

CURRENT STATUS OF TREATMENT FOR DIVERTICULITIS

PROEFSCHRIFT

Ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. H. Brinksma
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op donderdag 11 april om 12.45

door

Bryan Joost Marinus van de Wall

geboren op 19 augustus 1985
te Meyrin, Zwitserland.

Promotiecommissie

Promotor: Prof. Dr. I.A.M.J. Broeders

Co-promotoren: Dr. E.C.J. Consten en Dr. W.A. Draaisma

De promotor en co-promotoren hebben dit proefschrift goedgekeurd.

Cover design: Bryan van de Wall in cooperation with Okan Bastian

Lay-out: Bryan van de Wall

Drukwerk: Gildeprint Drukkerijen – The Netherlands

The production and distribution of this thesis was financially supported by:

Nederlandse Vereniging van Endoscopische Chirurgie (NVEC), ZonMW, Universiteit van Twente, Nycomed BV, Johnson & Johnson Medical BV, Covidien Nederland BV, Olympus BV, Gildeprint Drukkerijen.

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ISBN: 978-94-6108-426-2

Aan mijn ouders

Contents

Chapter 1	Introduction Outline of thesis
PART I:	CURRENT PRACTICE
Chapter 2	Treatment for diverticulitis not thoroughly researched.
Chapter 3	Dutch College of General Practitioners' practice guideline 'Diverticulitis' from a surgical perspective.
PART II:	ASPECTS ON DECISION-MAKING IN ACUTE DIVERTICULITIS
Chapter 4	The value of inflammation markers and body temperature in acute diverticulitis.
Chapter 5	Dietary restrictions for acute diverticulitis: Evidence based of expert opinion?
Chapter 6	Endoscopic evaluation of the colon after an episode of diverticulitis: a call for a more selective approach.
PART III:	ASPECTS ON DECISION-MAKING FOR ELECTIVE RESECTION
Chapter 7	Treatment of diverticulitis in young versus elderly patients: A meta-analysis of literature.
Chapter 8	Does the presence of diverticular abscess prelude surgery?
Chapter 9	Quality of life of patients with diverticular disease underestimated. A multicenter cross-sectional study.
Chapter 10	Effect of elective resection for diverticular disease on quality of life and discomfort caused by abdominal symptoms.
Chapter 11	DIRECT trial: Diverticulitis Recurrences or Continuing Symptoms Treatment; Operative versus Conservative Treatment. A MULTICENTER RANDOMISED CLINICAL TRIAL
Chapter 12	Summary and general discussion Future perspectives

Chapter 13

Nederlandse samenvatting

Curriculum vitae

List of publications

Dankwoord

Chapter 1

Introduction

Outline of thesis

Introduction

Diverticular disease

Diverticula are outpouchings that occur at weak points in the colonic wall where small blood vessels enter the circular muscle layer. Diverticula are most frequently found in the distal part of the colon, with 90% of patients having the sigmoid colon involved.¹ Most patients who have diverticulosis remain asymptomatic; however an estimated 15-20% will develop diverticulitis.² Acute diverticulitis is a complication of diverticulosis that occurs when these outpouchings become infected. It is theorised that inflammation occurs when the entrance to the diverticulum is obstructed by faecal matter leading to bacterial overgrowth and partial necrosis of the diverticular wall.

To date, consensus appears to be lacking on several aspects regarding the diagnostic approach and treatment of diverticulitis. This has led to a joint Dutch initiative, the Dutch Diverticular Disease Collaborative Study Group. This study group is a cooperation of the Academic Medical Center Amsterdam, Erasmus Medical Center Rotterdam, Kennemer Hospital Haarlem, Meander Medical Center Amersfoort, Saint Lucas Andreas Hospital Amsterdam aiming to deliver evidence in the form of both retrospective and prospective studies to end these persisting controversies.

Controversies in acute diverticulitis

Diverticulitis is a relatively mild disease. Approximately 5-10% of patients present with complications such as abscess and/or perforation. Computed tomography scanning (CT-scan) and, to lesser extent, ultrasonography are frequently used in discriminating complicated from uncomplicated episodes of diverticulitis.³⁻⁵ Several studies have suggested that infection markers such as temperature, white blood cell count and C-reactive protein might also help to determine which patients are at higher risk of having complications.⁶⁻⁸ The exact role of these factors however remains unclear.

When complications are excluded, patients are principally treated conservatively. Several guidelines have been published advocating the use of dietary restrictions for treating the acute phase of a diverticulitis episode.⁹⁻¹¹ Notably, there appears to be no consensus with regard to the degree of restrictive measures. Diets ranging from nil per os to solid foods are advised. Moreover, evidence supporting the use of dietary restrictions is lacking. In the Netherlands approximately 10% of physicians use a normal unrestricted diet.¹² Based on these facts it is questionable whether dietary restrictions are necessary for treating acute diverticulitis.

After successful conservative management of an episode of diverticulitis, routine colonoscopy is traditionally advised to exclude colorectal malignancy.¹¹ The possible association between diverticular disease and colorectal cancer, however, is still under debate.¹³⁻¹⁴ Evidence supporting the guidelines is controversial. As suggested in the study of Lau et al, potentially a more selective use of colonoscopy in patients with diverticulitis is in order.

Controversies in elective resection

The indication for elective sigmoid resection currently is one of the most controversial topics. Approximately 20% of patients develop recurrences after a conservatively treated episode of diverticulitis.¹⁵ Traditionally elective resection was advised after a second episode of diverticulitis. It was thought that patients with recurrent attacks were at 60% risk to develop complications and were less likely to respond to medical treatment.¹⁶ More recent studies have demonstrated that complications mostly occur during a primary manifestation of diverticulitis. Complications occur in only 5% of patients with recurrent episodes.¹⁷⁻¹⁸ Elective resection as a prophylactic procedure to prevent further complications does not seem warranted. More recent guidelines recommend a more tailored approach taking age, the severity of diverticulitis episodes and quality of life into account.³

Age is generally thought to be related to the course of disease. Several studies have demonstrated that patients younger than 50 years have a higher risk to develop diverticulitis recurrences and complications compared to older patients.¹⁹⁻²⁰ An equal amount of studies however did not find such a relation.²¹⁻²² Due to the great amount of studies published on this matter it is difficult to determine which role age should play in the decision to perform elective resection.

The presence of abscess in patients presenting with diverticulitis has also been described to be related to further complicated recurrences. Guidelines typically advise that elective resection should be performed after an episode of complicated diverticulitis.³ This recommendation is based on a study reporting that 41% of patients with diverticular abscess develop severe recurrent sepsis.² Guidelines also suggest that expectant management is possible. New evidence is needed to clarify this contradiction.

Quality of life is becoming the most important factor in the decision whether or not to perform elective resection.²³ As described previously 20% of patients with diverticulitis develop recurrences. Approximately 40-80% also has persisting abdominal complaints.¹⁵ Both recurrences and ongoing complaints have a detrimental effect on the quality of life. A major pitfall of quality of life is the fact that there frequently is a discrepancy between how patients experience their quality of life and how physicians perceive the quality of life of their patients.²⁴⁻²⁵ Understanding this difference is important when surgeons are taking decisions on elective resection based on their own perception of the quality of life of their patients.

Another major component that should be considered is the effect of elective resection on quality of life. Although resection minimizes the risk of recurrent disease and relieves the majority of patients from ongoing complaints, the actual effect on quality of life is not well understood. This uncertainty combined with the risk of complications and mortality, has led to reluctance among surgeons to perform resection.^{23,26} Studies on subjective improvement are therefore needed.

Outline of the thesis

As an introduction to this thesis, **chapter 2 and 3** describe the clinical features of different stages of diverticulitis and discusses controversies in current treatment strategies. The controversies clarify the need for new evidence to optimise decision-making in all aspects of the disease.

In **chapter 4-6** several aspects are addressed involving decision-making around the acute phase of a diverticulitis episode. Controversies in key-components of the decision on elective sigmoid resection are discussed in **chapter 7-10**. We end our thesis with the protocol of a randomised clinical trial aiming to compare elective resection with conservative treatment in patients with recurring and ongoing complaints after an episode of diverticulitis (**chapter 11**).

The studies presented in this thesis were guided by the following research questions:

- What is the value of body temperature, white blood cell count and C-reactive protein in discriminating complicated from uncomplicated diverticulitis in patients presenting at the emergency department (**chapter 4**)?
- Does the use of dietary restrictions for treating acute diverticulitis shorten hospital stay (**chapter 5**)?
- What is the benefit of performing colonoscopy after a conservatively treated episode of diverticulitis (**chapter 6**)?
- Is diverticulitis a more aggressive disease among patients younger than 50 years with regard to recurrences, complications and the need for surgery compared to older patients (**chapter 7**)?
- Are patients with diverticular abscess at higher risk of developing recurrences, complications or requiring surgery compared to patients with uncomplicated diverticulitis (**chapter 8**)?
- Is there a discrepancy in how patients and surgeons perceive quality of life (**chapter 9**)?
- What is the effect of elective resection on quality of life and abdominal symptoms in patients with recurrent or ongoing complaints after an episode of diverticulitis (**chapter 10**)?

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Chapter 2

Treatment for diverticulitis not thoroughly researched

Werner Draaisma
Bryan van de Wall
Jefrey Vermeulen
Cagdas Unlu
Niels de Korte
Hilko Swank

Nederlands Tijdschrift voor Geneeskunde 2009; 153(39):1919-1923

(Translated by Jefrey Vermeulen)

Abstract

In the Netherlands approximately 14,000 patients are referred to hospital for diverticular disease each year. Overall controversy persists about four aspects of treatment of the different stages of diverticulitis, i.e. the role of antibiotics in the treatment of mild diverticulitis, the question of whether elective surgical resection is justified in recurrent diverticulitis or in persisting abdominal symptoms after an episode of diverticulitis, the question of whether patients with purulent peritonitis due to perforation may be treated with laparoscopic peritoneal lavage instead of Hartmann's procedure, and finally, whether resection with a primary anastomosis is a feasible and safe alternative to Hartmann's procedure in the surgical treatment of Hinchey III or IV diverticulitis. These questions will be addressed in four upcoming Dutch randomized trials.

Introduction

Diverticulosis is a common disorder of the colon wall in westernized countries. The pathogenesis of this structural abnormality is probably multifactorial involving low-fibre-dietary habits, changes in colonic motility and wall structure associated with aging. The prevalence of diverticulosis is estimated at 50-70% in individuals older than 80 years. Below the age of 40, it is observed in less than 10% of the people.¹ Diverticulosis is most notable in the left colon, with up to 99% having some degree of sigmoid involvement. Several symptoms can be related to the presence of diverticulosis. Symptomatic diverticulosis refers to the condition in which the patient experiences recurrent abdominal pain and bloating. Complicated diverticulosis (diverticular disease) refers to the different stages of diverticulitis or diverticular bleeding. Left lower quadrant pain whether or not accompanied by fever is almost universal in sigmoid diverticulitis. The incidence of diverticular disease is estimated at 75-150 per 100.000 patients each year, which results in 14.000 hospital admissions each year. The annual costs to treat diverticular disease are 40-80 million Euros.¹⁻²

Diverticulitis is the most usual complications of diverticulosis, affecting 15-20% of patients.³ The pathophysiology of diverticulitis remains poorly understood. Due to a lack of good quality research, the optimal treatment of this ever more common disease is still debatable.

Four trials with different research questions all involving important issues concerning the treatment of different manifestations of diverticulitis have evolved in 2008. This has led to a joint Dutch initiative: the "Dutch Diverticular Disease Collaborative Study Group" (3D-study group). Herein we outline the different trials of the 3D-study group and discuss their importance.

Clinical features of diverticulitis

Patient suffering from diverticulitis will present with abdominal pain at the left lower quadrant, fever and an elevated white blood cell count (table 1).⁴ Most often the diagnosis of diverticulitis can be made on clinical ground, but sometimes clinical features can be non-specific and misleading. Other diagnosis like irritable bowel syndrome or gynaecological disorders must be excluded. In case of mild symptoms, additional radiographic modalities are not necessary to justify clinical diagnosis. These patients can be treated conservatively with oral fluids with or without additional antibiotics on an out-patient basis. Relief of symptoms is expected within 2-3 days. Imaging is indicated when complaints persist or worsen⁵⁻⁶ if necessary, in-hospital treatment of diverticulitis with restricted oral intake and intravenous antibiotic treatment is initiated.⁶⁻⁷

Abdominal ultrasound is known as a relatively cheap and reliable non-invasive method to diagnose diverticulitis. In the hands of an experienced radiologist, ultrasonography has a reported sensitivity of 92% and a specificity of 90%. In computed tomography (CT) scanning, sensitivity and specificity are reported as high as 94 and 99%, respectively.⁸⁻⁹ CT

has the advantage that it defines the extent of the affected colon as well as it identifies abscesses and perforations more accurately than ultrasonography. However, CT is more expensive and involves radiation.⁸⁻⁹

Table 1. Frequency of symptoms in diverticulitis.

Symptom	Frequency (%)
Abdominal tenderness in the left lower quadrant	93-100
Elevated white blood cell count	69-83
Fever	57-100
Nausea	10-30
Vomiting	15-25
Constipation	10-30
Diarrhea	5-15
Dysuria	5-20
Change in urinary habits	6-25

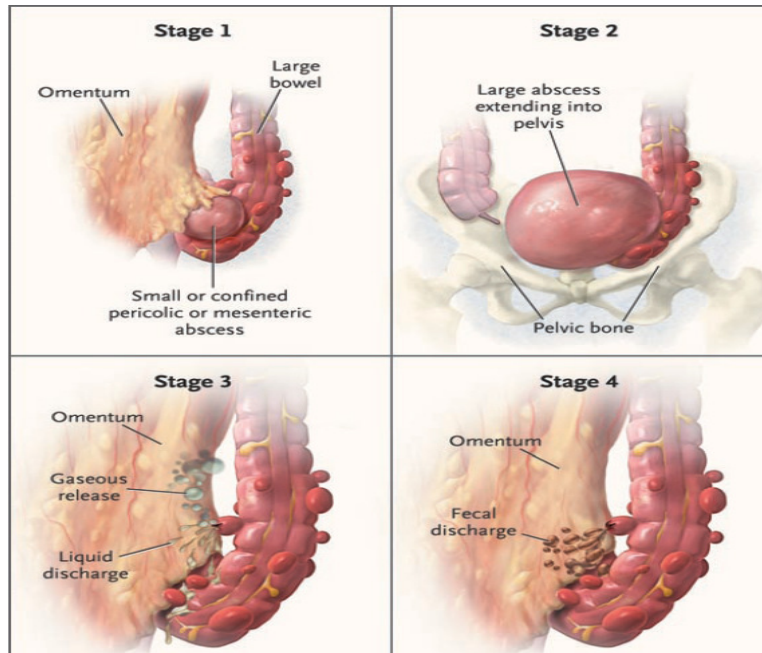
The Hinchey classification

Several classifying systems have been introduced to describe the different stages of diverticular disease. The Hinchey classification is most widely recommended.¹⁰ Traditionally, Hinchey's classification has been used to distinguish four different stages of perforated diverticulitis (figure 1), but improvements in imaging modalities has led to a modification of this classification. The modified Hinchey classification describes five categories of diverticulitis, with two sub-categories in case of a Hinchey stadium I (table 2).¹¹ In general Hinchey Ia is regarded as mild diverticulitis, Hinchey Ib-II as moderate diverticulitis and Hinchey III-IV as severe complicated diverticulitis.

Table 2. Original and modified classification of (perforated) diverticulitis by Hinchey.

Hinchey classification		Modified Hinchey classification	
Stadium	Findings	Stadium	Findings
		0	Mild non-complicated diverticulitis
I	Pericolic phlegmon or abscess	Ia	Localized pericolic inflammation or phlegmon
		Ib	Localized pericolic abscess
II	Pelvic, abdominal or retroperitoneal abscess	II	Pelvic, abdominal or retroperitoneal abscess
III	Purulent peritonitis	III	Purulent peritonitis
IV	Faecal peritonitis	IV	Faecal peritonitis

Figure 1. The Hinchey Classification of (perforated) diverticulitis.



Controversies in the treatment of diverticulitis

Literature

When discussing the optimal treatment for the different stages of diverticulitis, three main questions remain unanswered: 1) Is there a benefit of additional antibiotics in the treatment of mild diverticulitis?; 2) What is the benefit of elective surgery in case of recurrent or persistent complaints in diverticulitis?; and 3) What is the optimal treatment strategy in Hinchey III and IV perforated diverticulitis? Recently, a systematic concerning the above-mentioned issues was published, which showed that hard evidence is still missing.¹²

Randomised trials are lacking in the current literature, at present evidence is only based on retrospective studies and some prospective cohort studies with limited numbers of patients.

Antibiotics or not?

Most patients with mild (Hinchey I-II) diverticulitis can be treated conservatively without surgical intervention.⁵ Recently, the benefit of additional antibiotics in the conservative treatment of these patients is debated. In 2007 the results of the retrospective study in which patients with mild diverticulitis treated with antibiotics (n=118) were compared

with patients without additional antibiotics (n=193), were published.¹³ Of the patients who were treated with antibiotics, 3% needed to undergo surgical intervention in a later stage during initial hospital admission, compared to 4% of the patients that were initially treated without antibiotics. After a mean follow-up 30 months, 29% of the patients with antibiotics developed complications that needed surgical intervention or recurrence of diverticulitis. This was 28% for the patients that were initially treated without antibiotics. In conclusion, the authors of the study stated that additional antibiotics probably will not provide better outcome in the treatment of mild diverticulitis. However, selection bias may have played an important role, as the more severely affected patients are more likely to have been treated with additional antibiotics.

In 1996 questionnaires regarding the treatment of diverticulitis were sent to all surgeons and internists in the Netherlands. The results of this questionnaire showed that both specialists had different thoughts about the benefit of antibiotics in diverticulitis treatment. Surgeons were more conservative in prescribing antibiotics compared to internists: 55% versus 77%, respectively.¹⁴ A similar questionnaire, provided by the 3D-study group in 2009, demonstrated a significant decrease in antibiotic use: currently, only 10% of both the surgeons and internists recommended additional antibiotics in the treatment of mild diverticulitis (unpublished data).

As cost-effectiveness and antibiotic resistance are important issues in improving current health care, and hard evidence is lacking in current literature, prospective assessment of the benefit of antibiotics in the treatment of mild diverticulitis is warranted.

Diverticular recurrences or persistent complaints: resection or not?

After a conservatively treated first episode of diverticulitis, 20-25% of patients will develop a recurrence of diverticulitis.¹² Traditionally, patients were advised to undergo resection of the affected colon segment after a second episode of diverticulitis,⁶⁻⁷ because of a supposed higher risk on complications (fistulae/abscess formation/ perforation) and morality in case of another recurrence.¹⁵ Today, surgeons and internists are more conservative. Recent studies have observed that the severity of recurrent diverticulitis is comparable to previous episodes. Only 5-8% of the patients that were treated conservatively for diverticulitis will develop complications during follow-up.¹⁶⁻¹⁷ Subsequently the benefit of elective surgery to prevent perforated recurrent diverticulitis is debatable.

On the other hand, a more specified subgroup of patients might benefit from prophylactic surgery. After conservative treatment, 40-80% of the patients will present with persistent complaints related to diverticular disease.¹⁷⁻¹⁸ These patients complain of prolonged abdominal tenderness with or without changed stool habits for more than three months after recovery from the initial diverticular inflammation. It is important that other colonic disorders have been excluded.¹² The daily presence of abdominal tenderness affects the quality of life of these patients and is associated with higher costs due to frequent specialist consultation, analgesic use and absence from work.¹⁸⁻¹⁹ The question remains, for how long can a conservative strategy be acceptable for patients with prolonged abdominal complaints after diverticulitis?

Elective resections will not only prevent complicated recurrences, but might also be beneficial in treating prolonged abdominal complaints after diverticulitis.²⁰ However, the

supposed benefit of elective surgery must be weighed against possible perioperative complications. Major complications, such as anastomotic leakage is observed in 5-10% of patients and there is even a risk on mortality (0-1%).²¹ As good randomised clinical trials are lacking in current literature, the optimal treatment of patients suffering from recurrent diverticulitis or ongoing abdominal complaints after diverticulitis, is still a matter of debate.

Surgical treatment of Hinchey III-IV diverticulitis

Free bowel perforation caused by diverticulitis is one of the most severe and complicated forms of diverticular disease. Perforation of a large diverticular abscess (Hinchey III) or the bowel wall itself (Hinchey IV) into the abdominal cavity is found in about a quarter of patients with acute diverticulitis. It will lead to generalized peritonitis, with a mortality rate up to 35%.²² In this category of patients emergency surgery is indicated. The optimal strategy remains debatable.

Hartmann's procedure (HP). The most commonly performed surgical procedure in these cases is HP, in which the affected sigmoid is removed with the establishment of an end-colostomy.²³ Restoration of bowel continuity can eventually take place in a second operation, but with a significant risk on postoperative morbidity and even mortality. This is the main reason why almost 40% of patients after HP will be left with a permanent end-colostomy.²⁴

Resection with primary anastomosis (PA). Alternatively, resection of the affected bowel with primary anastomosis with or without temporary "protective" diverting loop ileostomy can be performed. Reversal of this loop ileostomy can be performed as a local procedure without the need for laparotomy.

Several studies have tried to compare both surgical strategies, including three systematic reviews.^{22-23,25} In the latest review of 2007, postoperative mortality is estimated at 18% after HP and 9.9% after PA.²³ Anastomotic leakage was observed in 3% and 6% respectively. Postoperative complication rates varied from 25% to 50% and were not different between both procedures. However, patients with higher risks on postoperative complications were found to undergo more often HP than PA. The effect of this selection bias on the presented results is unknown, but makes it hard to make a good comparison between both surgical strategies. A randomised controlled trial between both strategies is warranted.

Laparoscopic lavage. Recently a new strategy for treating Hinchey III diverticulitis has been introduced: laparoscopic lavage and drainage without resection. A prospective cohort study of 92 patients, who were treated with laparoscopic lavage with 4 liters of warm saline and the placement of two abdominal drains, showed an uncomplicated outcome in 89%.²⁶ Three patients died due to multi organ failure (3%). Laparoscopic lavage seems to be a promising alternative for HP or PA, as the latter have higher mortality rates. It is therefore of interest to compare this new laparoscopic strategy with the current mostly performed open resectional strategies in a randomized controlled trial.

Considerations

The optimal treatment for the several different stages of diverticular disease is still a matter of debate. Patients with mild and non-complicated diverticulitis can be treated conservatively, without the need for surgical intervention. It remains unclear if these patients need to be treated with antibiotics and if the use of antibiotics in the treatment of mild diverticulitis indeed leads to a faster recovery, shorter hospital stay and faster return to work, which have important socio-economic implications.

Prophylactic surgery seems not to be indicated for patients after one episode of diverticulitis as only a small number of these patients will develop complications in the future that require emergency surgery. Nevertheless, patients with persistent complaints after diverticulitis could benefit from elective surgery. The suspected benefit from surgery needs to be weighed against general postoperative morbidity like wound infection, bleeding and severe complications like anastomotic leakage and even mortality.

The optimal treatment of Hinchey III and IV diverticulitis also remains controversial.

Patient with generalized purulent peritonitis (Hinchey III) might benefit from laparoscopic lavage and drainage, if in these patients sigmoid resection by laparotomy, with accompanying high morbidity and mortality rates, can successfully be withheld.

Understandably, patients with generalized faecal peritonitis (Hinchey IV) need to undergo emergency surgery. The question remains which strategy is superior. Possibly PA is a better and safer option in this category of patients than HP.

Dutch trials

Recently, in the Netherlands the 3D-study group is established that will assess the abovementioned aspects with regard to the treatment of diverticulitis. Four randomized clinical trials have been designed in different hospitals under auspices of the 3D-study group. From the Amsterdam Academic Medical Center, the Saint Lucas Andreas Hospital and the Haarlem Kennemer Gasthuis Hospital, the DIABOLO-trial is initiated. This study will randomize patients with mild diverticulitis between treatment with intravenous administered antibiotics, outpatient treatment with oral antibiotics, or treatment without antibiotics.

The Amersfoort Meander Medical Center has designed another randomized trial: the DIRECT-trial. In this study patients with persistent complaints after one or more episodes of diverticulitis will be randomized between elective resection of the affected bowel segment and a conservative policy.

From the Rotterdam Erasmus University Medical Center and Amsterdam Academic Medical Center the LADIES-trial is initiated. The LADIES-trial will assess the optimal surgical treatment for perforated diverticulitis. Patients with Hinchey III diverticulitis will be randomized between laparoscopic lavage and open resectional surgery (LOLA-arm). In addition, the patients with Hinchey III diverticulitis that are randomized for open resectional surgery and all patients with Hinchey IV will be randomized between HP and

PA (DIVA-arm). The studies have started in 2010 and are intended to provide more evidence with regard to the optimal treatment for different stages of diverticular disease.

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Chapter 3

Dutch College of General Practitioners' practice guideline "Diverticulitis"

from a surgical perspective

Bryan van de Wall
Werner Draaisma
Esther Consten

On behalf of the Dutch Diverticular Disease Collaborative Study Group

Nederlands Tijdschrift voor Geneeskunde 2011;155:A4140

Abstract

Diverticulitis is a common disease which, in the Netherlands, leads to approximately 13.500 hospitalizations annually. This figure represents merely 12% of actual cases encountered by general practitioners. The combined factors of older age, pain in the left lower abdomen which increases on movement, an elevated C-reactive protein level, the absence of vomiting and a prior episode of diverticulitis are highly predictive for this clinical diagnosis. This prediction model has been developed in secondary care centres. Its diagnostic value has yet to be proven in general practice.

Discriminating between complicated and uncomplicated episodes of diverticulitis in the primary care setting is challenging. As clear practice guidelines for referring patients are lacking, collaboration between primary and secondary care must be enhanced for the development of a prediction tool that can help identify the complicated cases at an earlier stage.

Introduction

Recently, the Dutch College of General Practitioners published practice guidelines on diverticulitis. The full text of this document can be found on the NHG-website (<http://nhg.artsennet.nl>).

Despite the high incidence of diverticulitis in the Netherlands, hard evidence on diagnostic work-up and treatment is scarce. To our opinion, the General Practitioners' (GP) guideline suffers from several short-comings. Firstly, should the GP perform radiological examination and, if so, what is the preferred modality? Secondly, when should the GP refer the patient to secondary care?

Serologic and radiological examination

Approximately 13.500 patients are hospitalised for diverticulitis on a yearly basis in the Netherlands.¹ This group encompasses 12% of the 112.000 patients presenting with clinical signs of diverticulitis at the GP's office.² Logically, the authors of the GP guideline conclude that the diagnosis should preferably be made on a clinical basis in primary care. Radiological examination should be used sparingly. They suggest that a reliable diagnosis can be made based on a combination of pain in the left lower abdomen, elevated C-reactive protein and the absence of vomiting.³

This triad of symptoms however only occurs in a quarter of all patients with diverticulitis. Moreover, the authors based their advice on a study that was performed in secondary care. It is likely that the population of this study differs from patients encountered in primary care with regard to disease severity. As the a-priori chance of finding diverticulitis in secondary care is probably higher, the diagnostic value if this triad of symptoms in a primary setting remains doubtful.

A valuable addition to this triad is a history of previous episodes of diverticulitis.⁴ A recent study has demonstrated this to be the most predictive factor in the diagnosis of diverticulitis. The diagnosis can be made in approximately 86% of patients by using the triad in combination with a positive history of diverticulitis, high age (>71 years) and aggravation of pain on movement. Unfortunately, this study was also performed in secondary care. The value of this diagnostic model remains uncertain in primary care.

In light of the high incidence and the fact that diverticulitis is a relatively mild disease, we agree that establishing the diagnosis on a clinical basis at the GP's office is warranted. It must be emphasized however that a diagnostic model should be developed specifically for a primary care setting. Until then, diverticulitis will predominantly remain a radiological diagnosis.

To our opinion, the preferred radiological modality for diverticulitis should be computed tomography scanning (CT-scan). The sensitivity of ultrasonography is much lower compared to CT-scan (61% versus 81%).⁵ CT-scan also has a higher accuracy in assessing the extent and severity of the disease and can exclude other pathology.⁵

Referral to secondary care

More important than the question regarding the diagnostic work-up is the question when to refer the patient to secondary care. As previously described, diverticulitis is a relatively mild disease. Approximately 10% develop potentially life-threatening complications such as abscess and perforation. As it is difficult to predict which patients develop these complications, an unambiguous advice regarding whom to refer to secondary care is practically impossible.

Authors of the GP's guideline advise referring patients in case of *défense musculaire*, signs of ileus, palpable mass in the abdomen, rectal blood loss, hypotension or high fever.

Despite these criteria, it is likely that some patients with complications will be missed. To our opinion, the general condition of the patient should form the most compelling factor for patient referral. Patients should be frequently reassessed to determine deterioration. The previously described symptoms should increase the index of suspicion for complications. They should not be used as absolute criteria for referral.

It should be emphasized that all previously described advices are based on expert-opinion. Collaboration between primary and secondary care is mandatory to develop prediction models that may help the GP in patient referral.

In the Netherlands a study group has been formed aiming to provide high level evidence for treatment guidelines on diverticulitis (Dutch Diverticular Disease Collaborative Study Group – 3D study group). Three randomised clinical trials have been initiated investigating the use of antibiotics for mild diverticulitis, the benefit of elective resection for persisting and/or recurrent disease and a trial comparing laparoscopic lavage to resection (Hartmann's procedure versus primary anastomosis) for perforated diverticulitis. This group forms a solid basis for a joint effort in developing the highly anticipated predictive and diagnostic models for use in the GP's office.

Conclusion

To date diverticulitis predominantly remains a radiological diagnosis. Diagnostic models are necessary for establishing the diagnosis on a clinical basis in primary care.

CT-scan should be the preferred modality in case radiological examination is required. It both has a high sensitivity and creates the opportunity to accurately assess the extent of the disease and exclude other pathology.

The most important factor in the decision on patient referral to secondary care, should be the general condition of the patient. Symptoms such as *défense musculaire*, signs of ileus, palpable mass in the abdomen, rectal blood loss, hypotension or high fever should increase the index of suspicion for complications.

Collaboration between primary and secondary care is necessary to develop prediction and diagnostic models that can help the GP in all aspects of decision-making.

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Chapter 4

The value of inflammation makers and body temperature in acute diverticulitis

Bryan van de Wall
Werner Draaisma
Rosa van der Kaaij
Esther Consten
Marinus Wiezer
Ivo Broeders

Colorectal Dis. 2012 Oct 22. doi: 10.1111/codi.12072. [Epub ahead of print]

Abstract

Background: To determine the diagnostic value of serologic infection markers and body temperature in discriminating complicated from uncomplicated diverticulitis.

Methods: Patients in whom diverticulitis was pathologically or radiologically proven at presentation were included. Patients were classified as either complicated (Hinchey Ib, II, III and IV) or uncomplicated (Hinchey Ia) diverticulitis. The discriminative value of C-reactive protein (CRP), white blood cell count (WBC) and body temperature at presentation was tested.

Results: A total of 426 patients were included in this study of which 364 (85.4%) presented with uncomplicated and 62 (14.6%) with complicated diverticulitis. Only CRP was of sufficient diagnostic value (AUC 0.715). The median CRP in patients with complicated diverticulitis was significantly higher than patients with uncomplicated disease (224 mg/l, range 99-284 versus 87 mg/l, range 48 – 151). Patients with a CRP of 25 mg/l had a 14.7% chance of having complicated diverticulitis. This increased from 23.2% at CRP value of 100 mg/l to 47.1% for 250 mg/l or higher. The optimal threshold was reached at 175 mg/l with a positive predictive value of 36.3%, negative predictive value of 92.3%, sensitivity of 60.7% and a specificity of 81.6%.

