Treatment of Acute Uncomplicated Colonic Diverticulitis

DANIEL ISACSON
Abstract


The overall aim of this thesis was to evaluate the clinical management of AUD with regard to the no-antibiotic policy and its long-term effect, treatment on an outpatient basis and the potential health-care cost savings.

Study I: a retrospective study at Västmanlands Hospital that evaluated and confirmed the adherence to the no-antibiotic policy in patients with AUD and its safety regarding complications and recurrences. A total of 246 patients with acute diverticulitis were identified, of which 195 had computed tomography (CT) confirmed AUD. In total, 91.3% of these patients did not receive any antibiotics and only two developed complications.

Study II: a retrospective study with the aim to conduct a long-term follow-up of all Swedish patients who participated in the AVOD trial in terms of recurrences, complications, surgery and quality of life. The medical records of 96% of the patients were reviewed with a mean follow up of 11 years. Quality of life questionnaires were sent out to all patients. There were no differences regarding the rates of recurrence, complications or surgery for diverticulitis. There were no differences in the quality of life between groups according to the EQ-5D questionnaire.

Study III: a prospective study where 155 patients with CT-verified AUD as were treated as outpatients without antibiotics. On day 3, patients reported an average pain score of 1.8 of 10 on the VAS scale and only 30% of patients were using analgesia. Four patients returned to hospital because of treatment failure.

Study IV: a retrospective cohort study at Västmanland’s Hospital evaluated the impact on admissions, complication rates and health-care costs of the policy of outpatient treatment without using antibiotics. Medical records of all patients diagnosed with AUD in the year before (2011) and after (2014) the implementation of outpatient management without antibiotics were reviewed. Overall 494 episodes of AUD were identified: 254 in 2011 and 240 in 2014. Three patients developed complications in 2011 and four in 2014. The proportion of patients managed as outpatients was 20% in 2011 compared with 61% in 2014. The hospital admissions, total length of stay of and total health-care costs were almost halved.

In conclusion, these studies confirm the low complication and recurrence rates of AUD and strengthens findings that antibiotics have no benefit in the treatment of this disease. The no-antibiotic policy had no impact on short- or long-term outcomes regarding the rates of recurrence, complications, surgery or quality of life. Outpatient management was found to be feasible and safe, and significantly reduced admissions, which led to large health-care cost savings.

Keywords: Colonic diverticulitis, antibiotics, health-care cost, follow-up

Daniel Isacson, Centre for Clinical Research, County of Västmanland, Västmanlands sjukhus Västerås, Uppsala University, SE-72189 Västerås, Sweden. Department of Surgical Sciences, Upper Abdominal Surgery, Akademiska sjukhuset 70 t tr, Uppsala University, SE-751 85 Uppsala, Sweden.

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Twenty years from now you will be more disappointed by the things that you didn’t do than by the ones you did do, so throw off the bowlines, sail away from safe harbor, catch the trade winds in your sails. Explore, Dream, Discover.

—Mark Twain
List of Papers

This thesis is based on the following papers, which are referred to in the text with roman numerals.


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## Abbreviations

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<tr>
<td>ACD</td>
<td>Acute complicated diverticulitis</td>
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<td>AD</td>
<td>Acute diverticulitis</td>
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<td>AUD</td>
<td>Acute uncomplicated diverticulitis</td>
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<td>AVOD</td>
<td>Swedish acronym for “Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis” by Chabok et al. (1)</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>ED</td>
<td>Emergency Department</td>
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<td>IV</td>
<td>Intravenous</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>PO</td>
<td>Per oral</td>
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<td>QOL</td>
<td>Quality of life</td>
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<td>RR</td>
<td>Relative risk</td>
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<td>VAS</td>
<td>Visual analogue scale</td>
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<td>WBC</td>
<td>White blood cell count</td>
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Introduction

Definitions
A diverticulum is a sac-like protrusion or herniation of the mucosa. Diverticula can be either false or true. A true diverticula contains all layers of the colonic wall (mucosa, muscularis propria and adventitia) (1). A false diverticula, or pseudo-diverticula do not contain the muscular layers or adventitia. It only involves the submucosa and mucosa. Diverticulosis is defined as the presence of diverticula, which may be asymptomatic or symptomatic (1). Diverticulitis is defined as inflammation of one or more diverticula. Diverticular disease is defined as symptomatic diverticulosis caused by diverticular bleeding, diverticulitis, segmental colitis associated with diverticula, or symptomatic uncomplicated diverticular disease. Complicated diverticulitis is defined as acute diverticulitis with the presence of abscesses, free perforations, stenosis or fistulae (2).

History
A diverticulum was first described anatomically by Littré in 1700, according to a book by Morgagni (3). In the 19th century, several anatomists gave clear descriptions on the pathological appearances at post-mortem examinations and diverticulitis was recognized as a clinical entity. In 1896, William Mayo operated on his first case of internal ceecal fistula into the bladder, and later had resected the colon in cases thought to be cancer which were found to be diverticulitis(4). Hansemann (1896) found on experiments on animals that raising the intestinal pressure in the intestine caused rupture before there was evidence of sacculcation. He found that he could blow out these small herniae in adults and still more easily in the elderly but not in children. He postulated a lowered resistance of the bowel wall with ageing. During the latter half of the 19th and 20th century the prevalence of diverticulosis increased progressively(5). Denis Burkitt, an Irish surgeon working in Uganda, stimulated much of the interest in diverticulosis in the 1960s and 1970’s by observing that it occurred exclusively in the expatriate community there.
Pathophysiology/Aetiology

Diverticula are small mucosal herniations protruding through the intestinal layers including the smooth muscle. True diverticula contain all layers of the gastrointestinal wall, the mucosa, muscularis propria and adventitia (1). The muscle layer consists of an inner circular layer and an outer layer concentrated mainly in three narrow bands along the colon called taeniae coli. One of these bands is located on the mesenteric border of the colon and the other two are located on the antimesenteric side. The muscle layer becomes progressively thicker in the distal sigmoid colon and the taeniae eventually fuse in the proximal rectum (1).

