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New Treatment Aspects of Acute Diverticulitis

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DOCTORAL DISSERTATION

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Abstract

Background: Acute diverticulitis is a common disease in the Western world and causes considerable morbidity and mortality. It can be divided into acute uncomplicated and complicated diverticulitits (AUD and ACD) depending on whether the inflammation extends the colon wall or not. Treatment for AUD used to be antibiotics and bowel rest and resection surgery for perforated ACD. Follow-up was conducted with a colon examiniation 6-8 weeks after discharge to rule out colorectal cancer (CRC). Recently studies have questioned these practices and this thesis aimed to evaluate changes in clinical management/treament of acute diverticulitis.

Method: Paper I-III were retrospective cohort studies, where in the first two, mangement of AUD was assesed at two different hospitals and the main outcome was proportion of patients managed without antibiotics. Paper III looked at the risk of colorectal cancer being misdiagnosed as acute diverticultiis, by calcualting a standard morbidity ratio (SMR) evaluating if colon examination after diverticulitis is necessary. Paper IV was a long-term follow-up (5 years) of the Scandinavian Diverticulitis (SCANDIV)-study, a RCT comparing laparoscopic lavage to resection surgery for perforated purulent diverticulitis.

Results: The use of a protocol limiting antibiotic use for AUD patients at one of the hospitals resulted in that 60% were managed without antibiotics, but after two years, the proportion lowered to 48% . At the hospital without a protocol, 11% were managed without antibiotics. SMR was higher both after AUD and ACD**, (**6.23 and 16.34) overall respectively compared to the CRC rate in the population. The median follow-up was 59 months in paper IV and three patients were lost to follow-up, leaving 73 patients in the laproscopic lavage and 69 patients in the resection group respectively. There were no statistically significant differences in severe complications or overall mortality. Secondary operations, including stoma reversal, were similar in the two groups. Among patients who were alive, the stoma prevalence was higher in the resection group (8% vs. 33%) p=.002.

Conclusions: Adherence to treatment protocol and best clinical practice was lower than expected, and reasons need to be further investigated. Colon examination post acute diverticulitis should still be recommended. Laparoscopic lavage has similar long-term outcomes as resection surgery, more early re-interventions but fewer stomas at both short-and long-term. Shared decision-making should be encouraged.

Key words: acute diverticulitis, antibiotics, compliance, follow-up colonoscopy, laparoscopic lavage, management

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MADE IN SWEDEN

To strong women,

may we know them,

may we be them,

may we raise them

and to my parents who did

"Real knowledge is to know the extent of one's ignorance"

-Confucius

Table of Contents

Original papers

This thesis is based on the following original papers, referred to in text as their Roman numerals (I-IV):

I. Azhar N, Kulstad H, Pålsson B, Schultz JK, Lydrup ML, Buchwald P. Acute uncomplicated diverticulitis managed without antibiotics - difficult to introduce a new treatment protocol but few complications. Scand J Gastroenterol. 2019: 54: 64-68.

II. Azhar N, Aref H, Brorsson A, Lydrup ML, Jörgren F, Schultz JK, Buchwald P. Management of acute uncomplicated diverticulitis without antibiotics: compliance and outcomes -a retrospective cohort study. Submitted for publication

III. Azhar N, Buchwald P, Ansari HZ, Schyman T, Yaqub S, Oresland T, Schultz JK. Risk of colorectal cancer following CT-verified acute diverticulitis: a nationwide population-based cohort study. Colorectal Dis. 2020; 22:1406-14.

IV. Azhar N, Johanssen A, Sundström T, Folkesson J, Wallon C, Kørner H, et al. Laparoscopic Lavage vs Primary Resection for Acute Perforated Diverticulitis: Long-term Outcomes from the Scandinavian Diverticulitis (SCANDIV) Randomized Clinical Trial. JAMA Surg. 2021; 156:121-127.

Abbreviations

ACD	Acute Complicated Diverticulitis
AUD	Acute Uncomplicated Diverticulitis
BMI	Body Mass Index
CRC	Colorectal Cancer
CRF	Case Report Form
CRP	C-reactive protein
CT	Computed Tomography
ICD-10	International classification of diseases (10th version)
IQR	Interquartile range
GP	General Practitioner
HH	Helsingborg Hospital
QoL	Quality of Life
RCT	Randomised Clinical Trial
SMR	Standard Morbidity Ratio
SCANDIV	Scandinavian Diverticulitis Trial
SUS	Skåne University Hospital
WBC	White Blood Cells

Thesis at a glance

Paper	Aim	Study design	Outcomes	Conclusion
I	To analyse the adherence to a new treatment protocol for AUD limiting the use of antibiotics.	Retrospective, single centre register-based cohort study	Proportion of patients with antibiotic-free management	Protocol adherence was lower than expected (60%) indicating that implementation of new management is challenging. Complications were rare.
II	To investigate whether a treatment protocol facilitates the implementation of new knowledge in clinical practice.	Retrospective, register-based cohort study	Proportion of patients with antibiotic-free management	A treatment protocol led to reduced antibiotic use and a higher standard of care. Adherence to treatment protocol and best clinical practice was poor.
III	To compare the incidence of colorectal cancer in patients with acute diverticulitis with the incidence in the general population to assess the need for follow-up colon examination after acute diverticulitis..	Retrospective, register-based national cohort study	Standard Morbidity Ratio	CRC diagnosis is more frequent in the first year after an episode of CT-verified acute diverticulitis. Highest risk was observed in ACD patients, but the increased risk in AUD patients cannot be neglected. Colon examination should still be advised.
IV	To analyse the long-term results of the (SCANDIV) trial, comparing laparoscopic lavage vs colon resection in patients with acute perforated purulent diverticulitis in terms of severe complications and QoL.	Multicentre, randomised clinical trial	Severe complications (Clavien Dindo>IIIa) and functional outcomes+QoL	No differences in severe complications or functional outcomes. Higher recurrence rate but lower stoma prevalence in the laparoscopic lavage group. Shared decision-making considering both short-term and long-term consequences is encouraged.

Introduction

History

The term "divertikel" was first used by Fleischman in 1815. Subsequently diverticula in the colon were mentioned in some anatomical books but were considered a medical and surgical curiosity until the late 1800s(1). As late as around 100 years ago, diverticular disease was not mentioned in medical textbooks but after this, diverticulitis started being recognised as a clinical problem. In 1859 the first colovesical fistula from diverticulitis was described. One of the first articles in medicine, referencing diverticulitis was published in 1916 and included a definition, aetiology, pathological and clinical aspects including treatment and several illustrations of the disease(2). The first review article on diverticular disease saw the light. That diverticula in the colon was an acquired condition mainly located in the sigmoid colon, and that the number of diverticula could vary from one to hundreds was described as well as what might cause their “mischief”. Treatment was stated with one word -surgery. Early on, the association with increasing age was established(2, 3). The theories on aetiology and pathophysiology have not changed much since, but treatment certainly has, especially with the emergence of antibiotics. In the 1970’s there was surge in medical attention given to diverticular disease and several attempts to describe the cause and natural course were made and are still often referenced(1, 4, 5).

Terminology

Diverticulosis of the colon is defined as the existence of false diverticula –outpouchings of mucosa and submucosa through openings in the muscular layer of the bowel wall at weak points where blood vessels, the vasa recta, enter. The diameter is usually between 3-10 mm, and they can be found at any location in the gastrointestinal tract(6). In Western populations they are usually located in the sigmoid colon (6). Diverticulosis is common in the majority of individuals in Western countries with increasing age(6, 7). There is a difference between diverticulosis (presence of diverticula) and diverticular disease, which is the symptoms caused by diverticula which usually arises from inflammation of diverticula, but also bleeding and the complications of both. Most people with diverticulosis will remain asymptomatic(8). There are several different classifications for acute diverticulitis (uncomplicated; AUD, complicated; ACD). AUD is when the inflammations in contained in the mucosal wall or in close proximity there of i.e. a peri-diverticular inflammation and in ACD the inflammation exceeds beyond the mucosal wall, most commonly causing perforation with either free air or abscess formation. To classify ACD the Hinchey classification(9), was developed in 1978 intending to serve as an intra-operative stratification of perforated diverticulitis with abscess or peritonitis, enabling surgeons to adjust their surgical approach (Table 1). Lately the use has extended to radiological classification, but the transition has not been completely seamless(10).

Table.1 Hinchey classifcation(9)

Hinchey grade	Description
I	Pericolic abscess
II	Pelvic, intraabdominal, or retroperitoneal abscess
III	Generalised purulent peritonitis
IV	Generalised fecal peritonitis

Chronic diverticulitis is an entity within the diverticular disease spectrum and some include “Segmental colitis associated diverticulitis” (SCAD) there. SCAD is an incompletely understood disease which resembles inflammatory bowel disease and is characterised by macroscopic mucosal inflammation in segments of the colon that are affected by diverticulosis(11). Symptomatic Uncomplicated Diverticular Disease (SUDD) is often defined as gastrointestinal symptoms (usually abdominal pain or change in bowel habits) in the setting of diverticulosis without evidence of inflammation or diverticulitis(11-13). There is no real consensus over which classification to use, when describing diverticular disease.

The recently published “Guidelines on diverticular disease of the colon” from the European Society of Coloproctology has proposed this figure (Figure 1) for the terminology of diverticular disease including a proposed pathway for development. They all arise from diverticulosis but are not all a progression of each other.

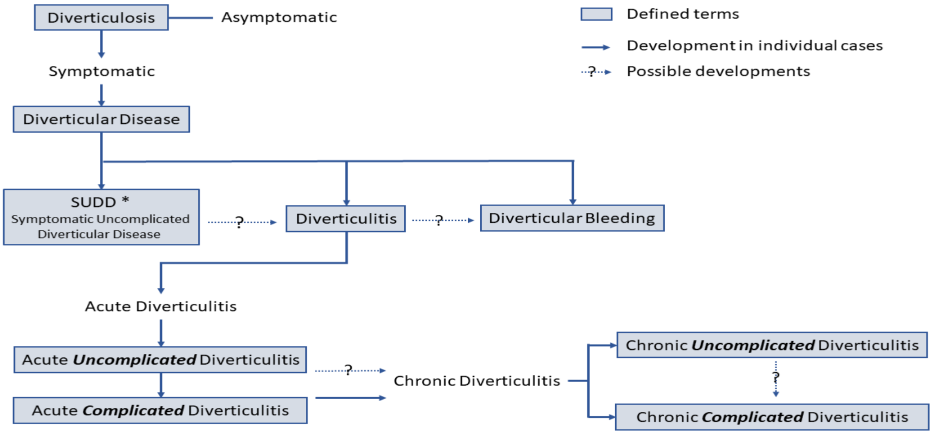

Figure 1. Flowchart showing terminology for diverticular disease and proposed pathways. *SUDD is controversial, it is unclear if it is a disease of its own or whether it represents the coexistence of irritable bowel syndrome and diverticulosis. Reprinted with permission from Wiley.