Conclusion: WBC and body temperature are of no value in discriminating complicated from uncomplicated diverticulitis. CRP can only be used as an indicator for the presence of complications. A low CRP does not mean that complicated disease can safely be excluded. Therefore, radiological examination remains a vital part in the diagnostic work-up of patients presenting with diverticulitis.

Introduction

Acute diverticulitis is a common disease and results in more than 13.000 hospitalizations per year in the Netherlands.¹ Approximately 10-15% of all patients with acute diverticulitis present with complications such as abscess, fistulae and perforation.² When suspected, these patients require adequate radiological examination by ultrasound and/or computed tomography (CT-scan) in order to accurately assess disease severity and the need for surgical intervention. Clinical evaluation alone has proven insufficient in order to distinguish complicated from uncomplicated episodes of diverticulitis.³⁻⁴

The objective parameters body temperature and serologic inflammation markers, C-reactive protein (CRP) and white blood cell count (WBC), are often determined when diverticulitis is suspected. It has been suggested that these parameters might help to differentiate between complicated and uncomplicated diverticulitis in daily practice.⁴⁻⁶ The exact role and clinical value remains unclear.

Our study aims to investigate the relation between body temperature, serologic inflammation markers and abnormalities on radiologic imaging in patients with diverticulitis in two hospitals.

Methods

Study design and setting

This retrospective cross-sectional study was performed in the Meander Medical Centre Amersfoort and St. Antonius Hospital in Nieuwegein, two large regional teaching hospitals in the Netherlands. Data was collected between January 2005 and June 2011.

Study population

A diagnosis specific code was used to identify all patients presenting with an episode of diverticulitis at the emergency department. All patients underwent a standard diagnostic work-up including an auricular measurement of body temperature and serologic blood testing (CRP, WBC).

Only patients in whom diverticulitis was proven on the day of presentation by computed CT-scan or pathological examination were included. Radiological criteria for diagnosing diverticulitis were the presence of diverticulae in the descending and/or sigmoid colon, localised colonic wall thickening, surrounding fat stranding, free fluid, abscess formation or extraluminal air on CT-scan.⁷ The CT-scan had to be performed on the day of presentation. Patients who underwent sonography only were excluded. Additionally, patients who underwent CT-scan on another day than the day of presentation were excluded.

Pathological criteria were the presence of diverticulae, signs of inflammation (and/or perforation) in the resected sigmoid specimen of patients who underwent emergency surgery on the same day as the day of presentation.

Baseline characteristics

Baseline characteristics were gathered for both in- and excluded patients. Patient characteristics, symptoms during presentation and American Society of Anesthesiologists (ASA) Physical Status classification scores were collected from the hospital uptake and discharge forms. The total number of hospitalizations and/or presentations at the emergency department for diverticulitis was registered.

Study outcome and markers

All included patients were divided into two groups. Patients presenting with a Hinchey Ia diverticulitis were classified as “uncomplicated diverticulitis.” Patients who presented with either Hinchey Ib, II, III or IV diverticulitis were classified as “complicated diverticulitis.” The Hinchey classification is described in table 1.⁸ The classification was based on the radiological reports of CT-scans. Distinction between Hinchey III and IV was performed based on the surgical reports of patients who underwent emergency surgery for perforated diverticulitis on the day of presentation. The values of the serologic markers, CRP (milligrams/Liter) and WBC count (10^9 /Liter) were extracted from the laboratory records. Body temperature (degrees Celsius) at presentation was collected from the hospital admission forms.

Table 1. Modified Hinchey Classification.

Hinchey	Description
Ia	Pericolic inflammation
Ib	Localised para colonic or mesenteric abscess
II	Pelvic abscess
III	Perforated diverticulitis with purulent peritonitis
IV	Perforation of diverticulitis in the abdominal cavity with faecal contamination

Statistical analysis

Statistical software package SPSS 19.0 was used to analyze the results. Descriptive statistics were provided of all variables for excluded, complicated and uncomplicated cases separately. Continuous variables were described as means (with standard deviation) or medians (with range between first and third tertile) according to their distribution. For categorical variables, the counts and percentages were calculated. For explorative purposes, differences in baseline characteristics between patients with uncomplicated and complicated diverticulitis were analyzed using an independent T-test or Kruskal-Wallis according to the distribution of continuous variables and the Fisher’s exact test for categorical variables. These tests were also used for analyzing differences between included and excluded patients. A p-value < 0.05 was considered significant. Receiving operating characteristics (ROC) analysis was used for analyzing the diagnostic value of CRP, WBC count and temperature. Only markers with an area under the curve (AUC) > 0.7 were selected for further analysis. The sensitivity, specificity, positive and negative predictive value of these selected markers was calculated for different

thresholds. Histograms were constructed for patients with complicated and uncomplicated diverticulitis separately.

Results

Participants

A total of 1277 consecutive patients presented with a clinically suspected episode of diverticulitis. Eight hundred and fifty-one patients were excluded because they either did not undergo CT-scan on the day of presentation (n=256), underwent sonography only (n=427) or no radiological examination at all (n=168). Analysis of these excluded patients demonstrated that they more frequently presented with a medical history of prior episodes of diverticulitis (19.0% versus 12.2%) compared to included subjects (table 2). Furthermore, excluded patients were less frequently hospitalised (65.7% versus 74.3%) and presented more frequently with typical pain in the left lower abdomen (64.0% versus 41.0%). Median values of CRP (64 mg/l versus 93 mg/l), WBC (11.0×10^9 /liter versus 12.2×10^9 /liter) and body temperature (37.4° Celsius versus 37.5° Celsius) at presentation were also lower among excluded patients.

A total of 426 patients were included in this study of which 364 (85.4%) presented with uncomplicated and 62 (14.6%) with complicated diverticulitis.

Baseline characteristics

Patients with complicated diverticulitis were of a significantly higher age (63.9 years) compared to patients with an uncomplicated episode (57.1 years) (table 2). In general, the group of patients with complicated diverticulitis consisted of patients with a higher ASA classification (ASA I: 25.8%; ASA II: 64.8%) compared to the group with uncomplicated diverticulitis (ASA I: 40.9%; ASA II: 50.5%).

Significantly more patients with a complicated episode presented with vomiting (25.8% versus 11.0%) and diffuse pain in the abdomen (19.6% versus 9.3%). Furthermore, patients with complicated diverticulitis were more frequently hospitalised (93.5% versus 71.2%).

Study outcome and markers

The median body temperature at presentation in patients with uncomplicated diverticulitis was equal to that of patients with a complicated episode (37.5° Celsius, range 36.2 – 38.9 versus 37.6° Celsius, range 36.3 – 39.0). The median WBC was significantly elevated in patients with complicated (15.3×10^9 /liter, range 11.5 – 20.5) compared to uncomplicated diverticulitis (12.0×10^9 /liter, range 10.1 – 15.0). Similarly, CRP was significantly higher in patients with a complicated episode (224 mg/l, range 99-284 versus 87 mg/l, range 48 – 151). The median CRP in patients with Hinchey Ib diverticulitis was 191 mg/l (range 80 – 270), Hinchey II 214 mg/l (range 128 – 295), Hinchey III 189 mg/l (range 85 – 305) and 263 mg/l (range 109 – 385) in patients with Hinchey IV diverticulitis. AUC statistics showed that only CRP had sufficient diagnostic value in discriminating between complicated and uncomplicated diverticulitis (AUC 0.715). The diagnostic value of body temperature (AUC 0.544) and WBC (AUC 0.578) was poor. The different

Table 2. Baseline characteristics of included and excluded patients.

		Uncomplicated diverticulitis (n=364)	Complicated diverticulitis (n=62)	Excluded patients (n=851)
Age at presentation		57.1 (SD 12.9)	63.9 (SD 13.6) [§]	56.8 (SD 13.4)
Male gender		156 (42.9%)	29 (46.8%)	376 (45.4%)
ASA	I	149 (40.9%)	16 (25.8%) [§]	412 (44.2%)
	II	184 (50.5%)	40 (64.5%) [§]	416 (48.4%)
	III	30 (8.2%)	6 (9.7%)	61 (7.2%)
	IV	1 (0.3%)	0	2 (0.2%)
Number of episodes	First	321 (88.2%)	53 (85.5%)	689 (81%)*
	Recurrent	43 (11.8%)	9 (14.5%)	159 (19%)
N days symptoms		3 (1-21)	5 (1 – 14)	3 (1-14)
Nausea		137 (37.7%)	24 (38.7%)	268 (31.5%)
Vomiting		40 (11.0%)	16 (25.8%) [§]	87 (10.2%)
Location abdominal pain				
	Left lower	154 (42.4%)	23 (37.5%)	546 (64%)*
	Right lower	67 (18.4%)	4 (7.1%)	51 (6%)
	Lower	98 (26.8%)	20 (32.1%)	159 (18.7%)
	Diffuse	34 (9.3%)	12 (19.6%) [§]	68 (8.0%)
	Other	11 (3.1%)	2 (3.6%)	27 (3.2%)
Hospitalised		259 (71.2%)	58 (93.5%) [§]	559 (65.7%)*
Hinchey	Ia	364 (85.4%)		n.a.
	Ib	-	23 (5.4%)	n.a.
	II	-	11 (2.6%)	n.a.
	III	-	20 (4.7%)	n.a.
	IV	-	8 (1.9%)	n.a.
CRP		87 (48–151)	224 (99–284) [§]	64 (4–268)*
WBC		12.0 (10.1–15.0)	15.3 (11.5–20.5) [§]	11 (6.1–18.6)*
Temperature		37.5 (36.2–38.9)	37.6 (36.3–39.0)	37.4 (36.2–38.8)*

* Significant difference between included (complicated and uncomplicated) and excluded cases.

[§] Significant difference between uncomplicated versus complicated cases.

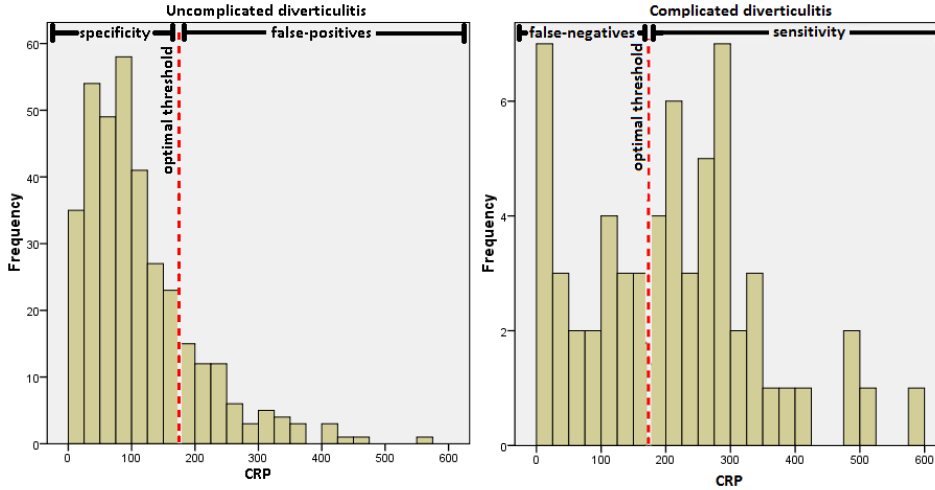


Figure 1. Frequencies of values for C-reactive protein encountered in patients with complicated and uncomplicated diverticulitis at presentation

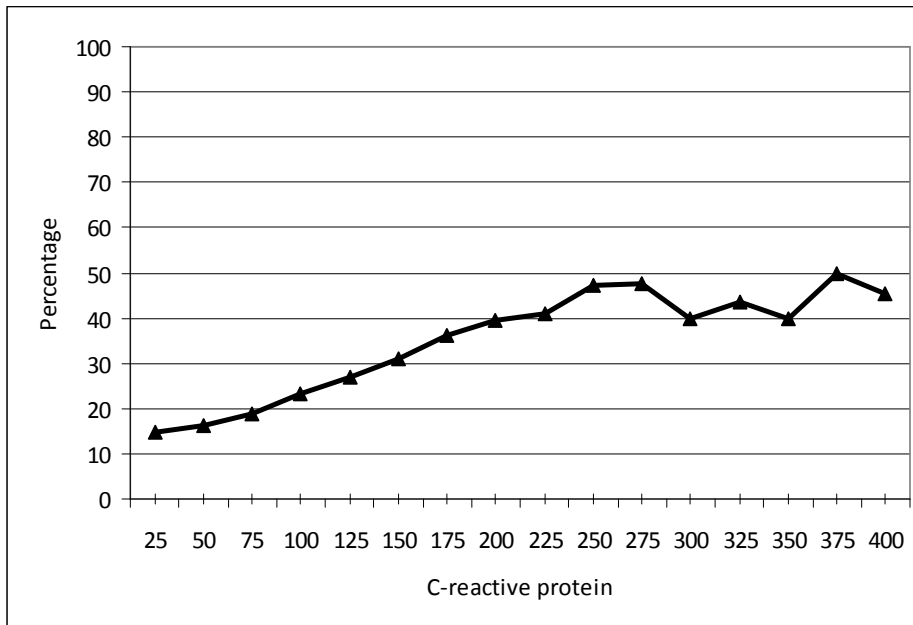


Figure 2. Positive predictive value plotted against C-reactive protein values.

frequencies CRP at presentation are depicted in figure 1 for both uncomplicated and complicated diverticulitis.

The results of ROC analysis of CRP are demonstrated in table 3. Patients with a CRP higher than 50 mg/l had a 16.2% chance of having complicated disease. This increased from 23.2% at a threshold of 100 mg/l to 47.1% for CRP higher than 250 mg/l (figure 2). The most optimal sensitivity and specificity was reached at a threshold of 175 mg/l. At this value the positive predictive value was 36.3%, negative predictive value 92.3%, sensitivity 60.7% and a specificity of 81.6%.

Table 3. Sensitivity, specificity, positive and negative predictive values of several cut-off points for C-reactive protein in distinguishing uncomplicated from complicated episodes of diverticulitis.

Cut-off point C-reactive protein	Positive predictive values	Negative predictive values	Sensitivity	Specificity
>25	14.7%	84.4%	88.5%	11.0%
>50	16.2%	90.0%	83.6%	25.5%
>75	18.7%	92.1%	80.3%	39.7%
>100	23.2%	93.4%	77.0%	55.8%
>125	27.0%	92.9%	70.5%	67.1%
>150	31.0%	92.6%	65.6%	74.8%
>175	36.3%	92.3%	60.7%	81.6%
>200	39.3%	91.5%	54.1%	85.6%
>225	40.9%	90.2%	44.3%	89.0%
>250	47.1%	89.8%	39.3%	92.4%
>275	47.5%	88.8%	31.1%	94.1%
>300	40.0%	87.2%	19.7%	94.9%
>325	43.5%	87.0%	16.4%	96.3%
>350	40.0%	86.2%	9.8%	97.5%
>375	50.0%	86.3%	9.8%	98.3%
>400	45.5%	86.1%	8.2%	98.3%

Discussion

Serologic inflammation markers and body temperature are frequently used to support the clinical diagnosis of acute diverticulitis. Although studies have suggested that these elevated markers can be used to differentiate between a complicated and uncomplicated episode, the exact role remains undefined.⁴⁻⁶

In general, patients with a complicated episode of acute diverticulitis present with considerably higher CRP compared to patients with uncomplicated episodes. The highest values are found in patients with Hinchey IV perforated diverticulitis with fecal peritonitis. Patients with Hinchey Ib, II and III diverticulitis have a relatively similar elevated median

CRP of approximately 200 mg/l. ROC statistics demonstrated that CRP at presentation may help to discriminate complicated from uncomplicated diverticulitis. To our opinion, however, its accuracy is not robust enough to completely abstain from additional radiological examination. This is best explained by examining the discriminative performance of CRP at its optimal threshold (175 mg/l). Approximately 81.6% of patients with uncomplicated diverticulitis present with a CRP lower than 175 mg/l (=specificity) (figure 1). Unfortunately, 39.3% of patients with a complicated episode also have a CRP below this threshold (false-negative). In other words, a low CRP does not mean that complications can safely be excluded.

CRP is only helpful as an indicator for the presence of complicated disease. Patients with a CRP of 25 mg/l have a 14.7% chance of having complicated disease (figure 2). This increases linearly to almost 50% in patients with 250 mg/l or higher after which the linear relation smooths out and the PPV remains approximately 50%.

Noteworthy, the high negative predictive values of approximately 90% for several CRP thresholds is mostly attributable to the relatively large amount of patients with uncomplicated (n=364) compared to patients with complicated (n=62) diverticulitis in this study. In other words, the high value is mostly induced by the high a-priori chance of finding no complications and not attributable to the diagnostic value of CRP. This further supports that CRP should not be used for excluding complicated diverticulitis.

Käser et al performed a similar study among 247 patients and reached the same conclusions with regard to the use of CRP in predicting complicated disease.⁵ Käser's study, however, found slightly different sensitivities, specificities, positive and negative predictive values and a higher optimal threshold (200 mg/l). This can partly be explained by the fact that the present study, for unknown reasons, had a different ratio between uncomplicated and complicated cases (5.9 : 1) when compared to Käser's study (2.8 : 1). No diagnostic value in WBC count was detected. Although the median WBC count was generally higher among patients with complicated diverticulitis, WBC count proved inadequate in discriminating complicated from uncomplicated disease. In addition, body temperature was of no diagnostic value as well.

As suggested in several studies, other parameters may be beneficial to discriminate between complicated and uncomplicated diverticulitis. Tursi et al described that patients with complicated disease had higher symptom scores (abdominal tenderness, pain at the lower left or right quadrant and fever) and elevated serologic markers.⁴ This is also underlined by the differences found in baseline characteristics in the current study. Patients with a complicated episode of diverticulitis were of a higher age and presented more frequently with vomiting and diffuse abdominal pain.

Possibilities for creating a full diagnostic model incorporating all the aforementioned factors were explored. As information bias was likely to have occurred in the collection of data on symptoms due to the retrospective nature of this study, we abstained from developing this model. However, measurements of serologic markers and body temperature as conducted for this study were part of the standard diagnostic work-up of patients presenting at the participating hospitals and systematically registered in a digital database. The quality of this data was therefore adequate in order to analyze these parameters.

The present study has some considerations that should be taken into account. Patients who underwent sonography (n=427) at presentation were excluded. The main reason for excluding these patients was because sonography has a low sensitivity of 61% and can less accurately assess disease severity compared to CT-scan.⁹ Including these patients would likely have led to severe misclassification bias.

By excluding these patients, and thus minimizing misclassification bias, selection bias might have occurred. Analysis demonstrated there was a statistical significant difference in location of abdominal pain, number of previous diverticulitis episodes, serologic markers and body temperature. Although statistically significant, the absolute difference is relatively small (table 2) and with it, the amount of selection bias. The exact effects of this selection bias on the study results, however, remain unclear.

In conclusion, WBC and body temperature are of no value in discriminating complicated from uncomplicated diverticulitis. CRP should only be used as an indicator for the presence of complications. A low CRP does not mean that complications can safely be excluded. Therefore, routine radiological examination will remain a vital part in the diagnostic work-up in patients presenting with diverticulitis. .

Acknowledgments

None

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Chapter 5

Dietary restrictions for acute diverticulitis:

Evidence based or expert opinion?

Bryan van de Wall
Werner Draaisma
Jan van Iersel
Rosa van der Kaaij
Esther Consten
Ivo Broeders

Submitted to the International Journal of Colorectal Disease.

Abstract

Background: Diet restrictions are usually advised as part of the conservative treatment for the acute phase of a diverticulitis episode. To date, the rationale behind diet restrictions has never been thoroughly studied. This study aims to investigate which factors influence the choice of dietary restriction at presentation. Additionally, the effect of dietary restrictions on hospitalization duration is investigated.

Methods: All patients hospitalized for Hinchey 0, Ia or Ib diverticulitis between 2009 and 2011 were included. Patients were categorized according to the diet imposed by the treating physician at presentation and included nil per os, clear liquid, liquid diet and solid foods. The relation between Hinchey classification, C-reactive protein, leucocyte count and temperature at presentation and diet choice was examined. Subsequently, the relation between diet restriction and number of days hospitalized was studied.

Results: Of the 256 patients included in the study 65 received nil per os, 89 clear liquid, 75 liquid diet and 27 solid foods at presentation. Solely high temperature appeared to be related to a more restrictive diet choice at presentation.

Patients who received liquid diet (HR 1.66 CI 1.19–2.33) or solid foods (HR 2.39 CI 1.52–3.78) were more likely to be discharged compared to patient who received clear liquid diet (HR 1.26 CI 1.52–3.78) or nils per os (reference group). This relation remained statistically significant after correction for disease severity, treatment and complications.

Conclusion: Physicians appeared to prefer a more restrictive diet with increasing temperature at presentation. Notably, dietary restrictions prolong hospital stay.

Introduction

Diverticulitis is a common disease and leads to approximately 13.500 hospitalizations per year in the Netherlands.¹ Despite diverticulitis being one of the most frequent gastrointestinal diseases, much remains unclear on the optimal treatment during admission. The majority of patients present with an Hinchey 0, Ia or Ib diverticulitis and can often be treated conservatively.²⁻³ Diet restrictions are usually advised as part of the conservative treatment. The European Association of Endoscopic surgery advises clear liquid diets for mild and nil per os (NPO) for moderate and severe cases of diverticulitis.⁴ The American Society of Colon and Rectal Surgeons recommend a liquid diet for all patients with diverticulitis.⁵ In a more recent article on the clinical management of diverticulitis, an easy digestible low-residue diet is advocated.² Notably, consensus between guidelines is lacking. The guidelines do agree on the lack of conclusive data supporting their diet recommendation.

The rationale behind diet restrictions for treating the acute phase of a diverticulitis episode has never been thoroughly studied. Many physicians recommend diet restrictions assuming that this may result in a less active bowel with a positive effect on the healing of the site of infection and ultimately shortening hospitalization time.⁴ Furthermore, it is thought that a more restricted diet is mandatory with increasing disease severity.² This study aims to determine whether these assumptions hold. To date the most objective instrument for determining disease severity in patients with diverticulitis is the Hinchey classification.³ It is primarily hypothesized that the diet choice is based on the Hinchey classification in such a way that a higher classification leads to a more restricted diet. Secondly, this study aimed to investigate the relation between dietary restrictions and hospital stay.

Methods

Study population

The hospital records were searched for all patients who were diagnosed with diverticulitis at the emergency unit using a diagnosis specific code for diverticulitis between January 2010 and June 2011. Patients were included in the study if they were hospitalized with initial conservative treatment for, and during the entire hospital stay were treated under, the diagnosis diverticulitis. All patients included had either a CT-scan or sonography at presentation to determine the modified Hinchey classification (table 1).³ Patients with a Hinchey II at presentation were excluded.

Baseline characteristics

Data of all patients included in this study regarding patient characteristics, treatment and complications during hospital stay were collected from the hospital uptake and discharge forms. The American Society of Anesthesiologists (ASA) Physical Status classification was collected from the anesthesiologist report made within half a year before or after presentation. If these reports were not available, one of the researchers determined the

ASA classification based on the medical history reported in the hospital uptake forms at presentation. Baseline characteristics were described per diet.

Table 1. Modified Hinchey Classification.³

Modified Hinchey Classification	
0	Mild clinical diverticulitis
Ia	Confined pericolic inflammation-phlegmon
Ib	Confined pericolic abscess (<5cm)
II	Pelvic, distant intraabdominal, or retroperitoneal abscess
III	Generalized purulent peritonitis
IV	Faecal peritonitis

Study outcome

The outcome for the primary hypothesis of this study was the diet restriction imposed by the treating physician at presentation. In the Meander Medical Center, consensus among dietitians has led to four standardized and predefined grades of diet restrictions for treating diverticulitis patients. These diet restrictions have been in use prior to the study period and consist of NPO, clear liquid diet, liquid diet and solid foods. NPO encompasses no intake whatsoever. Clear liquid diet consists of solely transparent liquids (e.g. water, apple juice or lemonade). A liquid diet comprises of foods with a liquid consistency, consequently avoiding the need to chew (e.g. custard and porridge). Solid foods include all nutrients with a solid consistency ranging from easy digestible foods (e.g. chicken, soft fruit or white bread) to a normal, unrestricted diet. Data regarding the diet restrictions imposed at presentation were extracted from the patient's nursing records. These records contain a standardized form in which nurses are obliged to prospectively list the diet restrictions as prescribed by the treating physician at the start of each day of all patients hospitalized. For baseline purposes, the mean number of successive diet regimes was calculated per diet restriction imposed at presentation.

The outcome for the secondary hypothesis was the number of days hospitalized. This was calculated from the hospital admission and discharge dates stored in the digital hospital records.

Determinant and confounders

The primary outcome, diet restriction imposed at presentation, was related to disease severity as defined by the modified Hinchey classification and other parameters including temperature, C-reactive protein (CRP) and leucocyte count.⁶ An independent researcher (RK) determined the Hinchey stadium based on the findings described in the digital radiological reports of CT-scans and/or sonographies made at presentation.

The heights of CRP and leucocyte count at presentation were extracted from the digital biochemistry records. Data on the temperature, as measured in all patients at presentation, was extracted from the digital emergency unit records.

The secondary outcome, number of days hospitalized, was related to the aforementioned diet restriction imposed at presentation. Potential confounders in this relation were assumed to be age, gender and disease severity defined by the aforementioned Hinchey

classification, biochemistry results and temperature at presentation. Additionally, complications which are known to increase hospitalization duration (perforation, development of abscess) were included in the analysis. Antibiotic use was also considered to be a confounder. Data regarding antibiotic use was extracted from the hospital discharge forms.

Statistical analysis

For describing baseline characteristics the mean of normally distributed and median of non-normally distributed variables were used. Distributions were described as either standard deviation or range between the 5th and 95th percentile. Normality was determined using histograms. Categorical variables were described as counts and percentages.

Only complete cases were used for analyzing the primary and secondary research question. All incomplete cases were compared to complete cases with regard to baseline characteristics, determinants and outcome to exclude whether data was missing selectively.

For analyzing the relation between diet restriction and Hinchey classification, CRP (mg/l), leucocyte count ($n \cdot 10^{-9}/l$) and temperature (°Celsius) ordinal regression was used. Prior to the final analysis, the data was tested whether conditions for performing ordinal regression were met. This was done by constructing a cross-table with all categorical variables included in the final analysis and determining whether no cells contained zero counts and more than 80% of cells had a count of five or higher. Furthermore, non-normal variables were log-normal transformed for the analysis. Both univariate and multivariate logit ordinal regression of complete cases was used to analyze the crude relation between determinants and diet restriction. The proportional odds assumption was tested using the test for parallel lines. The relation was described as proportional odds ratio's calculated by exponentiation of the beta coefficients obtained from the multivariate logit ordinal model. A p-value under the 0.05 was considered significant.

Cox regression was used to analyze the relation between number of days hospitalized and the diet restriction imposed at presentation. Diet restriction and Hinchey classification were operationalized as categorical variables in the model. Non-normal continuous variables were log normally transformed. Univariate Cox regression was used to analyze the crude relation between number of days hospitalized and diet restriction. Correction for the aforementioned confounder was done using a multivariate Cox model. The results were described as hazard ratios (HR). A p-value under the 0.05 was considered significant.

Results

Participants

A total of 290 consecutive patients were seen at the emergency unit with a clinical suspicion for diverticulitis between January 2010 and June 2011 (figure 1). Twelve patients were excluded as they were either not hospitalized or had a concomitant ileus at presentation.

Of the 276 hospitalized patients, 18 did not receive subsequent radiological examination and were therefore excluded. Four patients were additionally excluded because of the need for an acute resection on the day of presentation due to signs of perforated diverticulitis on radiological examination or presenting with Hinchey II diverticulitis. Finally, 256 patients were included.

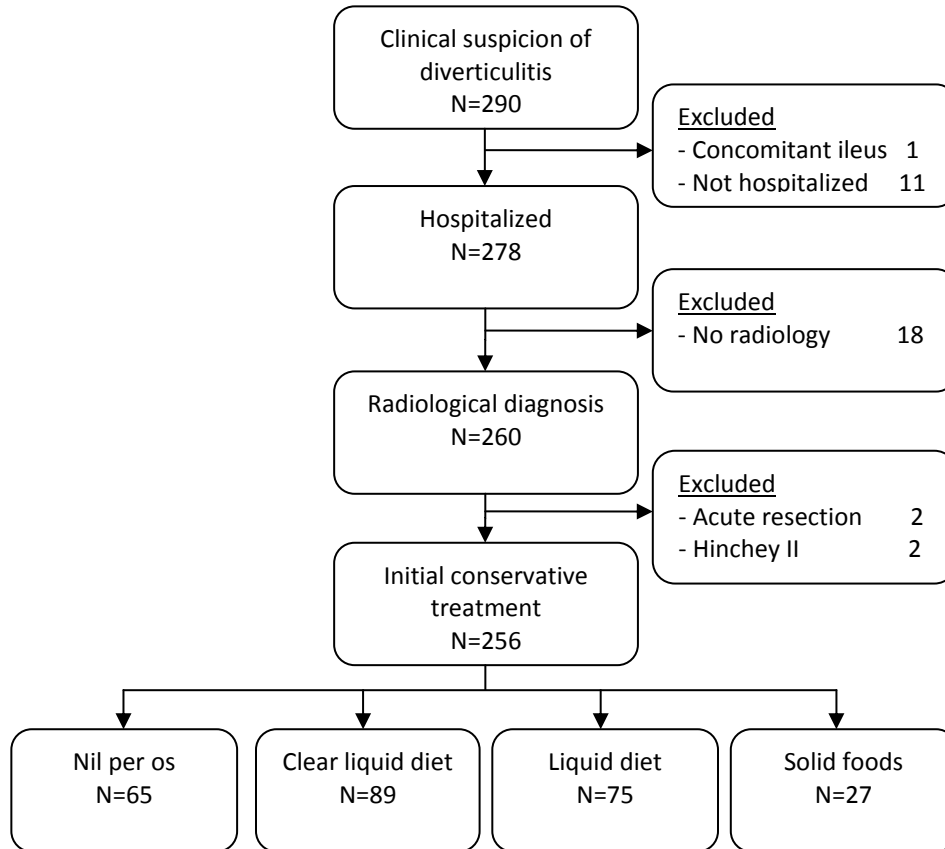


Figure 1. Flowchart: selection of study population

Main study results

Overall baseline characteristics of this study population are enlisted per diet restriction in table 2. The distribution of diet restriction according to the modified Hinchey classes is described in table 3. Of the 256 patients included in the study 65 received NPO, 89 clear liquid, 75 liquid diet and 27 solid foods. Patients who were hospitalized with NPO received a median of three successive diet regimes (including the starting diet) before being discharged. This amounted to three for clear liquid, two for liquid and, logically, one for patient who were hospitalized with solid foods as diet.

Table 2. Baseline characteristics of the 256 patients included in the study.