There is a weakness of the colon wall at the site where vasa recta penetrate through the circular muscle layer to supply the mucosa. It is at this weak point where diverticula can protrude (6, 7). Diverticula can be found throughout the colon, but are most common in the sigmoid colon where abnormalities include thickening and elastosis of the taeniae, shortening of the bowel and thickening and folding of the circular muscle layer (8, 9). The prevalence of diverticulosis of the colon increases with age suggesting it’s a progressive disease(10). Change in extracellular matrix and altered collagen structure with age partly explains this pattern (11).

Interestingly, studies of Western populations have demonstrated a tendency for diverticulosis to occur on the left side, primarily in the sigmoid colon (55–95%) (9, 10, 12). In contrast, diverticular disease in Asian people occurs much more commonly on the right, with as many as 70% of the diverticula isolated to the right side (13-15). Right-sided diverticulitis in the absence of sigmoid colon involvement usually consists of a single or a few true or false diverticula in the caecum or ascending colon; it develops at an earlier age than left-sided disease (16-18), and it is thought to reflect a genetic predisposition (19). This might be reinforced by a study that surveyed the Hawaiian Japanese community and found the dominant site has remained right-sided, as it is in the indigenous Japanese population (20).

The causes of colonic diverticular disease have not yet been established conclusively. Epidemiologic studies from the 1970s demonstrated associations between diverticulosis and diets that are low in dietary fibre and high in refined carbohydrates(21) (22, 23). The presumption was based on observations that diverticulosis is rare in rural Africa (24, 25). Painter and Burkitt presumed that the rural African diet is high in fibre and that the Western diet is low in this component(22, 24). They did not measure diet or diverticulosis in their studies nor did they account for confounding variables such as age and sex. They also conducted a trial to support their theory that a low intake of dietary fibre results in less bulky stools, which then retain less water, causing constipation; this raises intracolonic pressure and increases the gastrointestinal transit time. This could then lead to diverticula. Based on their results, a high-fibre diet has traditionally been recommended for patients
with diverticular disease. Studies in populations with colonic diverticula, on the other hand, have shown shorter colonic transit times and increased colonic pressure compared with controls (26).

More recent studies have now shown that a high-fibre diet does not protect against the development of diverticulosis but may protect against diverticular disease. A high-fibre diet has also been suggested for symptomatic control in patients with diverticular disease, but a recent systematic review concluded that “single low quality studies suggest that fibres, both dietary and supplemental, could be beneficial in the treatment of symptomatic uncomplicated diverticular disease” but further well designed studies are needed (27). A vegetarian diet was associated with a 31% lower risk of admission to hospital or death from diverticular disease compared with meat eaters in a large cohort study(28). Nut, corn, or popcorn ingestion was found not to be associated with diverticulitis (29).

Associations between diverticular disease and chronic idiopathic inflammatory bowel disease (irritable bowel, Crohn’s disease or ulcerative colitis) have been demonstrated on biopsies(30, 31). These findings, together with similar chronic symptoms of disease entities such as abdominal pain, bloating, tenesmus and diarrhea, have raised interest in the role of gut microbiota for both understanding the disease as a potential target for intervention (32). A systematic review concluded that evidence on probiotics in this regard is scant and does not support a clear benefit as a treatment option (33).

Risk factors for left-sided diverticulosis and diverticulitis

Non-modifiable risk factors for diverticulosis and diverticulitis include age, sex and genetics. The prevalence of diverticulosis is difficult to estimate, since in the majority of cases it does not cause any symptoms. Varying incidence rates are reported in studies in Western industrialized nations but these are similar to reports from a recent population-based colonoscopy study on 624 patients, where 42% had one or more diverticula with the proportion increasing with age. The rates were 30–35% for persons aged < 50, 40% for persons aged 50–70 years, 58% for persons aged 60–70 years and 30% for those aged > 70 years (10, 34, 35). The incidence of diverticular disease also demonstrates a clear age dependency, although a slight increase in younger patients has been observed during the last decade (36). Reports suggest that 60% of patients admitted with diverticulitis are female (35, 37). The Swedish twin registry study concluded that genetic susceptibility is an important component, along with individual specific environmental factors, for the development of diverticular disease (38). Heritability was estimated at 40% and non-shared environmental effects at 60%. Patients with some rare syndromes such as Marfan, Ehler–Danlos and polycystic kidney disease demonstrate a strong predisposition for the formation of colonic diverticula (34).
These syndromes have in common a defect in extracellular matrix components or connective tissue fibres. Modifiable risk factors include dietary and lifestyle factors such as obesity (body mass index (BMI) > 30), alcohol dependence and smoking (11). A Danish cohort study on 28,817 patients reported that the risk of diverticulitis was increased 3-fold in those with alcoholism (39). The relative risk of alcohol abuse decreased only slightly with time after diagnosis and the increase persisted after 5 years. A large prospective cohort study on 47,228 male health professionals found that a higher BMI, and greater waist circumference and waist-to-hip ratio significantly increased the risks of diverticulitis and diverticular bleeding (40). A similar increase in risk with a BMI > 25 was reported in women (41). A systematic review reported a 36%, 17% and 29% increase in the relative risks (RRs) of diverticular disease among current, former and ever smokers, respectively. Increased risk was also observed for complications of diverticular disease. (42). Other risk factors for developing diverticular disease include arterial hypertension and immunosuppression, while using non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and corticosteroids increased the risk of diverticular haemorrhage (34). Two large cohort studies have reported that increased physical activity is associated with a reduced risk of acute diverticulitis (40, 41). Diverticular pathology is associated with a 5-fold increased risk of developing chronic gastrointestinal symptoms or a mood disorder (43).
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<td>Environmental factors</td>
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Risk factors for complicated diverticular disease