Pathophysiology

Reasons for diverticular development are unclear and multifactorial. They can be divided into changes in the colon *structure, motility, microbiome and inflammation*. Several different theories have been discussed as to what causes these changes such as dietary fibre deficiency, genetics and microinflammation in the bowel, result of translocation of intestinal bacteria through the mucosa of the diverticulum on the basis of a weak barrier etc. The scientific support for most theories is low. It was believed that localised high-pressure zones in the colon lead to formation of diverticula at weak spots in the colonic musculature. This has been proposed as the reason to why diverticula are predominantly found in the sigmoid colon, and hardly any in the rectum which is a distensible organ. Elastin deposition has been observed to be amplified by more than 200% in the taenia muscle cells in colons with diverticula compared to those without in electron microscopy(14). Diverticulosis develops earlier in individuals with connective tissue disorders indicating that this plays a role in the diverticula formation(15). Ganglionic and neuronal cells can be reduced, and imbalances in neurotrophic factors and neuropeptides, have been found in patients with diverticular disease and these alternations might cause symptoms in patients with diverticulosis(16-18). Low fibre intake was for long thought to play an important role in diverticula formation. The theory was that low fibre intake reduces stool volume, and makes the consistency firmer, prolonging transit-time and thereby increasing intraluminal pressure aiding in herniation of mucosa(6, 19). In the 1960's, studies concluded that intraluminal pressure in diverticulosis patients was higher than in non-diverticulosis individuals(6, 20, 21). Dietary fibre intake also causes bacterial production of short chain fatty acids which can increase microbial diversity in the colon, enhancing mucosal barrier and immune function(22, 23).

Risk factors can be divided into modifiable (diet, smoking, medication, obesity, exercise) and unmodifiable such as genetics, sex and age. Recently, models for chronic inflammation and alterations in the gut microbiome have gained more attention. General risk factors for chronic inflammation in other diseases (such as arteriosclerosis) are also correlated to inflammation of diverticula. These include obesity, Western diet and smoking(24-26). Factors associated with intestinal inflammation such as increased expression of matrix metalloproteases and histamine, have been associated with diverticulitis(27, 28). Gut bacteria have been studied and established to differ between patients with diverticulitis and healthy samples(29). This difference has also been noted in inflammatory bowel disease patients, but it is difficult to draw any certain conclusion about causality from this. It is known that low-fibre diet, obesity and physical inactivity can alter the gut microbiota(30).

Genetic factors are considered to play a role and twin studies from Sweden concluded that the odds of developing diverticular disease was significantly higher among monozygotic twins than dizygotic twins and higher in siblings than the general population(31). Statistical modelling estimated that genetic factors accounted for 40%– 50% of risk for diverticular disease but a limitation was that the study couldn't distinguish between diverticulosis or diverticular disease.

The transformation of diverticulosis to diverticulitis is not completely elucidated. One theory is that an obstructing fecalith (often caused by longer transit-time or faster stool) can cause low-grade inflammation, bacterial overgrowth and then a mucosal breach with or without transmural reach, leading to perforation(12) (Figure 2).

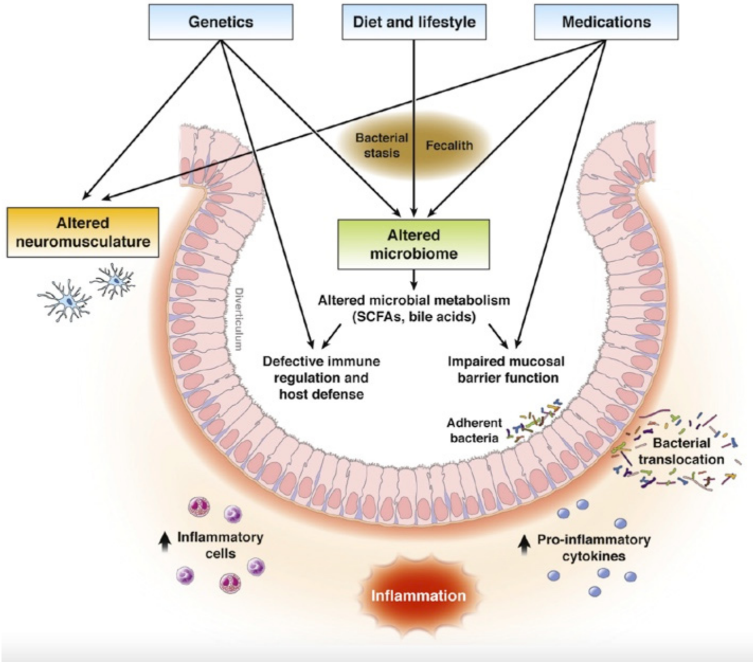

Figure 2. Proposed pathophysiology of acute colon diverticulitis.
Diverticulitis is hypothesized to arise from the complex interaction of diet and lifestyle factors, medications, genetics, and the gut microbiome. Alterations in the gut microbiome composition (eg, Y-short chain fatty acid, SCFA, producers, (invasive pathogens) and function (Y-SCFAs, altered bile acids) result in defects in the mucosal barrier and immune function leading to an inflammatory cascade and mucosal inflammation.
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Epidemiology

Lifetime risk of diverticulitis is unknown, since it has been difficult to distinguish diverticulosis from diverticulitis on radiological findings and autopsy studies. It is estimated that only 1-4% of people with known diverticulosis will develop diverticulitis(8). Most estimates are based on hospitalisations. A large Swedish population study showed that the incidence for first time hospitalisation (per 100 000 person-years) between 1987-2010 was around 8, and increased with age, to 27 in ages above 70. It was also more common in women than men after the age of 45, in younger age groups the rates were similar between the sexes(32, 33). This study did not show increasing incidence over time. A large study from the United States however, found an increase specifically noted in younger age groups, the incidence there was 188 per 100 000 person-years(34)

The morbidity from diverticular disease accounts for a large and increasing health-care burden and it is estimated the diverticulitis related morbidity accounted for between $1.6 -2.6 billion annually 2009- 2013 only in hospital costs in the United States(35, 36). Though it is often claimed that diverticulitis has a rising incidence, this is based on increasing incidence in hospitalisation and associated costs. In Sweden for instance the incidence is stationary in the overall population (32), but most studies agree that the incidence is rising in younger age groups, especially in males(34, 36).

Early on the geographical differences in incidence were established, where Painter introduced the theory of diverticular disease being a fibre deficiency disease affecting the West(1). Several studies have thereafter concluded that the incidence in the Western world for left sided diverticulosis is much higher than in Asia or Africa(37, 38). Diverticulosis location often differs, where Asians have their diverticula in the right colon and instead of pseudo-diverticula, their diverticula includes the whole bowel wall and believed to be congenital(38, 39). Migration and adaptation to a Western lifestyle affects incidence. A Swedish study found that despite lower incidence of diverticulosis in non-Western ethnicities, the rates quickly increase after immigration, indicating that diverticular disease is an acquired disorder and life-style changes impacts the risk for development(40).

Diagnosis

Diagnosis of acute diverticulitis was made previously, by a clinical examination and with the aid of blood tests showing an inflammatory response. Pain in the left lower quadrant, with fever, nausea and elevated white blood cells (WBC) and C-reactive protein (CRP) were sufficient for a diagnosis until recently. Radiological examination was only conducted on the suspicion of ACD, usually perforation. However, studies have shown that the clinical accuracy of diagnosis varies between 43-68%(41, 42) and therefore most current guidelines support the use of radiological imaging, preferably with computer tomography (CT) to verify the diagnosis and to assess complications(43, 44). Other radiological modalities that can be used include MRI or ultra-sonography, but MRI might not be readily available and ultrasound is user- and patient dependent. Therefore, it is recommended that they be reserved for situations where CT might be contraindicated (e.g. pregnancy or contrast allergy)(44). CT with its widespread availability and use is by far the most used imaging modality in the Scandinavian countries.

Treatment/Management

Treatment and management of acute diverticulitis can be divided into the treatment of the acute episode and the prophylactic measures, aiming to reduce the risk for recurrence. The treatment of the acute episode depends on its severity, but the management afterwards is usually the same. Prophylactic management can be divided into medical or surgical treatments both aimed to reduce recurrent episodes. The cornerstone in acute diverticulitis is antibiotic treatment. Antibiotics is used since the inflammation was believed to be bacterial(6).

Acute Uncomplicated Diverticulitis

AUD has historically been treated with antibiotics, analgesia and bowel rest. Evidence for this treatment is scarce and lately, randomised control trials (RCT)s have concluded that the use of antibiotics for AUD makes no difference in recovery, complications or recurrence(45-47). This has been supported by a Cochrane review and several systematic reviews and meta-analyses(48-51). Antibiotic-free management is also cost effective(52). Until recently, antibiotics were recommended in most national guidelines in the treatment of acute diverticulitis(53-55). Regardless of the use of antibiotics, complication rates after AUD are around 4%(46, 56). This has led to changes in recent diverticulitis management guidelines, where routine use of antibiotics in AUD is discouraged and the use is suggested to be reserved for patients with immunodeficiency or sepsis(43, 44). With the increasing awareness of antibiotic resistance and other adverse effects (allergic reactions, Clostridium difficile infections) there is a global movement towards reducing antibiotic use(57). One reason for antibiotics prescription has also been the outpatient management, which might have seemed safer with antibiotics. Bowel-rest and intravenous fluids have been administrated frequently but the evidence for dietary recommendations is limited. There is one prospective study including 86 patients concluding that an unrestricted diet is well-tolerated, although 8% had serious adverse events and 20% had ongoing symptoms(58). There are three recent systematic reviews studying out-patient management, where readmission rates are similar compared to hospitalised treatment(59-61). Recent practice is that outpatient treatment without antibiotics is safe for patients with a CT-verified AUD if oral intake is tolerated(43).