		Nil per os N=65	Clear liquid diet N=89	Liquid diet N=75	Solid foods N=29
Patient characteristics					
Gender	<i>Male</i>	30 (46,2%)	37 (41,6%)	28 (37,3%)	15 (55,6%)
Age (mean)	<i>years</i>	56,6 (13.1)	59,6 (12.3)	59,9 (14.7)	57,6 (14.8)
ASA	<i>I</i>	23 (35,4%)	44 (49,4%)	29 (38,7%)	11 (40,7%)
	<i>II</i>	36 (55,4%)	34 (38,2%)	41 (54,7%)	15 (55,6%)
	<i>III</i>	5 (7,7%)	10 (11,2%)	5 (6,7%)	1 (3,7%)
	<i>IV</i>	1 (1,5%)	1 (1,1%)	0 (0%)	0 (0%)
Physical/serologic examination					
Temperature (mean)	<i>Celsius</i>	37.7 (0.80)	37,5 (0.75)	37,4 (0.75)	37,3 (0.97)
CRP (mean)	<i>mg/liter</i>	118 (92.7)	114 (92.6)	103 (93.3)	83 (74.1)
Leucocyte count(mean)	10^{-9} /liter	12,9 (4.7)	12,5 (3.6)	11,9 (3.7)	11,9 (5.1)
Treatment					
Antibiotics		26 (40,6%)	25 (28,1%)	24 (32,0%)	7 (25,9%)
Days hospitalized (median)		5 (1-16)	4 (1-15)	3 (1-8)	3 (2-4)
Complications	<i>operatively</i>	1 (1.5%)	1 (1.1%)	0 (0%)	0 (0%)
	<i>conservatively</i>	1 (1.5%)	2 (2.2%)	1 (1.3%)	0 (0%)
N successive diets (median)		3 (2-4)	3 (1-3)	2 (1-2)	1

For analysis of the relation between diet restriction imposed by the treating physician at presentation and Hinchey classification, CRP, leucocyte count and temperature, 10 patients (7 in NPO and 3 in clear liquid diet group) of the 256 patients were excluded because data on the temperature at presentation was not available. Analysis of these 10 incomplete cases showed no differences in baseline characteristics, determinants or outcome compared to complete cases.

Table 3. Distribution of diet restriction according to Hinchey classification.

	NPO	Clear Liquid	Liquid	Solid foods	Total
Hinchey 0	11 (32,4%)	12 (35,3%)	6 (17,6%)	5 (14,7%)	34
Hinchey Ia	39 (21,1%)	64 (34,6%)	61 (33,0%)	21 (11,4%)	185
Hinchey Ib	15 (40,5%)	13 (35,1%)	8 (21,6%)	1 (2,7%)	37

Univariate analysis showed that patients with a Hinchey Ia diverticulitis episode tended to receive a less restrictive diet (OR 1.57 95% CI 0.80 – 3.06) and patients with Hinchey Ib diverticulitis a more restrictive diet (OR 0.62 95% CI 0.26 – 1.46) when compared to patients with Hinchey 0 diverticulitis. Furthermore, patients tended to receive a more restrictive diet with increasing titers for CRP (OR 0.92 CI 0.76 – 1.11), leucocyte count (OR 0.95 CI 0.90 – 0.99) and increasing temperature (OR 0.67 CI 0.51 – 0.90) at presentation. Only leucocyte count and temperature reached statistical significance (table 4).

After multivariate analysis, solely body temperature remained significantly related to the diet choice with an odd's ratio of 0.72 (CI 0.53 – 0.98) indicating that patients with fever tend to receive a more restrictive diet.

Table 4. Results of univariate and multivariate analysis of relation between diet restriction imposed by the treating physician at presentation and Hinchey classification, CRP, leucocyte count and body temperature.

	Proportional odds ratio	95% Confidence interval	P-value
<i>Univariate</i>			
Hinchey 0*	0	-	-
Hinchey Ia	1.57	0.80 – 3.06	0.18
Hinchey Ib	0.62	0.26 – 1.46	0.27
CRP	0.92	0.76 – 1.11	0.36
Leucocyte	0.95	0.90 – 0.99	0.04
Temperature	0.67	0.51 – 0,90	0.008
<i>Multivariate</i>			
Hinchey 0*	1	-	-
Hinchey Ia	1.80	0.90 – 3.60	0.10
Hinchey Ib	0.76	0.30 – 1.93	0.56
CRP	1.00	0.99 – 1.01	0.79
Leucocyte	0.97	0.92 – 1.03	0.35
Temperature	0.72	0.53 – 0.98	0.03

* Reference group for categorical variables

For the analysis of the relation between number of days hospitalized and diet restriction imposed at presentation, 10 patients were excluded for similar reasons as previously described. The median length of hospital stay for NPO, clear liquid, liquid diet and solid foods was 5 (1-16), 4 (1-15), 3 (1-8) and 3 (2-4), respectively. Univariate analysis confirmed that patients who received a less restrictive diet at hospitalization were more likely to be discharged (table 5)(figure 2). Notably this relation reached statistical significance in patient who received a less restrictive diet than a clear liquid diet (HR 1.26 CI 0.91 – 1.73). Patients who were given a liquid diet had a 1.66 (CI .19 – 2.33) and patients who started with solid foods had a 2.39 higher likelihood (CI 1.52- 3.78) to be discharged compared to patient who received NPO at hospitalization. This relation remained statistically significant after correction for age, gender, complications, antibiotic use, Hinchey classification and other parameters that are assumed to be related to disease severity (C-reactive protein, leucocyte count and temperature at presentation). The hazard ratios were 1.21 (CI 0.86 – 1.69) for clear liquid, 1.53 (CI 1.06 – 2.20) for liquid and 2.04 (CI 1.27 – 3.29) for solid foods respectively.

Complications requiring operative management during hospitalization occurred in one (1.5%) patient who received NPO and one (1.1%) in the liquid diet group (table 2).

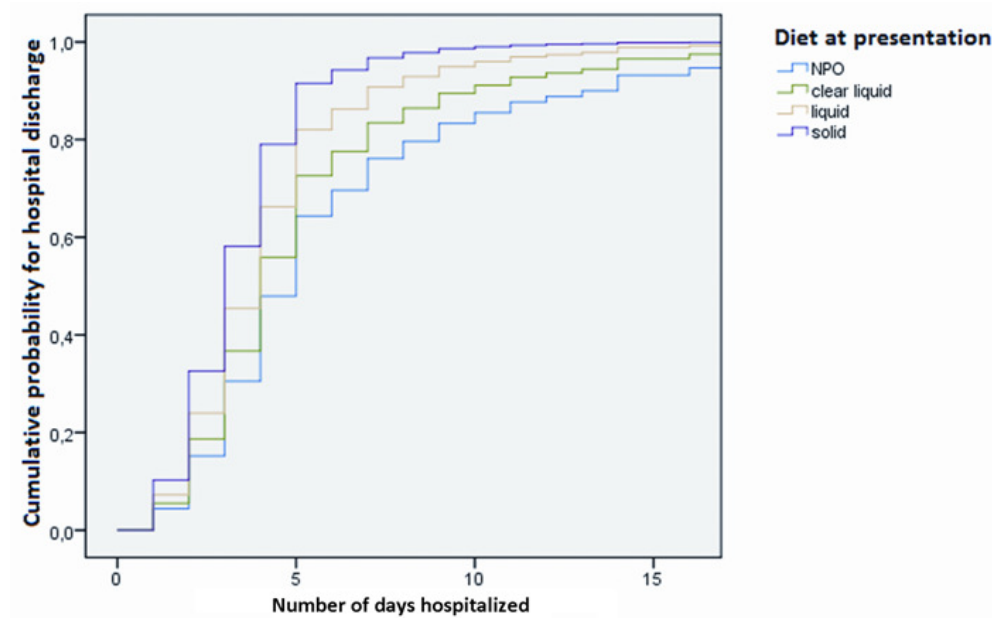


Figure 2. Cumulative probability curve of number of days hospitalized for nil per os, clear liquid, liquid diet and solid foods.

Table 5. Results of univariate and multivariate analysis of relation between diet restriction imposed by the treating physician at presentation and number of days hospitalized.

	Hazard ratio	95% Confidence interval	P-value
<i>Univariate</i>			
Nil per os*	1	-	-
Clear liquid diet	1.26	0.91 – 1.73	0.17
Liquid diet	1.66	1.19 – 2.33	0.003
Solid foods	2.39	1.52 – 3.78	0.0008
<i>Multivariate</i>			
Nil per os*	1	-	-
Clear liquid diet	1.21	0.86 – 1.69	0.28
Liquid diet	1.53	1.06 – 2.20	0.02
Solid foods	2.04	1.27 – 3.29	0.003
Age	0.994	0.987- 0.999	0.21
Gender (female)*	1	-	-
Gender (male)	1.45	1.10 – 1.90	0.007
Antibiotic (no)*	1	-	-
Antibiotic (yes)	0.86	0.64 – 1.16	0.33
CRP	0.91	0.80 – 1.03	0.13
Leucocyte	1.00	0.97 – 1.04	0.82
Temperature	0.89	0.75 – 1.07	0.20
Hinchev class 0*	1	-	0.58
Hinchev class Ia	0.95	0.63 – 1.42	0.80
Hinchev class Ib	0.78	0.46 – 1.32	0.36
Complication (no)*	1	-	-
Complications (yes)	0.23	0.09 – 0.59	0.002

* Reference group

Discussion

This retrospective study demonstrates that both nil per os, clear liquid, liquid diet and solid foods are all prescribed for patients with an acute phase of a diverticulitis episode in daily practice. The diet choice does not seem to depend on the Hinchev classification, nor does it relate to the height of C-reactive protein or leucocyte count. Physicians, however, seem to advice a more restricted diet with increasing fever at presentation. Notably, advising a more restrictive diet at presentation and hospitalization for a diverticulitis episode decreases the probability to be discharged and therefore might lead to longer hospitalization duration. This relation does not change after correction for age, gender,

complications, antibiotic use, Hinchey classification and several other factors that are assumed to be related to disease severity.

This is the first study to investigate diets in the acute phase of a diverticulitis episode. Essentially, this study demonstrates that consensus regarding the optimal diet for the acute phase of diverticulitis is lacking. As a result, potentially unnecessary restrictive measures with regard to the diet are taken that might lead to needlessly long hospitalizations.

It was an unexpected finding that the Hinchey classification was not related to diet choice. Moreover, patients with a Hinchey 0 received a more restricted diet compared to patients with Hinchey Ia. The fact that the diet choice does not depend on Hinchey classification, could imply that the choice is a more subjective matter based on old principles, personal preferences and the interpretation of symptoms. If the physician's choice of the diet is indeed a subjective issue, it may be questioned whether diet restrictions are even necessary. Ultimately, patients could be given the freedom to determine their diet according to their own needs without any restrictions in case of a Hinchey 0, Ia or Ib diverticulitis.

We did not include clinical parameters in the analysis as study design did not allow for accurate assessment. However, it should be questioned whether clinical parameters truly warrant a restricted diet. Is it because these parameters form an indicator for risk of developing complications? If true, then one should ask him/herself whether the choice of diet will influence this chance of complications at all. To our opinion, clinical parameters should not play a role in diet choice. There is no evidence supporting a relation between diet and the development of complications in patients hospitalized with Hinchey 0, Ia or Ib diverticulitis; Nor do the results of this study support the existence of such a relation. Complications in this study population were extremely rare and did not occur among patients who received solid foods.

The results of this study also demonstrate an inverse relation between length of hospital stay and dietary restrictions. This inverse relation can principally be explained by the ordinal nature of the diet restrictions. It is plausible to assume that physicians tend to discharge patients more easily when they ascertain that patients thrive on a less restrictive diet than initially hospitalized with. Patients starting with a NPO diet, will logically first receive a clear liquid diet before moving to less restricted diets and will, therefore, be hospitalized for a longer period than patients initially hospitalized with solid foods. Results found in this study regarding the number of successive diets per diet imposed at hospitalization support this concept.

This study has certain considerations that must be taken into account when interpreting the results. The retrospective nature of this study inevitably leads to certain amounts of selection and information bias. Nevertheless, the standardized fashion in which data on dietary restrictions was gathered minimizes information bias. Analysis of incomplete cases also did not show any signs for selectively missing data.

Selection bias could not be completely excluded. The flowchart for selection of the study population however did not raise any concern regarding this issue. Moreover, all causal relations were corrected for any residual confounding factors.

One may question whether the study population is large enough to reach statistical significance for describing the relation between Hinchey classification and the diet

imposed by the treating physician at presentation. As previously described, the results of this study indicate that patients with a Hinchey Ia episode tend to receive a less restricted diet compared to patients with Hinchey 0. This is in conflict with the hypothesis that a Hinchey classification and diet type are inversely related. Increasing the sample size might therefore yield a significant result but will not change the conclusion.

With regard to the generalizability of the results, this study was performed in a single center. However, due to the lack of literature and guidelines regarding diet restrictions during the acute phase of diverticulitis, it is likely that the same situation may be found in other centers. This is further strengthened by the diversity of diet regimes used in studies on the efficacy of antibiotic treatment in patients with diverticulitis.⁷⁻¹⁰

In conclusion, a diversity of diet restrictions is being used for the treating patients hospitalized with a Hinchey 0-Ib diverticulitis. There is currently no evidence supporting the use of dietary restrictions. Based on our results, employing dietary restrictions might unnecessarily prolong hospital stay. In our medical center we abandoned the use of dietary restrictions in the treatment of diverticulitis.

Acknowledgements

The authors thank Prof. Y. van der Graaf from the Julius Center of Health Sciences and Primary Care, Utrecht (the Netherlands) for her contribution in conceiving this study and data analysis.

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Chapter 6

Endoscopic evaluation of the colon after an episode of diverticulitis:

A call for a more selective approach

Bryan van de Wall
Ellen Reuling
Esther Consten
Janneke van Grinsven
Matthijs Schwartz
Ivo Broeders
Werner Draaisma

International Journal of Colorectal Disease 2012 Mar 13. [Epub ahead of print]

Abstract

Background: Routine colonic evaluation is advised after an episode of diverticulitis to exclude colorectal cancer. In the recent years, the possible relation between diverticulitis and colorectal cancer has been subject of debate. The aim of this study is to evaluate the benefit of routine colonic endoscopy after an episode of diverticulitis.

Methods: Records of all consecutive patients presenting with a radiologically confirmed episode of diverticulitis between 2007 and 2010 were retrieved from an in-hospital database. Patients who subsequently underwent colonic evaluation were included. The endoscopic detection rate of hyperplastic polyps, adenomas and advanced colonic neoplasia was assessed. Findings were categorized on the basis of the most advanced lesion identified.

Results: Three hundred and seven patients presented with a radiologically confirmed primary episode of diverticulitis. Two hundred and five patients underwent colonic evaluation. Hyperplastic polyps were found in 15 (6.8%), adenomas in 18 (8.8%) and advanced neoplastic lesions in 7 (3.4%) patients. Only two patients had a colorectal malignancy.

Conclusion: There appears to be no benefit in performing routine colonic evaluation after an episode of diverticulitis as the incidence of colorectal cancer is almost equal to that of the general population. A more selective approach might therefore be justified. Potentially, only patients with persisting abdominal complaints after an episode of diverticulitis should be offered colonic evaluation to definitively exclude causal pathology.

Introduction

Diverticular disease is a common problem in Western countries and leads to approximately 152,000 hospitalizations on a yearly basis in the USA.¹⁻³ The total yearly costs for diverticular disease are estimated around 2.7 billion US dollars, thus placing a significant burden on health care.⁴

Diverticular disease is associated with a low-fibre diet and structural changes in the bowel wall musculature. Microscopic changes in the extracellular matrix due to a collagen switch in the mucosa and submucosa and increased epithelial turnover of the colon are seen in patients with diverticular disease. These alterations have also been observed in patient with a colorectal malignancy.⁵⁻⁶ Therefore, expert opinion and international published guidelines traditionally advise routine colonic evaluation approximately 6 weeks after an episode of acute diverticulitis in order to exclude a potential malignancy.⁷⁻⁸ These endoscopies can be accompanied by procedure-related morbidity and may amplify both the health care burden and costs related to diverticular disease.⁴

The possible association between diverticular disease and a colorectal malignancy is still under debate. Furthermore, evidence supporting the assumption that all patients should undergo routine endoscopy after an uncomplicated episode of diverticulitis currently is controversial. Recently two reports have been published questioning the benefit of routine colonic evaluation after a conservatively managed episode of diverticulitis with contradictory results.⁹⁻¹⁰ Therefore, this cross-sectional study aims to describe the yield of colonic evaluation after a radiologically confirmed episode of uncomplicated diverticulitis and to provide recommendations for follow-up of these patients in daily practice.

Patients and methods

Design and setting

This study had a retrospective cross-sectional design and was performed in the Meander Medical Center, a large district teaching hospital in the Netherlands. The study period ran from January 2007 to January 2010.

Participants

A diagnosis specific code was used to identify all patients presenting with an episode of diverticulitis at the emergency department in the aforementioned study period. All patients with a clinical suspicion for a primary episode of diverticulitis underwent either ultrasonography or computed tomography (CT scan) at presentation. If the ultrasonography was negative, a CT scan was made to definitely exclude diverticulitis. Diagnostic criteria which were applied for diagnosing diverticulitis were the presence of diverticulae in the descending and/or sigmoid colon in combination with localized colonic wall thickening and/or surrounding fat stranding. Solely patients who have had a radiologically confirmed primary episode of diverticulitis and subsequently underwent colonic evaluation (sigmoidoscopy or colonoscopy) within 6 months during follow-up were included for final analysis.

Baseline characteristics

Data regarding patient characteristics, co-morbidity, symptoms at presentation and abnormalities at physical examination were collected from the hospital admission and discharge forms. The radiological reports of abdominal ultrasonographies and/or CT scans performed at presentation were used to determine the disease severity graded by the modified Hinchey classification (Table 1).¹¹ The quality of the colonic evaluation was determined by assessing the technique (sigmoidoscopy or colonoscopy), the caecal intubation rate and the amount of faecal pollution encountered during the procedure.

Table 1. Modified Hinchey Classification.

Hinchey	Description
Ia	Pericolic inflammation
Ib	Localised para colonic or mesenteric abscess
II	Pelvic abscess
III	Perforated diverticulitis with purulent peritonitis
IV	Perforation of diverticulitis in the abdominal cavity with faecal contamination

Study outcome

The endoscopy reports of all patients were searched for abnormalities. Abnormal findings at colonic evaluation were categorized based on the histological reports of the most advanced lesion and included either advanced colonic neoplasia, adenoma or hyperplastic polyps. Advanced colonic neoplasia was defined as an adenoma of 10 mm or greater in diameter, or with high-grade dysplasia, or with more than 25% villous components or an invasive cancer.⁹ Abnormalities classified as adenoma included adenomas smaller than 10 mm in diameter with low-grade dysplasia and less than 25% villous components, and serrated adenoma. Hyperplastic polyps were defined as benign small sessile polyps with lengthening and cystic dilation of mucosal glands. Additionally, all non-neoplastic abnormalities were recorded (for example inflammatory process/stenosis, and inflammatory polyps or small polyps that did not require additional histological investigation based on macroscopic examination).

The hospital records of all patients presenting with a primary episode of diverticulitis were searched for whether colon surgery had been performed. The pathological reports of all resected specimens were screened for colorectal malignancies.

Statistical analysis

Software package SPSS 17.0 was used for analysis. Baseline characteristics were described as counts and percentages for categorical variables. Continuous variables were summarized as either means with corresponding standard deviations or medians with interquartile range depending on normality. Normality was assessed using Q–Q plots. For analysing the difference in characteristics between patients who did and did not undergo endoscopy, the Students t test was used for continuous normally distributed variables and chi-square test for categorical variables.

Results

Descriptive data

A total of 307 patients presented with a radiologically confirmed primary episode of diverticulitis. One hundred and two patients did not undergo colonic evaluation. Reasons for not performing endoscopy included the need for acute resection due to perforation or disease progression during initial hospitalization in 19 patients. Twenty-six patients were directly planned for elective resection for frequently recurring out-hospital diverticulitis episodes or fistulae. Forty-four patients did not receive colonoscopy as the treating physician found them to be completely asymptomatic at the outpatient clinic. In combination with a clinically mild initial diverticulitis episode, the treating physician deemed colonoscopy not to be warranted. Other reasons for not performing colonoscopy included severe co-morbidity in combination with high age (n=5), colonoscopy being planned outside the study period or in another hospital (n=5) and CT-colonography being used (n=3).

A total of 205 (66.8%) patients received endoscopy. The mean age of patients undergoing endoscopy was 57.3 (SD 13.2) years with a male to female ratio of 97:108 (Table 2). This was comparable to patients who did not receive endoscopy in which the mean age was 59.6 (SD 14.5) with a ratio of 43:59.

With respect to alarm symptoms for colorectal malignancies, no significant differences between patients who did and did not receive endoscopy were identified. Abnormalities at rectal examination were found in one patient (0.5%) in the endoscopy group versus two patients (2%) in the no endoscopy group. Rectal blood loss was reported in 15 (7.3%) versus 8 (7.8%). The eight patients with rectal blood loss in the no endoscopy group were previously diagnosed with haemorrhoids or anal fissures. Therefore, no additional examination was planned. Weight loss was reported in 77 (37.6%) of patients who did versus 45 (44.1%) who did not undergo endoscopy.

Diverticulitis was radiologically confirmed using CT-scan in 61% in the endoscopy group versus 68.6% in the no endoscopy group. In the remaining patients, the diagnosis was based on findings at ultrasonography. The majority of patients presented with Hinchey Ia (90.2%) and Ib (8.3%) diverticulitis in the group who underwent endoscopy. In patients who did not receive endoscopy, these proportions were 84.3 and 8.8%, respectively.

Main study results

Of the 205 performed endoscopies, 42 (20.7%) were sigmoidoscopies and 163 (79.3%) colonoscopies. The caecal intubation rate of all colonoscopies was 90.6% (n=146). The main reason for not reaching the caecum at colonoscopy was due to either an inflammatory process/stenosis or a fixated, painful sigmoid impeding further investigation (Table 3). Faecal pollution was encountered in 28 (13.6%) of all endoscopies. Two patients were re-examined due to severe faecal pollution. Despite the suboptimal examination in the remaining patients, the endoscopist regarded the examination reliable enough to abstain from re-examination. There were no perforations from any endoscopy. The mean interval between presentation and colonic evaluation was 8.9 weeks (SD 10.6). In 42 (20.5%) patients non-neoplastic abnormalities were found (Fig. 1). Fourteen of these patients had an inflammatory process protruding in the colonic lumen and subsequently

Table 2. Baseline characteristic of patients who did and did not undergo colonic evaluation.

	Endoscopy N=205	No endoscopy N=102	P-value
Age	57.4 (SD 13.2)	59.6 (SD 14.5)	0.226
Male:Female	97:108	43:59	0.616
Abnormalities in rectal examination	1 (0.5%)	2 (2.0%)	0.223
Rectal blood loss	15 (7.3%)	8 (7.8%)	1.000
Weight loss	77 (37.6%)	45 (44.1%)	0.310
Radiologic examination			
Ultrasonography	80 (39%)	32 (31.4%)	0.92
CT-scan	125 (61%)	70 (68.6%)	
Hinchey classification			
Hinchey Ia	185 (90.2%)	86 (84.3%)	0.702
Hinchey Ib	17 (8.3%)	9 (8.8%)	
Hinchey II	2 (0.8%)	2 (3.5%)	
Hinchey III/IV	2 (0.7%)	2 (3.4%)	

underwent elective sigmoid resection. No colorectal malignancies were found in the resected specimens. The remaining 28 patients either had inflammatory (pseudo)polyps as described in the histological reports or small polyps that did not require additional histological investigation based on macroscopic examination.

Histologically proven neoplastic lesions were found in 40 (19.5%) patients. Fifteen (6.8%) patients had hyperplastic polyps and 18 (8.8%) adenomas. Advanced colonic neoplasia was found in seven (3.4%) patients, diagnosed at a mean age of 62.7 years (range 37–83 years). There were two adenomas with more than 25% villous components, two with a tubular adenoma with a diameter greater than 10 mm and one with high-grade dysplasia. Colorectal cancer was found in two patients encompassing 1.0% of all patients who underwent colonic evaluation after a primary episode of diverticulitis. The two colorectal cancer cases were a pT4N0M2 in a 65-year-old woman and a pT3N2Mx in male of 83 years. In retrospect, the radiological reports of the CT-scans performed at presentation of these two patients did not mention any suspicion for colorectal malignancy. Notably, both patients underwent additional CT scans for ongoing abdominal symptoms approximately 1 month after presentation.

Of the 102 patients who did not receive colonoscopy, 45 underwent sigmoid resection, as previously described. No malignancies were found in the resected specimens of these patients.

Table 3. Quality of endoscopies defined by the technique, extent and amount of fecal pollution.

Quality of colonic evaluation		
Technique of colonic evaluation		
Sigmoidoscopy	42	(20.7%)
Colonoscopy	163	(79.3%)
Cecal intubation rate (colonoscopies)	146	(90.6%)
Fecal pollution	28	(13.6%)

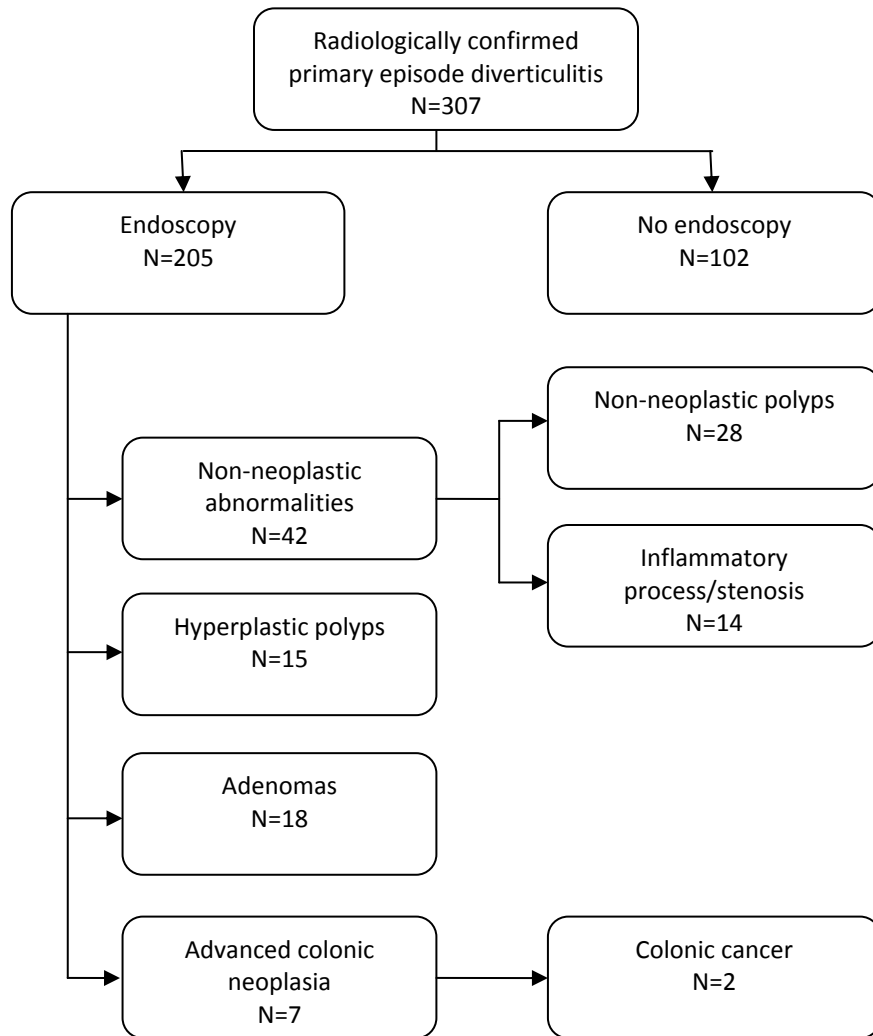


Figure 1. Lesions found at endoscopy performed after a primary episode of diverticulitis.

Discussion

This study demonstrated that hyperplastic polyps are found in 15 (6.8%), adenomas in 18 (8.8%) and advanced neoplastic lesions in 7 (3.4%) of the 205 patients who underwent colonic evaluation after an episode of uncomplicated diverticulitis. Colorectal malignancies were rare and only found in the two (1.0%) patients.

The use of routine colonic evaluation after an episode of diverticulitis remains a point of debate. Both the American Society of Colon and Rectal Surgeons and a more recent clinical practice guideline by Jacobs et al. advise endoscopy to exclude potential advanced neoplastic disease.⁷⁻⁸ Both guidelines emphasize this advice to be based on expert opinion. In the recent years, increasing amounts of evidence have been published contradicting the existing guidelines. The results of this study support the vision of more recent studies. Westwood et al. and Lam et al. found comparable results.^{9,12} Advanced colonic neoplasia was found in 5.4 and 6.3%, and colorectal cancer was diagnosed in 0.5 and 1.7%, respectively, of patients after an episode of diverticulitis, which is comparable to the results demonstrated in this study. Both studies concluded no additional benefit of routine colonic evaluation after an episode of diverticulitis.

The main question on the benefit of routine endoscopy revolves around whether patients with diverticulitis have an increased incidence of colorectal cancer compared to the general healthy population of similar age. A meta-analysis performed in 2008, aiming to determine the diagnostic yield of colonic evaluation in asymptomatic populations of 50 years and older, demonstrated that the overall prevalence of advanced colonic neoplasia and colorectal cancer was 5% (CI 4–6) and 0.78% (CI 0.001–2.97).¹³ A more recent nationwide study analysing 269,000 asymptomatic patients found a prevalence of 5.4% for advanced adenoma and 0.52% for colorectal cancer in patients between 55 and 64 years and a prevalence of 8.2% and 0.95% between the age of 65 and 74 years.¹⁴ This study found a lower proportion of patients with advanced adenoma (3.4%) and an almost equal proportion with colorectal cancer (1.0%) which is well within the confidence interval and near the mean prevalence of the first study. Furthermore, the mean age in this study was 57.4 with a standard deviation of 13.2 years. This variation in age covers both of the aforementioned age groups of the second study which found an average prevalence of 7.4% for advanced colonic neoplasia and 0.74% for colorectal cancer. Therefore, there appears to be no additional benefit in performing routine colonic evaluation in patients with diverticulitis compared to screening the general population for colorectal cancer. The fact that the two patients in this study who eventually had colorectal cancer were diagnosed with diverticulitis at presentation demonstrates the very origin of the question whether or not patients should be subjected to routine colonic evaluation after an episode of diverticulitis. This doubt in combination with the inherent nature of any physician to seek certainty with a diagnosis, especially in excluding cancer, ultimately may lead to over-diagnosing. This may cause more harm than benefit.

Potentially, the indication can be narrowed down to a more selective group. The two patients in this study with colorectal cancer suffered from persisting abdominal complaints after their initial episode of diverticulitis. Although persisting abdominal complaints are common after an episode of diverticulitis, it may comprise a distinct group

who does have an indication for colonic evaluation in order to definitively exclude underlying pathology.¹⁵

There are certain considerations that must be taken into account when interpreting the results of this study. One hundred and two patients presenting with diverticulitis did not undergo endoscopic colonic evaluation. This group appeared to be comparable to patients who did receive endoscopy with regards to alarm symptoms for colorectal cancer, although these symptoms might have been underreported due to the retrospective design of this study. Therefore, selection bias cannot be ruled out with certainty.

Additionally, of these 102 patients who did not undergo endoscopy, 45 underwent sigmoid resection, creating the opportunity to screen the resected specimens for colorectal cancer. A total of 57 patients remain in whom neither colonic evaluation nor resection was performed to rule out cancer. Therefore, the prevalence found in this study might have been under-reported.