A systematic review aimed to identify risk factors that can predict complicated diverticulitis. Twelve studies with 4,619 patients were included. Age and sex were the only risk factors eligible for meta-analysis and showed no significant effect on the risk for complicated diverticulitis. There was reasonable quality of evidence suggesting that high C-reactive protein (CRP) levels (cut-off values ranging from 50 to > 175 mg/L) and white blood cell counts (WBCs) generally higher in those with complicated diverticulitis 14.4 × 10⁹ vs 10.4 × 10⁹) were associated with complicated disease. Clinical signs including severe and generalized abdominal pain rather than localized left-sided pain, constipation and vomiting, as well as steroid use, a primary episode and comorbidity are also risk factors for complicated diverticulitis (44). Individually, the evidence for these risk factors was low but when combined, the factors may be used to predict complicated disease.
Figure 1. Illustration of multifactorial influences on the development of diverticulitis and the risk of progression with a lifetime perspective (reused with permission from Seretide et al) (11).
Incidence/Prevalence

Diverticulitis is a disease of Western and industrialized societies with recent increase in prevalence. The highest prevalence is in the United States, Europe and Australia, where approximately half the population over the age of 60 have the disease (24, 45). The prevalence of diverticulosis increases with age, and is present in up to two thirds of the population aged over 85 years (46). In men there’s a higher incidence in younger age groups but in women it’s higher in older age groups (45, 47, 48). In the Asian populations the prevalence of diverticulosis is increasing compared with data from two decades ago (49, 50).

In 1975, Parks suggested that between 10% and 25% of patients with diverticulosis will develop diverticulitis. This was based on studies on the prevalence of diverticulosis in post-mortem and barium enema data (3). More recent evidence suggests that the lifetime risk of developing acute left-sided colonic diverticulitis varies, but the true incidence is unknown because studies reporting rates of acute diverticulitis have focused solely on those patients admitted to secondary care despite substantial numbers of patients being treated in primary care (11). One cohort study on 2,222 patients in Los Angeles reported that 4% of patients with diverticulosis developed diverticulitis over an 11-year period (51) but other studies have reported a prevalence of 10–25% (21, 52). Of these patients, up to a quarter can develop life-threatening complications such as obstructions, perforations and intraperitoneal abscess formation (53).

<table>
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<th>Box 2: Prevalence of Diverticulosis</th>
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<td>5–10% before age 50</td>
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<td>30% after age 50</td>
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<td>50% after age 70</td>
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<td>66% after age 85</td>
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Health-care costs

Diverticulitis is now ranked as the fifth most important gastrointestinal disease in terms of direct and indirect health-care costs in Western countries and is seen as the third most common gastrointestinal disorder requiring hospitalization, costing 2.6 billion dollars per year in the United States alone (54). In Europe, acute diverticulitis accounts for more than 200,000 annual hospital admissions and poses a health burden exceeding 300 million Euros (€) (55). According to a report from the United States national inpatient database, the incidence of diverticulitis has increased similarly in both sexes with an incidence of diverticulitis-related hospital admissions has increasing from 61.8 per 100,000 in 1998 to 75.5 per 100,000 in 2005 (56). Another study reports a 41% increase in hospital admissions for diverticulitis without hemorrhage from 2000 to 2009, totaling 2.1 billion dollars in inpatient costs in 2009 (54). A study using data from the United States national emergency department (ED) sample records found that between 2006 and 2013, the rate of diverticulitis-related ED visits increased by 26.8% from 89.8 to 113.9 visits per 100,000 population (57). The aggregate national cost of diverticulitis-related ED visits increased by 105%, from approximately $822 million in 2006 to over $1.6 billion in 2013. Similar trends have been observed from Canadian and European data during the same time period (45, 53, 58).

While the prevalence and hospitalization rate of diverticulitis have increased, the overall rate of patients undergoing surgery has decreased. At the turn of the millennium, several scientific organizations agreed on the necessity of prophylactic interval sigmoidectomy for patients aged < 50 years, patients with complicated disease and patients who had experienced two or more episodes of uncomplicated diverticulitis (46, 59, 60). This was based on the rationale that diverticulitis has a high recurrence rate.

