Outcome and treatment of acute diverticulitis
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CHAPTER 13
Summary and conclusions
Future perspectives
SUMMARY AND CONCLUSIONS

The incidence of acute diverticulitis and subsequent hospital admissions are increasing in Western countries, imposing a significant burden on health care resources. The natural history of mild diverticulitis is usually mild, and most patients are treated by conservative means often including antibiotics. However, major differences in clinical practice exist between countries and medical disciplines. Due to the lack of evidence, most recommendations in international guidelines are based on expert opinion. With the rising incidence, there is an emerging need for evidence-based practice in the treatment and follow-up of patients with acute diverticulitis. This thesis consists of two parts: Part 1 entitled “diagnosis and treatment of diverticular disease” discusses the different classifications and the variety of conservative treatment measures of acute diverticulitis. Part 2 entitled “follow-up after acute diverticulitis” in which follow-up with or without colonoscopy and risk factors for recurrent disease are discussed.

Part 1. Diagnosis and Treatment of diverticular disease

In a mixed cohort, the inter-observer variability of three computed tomography (CT) based classification systems for diverticulitis are described in Chapter 2. This study showed that the Ambrosetti classification is the most reproducible classification. The Ambrosetti and modified Hinchey classifications have a substantial agreement with the reference standard and therefore produce a reliable classification. The Dhamarajan classification is applicable only in complicated diverticulitis and is an important complementary classification to the other more general classifications of diverticulitis.

One of today’s controversies remains the treatment of uncomplicated diverticulitis. Treatment can consist of dietary advises and several medical therapies, and can be directed by risk factor assessment. In Chapter 3, Chapter 4 and Chapter 5 an overview of published data is presented in three systematic reviews. In Chapter 3 the hypothesis that a low-fibre diet results in diverticulosis and a high-fibre diet will prevent symptoms or complications of diverticular disease is discussed. High-quality evidence for a high-fibre diet in the treatment of diverticular disease is lacking. Most recommendations are based on inconsistent level 2 and mostly level 3 evidence. Nevertheless, high-fibre diet is still recommended in several guidelines, notwithstanding the fact that there is no evidence.

Another classical dogma is that immunosuppression could increase the incidence and complication rates in patients with acute diverticulitis. This would justify a low threshold for elective sigmoid resection in these patients after an episode of diverticulitis. Well-documented groups of immunocompromised patients are transplant patients, in which many prospective studies have been conducted. In Chapter 4, a total of 11,966 post-transplant patients from 17 publications were included in a systematic review. The
incidence of a complicated disease course is higher in transplanted patients compared to the normal population, about one in hundred transplant patients seems to develop complicated diverticulitis. Additionally, when a transplant patient develops an episode of acute diverticulitis, a high proportion (40%) of the patients have a complicated disease course. Immunosuppression is therefore a risk factor in developing complicated diverticulitis. There is a major discrepancy in the use of antibiotics in the treatment of acute diverticulitis between countries in Northwest Europe and other countries, including the United States and United Kingdom. In Chapter 5 we present an overview of the literature and guidelines on the use of antibiotics. In the Netherlands and in Scandinavian countries, antibiotic use for uncomplicated diverticulitis is less common compared to other countries, where antibiotics are usually considered mandatory. A Dutch survey showed that many gastro-enterologists prescribed antibiotics in the treatment of acute uncomplicated diverticulitis, but only a minority of Dutch surgeons did so. In contrast, all UK surgeons responding to a survey prescribed antibiotics in the initial treatment of diverticulitis. Six professional organisations have issued formal guidelines concerning the use of antibiotics in uncomplicated diverticulitis. Five of these guidelines advice the use of antibiotics. In the Netherlands, the Dutch Antibiotic Policy Committee considers antibiotics not primarily indicated in the treatment of uncomplicated diverticulitis.

Traditionally, treatment of acute diverticulitis has mostly been based on inpatient care, with bowel rest and administration of intravenous antibiotics. The question arises whether these patients can be treated on an outpatient basis although the admissions for diverticular disease have been shown to be increasing. We studied in Chapter 6 whether outpatient treatment of acute uncomplicated diverticulitis is feasible and safe, and which patients could benefit from outpatient care. Despite inherent patient selection in a retrospective cohort of 312 patients, ambulatory treatment of patients presenting with uncomplicated acute diverticulitis seems feasible and safe. In mildly ill and younger patients, hospital admission can usually be avoided.

The lack of evidence for the role of antibiotics in the treatment of uncomplicated diverticulitis necessitates a scientific judgement. Therefore, we initiated a randomized multicenter trial to investigate the effect of antibiotics on disease course in patients with mild acute diverticulitis. In Chapter 7 the protocol is presented. In Chapter 8 we discuss the results of the DIABOLO trial. Observational treatment for uncomplicated acute diverticulitis is not associated with a longer time-to-recovery nor with higher rates of readmission, complicated, recurrent or ongoing diverticulitis or sigmoid resection. The short-term benefits of observational treatment without repercussions during longer-term follow-up indicate that antibiotic treatment can safely be omitted in uncomplicated diverticulitis and guidelines need to be adjusted.
Part 2. Follow-up after acute diverticulitis

