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TREATMENT OF



ACUTE DIVERTICULITIS

AND APPRAISAL
OF EVIDENCE

Stefan van Dijk

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Treatment of acute diverticulitis and appraisal of evidence

ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

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INTRODUCTION AND OUTLINE OF THESIS

INTRODUCTION

Diverticulosis, acute diverticulitis and (symptomatic uncomplicated) diverticular disease

Various terminology is used in diverticular literature which should be clearly defined for adequate interpretation of its findings. Patients with colonic diverticulosis have one or more diverticula of the colon. Diverticula are outpouchings of the colonic wall that mostly occur in the sigmoid colon in the Western world, opposed to the Asian population in which right-sided diverticulosis is much more common. Acute diverticulitis is the inflammatory complication of colonic diverticulosis. Acute diverticulitis can be further divided into uncomplicated diverticulitis – peridiverticular inflammation only – and complicated diverticulitis comprising diverticular abscess, perforation, colonic obstruction and fistula. Diverticular disease is another frequently used term, however the meaning differs between studies leading to misinterpretation. Some use diverticular disease for patients with diverticulosis only, some use the term for diverticulosis accompanied by abdominal complaints, and others even use the term for the entire spectrum of diverticular diseases from diverticulosis to complicated diverticulitis. Increasing the confusion in terminology, for some complicated diverticular disease can mean uncomplicated acute diverticulitis. Another term that is frequently used is symptomatic uncomplicated diverticular disease, which is mostly defined by abdominal complaints (probably) related to colonic diverticulosis with or without increased inflammatory markers such as C-reactive protein or white blood cell count.

This thesis focusses on patients with acute diverticulitis, meaning patients with at least diverticular inflammation confirmed by imaging. Whereas ultrasonography is sufficiently accurate for the diagnosis acute diverticulitis, computed tomography (CT) is better in finding complicated diverticulitis or alternative diagnoses.^{1,2} Since most chapters of this thesis focus on uncomplicated diverticulitis or on a specific diverticular complication, most studies only include CT-proven acute diverticulitis patients.

Classification

Several acute diverticulitis classifications have been developed to grade the disease severity and to select the adequate treatment strategy. The Hinchey classification is most commonly used in literature. It was originally introduced in 1978 but the modified Hinchey classification that has been introduced in 1999 is used nowadays.^{3,4} This modification incorporated CT findings into the classification. (Table 1)

Epidemiology

The prevalence of colonic diverticulosis ranges from 10% in individuals under the age of 40 up to 50% to 70% in elderly patients. The vast majority of these patients remain asymptomatic. Approximately 4% to 7% of patients will develop one or more episodes of acute diverticulitis.^{5,6}

Table 1. Modified Hinchey classification.⁴

Stage	Definition
1a	Confined pericolic inflammation or phlegmon
1b	Pericolic or mesocolic abscess
2	Pelvic, distant intra-abdominal or retro-peritoneal abscess
3	Purulent peritonitis
4	Faecal peritonitis

Roughly two-third of patients present with uncomplicated diverticulitis, and one-third has a diverticular complication at presentation.^{7,8} The incidence of acute diverticulitis is rising in the Western world, and probably will keep rising because of the increased life expectancy and increasing incidence with age.⁹⁻¹¹ The entire spectrum of diverticulosis-related diseases is the eight most frequent outpatient gastrointestinal diagnosis with over 2.7 million visits each year in the US. In 2012, acute diverticulitis accounts for over 200,000 admissions annually with an aggregate cost of 2.2 billion US dollars.¹¹ After an episode of acute diverticulitis has resolved, patients can develop one or more recurrent episodes. The proportion of patients that develops a recurrence varies widely in literature, depending on diagnostic criteria used and the reported follow-up duration, but mostly ranges between 13% and 40%.

Treatment

The treatment of acute diverticulitis has been evolving in last decades. In almost all stages of the disease, treatment has become more conservatively. Percutaneous abscess drainage has become the preferred approach rather than surgical abscess drainage in diverticulitis. Laparoscopic lavage rather than sigmoid resection has become an option for perforated diverticulitis with purulent peritonitis, and a primary anastomosis may be created rather than performing the formerly golden standard Hartmann's procedure. Surgery for recurrent diverticulitis has been debated but positively affected quality of life when more recurrences are encountered. In contrast to these evidence-based shifts towards more conservative treatment strategy, several other treatment strategies are widely implemented into daily practice without scientific grounds. Expert opinion and tradition play an important role in the management of acute diverticulitis. An example of such a treatment strategy that lacks scientific grounds is dietary restrictions as part of the treatment of acute diverticulitis. No benefits of dietary restrictions have even been proven. Two studies have even shown the safety of an unrestricted diet, nevertheless dietary restrictions are still regularly imposed by physicians worldwide.

Antibiotic treatment of uncomplicated acute diverticulitis is another treatment strategy that has been adopted worldwide without any evidence in favour of it, and one of the main issues in this thesis. In recent years, two randomized controlled trials showed the safety of

omitting antibiotics for uncomplicated acute diverticulitis. The Scandinavian AVOD trial¹² was published in 2012 and found comparable rates of complicated diverticulitis and surgery among groups within 1 year. The Dutch DIABOLO trial¹³, which is the foundation of this thesis, published short-term results in 2017 and demonstrated a comparable time-to-recovery and rates of complicated diverticulitis and surgery within 6 months for observational compared to routine antibiotic treatment. However, to provide a complete overview on the consequences of omitting antibiotics for uncomplicated diverticulitis, additional outcomes need to be assessed. Important secondary outcomes of the DIABOLO trial were long-term results, quality of life, cost-effectiveness and the effect of antibiotic on the gut microbiome which are assessed in this thesis. Antibiotic treatment of acute diverticulitis usually comprises an intravenous antibiotic start and thereby admission, whereas non-antibiotic treatment facilitates the possibility for outpatient treatment. If patients can be treated without antibiotics, some patients may be candidates for outpatient rather than inpatient treatment.