In several patients suboptimal colonic evaluation was performed due to the fact that these patients either underwent sigmoidoscopy (n=42), the caecum could not be reached (n=17) or evaluation was impeded by faecal pollution (n=28). The majority of previously published studies excluded all these suboptimal endoscopies inducing certain amounts of selection bias.^{9-10,12} This study aimed to incorporate these daily practice issues for describing the study results, reflecting a more realistic situation. Although this approach reduces the amount of selection bias, it increases the chance of under-reporting as lesions might have been missed. Nevertheless, comparable results are found indicating that relatively solid conclusions may be drawn.

In conclusion, there appears to be no benefit in performing routine colonic evaluation after an episode of uncomplicated diverticulitis as the incidence of colorectal cancer is equal to that of the general population. A more selective approach might therefore be justified. Potentially, only patients with persisting abdominal complaints after an episode of diverticulitis treated conservatively could be offered an endoscopy to definitively exclude causal colonic pathology.

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Chapter 7

Diverticulitis in young versus elderly patients:

A meta-analysis.

Bryan van de Wall
Jolien Poerink
Werner Draaisma
Johannes Reitsma
Esther Consten
Ivo Broeders

Accepted for publication Scandinavian Journal of Gastroenterology (December 2012)

Abstract

Objective: To compare patients younger and older than 50 years with diverticulitis with regard to complications, disease recurrence and to the need for surgery.

Methods: A literature review and meta-analysis was conducted according the PRISMA guidelines. MEDLINE, Embase and the Cochrane databases were searched for longitudinal cohort studies comparing patients younger and older than 50 years with diverticulitis.

Results: Eight studies were included with a total of 4.751 (male: female 1: 0.66) patients younger and 18.328 (male: female 1: 1.67) older than 50 years of age. The risk of developing at least one recurrent episode was significantly higher among patients younger than 50 years (pooled RR 1.73; 95% CI 1.40 – 2.13) with an estimated cumulative risk of 30% compared to 17.3% in older patients. The risk of requiring surgery during hospitalization for a primary episode of diverticulitis was equal in both age groups (pooled RR 0.99; 95% CI 0.74 – 1.32) and estimated at approximately 20%. Patients younger than 50 years more frequently required urgent surgery during hospitalization for a subsequent recurrent episode (pooled RR 1.46; 95% CI 1.29 – 1.66); the cumulative risk was 7.3% in younger and 4.9% in patients older than 50 years.

Conclusion: Patients younger than 50 years only differ substantially in risk for recurrent disease from patients older than 50 years of age. Although the relative risk for requiring urgent surgery for recurrent disease was higher in younger patient, one should consider that the absolute risk difference is relatively small (7.3% versus 4.9%).

Introduction

Diverticular disease frequently occurs in Western countries and puts a significant burden on health care.¹ The prevalence of this disorder rises with increasing age, occurring in approximately 65% of the population aged 65 years or more. Diverticular disease is relatively rare amongst patients under the age of 50 years with a prevalence of 10%. Approximately 20% of all patients with diverticulae develop acute diverticulitis.² There is a general belief that diverticulitis may be more severe in patients younger than 50 years of age in terms of a higher risk of recurrences and complications.³ Early studies performed in the 70's and 80's demonstrated that patients younger than 50 years were more prone to develop recurrences and up to 88% required emergency surgery for diverticulitis related complications such as perforation and abdominal abscesses.³⁻⁴ More recent studies no longer confirm this hypothesis.⁵⁻⁶ Due to the large amount of controversial results found in literature it is difficult to draw solid conclusions. A meta-analysis was performed to compare recurrence, complications and the need for urgent and elective surgery among patients younger and older than 50 years of age with diverticular disease.

Methods

Search strategy

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The aim was to determine pooled relative risk ratios of several outcomes and gain insight on the absolute cumulative risks.

A search on Pubmed and Embase was performed on the 11th of November 2011, using all possible synonyms for the domain (diverticulitis), determinant (age) and outcome (recurrences, complications, surgery). The exact search terms are enlisted in table 1. No restrictions for language or methodological filters were used. All studies published between 1986 and 2012 were considered for inclusion.

The initial search results were filtered for doubles and the remaining articles were screened on title and abstract for whether they reported on both the domain (diverticulitis) and determinant (age groups) of interest. All other studies including reviews and non-English articles were excluded.

The full text of the remaining articles was read. In order to obtain reliable estimates of the pooled relative risk ratios, studies with a longitudinal cohort design (both prospective and retrospective) with a median follow-up of at least 12 months that included patients with a primary episode of diverticulitis were considered for inclusion. Studies with a cross-sectional design or studies that included patients with recurrent episodes of diverticulitis were excluded. Studies had to directly compare at least two age groups and report on the cumulative incidence of at least one outcome of interest. Age groups had to be defined according to a cut-off point of 50 years. Studies comparing three age groups (<40 years versus 40-50 versus >50 years) were also included if the possibility existed to merge the results of the <40 and 40-50 years age groups. The references of all selected studies were hand-searched for other relevant studies.

Critical appraisal

All included articles were critically appraised independently by two reviewers (BW, JP). The relevance of these articles was assessed according to the SIGN Methodology Checklist. Studies that were graded 'poorly' with regard to attempts to minimize the risk of bias and confounding were excluded.

Data extraction

The same reviewers independently extracted data regarding study characteristics and all relevant outcomes. Disagreement was resolved by discussion between the two reviewers. As it was not possible to reliably distinguish between the frequency of emergency surgery (e.g. for perforation) and semi-emergency surgery (e.g. for failure of conservative treatment, abscess progression, intestinal obstruction), both types of surgery were grouped to obtain the pooled risk of surgery performed during hospitalization (defined as "urgent surgery"). Elective resection was defined as planned surgery after hospital discharge. A recurrence was defined as presentation at the hospital with clinical signs of diverticulitis (with or without additional radiology).

Table 1. Synonyms domain, determinant, outcome used in Pubmed and Embase search.

Domain	Determinant	Outcome
Diverticulitis	Age	Recurrence
Diverticular	Young	Relapse
Diverticulosis	Old	Repeat
Diverticulose	Adolescent	Return
	Youth	Fistulae
	Adult	Abscess
		Perforation
		Perforated
		Conservative
		Conservatively
		Complication
		Complaint
		Resection
		Surgery
		Operation
		Operative
		Surgical

Data analysis

Review Manager (Revman) software version 5.1 was used for the meta-analysis. Pooling of data was only performed when at least four studies reported on the outcome of interest. Consequently, only the outcomes "urgent surgery for primary episode of diverticulitis", "diverticulitis recurrences", "urgent surgery for recurrent episode of diverticulitis" and

“elective resection” were subjected to meta-analysis. The remaining outcomes were described qualitatively.

Pooled risk ratios (RR) comparing young versus old were calculated using a random-effects model allowing for variation beyond chance in estimates across studies. The I^2 statistic was used to quantify the amount of heterogeneity.

To obtain insight on the absolute cumulative risk of outcomes which depend on the follow-up duration (diverticulitis recurrence, acute surgery for recurrent episodes, elective resection) we used the average risk across studies in older patients. Insight on the cumulative risk among younger patients was obtained by multiplying RR with the average risk among older patients.

Sensitivity analysis was performed on study design by comparing results of meta-analysis with and without population-based studies.

Results

Search

Search results and study selection are described in figure 1. A total of 10 articles were critically appraised.^{3,6-14} Two studies were graded poorly regarding attempts at minimizing the risk of bias and confounding and therefore had to be excluded (table 2).^{3,14} Eight articles of adequate methodological quality were finally included in this study.⁶⁻¹³

Baseline characteristics

Study characteristics of included studies are described in table 3. Of the eight included cohort studies, six studies had a retrospective^{7,9-13} and two had a prospective^{6,8} design. There was one population-based cohort study (table 3).¹⁰ The median follow-up was 48 months (range 15 – 114) as reported in seven studies.^{6-11,13}

Eight studies included a total of 4.751 patients younger than 50 and 18.328 older than 50 years of age. Four studies reported on gender with a pooled male to female ratio of 1: 0.66 in patients younger than 50 years and 1: 1.67 in older patients.^{6,8,11,12}

Main outcomes – Primary diverticulitis episode

Urgent surgery

Six studies reported on urgent surgery performed during hospitalization for a primary episode of diverticulitis.^{6,8-11,13} Indications included diffuse peritonitis, septic shock, perforation, intestinal obstruction, abscess progression and failure of conservative treatment. There was no significant difference in risk to require urgent surgery between both age groups (figure 2). The pooled risk ratio was 0.99 (95% CI 0.74 – 1.32) in a random-effects model ($I^2=62\%$). Sensitivity analysis on study design, by excluding the population-based study¹⁰, did not show any difference. The pooled risk ratio of meta-analysis without the population-based study was 0.75 (95% CI 0.45 – 1.26).

The absolute risk to require urgent surgery for a primary episode of diverticulitis varied between 1.7% and 26.4% in patients younger than 50 years with an estimated average risk of 22.4%. Patients older than 50 years had an absolute risk that varied between 6.8% and 22.5% with a estimated average of 18.9%.

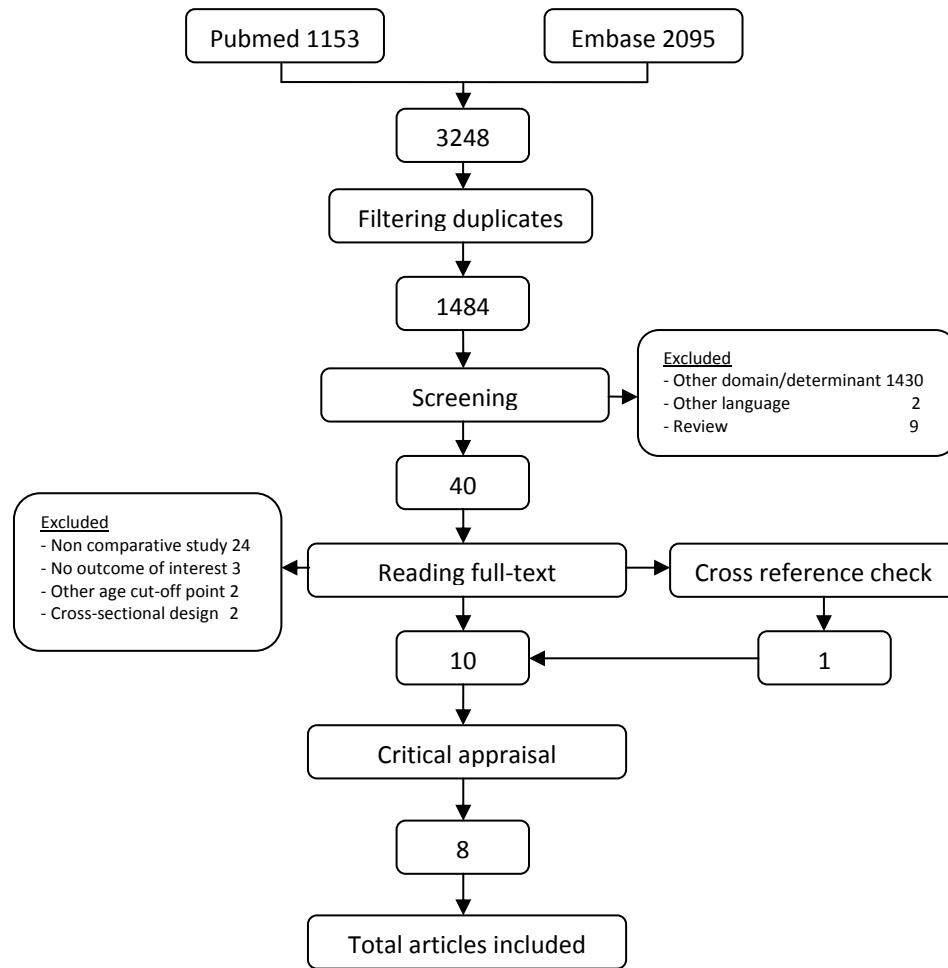


Figure 1. Flowchart.

Table 2. Critical appraisal. According to: Methodology Checklist 3: Cohort studies. Scottish Intercollegiate Guidelines Network (SIGN), March 2004.

Author	Internal validity													Overall assessment of the study		
	Clear question	Comparable populations	Selection study population	Loss to follow up	Comparison full and lost participants	Clear outcomes	Blind exposure status	Influence assessment outcome	Reliable measure of exposure	Evidence for outcome assessment	Assessment exposure level	Confounders identified	Confidence intervals	Applicable results	Minimize risk bias and confounding	
Faria 2011	+	+	+	2%	-	+	n.ap.	n.ad.	+	+	n.ap.	n.ap.	n.ap.	+	++	
Hjern 2008	+	+/-	+	25.6%	-	+	n.ap.	n.ad.	+	+	n.ap.	n.ap.	n.ap.	+	+	
Biondo 2002	+	+/-	+	7%	+/-	+	n.ap.	n.ad.	+	+	n.ap.	n.ap.	n.ap.	+/-	+	
Anaya 2005	+	n.r.	+	2.8%	-	+	n.ap.	n.ad.	+	-	n.ap.	n.ap.	n.ap.	+/-	+	
Chautems 2002	+	n.r.	+/-	25.4%	+/-	+	n.ap.	n.ad.	+	+	n.ap.	n.ap.	n.ap.	+/-	+	
Guzzo 2004	+	n.r.	+	n.r.	n.r.	+/-	n.ap.	n.ad.	+	-	n.ap.	n.ap.	n.ap.	+	+	
Ambrosetti 1994	+	+/-	+	0.6%	-	+	n.ap.	n.ad.	+	+	n.ap.	n.ap.	n.ap.	+/-	+	
Mäkälä 2009	+	-	+	2%	+/-	+	n.ap.	n.ad.	+	+	n.ap.	n.ap.	n.ap.	+/-	+	
Pautrat 2006	+	+/-	-	n.r.	n.r.	+	n.ap.	n.ad.	+	+	n.ap.	n.ap.	n.ap.	+	-	
Freischlag 1986	+	-	-	n.r.	n.r.	+	n.ap.	n.ad.	+	-	n.ap.	n.ap.	n.ap.	-	-	

+; well covered, +/-; adequately addressed, -; poorly addressed, n.a.: not addressed, n.r.; not reported, n.ap.; not applicable

Fistulae

One study reported on the frequency of fistulae encountered in patients with a primary episode of diverticulitis.¹² Fistulae were found in 0.7% of patients younger and 2.2% of patients older than 50 years.

Abscess

The frequency of abscess was reported in two studies. One of these studies found pericolic abscess in 13.1% of patients younger than 50 years versus 14.2% among older patients presenting with a primary episode of diverticulitis.⁶ The other study reported a lower proportion among patients younger than 50 years (9.7% versus 23.8%).¹³

Mortality

Deriving mortality per age group for a primary episode of diverticulitis was only possible in four studies. One study found a mortality of 2.7% in patients older than 50 years with a primary episode of diverticulitis.¹² The exact cause was not described, however, 7 patients presented with uncomplicated diverticulitis, 12 with perforation and three with diverticular bleeding. No mortality occurred among younger patients.

Another study found 0% mortality among younger patients and 9.0% in older patients.⁸ Mortality only occurred after acute surgery (due to persistent septic shock, myocardial infarction, anastomotic dehiscence, hemorrhage).

A third study only reported mortality among patients treated conservatively for a primary episode.¹⁰ In-hospital mortality was 0.2% and 30-days mortality 0.2% in patients younger than 50 years. This was 2.8% and 3.4% in older patients. Causes for mortality were not reported.

In the last study no mortality was found in either age groups.¹³

Main outcomes during follow-up (after conservatively treated primary diverticulitis)

Diverticulitis recurrence

Seven studies reported on the number of patients who developed at least one diverticulitis recurrence during follow-up after a conservatively treated primary episode of diverticulitis.^{6-8,10-13} The overall mean follow-up of these studies was 45 months (range 12-114). Two studies mandated radiological confirmation.^{8,13}

Patients younger than 50 years more frequently developed a recurrence (figure 3). The pooled risk ratio was 1.73 (95% CI 1.40 – 2.13) in a random-effects model ($I^2 = 63\%$). Sensitivity analysis on study design, by excluding the population-based study¹⁰, did not show any difference. The pooled risk ratio of meta-analysis without the population-based study was 1.86 (95% CI 1.31 – 2.63).

The cumulative risk of developing at least one diverticulitis recurrence varied between 20.9% and 53.6% in patients younger than 50 years with an estimated average risk of 29.9%. Patients older than 50 years had an estimated average risk of 17.3% (range 5.6% - 28.6%).

Table 3. Study characteristics of included studies.

Author	Design	Median follow-up (months)	Study population	Total number of patients	Gender (M/F)	
				< 50 years	> 50 years	
Ambrosetti 1994	Prospective cohort	32	Radiologically or pathologically confirmed primary episode	61	49/12	82/122
Chautems 2002	Retrospective cohort	114	Radiologically confirmed primary episode	28	-	-
Biondo 2002	Prospective cohort	24-90	Clinically or radiologically confirmed primary episode	71	51/21	105/150
Guzzo 2004	Retrospective cohort	62	Clinically confirmed primary episode	259	-	-
Anaya 2005	Retrospective population-based cohort	52	Clinically or radiologically confirmed primary episode	3970	-	-
Hjern 2008	Retrospective cohort	30	Pathologically or radiologically confirmed primary episode	58	30/28	60/116
Mäkälä 2009	Retrospective cohort	> 12 months	Radiologically, pathologically or endoscopically confirmed primary episode	273	150/123	293/515
Faria 2011	Retrospective cohort	15	Pathologically or radiologically confirmed primary episode	31	-	-

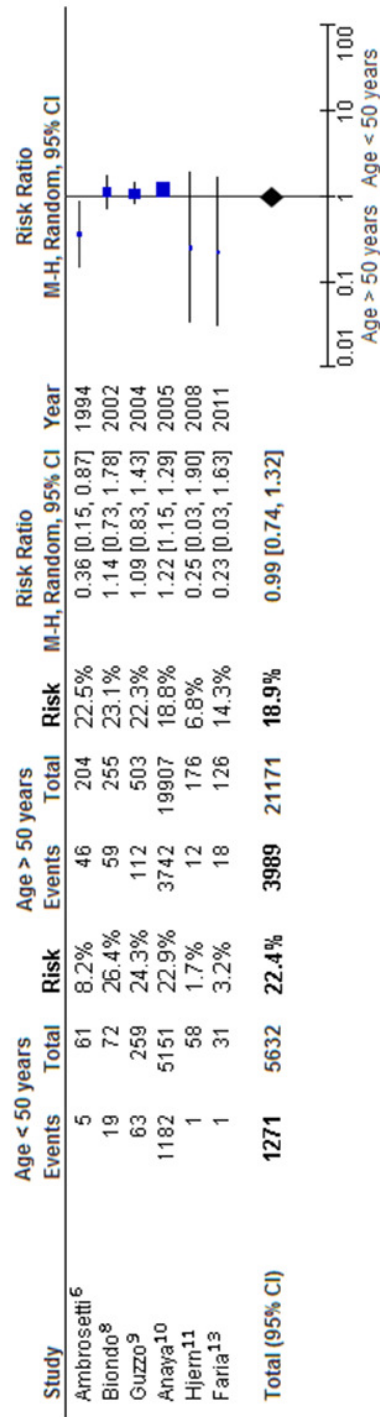
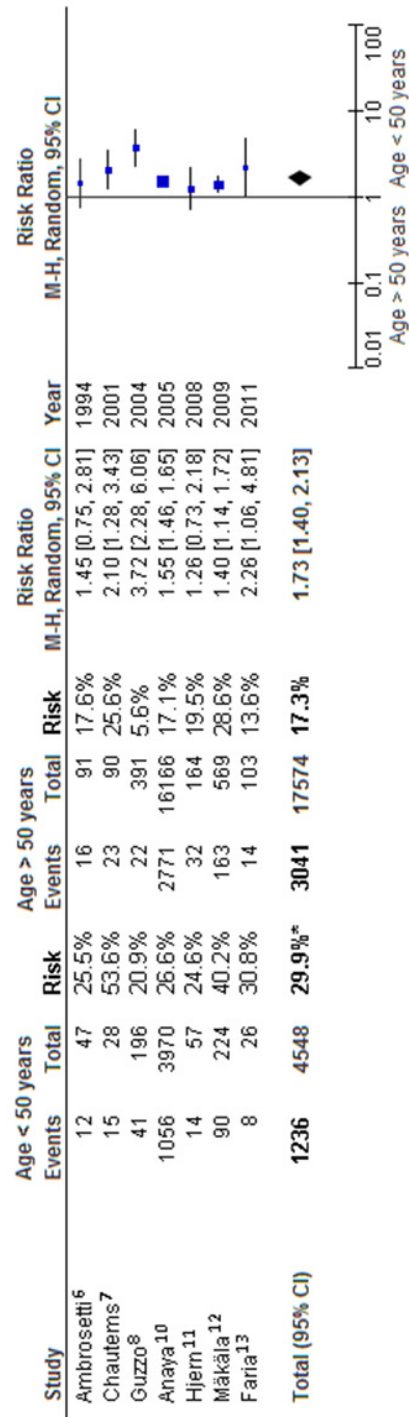


Figure 2. Risk ratio of urgent surgery during a primary episode of diverticulitis. Risk ratios are shown with 95 per cent confidence intervals.



* Calculated by multiplying the risk in patient > 50 years with the risk ratio.

Figure 3. Risk ratio of developing at least one diverticulitis recurrence. Risk ratios are shown with 95 per cent confidence intervals.

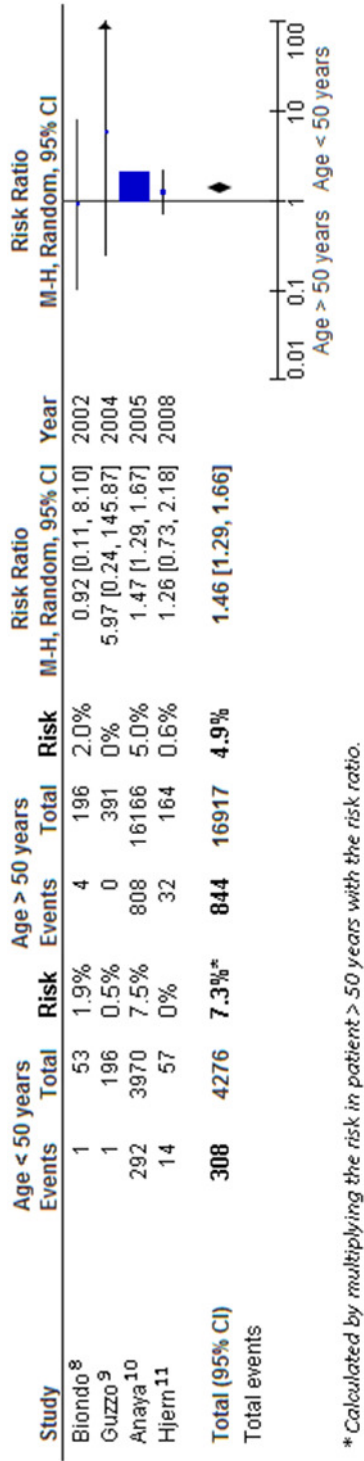


Figure 4. Risk ratio of urgent surgery for a recurrent episode of diverticulitis. Risk ratio's are shown with 95 per cent confidence intervals.

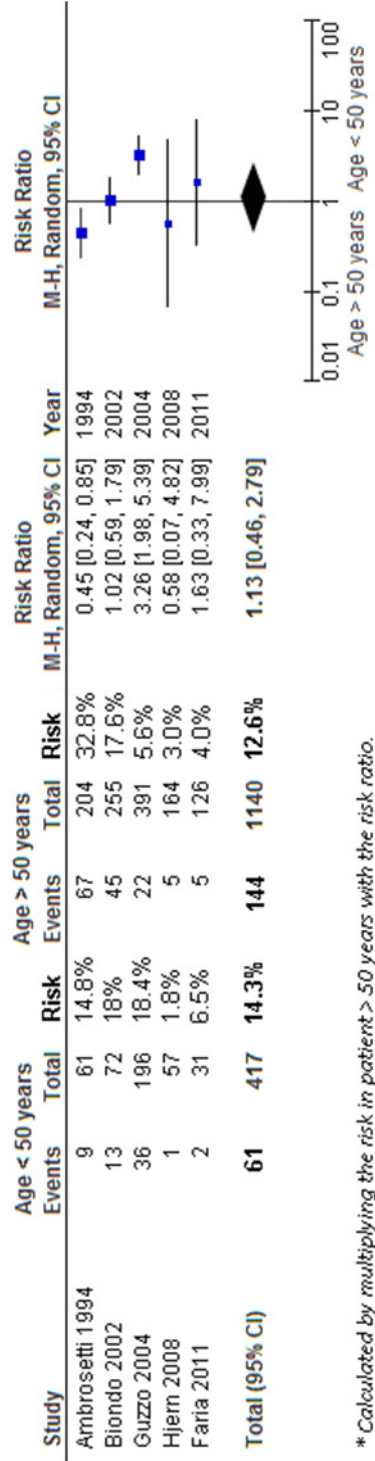


Figure 5. Risk ratio of elective resection for recurring diverticulitis. Risk ratio's are shown with 95 per cent confidence intervals.

Two studies described the time interval between primary and recurrent episodes of diverticulitis. One study found a median of 4 months (range 1 – 40) in patients younger than 50 years compared to 6 months (range 1 – 150) in older patients.¹³ The second study also found a shorter interval among younger patient (median 7.4 months versus 8.4 months).⁸

Two studies reported on additional recurrent episodes. The first found that during a median follow-up of 30 months 5.3% of patients younger than 50 years developed two and 1.7% three recurrences.¹¹ Among older patients 4.9% had two, 1.2% three and 1.2% five recurrences. The other study reported a higher frequency and demonstrated that 23.7% of patients younger than 50 years had two diverticulitis recurrences, 10.3% three and 7.0% four recurrences during a follow-up of at least 12 months.¹² Among patients older than 50 years, this was 19.0%, 7.4% and 2.1% respectively. Notably, the first study defined a recurrence as presentation with clinical signs of diverticulitis at least one month after discharge for a previous episode while the other did not apply a minimal time-interval.

Urgent surgery

Four studies reported on urgent surgery for complicated (perforation, failure of conservative treatment) diverticulitis recurrences during follow-up after a conservatively treated primary episode of diverticulitis.⁸⁻¹¹ Younger patients more frequently required urgent surgery with a pooled risk ratio of 1.46 (95% CI 1.29 – 1.66, $I^2 = 0\%$). The estimated average cumulative risk was 7.3% (range 0% - 7.5%) for patients younger and 4.9% (range 0% - 5%) for patients older than 50 years.

Sensitivity analysis demonstrated that the difference became smaller with a pooled risk ratio of 1.29 (95% CI 0.76 – 2.18) when the population-based study (10) was excluded.

Fistulae and abscess

None of the included studies described the number of patients who developed fistulae or abscess separately after a conservatively treated primary diverticulitis. Three studies reported the combined frequency of fistulae, abscess and perforation among patients with recurrent diverticulitis. One study found an incidence of 7.7% in younger and 3.8% in older patients.¹³ The other described a frequency of 13.9% and 12.2%.¹⁰ The latter found that 8.9% of younger patients had fistulae, abscess or perforation at recurrent presentation.¹² This was 12% among patients older than 50 years.

Elective resection

Five studies reported on elective resection during a mean follow-up of 39 months (range 24 – 90).^{6,8,9,11,13} The main indication for performing elective resection was recurrent disease. One study did not describe indications, however, it was assumed that elective resection was performed for the same reason as in the other studies.¹³

Analysis demonstrated that the risk for requiring elective resection during follow-up was equal in both age groups with a risk ratio of 1.13 (95% CI 0.46 – 2.79, $I^2 = 84\%$). The risk varied between 6.5% and 18.4% with an estimated average cumulative risk of 14.3% in patients younger than 50 years. This was 12.6% (3.0% - 32.8%) among older patients.

None of the studies reported on the time interval between primary episode and elective resection.

Mortality

Only one study reported on mortality per age group during follow-up after a conservatively treated primary episode of diverticulitis. No mortality occurred in patients younger than 50 years.⁸ One patient (0.5%) died due to myocardial infarction during follow-up among older patients. The follow-up ranged from 24 to 90 months in this study.

Discussion

This meta-analysis summarizes all evidence currently available in the literature concerning the course of disease of diverticulitis in patients younger and older than 50 years of age. Although high level evidence is lacking this review demonstrated that the risk of requiring urgent surgery during a primary episode of diverticulitis is equal in both age groups (pooled RR 0.99; 95% CI 0.74 – 1.32) and estimated at approximately 20%. The risk of developing at least one diverticulitis recurrence after a conservatively treated primary episode is significantly higher among patients younger than 50 years (pooled RR 1.73; 95% CI 1.40 – 2.13) with an estimated cumulative risk of 30% compared to 17.3% in older patients. Patients younger than 50 years also more frequently required urgent surgery during a subsequent recurrent episode (pooled RR 1.46; 95% CI 1.29 – 1.66). The estimated cumulative risk was 7.3% in younger patients and 4.9% in patients older than 50 years. The risk of elective resection for recurrent disease was equal in both age groups (pooled RR 1.13; 95% CI 0.46 – 2.79) and approximately 12-14%.

Several guidelines have been published on the treatment of diverticulitis.¹⁵⁻¹⁷ Despite several revisions in the past decade the guidelines remained unclear about the exact role that age should play in the treatment for diverticulitis.¹⁸

With regard to patients presenting with a primary episode of diverticulitis, patients younger than 50 years should not be treated differently than older patients. There was no difference in the need for urgent surgery (pooled RR 0.99; 95% CI 0.74 – 1.32). Although low-quality data showed that older patients more frequently presented with fistulae and abscess (11-13), the equal risk of requiring urgent surgery suggest a similar disease course in both age groups.

The risk of urgent surgery for a primary episode of diverticulitis, approximately 20% in both age groups, appeared rather high. It must be emphasized that urgent surgery as defined in this study included all surgery performed during hospitalization. Indications not only encompassed perforation but also abscess progression, failure of conservative treatment and intestinal occlusion. Remarkably, more recent studies reported a lower risk of urgent surgery for primary diverticulitis in both age groups compared to older studies performed before 2005. This suggests a more conservative or minimally invasive approach in the management of a primary diverticulitis in the past years.

With regard to the period after a conservatively treated primary episode of diverticulitis, there are a few differences between age groups which should be considered when taking treatment decisions. Younger patients have a significantly higher risk to develop a

recurrent episode (pooled RR 1.73; 95% CI 1.40 – 2.13). Many studies attribute the greater risk among younger patients to the longer life-time at risk.¹⁹ The fact that several studies in this review described the interval between primary and recurrent episode to be shorter among patients younger than 50 years contradicts this statement.^{8,13} It appears that higher recurrence risk in younger patients is attributable to the higher rate at which recurrences occur and not the longer life-time at risk.

Although patients younger than 50 years have a higher risk of developing a subsequent recurrence after a primary episode, these recurrences do not seem to be more virulent compared to older patients. This meta-analysis produced a pooled risk ratio of 1.46 (95% CI 1.29 – 1.66) indicating a statistically significant higher relative risk to require urgent surgery for recurrent disease among younger patients. From a clinical point of view, the cumulative risks are low and do not differ substantially (7.3% versus 4.9%). Additionally, sensitivity analysis demonstrated that the difference was mostly attributable to the large population-based study (10). When excluded, the difference became smaller.

It was an unexpected finding that there was no difference in cumulative risk of requiring elective resection for recurrent disease between both age groups. Although no clear explanation could be identified, a notable decline in the use of elective resection in the past years was found. Studies published before 2005 reported cumulative risk for elective resection between 5.6% and 32.8% while more recent studies described this risk to range from 1.8% to 6.5%.

