Outcome and treatment of acute diverticulitis
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CHAPTER 1

General introduction
Diverticular disease
Colon diverticula are actually “pseudodiverticula” because herniation only involves the mucosal and submucosal layers and not all layers of the colonic wall. Diverticula are common in the colon because of anatomic features such as an outer longitudinal muscle layer divided into distinct taenia coli and areas of weakness where the vasa recta penetrate the smooth muscle layer. (1)

Aetiology theories were developed in the 1970’s. These are based on diets low in fiber, together with altered colonic motility, which eventually contribute to the pathogenesis of diverticulosis coli. Increased pressure on the wall results in the formation of diverticula at the weakest point in the wall. (2, 3) This theory is probably outdated, since nowadays diverticulosis is thought to be a disease of ageing. (4, 5) Interest has been generated in the role of altered peridiverticular colonic flora and low-grade chronic inflammation leading to periods of symptomatic disease, similar to periods of exacerbation and remission in inflammatory bowel disease. (6, 7) For all of these theories there is no conclusive evidence.

Fact is that diverticular disease is becoming increasingly more prevalent with the aging Western population. Colonic diverticulosis affects one-third of the population over 40 years of age and two-thirds of the population over 85 years of age in the western world. It is estimated that approximately 10–25% of those with colonic diverticulosis will experience an episode of acute inflammation (8, 9). In the Netherlands, the annual number of patients admitted with some form of diverticular disease increased, from 15,822 patients in 2008 to 22,450 patients in 2010. (10) Costs associated with diverticular disease increase every year. (11) Although a common disease with rising prevalence, over the years little has changed in terms of diagnosis and treatment of diverticular disease. The treatment policy of diverticulitis is based upon many dogmas and little evidence.

Acute uncomplicated diverticulitis
The majority of mild diverticulitis patients improve with conservative treatment; less than 10% need percutaneous or operative treatment for disease progression and/or complications. Therefore, it can be considered a self-limiting disease. (12, 13)

Conservative treatment of mild diverticulitis usually comprises hospital admission, careful observation, restriction of oral intake, and intravenous fluids, and antibiotic therapy. (14) In the last decade, many of these treatments and especially the use of antibiotics have been debated. New studies show no advantage of antibiotics in respect to complications but were not convincing. (15) The main goal of the DIABOLO trial, in this thesis, is
to study whether a strategy without initial antibiotics is more cost-effective with respect to time to full recovery. Restriction of oral intake is also debated taken the results of fast track programs after colorectal surgery into consideration, in which early oral feeding is safe in postoperative care. (16) Careful observation does not mean in-patient care. Ambulatory treatment of uncomplicated acute diverticulitis may be safe, effective and applicable to patients who tolerate oral intake and are without severe co-morbidity. (17)

**Follow-up after acute uncomplicated diverticulitis**

An initial episode of uncomplicated diverticulitis can be managed non-operatively in the majority of cases. (13, 15) Most patients will have a routine colonoscopy after an episode of diverticulitis. Routine colonoscopy after an uncomplicated episode of diverticulitis was introduced as common practice in a time where imaging was not widely used. (18) Nowadays in clinical practice computed tomography (CT) is widely used because of its diagnostic superiority in sensitivity and specificity. (19) Still most international guidelines and clinical practice guidelines advise endoscopy to exclude malignancy or potential advanced neoplastic disease. (14, 20-23) The recent Dutch diverticulitis guideline and a systematic review, based on newer studies, contradict these earlier advices. (24, 25)

During follow-up, patients are at risk for developing recurrent disease. Until recently, elective resection was advised after two documented attacks of uncomplicated diverticulitis requiring hospitalization and/or after one episode of “complicated” diverticulitis. (20-23) These recommendations were based on older studies with recurrence rates of up to 60%. These high rates were based on mainly incorrect diagnoses of recurrence. The wider use of imaging modalities to confirm diagnosis showed lower recurrence rates. (19) In recent literature the reported recurrence rates are lower and the number of attacks of uncomplicated diverticulitis is not necessarily an indication for surgery (26, 27). Surgery may be needed for high-risk patients, but correct identification of these patients seems difficult.

Age is regarded as a potential risk factor for recurrent diverticulitis. (24) There is some evidence that younger patients (younger than 50 years) with diverticulitis have a higher risk for complications or recurrent disease. Guidelines and a recent review advise elective resection in younger patients. (20-23, 28) However, other studies dispute this advice. (13, 29, 30).