Other medical agents such as mesalamine (anti-inflammatory agent), rifaximin (non-absorbable antibiotic agent) and probiotics have been studied with the hope both to achieve a faster recovery after AUD and to reduce the risk for recurrence. Mesalamine has showed to reduce symptoms in Symptomatic Uncomplicated Diverticular disease (SUDD) according to one systematic review(62) and another meta-analysis including 13 trials showed similar results but no effect on disease remission or recurrence(63). One prospective study demonstrated Mesalamine more effective in reducing recurrence compared to Rifaximin(64). Rifaximin has mostly been studied with high fibre diets and has in some studies displayed some promising results in symptom reduction(65, 66). Probiotics have been studied lately in many different aspects of bowel health and the results on diverticulitis are unclear since probiotics are given in addition to other medication(67). Most studies on all these agents are very heterogenous and none have proven very effective and current guidelines don't recommend their use(43, 44, 68)

Acute Complicated Diverticulitis

ACD is defined as diverticular inflammation with free perforation, abscess, fistula, obstruction or stricture(44). The most common complication is perforation. The incidence rate is believed to be 1.85 per 100 000 population per year(69, 70) but in a study from the UK the age-adjusted incidence was 3.5 per 100 000(71). Acute perforation with free air and sepsis is a very serious condition with a mortality rate between 10-25% in some studies(71, 72). Perforated diverticulitis is often classified using the Hinchey classification(9) (Table 1). The different stages are visualised in Figure 3. Free perforations would be classified as Hinchey III or IV. Treatment of ACD always includes antibiotics irrespective of Hinchey grade.

Other complications from ACD are abscess formation, probably caused by micro-perforations in the colon wall during an episode of acute diverticulitis which leads to a cavity, forming a peri- or paracolic abscess. This is classified as Hinchey I or II(9). The treatment has been antibiotics +/- percutaneous drainage or surgery, usually with resection. The evidence is varying as there are no randomised trials and the available studies are observational studies that are sometimes heavily biased, as more invasive procedures usually are undertaken in patients with larger abscesses or worse clinical status(73, 74). A meta-analysis concludes that abscesses smaller than three cm, can usually be treated with antibiotics only, whereas larger ones might need drainage(75). A multicentre study showed that abscess size of five cm or more was an independent risk factor for the need of emergency surgery(76)

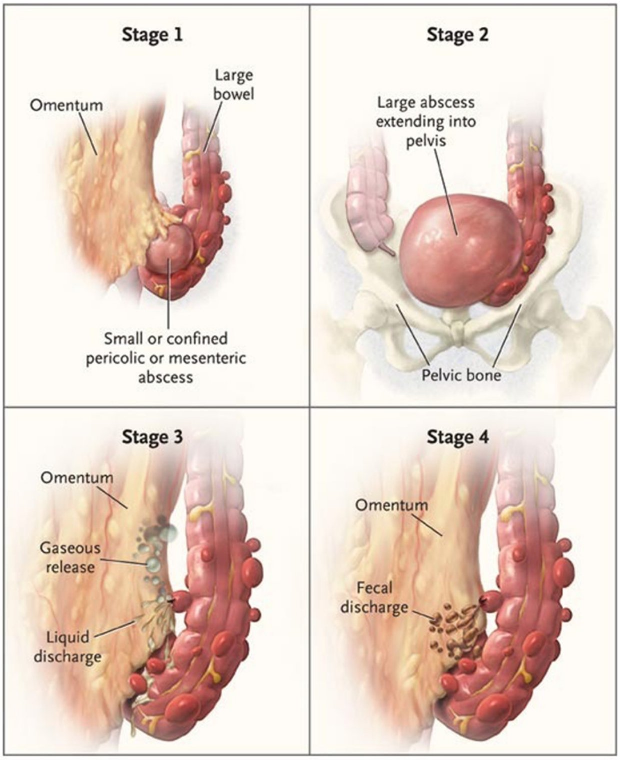

Figure 3. Hinchey stage I-IV visualised. Reproduced with permission from Jacobs DO. Diverticulitis N Engl J Med 2007;357:2057-2066, © Massachusetts Medical Society.

Treatment has traditionally been surgery in addition to antibiotics for Hinchey stages >II, usually colon resection of the perforated bowel and often with stoma creation i.e., Hartmann's procedure (Figure 4).

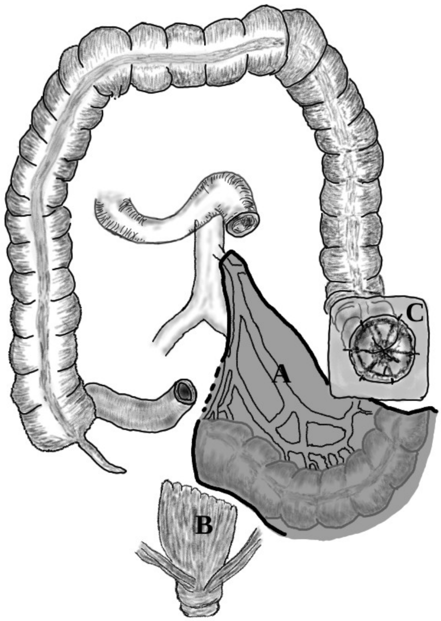

Figure 4. Illustration of Hartmann's procedure ©CC
A= showing resected area=sigmoid colon
B= Rectal stump which is closed
C= Stoma formation

This practice has been based on empirical knowledge. In the 90's case series started emerging showing that less aggressive approaches may be taken, such as laparoscopic lavage, in case of purulent peritonitis, reserving resection for the fecal peritonitis cases. Myers showed very good results(77), and thereafter three European RCTs have been conducted to examine this technique (our study, the Swedish/Norwegian "SCANdinavian DIVerticulitis trial"; SCANDIV, the "DIverticulitis—LAparoscopic LAvage vs resection (Hartman procedure) for acute diverticulitis with peritonitis"; DILALA and the"LaparOscopic LAvage"; LOLA arm of the "Laparoscopic peritoneal lavage or resection for purulent peritonitis and Hartmann's procedure or resection with primary anastomosis for purulent or faecal peritonitis in perforated diverticulitis"; LADIES trial (78-80). None of these trials have been able to reproduce the initial good results, and the only clear conclusions have been that there are more reinterventions in the laparoscopic lavage group in the short-term follow-up, similar mortality rate, and that the stoma prevalence is lower in the laparoscopic lavage group. Hence, the latest European guidelines deem it feasible to use laparoscopic lavage on selected patients, but the American guidelines still don't recommend laparoscopic lavage, mainly because of the risk of unresolved septic foci requiring secondary intervention(43, 44).

Fistulation, often to the urinary bladder can be a complication to acute diverticulitis, which usually presents after the acute episode. Stenosis, sometimes causing colon obstruction is also a complication to diverticulitis but considered to be caused by a chronic inflammation. Both will not be further addressed in this thesis and the same applies to acute bleeding from diverticula which must not coincide with an inflammation of diverticula (but it may).

Recurrence

Recurrence is not always defined in a coherent way, but a common definition is "a new episode of acute diverticulitis >30 days after recovery from a previous episode". It should be separated from the term "ongoing symptoms" which refers to a prolonged course of one episode. Around 8% of patients with acute diverticulitis have recurrences within the first year after complete recovery, and 20% have recurrences within 10 years(34). Most estimates of recurrence are derived from selected populations, such as patients previously hospitalised for treatment. Risk factors for recurrence specifically involving surgery include young age at onset, female sex, smoking, and obesity(34, 81, 82). A large study from California revealed that >80% of patients with acute diverticulitis, never have a recurrence, while the rest may have multiple recurrences(83). Recurrence risk is also believed to increase in ACD patients with abscess formation(84). The risk for recurrence has previously been overestimated and because of this guidelines have recommended an elective sigmoid resection, even after only two episode of acute diverticulitis, regardless of severity(6, 85). Lately this has been challenged and the recommendation for elective sigmoid resection should now be individualised with focus on quality of life (QoL)(43, 86). Changes in recommendation are mainly because of the low recurrence rate and low risk of a complicated episode after AUD(87-89) which previously had been of concern . A RCT comparing elective surgery to conservative treatment in patients with recurrent diverticulitis, with the main outcome being differences in QoL, presented that 11% had anastomotic leaks and 70% in the surgical group has serious adverse events compared to 80% in the conservative arm at five-year follow-up(86). Recurrence rate was 11% compared to 30% respectively, but QoL was better in the surgical group. Likewise, improvements in QoL after elective surgery compared to conservative treatment for recurrent diverticulitis was established in a similar RCT from the United States at six months, where recurrences were more common in the conservatively managed group (5% vs 27%) but all of them were Hinchey grade I(90). Major complications after surgery were 10 % compared to none in the conservatively managed group. These results further emphasises the complexity of this subject, concluding that QoL and patient involvement should be guiding in decision making. In the United States however, one episode of conservatively treated ACD still demands the consideration for elective surgery but the discussion is becoming more nuanced(12, 44).

Follow-up

Follow-up after an episode of acute diverticulitis has been reason for much debate. With the increasing use of radiological imaging to first establish the diagnosis, the indication for colonic follow-up has become controversial. There is no elevated risk for perforation when performing colonoscopy after an episode of acute diverticulitis(91) but still it is an invasive procedure that requires considerable resource utilisation. The main reason for colonic evaluation has been to confirm the diagnosis, since acute diverticulitis used to be a clinical diagnosis. It has also been important to rule out a misdiagnosed cancer. Acute diverticulitis is not thought to increase the risk of colon cancer (CRC)(92), instead the cases with diverticulitis and cancer are thought to be misdiagnosed at first clinical presentation. This conclusion is derived from studies showing that the association between CRC and diverticular disease is highest within 6-12 months after a diverticulitis diagnosis, after that CRC rates are similar to the general population(93, 94). For patients with a CT-verified AUD, who are asymptomatic after one episode, a low prevalence of misdiagnosed cancer is noted in some studies(95-100). These studies are however somewhat heterogenous, in some ACD patients are included and comparisons have been made to the prevalence of CRC in the normal population, which has been difficult to assess, resulting in a possible underestimation of relative risk. Patients with ACD however have a higher prevalence of CRC and consensus is still to recommend a colonoscopy for them after discharge(101-103). Current guidelines advocate that AUD patients, who fully recover and have undergone one colon examination within the last three years, can refrain from further examination(43).

Aims of the thesis

The overall aims of this thesis were to assess and evaluate the changing management, treatment and follow-up options for acute uncomplicated and complicated diverticulitis.

The specific aims for each study were

I. To analyse the adherence to a new treatment protocol for AUD, limiting the use of antibiotics. Secondary objective was to study complications and the recurrence rate after AUD.

II. To investigate whether a treatment protocol facilitates the implementation of new knowledge in clinical practice, its influence on outcomes and how adherence to protocol is changed over time.

III. To compare the incidence of CRC in patients with acute diverticulitis with that in the general population in order to assess the need for follow-up colon examination.

IV. To analyse the long-term results of the Scandinavian Diverticulitis (SCANDIV) trial in terms of severe complications (Clavien-Dindo score >IIIb) in patients with acute perforated purulent diverticulitis. Secondary outcomes included mortality, secondary operations, recurrences, stoma prevalence, functional outcomes and QoL.