In the shift towards less invasive and more conservative treatment of acute diverticulitis, patient selection plays an important role. Patients at risk for complications may need a different approach than the majority of patients in which treatment strategies have been studied. Patients can be at risk for a deviant clinical course in two ways. First, patients with a CT-proven uncomplicated acute diverticulitis may progress into diverticular complications in the days or months after presentation. The identification of patients at risk for this progression barely have been studied, but are needed when patient tailored management will become increasingly important. Secondly, features that may be predictive for a less favourable clinical course may already be present at first presentation, such as an abscess or pericolic extraluminal air. Physicians have their own experiences and opinions about these features and how to treat them, but little research has been done. Therefore, patients are treated based on expert opinion rather than evidence based treatment, possibly resulting in over- or under treatment and a great variety in treatment strategies between and within countries.

After an episode of acute diverticulitis has passed, the question rises whether or not to perform a screening colonoscopy. Acute diverticulitis has been associated with colorectal malignancy for decades, which led to routine colonoscopy in acute diverticulitis patients to rule out such a malignancy. However, probably there is no causal association but colorectal carcinoma being misdiagnosed as acute diverticulitis. Improved diagnostics by means of CT increased the diagnostic accuracy and decreased the number of misdiagnoses. However, most guidelines still recommend routine colonoscopy after an episode of acute diverticulitis. Colonoscopy is not a harmless procedure due to the risk of perforation, costs and patients' discomfort. Therefore, it is important to assess the association between acute diverticulitis and colorectal malignancy in this modern era.

Aim of the thesis

In summary, the treatment of acute diverticulitis has become more conservatively, or rather less aggressive. This shift requires better selection of patients that may or may not be candidates for a more conservative approach. Furthermore, several treatment strategies are widely implemented without any scientific grounds, whereas other strategies may be old-fashioned and current evidence deemed too weak or implemented insufficiently. This thesis aimed to make a contribution to these issues. Whereas the short-term safety of omitting antibiotics for uncomplicated acute diverticulitis has been demonstrated in the publication by Daniels et al¹³, this thesis aimed to reveal all consequences of omitting antibiotics by assessing the long-term results, quality of life, cost effectiveness and effects on the gut microbiome. Furthermore, this thesis aimed to assess whether specific patient subgroups could be considered uncomplicated diverticulitis by assessing the virulence of patients with a small abscess or pericolic air, and by identifying uncomplicated diverticulitis patients that are at risk of a complicated course. Last, this thesis aimed to aggravate current evidence on controversial topics, providing evidence based conclusions to physicians.

OUTLINE OF THESIS

Chapter one provides a narrative overview of evidence in (uncomplicated) acute diverticulitis at the time this thesis was initiated. It includes the conservative treatment of acute diverticulitis, patient subgroups that may have a deviant clinical course and the prevention of recurrent diverticulitis. Moreover, it discusses the short-term results of the DIABOLO trial. Hereafter, this thesis is divided into three parts. Part one covers the consequences of omitting antibiotics for uncomplicated diverticulitis in which the chapters are mainly based on results of the DIABOLO trial. Part two defines the border between uncomplicated and complicated diverticulitis by assessing the disease virulence in specific subgroups of patients. Part three aggravates current evidence on several controversial topics.

Part 1

In **chapter two**, short-term results of the two randomized clinical trials (AVOD trial and DIABOLO trial) are merged in an individual patient data meta-analysis. Somewhat but non-significant higher rates of complicated diverticulitis and sigmoid resection are assessed again, using the increased power of this combined sample size. Also, and more importantly, it is tested whether patient subgroups that may benefit from antibiotic treatment could be identified. Subsequently, the long-term results of the DIABOLO trial are reported in **chapter three**, followed by the quality of life in **chapter four** and cost-effectiveness in **chapter five**. The effects of antibiotics on the gut microbiome in acute diverticulitis patients are assessed in **chapter six**.

Part 2

Uncomplicated diverticulitis patients may progress to complicated diverticulitis in the days to months after presentation. **Chapter seven** assesses whether CT imaging may reveal risk factors that are already present at presentation, which predict complications later on. **Chapter eight** also studies risk factors for such a complicated disease course, but focusses on patient characteristics and clinical parameters as potential predictors. **Chapter nine** analyses the virulence of small diverticular abscesses, to assess whether patients with a small abscess could be managed as uncomplicated diverticulitis. Whereas free perforation is a known risk factor for complications and therefore patients need an intervention, pericolic extraluminal air may be candidate for an initially conservative approach. **Chapter ten** summarizes current evidence on this patient subgroup. Since the level of evidence appeared to be very low, **chapter eleven** covers an additional observational study on this patient subgroup.

Part 3

Many physicians believe that young patients are at higher risk of complicated diverticulitis and recurrent diverticulitis. **Chapter twelve** tests the validity of these beliefs by summarizing all current evidence on this topic. Whereas all diverticulitis patients were traditionally admitted

to the hospital, a large group of patients may be treated as outpatients. Nevertheless, currently only few patients are treated as outpatients and therefore **chapter thirteen** assesses the safety of outpatient treatment and identifies the subgroup of patients that is candidate for outpatient treatment. Many patients undergo a colonoscopy after an episode of acute diverticulitis to rule out a colorectal malignancy. However, the association between acute diverticulitis and colorectal malignancy is questionable and is frequently studied in recent years. Therefore, **chapter fourteen** summarizes all current evidence and answers the question whether or not to perform colonoscopies routinely after an episode of acute diverticulitis.

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