Classification

Acute diverticulitis (AD) can be classified as uncomplicated (absence of abscesses, perforations or fistulae) or complicated. For the past three decades, the Hinchey classification has been the most commonly used classification in the international literature (2). Based on surgical findings of abscesses and peritonitis, Hinchey classified the severity of AD into four grades as follows:
Stage 1  Periolic abscesses  
Stage 2  Pelvic, intra-abdominal or retroperitoneal abscesses  
Stage 3  Generalized purulent peritonitis  
Stage 4  Generalized faecal peritonitis  

Since the introduction and evolution of computed tomography (CT) scanning, the Hinchey classification has been modified on several occasions. The most recent classification system by the World Society of Emergency Surgery (WSES) proposes a system based on CT-guided classification of left colonic AD (61). It is a simple classification system that aims to guide clinicians in daily practice. It classifies AD into two groups: uncomplicated and complicated. In cases of acute uncomplicated diverticulitis (AUD), the phlegmon does not extend to the peritoneum. In cases of complicated diverticulitis (CD), the infectious process proceeds beyond the colon. CD is then classified into four stages as follows:

- **Uncomplicated**
  - Stage 0: diverticula, thickening of the colonic wall or increased density of the periolic fat
- **Complicated**
  - Stage 1a: periolic air bubbles or little periolic fluid without abscesses (within 5 cm from the inflamed bowel segment)
  - Stage 1b: abscesses ≤ 4 cm in diameter
  - Stage 2a: abscesses > 4 cm in diameter
  - Stage 2b: distant air (> 5 cm from the inflamed bowel segment)
  - Stage 3: diffuse fluid without distant free air (no hole in the colon)
  - Stage 4: diffuse fluid with distant free air (persistent hole in the colon)

**Symptoms/Diagnosis**

Clinical manifestations in patients with AD vary depending on the severity of the inflammatory process of the disease and the presence or absence of complications. The most common symptom is left lower quadrant pain, occurring in 70% of cases and lasting for more than 24 h in most. Other manifestations include nausea and vomiting, changes in bowel movements and urinary symptoms. Physical findings are left lower abdominal tenderness in
most cases, which might be associated with fever. Blood tests may reveal increased levels of inflammatory markers including CRP and WBC. Clinical diagnosis of diverticulitis was concluded to lack accuracy in a prospective analysis with a positive and negative predictive value of 0.65 and 0.98 respectively (62). A clinical decision rule for diagnosis of diverticulitis was developed in 2010 by Lameris et al. They used three criteria: direct tenderness in the left lower quadrant, CRP > 50 mg/L and absence of vomiting. In their study, 29 of 30 patients with all three features had a final diagnosis of AD. Of the patients who did not have all three features, 47% did not have diverticulitis (63).

Examinations that can diagnose diverticulitis are contrast enemas combined with ultrasonography, CT and magnetic resonance imaging (MRI). Contrast enemas can be used in the acute setting with water-soluble contrast instead of barium, in cases when perforation is present. Early reports favored diagnostic accuracy with barium enemas (64), but with improving CT technology it is now considered the gold standard because of its high sensitivity and specificity (65-67), and is recommended by most international guidelines (68). Ultrasound diagnosis is emerging as an alternative approach, sparing patients exposure to radiation. However the results are operator dependent (69). MRI is also a good diagnostic tool with similar specificity and sensitivity to CT with the benefit of no radiation exposure, but it is still expensive and not as readily available (70, 71).

**Treatment**

Antibiotics have been the unquestioned cornerstone of treatment for diverticulitis, consistently recommended by early guidelines, textbooks and expert reviews (72). Treatment also consisted of admission to hospital, antibiotics, fasting and slow introduction of a liquid diet. The emerging belief that diverticulitis is an inflammatory rather than an infectious condition, as well as the increasing concerns about the overuse of antibiotics, led to research where the first multicenter randomized trial, the AVOD study, concluded that the use of antibiotics in patients with AUD neither accelerated recovery nor prevented complications or recurrence when compared to no-antibiotic management (73). Another large multicenter randomized trial published similar results in 2017 (74). One must keep in mind that the diagnoses of AUD were based on radiology with CT and that immunocompromised patients, pregnant women or patients with sepsis were excluded in the above studies.

Most recently revised international guidelines now do not recommend antibiotics in all patients with AUD but recommend that a case-by-case approach should be adopted (68). In general, clinically stable and reliable patients with AUD can be treated without the need for antibiotics. Successful outpatient management of patients with AUD with antibiotics has also been
demonstrated. However, outpatient management without antibiotics in patients with AUD had not been evaluated until it was conducted as part of this thesis (75, 76). The traditional dietary approach, changing from fasting to a fluid diet, has also been challenged recently and a prospective study has concluded that an unrestricted diet is just as safe (77).

Complicated diverticulitis

CD is a different disease entity from AUD and its treatment should also differ. One prospective study with the aim of analyzing the intra-abdominal bacteriome in cases of this disease and its relation to the clinical outcome concluded that early source control is mandatory to reduce the mortality rate in such patients. In treating it, every verified source of infection should be controlled. “Effective empirical antimicrobial agent therapy is necessary to reduce resistance and improve the clinical outcome” (78).