Methods

Patients and study design

Paper I

A retrospective study including consecutive patients admitted to Helsingborg teaching Hospital, Sweden between the January 1, 2013 and January 6, 2015 with CT-verified AUD. Patients were identified searching the inpatient registry using ICD-10 codes K57.2, K57.3, K57.8 and K57.9. A review of the medical records was conducted, and a database was created recording patient demographics, co-morbidities and outcome measures. During the first 16 months of the study period, antibiotic therapy during hospitalisation was the therapy of choice. On May 1, 2014, a new protocol was introduced stating that patients with suspected AUD without any signs of complication on CT should be treated without antibiotics. Patients were divided into two groups based on before/after protocol implementation and outcomes compared. Comparison was also done, by dividing patients with the use of antibiotics as the exposure. All data were retrieved retrospectively from patient charts and transferred to a case report form (CRF) modified from the one used in the "Antibiotika Vid Okomplicerad Divertikulit"- AVOD study. All patients were followed by manual review of medical files for at least one year.

Paper II

A retrospective observational study including all consecutive patients over 18 years with the main diagnosis of AUD hospitalised at Helsingborg Hospital (HH) and Skåne University Hospital (SUS) Sweden from January 1, 2015 to December 31, 2017. Patients were identified from the hospitals' inpatient registry by the discharge ICD-10 code K57.3. Patients were divided in two groups based on their admitting hospital. Baseline characteristics and outcome measures were recorded in a data base. All patients were followed for a minimum of one year after discharge by medical file review.

Paper III

A retrospective observational study linking data between the Norwegian Patient Registry and the Cancer Registry of Norway. All patients with an emergency admission to a Norwegian hospital between January 1, 2008 and December 31, 2010 discharged with a main diagnosis of diverticular disease (ICD code K57.1-9), were identified in the Norwegian Patient Registry and included in the study cohort. All included patients subsequently diagnosed with CRC within a year after the admission for diverticular disease were detected through cross-matching with the Cancer Registry of Norway. A three-year period was chosen to reduce the risk of the incidence being skewed for one particular year. To estimate the age-specific distribution of complicated and uncomplicated diverticulitis in the study population, and to assess the number of patients with a CT-verified episode of diverticulitis (population of interest), data from a consecutive series at Akershus University Hospital, investigating the in-hospital patients with acute diverticulitis for the study period, was used. During this period Akershus University Hospital covered approximately 7% of the Norwegian population. The incidence of CRC in the Norwegian population between 2008 and 2010 was extracted from the Cancer Registry of Norway. By using these calculations, the Standard Morbidity Ratio (SMR) was calculated for different age groups.

Paper IV

The Scandinavian Diverticulitis (SCANDIV) trial was designed as a two-armed, open-label, pragmatic, superiority, multicentre RCT. Twenty-one participating centres in Sweden and Norway were recruited and primary inclusion was conducted between February 5, 2010 and June 28, 2014. Patients were analysed in an intention to treat basis. The CONsolidated Standard Of Reporting Trials; CONSORT statement was used for reporting(104). The long-term follow-up was conducted with patient file reviews and telephone interviews between March 2018 and November 2019. The information was registered into a web based electronic CRF. Severe complications were defined as Clavien-Dindo >IIIa. The Clavien-Dindo classification of surgical complications, is a system of grading postoperative complications based on the type of therapy that is required to treat the complication (Table 2)(105).

Table 2. **Clavien-Dindo classifcation of surgical complications(105)**

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
III **IIIa** **IIIb**	Requiring surgical, endoscopic or radiological intervention Intervention not under general anesthesia Intervention under general anesthesia
IV **IVa** **IVb**	Life-threatening complication requiring ICU management Single organ dysfunction (including dialysis) Multiorgan dysfunction
V	Death

Functional outcomes were assessed using the EuroQoL (EQ-5D) questionnaire, which is used to evaluate health status(106). The EQ-5D-5L official user guide was used to present collected information. The current version was developed in 2005 and consists of five dimensions, each describing a different aspect of health (Figure 5).

Figure 5 showing the 5 dimensions in EQ-5D

Each dimension has three response levels depending on severity: no problems, some problems and extreme problems.

The Cleveland Global QoL questionnaire was used to evaluate QoL. It includes three questions, and the total calculated score ranges from 0 to 1 (with 1 being excellent); a change in score of 0.1 was considered clinically important.

Methodological Considerations

Study design

There are different ways to conduct studies and gain further knowledge. The study designs have different levels of strength and to attain this knowledge, studies are performed which can be either observational or experimental, depending on whether or not the exposure is supplied by the researchers(107). Mainly there are two types of observational studies: including group comparisons (analytic studies, e.g. cohort, case-control, or cross-sectional studies) and descriptive studies (no comparison, e.g. case series)(108). Likewise, there are two main categories of experimental studies: RCTs where patients are assigned to the interventions based on a truly random process (e.g. coin flip, a computer-generated random allocation sequence) and non-randomised controlled trials where patients are assigned to the interventions based on a non-random process (e.g. admission date, hospital number).

The evidence pyramid (Figure 6) is commonly used to grade clinical evidence in an established hierarchy. The lowest grade is given to expert opinions and case reports. RCTs are ranked highest among clinical studies surmounted only by systematic reviews and meta-analysis of several RCTs. In this thesis, cohort studies and a RCT design have been used.

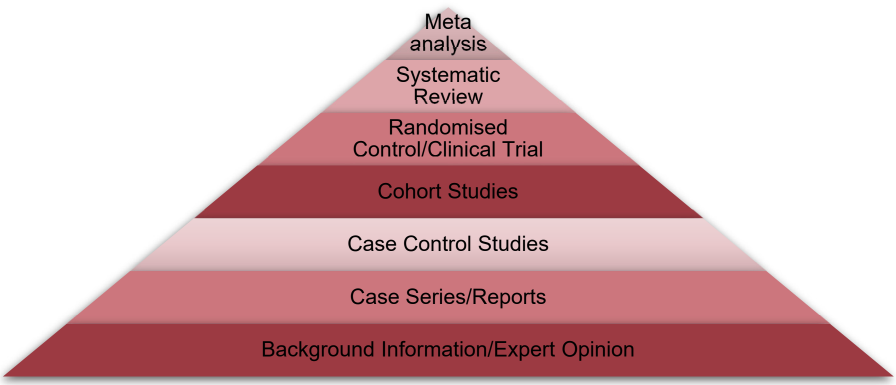

Figure 6. The hierarchial evidence pyramid

RCTs have emerged in the last 50 years and are now considered the best quality of evidence when studying changes in clinical practice(107). In the beginning their use was limited to therapeutic studies, comparing medical treatment. One of the great strengths of this design is that allocation to exposure by randomisation ensures an equal distribution of baseline characteristics between the groups, limiting selection bias. "Provided that such trials are large enough, the problem of confounding is thus avoided because the treatment and control groups will be similar in all respects other than those under trial"(109). Randomisation can be conducted by different measures; open labelled (researcher and subject know the treatment allocation), single-blinded (subject doesn't know which treatment allocation) or even double-blinded (neither researcher nor subject knows which treatment allocation) and in blocks. RCTs in surgical research are relatively new, mainly due to the demanding design of such a study but also because certain factors in surgery, sets it apart from medical research. Surgery is skill dependent and standardisation of the surgical method can be difficult to achieve. Blinding in surgical procedures is possible but can be difficult if the two surgical procedures being compared are very different (e.g. laparoscopic vs. open surgery). Despite these limitations, RCTs have emerged as the best quality evidence in clinical practice even in surgical research. There are however fields, where an RCT is difficult to perform. Clinical conditions/diseases that are very rare, the study of exposures that cannot be randomised (complications) are examples of such, since RCTs require a large sample size to achieve good power, to adequately answer a proposed question. It can also be considered unethical to randomise between two exposures, e.g. active medical treatment and placebo. Observational studies are therefore an adequate way to study some areas, especially if large cohorts are available.

Cohort studies are longitudinal studies that sample a group of people who share a defining characteristic (an outcome, disease etc.). Subjects are followed over time and often incidence rates are calculated. They can be retrospective (using data from registries, medical files) or prospective (collection of new data). Large cohorts that are collected prospectively can often be used to study different outcomes (birth registries, cancer registries). The advantages include faster data collection and thereby lower costs, and since there is no exposure supplied; no harm to study subjects. The main disadvantages are the risks of confounding, and bias and that the amount of data that exists is restricted.

The studies in this thesis use different methodologies, depending on current available evidence. The use of antibiotics in AUD has been studied in two large European RCTs and concluded to have no effect on complications, hospital stay or adverse events in short or long-term follow-up(46, 47, 52, 56), so there was no need to reproduce those results. How clinical research is converted into clinical practice has not been studied in great detail, which is surprising since that's the goal of clinical studies. The implementation of results from trials into clinical practice can be challenging and the external validity of results is usually unknown(110). Results from studies are often difficult to reproduce in clinical practice, due to different reasons e.g. better compliance from both patients and health-care providers and better follow-up during the study period. A need to assess the implementation of change in management emerged and how this translated into everyday clinical practice in terms of outcomes for the patients. Paper I and II were therefore designed as register based retrospective observational cohort studies looking at the clinical management at different hospitals in the same region. A structured protocol was introduced at HH and adherence followed, as well as clinical outcomes of the patients. SUS never had such a protocol implementation, but best clinical practice was a shift in clinical management towards non-antibiotic management on a national and international level. A retrospective cohort study therefore seemed like an adequate study design.

In paper III, the aim was to study if the increasing use of CT to diagnose acute diverticulitis made follow-up colonoscopy obsolete. Particularly since misdiagnosing CRC as diverticulitis has been the main reason for colonoscopy. Some recent studies have concluded that colonoscopy may be omitted in asymptomatic patients post-AUD (100, 111). A prospective RCT was unfeasible since it would require a very large cohort.

Laparoscopic lavage for perforated purulent peritonitis had only been studied in case series and observational studies when the SCANDIV study was set up(77) and the results needed to be confirmed with a RCT. Two other RCTs investigating the same topic were conducted during the same time-period(79, 80). The primary outcomes were different in all studies and the LADIES trial was terminated prematurely due to many re-interventions in the laparoscopic lavage arm at interim analysis. The SCANDIV trial was designed as a two-armed, open-label, pragmatic, superiority, multicentre RCT. For all studies short-term (90 days-2 years) have been published but long-term follow-up was missing(80, 112, 113). Block randomization was used, and patients were analysed in an intention to treat manner, i.e. analysed in the intervention group in which they were allocated irrespectively to the intervention they received.

Sources of error

All scientific research is at risk of errors. Differentiation is made between random errors, which can be adjusted by increasing the sample size in the study population and systematic errors (bias) which can be reduced by a proper study design(114).

