Diverticulitis Insights in Aetiology and Treatment

de Korte, N.

2015

document version
Publisher's PDF, also known as Version of record

CHAPTER 13

Summary, general discussion
and future perspectives.

SUMMARY

Colonic diverticulosis is one of the most common disorders of the gastro-intestinal tract. Diverticulitis is a common complication of diverticulosis and imposes a significant health care burden. International guidelines until now have been based on low-level evidence. No universal classification system exists and still much debate exists over optimum treatment strategies. Furthermore the aetiology of diverticulitis remains unclear; especially in relation to the colonic microbiome.

In this thesis we have tried to answer a number of questions concerning the aetiology, current treatment of diverticulitis and the use of antibiotics. All research questions postulated in the introduction are answered separately below.

PART I: AETIOLOGY. COLONIC MICROBIOME AND MUCOSAL CHANGES IN PATIENTS WITH DIVERTICULOSIS AND DIVERTICULITIS.

What is the colonic microbiome composition in patients with diverticulosis compared to a control population?

Chapter 2 presents the results of the PADIFLORA study. As a first step in further understanding the development of diverticulitis we compared the colonic microbiome of individuals with diverticulosis on colonoscopy, but without symptoms, and compared it to a matched control population. It has been suggested that a low fibre diet that may lead to diverticula formation could also alter the colonic microbiome. A high-throughput polymerase chain reaction (PCR)-based profiling technique (IS-pro) was performed on DNA isolates from mucosal samples. We found that the microbiome of patients with diverticulosis is not different to that of a control population. This is true for the sigmoid colon as well as the transverse colon. The *Firmicutes* to *Bacteroidetes* ratio is commonly used to describe and characterize a dysbiosis of the gut microbiota. Therefore, we compared their relative abundance between patients and controls. For diverticulosis patients, *Bacteroidetes* represented 62% and *Firmicutes* 38% of the total abundance in the *Firmicutes/Bacteroidetes* PCR. Almost identical proportions were found for the patient group (*Bacteroidetes* 63%, *Firmicutes* 37%) (p=0.69 vs patients). The total load of bacteria of the *Proteobacteria* phylum was also similar between patients and controls (*P*=0.56).

Are there histological changes in the mucosa of patients with diverticulosis?

Chapter 2 also describes the histological evaluation of the colonic mucosa in a group of patients with diverticula on colonoscopy compared to individuals with no diverticula. It has been hypothesized that clinically manifest forms of diverticulitis could have a precursor stage with a form of low grade mucosal inflammation not leading to clinical manifest symptoms yet. To assess this, mucosal biopsies were taken from individuals with diverticulosis on colonoscopy but without symptoms and compare this to the mucosa of patients

without diverticula. The presence of inflammation was assessed. We found no difference in mean lymphocyte count between the groups, neither in the bottom of the crypts or in the whole crypts. This was also true for the sigmoid colon as well as the transverse colon.

Is the colonic microbiome in patients with diverticulitis different from healthy individuals?

Chapter 3 describes the results of the DIBIOTA study. Thirty-one patients with Computed Tomography (CT) proven left-sided, uncomplicated diverticulitis were included and compared with 25 matched control subjects evaluated for a range of other gastrointestinal indications.

Differences in bacterial phylum abundance and diversity (Shannon index) of the resulting profiles were assessed by conventional statistics. Dissimilarity in microbiome composition was analysed with principal coordinate analysis (PCoA) based on cosine distance measures. To develop a prediction model for the diagnosis of diverticulitis, we used cross-validated partial least squares discriminant analysis (PLSDA). Firmicutes/Bacteroidetes ratios and Proteobacteria load were comparable among patients and controls (p=0.20). The Shannon index indicated a higher diversity in diverticulitis for Proteobacteria (p<0.00002) and all phyla combined (p= 0.002). PCoA based on Proteobacteria profiles resulted in visually separate clusters of patients and controls. The diagnostic accuracy of the cross-validated PLS-DA regression model was 84 %. The most discriminative species derived largely from the family Enterobacteriaceae.