**Classifications**

Since Hinchey’s traditional classification for perforated diverticulitis in 1978, several modifications and new grading systems have been presented to display a more contemporary overview of the disease. The original Hinchey classification was based on both clinical and surgical findings. (31)
Recent development in imaging modalities showed that the clinical diagnosis of acute diverticulitis is correct in only 43%-68% of the patients. (32, 33) Therefore, imaging is important to increase diagnostic accuracy. CT became the gold standard with a superior sensitivity of 94% and specificity of 99%. (19) The Hinchey classification was modified becoming both based on clinical and CT findings. (34) This resulted in a fully CT-based modification of the original Hinchey classification. (35) Also Ambrosetti defined a new classification based on CT imaging. (36) CT findings during the acute phase of inflammation were correlated with primary outcome and secondary complications. Both classifications do not specify the various stages of complicated diverticulitis. Since old treatment dogmas have been challenged and individualized treatment of patients with complicated diverticulitis has become important, it is essential to adequately distinguish between different forms of complicated acute diverticulitis. (37) Therefore, a new classification has emerged focussing on complicated diverticulitis only, especially on different free air depositions. This Dharmarajan classification comprises a four-grade CT classification system for complicated diverticulitis. This is an important extension of existing classifications. Based on CT findings patients may be selected for successful conservative treatment of complicated diverticulitis. The authors claim a successful non-operative management with avoidance of an emergency operation in 91% of qualifying patients with acute complicated diverticulitis based on this classification. Similar results are reported elsewhere. (37) All classifications are summarized in table 1.

<table>
<thead>
<tr>
<th>Classification (31)</th>
<th>Modified Hinchey classification (34)</th>
<th>Modified Hinchey classification with CT findings (35)</th>
<th>Ambrosetti CT classification (36)</th>
<th>Dharmarajan (37) Complicated diverticulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Mild clinical diverticulitis</td>
<td>0 Diverticuli ± colonic wall thickening</td>
<td>Moderate diverticulitis</td>
<td>1 Localized free air (mesocolic) without abscess</td>
<td></td>
</tr>
<tr>
<td>I Pericolic abscess or phlegmon</td>
<td>Ia Confined pericolic inflammation or phlegmon</td>
<td>1a Colonic wall thickening with pericolic soft tissue changes</td>
<td>Localized sigmoid wall thickening (&gt;5 mm) Pericolic fat stranding</td>
<td></td>
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<tr>
<td>1b Pericolic or mesocolic abscess</td>
<td>1b changes + pericolic or mesocolic abscess</td>
<td>Severe diverticulitis Abscess</td>
<td>2 Collection of free air (&lt; 2cm) or Abscess (&lt; 4cm)</td>
<td></td>
</tr>
<tr>
<td>II Pelvic, intraabdominal, or retroperitoneal abscess</td>
<td>II Pelvic, distant intraabdominal, or retroperitoneal abscess</td>
<td>II changes + distant abscess (generally deep in the pelvis or interloop regions)</td>
<td>Extraluminal air Extraluminal contrast</td>
<td></td>
</tr>
<tr>
<td>III Generalized purulent peritonitis</td>
<td>III Generalized purulent peritonitis</td>
<td>Free gas associated with localized or generalized ascites and possible peritoneal wall thickening</td>
<td>3 Collection of free air (&gt; 2cm) or Abscess (&gt; 4cm)</td>
<td></td>
</tr>
<tr>
<td>IV Generalized fecal peritonitis</td>
<td>IV Generalized fecal peritonitis</td>
<td>Same findings as III</td>
<td>4 Free air with nonloculated free fluid in the peritoneal cavity</td>
<td></td>
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</tbody>
</table>
Outline of the thesis

In this thesis we present different studies to provide evidence in the treatment and follow-up of patients with acute diverticulitis. We divided this thesis in two parts. In Part I Diagnosis and treatment of acute diverticulitis, different classification systems and various medical treatments, such as diet therapy and antibiotics, are studied in relation to patient outcome. In chapter two we evaluate the different CT classifications and provide evidence for reproducibility of the different classifications in daily practice. In chapter three we describe a systematic review on the evidence for high fiber diet in patients with diverticular disease, as has been advocated for more than half of a century. In chapter four a systematic review with pooled analyses is presented of the incidence of complicated diverticulitis in post-transplant patients. In chapter five a study is presented investigating the feasibility of outpatient care of patients with uncomplicated diverticulitis. In chapter six a systematic review of the available evidence on the treatment of diverticulitis with antibiotics is presented. Chapter seven is the protocol of the DIABOLO trial en the results of this randomized trial are presented in chapter eight. Part II Follow-up after acute diverticulitis assesses routine colonoscopy after acute diverticulitis, risk factors for recurrent diverticulitis, and possible medical treatments to prevent recurrent diverticulitis. Chapter nine is a systematic review on routine colonoscopy after uncomplicated diverticulitis. In chapter ten, evidence on the use of routine colonoscopy after uncomplicated diverticulitis is provided in two parallel, large prospective series, one with diverticulitis patients and one screening population. Chapter eleven reports a systematic review on medical treatments aimed to prevent recurrent diverticulitis. Chapter twelve is a large retrospective cohort study that analyzes age as a potential risk factor for recurrent diverticulitis.
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General introduction