Sample size

To adequately answer a proposed question, a null hypothesis is formulated, usually that there is no effect of an exposure/intervention being studied on the main outcome. This hypothesis can either be accepted or rejected (if there is a difference in the main outcome). Sample size or the number of patients in the studied cohort is important to study this correctly. It should be large enough to supply sufficient statistical power which is the probability that we will succeed in rejecting null hypothesis when it is false (avoiding a type II error) while minimizing the risk of type I errors.

Type I error is also called the significance level and is the possibility of rejecting the null hypothesis, when it is true, i.e. falsely confirming causality when there is none. This also called alpha(α) and is usually set to .05.

Type II error is not finding a difference, where there is one, due to lack of statistical significance i.e., falsely accepting the null hypothesis. The rate of type II error, often called beta(β) is related to the statistical power of a test, which equals 1- ß. The ability to establish an effect related to the exposure, is dependent on sample size, magnitude of difference in incidence (or means and variation) and an accepted level of making a type I error.

Sample size calculations are important to determine the number of patients needed to establish sufficient power. A small sample size will not show effect of exposure on outcome with sufficient statistical power. However, the sample size should not be too large either, since it can prolong the study, cause unnecessary discomfort to subjects being studied, be costly, and also, a too large sample might show statistically significant differences, which are clinically irrelevant.

Sources of bias

Bias should be recognised and managed in the study design, or in its interpretation and includes selection bias, information bias and confounding among others.

Selection bias arise when the selection of the study population, by selection procedures or factors, influence the inclusion and/or exclusions of study participants.

Information bias is sometimes called misclassification bias and may result from wrongful or inexact sampling of information. Misclassification occurs if a participant is wrongly classified into an incorrect category (e.g. light smoker instead of heavy smoker). Non differential vs. differential misclassification further differentiates if the misclassification is unrelated to other study variables vs. differs according to the value of other study variables, such as exposed or unexposed or if they reach the study outcome or not(114).

Confounding is a recurrent issue in epidemiological studies and must be adjusted for. It can be defined as the "confusion of effect"(114). A confounder is something that can influence outcomes and is by definition linked with both outcome and exposure. It is a systematic error and might be unevenly distributed when comparing two groups, when groups are not randomised (e.g. more women, or older patients in one group). Three steps can be taken to control for confounders; randomisation, restriction and matching. Ways to adjust for confounders in data analysis can be done by using stratification or regression analysis(114).

Missing data can occur in any type of study design and reduces the representativeness of the sample. Clinical variables can be missing from registries and specifically in QoL studies, some questions might not be answered by all participants. Missing data is usually classified as missing completely at random (the missing information is unrelated to factors with potential impact on the outcome), missing at random (missing due to factors that can be accounted for). Both these result in reduced statistical power by wider confidence intervals but the estimated treatment effects remains unbiased. The data can also be missing not at random, which effects results the most. Missing data are then related to factors influencing outcome. Efforts should be made to reduce the number of missing data, e.g. by approaching study subjects on multiple occasions, by having questionnaires that are easy to comprehend, not be too extensive and easy to fill in. In the data analysis, missing data can be handled by imputations (missing data is replaced) or omission (missing data is discarded from further analysis).

Internal and External Validity

Internal validity is the degree to which the results of a study are attributable to the independent variable being studied and not some other rival explanation. This is the study of causality. One could say that it is the degree to which causality can be proven, and not be influenced by other factors (than the variables studied). The cause must precede the effect, cause and effect must correlate and there should be no third variable involved. Usually this is affected by confounders.

External Validity is the extent to which the results of a study can be generalised. This is important since the main aim of clinical research is its translation into a broader clinical setting. This can be influenced by selection bias.

Outcome Measures

Choosing the outcome measures is an important part of the study design. For paper I & II the proportion of patients managed without antibiotics were the main outcomes. In paper III it was the risk for having CRC one year after an episode of acute diverticulitis, used as marker for misdiagnosis. In paper IV, severe complications were the main outcome measure and functional and QoL outcomes were secondary outcome measures. Complications were measured using the Clavien-Dindo classification of surgical complications, which is a system of grading postoperative complications based on the type of therapy that is required to treat the complication(105). Since published in 2004, the Clavien-Dindo classification has become one of the standard methods to grade surgical complications. The different grades can be seen in Table 2. Clavien-Dindo>IIIa was chosen as cut-off for severe complications, since it requires an intervention in general anaesthesia. Measuring all Clavien-Dindo grades could have been chosen but the first two grades include symptoms such as paralysis and nausea, which can be accountable to the "expected" post-operative process and were therefore of less interest.

Functional outcomes and QoL was measured by using EQ-5D questionnaire and the Cleveland GlobalQoL tool respectively. The EQ-5D is a questionnaire that was developed in the late 80's and was specifically designed to generate a cardinal index of health providing a standardized measure of health status. The answers can be summarised into an index value which reflects how good or bad a health state is according to the preferences of the general population of a country/region. An EQ-5D summary index is derived by applying a formula attaching values (weights) to each of the levels in each dimension. The index is calculated by deducting the appropriate weights from 1, which is the value for full health. The collection of index values for all possible EQ-5D health states is called a value set and this is obtained from a standardised valuation exercise, in which a representative sample of the general population in a country/region is asked to place a value on EQ-5D health states and this is then used in comparison. So far 34 countries have value sets but unfortunately neither Sweden nor Norway (although when this method was chosen it was believed to be underway soon). The tool is therefore only used for group comparisons in our study.

The amount of missing data was low in all our studies. Several efforts were made to reduce missing data by reviewing patient files on multiple occasions in the first three studies to ensure complete data bases for further analysis. Missing variables were considered missing at random and therefore expected to have a minor impact on outcomes. For the SCANDIV study the results were reported with accounting for missing variables in each category.

Limitations

All study designs have their benefits and disadvantages. Observational studies have a high risk of selection bias resulting in confounding. There is a risk that the two groups being compared are different from the beginning. Why choose such a design then? As previously mentioned, it can be used to study rare events, or diseases. Also, if the study cohort is large, the risk of confounders decreases. Furthermore, it is a less resource consuming design than a RCT which can be very costly, both in terms of finance and time. The first three studies are register-based cohort studies and are at risk of misclassification bias. The data can only be as reliable as the registries. The Melior database has not been validated, but a manual review of all patient files was conducted to account for all diagnosing errors. This is the reason for the wide range of ICD-codes used in the first study, to ensure that no patients were missed. In the second study the diagnosis codes were narrower since the manual review from the first study showed that it was not necessary to include all diverticular disease codes. The data in paper III came from the Norwegian Cancer registry which had been validated(115) and the Norwegian Patient registry which had not. A text search at Akershus University Hospital however showed high validity of the Norwegian Patient registry data from case series. Highly validated registries decrease the risk for misclassification bias.

Sample size is important as mentioned previously to adequately show an effect of the exposure being studied and a calculation was done for the SCANDIV study. In paper I the sample size is too small, notably after protocol introduction, which is why the two groups comparing clinical outcomes are based on antibiotic treatment for the whole study period. In paper II, sample size is much larger and therefore even small differences between groups can be stated as statistically different (e.g. Temperature (median 37.8 vs 37.6 degrees Celsius p=.011) but a difference of .2 degrees where both are in the normal range, is not of clinical importance.

In Paper III, to calculate the SMR in different age-groups, the number of patients with CT-verified AUD/ACD in the whole country was needed and not available. To acquire this information an estimation was done, using extrapolated data from a case series from Akershus University Hospital, which covers around 7% of the Norwegian population from the same time period. This estimation can result in proportion skewness.

In paper IV some biases have been eliminated due to the prospective RCT design. However, many patients eligible for inclusion had not been included. Of 415 eligible patients, 216 were not enrolled and the main reason for this was that the on-call surgeon had not asked (n=162). So clearly there is a risk of selection bias, possibly affecting the external validity. However, only three patients were lost to follow-up and there were no differences between the treatment groups, accounting for a high internal validity of the study. The high rate of eligible but not included patients reflects how difficult it can be to perform high quality studies in an acute setting were time-constraint and the need for written informed consent can hamper inclusion(116). A secondary analysis revealed that the not included patients had a higher ASA score, which might indicate that the frailest patients are not included in the study and the findings might not be generalisable to them.

Ethical Considerations

Ethical aspects are essential when conducting human studies. Since the results from the studies are often not directly beneficial to the included patients (if this was known, no need for a trial), it is important to not cause any unnecessary harm, while still being able to study and evaluate new treatments/procedures. In the "DECLARATION OF HELSINKI" the World Medical Association (WMA) has defined Ethical Principles for Medical Research Involving Human Subjects to provide guidelines for human studies(117). The declaration has been revised several times since 1965 and the last revision is from 2008. In accordance with the declaration, all studies in this thesis were approved by Ethical boards, the SCANDIV study both in Sweden and in Norway. As recommended for interventional studies, written informed consent was mandatory in the SCANDIV study. This provided a challenge during the inclusion as the ethical implications of including acute, severely ill patients in studies can be discussed from several aspects. Are they able to provide informed consent, when they're severely ill? Is it ethical to attain consent? Should next-of-kin provide consent? Some surgeons' might have refrained to ask for inclusion due to these aspects. Despite obstacles, ethical principles are very important when conducting studies, testing of knowledge without a study setting would also be unethical.

Statistical analysis

Paper I, II, IV

Statistical analyses were done using IBM SPSS software version 22 and 25 for Windows and Macintosh (IBM Corp, Armonk, NY) and Stata 12 (StataCorp, College Station, TX). Continuous variables were presented as median and interquartile range (IQR). χ^2-test, independent sample T-test and Mann Whitney-U-test were used when appropriate to test for statistical significance. A P-value of < 0.05 was considered significant.

Paper III

SMR was calculated, including the 95% confidence interval (CI). The SMR is the ratio between the actual number of CRC cases among patients with acute diverticulitis and the expected number of CRC cases among patients with acute diverticulitis, assuming the same incidence as in the Norwegian population, with standardization being done for age and sex. A SMR above 1 indicates a higher incidence of CRC in acute diverticulitis patients compared with the Norwegian population. SMRs were calculated for different age groups (20–39, 40–59, 60–79 and 80+ years) and an overall SMR was calculated by summarizing numbers for acute diverticulitis patients, person-years at risk, actual cases and expected cases from age groups. Statistical calculations were made using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

$$\frac{\text{Number of patients with CRC in AUD/ACD patients in Norway 2008 – 2010}}{\text{Expected number of CRC in AUD/ACD patients in Norway 2008 – 2010}}$$

Results

Paper I

During the study period a total of 249 patients were identified, and after exclusion 132 patients remained. They were divided into an antibiotic and a non-antibiotics group as shown in the flowchart (Figure 7). Except for more comorbidities in patients receiving antibiotics, there were no statistically significant differences in baseline characteristics between the groups. There were no differences in complications between the groups (Table 3.) After introducing the treatment protocol, limiting the use of antibiotics, a total number of 47 patients were assessed out of which 28 (60%) did not receive antibiotics and 19 (40%) did. This can be compared 3/85 (4%) patients not receiving antibiotics before the protocol implementation. Patients receiving antibiotics had a higher CRP at admission (median 117 mg/L vs. 52, p=.008) compared to those not receiving antibiotics (Table 4) and a one day longer hospital stay (3 compared to 2 days; p=0.004).