Antibiotic resistance

Despite many proposals and initiatives in recent decades, the world has failed to keep pace with microbes becoming increasingly resistant to available antibiotics. Deaths from drug-resistant infections are projected to increase from the current 700,000 to 10 million annually and cost estimates are as high as 100 trillion US dollars worldwide by 2050 as reported by the review on antimicrobial resistance in London, UK. Resistance against the carbapenem class of antibiotics, widely regarded as the class of last resort for drug-resistant infections was tested in the UK. Until 2003, carbapenem-resistant strains were extremely rare in both the UK and Europe. Since then, there has been an exponential rise in the number of carbapenem-resistant infections in the UK. Most worrying of all, surveillance has recently identified half a dozen clinical isolates within the UK that are resistant to all tested antibiotics as follows:
Surgery for diverticulitis

The view of the efficacy of surgery has now changed, with recent guidelines suggesting against elective colonic resection in patients with an initial episode of AUD. They recommend surgeons to adopt an individualized approach, because only approximately 20% of patients with AUD experience recurrent episodes of diverticulitis in the following 5 years (80-82). The risk of further complications and need for emergency surgery is low at < 5%. Eighteen patients need treatment to avoid one emergency operation (83). One must also consider the potential need for colostomy, short term postoperative complications in approximately 10% of patients and long-term complications such as abdominal distension, cramping, altered defecation and
faecal incontinence reported in 25% of patients after elective surgery (81). A Canadian study reported a decline in the rate of elective colectomy of patients initially medically treated for AD. Within 1 year of discharge the rate decreased from 9.6% of patients in 2002 to 3.9% by 2011(84). Despite this, diverticulitis remains the leading indication for elective colectomy (54).

In about 15–25% of patients with AD there is an associated complication that require surgery (82). Until recently, a peri-diverticular abscess was the main indication for surgery, but following improvements in imaging and drainage techniques, it is now usually manageable by percutaneous drainage and intravenous antibiotics (85). Recent studies report a surgery rate of < 30% for perforated diverticulitis suggesting that most patients can be treated without surgery (86, 87). The main indication for surgery is perforated colonic diverticulitis, with an incidence of 3–4 per 100,000 persons per year, which can lead to uncontained purulent or faecal contamination (88, 89).

Emergency sigmoid colectomy with or without primary anastomoses might be required for patients with perforation and diffuse peritonitis, persistent sepsis and in those subjected to immunosuppression (82). There are different surgical strategies, both open and laparoscopic techniques and with or without diverting stomas. Resections for perforated diverticulitis have a high morbidity rate (30–50% complication rate) and a mortality rate of 10–20%. Laparoscopic lavage with no resection was proposed as a safer alternative in a systematic review (90). One recent systematic review compared the two methods and found lavage is a safe alternative but led to higher rates of postoperative abscess formation requiring more percutaneous drainage interventions without any difference in perioperative mortality and serious morbidity(91). Another systematic review demonstrated no significant difference between laparoscopic peritoneal lavage and traditional surgical resection in patients with peritonitis from perforated diverticular disease in terms of postoperative mortality and early reoperation rate. Laparoscopic lavage was associated with a lower rate of stoma formation but a significantly higher rate of postoperative intra-abdominal abscesses (92).

Follow-up after diverticulitis:

Colon investigation following AD to exclude a colon malignancy has consistently been recommended by most international guidelines. Two recent large cohort studies have shown that diverticular disease does not increase the risk of colon cancer after the first year of diagnosis (93, 94). Within the first year of diagnosis, the association is strong, most probably because of similar symptoms, difficulties with differential diagnosis and misclassifications. A cohort study from 2016 on 890 patients who were treated conservatively for AUD identified a standardized incidence ratio of 20 for sigmoid cancer within 1 year (95). It concluded that these patients were at high risk
for an underlying colorectal malignancy, which might be missed or misinterpreted on the initial imaging modality. A systematic review from 2012 concluded that there are limited data to support the recommendation to perform colonoscopy after diagnosis of AD, (96) whereas a systematic review of international guidelines from 2014 found that most guidelines recommend imaging following CT-diagnosed diverticulitis (68). This might have led to the conclusion that colon cancer has to be excluded using modern techniques after at least the first episode of suspected diverticulitis.
Rationale for this thesis

The overall aim of this thesis was to evaluate the clinical management of AUD with regard to a no-antibiotic treatment policy and it’s safety in the short- and long term, treatment on an outpatient basis and potential health-care cost savings.
Aims of this thesis

The specific aims were as follows:

Study I
To evaluate and confirm the adherence and safety of the no-antibiotic policy in patients with AUD at a county hospital and the consequences regarding complications and recurrence.

Study II
To assess the long-term effects of the no-antibiotic policy regarding recurrences, complications, surgery and quality of life.

Study III
To evaluate outpatient, non-antibiotic management in patients with AUD with regard to admissions, complications, and recurrences, within a 3-month follow-up period.

Study IV
To evaluate the impact on admissions, complication rates and health-care costs of the new policy of outpatient treatment without using antibiotics.
Methods

Study I

This was a retrospective study. A search was conducted on the hospital record system, which contains data on all ED visits, admitted and discharged patients at Västmanland’s Hospital, Västerås, Sweden. Patients were identified according to the International Classification of Diseases coding system (ICD-10) (K 57.0–9) and the specific Swedish surgical procedure codes.

The search criterion was patients diagnosed with all types of colonic diverticular disease from 1 January to 31 December 2011. The medical records of all the identified patients could be retrieved and were carefully reviewed by two researchers. A predefined protocol was used. AUD was defined as CT-verified signs of AD without complications.

Study II

This was a long-term follow-up of all Swedish patients who participated in the AVOD study. Icelandic patients were excluded as we were unable to obtain approval for follow-up from the Icelandic ethics committee. All 580 patients who participated in the AVOD trial in Sweden were identified and we were able to obtain 556 (96%) patient medical records, which were reviewed. Data extraction included any admission for recurrences of diverticulitis, surgery for diverticulitis, acute or planned, and the development of colorectal cancer. Recurrent diverticulitis was defined as clinical recurrence diagnosed at a hospital, CT verification was not a criterion.