Diverticulitis patients have a higher diversity of faecal microbiota than controls from a mixed population, with the phylum Proteobacteria defining the difference. The analysis of intestinal microbiota offers a novel way to diagnose diverticulitis and may play a role in the aetiology of diverticulitis.

In conclusion, much remains unclear in the aetiology of diverticulitis and the role the colonic microbiome plays in it.

PART II: CURRENT CLASSIFICATION AND MANAGEMENT OF DIVERTICULITIS

Which classification systems exist and what are the differences between the systems?

Chapter 4 reviews the current classification systems for diverticulitis. A total of nine different classification systems were identified. Some were only based on imaging and some incorporated all aspects of diverticular disease including chronic complications and bleeding.

A new classification system more in line with current evidence incorporating all aspects of complicated diverticular disease, imaging and its treatment is proposed.

What is the current approach to the diagnosis and treatment of diverticulitis in the Netherlands?

Chapter 5 describes the results of a questionnaire on the treatment and diagnosis of diverticulitis in the Netherlands among gastro-enterologists and surgeons. Eighteen percent of gastro-enterologists consider a CT mandatory for every patient compared to 39% of surgeons (p=0.001). A CT however is considered mandatory in all guidelines. 90% percent of respondents (both gastro-enterologists and surgeons) treat mild diverticulitis *without* antibiotics, although antibiotics are recommended in all international guidelines. The majority of both surgeons and gastroenterologists use a form of bowel rest, would consider outpatient treatment, and perform a colonoscopy at follow-up. For Hinchey 3 diverticulitis 78% of surgeons would consider a resection and primary anastomosis. Laparoscopic lavage is viewed as a valid alternative for Hinchey 3 diverticulitis by 30% of gastro-intestinal surgeons and 2% of non-gastrointestinal surgeons. For Hinchey 4 diverticulitis 46 % of gastro-intestinal surgeons and 72% of non-gastrointestinal surgeons would always perform a Hartmann procedure.

Recent publications show that bowel rest and antibiotics are not needed for mild diverticulitis, follow-up colonoscopy is not needed, and primary anastomosis after resection for complicated diverticulitis is usually safe and feasible. Much of these new insights are not widely practiced.

What is the evidence base for diagnosing diverticulitis?

Chapter 6 reports a case vignette study in which the current evidence base for diagnosing diverticulitis is evaluated.

A strategy of ultrasound first followed by Computed Tomography (CT) in case of inconclusive ultrasound is a safe strategy and results in the lowest exposure to radiation. In case of a critically ill patient a CT should be performed as the first choice. The role of Magnetic Resonance Imaging (MRI) for diverticulitis remains unclear.

Which risk factors predict treatment failure of diverticulitis in patients treated non-operatively?

In chapter 7 a cohort of patients with diverticulitis treated non-operatively is described. A total of 20 patients (6%) failed treatment. On univariate analysis age above 70, ASA grade higher than 2, abscess formation on CT scan, steroid use and NSAID use were associated with an increased risk of treatment failure. Multivariate analysis showed abscess formation (odds ratio 8.76 [95% confidence interval 2.88-26.64]), NSAID use (odds ratio 13.35 [95% confidence interval 2.84-64.20]) and ASA grade (odds ratio 4.50 [95% confidence interval 1.52-13.33]) to be independent risk factors. There were 6 (2%) deaths in the entire cohort, all of which were in the treatment failure group. When treatment failed mortality was as high as 31.6 percent.

A more aggressive approach should be considered in a high-risk group of patients.

PART III: TREATMENT OF DIVERTICULITIS WITH ANTIBIOTICS

What is the value of treating uncomplicated diverticulitis with antibiotics?