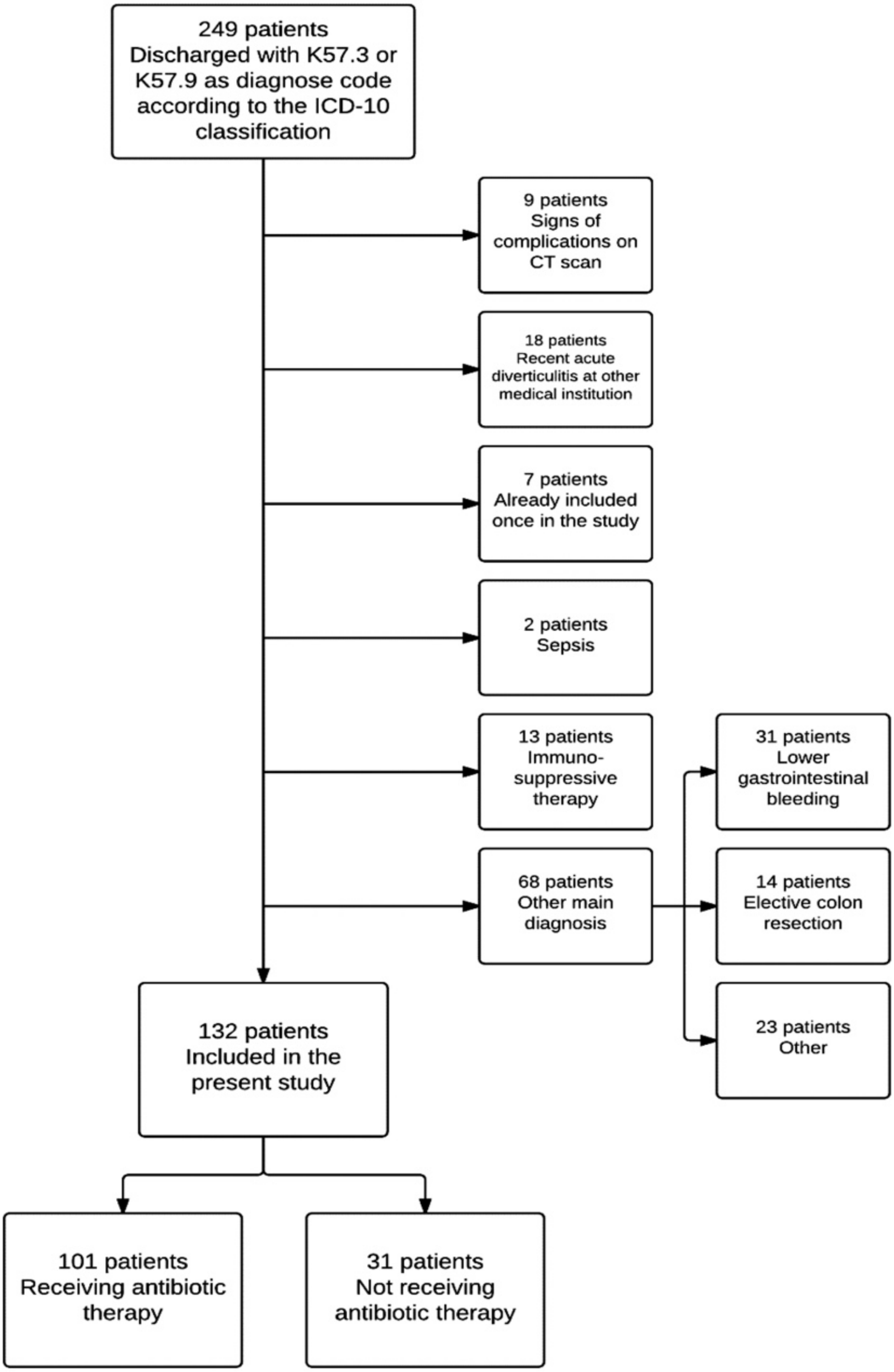

Figure 7. Study flowchart paper I

Table 3. Complications paper I

Variable	Total (n=132)	Antibiotics (n=101)	No antibiotics (n=31)	p
Any complication	21 (16)	19 (19)	2 (6)	.10
Abscess (n;%)	0 (0)	0 (0)	0 (0)	-
Perforation (n;%)	2 (2)	2 (2)	0	.43
Stenosis (n;%)	0	0	0	-
Sepsis (n;%)	0	0	0	-
Fistula (n;%)	1 (0.8)	1 (1)	0	.58
Recurrence (n;%)	18 (14)	16 (16)	2 (6)	.18

Table 4. Background characteristiics after protocol implementation

Variable	Total (n=47)	Antibiotics (n=19)	No antibiotics (n=28)	p
Age (years)	62 (51-70)	63 (48-68)	63 (59-70)	.47
Female sex (n;%)	29 (62)	9 (47)	20 (71)	.10
BMI (kg/m^2)	25.9 (23.9-29.5)	25.4 (23.8-28.9)	26.3 (24.0-30.1)	.72
CRP (mg/L)	61 (33-157)	117 (48-197)	52 (34-102)	.008
WBC (x 10^9 cells/L)	12.8 (11.0-14.6)	12.8 (10.9-15.0)	12.8 (10.4-14.0)	.79
Body temperature (ºC)	37.4 (36.7-37.9)	37.9 (37.4-38.1)	37.2 (36.7-37.8)	.09
Previous diverticulitis (n;%)	15 (32)	8 (42)	7 (25)	.22
Comorbidity (n;%)	18 (38)	9 (47)	9 (32)	.29

Data presented as median (IQR) or as absolute frequency (relative frequency).

Paper II

A total of 1082 admissions registered with the ICD-10 code K57.3 were identified. After exclusion the final cohort consisted of 583 patients; 388 and 195 cases treated at SUS and HH respectively (Figure 8).

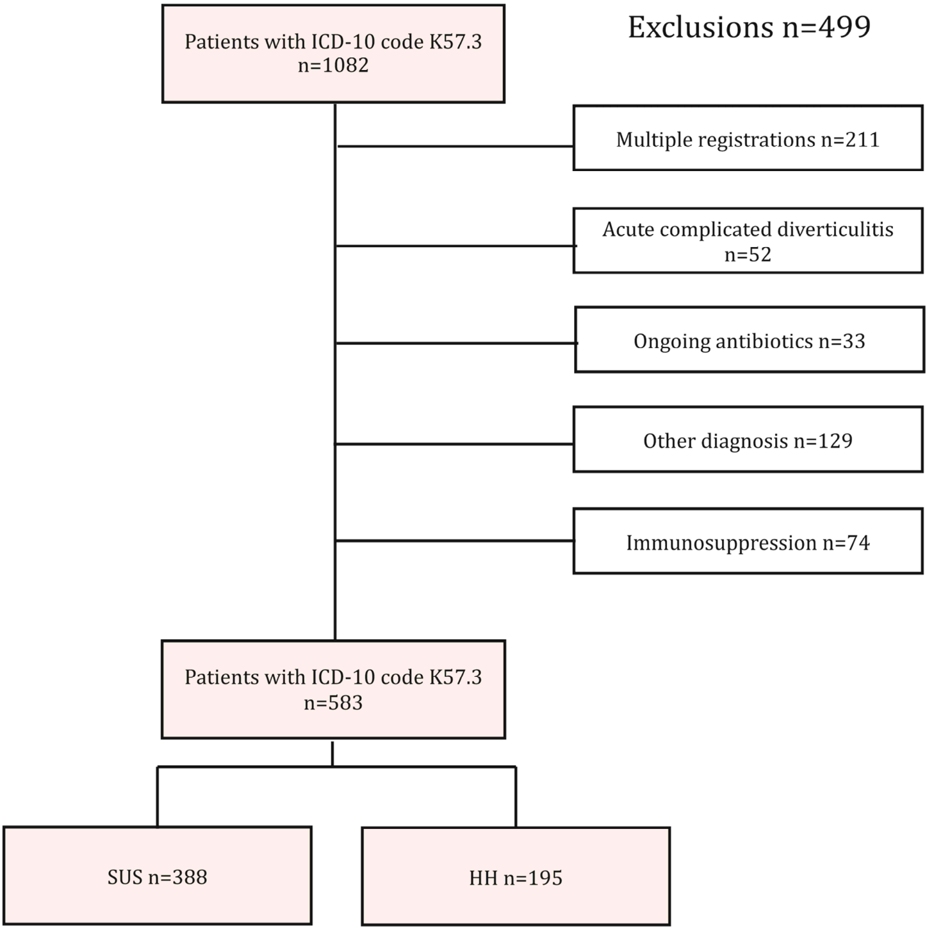

Figure 8. Study flowchart paper II

A total of 137 patients (24%) were managed without antibiotics and 437 (76%) with antibiotics. Forty-three (11%) and 94 (48%) of patients from SUS and HH respectively did not receive antibiotics during hospitalisation (p < 0.001) (Table 5). Clinical characteristics of the whole study cohort are shown in Table 5 comparing hospitals and Table 6 comparing groups with and without antibiotic use. CT-verification of the AUD diagnosis was lower in patients at SUS compared to 320 (83%) vs HH 186 (95%) respectively; p < 0.001). Colon evaluation follow-up was conducted in 430 (74%) of all cases with no statistically significant difference between SUS and HH, 280 (72%) vs 150 (77%); p=0.22. CRP at admission was higher in patients receiving antibiotics (65 vs 90 p=.016) as was temperature and WBC. (Table 6). There was no significant difference in recurrences (22% vs 23% ; p = 0.87), complications (3% in both groups ; p = 0.77) or length of hospital stay, median 3 (2-4) days between the groups.

Table 5. Clinical characteristics of the patient cohort divided into three groups total, patients treated at Skåne University Hospital and Helsingborg Hospital respectively.