A quality of life (QOL) questionnaire (EQ-5D) with a letter of consent was mailed to all patients. We tried calling all patients who responded to answer further questions. The patient was registered as a dropout from the questionnaire and QOL study if no answer was received after three reminders by letter. Once all data collection had been concluded, the data were linked to the database of the AVOD study. The groups were compared regarding antibiotic therapy and the above outcome measures.
Study III

The study design was a prospective, observational study and involved two Swedish hospitals. Patients presenting at the EDs in Mora and Västmanland’s hospitals with clinical signs of acute colonic diverticulitis (ACD) were screened for potential eligibility.

Inclusion criteria:
- Adults aged 18 years and over
- Acute lower abdominal pain with duration of less than 3 days
- Elevated CRP levels or WBC
- Signs of uncomplicated AD on CT scans
- Informed and written consent provided

Exclusion criteria:
- High fever affecting general conditions, peritonitis or septicemia
- Pain requiring intravenous or subcutaneous pain medication
- Immunologically compromised patients
- Ongoing antibiotic therapy
- Pregnancy, dementia or language barrier
- Patients unable to take care of themselves at home

Eligible patients underwent an abdominal CT scan to confirm diagnosis and were included after giving informed consent. Diverticulitis was classified radiologically as uncomplicated when there were no signs of perforation, abscess, fistula or colonic obstruction. Outpatient management was defined as patients being discharged within 24 h of presentation at the ED. All patients were given a day journal questionnaire to fill out. Prior to discharge, all patients received written information with recommendations on oral intake involving fluids for the first 48 hours, followed by a liquid diet before moving on to a solid diet when tolerated. To ensure safety, all patients were contacted daily by telephone by a nurse who assessed their general condition. Patients were monitored with blood tests at the surgical clinic after 1 week. At 3 months, they were again followed by a physician. The patients were offered a colonic investigation (CT colonography or colonoscopy) if this had not been performed during the previous year.

Study IV

This was a retrospective cohort study where medical records of all patients diagnosed with AUD in the year before (2011) and after (2014) the imple-
mentation of outpatient management without antibiotics in Västmanland County were reviewed. Hospital presentations, admissions, investigation finding and complications within 30 days was registered. The cost per patient (CPP) was calculated according to the Swedish CPP (KPP in Swedish) method used by the Swedish Association of Local Authorities and Regions (SALAR, Sveriges Kommuner och Landsting, www.skl.se). This system ensures that all costs, both fixed and variable, are included. For an approximation of costs, the cost for each patient contact (admitted or discharged from the ED) was obtained from our local patient registry. Once the total cost for each patient was obtained, the total costs for patients diagnosed in 2011 and 2014 were calculated. Costs were adjusted to match the price increase in 2014.
Statistical analysis

Data were analyzed using the IBM SPSS statistics package (IBM Corp., Armonk, NY, USA). Differences in proportions were calculated using the chi-squared test or Student’s t-test for independent samples. Unpaired numerical data were analyzed by the Mann–Whitney non-parametric $U$ test. Fisher’s exact test was used for low numbers. Analysis of variance (ANOVA) was used for contingent variables. Univariable and logistic regression analyses were performed to identify risk factors for recurrent and CD in Study IV. Significant values identified using the univariable regression model were entered into a multivariable regression analysis. A $p$ value of $< 0.05$ was considered statistically significant.
Ethical considerations

All four studies were approved by the Ethics Committee of the Faculty of Medicine, Uppsala University, and followed the Declaration of Helsinki guidelines.
Summary of the results

Study I
A total of 246 patients were identified, of which 195 had CT-verified AUD and 51 ACD. Of the 195 patients in the AUD group, 178 (91.3%) did not receive any antibiotic therapy and 17 (8.7%) were treated with at least one dose of antibiotics for various reasons. Most patients were admitted to the hospital. A total of 13 patients were managed without antibiotics as outpatients once diagnosis had been made in ED. There were no significant differences regarding age, body temperature, or CRP levels between the patients with and without antibiotic treatment but the WBC count was significantly higher in the antibiotic group. The mean hospital stay for treating AUD was 1.9 days for patients in the no-antibiotic group versus 5.4 days for patients in the antibiotic group ($p < 0.001$). A total of six (3.4%) patients in the no-antibiotic group were re-admitted. In only two of these was the admission because of an abscess, which was treated with antibiotics. The other four admissions were because of persistent pain and were treated successfully with analgesics. One patient in the antibiotic treatment group returned within 1 week with an abscess and was treated with further antibiotics.

Study II
In all, 623 patients with CT-verified left-sided uncomplicated diverticulitis were randomized to management without or with antibiotics. The medical records of 556 of 580 patients (96%) were retrieved and reviewed. The median follow-up was 11 years for both groups ($p = 0.492$). There were no significant differences regarding recurrence (86 vs 88; $P = 0.986$), complications (12 vs 14; $P = 0.737$) or surgery for diverticulitis (17 vs 20; $P = 0.719$) in the non-antibiotic group compared with the antibiotic group. There were no differences in the quality of life between groups according to the EQ-5D questionnaire.
Study III
A total of 155 patients were included in the study and managed as outpatients without antibiotics: 101 women and 54 men. In 4 patients (2.6 %), there was management failure; all were treated successfully with antibiotics and without surgery. Three of these patients had CD at the time of treatment failure, although a small pericolic abscess was overlooked in one of these patients on the initial CT report. All the other 151 patients (97.4%) were successfully managed without any complications or hospital admissions. On day 3, patients reported a mean pain score of 1.8 of 10 and only 30% of them used analgesics. After 1 week, the WBC count and CRP had normalized in most (84%) of the patients. Recurrences were diagnosed in five patients and they were treated as outpatients without antibiotics. At follow-up with colonic investigation, two patients had cancers and 13 had polyps.