There are several considerations that should be taken into account when interpreting the results of this study. There was considerable heterogeneity among study results of studies included in the meta-analysis. This has most likely been caused by information bias. The risk of urgent surgery for primary diverticulitis and elective resection during follow-up differed substantially between studies. More recent studies reported much lower risks compared to older studies. The underlying cause may lie in the fact that the threshold to perform and indications for surgery change over time. Likewise, definitions for several other outcomes may have differed between studies despite attempts to minimize these differences.

It must be emphasized that the pooled cumulative risk of diverticulitis recurrences, urgent surgery during hospitalization for a recurrent episode and elective resection only give an impression of the true cumulative risks. The follow-up duration differed between included studies (12 – 114 months). This contributes to the aforementioned heterogeneity in results and impedes calculating the exact cumulative risk at a fixed point in time. The pooled risk ratio's, however, are less dependant on variation in follow-up duration between studies.

It should be considered that diverticulitis recurrence, as defined in this review, included all presentations with clinical signs consistent with diverticulitis at the hospital after a conservatively managed primary episode. No distinction was and could be made between persistent disease and actual recurrent disease.

Although studies included in the meta-analysis comprise the best available evidence to our knowledge, the low number of studies impedes additional (sensitivity) analysis. Other causes for heterogeneity between studies could not be investigated.

Conclusively, apart from minor differences, patients younger than 50 years only differ substantially in risk for recurrent disease from patients older than 50 years. Although

patients younger than 50 years had a higher relative risk to require acute surgery during recurrent episodes of diverticulitis compared to older patients, one should consider that the absolute risk difference is relatively small (7.3% versus 4.9%).

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Chapter 8

**Does the presence of abscesses in diverticular disease
prelude surgery?**

Bryan van de Wall
Werner Draaisma
Esther Consten
Rosa van der Kaaij
Marinus Wiezer
Ivo Broeders

Journal of Gastrointestinal Surgery. 2012 Dec 14. [Epub ahead of print]

Abstract

Background: Information on long-term outcome of patients treated conservatively for diverticular abscess is scarce. This study aims to compare diverticulitis patients with abscess to patients without abscess with regard to readmission, complications and surgical treatment during a follow-up period of at least 12 months

Methods: A chart review of all patients admitted for a primary manifestation of diverticulitis between January 2005 and January 2011 was performed.

Results: Fifty-nine patients with abscess and 663 without abscess were identified. Median follow-up was 28 months (range 12-103). Initial conservative management was achieved in 54 (91.5%) of patients with diverticular abscess and 635 (96.8%) without abscess. Readmission occurred more frequently among patients with abscess (HR 2.6 CI 1.51 – 4.33) with a first-year-risk of 27.3% versus 10.7% and second-year-risk of 8.2% versus 4.6%. Surgery was more frequently performed in patients with diverticular abscess (HR 2.3 CI 1.42 – 3.66). The first-year-risk was 35.1% versus 16.6% and second-year-risk 12.9% versus 2.4%. The most frequent indication for surgery was persisting or recurrent disease.

Conclusion: Patients with diverticular abscess have a higher risk of being readmitted and requiring surgical treatment. The pattern suggests that readmission and need for surgery is the result of ongoing inflammation of the initial episode.

Introduction

Diverticulitis puts a significant burden on health care. Approximately 112.000 patients present with symptoms consistent with diverticulitis at the general practitioners' office annually in the Netherlands.¹ Hospitalization for confirmed diverticulitis occurs in 13.500 of these patients.²

The majority of patients present with uncomplicated diverticulitis. Between 10-20% present with complications including abscess, perforation, stricture or fistulae.³⁻⁴ Although consensus exists on the surgical management of the latter three, controversy persists on the optimal treatment of patients presenting with abscess.

After conservative management of patients with diverticular abscess, elective resection is typically advised.⁵ It is thought that 40% of these patients will develop severe recurrent disease.⁴⁻⁵ However, with evolving knowledge on diverticular disease indications for elective resection are shifting and principles on treatment strategies should be reconsidered.⁶

Literature on long-term outcome of patients treated conservatively for diverticulitis with concomitant abscess is scarce. This study aims to compare patients with abscess at presentation for a primary episode of diverticulitis to patients without abscess with regard to readmission, complications and surgical treatment during a follow-up period of at least 12 months.

Patients and methods

Study population

This study was a retrospective chart review of all patients presenting with diverticulitis at the emergency department of two large teaching hospitals between January 2005 and January 2011.

Potentially suitable patients were identified using a diagnosis specific discharge code for diverticulitis. Patients were considered for inclusion if it was a first presentation with clinical signs consistent with diverticulitis (local tenderness in the lower or left-lower abdomen in combination with C-reactive protein >10mg/l, white blood cell count >11.0*10⁹/l or body temperature > 38°Celsius).³ Confirmation by computed tomography (CT-scan), sonography or operative findings was mandatory. Radiological criteria for diagnosing diverticulitis were the presence of diverticulae in the descending and/or sigmoid colon and localized colonic wall thickening with or without surrounding fat stranding, free fluid, abscess formation or extraluminal air.⁴

Only patients with Hinchey Ia, Ib and II diverticulitis were included and divided into two groups: patients without (Hinchey Ia) and patients with concomitant diverticular abscess (Hinchey Ib-II). Patients with a Hinchey III or IV were excluded. The Hinchey classification was based on the radiological reports of radiology obtained at presentation (table 1).⁴

Table 1. Modified Hinchey Classification.

Hinchey	Description
Ia	Pericolic inflammation
Ib	Localised para colonic or mesenteric abscess
II	Pelvic abscess
III	Perforated diverticulitis with purulent peritonitis
IV	Perforation of diverticulitis in the abdominal cavity with faecal contamination

Treatment

Both in- and outpatient treatment and follow-up was predominantly performed by surgeons due to local logistic preferences. All included patients were primarily treated conservatively. Hospital admission and the use of antibiotics was left at the discretion of the treating surgeon and included a regime of oral, when tolerated, or intravenous augmentin (or metronidazol in case of penicillin allergy) for 7-10 days. Percutaneous drainage was performed in patients with abscess larger than 5 cm in diameter and radiologically feasible. Acute surgery during a primary episode of diverticulitis was performed in patients with colonic obstruction and in case of failure of conservative management due to disease progression, sepsis and perforation.

Baseline characteristics

Demographic data, American Society of Anesthesiologists' (ASA) Physical Status classification scores, abscess location and diameter in centimeters (of the largest abscess), concomitant complications (fistulae, stenosis and/or free perforation) and management were collected from the hospital database. Characteristics were described for both in- and excluded patients.

Follow-up and study endpoints

All included patients who had been treated conservatively for their primary episode of diverticulitis were followed up to January 2012. The hospital records were searched for readmissions and surgical intervention.

Readmission was defined as secondary presentation to the emergency department with clinical signs of diverticulitis (local tenderness in the lower or left-lower abdomen in combination with C-reactive protein >10mg/l, white blood cell count >11.0*10⁹/l or body temperature > 38°Celsius). Distinction was made between readmission for diverticulitis without abscess, with abscess and free perforation (free intra-abdominal air on radiological examination requiring emergency surgery).

Surgery performed during follow-up was categorized according indication and included symptomatic stenosis, fistulae, perforation and elective resection for ongoing or recurrent complaints. Surgical treatment for symptomatic stenosis was considered when patients developed obstructive complaints after hospital discharge with impassable or hardly passable stenosis in the sigmoid colon at colonoscopy during follow-up. Surgical intervention for fistulae was performed when patients developed clinical signs of fistulae

(pneumaturia, purulent vaginal discharge and purulent discharge in urine) after hospital discharge for their primary episode of diverticulitis. Patients with recurring or persisting abdominal complaints were also treated surgically. Recurring or persisting complaints were defined as multiple bouts of diverticulitis (radiologically or clinically proven) or chronic abdominal pain in the left lower abdomen. The decision to operate was made on a case-by-case basis taking into account the age, comorbidities, severity and frequency of complaints.

Statistical analysis

Statistical software package SPSS 19.0 was used to analyze the results. Descriptive statistics were provided of all baseline characteristics and study endpoints. Continuous variables were described as means (with standard deviation) or medians (with range). For categorical variables, the counts and percentages were calculated.

Cox regression was used to determine whether the presence of abscess at presentation with primary diverticulitis (treated conservatively) was predictive for being readmitted or undergoing surgery during follow-up. Risk estimates were corrected for age, gender, ASA classification and antibiotic use. Analysis was limited to endpoints which occurred more than 10 times during follow-up ensuring sufficient number of events for the degrees of freedom in the Cox model. Results were described as Hazard Ratio's (HR) with corresponding confidence interval (95% CI). A p-value under 0.05 was considered significant.

Results

Participants

A total of 996 patients with the discharge code for a primary episode of diverticulitis were identified from the hospital database (figure 1). Nine-hundred and twenty-nine presented with clinical signs consistent with diverticulitis. Radiological confirmation at presentation was obtained in 768 patients. Diverticulitis without abscess (Hinchey Ia) was found in 663 patients, diverticulitis with abscess (Hinchey Ib-II) in 59 and perforated (Hinchey III-IV) diverticulitis was encountered in 46 patients at presentation.

Baseline characteristics

Patient characteristics are described in table 2 for both in- and excluded patients. Of the 663 patients who initially presented with a primary Hinchey Ia diverticulitis, 28 (4.2%) underwent surgery for the development of perforation (n=9) or disease progression (n=8) during hospitalization and concomitant fistulae (n=8) or ileus caused by colonic stenosis (n=3) at presentation. The remaining 635 (96.8%) patients were treated conservatively either with (n=103) or without antibiotics (n=532).

Fifty-nine patients initially presented with a primary Hinchey Ib-II episode of diverticulitis with pericolic (n=57) or pelvic (n=2) abscess. The abscess diameter ranged from 0 - 2 cm in 27 (45.8%), 2 - 5 cm in 18 (55.9%) and in 14 (23.7%) patients the diameter was greater than 5 cm. A total of 5 (8.5%) patients required surgical intervention for concomitant

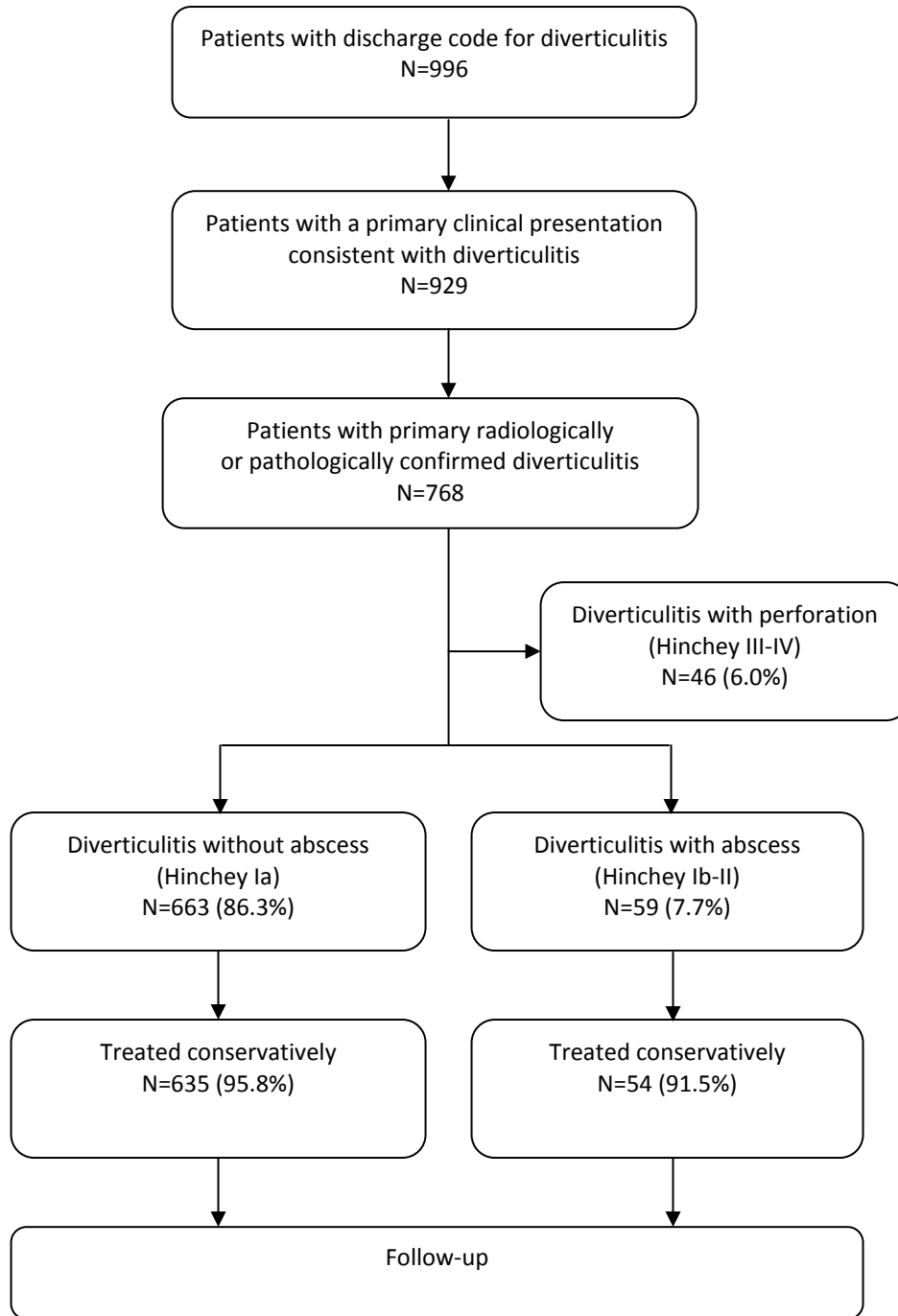


Figure 1. Flowchart of study population.

Table 2. Baseline characteristics of patients with a primary episode of diverticulitis.

	Included patients		Excluded patients
	Diverticulitis <i>without abscess</i> (Hinchey Ia)	Diverticulitis <i>with abscess</i> (Hinchey Ib-II)	Diverticulitis <i>with perforation</i> (Hinchey III-IV)
	N=663	N=59	N=46
Age at presentation (years)			
Mean (SD)	56.7 (13.1)	59.8 (14.4)	66.4 (12.2)
Gender			
male	307 (46.3%)	22 (37.3%)	19 (41.3%)
ASA			
I	290 (43.7%)	23 (39.0%)	10 (21.8%)
II	320 (48.3%)	33 (55.9%)	30 (65.2%)
III or higher	53 (8.0%)	3 (5.1%)	6 (13.0%)
Hospital admission	492 (74.2%)	52 (88.1%)	46 (100%)
Abscess diameter			
0 – 2 cm	-	27 (45.8%)	-
2 – 5 cm	-	18 (30.5%)	-
>5 cm	-	14 (23.7%)	-
Location abscess			
Pericolic	-	57 (96.6%)	-
Pelvic	-	2 (0.4%)	-
Surgical treatment			
Overall	28 (4.2%)	5 (8.5%)	40 (87%)
Development of perforation	9 (1.4%)	-	-
Disease progression/sepsis	8 (1.2%)	4 (6.8%)	-
Fistulae*	8 (1.2%)	1 (1.7%)	-
Ileus caused by stenosis	3 (0.4%)	-	-
Surgical procedure			
Hartmann	15 (2.2%)	4 (6.8%)	17 (37%)
Primary anastomosis	13 (2.0%)	1 (1.7%)	23 (50%)
Conservative treatment			
Overall	635 (96.8%)	54 (91.5%)	6 (13.0%)
Wait-and-see policy	532 (80.2%)	30 (50.8%)	-
Only antibiotics	103 (16.6%)	17 (28.8%)	-
Percutaneous drainage + antibiotics	-	7 (11.9%)	6 (13%)
Laparoscopic lavage	-	-	-

* Numbers described included both patients who underwent surgical treatment during hospitalization and patients planned for elective resection directly at discharge.

fistulae at presentation (n=1) and disease progression during hospitalization (n=4). The remaining 54 (91.5%) patients were treated conservatively with percutaneous drainage and antibiotics (n=7), antibiotics only (n=17) or wait-and-see policy (n=30).

Follow-up

The median follow-up of patients who were treated conservatively for a primary Hinchey Ia diverticulitis was 28 months (range 12-103). This was 27.5 months (range 12-81) among conservatively treated Hinchey Ib-II patients.

Readmission

Patients who have had a Hinchey Ib-II diverticulitis had a higher risk for being readmitted within one month (HR 2.7 CI 1.64 - 4.52), after one month (HR 2.7 CI 1.47 – 4.79) and during the entire follow-up duration (HR 2.6 CI 1.51 – 4.33) compared to patients with a primary Hinchey Ia diverticulitis (table 3). The overall proportion of patients readmitted was 14.8% with a median time-to-event of 7.5 months (range 0-73) among Hinchey Ia individuals. This was 33.4% with a median time-to-event of 3 months (range 0-58) in the other group of patients. Figure 2 shows a cumulative probability curve of readmission for both groups. The majority of readmissions occurred during the first year follow-up with a first-year-risk of 10.7% for Hinchey Ia patients and 27.3% for Hinchey Ib-II patients. After this interval the yearly risk of readmissions decreased with a second-year-risk of 4.6% versus 8.2% and third-year-risk of 4.2% versus 8.7%.

When readmission occurred, patients with a conservatively treated primary Hinchey Ib-II diverticulitis were much more likely to present with complicated disease during follow-up (HR 23.2 CI 7.57-71.28). A total of 5 patients (0.8%) with Hinchey Ia primary diverticulitis were readmitted with complicated disease, of which four presented with abscess and one with perforation. This occurred in 8 (15%) of the conservatively treated Hinchey Ib-II patients of which four presented with abscess and another four with perforation. The median time-to-event was 14 months (range 0-21) compared 8.5 months (range 0-51) in patients who have had a Hinchey Ib-II primary diverticulitis.

Surgical treatment

When analyzing the overall risk of requiring surgery during follow-up, a significantly larger proportion of Hinchey Ib-II patients underwent surgical treatment compared to patients with Hinchey Ia primary diverticulitis (19.5% versus 40.7%; HR 2.3 CI 1.42 – 3.66). Indications for surgery are described in table 3. The majority of patients were treated for recurring or persisting abdominal complaints. Median time-to-event was 5 months (range 0-64) in the Hinchey Ia group and 4.5 months (range 0-58) in the other group. Figure 3 shows a cumulative probability curve for both groups. Comparable to readmission, the risk for surgical treatment was greatest in the first year of follow-up. The first-year-risk was 16.6% in Hinchey Ia patients compared to 35.1% in Hinchey Ib-II patients; Second-year-risk was 3.6% versus 12.9% and third year risk was 2.4% versus 0%.

Table 3. Incidence and risk of study endpoints during follow-up after conservative treatment for a primary episode of diverticulitis.

	Diverticulitis without abscess (Hinchey Ia)	Diverticulitis with abscess (Hinchey Ib-II)	Hazard ratio (95% CI)
	N=635	N=54	
Total follow-up (range)			
Median (months)	28 (12-103)	27.5 (12-81)	
Readmission			
Overall	94 (14.8%)	18 (33.4%)	2.6 (1.51 – 4.33) ^π
Within one month	20 (3.1%)	5 (9.3%)	2.9 (1.10 – 7.82)
After one month	74 (11.7%)	13 (24.1%)	2.7 (1.47 – 4.79)
Readmission disease severity			
Uncomplicated	89 (14%)	10 (18.4%)	1.6 (0.83 – 3.07)
Complicated	5 (0.8%)	8 (15%)	23.2 (7.57- 71.3)
Abscess	4 (0.6%)	4 (7.5%)	-
Perforation	1 (0.2%)	4 (7.5%)	-
Surgical treatment			
Overall	124 (19.5%)	22 (40.7%)	2.3 (1.42 – 3.66) ^π
Symptomatic stenosis	17 (2.7%)	4 (7.4%)	-
Fistulae	5 (0.8%)	1 (1.9%)	-
Perforation	2 (0.3%)	5 (9.3%)	-
Ongoing/recurring complaints	100 (15.7%)	12 (22.2%)	-
Median time-to-event (range)			
Readmission: overall (months)	7.5 (0-73)	3 (0-58)	
< one month (days)	8 (1-30)	24 (9-31)	
> one month (months)	11 (1-73)	12 (1-58)	
uncomplicated (months)	7 (0 – 73)	2.5 (0 – 58)	
complicated (months)	14 (0-21)	8.5 (0-51)	
Surgery: overall	5 (0-64)	4.5 (0-58)	
symptomatic stenosis	3 (1-38)	2 (2-17)	
(months)	2.5 (1-9)	12 (n.a.)	
fistulae (months)	10.5 (0-21)	42 (1-58)	
perforation (months)	6 (1-64)	4.5 (1-23)	
persisting/recurring (months)			

^π Corrected for age, gender, antibiotic use and ASA classification.

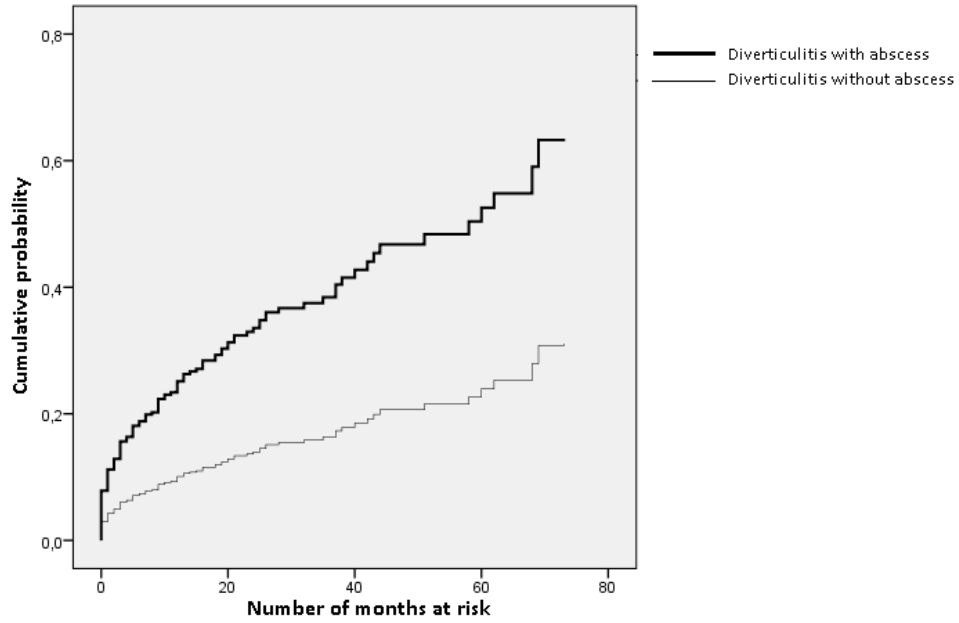


Figure 2. Cumulative probability curve for readmission during follow-up for patients with (Hinchey Ia) and without abscess (Hinchey Ib-II) treated conservatively.

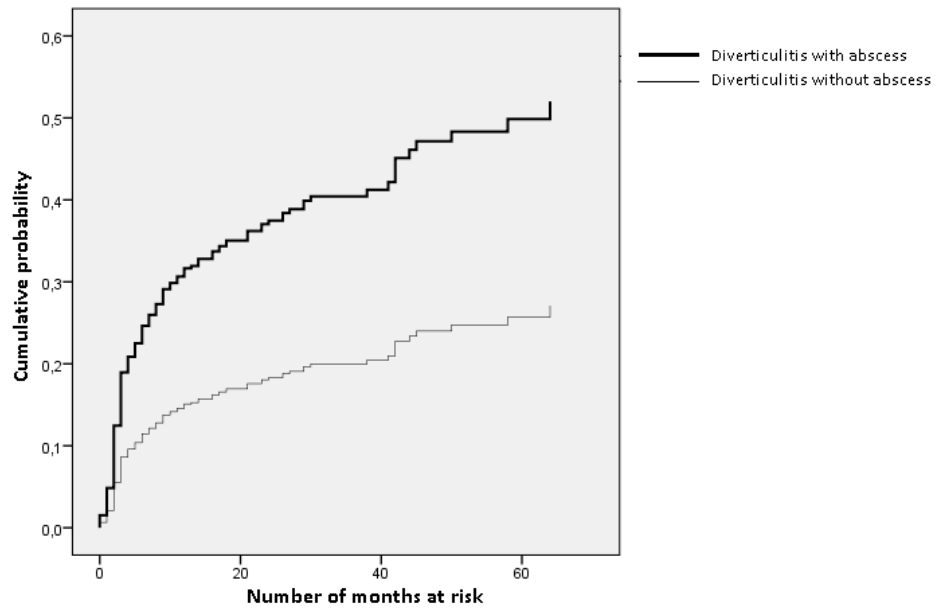


Figure 3. Cumulative probability curve for requiring surgical treatment during follow-up for patients with (Hinchey Ia) and without abscess (Hinchey Ib-II) treated conservatively.

Discussion

The presence of abscess in patients with a primary episode of diverticulitis is relatively rare with a prevalence of 7.7% in this large study population. Controversy exists on the long-term clinical consequences of diverticular abscess.

This study demonstrated that patients with abscess were readmitted more frequently (33.4% versus 14.8%; HR 2.6 CI 1.51 – 4.33) which is consistent with previously published studies.^{3-4,6} Notably, 8 of the 18 readmissions among patients with abscess were for complicated disease. This was 5 out of 94 in patients without abscess. It appears that when readmission occurs, it is more frequently associated with complicated disease in patients treated conservatively for diverticular abscess compared to patients without abscess (HR 23.2 CI 7.57 – 71.28). Nevertheless, the overall risk for readmission with complicated disease is relatively small in both groups (15% versus 0.8%).

The pattern of readmission in this study suggests that readmission usually occurs in the first few months after primary episode and decreases to a low persistent rate after 12 months. This feature is more distinct among patients with abscess (median time-to-readmission: 3 months versus 7.5 months). It seems likely that early readmission is the result of ongoing inflammation of the primary episode, as opposed to “de novo” recurrence.^{3,7}

The most notable difference between both groups was that, despite initial conservative management, 40% of patients with diverticular abscess eventually underwent surgical treatment during follow-up. This was one fifth in patients without abscess. The pattern of requiring surgery is comparable to that of readmission with the majority of patients undergoing surgery in the first few months.

The presence of abscess in patients with diverticulitis is currently used as an indication for elective resection based on the assumption that patients with abscess have a risk of 41% to develop complicated disease.^{5,8} The present study found a considerably lower risk. Based on our results, elective resection should not be performed to prevent further complications. However, it must be emphasized that 40.7% of all patients with diverticular abscess in this study eventually underwent surgery mainly for recurring and/or persisting abdominal complaints. It appears that patients presenting with Hinchey Ib-II diverticulitis are more prone to develop chronic disease. This might form a valid reason to perform elective resection in patients presenting with diverticular abscess.⁹ Elective resection has proven to be effective for treating recurrent and/or persisting abdominal complaints after an episode of diverticulitis.⁹⁻¹¹ On the other hand, by routinely performing elective resection in patients with diverticular disease, a large proportion of patients is operated who would otherwise never have developed chronic complaints.

It is difficult to predict which patients with diverticular abscess develop chronic complaints or complicated disease. The presence of an abscess in itself should not be a reason to perform elective resection. Patients, however, should be informed on the prognosis of this disease with the majority being readmitted or requiring surgical intervention on short-term.

This study has several limitations associated with evaluation of a retrospective cohort. Firstly, this study only included patients with a radiologically confirmed episode of

diverticulitis. As such, it is possible that patient with diverticulitis who did not undergo radiological examination have been missed. Secondly, it should also be considered that the readmission rate does not accurately reflect the actual diverticulitis recurrence rate. Outpatient recurrent episodes of diverticulitis or readmission in other hospitals could have been missed. Lastly, the number of patients with diverticular abscess is relatively small. Nevertheless, as evidence on long-term outcome of patients with diverticular abscess is scarce, this study still provides valuable insight on disease progression after conservative treatment.

Conclusively, patients presenting with a primary episode of diverticulitis with concomitant abscess have a higher risk of being readmitted and requiring surgical treatment compared to patients without abscess. This predominantly occurs during the first few months and suggests that early readmission and need for surgery is the result of ongoing inflammation of the initial episode. Notably, the need for surgical intervention after a disease free interval of one year, is relatively low

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Chapter 9

Patients' and surgeons' perspectives on elective resection for diverticular disease

Bryan van de Wall
Werner Draaisma
Esther Consten
Annemiek Doeksen
Eric Sonneveld
Boudewijn Toorenvliet
Toine Bell
Robert de Vos
Eric Belgers
Eric Hazebroek
Joost Leijtens
Huib Cense
Ivo Broeders

Submitted to Colorectal Disease

Abstract

Background: Quality of life (QoL) is one of the most compelling factors in the decision to perform elective sigmoid resection for diverticular disease. Understanding differences in how patients value their QoL compared to health providers is imperative for shared decision making. A prospective cross-sectional pilot study was performed to explore how surgeons and patients value QoL and their perspectives on the risks associated with elective resection.

Methods: Patients planned for elective resection for diverticular disease were included. Health state utilities were measured in both patient and surgeon using the Standard Gamble method to quantify preferences for different health outcomes after resection including death, living with a temporary or permanent stoma. Scores ranged from 0, in case patient or surgeon preferred the health outcome over the patients' current health state, up to 1.0 when remaining in the current health state was preferred over the health outcome.

Results: Twenty patients (10 males) with a mean age of 62 years were included. For the outcome "death" surgeons assigned a significantly higher mean utility of 0.97 compared to patients who reported a mean of 0.71 ($p=0.000$). This was 0.55 versus 0.11 ($p=0.005$) for living with a temporary and 0.83 versus 0.39 ($p=0.001$) for living with a permanent stoma.

Conclusion: Surgeons appear to consistently underestimate the impact of diverticular disease on QoL of their patients. Patients are willing to accept higher operative risks of death and complications to improve their current health state compared to surgeons.

Background

Diverticulitis represents one of the most frequent colonic pathologies in the United States and Europe with over 200.000 hospitalisations annually.¹ In the past decades, the indication for elective resection has been a continuous matter of debate. Recent guidelines suggest that the number of recurrences is not necessarily a prevailing factor in defining the suitability for elective resection.² These guidelines recommend a tailored approach taking the number and severity of recurrences into account and whether persistent symptoms after an episode of diverticulitis exist. As such, quality of life has become the most compelling factor in the decision to operate.³

It has frequently been suggested that there is a discrepancy in how patients and health providers value quality of life.⁴⁻⁶ This discrepancy however has never been investigated among patients with diverticular disease. Understanding this difference is important when surgeons are taking decisions on elective resection based on their preferences and their own perception of the quality of life of their patients.⁵

This pilot study aims to explore whether there is a difference in how surgeon and patient value quality of life and their perspectives on the risks associated with elective resection by employing a Standard Gamble, the golden standard for measuring health state utility.^{5,7}

Methods

Study design and setting

This was a prospective single-blinded cross-sectional pilot study. Patients were recruited from ten large district teaching hospitals. The reason for the relatively large number of participating centres lies in the fact that we aimed to measure discrepancies on a nationwide basis instead of regional or local differences. Each centre had one dedicated gastrointestinal surgeon responsible for patient enrolment. Patients were included from the outpatient clinic between September 2011 and May 2012.