Variable	Total n=583	SUS n=388	HH n=195	P
Female n (%) **Male n (%)**	356 (61) 227 (39)	227 (56) 161 (44)	129 (66) 66 (44)	0.07
Age, years	61.0 (51-72)	61.0 (51-72)	61.0 (51-71)	0.94
BMI	27.5 (24.7-30.5)	27.6 (25.8-30.5)	27.2 (24.2-30.4)	0.19
Previous diverticulitis n (%)	233 (40)	159 (41)	74 (38)	0.60
CT n (%)	506 (87)	320 (83)	186 (95)	<0.001
***CRP (mg/L)**	87 (40-136)	84 (40-144)	90 (39-141)	0.54
Peak CRP (mg/L)	127 (80-183)	128 (77-186)	124 (86-172)	0.50
***WBC (x10^9 cells/L)**	12.4 (10.4-14.7)	12.5 (10.4-14.8)	12.3 (10.3-14.6)	0.16
Temperature (Celsius)	37.7 (37.2-38.2)	37.7 (37.2-38.2)	37.8 (37.3-38.3)	0.63
Antibiotics n (%)	437 (75)	345 (89)	101 (52)	<0.001
Recurrence n (%)	128 (22)	83 (21)	45 (23)	0.24
Complications n (%)	15 (3)	8 (2)	7 (4)	0.18
Charlson score	2 (1-4)	2 (1-4)	2 (1-4)	0.82
Hospital stay (days)	3 (2-4)	3 (2-4)	3 (2-4)	0.79
Colon evaluation within 6 m n(%)	430 (74)	280 (72)	150 (77)	0.22

*at admission, Values in median and IQR unless specified otherwise

Table 6. Clinical characteristics of the patient cohort divided into three groups total, with and without antibiotics respectively

Variable	Total n=583	Antibiotics n= 446 (%)	No antibiotics n=137 (%)	P
Female n (%) **Male n (%)**	356 (61) 227 (39)	267 (60) 179 (40)	89 (65) 48 (35)	0.28
Age, years median	61 (51-72)	60 (50-71)	64 (54-73)	0.05
BMI	27.8 (24.7-30.5)	27.2 (24.-30.9)	26.8 (24.3-29.8)	0.16
Previous diverticulitis n (%)	233 (40)	181 (40.6)	52 (38.0)	0.58
CT n (%)	506 (87)	377 (85)	129 (94)	0.004
***CRP (mg/L)**	87 (40-136)	90 (46-151)	65 (22-115)	0.016
CRP (mg/L)	127 (80-183)	138 (89-199)	97 (57-129)	< 0.001
***WBC (x10^9 cells/L)**	12.4 (10.4-14.7)	12.6 (10.6-15.1)	11.7 (9.9-13.9)	0.004
Temperature (Celsius)	37.7 (37.2-38.2)	37.8 (37.3-38.3)	37.6 (37.138.0)	0.011
Recurrence n (%)	127 (22)	96 (22)	31 (23)	0.87
Complications n (%)	15 (3)	11 (3)	4 (3)	0.77
Charlson score	2 (1-4)	2 (1-4)	2 (1-4)	0.07
Hospital stay (days)	3 (2-4)	3 (2-5)	3 (2-4)	<0.001
Colon evaluation within 6 m n (%)	430 (74)	338 (76)	92 (67)	0.04

*at admission, Values in median and IQR unless specified otherwise

Paper III

Between 2008 and 2010, 7473 patients were admitted to Norwegian hospitals with any ICD-10 code for diverticular disease (Figure 9). By crossmatching the data with the Cancer Registry of Norway, 155 patients were identified who had been diagnosed with CRC within one year of an admission for diverticular disease and had a CT-verified episode of acute diverticulitis. Out of these five were excluded due to missing medical records. Of the remaining 150 patients 80 had acute diverticulitis without radiological suspicion of CRC or other colon pathology, 41 (51.3%) with AUD and 39 (49.3%) with ACD.

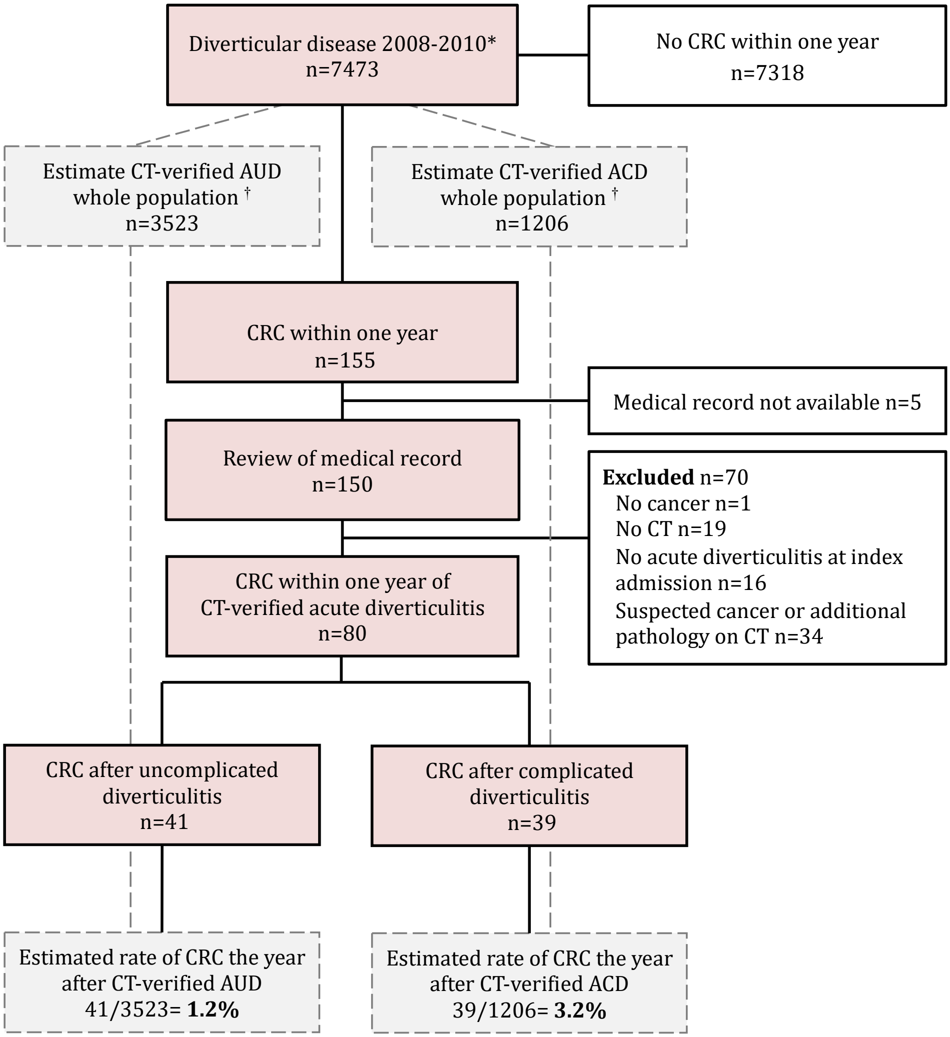

Figure 9. Study flowchart Paper III
*Patients admitted with ICD-10 codes K.571-K57.9
† Estimates based on a cohort from Akerhus University Hospital

Clinical characteristics of the patients are seen in Table 7.

Table 7. Clinical characteristics of patients with cancer and CT-verified diverticulitis.

	Total n=80	**AUD n=41**	**ACD n=39**
Mean age; years (range)	71.9 (40-94)	72.0 (40-92)	71.7 (47-94)
Female; n (%)	44 (55.0)	21 (51.2)	23 (59.0)
Previous diverticulitis; n (%)	12 (15.0)	8 (19.5)	4 (10.3)
Previous colonoscopy < 3 years; n (%)	4 (5.0)	2 (4.9)	2 (5.1)
>1 admission; n (%)	13 (16.3)	7 (17.1)	6 (15.4)
Persistent symptoms; n (%)			
Yes	40 (50.0)	19 (46.3)	21 (53.8)
No	8 (10.0)	6 (14.6)	2 (5.1)
Unknown	32 (40.0)	16 (39.0)	16 (41.0)
Diverticulitis location; n (%)			
Sigmoid	71 (88.8)	37 (90.2)	34 (87.2)
Left colon	6 (7.5)	3 (7.3)	3 (7.7)
Transverse colon	0 (0)	0 (0)	0 (0)
Right colon	3 (3.8)	1 (2.4)	2 (5.1)
Cancer location; n (%)			
Rectum	3 (3.8)	3 (7.3)	0 (0)
Rectosigmoid/sigmoid	63 (78.8)	33 (80.5)	30 (76.9)
Left colon	7 (8.8)	2 (4.9)	5 (12.8)
Transverse colon	1 (1.3)	0 (0)	1 (2.6)
Right colon	6 (7.5)	3 (7.3)	3 (7.7)
Colonic examination < 8 weeks from discharge			
Yes	32 (40.0)	18 (43.9)	14 (35.9)
>8 weeks	22 (27.5)	16 (39.0)	6 (15.4)
No	14 (17.5)	4 (9.6)	10 (25.6)
Not applicable*	12 (15.0)	3 (7.3)	9 (23.1)
Colonic examination as planned			
Yes	48 (88.9)	33 (97.1)	15 (75.0)
No, Emergency procedure	6 (10.1)	1 (2.9)	5 (25.0)

The tumour was located in the same colon segment as the diverticulitis in 66 (82.5%) patients, most frequently in the sigmoid colon n=31 (93.9%) following AUD, and for all of the ACD patients (n=30). Three right-sided cancers were found in the AUD group, none of whom had right-sided diverticulitis. In the ACD group, two of the three patients with right-sided cancers had right-sided diverticulitis on CT. Sixty-two patients (67.5%) had a colonic examination after discharge, 34 (82.9%) in the AUD group and 20 (51.3%) in ACD group. SMR was highest in the younger age-groups for both AUD and ACD (Figure 10). It was higher after ACD than AUD.