Chapter 8 is the result of a systematic review on the use of antibiotics in uncomplicated diverticulitis. The results show that evidence for antibiotic treatment of diverticulitis is extremely sparse. The review concludes that there is no evidence supporting the use of antibiotics in uncomplicated diverticulitis.

Chapter 9 describes a retrospective cohort study in which a group of patients with uncomplicated diverticulitis is treated with antibiotics and one is treated without antibiotics. A total of 191 patients were treated without antibiotics and 81 with antibiotics. Groups were comparable at baseline with respect to age, sex, co-morbidity, NSAID, steroid and aspirin use. All patients had imaging confirmed diverticulitis. C-reactive protein and white blood cell counts levels did not differ significantly. Treatment failure did not differ between groups (4% *versus* 6%, p=0.350).

Chapter 10 is the presentation of the protocol of the DIABOLO study, a randomized controlled trial comparing a regimen of antibiotics and hospital admission to observation alone in patients with uncomplicated diverticulitis.

Chapter 11 reports on the outcome of the DIABOLO study. The trial shows that there is no differences in time to recovery at six months follow up. 570 patients were randomly assigned to observation or antibiotics. Complete recovery occurred in 234 (89.3%) of patients assigned to the observation arm and in 248 (93.2%) patients assigned to the antibiotic arm (P=0.183) Over a median follow-up period of 731 days we found, after adjusting for multiple comparisons, no significant differences between both treatment strategies for main and secondary endpoints. Hospital stay was significantly shorter in the observation group.

In conclusion, omitting antibiotics in uncomplicated diverticulitis is safe. In the light of ever growing antibiotic resistance this is an important finding. Based on all research currently available, international guidelines should be amended.

What controversies exist in the current management of diverticulitis?

A review of the current management strategies for the treatment of diverticulitis is addressed in **chapter 12**. The use of antibiotics is controversial in the treatment of uncomplicated diverticulitis and according to the outcome of the DIABOLO trial not necessary. In complicated diverticulitis there is still much debate on the treatment of Hinchey 3 (purulent peritonitis) and Hinchey 4 diverticulitis (fecal peritonitis). A resection and anastomosis may be a save option as is laparoscopic lavage in selected cases. A less aggressive approach for all stages is advocated.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis focusses on several aspects of aetiology, classification and treatment of diverticulitis, where progress and clarification is needed. This has been one of the main reasons of the formation of the Dutch Diverticular Disease (3D) collaborative study group, addressing some of the most controversial aspects of management.

The aetiology of diverticulitis still remains partly unsolved. In this thesis we have tried to shed some light on the role of the colonic microbiome in the development of diverticulitis. For the first time in diverticulosis and diverticulitis patients we assessed the microbiome using the latest DNA technologies. We found that although the microbiome in diverticulis has changed significantly, this is not the case yet in asymptomatic diverticulosis. These findings need to be validated on a much larger set of patients with diverticulitis, and the cause and effect of a changed microbiome in this setting needs to be assessed. Furthermore, it would be interesting to know whether the microbiome changes again after diverticulitis subsides. Studies in children indicate that antibiotic use may alter the microbiome permanently, and this may be the case in adults as well. Along these lines of reasoning, antibiotic-induced changes superimposed upon an already altered microbiome in diverticular disease may play a role in the pathophysiology of recurrent episodes of diverticulitis. For future research the colonic microbiome can be evaluated using rectal swabs instead of mucosal biopsies. Evaluation in asymptomatic patients with diverticula but without the possible confounding of colonic lavage (as preparation for colonoscopy) is necessary to define whether shifts in the microbiome occur already before symptoms start. Furthermore, the microbiome inside diverticula may be different from the microbiome in the colonic lumen. Therefore, assessment of diverticula specimens of resected sigmoid for other reasons than diverticular disease may be an interesting approach.

The colonic microbiome harvests more than 5000 individual bacterial species and is a largely uncharted field for future research. In the coming years our understanding of the role of the microbiome in health and disease needs to increase. What is its role in the prevention, development and disease course of diverticulitis; which micro-organisms and which shifts in microbiome are important?