Study population

The choice to perform elective resection in participating centres was made on a case-by-case basis in accordance with the most recent treatment guidelines. All patients who were planned for elective resection were considered for inclusion. Notably, patients required to have had at least one well documented (sonography or computed tomography) episode of diverticulitis followed by either at least two subsequent episodes of diverticulitis and/or chronic abdominal complaints existing longer than three months.

Patients were asked to participate in the study directly after the decision had been made to plan the patient for elective resection. Informed consent was a prerequisite for participation.

Baseline characteristics

Baseline characteristics regarding age, gender, body mass index and American Society of Anaesthesiologists (ASA) Physical Status were gathered by the local surgeon at inclusion.

In case patients suffered from chronic abdominal complaints, data on the location and self-reported severity of complaints (graded as either mild, moderate or severe) were collected. Historical data on the number of diverticulitis episodes, Hinchey classification (table 1) and treatment were extracted from the hospital database. Surgeons were also asked to indicate their years of experience. All data was collected using paper case record forms. These records were sent to the study coordinator.

Table 1. Modified Hinchey Classification.

Hinchey	Description
Ia	Pericolic inflammation
Ib	Localised para colonic or mesenteric abscess
II	Pelvic abscess
III	Perforated diverticulitis with purulent peritonitis
IV	Perforation of diverticulitis in the abdominal cavity with faecal contamination

Outcome

The discrepancy in how patients and surgeons value quality of life was measured using the Standard Gamble (SG) technique.⁷ The SG is the golden standard for measuring health state utility. During a telephonic interview performed by the study coordinator, patient and surgeon were independently told that the patient could either live the rest of their life in their current health state, or take a “gamble” on healthy life. The “gamble” in this case was elective sigmoid resection. If the patient or surgeon were to take the gamble option, there is an X percent chance that the patient would die instantly, and 1-X chance that the patient would live a healthy remainder of their life. The interviewer, in this case the study coordinator, progressively increased X, until the probability of death was so high, that the patient or surgeon would prefer not to take the gamble and (let the patient) live the remainder of their life in the current health state. The utility associated with the health state would be equal to one minus the probability of death the participant was willing to risk. For example, if a subject said he/she was willing to take the gamble for a healthy life when the percent chance of death was 11% (probability of 0.11), but at 12% risk of death he/she would prefer to (let the patient) live the remainder of their life with recurring/persisting symptoms, the utility associated with the patients’ current health state would be $1-0.11=0.89$.

Patient and surgeon were also asked to choose between taking the “gamble” with a chance of living with a permanent stoma or living the rest of their life in the current health state. This was also done for living with a temporary stoma for three months. These three anchor points were chosen as these outcomes are possible after resection and the readiness to take risks depends on the worst outcome.

Notably, scores could range from 0, in case patient or surgeon preferred the health outcome over the patients’ current health state, up to 1.0 when remaining in the current health state was preferred over the health outcome

Statistical analysis

Statistical software package SPSS 20.0 was used to analyse the results. Descriptive statistics were provided of all variables. Continuous data was described as means with either standard deviation or, when appropriate, range. For categorical variables, the counts and percentages were calculated.

Differences in health state utility between surgeon and patient were analysed using the Mann-Whitney test for all three anchors. A p-value under 0.05 was considered significant. As the sample size was relatively small, bootstrapping (number of samples=1000) was used to test the robustness of found differences.

Cumulative frequency plots were made of reported probabilities of death the patient and surgeon were willing to risk to undergo/perform elective resection (risk acceptance curve). This was also done for living with a permanent or temporary stoma.

Results

Baseline characteristics

Twenty patients were included in this study with a mean age of 62 years (10 males; 10 females). The majority of patients was ASA I (n=7, 35%) or II (n=12, 60%) with only one patient graded as ASA III (5%). Nine patients (45%) had a history of abdominal surgery. Nine (45%) patients had a Hinchey Ia primary episode of diverticulitis, two (10%) Hinchey Ib and an additional two (10%) Hinchey II. In seven patients no radiology was performed during their primary episode. These patients underwent radiology during subsequent episodes.

Patient records showed that 17 (85%) patients had two, 12 (60%) had three and 8 (40%) had four or more episodes of diverticulitis prior to the decision to perform elective surgery. The mean interval between primary diverticulitis episode and decision to operate was 30 months (range 1 – 264). Additional information on treatment of primary and recurrent episodes is described in table 2.

Fifteen out of the 20 included patients reported chronic abdominal pain after their primary episode of diverticulitis (table 3). Self-reported intensity of these complaints varied from mild in five (33.3%) cases, moderate in eight (53.3%) and severe in 2 (13.3%). The pain was predominantly located in the left lower abdomen (n=8, 53.3%). The remaining patients reported their complaints to be located in the entire lower abdomen (n=5, 33.4%) and right lower abdomen (n=2, 13.3%).

A total of ten surgeons participated in this study. The mean experience was 12 years ranging from 7 to 21 years.

Health state utility

For the outcome "death" surgeons assigned a significantly higher mean utility of 0.97 (SD 0.02) compared to patients who reported a mean of 0.71 (SD 0.28, p=0.000). This was 0.55 (SD 0.35) versus 0.11 (SD 0.29, p=0.005) for living with a temporary and 0.83 (SD 0.22) versus 0.39 (SD 0.42, p=0.001) for living with a permanent stoma.

Figure 1, 2 and 3 demonstrate this discrepancy from a clinical point of view. None of the surgeons were willing to perform elective resection if the risk of death was greater than

10% (figure 1). Several patients however were willing to accept a mortality risk of up to 90% in order to improve their current health state.

Table 2. Baseline characteristics of all included patients.

Patient characteristics		20
Age (mean)	<i>years</i>	62 (SD 10.1)
Gender	<i>Male</i>	10 (50%)
Body Mass Index (mean)		26.9 (SD 4.1)
ASA	<i>I</i>	7 (35%)
	<i>II</i>	12 (60%)
	<i>III</i>	1 (5%)
History of abdominal surgery		9 (45%)
Primary diverticulitis episode		20
Hinchev classification	<i>0</i>	0 (0%)
	<i>Ia</i>	9 (45%)
	<i>Ib</i>	2 (10%)
	<i>II</i>	2 (10%)
	<i>No radiology</i>	7 (35%)
Hospitalized		12 (60%)
Antibiotics		4 (20%)
Dietary restriction		12 (60%)
Secondary diverticulitis episode		17
Time interval (median)	<i>weeks</i>	30 (range 1 – 264)
Hinchev classification	<i>0</i>	1 (5.9%)
	<i>Ia</i>	8 (47.1%)
	<i>Ib</i>	5 (29.4%)
	<i>II</i>	0 (0%)
	<i>No radiology</i>	3 (17.6%)
Hospitalized		12 (70.6%)
Antibiotics		4 (23.5%)
Dietary restriction		13 (76.5%)
Tertiary diverticulitis episode		12
Time interval (mean)	<i>weeks</i>	6 (range 5 – 82)
Hinchev classification	<i>0</i>	1 (8.3%)
	<i>Ia</i>	6 (50%)
	<i>Ib</i>	1 (8.3%)
	<i>II</i>	0 (0%)
	<i>No radiology</i>	4 (33.3%)
Hospitalized		7 (58.2%)
Antibiotics		0 (0%)
Dietary restriction		6 (50%)
4 or more diverticulitis episodes		8

Table 3. Characteristics of the 15 patients who reported chronic abdominal pain between diverticulitis recurrences.

Chronic abdominal pain > 3 months		15
Location	<i>Left lower abdomen</i>	8 (53.3%)
	<i>Lower abdomen</i>	5 (33.3%)
	<i>Right lower abdomen</i>	2 (13.3%)
Self-reported intensity pain	<i>Mild</i>	5 (33.3%)
	<i>Moderate</i>	8 (53.3%)
	<i>Severe</i>	2 (13.3%)

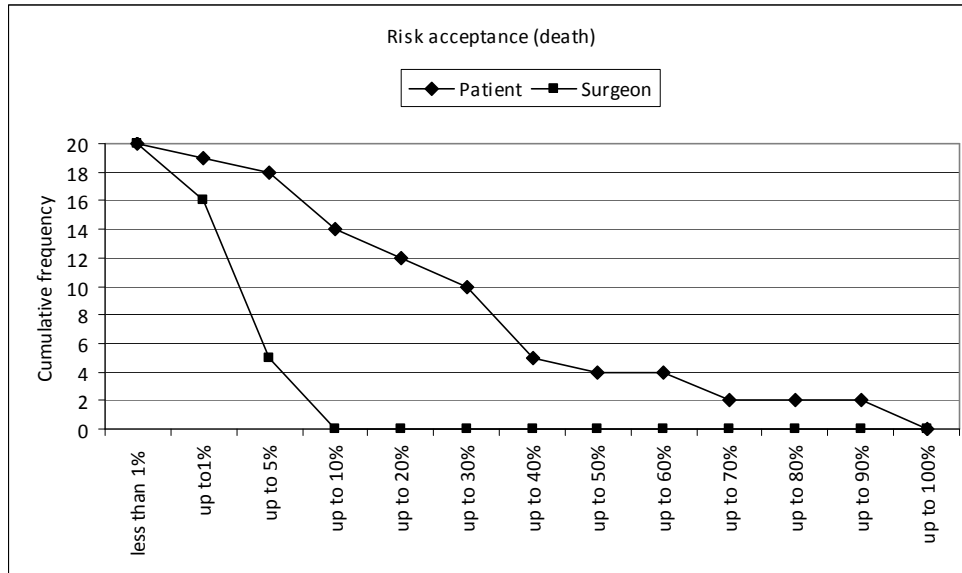


Figure 1. Cumulative frequency distribution of risk acceptance for mortality associated with elective resection of both surgeon and patient across risk levels.

Figure 2 shows the willingness of patients and surgeons to undergo/perform elective resection for several risk thresholds for having to live with a permanent stoma. Notably, 12 of the 20 patients would prefer living in a better health state with a permanent stoma than abstain from resection and remain in their current health state. Only one surgeon agreed on this matter.

Almost similar results were found in the risk acceptance analysis for risks of a temporary stoma as demonstrated in figure 3.

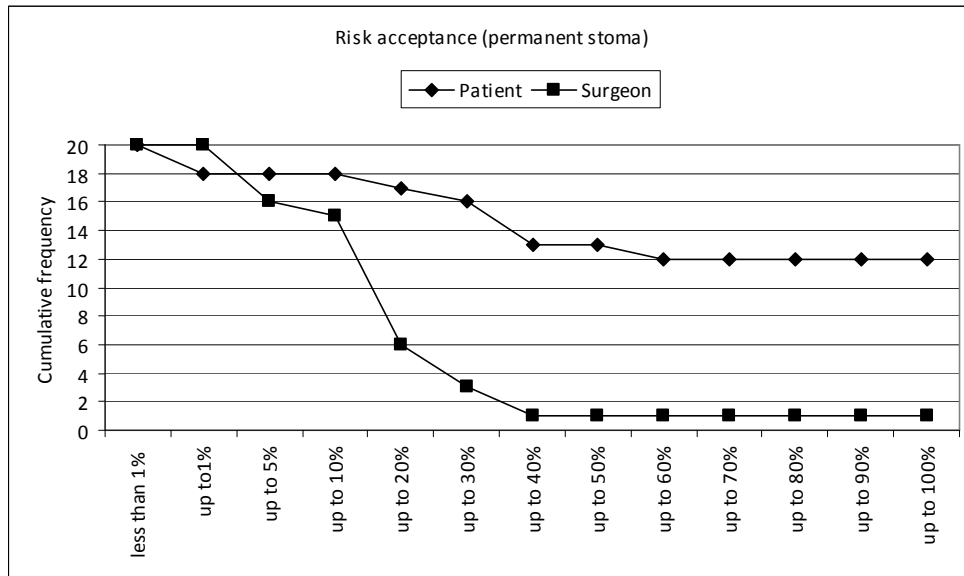


Figure 2. Cumulative frequency distribution of risk acceptance for living with a permanent stoma after with elective resection of both surgeon and patient across risk levels.

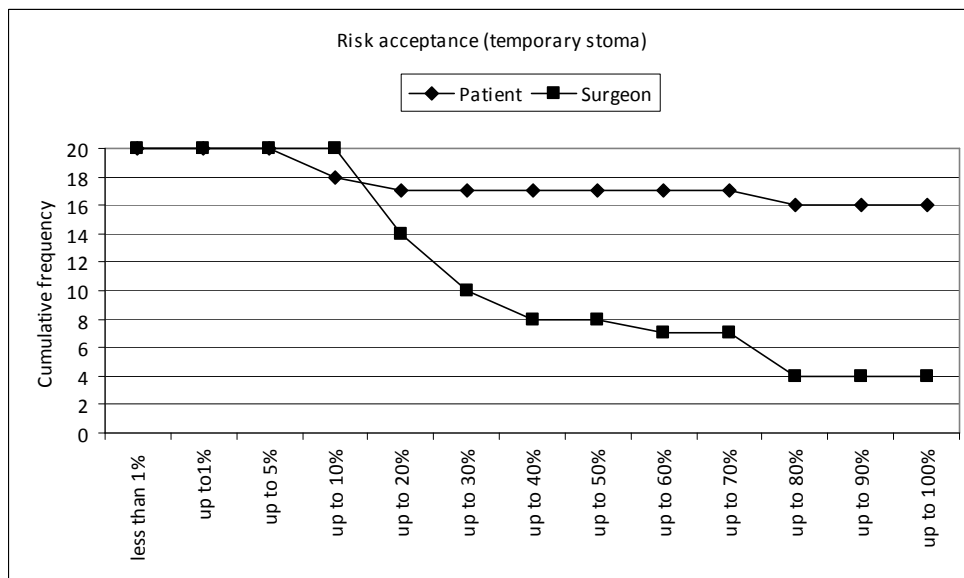


Figure 3. Cumulative frequency distribution of risk acceptance for living with a temporary stoma after elective resection of both surgeon and patient across risk levels.

Discussion

This study aimed to quantify the perceived impact of recurring and/or persisting complaints after an episode of diverticulitis from both a patients' and surgeons' point of view by employing a SG approach. Results suggest that there appears to be a considerable discrepancy. When anchored for several outcomes after resection, patients consistently reported a lower health state utility compared to surgeons. In other words, surgeons appear to consistently underestimate the impact of complaints on the quality of life of their patients. This results in a divergence in perspectives on elective resection and its' associated risks. Patients seem to be more willing to accept higher risks of death, living with a temporary and even permanent stoma after resection compared to surgeons. This study was not designed to identify reasons behind the difference in how patients and surgeons value the health state of patients suffering from persisting and recurring complaints after an episode of diverticulitis. However, it clearly shows that surgeons are more conservative than patients and less likely to risk death and other complications. Surgeons appear to downplay the impact of complaints on quality of life in favour of prolonging life or avoiding complications. Inversely, it is also possible that patients underestimate the impact of complications associated with elective resection on quality of life. Although this is the first study to have investigated this among patients with diverticular disease, similar results were found in studies on cervical cancer (Einstein et al).⁴

Knowledge of the existence of this discrepancy is imperative in decision-making on elective resection.⁸ Increasingly more treatment guidelines are advocating a more tailored approach taking age, medical condition of the patient, the frequency and severity of the attack(s), and whether there are persistent symptoms after the acute episode into account.² As patients appear to value these factors differently, including the patients' perspective is important in order to truly reach a tailored decision.

Elective sigmoid resection for diverticulitis has become increasingly feasible. A population-based study by Guller et al reported a total mortality of 0.1% among 2813 patients.⁹ In a recent randomised clinical trial comparing laparoscopic to conventional elective sigmoid resection for diverticulitis, a mortality of 3% was reported in 104 participants.¹⁰ Eleven (10.6%) of these patients were discharged from the hospital with a stoma. In three patients stoma reversal was performed after six months. It was not reported whether the stomas in the remaining eight patients were intended to be temporary or permanent. Notably, it should be acknowledged that the actual risks on mortality and living with a temporary or permanent stoma are considerably lower than the risk patients are willing to take as demonstrated in this study.

This study has several considerations that should be taken into account. The sample size was relatively small. Bootstrapping analysis, however, demonstrated the results to be robust. Increasing sample size or redoing the study would most certainly lead to similar conclusions.

We limited the number of anchors to death, living with a temporary or permanent stoma in order to avoid response fatigue. Although many other anchors could have been used (e.g. anastomotic leakage, reoperation, other complications), we found strong evidence

that surgeons consistently underestimate health state utility regardless of the anchor used for the SG.

The major strength of the study is that the data was acquired prospectively in multiple centres using the golden standard technique for establishing health state utilities in a standardized fashion by one trained study coordinator.

In conclusion, our findings highlight the differences in perceptions between surgeons and patients regarding the impact on the quality of life of recurring or persisting abdominal complaints after an episode of diverticulitis. Patients are willing to accept a higher risk of death and complications compared to surgeons and even the actual risks associated with elective sigmoid resection described in literature. This discrepancy mandates including a patients' point of view more vigorously in the decision whether or not to perform elective resection.

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Chapter 10

Elective resection for ongoing diverticular disease

significantly improves quality of life

Bryan van de Wall
Werner Draaisma
Jan van Iersel
Esther Consten
Marinus Wiezer
Ivo Broeders

Accepted for publication in Digestive Surgery (December 2012)

Abstract

Background: Although the risks of elective resection for diverticular disease are well studied, studies on subjective improvement are scarce. This study aims to investigate subjective improvement.

Methods: All patients who underwent elective resection for recurring or persisting complaints after an episode of diverticulitis were identified from an in-hospital database. Patients with at least one year follow-up were sent visual analogue scales (VAS) to grade their quality of life and the degree of discomfort caused by abdominal, abnormal defecation and fatigue before and after resection.

Results: One hundred and five patients responded to the questionnaire (response rate 76.6%). Median follow-up was 33 (15-53) months. Elective resection improved general quality of life (median VAS improvement 40) and reduced discomfort caused by abdominal pain (median VAS improvement 60) in up to 89.3% and 87.5% of patients. The effects of elective resection are less profound for discomfort caused by abnormal defecation (77.1%, median VAS improvement 33) and fatigue (75.2%, median VAS improvement 30).

Conclusion: Elective resection of the sigmoid for persisting or recurring symptoms after an episode of diverticulitis improves general quality of life and discomfort caused by abdominal pain, abnormal defecation and fatigue in the vast majority of patients.

Introduction

Elective surgery for recurring and ongoing abdominal complaints after an episode of diverticulitis has been a continuous point of debate. Recent guidelines suggest that the number of recurrences is not necessarily a prevailing factor in defining the indication for elective resection.¹ A more tailored approach is recommended by these guidelines.

Quality of life and the amount of discomfort caused by abdominal complaints should be weighed against the risk of complications when considering surgery.

Although many studies have been performed investigating the morbidity and mortality of elective sigmoid resection in patients with diverticular disease, little attention has been given to improvement as experienced by the patient.²⁻³ Objectifying this improvement is essential for balanced decision-making and offers both patients and surgeons better insight on expectations of elective surgery.

Therefore this study aims to investigate the effects of elective resection on general quality of life and the degree of discomfort caused by abdominal pain, abnormal defecation and fatigue as experienced by the patient.

Patients and methods

Study design and setting

This retrospective cohort study was performed in the Meander Medical Center Amersfoort and the St Antonius Hospital in Nieuwegein, two large regional teaching hospitals in the Netherlands.

Study population

Hospital records were searched for all patients who were diagnosed with diverticulitis at the emergency unit between January 2005 and January 2011 using a diagnosis specific code for this disorder. Only patients who were treated conservatively during the acute phase and received elective sigmoid resection during the study period were considered eligible for participation. Resections were deemed elective if the date of surgery was planned and surgery was preceded by standard preoperative screening and work-up. In the participating centers elective resection was considered in patients with at least one radiologically confirmed episode of diverticulitis who subsequently developed multiple bouts of diverticulitis or suffered from chronic abdominal complaints. Patients with an absolute indication for elective resection such as fistulae or impassable stenosis at colonoscopy were excluded.

Baseline characteristics

All patients had undergone standard preoperative screening by senior anesthesiologists. Patient characteristics (birth date, gender) and the the American Society of Anesthesiologists Physical Status (ASA) classification were extracted from these reports. The total number of hospitalizations and/or presentations at the emergency department for diverticulitis was registered. The severity of the primary in-hospital episode of

diverticulitis was determined by screening the radiological reports of computed tomography scans and ultrasonographies performed at presentation. Patients were categorized as either uncomplicated (Hinchey Ia) or complicated (Hinchey Ib and II) diverticulitis. The Hinchey classification is described in table 1.

Additionally, all included patients were sent a customized questionnaire in January 2012 in which they were asked to describe their symptoms in the period preceding resection. The questionnaire is described in appendix 1.

Table 1. Modified Hinchey Classification.

Hinchey	Description
Ia	Pericolic inflammation
Ib	Localised para colonic or mesenteric abscess
II	Pelvic abscess
III	Perforated diverticulitis with purulent peritonitis
IV	Perforation of diverticulitis in the abdominal cavity with faecal contamination

Elective resection

Data regarding elective colonic resection were extracted from the surgical reports which contained detailed information on procedure, technique, conversion, intra-operative complications, the construction of the anastomosis and stomas. The hospital discharge forms were screened for post-operative complications. Anastomotic leakage was defined by radiological signs of a deficient anastomosis (abscess at the site of the anastomosis and/or free abdominal fluid and/or air). A wound infection was defined as a superficial infection of the surgical entry wound. Postoperative bleeding requiring surgical reintervention and/or blood transfusion was deemed as a severe bleeding. All other minor complications such as respiratory- and urinary tract infections and long-term complications (incisional hernia) were also registered.

General quality of life and degree of discomfort scores

General quality of life (QoL) was measured by asking patients to estimate their quality of life in the period preceding- and after resection using a visual analogue scale (VAS) embedded in the aforementioned questionnaires (appendix 1). A score of 0 was regarded as the worst and 100 as the best general quality of life.

Additionally patients were asked to score the degree of discomfort caused by abdominal pain (DDP), abnormal defecation (DDD) and fatigue (DDF) on a VAS prior to and after resection. A score of 0 was regarded as no discomfort and 100 as incapacitating discomfort.

The VAS instrument is a psychometric response scale, where symptom impact is registered by indicating a position along a continuous line between two endpoints representing the extremes of a given symptom. The distance from the lowest extreme to the marked position (in millimeters) reflects the symptom impact. This method is established as a valid and reliable tool with a range of clinical and research applications including assessment of symptoms, pain, fatigue, and general health status.⁴⁻⁷

The questionnaire including VAS was sent a second time to all patients who did not return the questionnaire within 4 weeks. Patients, in whom no response was attained after another interval of 4 weeks, were contacted by phone to encourage responding to the questionnaire. Reasons for refusal were registered.

Statistical analysis

Statistical software package SPSS 19.0 was used to analyze the results.

Descriptive statistics were provided for all variables. Continuous data was firstly tested for normality using de Q-Q plots. Normally distributed continuous variables were described using the mean and standard deviation. Non-normally distributed continuous variables were described as medians and range. For categorical variables, the counts and percentages were calculated. The median VAS scores for QoL, DDP, DDD and DDF in the period preceding and after resection were described graphically.

Sub-analysis

VAS scores were also described for both patients with a primary uncomplicated and complicated episode of diverticulitis separately. Differences in scores of the period preceding resection and improvement after resection were compared using the Mann-Whitney test in order to investigate whether there was a significant difference between both groups.

Additionally, this study aimed to investigate how scores prior to resection relate to chances of benefit from elective resection. Benefit was defined as improvement by more than half a standard deviation of preoperative scores of QoL, DDP, DDD and DDF (>10 points on VAS) which corresponds to the minimal clinically important difference.⁸ The minimal clinically important difference is defined as the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate a change in the patient's (health care) management.

Positive predictive values for every level on the VAS score prior to resection were calculated. The area under the curve (AUC) was calculated to study whether the height of VAS scores prior to resection was an adequate indicator for determining the effect of elective resection. An AUC greater than 0.9-1.0 was considered to be optimal, 0.8-0.9 good, 0.7-0.8 fair, 0.6-0.7 poor and 0.5-0.6 a failure.

Results

Participants

One thousand and twenty-four consecutive patients were identified who were treated conservatively for an episode of diverticulitis during the study period. A total of 161 patients underwent elective resection. Twenty-four of these patients were excluded as elective resection had been performed for either colonic fistulae (n= 16) or impassable stenosis at colonoscopy for which conservative treatment was not deemed warranted by the treating physician (n=8).

Elective resection for recurring or persisting abdominal complaints was performed in 137 (13.6%) patients. A total of 105 (76.6%) out of 137 patients responded to the

questionnaires. Of the twenty-six non-responders 5 patients refused to answer the questionnaire due to either non-related severe comorbidity (n=2), lack of time (n=2) or because their condition improved and felt no need to participate (n=1). The other 21 non-responders remained unattainable after repetitive attempts. No mortality occurred in the study period.

The median interval between resection and response date was 33 (15-52) months .

Table 2. Baseline characteristics

Patient characteristics		Responders (N=105)
Gender	<i>Male</i>	59 (56.2%)
	<i>female</i>	46 (43.8%)
Age at resection (mean)		56.2 (SD 11)
ASA	<i>I</i>	39 (37.1%)
	<i>II</i>	57 (54.3%)
	<i>III</i>	9 (8.6%)
Severity of primary diverticulitis episode	<i>Uncomplicated</i>	85 (81.0%)
	<i>Complicated</i>	12 (11.4%)
	<i>No radiology</i>	8 (7.6%)
Number of in-hospital episodes prior to resection	<i>1</i>	67 (63.8%)
	<i>2</i>	33 (31.4%)
	<i>3</i>	5 (4.8%)
Start abdominal symptoms	<i>Around first episode diverticulitis</i>	63 (59.6%)
	<i>Always existing</i>	42 (40.4%)
Abdominal pain	<i>Continuous</i>	33 (31.4%)
	<i>Intermittent</i>	72 (68.6%)
Defecation	<i>Predominantly diarrhea</i>	13 (12.4%)
	<i>Predominantly constipation</i>	17 (16.2%)
	<i>Predominantly altering</i>	64 (61.0%)
	<i>Predominantly normal</i>	11 (10.5%)
Frequent blood loss in faeces		15 (14.3%)
Months between primary episode and resection (median)		7 (3-55)
Months between resection and response date (median)		33 (15-52)

Baseline characteristics

Baseline characteristics of the 105 responders are described in table 2. Notably 8 (7.6%) patients did not undergo radiological examination during their primary episode of diverticulitis. The diagnosis was made on a clinical basis. These patients however underwent radiological examination during their secondary manifestation and presented with uncomplicated diverticulitis.

Elective resection

The median interval between the primary episode of diverticulitis and elective resection was 7 (3-55) months. Eighty-six per cent (n=97) of elective resections were started with minimally invasive techniques (table 3). Conversion to an open procedure occurred in 3.8% (n=4) all due to adhesions.

A protective stoma was constructed in 3.8% (n=4). In one patient no stoma reversal was performed in a later phase due to severe co-morbidity. In the other three patients the stoma was successfully reversed without any complications.

Reoperation was required in 5.8% (n=6) due to either anastomotic leakage (n=5) or severe bleeding (n=1) originating from the trocar entry site. Two patients (1.9%) had anastomotic abscess which were treated conservatively.

Minor complications included 9 (8.6%) patients with wound infection, 5 (4.8%) with urinary tract and 4 (3.8%) with respiratory tract infection (3.6%). During follow-up 6 (5.7%) patients developed a incisional hernia.

Table 3. Complications of elective resection.

Elective sigmoid resection		Responders (N=105)
Technique	<i>Laparoscopic</i>	97 (85.8%)
	<i>Conventional</i>	8 (7.1%)
Conversion		4 (3.8%)
Protective stoma		4 (3.8%)
Complications	<i>Anastomotic leakage</i>	5 (4.8%)
	<i>Anastomotic abscess</i>	2 (1.9%)
	<i>Severe bleeding</i>	1 (1.0%)
	<i>Wound infection</i>	9 (8.6%)
	<i>Urinary tract infection</i>	5 (4.8%)
	<i>Respiratory tract infection</i>	4 (3.8%)
	<i>Incisional hernia</i>	6 (5.7%)

General quality of life and degree of discomfort scores

The median VAS score for general Qol prior to resection was 40 (30-55). This score improved to 80 (70-90) after resection (figure 1). There were no significant differences in scores before resection and improvement after resection between patients who had an uncomplicated and complicated primary episode of diverticulitis. Elective resection had an overall beneficial effect on the Qol in 89.3% of patients. Positive predictive values (PPV) of

elective resection improving general QoL increased with lower QoL scores prior to resection (table 4). The PPV reached 100% for patients with a QoL score of 30 or lower prior to resection. The predictive value of using QoL scores prior to resection for predicting improvement was considered to be good to optimal (AUC 0.886).

The VAS score for DDP (abdominal pain) decreased from 80 (70-90) to 20 (10-40). Scores did not significantly differ between patients with an uncomplicated and complicated primary episode of diverticulitis. Elective resection improved abdominal pain in 87.5% of patients. Similar to general QoL, the scores for DDP prior to resection strongly related with the PPV for benefitting from elective resection (AUC 0.869). The PPV reached 100% at a score of 80 or higher (table 5).

The median score for DDD (abnormal defecation) was 63 (38-80) prior to resection. This decreased to 30 (10-50) after surgery. There was no difference between patients with a complicated and uncomplicated primary episode. Improvement of DDD after resection was seen in 77.1% of patients. In contrast to QoL and DDP, the scores prior to resection did not appear to be of predictive value (AUC 0.595).

The DDF (fatigue) decreased from 70 (40-80) to 40 (15-60) after surgery with 75.2% of patients having benefitting from resection. No difference existed between patients with an uncomplicated and complicated primary episode of diverticulitis. Similar to DDD, scores for DDF prior to resection were of poor predictive value (AUC 0.616).

Table 4. Positive predictive value* of beneficial effect of elective resection for general quality of life scores.

QoL scores prior to resection	General condition (n patients within corresponding score range)
0 (worst)	100% (n=0)
≤10	100% (n=0)
≤20	100% (n=8)
≤30	100% (n=25)
≤40	97.8% (n=45)
≤50	98.3% (n=58)
≤60	97.5% (n=79)
≤70	96.5% (n=85)
≤80	94.7% (n=94)
≤90	92.0% (n=100)
≤100 (best)	89.3% (n=105)

* Proportion of subjects with positive test results (score equal or lower than described in table) who will benefit from elective resection.

Table 5. Positive predictive value* of beneficial effect of elective resection for discomfort scores of abdominal pain, abnormal defecation and fatigue.

Discomfort scores prior to resection	Abdominal pain (n patients within corresponding score range)	Abnormal defecation (n patients within corresponding score range)	Fatigue (n patients within corresponding score range)
≥0 (not present)	87.6% (n=105)	77.1% (n=105)	75.2% (n=105)
≥10	88.5% (n=105)	76.8% (n=99)	74.2% (n=93)
≥20	88.5% (n=104)	76.3% (n=93)	73.9% (n=88)
≥30	91.1% (n=101)	78.3% (n=83)	74.1% (n=81)
≥40	93.8% (n=97)	78.6% (n=70)	74.0% (n=77)
≥50	93.5% (n=92)	82.3% (n=62)	81.3% (n=64)
≥60	94.5% (n=91)	84.9% (n=53)	86.0% (n=57)
≥70	91.1% (n=74)	87.2% (n=39)	88.9% (n=45)
≥80	100% (n=38)	81.3% (n=16)	90.5% (n=21)
≥90	100% (n=12)	66.7% (n=6)	75.0% (n=8)
100 (incapacitating)	100% (n=6)	75.0% (n=4)	100% (n=5)

* Proportion of subjects with positive test results (score equal or lower than described in table) who will benefit from elective resection.