Study IV
In total, 494 episodes of AUD were identified: 254 in 2011 and 240 in 2014. The proportion of patients managed as outpatients was 20% in 2011 compared with 60% in 2014 ($p < 0.001$). There were 203 hospital admissions and a total length of stay of 677 days in 2011 compared with 95 admissions and 344 days in 2014 (both $p < 0.001$). The total health-care cost was €558,679 in 2011 compared with €370,370 in 2014 ($p < 0.001$). Three patients developed complications in 2011 and four in 2014 ($p = 0.469$).
**Table 3:** Cost analysis of acute uncomplicated diverticulitis (AUD) treated in 2011 and 2014

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2014</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of diagnosed episodes of AUD</td>
<td>254</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Admitted</td>
<td>80%</td>
<td>39%</td>
<td>−41%</td>
</tr>
<tr>
<td>Total hospital LOS (days)</td>
<td>677</td>
<td>334</td>
<td>−51%</td>
</tr>
<tr>
<td>Total cost of inpatient treatment</td>
<td>536 675</td>
<td>282 297</td>
<td>−48%</td>
</tr>
<tr>
<td>Total cost of patients presenting to the ED and managed as outpatients</td>
<td>22 004</td>
<td>88 080</td>
<td>+75%</td>
</tr>
<tr>
<td>Average cost per inpatient</td>
<td>2 643</td>
<td>3 442</td>
<td>+23%</td>
</tr>
<tr>
<td>Average cost per patient presenting to the ED and managed as an outpatient</td>
<td>431</td>
<td>603</td>
<td>+29%</td>
</tr>
<tr>
<td>Total cost of inpatients and outpatients</td>
<td>558 679</td>
<td>370 370</td>
<td>−44%</td>
</tr>
</tbody>
</table>

All costs are in euros (€).

ED – emergency department; LOS – hospital length of stay
Discussion

Study I demonstrated that the no-antibiotic policy for treating patients with AUD is safe, with low complication and recurrence rates in a population-based cohort study. Of all patients with AUD, only 8.7% received antibiotics. Only 2/178 patients (1.1%) with AUD managed without antibiotics were re-admitted because of development of an abscess.

Study II demonstrated no long-term (> 10 years) differences in outcomes regarding recurrences, complications, surgery rates or QOL measures between the two groups managed with or without antibiotics, suggesting that antibiotics have no beneficial effect and could be omitted in the management of AUD.

Study III was, to our knowledge, the first prospective study that evaluated outpatient treatment of AUD without antibiotic therapy. This study not only strengthened previous findings that the no-antibiotic policy in such cases is safe and applicable in clinical practice, but also added evidence that it is safe to discharge patients directly from the ED. Given that antibiotic resistance has become a major health problem worldwide, and antibiotic use is being increasingly recognized as the main selective pressure driving this resistance, this further strengthens the idea that the routine use of antibiotics in treating AUD should be avoided. A recent meta-analysis found that outpatient management of AUD resulted in low readmission and very low complication rates and reduced the medical costs substantially (average health-care cost savings for outpatient vs inpatient treatment ranged between 42% and 82%(97).

Study IV evaluated health-care cost savings in outpatient management without using antibiotics in cases of AUD. It found a dramatic change in the management of patients with AUD from inpatient treatment without antibiotics to outpatient treatment without antibiotics. The study found an almost 50% reduction in total hospital length of stay and total health-care cost savings without worsening patient outcomes or complication rates. The results also strengthen the findings of previous work on the safety of the policy of treating patients with AUD as outpatients and without the use of antibiotics. Outpatient antibiotic treatment has previously been suggested as a safe approach in up to 93–97% of patients (98-100).

All these studies indicate that patients with uncomplicated diverticulitis have a very low risk of developing severe complications and that antibiotics have no value in preventing or reducing the rates of these complications. The
above findings question the traditional treatment of AUD by hospital admission and antibiotics.

Given these results it should also be safe to manage patients with AUD without antibiotics as outpatients. This new policy has the potential to reduce unnecessary admissions significantly and allow important cost savings for health-care systems. It should also lead to reducing the unnecessary prescription of antibiotics, which is a contributing factor to worldwide resistance.

Limitations and strengths of the studies

Limitations with these studies include the inherent limitations of a retrospective design in studies I and IV. Patients might have developed diverticulitis, complications or cancers treated elsewhere than in their main hospital and could therefore be missing from our data.

Study III was a prospective trial that could be argued should have been randomized. Given the results from our previous two studies that demonstrated no value in using antibiotics in AUD, we decided that treating these patients with AUD for the purpose of a study would not benefit our patients. It would also be a step backwards in the treatment of AUD. Another limitation was that not all patients who were eligible for the study were included, suggesting that there could have been selection bias.

In Study IV, not all patients underwent CT scans to confirm their diagnosis. This reflects routine health-care practice but is a limitation of this study since some patients may have been misdiagnosed. However, there were no differences between the rates of CT scanning in 2011 and 2014 suggesting an equal distribution of potential misdiagnosed patients in the 2 study groups. Another limitation is that no cost analysis was carried out for the patients who might have presented to their general practitioner. Therefore, the total cost for outpatient management might be higher for the community but there should in theory be no difference between the two study groups. The CPP was used to calculate health costs, which makes it difficult to compare with another county or country. However, the same method was used for patients in 2011 and 2014, giving a good model for evaluating any changes in the costs, which was the aim of the study.