We found no inflammatory changes in the mucosa of symptom-free diverticulosis patients as had been suggested by others. Future research could focus on identifying changes in regulatory pathways of mucosal cytokines in individuals with diverticulosis that could play a role in developing clinically manifest diverticulitis.

A universally adopted classification system is paramount for standardizing diagnosis and treatment of a disease, for evaluation of new imaging and treatment advances, and for international comparison of study results. For diverticulitis this is however not the case. We reviewed all classification systems and propose a new system incorporating all elements of diagnosis and treatment of diverticular disease. Future research must evaluate and validate this new comprehensive classification and other promising new classification systems like the Dharmarajam classification in prospective series. Research on diverticular disease would benefit greatly if a classification system would be universally adopted, as has been the case for the international TNM system in cancer.

In this thesis we demonstrated large variations in diagnosis and treatment of diverticulitis in the Netherlands. Large practice variations of a condition are unwanted both from a medical and a socio-economical point of view. Surgical societies and health care insurers could play an important role in making these differences clear by providing data on the sort of diagnostic modality and treatment used in individual hospitals and comparing them to other hospitals and guidelines. Since the publication of our survey a guideline on the treatment of diverticulitis has been issued. It would be interesting to see whether emerging evidence and guidelines alter treatment for diverticulitis. Limited funds for diverticulitis research, as for other non-malignant diseases, are a problem that needs to be addressed. The health care burden of diverticulitis is enormous and research resources should not by predominantly aimed at cancer research.

It appears that although mild or uncomplicated diverticulitis usually runs a benign course of disease, when comorbidity, NSAID use or abscess formation is present, failure of conservative treatment may result in high mortality. Further research should focus on these risk factors and determine the best treatment strategy for them. Ideally treatment choices should be tailored to a patients individual risk profile. National prospective audits, similar to cancer treatment, may prove a valuable quality control method in evaluating diverticulitis treatment in the future.

The use of antibiotics in the treatment of uncomplicated diverticulitis has been a long-standing dogma. Until only a few years ago there was no evidence whatsoever to justify this. The Dutch surgeon Roumen, already in 1996, was the first who published data on the use of antibiotics in diverticulitisin the Netherlands Journal of Surgery. His prospective DIVAN trial however proved difficult to complete. More than 15 years later we completed the DIABOLO trial which together with the Swedish AVOD study by Chabok et al. and two retrospective cohort studies, of which one is presented in this thesis, firmly prove the safety of omitting antibiotics in uncomplicated diverticulitis. The recently published Dutch national guideline does not advise the use of antibiotics in uncomplicated diverticulitis and more emphasis on restrictive use is appearing currently in review articles on diverticulitis. The next update of the Dutch national guideline should include the evidence of the DIABOLO trial. International guidelines however appear to be rigid and still recommending the use of antibiotics. This should be altered in upcoming updates. Restrictive use of antibiotics is extremely important in the light of ever growing antibiotic resistance. In 2014 the World Health Organization stated that antibiotic resistance is a serious worldwide threat to public health that should be firmly combated. The use of antibiotics without evidence and published clinic benefit should be banned.

The Dutch LOLA trial and three other foreign trials evaluate the use of laparoscopic lavage in Hinchey 3 diverticulitis. Furthermore the Dutch DIVA trial examines primary anastomosis versus Hartmann's procedure in Hinchey 3 and 4 diverticulitis. In the near future these trials hopefully will provide more definitive answers to the many other unsolved questions regarding the treatment of diverticulitis.

All and all, recent years have seen a shift from an approach of the disease with antibiotic use, hospitalization, resection and stoma formation to a *less aggressive* approach without antibiotic use and with outpatient treatment in uncomplicated disease and the possibility of primary anastomosis or peritoneal lavage in selected cases of complicated disease.