Discussion

The decision whether or not to perform elective resection for diverticular disease remains difficult. The physician should balance the severity of complaints and chances for improvement against the risk of severe complications. Although both the impact of symptomatic disease and occurrence of complications are extensively studied, little is known about outcome after surgery.⁹⁻¹²

The results of this study demonstrate that elective resection will improve general quality of life (median VAS improvement of 40) and discomfort caused by abdominal pain (median VAS improvement of 60) in up to 90% of patients with recurring or persisting abdominal complaints after an episode of diverticulitis regardless whether they have had an uncomplicated or complicated primary episode of diverticulitis. The effects of elective resection are substantial but less profound for discomfort caused by abnormal defecation (median VAS improvement 33) and fatigue (median VAS improvement 30) with approximately three quarters of patients reporting clinical improvement. The percentage of severe complications in this study population was in accordance with results published in previous studies.³

The high success rate support the decision for elective surgery in patients with recurring or persisting complaints after an episode of diverticulitis. The results can be used when informing patients on the chances on benefit from elective sigmoid resection with regard to their general quality of life, abdominal pain, abnormal defecation and fatigue.

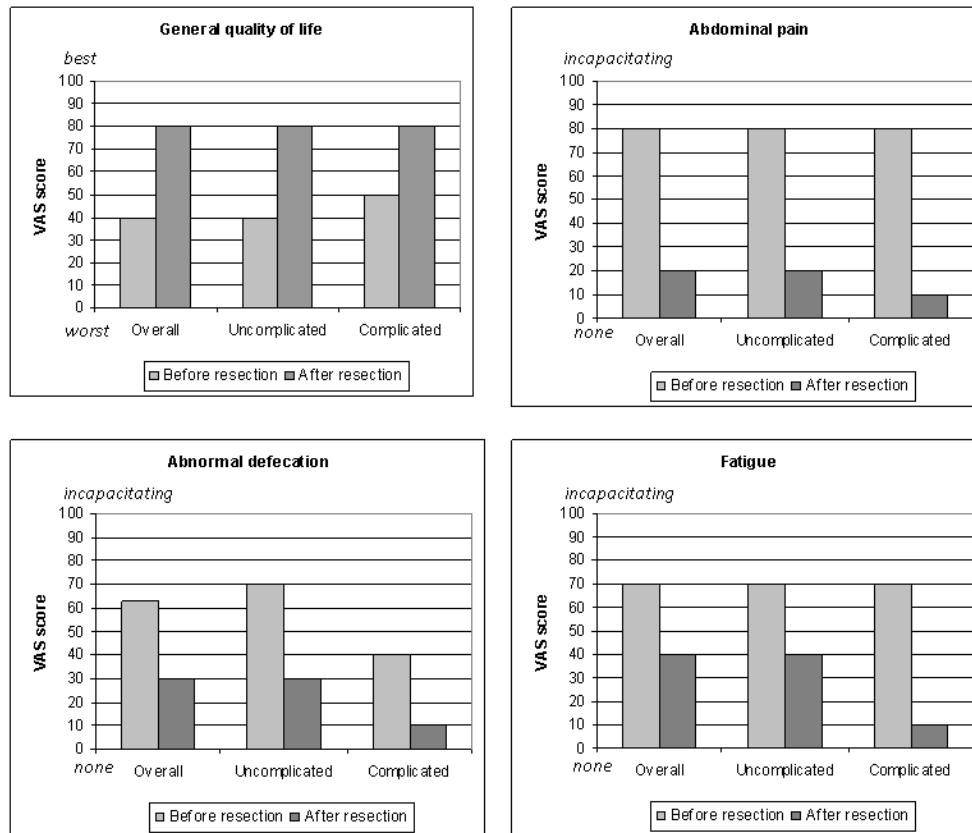


Figure 1. Median scores of general quality of life, degree of discomfort caused by abdominal pain, abnormal defecation and fatigue before and after resection.

Additionally, it is acknowledged that chances on benefit increases with worse scores on quality of life and abdominal pain prior to resection.² This does not apply to discomfort caused by abnormal defecation and fatigue.

Despite the major improvement in quality of life and symptoms, it should also be emphasized that the majority of patients remain mildly symptomatic after resection. This study demonstrated that after resection patients have a median score of 40 for abdominal pain, 30 for abnormal defecation and 40 for fatigue indicating the existence of residual symptoms. This should be taken into account when considering elective resection and informing the patient.

Before generalizing these results to daily practice, it is important to comprehend to which group of patients these results apply. In the past, indications for elective resection in diverticular disease focused on the number of diverticulitis episodes.¹³ Present-day guidelines abandoned these general principals.¹ Elective resection is currently evaluated on a “case by case” basis in which not just the number and severity of diverticulitis recurrences or duration of persisting abdominal complaints individually is important but

the product and impact of these factors on quality of life and the amount of discomfort. The institutions at which this study was performed adopted a similar policy. Patients reporting impairment of their daily activities were offered elective resection. Comparable studies with similar study populations were performed by Forgione et al in 2009 and more recently by Pasternak et al.^{2, 14} Both studies found a substantial improvement of gastro-intestinal symptoms on the Gastro-intestinal Quality of Life Index (GIQLI) after elective resection for diverticular disease. Pasternak et al reported an overall success rate of 96% in gastro-intestinal symptoms which corresponds well with success rates found in this study. Notably, a major difference between the above mentioned studies and this study is the instrument for measuring quality of life and symptoms. The GIQLI produces an overall score of both quality of life and gastro-intestinal symptoms combined.¹⁵⁻¹⁶ This study applied visual analogue scales in order to measure improvement of these dimensions separately.

There are certain considerations regarding the design of the current study that must be taken into account. Firstly, patients were asked to grade their general quality of life, DDP, DDD and DDF in retrospect. We cannot definitely know whether patients over- or underestimated their health and symptoms in the period preceding resection. Nevertheless, it is assumed that patients are perfectly capable to indicate the direction of the treatment effect (improvement of deterioration) in both prospective and retrospective setting. Therefore, caution should be applied when directly comparing scores prior and after resection. However, the proportion of patients reporting improvement (> 10 on VAS) is reliable.

Secondly, in this study subjective evaluation of quality of life and symptom severity was of central importance. Subjective outcomes share the weakness of inter-patient variation due to individual differences in quality of life and symptom perception, interpretation, management and coping.

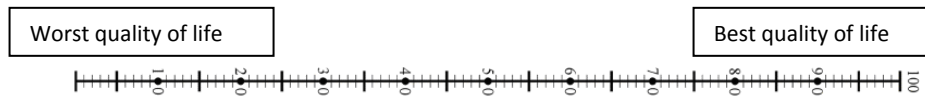
Lastly, in 21 patients reasons for not responding to the questionnaire remained unclear. Response bias cannot be ruled out with certainty.

In conclusion, this study demonstrates that elective sigmoid resection substantially improves both general quality of life and discomfort caused by abdominal pain, abnormal defecation and fatigue in patients with persisting or recurring abdominal complaints after an uncomplicated and complicated episode of diverticulitis. To our opinion, elective resection should play an important role in the treatment of these patients.

Appendix 1. Questionnaire sent to all included patients (translated into English)

1. Please indicate on the scale below how you experience/experienced your quality of life:

Now

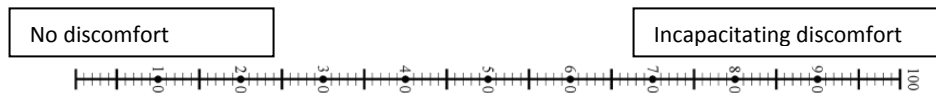


In the period preceding surgery

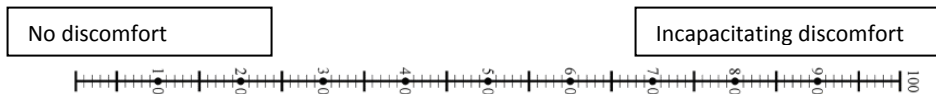


2. Please indicate on the scale below how much discomfort from abdominal pain you experience/experienced:

Now



In the period preceding surgery



3. Please indicate on the scale below how much discomfort from abnormal defecation you experience/experienced:

Now

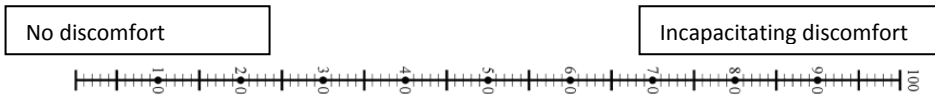


In the period preceding surgery



4. Please indicate on the scale below how much discomfort from fatigue you experience/experienced:

Now



In the period preceding surgery



5. When did the abdominal complaints start?

- *Around the first episode of diverticulitis.*
- *I always have had abdominal complaints.*

6. Regarding your abdominal complaints, were they continuously present or with pain-free intervals?

- *Continuous.*
- *With pain-free intervals.*

7. How was the consistency of your stool prior to the operation?

- *Predominantly diarrhea.*
- *Predominantly constipation.*
- *Predominantly altering.*
- *Predominantly normal.*

8. Did you frequently (more than once a month) lose blood in your stool prior to the operation?

- *Yes*
- *No*

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Chapter 11

**DIRECT trail: diverticulitis recurrences or continuing symptoms treatment;
operative versus conservative treatment.**

A multicenter randomised clinical trial

Bryan van de Wall
Werner Draaisma
Esther Consten
Yolanda van der Graaf
Marten Otten
G de Wit
Henk van Stel
et al.

BioMed Central Surgery, 2010 6;10:25.

Abstract

Background: Persisting abdominal complaints are common after an episode of diverticulitis treated conservatively. Furthermore, some patients develop frequent recurrences. These two groups of patients suffer greatly from their disease, as shown by impaired health related quality of life and increased costs due to multiple specialist consultations, pain medication and productivity losses.

Both conservative and operative management of patients with persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis are applied. However, direct comparison by a randomised controlled trial is necessary to determine which is superior in relieving symptoms, optimising health related quality of life, minimising costs and preventing diverticulitis recurrences against acceptable morbidity and mortality associated with surgery or the occurrence of a complicated recurrence after conservative management.

We, therefore, constructed a randomised clinical trial comparing these two treatment strategies.

Methods: The DIRECT trial is a multicenter randomised clinical trial. Patients (18-75 years) presenting themselves with persisting abdominal complaints after an episode of diverticulitis and/or three or more recurrences within 2 years will be included and randomised. Patients randomised for conservative treatment are treated according to the current daily practice (antibiotics, analgetics and/or expectant management). Patients randomised for elective resection will undergo an elective resection of the affected colon segment. Preferably, a laparoscopic approach is used.

Outcome: The primary outcome is health related quality of life measured by the Gastro-intestinal Quality of Life Index, Short-Form 36, EQ-5D and a visual analogue scale for pain quantification. Secondary endpoints are morbidity, mortality and total costs. The total follow-up will be three years.

Discussion: Considering the high incidence and the multicenter design of this study, it may be assumed that the number of patients needed for this study ($n = 214$), may be gathered within one and a half year.

Depending on the expertise and available equipment, we prefer to perform a laparoscopic resection on patients randomised for elective surgery. Should this be impossible, an open technique may be used as this also reflects the current situation.

Trial register number: NTR1478

Introduction

The recurrence rate of patients treated conservatively for an episode of diverticulitis is approximately 25%.¹ Elective resection has traditionally been advised after a second episode of diverticulitis. It has been thought that patients with a diverticulitis recurrence are at greater risk of developing complications, have higher mortality rates and are less likely to respond to medical treatment.²

However, recent studies have demonstrated that the number of attacks of diverticulitis is not necessarily a prevailing factor in defining the suitability of surgery. Most patients who present with complicated diverticulitis do so at the time of their first attack. Furthermore, only a fraction (5-7%) develops complicated diverticulitis during subsequent attacks.³⁻⁴

This and the fact that operation itself carries significant morbidity and mortality, has led to reluctance in gastroenterologists and surgeons towards elective resection after a recurrence of the disease.

However, elective resection may be an appropriate solution for a more selective group of patients who suffer greatly from their disease. Many studies have consistently shown that 40-80% remain symptomatic after conservative treatment, leading to impaired health-related quality of life (HRQoL) and increased costs due to multiple specialist consultations, pain medication and productivity losses.¹ Logically, this is also the case for patients who continue developing diverticulitis recurrences on a frequent basis. Also, these patients often remain symptomatic in between the recurrences.

In addition of possibly preventing further recurrences and complications of diverticulitis, elective resection has frequently been demonstrated to relieve persisting symptoms after an episode of diverticulitis.⁵⁻⁶ Therefore, many physicians and patients seem to abandon expectant/conservative management and subsequently choose elective resection.

Both conservative and operative management of patients with persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis are applied. However, direct comparison by a randomised controlled trial is necessary to determine which is superior in relieving symptoms, optimising HRQoL, minimising costs and preventing diverticulitis recurrences against acceptable morbidity and mortality associated with surgery or the occurrence of a complicated recurrence after conservative management.

Methods

Study objective

The DIRECT trial is a multicenter randomised clinical trial. The objective is to compare conservative management to elective resection of the diseased colon segment in patients with persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis. We hypothesize that elective resection is superior in relieving abdominal complaints, preventing further hospitalisation and specialist consultation and minimising direct and indirect hospital costs against acceptable morbidity and mortality compared to conservative management.

Study population

Inclusion criteria

- Age 18-75 years.
- Patients presenting with either persisting abdominal complaints and/or frequently recurring diverticulitis after a well documented (CT-scan or ultrasonography) episode of diverticulitis.

Persisting abdominal complaints may include patients with:

- *continuing lower left abdominal pain AND/OR persistent change in bowel habits AND/OR persistent blood loss.*
- *Symptoms must exist longer than 3 months after a previous episode of diverticulitis*

Frequently recurring diverticulitis is defined as:

- *Three or more diverticulitis recurrences within 2 years.*
- *A minimal interval of 3 months between the recurrences is mandatory.*
- Persisting abdominal complaints and/or frequently recurring diverticulitis must be accompanied by inflammatory changes (CT-scan or ultrasonography) in the bowel wall: Bowel-wall thickening with or without abscess.
- ASA I-III.

Exclusion criteria

- Patients with elective or emergency surgery for acute diverticulitis in the past.
- Patients with an absolute operation indication (perforation with purulent/fecal peritonitis, symptomatic bowel stenosis or fistula).
- Patients with colorectal malignancies.
- Patients in ASA class III who are at high risk for per- and postoperative complications due to severe co-morbidity as regarded by the surgeon and/or the patients specialists
- Patients with a psychiatric disease or other conditions making them incapable of filling out the questionnaires or completing the objective follow up tests.

Study endpoints

Primary endpoint

Health-related quality of life (HRQoL) objectified primarily by the Gastro-intestinal Quality of life Index (GIQLI) and secondarily by EuroQol-5D (EQ-5D), Short-form 36 (SF-36) and Visual Analogue Score (VAS) for pain. Patients are also asked to point out on a 7 point Likert scale whether their health and complaints have improved or deteriorated in comparison to the previous assessment.

Secondary endpoints

1. Mortality defined as:

- *Elective surgery:* 30-days mortality.
- *Both groups:* Mortality associated with the development of complications related to diverticulitis during follow-up.

2. Morbidity defined as:

- Diverticulitis recurrence
- Perforation (with purulent/fecal peritonitis)
- Fistula
- Symptomatic stenosis
- Abscess
- Stoma formation
- Emergency surgery or re-operation
- Peri- and postoperative complications

3. Direct health care costs. In-hospital resource use will be recorded. During follow-up medication use, general practitioner and specialist visits will be measured at baseline and regular intervals with customized questionnaires.

4. Indirect non-health care costs, using a standardised ShortForm-health and labour questionnaire (SF-H&L) at baseline and regular intervals during follow-up.

All questionnaires are asked to be filled in at baseline and 3, 6, 9, 12, 24 and 36 months after treatment

Sample size

The sample size calculation is based on the minimum important difference* (MID) of the GIQLI score. The MID can be estimated by taking half a standard deviation of a quality of life instrument.⁷⁻⁸

Based on the studies of Forgione et al and Zdichavsk et al the MID of the GIQLI score is estimated at 10 points.⁵⁻⁶ They also demonstrated that patients improve with 10 points on the GIQLI score one month to one year after elective resection (111 ± 20.4 and 105.8 ± 15.5) for diverticulitis compared to preoperatively (100 ± 22.1 and 95.3 ± 21.4). In conclusion, a difference of 10 points corresponds with the MID and the expected improvement after elective resection.

To demonstrate this difference using an independent t-test ($\alpha = 0.05$, $\delta = 10$, $\sigma = 21$, $\text{power} = 0.9$) approximately $N = 97$ patients per group are needed for this study. Therefore a total study population of 194 patients is required to attain statistical significance.

To compensate for a potential loss to follow-up of 10%, 214 patients will be included.

** Minimum important difference (MID): The smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's (health care) management.*

Treatment of Subjects

Conservative treatment

Patients randomised for conservative treatment are treated according to the current daily practice. In other words, conservative treatment is determined by the preferences of the treating physician. Conservative treatment may consist of expectant management, antibiotics and/or analgetics. Should there be radiologic evidence for the presence of

pericolonic abscesses, percutaneous drainage may be performed depending on the size and opinion of the local radiologist regarding accessibility.

Elective surgery

Patients randomised for elective surgery will undergo an elective colonic resection within approximately 6 weeks. In the interval between randomisation and elective surgery, patients are treated conservatively (see above). Intentionally, a laparoscopic approach is used. The extent to which the colon is resected in the proximal direction should cover the entire macroscopically involved colon. In other words, the proximal resection line should be where no diverticula exist or at the level where a considerable decline in number of diverticula is noted. Distally, the margin of resection should be where the taenia coli splay out onto the upper rectum. After resection a primary anastomosis will be performed between the distal colon and rectum.

Randomisation

All patients presenting themselves with persisting abdominal complaints after an episode of diverticulitis and/or a third (or more) diverticulitis recurrence, require to have had a recent radiological examination of the abdomen. Preferably a CT-scan is used. However, ultrasonography may also be used on the condition that bowel wall thickening and abscess size can be assessed accurately. Colonoscopy may be performed on indication to exclude malignancy.

If all inclusion criteria are met, patients are informed about the study protocol by their treating physician. They are given a 3 day reflective period, together with the information package. After the reflective period, the patient is contacted and asked for participation. If the patient decides to take part in the trial, he/she is invited to the local hospital to sign the informed consent. After receiving this consent form, randomisation will be performed centrally by the study coordinator using block randomisation (block size 6) stratified for center and inclusion criteria (persisting abdominal symptoms or frequent recurrences). Both patients in the conservative and elective resection group will be treated conservatively in case of events during follow-up unless there is an absolute indication for surgery according to the treating physician (e.g. fistula, symptomatic stenosis, perforation with purulent/fecal peritonitis). In addition, in case of persisting abdominal symptoms during follow-up (in the conservative group) which are regarded as unbearable by both patient and treating physician, the treating physician may consult an independent event adjudication committee. The independent committee will advise the treating physician whether or not to abandon conservative management and proceed to elective resection. The final decision is made by the treating physician.

Data collection

Data are collected by a local research fellow and/or treating physician at baseline, postoperatively (if randomised for elective resection), during outpatient visits and in case of adverse events leading to hospitalisation during follow-up. Case record forms on paper are used and faxed to the data manager.

Patients are asked to fill out HRQoL questionnaires at baseline. These questionnaires, as well as resource use and productivity losses questionnaires, are also sent to the patients at 3,6,9,12,24 and 36 months follow-up.

Data integrity will be checked when receiving the questionnaire. Any missing items will be collected by contacting the patient by telephone. Reminders (including a new copy of the questionnaire) will be sent after two weeks.

Statistical analysis

The statistical package SPSS will be used for analysis. All analyses will be performed according to the intention to treat principle.

Baseline characteristics will be described as means and standard deviations. Large differences between treatment groups will be analysed with an independent Student's T-test to verify significance (p -value < 0.05). Significant differences will be adjusted for in the final analysis.

The primary outcome will be analysed using mixed linear models with random effects. The covariates of the random part of the model will be determined using restricted maximum likelihood estimation (REML) and selected on the basis of Akaike Information Criterion (AIC). For the fixed part, models will be constructed containing either the treatment effect adjusted for time with or without an interaction term of these components. The models will be compared using AIC. Missing data will be imputed using multiple imputation.

The estimates of the final model will be used to test whether or not there is a clinical difference between the treatment groups. As described before, the MID is 10 points on the GIQLI scale. Therefore, the MID will be subtracted from the estimated difference between treatment groups and tested with Wald's test against a p -value of 0.10.

Additionally, the 7 point scale reflecting self-reported improvement of complaints over time, will be used to confirm whether the assumption of MID being the equivalent of half a standard deviation, holds.

Categorical outcome measures will be tested using the chi-square test (p -value < 0.05) and described as percentages and counts.

Economic evaluation

The cost analysis will be performed from a societal perspective including total direct health care costs and indirect non-health care costs (productivity losses).

Direct health care costs include costs related to hospitalization, imaging, blood tests, colonoscopy, medication, interventions, operations, consultations, complications and primary health care contacts. On an individual patient basis, resource use will be recorded. Subsequently, by multiplying resource use with unit price, actual costs per patient will be calculated. Unit costs will be derived from the Dutch costing manual or determined in co-operation with hospital administration.

Health care consumption including general practitioner or specialist visits and medication use will be assessed using customised questionnaires and case report forms.

Indirect non-health care costs include sick leave from paid work, own expenses of patients and time and travel costs. Sick leave from paid work will be assessed using the ShortForm-Health and Labour questionnaire. The remaining indirect non-health costs will be assessed using customised questionnaires to be completed by participants.

The cost-effectiveness will be expressed as incremental costs per quality-adjusted life year (QALY) gained. QALY gains over time will be assessed using the EQ-5D classification system as completed by patients, in combination with pre-defined value sets for all possible health states. The time perspective of the analysis will be 3 years.

Patient safety

After inclusion and completion of half a year follow-up of 25% of patients and after one year follow-up of 50% of patients in both groups, interim analysis will take place. A safety-monitoring committee consisting of independent physicians will review the results and advise the steering committee of the trial. The steering committee will decide on the continuation of the trial.

In addition all severe adverse events will be reported to the central Medical Ethics Committee and the independent safety-committee. The safety committee will discuss the events and will advise the trial steering-committee on the safety of the trial.

Ethics

The study is conducted in accordance with the principles of the Declaration of Helsinki and "good clinical practice" guidelines. The protocol has been approved by the the medical ethical committee "Verenigde Commissies Mensgebonden Onderzoek", located at the St. Antonius Hospital, Nieuwegein, the Netherlands. Prior to randomisation, informed consent will be obtained from all patients.

Discussion

Acute diverticulitis is diagnosed about 300 times alone at the department of surgery at the Meander Medical Center Amersfoort per year. A significant part consists of patients with persisting abdominal symptoms and frequent recurrences. Considering the high incidence and the multicenter design of this study, it may be assumed that the number of patients needed for this study (n = 214), may be gathered within one and a half year.

Depending on the expertise and available equipment, a laparoscopic approach is preferred for patients randomised for elective sigmoidresection. Preliminary results of the SIGMA trial have shown that elective laparoscopic sigmoid resection for diverticulitis leads to a better HRQoL compared to conventional resection. However, as this study aims to reflect the current situation (in which both conventional and laparoscopic approaches are used), conventional sigmoid resection may be used as an alternative.

Abbreviations

HRQoL: Health-related Quality of Life; ASA: American Society of Anesthesiologists classification of preoperative risk; VAS: Visual Analogue Score; SF-36: Short Form-36; GIQLI: Gastrointestinal Quality of Life Index; SF-H&L: Short Form Health and Labour; MID:

Minimum Important Difference; REML: Restricted maximum likelihood estimation; AIC: Akaike Information Criterion

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BJM and WA drafted the manuscript. ECJ and IAMJ co-authored the writing of the manuscript. All other authors and study groups participated in the design of the study during several meetings and/or are local investigators at the participating centers. All authors edited the manuscript and read and approved the final manuscript.

Acknowledgements

Approved by the medical ethical committee "Verenigde Commissies Mensgebonden Onderzoek", located at the St. Antonius Hospital, Nieuwegein, the Netherlands. The study is funded by ZonMW, the Netherlands Organisation for Health Research and Development.

The DIRECT trial is part of a national consortium (Dutch Diverticular Disease Collaborative Study Group) consisting of the researcher of the DIRECT and two other diverticulitis trials in the Netherlands (DIABOLO trial and Ladies trial).

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Chapter 12

Summary and general discussion

Future perspectives

Summary and general discussion

Over the past decade the incidence and health care expenses for diverticulitis have gradually increased.¹ Although our understanding of the disease has improved, much remains unclear (**chapter 2 and 3**). This thesis aims to address several key aspects in the decision-making around the acute phase of a diverticulitis episode and elective resection. The findings of the studies from this thesis and the answers to the central questions as formulated in the introduction are summarised and discussed here.

I What is the value of body temperature, white blood cell count and C-reactive protein in discriminating complicated from uncomplicated diverticulitis in patients presenting at the emergency department?

A small proportion (10-15%) of patients with acute diverticulitis present with complications such as abscess, fistulae and perforation.² We performed a study on the diagnostic value of inflammation markers and body temperature in discriminating complicated from uncomplicated diverticulitis among 426 patients (**chapter 4**). This study revealed that only C-reactive protein (CRP) might be helpful. Patients with a CRP of ≥ 25 mg/l had a 14.7% chance of having complicated disease. This increased linearly to almost 50% in patients with values of 250 mg/l or higher. It should however be emphasized that CRP should only be used as an indicator for the presence of complications. A low CRP does not mean that complicated disease can safely be excluded. Approximately 11.5% of patients with complicated diverticulitis presented with a CRP lower than 25 mg/ml. To our opinion, the diagnostic accuracy of CRP is not robust enough to completely abstain from additional radiological examination when aiming to exclude complications. Diagnostic models incorporating multiple factors (e.g. age, gender, medical history, symptoms, and inflammation markers) should be developed before exclusion of complications can be made on a solely clinical basis.³

II Does the use of dietary restrictions for treating acute diverticulitis shorten hospital stay?

Dietary restrictions are traditionally advised for treating the acute phase of a diverticulitis episode.^{2,4-5} It is assumed that the use of restrictive measures may result in a less active bowel with a positive effect on the healing of the site of infection and ultimately shortening hospitalisation time.⁴ In **chapter 5** these assumptions are challenged. We performed a study comparing several diets including nil per os, clear liquid diet, liquid diet and solid foods with regard to hospitalisation duration among patients with Hinchey 0, Ia and Ib diverticulitis.⁶ Of the 256 patients included in the study 25% received nil per os, 35% clear liquid, 29% liquid diet and 11% solid foods at initial presentation and hospitalisation. Multivariate analysis demonstrated that patients who were given a less restrictive diet at hospitalisation were more likely to be discharged. This relation remained

significant after correction for disease severity, treatment and complications. It may be concluded that the use of dietary restrictions prolongs hospital stay.

To our opinion the use of dietary restrictions should be omitted in the treatment of the acute phase of a diverticulitis episode. A clear trend can be seen towards less aggressive management of diverticulitis in the past years.⁷ Most recent guidelines advise a normal unrestricted diet for diverticulitis.⁸⁻⁹ In the Netherlands approximately 20% of gastroenterologists and surgeons treat their patients without dietary restrictions indicating its feasibility.¹⁰ Moreover, there is no evidence supporting a beneficial effect in terms of prevention of complications or time to recovery; only a detrimental effect on hospital stay as presented in this study.

III What is the benefit of performing colonoscopy after a conservatively treated episode of diverticulitis?

Routine colonic evaluation is traditionally advised after a primary episode of diverticulitis to exclude colorectal cancer. The relation between diverticulitis and colorectal malignancies however remains a point of debate. In **chapter 6** we investigated the benefit of routine colonic evaluation after an episode of diverticulitis. Among the 205 patients who underwent colonic endoscopy, hyperplastic polyps were found in 6.8%, adenomas in 8.8% and advanced neoplastic lesions in 3.4%. Colorectal malignancies were rare and only seen in 1.0% of patients. The prevalence found in this study was comparable to the prevalence in the general healthy population of comparable age. Both a meta-analysis and population-based study described the prevalence of advanced neoplastic lesions to be 5% and 5.4%.¹¹⁻¹² This was 0.8% and 0.5% for colorectal malignancies. Therefore, it may be concluded that there is no additional benefit in performing routine colonic evaluation in patients with diverticulitis compared to screening the general population for colorectal cancer.

The indication to perform endoscopic evaluation of the colon should be narrowed down to a more selective group of patients with diverticulitis. The two patients in this study with colorectal cancer suffered from persisting abdominal complaints after their initial episode of diverticulitis. The existence of these chronic complaints might form an indication for underlying pathology. Additionally it has been suggested that the presence of an abscess, local perforation or fistula on computed tomography scanning (CT-scan) at presentation with acute diverticulitis is associated with an increased risk of finding colorectal cancer.¹³

IV Is diverticulitis a more aggressive disease among patients younger than 50 years with regard to recurrences, complications and the need for surgery compared to older patients?

Diverticulitis is a rare disease under the age of 50 years.¹⁴ Traditionally it is thought that diverticulitis may be more severe among younger patients in terms of a higher risk of recurrences and complications.¹⁵ Therefore elective resection should be offered.⁴ More recent evidence contradicts this statement.¹⁶⁻¹⁷ Many studies have been performed on

this matter with controversial results. In **chapter 7** we describe a systematic review and meta-analysis summarizing the best available evidence in order to gain more insight on the exact implications of age on the course of disease. Eight studies were included with a total of 4.751 patients younger and 18.328 older than 50 years of age. We found that the risk of requiring urgent surgery during a primary episode of diverticulitis is equal in both age groups and estimated at approximately 20%. The risk of developing at least one diverticulitis recurrence after a conservatively treated primary episode is significantly higher among patients younger than 50 years (pooled RR 1.73; 95% CI 1.40 – 2.13) with an estimated cumulative risk of 30% compared to 17.3% in older patients. Younger patients also more frequently required urgent surgery during a subsequent recurrent episode (pooled RR 1.46; 95% CI 1.29 – 1.66). The estimated cumulative risk was 7.3% in younger patients and 4.9% in patients older than 50 years.

It may be concluded that patients younger than 50 years only differ substantially in risk for recurrent disease from patients older than 50 years. Although patients younger than 50 years had a higher relative risk to require acute surgery during recurrent episodes of diverticulitis, from a clinical point of view, the cumulative risks are low and do not differ substantially.

To our opinion, elective resection as a prophylactic procedure to prevent further complications in patients younger than 50 years does not seem warranted. Age should play a secondary role in the decision to operate. This meta-analysis showed that patients younger than 50 years are more prone to develop recurrences. Although the higher risk in itself should not be a reason to operate, the detrimental effect of having suffered from multiple recurrences on quality of life (described in the section below) coupled with the longer life-span of younger patients, however is.

V Are patients with diverticular abscess at higher risk of developing recurrences, complications or requiring surgery compared to patients with uncomplicated diverticulitis?