The use of routine colonoscopy after an episode of acute diverticulitis remains a point of debate. Most international and clinical practice guidelines advise endoscopy after conservatively treated diverticulitis. The rationale has always been to exclude an underlying malignancy (CRC) or advanced colonic neoplasia (ACN). However, with increased use of abdominal CT imaging, with a high sensitivity/specificity and a low interobserver variability, an underlying malignancy should be detected by CT. Nevertheless, it remains uncertain if the prevalence of colorectal carcinoma (CRC) and advanced adenoma (AA) in patients with imaging-proven diverticulitis is higher than in an average-risk population. Before we conducted our own study, we performed a systematic review, Chapter 9. The aim of this systematic review was to determine the pooled prevalence of ACN, thus CRC and/or AA, as detected with colonoscopy in patients after an imaging-proven diagnosis of acute diverticulitis. Eight studies met our inclusion criteria, with a total of 1796 patients. In conclusion, the available data presented in this systematic review suggest that the malignancy rate as detected with colonoscopy after imaging-proven uncomplicated diverticulitis is low; the ACN rate is lower and the CRC rate somewhat higher than in asymptomatic populations. However, because of limitations of included studies, such as moderate methodological quality, lack of adequate control groups, selection bias, and low quality of colonoscopies, strong conclusions cannot be made.

Since most existing studies were cohort studies without control group, we conducted a prospective, comparative study, Chapter 10. The two cohorts, a screening population and a cohort of uncomplicated AD patients, were derived from two multicentre randomized clinical trials that were performed in the Netherlands. In total, 424 patients with uncomplicated diverticulitis were compared to 1426 screening patients. We concluded that ACN prevalence does not differ significantly between patients with a recent episode of diverticulitis and (asymptomatic) screening individuals. Routine follow-up colonoscopy in patients with a primary episode of CT-proven uncomplicated left-sided diverticulitis may therefore be omitted. Follow-up colonoscopy may be targeted at patients with diagnostic uncertainty at CT or those with a protracted clinical course.

Since elective resection after an episode of recurrent diverticulitis is not standard therapy to prevent further recurrences, different medical therapies have been developed in the last decade. In Chapter 11 the systematic review assess these medical or dietary therapies that could prevent recurrent diverticulitis after a primary episode of acute diverticulitis. The evidence that supports medical therapy to prevent recurrent diverticulitis is of poor quality. Treatment with 5-aminosalicylic acid seems promising. Based on current data, no recommendation of any non-operative relapse prevention therapy for diverticular disease can be made.
In Chapter 12 the controversy about the treatment of acute colonic diverticulitis in young patients is studied. The discussion is focused on whether younger age is a risk factor for recurrence or a complicated course, and thereby whether these patients should be treated more aggressively (i.e., surgically). We investigated whether an episode of acute diverticulitis at a younger age (≤50 years) has a higher recurrence rate or a more severe outcome in a retrospective cohort study. A total of 1,441 consecutive patients were identified as having primary acute diverticulitis of the sigmoid colon. Younger age was neither associated with a more severe presentation of diverticulitis nor with a higher incidence in recurrence. In this regard, other factors played a significant role. In multivariate analysis, ASA III classification and the occurrence of abscesses were associated with recurrence.

**Future perspectives**

It is important to understand the pathophysiology of diverticular disease (DD) and address the treatments options on an evidence based manner. The last decade the dogmatic treatment principles of acute diverticulitis have been scrutinized more and more for evidence, but still additional clinical studies are needed on this topic. However, the holy grail of the treatment of patients with diverticulitis lies eventually in discovery of the unknown pathophysiology of the disease.

To date, the dominant pathophysiology theory, set in 1971, has been based on fibre deficiency. Current theories are shifting away from this traditional theory. New research implicates a role for low-grade inflammation and alterations of gut microbiota in this group of diseases. Last decade a new hypothesis has emerged which could be helpful in understanding the etiology. This hypothesis is based on the fact that DD is an age-related disorder: ageing eventually leads to altering colonic epithelia (diverticulosis) altering colonic mucosal flora and microbial environment. It is now known that the intestine harbors a complex bacterial community. However, very little is known about the composition of the intestinal microbiota in diverticular disease and its role in inflammation and its effect of mucosal change and mucosal flora. The interaction between changes in intestinal microbiota in the vicinity of changed mucosa may result in a low-grade chronic inflammatory condition. This low-grade colitis then has the potential to progress to microperforation and, ultimately, to acute diverticulitis. With a better understanding of the etiology, more tailored therapy could be conducted in the future.

To gain better understanding of the pathogenesis of DD, the interplay between genetic predispositions, in relation to environmental and nutritional exposures has to be studied. One of the molecular mechanisms that can dynamically respond to environmental and nutritional exposures is defined as epigenetic. Epigenetic changes
are mitotically heritable molecular modifications that affect gene expression potential without alteration in the DNA sequence.

In the field of gastrointestinal tract, the correlation between methylation of gastric mucosa and inflammation caused by Helicobacter pylori (H. pylori) infection has particularly been highlighted. H. pylori infection potently induces aberrant DNA methylation in gastric mucosa, and methylation levels of a unique set of individual markers in gastric mucosa decreased after H. pylori eradication. Future studies will focus on the reaction of microbiota and epigenetic changes. This hypothesis has not been evaluated yet.

More research is needed to explain its pathogenesis and multifactorial etiology and this could lead to new targets for treatment. Several unanswered clinical questions regarding the management of patients with acute diverticulitis will hopefully be answered in the nearby future by various ongoing trials that address the optimal treatment of different stages of diverticulitis including complicated diverticulitis. Main goal in the recent future is avoidance of overtreatment. This has obvious benefits: less in-hospital treatment, no antibiotics for uncomplicated diverticulitis, cost reduction, diminished development of antimicrobial resistance, reduction in complication rate and side effects, and presumably a better quality of life for the patient.