Because there were inclusion and exclusion criteria used in the studies, the results can only be applied to patients who fulfil these criteria. It is important to note that diverticulitis affects a heterogenous groups of patients, some of whom present contraindications for outpatient treatment without antibiotics according to their symptoms, general condition and associated medical diseases.

The strengths of the studies were the prospective randomized multicenter design of study III. The follow-up for Study II was long, with a median of
more than 11 years with data collection performed in a standardized way. Furthermore only 4% of patients were missed to follow-up. In Sweden, only one county hospital is usually available for patients according to where they live. We might have missed a few patients in our retrospective reviews, but this should not have affected our results given the even results spread between groups and assuming a similar proportion of patients between groups might have been missed. Our aim was to further minimize the number of patients who might have been treated for diverticulitis elsewhere as their treatment might not be reflected in their medical records. All patients who responded the QOL questionnaire received a phone call and were asked if they had experienced any complications or surgery. We were successful in 55% of the patients.

For Study III, an analysis of the 66 patients who were potentially eligible for the study but failed to be recruited was performed. All the patients’ medical records were reviewed. There were no statistical differences in age, gender distribution, CRP and WBC levels or outcomes between the potentially eligible patients and those included in the study, suggesting there was no bias. The main reason for this non-inclusion was most likely the high number of clinicians per hospital treating these patients.

The strength of the CPP model used in Study IV is that the costs were calculated for each patient episode, and therefore accurately reflect the real costs. Other methods such as diagnosis-related groups tend to group patients and calculate cumulative costs rather than individual costs and are therefore—according to staff members or hospital finance departments—inferior tools for calculating the total costs of different treatments of a specific disease.
Conclusions

It is safe to manage patients with AUD without antibiotics both in the short and long term without affecting the rate of recurrence, complications, surgery or quality of life. Furthermore, the outpatient, non-antibiotic policy did not affect patient recurrence rate, with a complication rate of < 3%. Since the studies were conducted on a selected group of patients, the results can only be applied to patients fulfilling these inclusion criteria. Adopting a new policy with a change to a more outpatient-based, non-antibiotic management of these patients will significantly reduce the number of patients with AUD who are admitted to hospital and lead to significant health-care cost savings without compromising patient safety.
Sammanfattning på svenska

Divertiklar i tjocktarmen, också kallade tarmfickor, är små utbuktningar som utgår från tarmen, vanligast i sigmoideum. Divertikulit definieras som inflammation i tjocktarmen, utgången från en eller flera divertiklar.


Tillståndet delas in i okomplicerad och komplicerad divertikulit. Akut okomplicerad divertikulit (AOD) har alltid behandlats med antibiotika sedan dess introduktion inom medicin. Behandling av AOD med antibiotika har varit fastslagen i medicinska riktlinjer trots total avsaknad av kontrollerade studier. Oftast har man behandlat patienter med inläggning på sjukhus, fasta och intravenös antibiotika.

2012 publicerades den första randomiserade studien som utvärderade behovet av antibiotikabehandling vid AOD (AVOD studien). Studien visade inga fördelar med antibiotika som varken kunde påskynda tillfrisknandet eller förhindra komplikationer.

Målsättningen med detta avhandlingsarbete är att med utgångspunkt från kliniska studier belysa följande:

I. Utvärdera om icke-antibiotika behandling av AOD kan tillämpas med liknande resultat i klinisk praxis.

II. Utvärdera långtidsresultat för samtliga patienter som medverkade i AVOD studien med avsände på recidiv, kirurgi, kolorektal cancer samt livskvalite.

III. Utvärdera om patienter med DT verifierad okomplicerad divertikulit kan behandlas polikliniskt, dvs i hemmet, utan antibiotika
IV. Utvärdera den nya polikliniska icke-antibiotika policyns påverkan på komplikationsfrekvens, antal vårdtillfällen, inläggningar och hälsokonomiska effekter i Västmanland.

Delstudie I i denna avhandling var en retrospektiv studie som utvärderade hur uvida icke antibiotika behandling vid AUD var tillämpad i klinisk praxis år 2011 på Västmanland sjukhus och hur det gått för dessa patienter i mån om tillfrisknade, komplikationer, kirurgi och recidiv.

Resultaten visade att den nya handläggningen var väl tillämpbar och säker. Drygt 91% av patienterna behandlades utan antibiotika. Endast 2 patienter fick komplikationer i form av abscess som behandlades framgångsrikt med antibiotika.


Delstudie III var en prospektiv studie som utvärderade poliklinisk behandling utan antibiotika av AOD och var den första studien av sitt slag. 155 patienter inkluderades i studien. Efter 1 vecka hade LPK samt CRP normaliserats hos 84% av patienterna. Dag 3 rapporterade patienterna en smärtnivå i snitt enligt VAS på 1.8 av 10 och endast 30% av patienterna använde analgetika. Fyra patienter (2.6%) fick komplikationer. Alla behandlades med antibiotika och ingen behövde opereras.


Samtliga studier styrker att AOD kan behandlas utan antibiotika och att komplikationsfrekvensen är låg både kort- och långsiktigt. Studie III samt IV styrker att dessa patienter kan också behandlas polikliniskt med bevarad medicinsk säkerhet. Tillämpas denna strategi så leder den till stora kostnadsbesparingar inom sjukvården samt minskar onödig användning av antibiotika.
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