Guidelines typically advise that elective resection should be performed after an episode of complicated diverticulitis.⁴⁻⁶ Evidence with regard to the long-term consequences of treating a diverticulitis episode complicated by abscesses, however is scarce. We performed a study with a follow-up of at least 12 months comparing patients with abscess (n=54) to patients without abscess (n=635) at presentation for a primary episode of diverticulitis (**chapter 8**). Readmission occurred more frequently among patients with abscess with a first-year-risk of 27.3% versus 10.7% and second-year-risk of 8.2% versus 4.6%. The overall risk for readmission with complicated disease was relatively small in both groups (15% versus 0.8%). Surgery was also more frequently performed in patients with diverticular abscess. The first-year-risk was 35.1% versus 16.6% and second-year-risk 12.9% versus 2.4%. The most frequent indication for surgery was persisting or recurrent disease. Interestingly, the pattern of all study events suggests that readmission and surgery usually occurs in the first few months after primary episode and decreases to a low persistent rate after 12 months.

Although this study demonstrates that patients with abscess have a higher readmission rate and require surgery more often during follow-up, the presence of an abscess in itself should, in our opinion, not be a reason to perform elective resection. By routinely performing a prophylactic resection in patients with diverticular abscess, a large proportion of patients is operated who would otherwise never have developed recurrences or complications. Patients however should be informed on the prognosis of this disease with the majority being readmitted or requiring surgical intervention on short-term.

VI Is there a discrepancy in how patients and surgeons perceive quality of life?

Quality of life is one of the most important factors in the decision to perform elective sigmoid resection in patients with diverticulitis. It has frequently been suggested that there is a discrepancy in how patients and health providers value quality of life.¹⁸⁻²⁰ In **chapter 9** we investigated this discrepancy in a multicenter prospective pilot-study. It appears that surgeons consistently underestimate the impact of chronic and/or recurrent complaints after an episode of diverticulitis on the quality of life of their patients. Patients are willing to accept higher operative risks of death and complications to improve their current health state compared to surgeons.

These findings are best explained by the fact that surgeons might be more conservative than patients and less likely to risk death and other complications. Surgeons appear to downplay the impact of complaints on quality of life in favour of prolonging life or avoiding complications. Inversely, it is also possible that patients underestimate the impact of complications associated with elective resection on quality of life.

Knowledge of the existence of this discrepancy is imperative in decision-making on elective resection.²¹ Increasingly more treatment guidelines are advocating a more tailored approach.^{2,4,22} As patients appear to value their quality of life differently, including the patients' perspective is important in order to truly reach a tailored decision.

VII VII What is the effect of elective resection on quality of life and abdominal symptoms in patients with recurrent or ongoing complaints after an episode of diverticulitis?

Many studies have been performed on complications of elective resection in patients with diverticulitis. Little is known with regard to subjective improvement. In **chapter 10** we performed a study among 105 patients who have undergone elective resection for chronic/recurrent complaints after an episode of diverticulitis. Elective resection improved general quality of life and reduced discomfort caused by abdominal pain in up to 89.3% and 87.5% of patients. The effects were less profound for discomfort caused by abnormal defecation and fatigue with 77.1% and 75.2%, respectively, reporting improvement. Additionally, chances of benefitting from elective resection increased with worse quality of life or more severe abdominal complaints prior to resection.

To our opinion, the high success rate supports the decision for elective surgery in patients with recurring or persisting complaints after an episode of diverticulitis. Suitable patients

should however be carefully selected. The fact that improvement of quality of life was greatest in patients who were more severely affected by their symptoms, emphasizes that the decision to operate should predominantly be based quality of life. It should not be based on a single factor such as age, a complicated episode or single recurrences but the product that all these factors have on quality of life.

Future perspectives

Although this thesis has given more insight on the management of diverticulitis, finding the optimal diagnostic approach and optimal treatment remains challenging.

We have identified CRP as a helpful indicator for the presence of complications at presentation with an episode of diverticulitis. Separately its diagnostic value is limited; combining it with other parameters in a full-diagnostic model might improve its value. Prognostic studies are required before additional radiological examination can become obsolete in the identification of complicated diverticulitis.

We have provided the first study on the optimal diet for treating acute diverticulitis. Although the results showed that using a restricted diet prolongs hospital stay, the feasibility and safety of a normal unrestricted diet has yet to be defined. Currently our study group is performing a prospective study (DiDi-study) comparing different diet regimes with regard to complications and subjective improvement. The results are expected in 2014.

The most challenging part in the management of diverticulitis is what to do after the acute phase has subsided; When should elective sigmoid resection be performed? To our opinion, elective resection should not be used for prophylactic purposes. The fact that younger age and a primary complicated episode of diverticulitis is related to a greater risk of recurrences and the need for surgery in the future, does not warrant resection. Instead we advocate using elective resection for therapeutic purposes; not to prevent what has yet to come but to treat what has come to pass. Inherently, the decision to operate should thus be based on the quality of life of the patient.

In light of our vision, the most important question that remains is whether elective resection is truly superior to conservative management in terms of quality of life, costs, morbidity and mortality. With the study described in **chapter 10** we have gained some insight of what to expect from resection. This was however a retrospective study without a control group. Before hard conclusions can be drawn, randomised clinical trials are needed. The DIRECT trial described in **chapter 11** will provide this evidence. Currently 75 patients have been randomised between conservative management and elective resection. Patient accrual is expected to be completed at the end of 2013. Results may be anticipated in 2014.

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Chapter 13

Nederlandse samenvatting

Curriculum vitae

List of publications

Dankwoord

Nederlandse samenvatting

Diverticulitis (ontsteking van uitstulpingen in de dikke darm) is een veelvoorkomende ziekte. Huisartsen zien jaarlijks ongeveer 112.000 patiënten met dit ziektebeeld. Tevens leidt het tot 13.500 ziekenhuisopnames per jaar. Ondanks de hoge incidentie, bestaat er nog veel onduidelijkheid betreffende de optimale behandeling (**hoofdstuk 2 en 3**). Dit proefschrift richt zich op enkele belangrijke aspecten omtrent de besluitvorming in de acute fase van een diverticulitis episode en omtrent electieve resectie. De belangrijkste resultaten van dit proefschrift en de antwoorden op de centrale vraagstellingen worden hieronder besproken.

I Wat is de diagnostische waarde van C-reactieve proteïne, leukocyten aantal en lichaamstemperatuur in het onderscheiden van gecompliceerde en ongecompliceerde episodes diverticulitis bij patiënten die zich presenteren op de spoedeisende hulp?

Diverticulitis is een relatief milde aandoening. Slechts 10-15% van patiënten met diverticulitis presenteren zich met complicaties zoals abscessen, fistels en perforatie. Bij deze patiënten dient radiologisch onderzoek verricht te worden om verder (operatief) beleid te bepalen. Wij hebben een studie (**hoofdstuk 4**) verricht waarin wij gekeken hebben of het mogelijk is om op basis van lichaamstemperatuur, het C-reactieve proteïne (CRP) en leukocyten aantal in het bloed onderscheid te maken tussen patiënten met gecompliceerde en ongecompliceerde diverticulitis. Hieruit bleek dat alleen CRP van enige diagnostische waarde was. De positief voorspellende waarde bij patiënten met een CRP van $\geq 25\text{mg/l}$ was 14.7%. Dit liep op tot bijna 50% in patiënten met een CRP gelijk aan of hoger dan 250mg/l . Echter, een laag CRP betekent niet dat complicaties met zekerheid uitgesloten kunnen worden. Ongeveer 11.5% van patiënten met een gecompliceerde diverticulitis presenteerden zich met een CRP lager dan 25mg/l . CRP kan dus gebruikt worden om complicaties aan te tonen maar niet om ze met zekerheid uit te sluiten. Om deze reden zullen CT-scans een belangrijk onderdeel blijven spelen bij patiënten die zich presenteren met diverticulitis op de spoedeisende hulp. Diagnostische modellen met meerdere variabelen (zoals leeftijd, geslacht, medisch geschiedenis, symptomen en biochemische waarden) dienen ontwikkeld te worden alvorens complicaties op zuiver klinische gronden met voldoende zekerheid kunnen worden uitgesloten.

II Leidt het gebruik van dieet restricties in de behandeling van acute diverticulitis tot een kortere opnameduur?

Artsen leggen patiënten met acute diverticulitis vaak een dieet restrictie op. Hiermee beoogt men een minder actieve darm te bewerkstelligen. Op zijn beurt zou dit een gunstig effect kunnen hebben op de genezing van de ontsteking en daarmee de opnameduur. In **hoofdstuk 5** worden deze veronderstellingen uitgedaagd. Wij hebben een retrospectieve analyse verricht onder 256 patiënten met een Hinchey 0, Ia of Ib diverticulitis. Bij 25% van deze patiënten werd bij opname volledige carentie opgelegd, 35% kreeg een helder

vloeibaar dieet, 29% vloeibaar dieet en 11% had een normaal dieet zonder restricties. Opvallend was dat patiënten met een normaal dieet eerder met ontslag gingen dan patiënten die dieet restricties opgelegd kregen. Deze bevindingen bleven significant zelfs na correctie voor leeftijd, geslacht, ziekte ernst, behandeling en complicaties gedurende opname.

Wij zijn van mening dat dieet restricties niet nodig zijn in de behandeling van acute diverticulitis. In de laatste jaren zijn wij steeds meer tot het besef gekomen dat diverticulitis minder agressieve behandeling behoeft (geen antibiotica of dieet restricties). Dit is ook duidelijk terug te zien in de richtlijnen. De meest recente richtlijnen adviseren een normaal dieet in tegenstelling tot oudere richtlijnen. Tevens is ongeveer 20% van de chirurgen en gastro-enterologen in Nederland afgestapt van het gebruik van dieet restricties. Er bestaat geen bewijs dat dieet restricties een gunstig effect hebben op complicaties en genezing; echter, nu is er middels deze studie wel bewijs dat dieet restricties de opnameduur onnodig verlengen.

III Wat is het nut van coloscopie bij patiënten die een episode diverticulitis hebben doorgemaakt?

Coloscopieën worden vaak ter uitsluiting van colorectale maligniteit verricht bij patiënten die een episode diverticulitis hebben doorgemaakt. Echter, de meningen omtrent het mogelijke verband tussen diverticulitis en darmkanker zijn verdeeld. Om deze reden hebben wij een studie verricht (**hoofdstuk 6**) waarin wij hebben gekeken naar de prevalentie van neoplastische laesies bij patiënten die een coloscopie hebben gehad voor diverticulitis. Benigne laesies zoals hyperplastische poliepen en adenomen werden gevonden bij 6.8% en 8.8% van de patiënten. Bij 3.4% werden premaligne laesies gevonden en 1.0% had darmkanker. De prevalentie van (pre)maligne laesies in onze studie was vergelijkbaar met die van de normale samenleving van gelijke leeftijd. Zowel een recente meta-analyse als een demografische studie hebben aangetoond dat premaligne laesies voorkomen bij ongeveer 5% en 5.4% van de gezonde samenleving. De prevalentie van colorectale maligniteiten was 0.8% en 0.5%. Er mag geconcludeerd worden dat screening middels coloscopie op darmkanker bij patiënten met diverticulitis geen toegevoegde waarde heeft ten opzichte van de normale populatie.

Wij pleiten voor een selectiever gebruik van coloscopieën bij patiënten met diverticulitis. Beide patiënten in onze studie waarbij darmkanker geconstateerd was, leden aan persisterende buikklachten na behandeling van de initiële episode diverticulitis. Het bestaan van dergelijke chronische klachten zou mogelijk een teken kunnen zijn van onderliggende pathologie. Coloscopie zou ook laagdrempelig aangeboden moeten worden aan patiënten die behandeld zijn voor een gecompliceerde episode diverticulitis. Een recente studie heeft namelijk aangetoond dat patiënten die zich presenteren met een abces, fistel of lokale perforatie een verhoogde kans hebben op het vinden darmkanker bij coloscopie.

IV Kent diverticulitis een agressiever beloop onder patiënten jonger dan 50 jaar wat betreft recidieven, complicaties en de noodzaak tot chirurgische behandeling ten opzichte van patiënten ouder dan 50 jaar?

Diverticulitis komt weinig voor bij patiënten jonger dan 50 jaar. Studies uit de jaren '80 en '90 hebben aangetoond dat jongere patiënten een hogere kans hebben op recidieven en complicaties. Om deze reden wordt vaak electieve resectie bij jongere patiënten geadviseerd. Echter, resultaten van recentere studies spreken dit advies tegen. Gezien het grote aantal studies met uiteenlopende resultaten, hebben wij besloten een systematische review en meta-analyse te verrichten van de beschikbare literatuur om meer vat te krijgen op de exacte invloed van leeftijd op het ziektebeloop (**hoofdstuk 7**). Er werden acht kwalitatief goede studies geïncludeerd met in totaal 4.751 patiënten jonger en 18.328 ouder dan 50 jaar. De kans op urgente chirurgie tijdens een eerste episode diverticulitis was even groot in beide groepen met een gemiddeld risico van ongeveer 20%. Diverticulitis recidieven kwamen aanmerkelijk vaker voor bij patiënten jonger dan 50 jaar (pooled RR 1.73; 95% CI 1.40 – 2.13). Het gemiddeld risico was 30% versus 17.3% bij patiënten ouder dan 50 jaar. Tevens was de kans op urgente chirurgie gedurende een diverticulitis recidief bij jongere patiënten ietwat verhoogd (pooled RR 1.46; 95% CI 1.29 – 1.66). Het absolute risico betrof 7.3% in de jongere groep patiënten en 4.9% bij de ouderen.

Concluderend kan men stellen dat patiënten jonger dan 50 jaar alleen substantieel verschillen in het risico op recidieven. Hoewel urgente chirurgie voor diverticulitis recidieven statistisch gezien vaker nodig was bij jongere patiënten, is (vanuit klinisch oogpunt) het absolute verschil met oudere patiënten erg klein.

Naar onze mening rechtvaardigt het lage risico op gecompliceerde recidieven niet het verrichten van een profylactisch electieve resectie bij patiënten jonger dan 50 jaar. Leeftijd zou een secundaire rol moeten spelen in de keuze tot electieve resectie. Het algemene risico op recidieven is groter bij jongere patiënten. Hoewel dit feit geen reden hoeft te zijn tot het verrichten van een profylactische operatie, dient wel electieve resectie aangeboden te worden aan jongere patiënten die een verminderde kwaliteit van leven ervaren als gevolg van recidiverende episodes diverticulitis; zeker gezien jongere patiënten nog een langere levensduur hebben in vergelijking met oudere patiënten.

V Hebben patiënten die zich presenteren met een gecompliceerde (met abscessen) eerste episode diverticulitis een grotere kans op het ontwikkelen van recidieven en complicaties in vergelijking met patiënten die zich presenteren met een ongecompliceerde eerste episode?

Richtlijnen adviseren electieve resectie bij patiënten die een episode diverticulitis gecompliceerd door abscessen hebben doorgemaakt. Ook bij deze patiënten wordt gedacht dat zij een agressiever ziektebeloop hebben. Echter, hier is weinig literatuur over bekend. In **hoofdstuk 8** beschrijven wij een studie met een follow-up van tenminste 12 maanden waarin wij patiënten met abces (n=54) hebben vergeleken met patiënten zonder abces (n=635). Patiënten met abces ontwikkelde vaker een recidief in vergelijking met patiënten zonder abces. Het eerstejaars risico bedroeg 27.3% versus 10.7% en

tweedejaars risico 8.2% versus 4.6%. Chirurgie gedurende follow-up was ook vaker nodig bij patiënten met abces. Het eerstejaars risico was 35.1% versus 16.6% en tweedejaars risico 12.9% versus 2.4%. De meest voorkomende indicatie voor operatie was recidiverende/persisterende klachten. Opvallend was dat recidieven en operaties voornamelijk in de eerste paar maanden follow-up plaatsvonden. Na 12 maanden werd het risico aanmerkelijk kleiner en bleef constant over de resterende follow-up duur. Hoewel patiënten met abces een grotere kans hebben op recidieven en vaker chirurgie nodig hebben gedurende follow-up, is deze kans naar onze mening niet groot genoeg om profylactische electieve resectie te rechtvaardigen. Routinematig resectie uitvoeren bij deze patiëntengroep zou alleen maar leiden tot onnodige operaties bij een groot deel van patiënten die anderszins nooit recidieven of complicaties zou hebben ontwikkeld. Patiënten dienen echter wel goed ingelicht te worden over de prognose. Hierbij dient benadrukt te worden dat de kans op recidiverende/persisterende klachten groot is en electieve resectie op korte termijn hoogst waarschijnlijk nodig zal zijn om deze klachten te behandelen.

VI Is er een discrepantie in hoe patiënten en chirurgen kwaliteit van leven ervaren/waarnemen?

Kwaliteit van leven in één van de belangrijkste factoren in de keuze om electieve resectie te verrichten bij patiënten met diverticulitis. Er wordt vaak gesuggereerd dat er een discrepantie bestaat in hoe patiënten hun kwaliteit van leven ervaren en zorgverleners dat van hun patiënten inschatten. In **hoofdstuk 3** gaan wij in op deze discrepantie. Wij hebben een multicentrum prospectieve pilot-studie verricht waaruit duidelijk blijkt dat chirurgen de impact van recidiverende/persisterende klachten na een episode diverticulitis op de kwaliteit van leven van hun patiënten onderschatten. Patiënten zijn bereid hogere risico's op operatieve morbiditeit en mortaliteit te accepteren om van hun klachten af te komen dan chirurgen.

Deze bevindingen worden waarschijnlijk verklaard door het feit dat chirurgen de voorkeur geven aan conservatieve behandeling en in mindere mate risico willen lopen op complicaties en mortaliteit. Eveneens is het ook mogelijk dat patiënten de impact van morbiditeit die gepaard kan gaan met electieve resectie onderschatten.

Desalniettemin achten wij het van groot belang dat artsen zich bewust zijn van deze discrepantie. Steeds meer richtlijnen stappen af van algemene behandelingsprincipes en adviseren een individuele benadering in de keuze tot electieve resectie. Juist om deze reden is het meenemen van de visies van de patiënt in deze tijden des te belangrijker geworden.

VII Wat is het effect van electieve resectie op kwaliteit van leven en buikklachten van patiënten die lijden aan persisterende of recidiverende klachten na een episode diverticulitis?

Er zijn veel studies verricht naar de morbiditeit en mortaliteit van electieve resectie bij patiënten met diverticulitis. Echter, studies naar subjectieve verbetering van kwaliteit van leven en klachten zijn schaars. Wij hebben een studie verricht onder 105 patiënten die een

electieve resectie hebben gehad voor recidiverende dan wel persisterende klachten na een episode diverticulitis (**hoofdstuk 10**). Hieruit bleek dat electieve resectie in 89.3% van patiënten een sterke verbetering gaf van de kwaliteit van leven. Eveneens ervaren 87.5% een sterke verbetering van hun chronische/recidiverende buikpijnklachten. Het effect van electieve resectie was minder groot op klachten veroorzaakt door een abnormaal defecatiepatroon (77.1%) en vermoeidheid (75.2%). Tevens werd in deze studie ook geconstateerd dat de kansen op verbetering toenamen naarmate de patiënt meer hinder ondervond van zijn/haar buikklachten (of een slechtere kwaliteit van leven had) voorafgaand aan de electieve resectie.

Naar onze mening, rechtvaardigt de grote kans op verbetering het verrichten van electieve resectie bij patiënten met recidiverende/persisterende klachten na een episode diverticulitis. Wij willen echter wel benadrukken dat patiënten zorgvuldig geselecteerd dienen te worden. Het feit dat kansen op verbetering groter werden naarmate patiënten meer hinder ondervonden van hun klachten, benadrukt het feit dat de keuze tot electieve resectie gebaseerd dient te zijn op de kwaliteit van leven; het moet niet gebaseerd worden op een enkele factor zoals leeftijd, het al dan wel of niet doorgemaakt hebben van een gecompliceerde episode diverticulitis of een enkel recidief maar juist het product van al deze factoren op de kwaliteit van leven.

Toekomstperspectieven

Hoewel dit proefschrift ons meer inzicht heeft gegeven, blijft het vinden van een optimaal diagnostische traject en de behandeling van diverticulitis een grote uitdaging.

Uit onze studies is gebleken dat CRP een nuttige indicator is voor de aanwezigheid van complicaties bij patiënten die zich presenteren met diverticulitis op de spoedeisende hulp. De diagnostische waarde van CRP kan echter versterkt worden door deze te combineren met andere potentiële indicatoren. Prognostische studies zijn hiervoor nodig. Tot die tijd zal de CT-scan een cruciale rol blijven spelen in het uitsluiten van complicaties. Wij zijn de eerste die een studie hebben verricht naar het optimale dieet voor acute diverticulitis. Hoewel uit deze studie is gebleken dat het gebruik van dieet restricties leidt tot een verlengde opnameduur, dient de veiligheid en het effect van een normaal dieet nog getoetst te worden. Momenteel loopt er een prospectieve studie (DiDi-studie) die deze vraag tracht te beantwoorden. Resultaten worden verwacht in 2014.

Het meest uitdagende gedeelte in de behandeling van diverticulitis begint zodra de acute fase tot rust is gekomen met als centraal vraagstuk: Bij welke patiënten moet een electieve resectie verricht worden? Naar onze mening dient electieve resectie niet voor profylactische doeleinden gebruikt te worden. Het feit dat jonge leeftijd en een gecompliceerde eerste episode diverticulitis de kans op recidieven en noodzaak tot chirurgie in de toekomst vergroot, rechtvaardigt niet een resectie. In plaats daarvan adviseren wij electieve resectie te gebruiken voor meer therapeutische doeleinden; niet voorkomen wat er kan gebeuren maar behandelen wat er is geschied. Inherent hieraan zou de keuze tot electieve resectie gebaseerd moeten worden op de kwaliteit van leven van de patiënt.

In het kader van onze visie, ontstaat hiermee het volgende essentiële vraagstuk: Is electieve resectie daadwerkelijk beter dan conservatieve behandeling wat betreft kwaliteit van leven, kosten, morbiditeit en mortaliteit. Met de studie beschreven in **hoofdstuk 10** hebben wij enig inzicht verkregen in de effecten van electieve resectie op de kwaliteit van leven. Echter was dit een retrospectieve studie zonder controle groep. Gerandomiseerde klinische trials zijn nodig voordat harde conclusies getrokken kunnen worden. De DIRECT trial, beschreven in **hoofdstuk 11**, zal voor dergelijk bewijs zorgen. Momenteel zijn er 93 patiënten geïncludeerd en gerandomiseerd tussen conservatieve therapie en electieve resectie. De inclusieperiode zal lopen tot eind 2013 waarna de eerste resultaten zullen verschijnen in 2014. Tot die tijd zal het debat omtrent electieve resectie voortduren.

Curriculum vitae

Bryan van de Wall was born on August 19th 1985 in Meyrin, Switzerland. In May 2003 he graduated from the Johan van Oldenbarnevelt Gymnasium in Amersfoort. The same year he commenced his medical training at the University of Utrecht, the Netherlands. During his internships at the Meander Medical Center in Amersfoort, he was invited to participate in the initiation of a multicenter randomised clinical trial on elective resection for diverticular disease (Dr. W.A. Draaisma, Dr. E.C.J. Consten). In 2009 he received a scientific fund for this study (DIRECT trial) from The Netherlands Organisation for Health Research and Development (NWO, ZonMW). After graduation from medical school in April 2010, he functioned as principal coordinator of the DIRECT-trial and started as a PhD-student with the work presented in this thesis at the Meander Medical Center (Dr. W.A. Draaisma, Dr. E.C.J. Consten) and the University of Twente (Prof. Dr. I.A.M.J. Broeders). He also attended a post-graduate master epidemiology at the University of Utrecht and obtained his masters degree cum laude in May 2012 (Prof. Dr. Y. van der Graaf, Dr. G.A. van der Heijden). With great pleasure he started his surgical residency in July 2012 at the Meander Medical Center (Dr. A. van Overbeeke). In January 2012 he will be applying at the University Medical Center (UMC) in Utrecht aiming to officially commence his surgical training.

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Dankwoord

Dit proefschrift is tot stand gekomen met de hulp en steun van velen. Een aantal personen wil ik in het bijzonder bedanken:

Prof. Dr. I.A.M.J. Broeders, beste Ivo, het was een eer je promovendus te zijn. Met veel plezier kijk ik terug naar de topsport om jou tussen alle drukte door te tackelen voor advies en correcties van mijn manuscripten. Keer op keer wist jij het geduld op te brengen om mij, in ieder geval diezelfde dag, te woord te staan. Je was een zeer toegankelijke en kritische promotor. Ik zal de congressen, skivakanties met sneeuwballengevecht “onder de volle maan” en mijn tijd onder jouw hoede ontzettend missen.

Dr. W.A. Draaisma, beste Werner, de onmisbare schakel in mijn promotie. Ik leerde jou kennen tijdens één van mijn eerste coschappen. Met knikkende knieën hoorden wij aan wat van ons verwacht werd tijdens ons coschap chirurgie.....en wát de consequenties waren van een passieve instelling. Streng was de karaktereigenschap die jij toegedicht kreeg; een eigenschap die mij (en anderen) deed presteren! Ik kan mij nog goed herinneren dat jij mij tijdens mijn coschap interne op de spoedeisende hulp in Amersfoort vroeg of ik geïnteresseerd was in wetenschappelijk onderzoek. Benieuwd naar het bereik van jouw kunnen, nam ik het aanbod aan. Wederom bewees jij je als zeer capabele mentor. Ik leerde jou ook kennen als een grappenmaker en iemand die altijd klaar staat wanneer het tegen zat. Ik bewonder je onvoorwaardelijke inzet voor de wetenschap. Je bent een bron geweest van inspiratie, de “zweep” achter mijn promotie en de “King” van mijn proefschrift. Ik ben je ontzettend dankbaar voor alles.

Dr. E.C.J. Consten, beste Esther, de “Queen” van mijn proefschrift. Naast jouw inzet en betrokkenheid, ben ik jou in het bijzonder dankbaar voor je toegankelijkheid. Jij wist tussen én tijdens de policontroles, operaties, vakanties en congressen door altijd tijd te vinden om mij te woord te staan. Ik trof jou dan ook frequent aan met 2 telefoons aan je oren, terwijl jij je lunch aan het eten was achter de computer van waar jij alle e-mails trachtte te beantwoorden. Ook jou wil ik hartelijk bedanken voor alle feedback en ondersteuning.

Geachte Prof. Dr. Boermeester, Prof. Dr. van der Graaf, Prof. Dr. Gooszen, Prof. Dr. Lange, Prof. Dr. Ijzerman en Prof. Dr. Veth, hartelijk dank dat u vanuit uw specialisme bereid bent geweest mijn proefschrift kwalitatief te beoordelen.

Henk, Stoma-Henkie, Henk-The-Tank, ironisch genoeg zit jij nu naast mij en zul jij dit pas over enkele maanden lezen. Aan onze tijd in de krochten van het Meander, kan een volledig hoofdstuk besteed worden. Ik zal jouw tekeningen over de email, waarin jij regelmatig jouw opvattingen over uiteenlopende zaken illustreerde, missen. Veel succes en plezier met jou toekomstige carrière als chirurg. Dank voor de briljante tijd!

Margueritte Stam, stampertje, mijn waardige opvolgster, ik wil je heel veel succes wensen met de afronding van de DIRECT trial. Ik kan mij geen beter persoon bedenken die deze zware kar kan trekken.

Okan, mijn paranimf, dank dat jij gedurende mijn kleuter-, peuter-, basis- en middelbare schooltijd, mijn studie geneeskunde en nu ook tijdens mijn verdediging aan mijn zijde staat.

Annemiek van de Wall, liefste tante, dankzij jou ben ik in contact gekomen met mijn promotoren. Daarvoor wil ik nogmaals hartelijk bedanken. Ik verheug mij om samen met jou de spoedeisende hulp te bemannen gedurende mijn toekomstige carrière.

Prof. Dr. H. Gooszen, Prof. Dr. C. Mulder, Prof. Dr. L. Stassen, Prof. Dr. K. Roes, Dr. B. Heggelman en Rebecca Stellato, hartelijk dank voor jullie inzet als Data Safety Monitoring Board voor de DIRECT trial.

Mijn student-onderzoekers, Rosa van der Kaaij, Jolien Poerink, Jan van Iersel en Janneke van Grinsven hartelijk dank voor al jullie bijdrage aan mijn studies.

Prof. Dr. Y. van der Graaf, beste Yolanda, jij hebt mij weten te enthousiasmeren voor de epidemiologie. Tevens heb jij een grote rol gespeeld in het opzetten van de DIRECT trial. Hiervoor wil ik je hartelijk bedanken. Ik wens jou veel voorspoed toe.

Dr. G. van der Heijden, hartelijk dank voor je begeleiding in het afronden van mijn master epidemiologie.

Kopstukkeraars, jaclubgenoten, ik hoop ik dat dit proefschrift een prominente plek krijgt in jullie boekenkast en niet op de WC.....)

Collega's van het Meander Medisch Centrum, ik heb jaar in jaar uit met ontzettend veel plezier gewerkt in het Meander. De skivakanties waren legendarisch! Ik hoop de komende vakantie nog mee te kunnen pakken; dan vier ik namelijk mijn jubileum! Dank voor alles.

Opa en oma, ik vind het geweldig dat jullie deze mijlpaal in mijn leven nog mogen meemaken. Opa, bedankt voor je nimmer aflatende interesse in mijn studies. Met veel plezier kan ik nu mijn proefschrift naast die van jou plaatsen in mijn boekenkast.

Papy et mamy, je suis très heureux de vous avoir ici. J'espère que vous rester encore longtemps dans ma vie.

Lieve pap en mam, mijn hele leven hebben jullie mij onvoorwaardelijk gesteund. Jullie thuis in scherpzeel is altijd een oase van rust en een vruchtbare bodem voor mijn proefschrift geweest. Jullie betekenen ontzettend veel voor mij. Ik houd ontzettend veel van jullie en ben blij dat ik dit moment met jullie kan delen. Bedankt voor alles!

Lieve Carolyn en Jane, Ik mag mijzelf rijk prijzen met dergelijke zussen. Ook jullie bedankt voor alle steun en met name de gezellige avondjes waar ik even al mijn perikelen kon vergeten.

Ed, Cathrien, Marjolijn en Laurien, hartelijk dank voor alle geweldige weekenden en zeiltochten. Ze waren een bron van energie voor het tot stand brengen van dit proefschrift. Ik hoop dat er nog vele zullen volgen en wij de Winner-cup blijven domineren.

Dan toch als laatste, Annemieke, Miekske, lief! Jij bent en blijft altijd de grootste overwinning in mijn leven. Leven met jou is één en al genieten; Ik geniet van de momenten dat ik weer eens dokter mag spelen wanneer jij besluit voor de zoveelste keer de grootste tegenstander omver te beuken tijdens een hockeywedstrijd...omdat die in de weg stond; Ik geniet van de momenten dat jij een straf-adje uitdeelt omdat ik te traag drink; ik geniet van de momenten dat ik genadeloos hard wordt afgeslacht bij Kolonisten van Katan door jouw familie omdat jullie stiekem samenspannen; ik geniet van de momenten dat ik met jou in een winkelwagentje door de straten van Utrecht race...om 4 uur 'snachts; van de eeuwige strijd wie beter kan skiën; van die lach die verschijnt wanneer jij de nieuwe Allerhande in de Albert Hein ziet liggen; van de rollende R wanneer jij mijn naam uitspreekt; Ik geniet van het moment dat ik naast jou wakker wordt wetend dat ik jou diezelfde avond weer zie; van de warmte die je mij geeft in zware tijden; maar ik geniet het meeste van de gedachte dat ik deze momenten de rest van mijn leven met jou zal hebben.