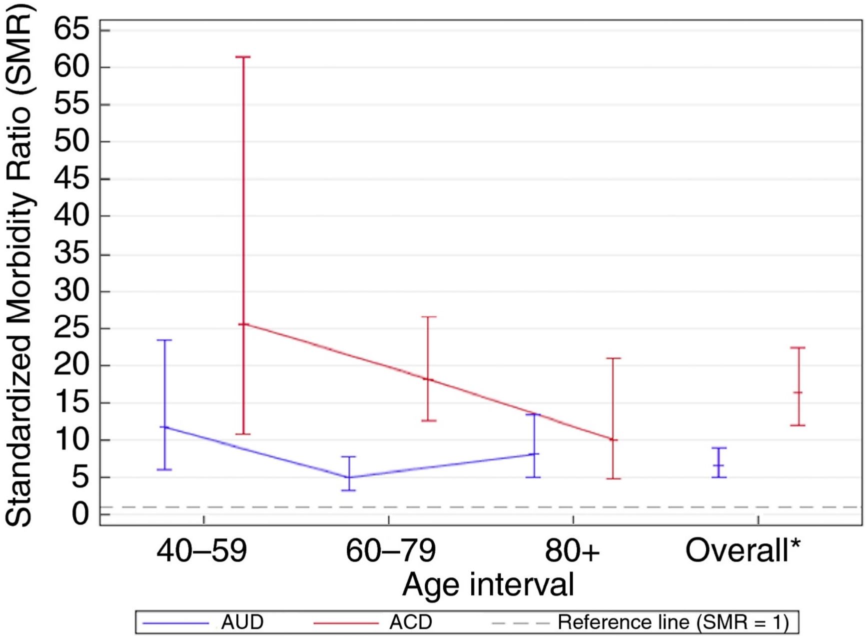

Figure 10.. Standard morbidity ratio (SMR) graph. Risk for colorectal cancer expressed as SMR following acute diverticulitis compared with the general population (dashed line). Graphs show SMR for different age groups and overall mean (95% CI)

Paper IV

Patients available for analysis can be seen in Figure 11. The median follow-up was 59 (IQR, 51-78) months, and three patients were lost to follow-up. Of 145 included patients 142 were available for analysis of 5-year results, 73 patients who had laparoscopic lavage and 69 who had received a resection.

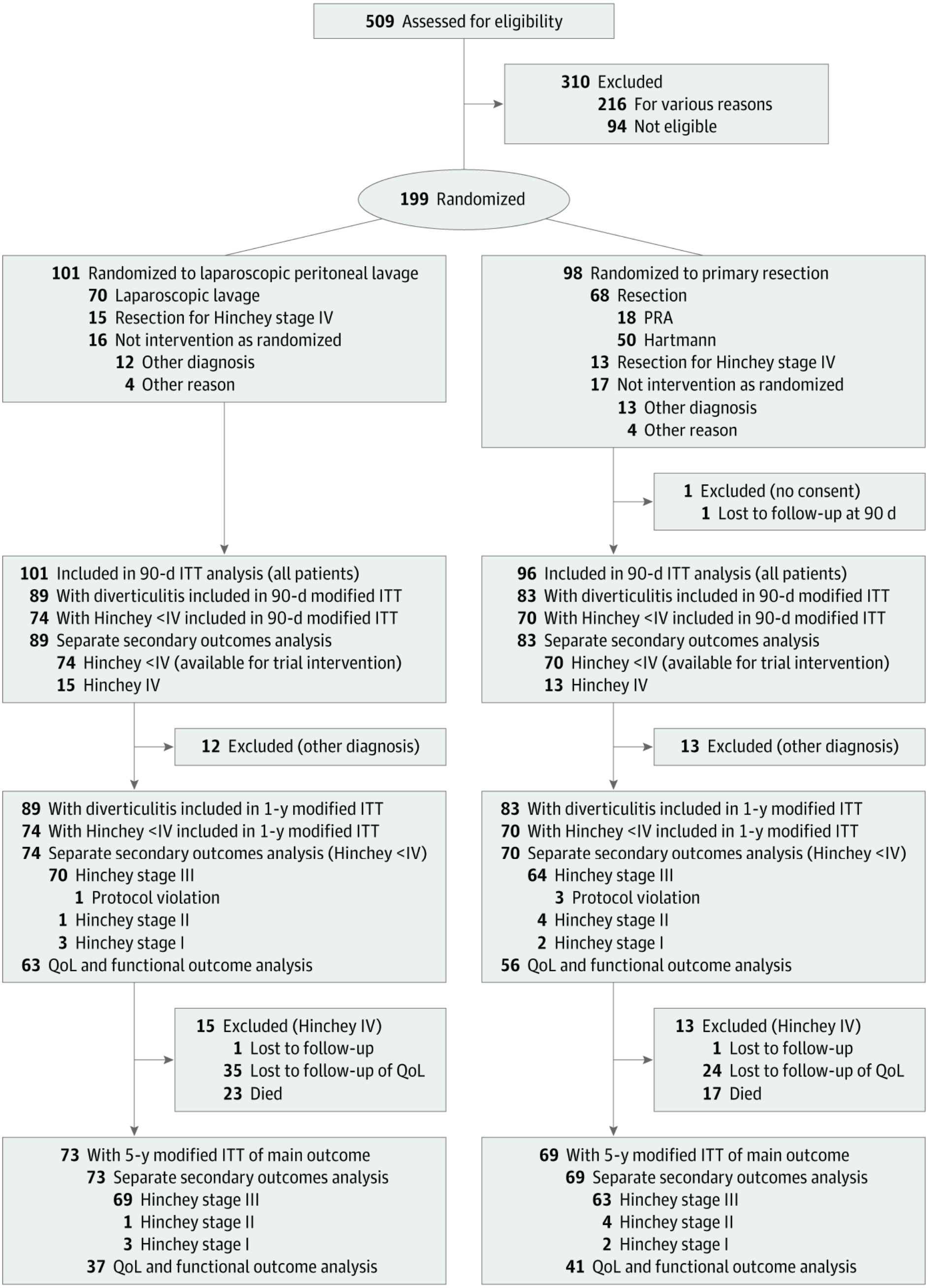

Figure 11. Study inclusion flowchart paper IV
IIT =intention to treat; PRA= primary resection with anastomosis

Baseline characteristics are seen in Table 8 and secondary outcomes in Table 9.

Table 8. **Baseline characteristics of patients included in long-term follow-up with Hinchey<4**

Characteristic	Lavage n=73 (%)	Resection n=69 (%)
Age years (s.d)	66.4 (13)	63.5 (14)
Sex ratio (M: F)	39: 34	36:33
BMI kg/m2 (s.d)	26.5 (5)	26.1 (4)
Previous abdominal surgery		
None	53 (73)	45 (65)
Single	13 (18)	15 (22)
Multiple	7 (10)	9 (13)
Previous episodes of diverticulitis		
None	57 (78)	51 (74)
Single	8 (11)	10 (15)
Multiple	8 (11)	8 (12)
Co-morbidity		
None	16 (22)	14 (20)
Anti-inflammatory medications	16 (22)	14 (20)
Chronic obstructive lung disease or asthma	9 (12)	14 (20)
Ischemic heart disease or heart failure	6 (8)	15 (22)
Cigarette smoking	8 (11)	12 (17)
Alcoholism or drug abuse	2 (2)	6 (8)
Active malignancy	5 (6)	3 (4)
Insulin-treated diabetes	3 (4)	2 (3)
Immunodeficiency or chronic hepatitis	1 (1)	2 (3)
Uremia needing dialysis	0 (0)	0 (0)
Other	45 (62)	45 (64)
ASA*		
I	12 (16)	11 (16)
II	38 (52)	26 (38)
III	20 (27)	31 (45)
IV	3 (4)	1 (1)
V	0 (0)	0 (0)
Charlson Comorbidity Index (s.d)	3.8 (2)	3.6 (2)

s.d=standard deviation *ASA American Society of Anesthesiology score

Table 9. Secondary outcomes in patients with diverticulitis of Hinchey grade <IV at long-term follow-up

	Laparoscopic lavage n=73 (%)	**Resection n=69 (%)**	**P**
Severe complications	26 (36)	24 (35)	0.92
Patients alive with stoma	4/50 (8)	17/52 (33)	0.002
Secondary reoperations (including stoma reversal)	26 (36)	24 (35)	0.92
Stoma reversal	5 (7)	17 (25)	0.003
Unplanned reoperations	19 (26)	8 (12)	0.028
Patients with readmissions	28/70 (40)	26/64 (41)	0.94
Patients with unplanned readmissions	24/70 (34)	7/64 (11)	0.001
Total days of hospital stay (median; IQR)	14 (6;20)	11 (7;19.5)	0.79
Diverticulitis recurrence	15 (21)	3 (4)	0.004
AUD	5 (7)	2 (3)	NA
ACD	10 (14)	1 (1)	NA

NA= Not applicable

Overall mortality was 32% (n = 23) in the laparoscopic lavage group and 25% (n = 17) in the resection group (p = .36). There were no statistically significant differences in severe complications (Table 9). Amongst patients still alive, the stoma prevalence was higher in the resection group. The total number of secondary operations, including stoma reversals, was similar between the two groups. Recurrence of diverticulitis was higher following laparoscopic lavage. In the laparoscopic lavage group, 30% (n = 21) underwent a sigmoid resection. There were no significant differences in the EQ-5D questionnaire (Table 10) or Cleveland Global Quality of Life scores between the groups.

Table 10. Functional Outomes EuroQoL-5D.

Level	Mobility		Self-care		Usual activities		Pain/discomfort		Anxiety/depression	
	Lap Lavage	Sigmoid resection	Lap Lavage	Sigmoid resection	Lap Lavage	Sigmoid resection	Lap Lavage	Sigmoid resection	Lap Lavage	Sigmoid resection
	n=37	n=43	n=37	n=43	n=37	n=43	n=37	n=43	n=37	n=43
1 no problems (%)	30 (81)	27 (63)	36 (97)	41 (95)	30 (81)	35 (81)	20 (54)	14 (33)	30 (81)	27 (63)
2 slight problems (%)	3 (8)	6 (14)	1 (3)	0	2 (5)	4 (9)	10 (27)	15 (35)	3 (8)	6 (14)
3 moderate problems (%)	2 (5)	8 (19)	0	1 (2)	3 (8)	2 (5)	2 (5)	9 (21)	2 (5)	8 (19)
4 severe problems (%)	2 (5)	2 (5)	0	1 (2)	1 (3)	1 (2)	4 (11)	5 (12)	2 (5)	2 (5)
5 unable / extreme (%)	0	0	0	0	1 (3)	1 (2)	1 (3)	0	0	0
Proportion reporting any problems (%)	7 (19)	16 (37)	1 (3)	2 (5)	7 (19)	8 (19)	17 (46)	29 (77)	7 (19)	16 (37)
P-value	p=0.09		p=1.00		p=1.00		p=0.07		p=0.34	

Discussion

The results presented in these studies emphasises the need to constantly challenge accepted practices in clinical management. Paper I and II show that despite high level evidence concluding no benefits of antibiotic treatment in patients with CT-verified AUD(46, 47, 52, 56), this is still very difficult to translate into clinical practice. A structured protocol and educational efforts when introducing such a protocol helps as shown in paper I but over time the compliance can decrease. There are many possible reasons for this. One may be the high turnover of doctors working at clinical departments not all of whom are updated on the latest protocols or guidelines. Studies show that barriers to implementation can be divided into three main factors; personal (related to physicians' knowledge and attitudes), guideline-related, and external factors(118). Paper II indicates that without a local treatment protocol, clinicians may not be updated at all with the latest guidelines. It is also possible that clinicians in general find it easier to start a therapy (such as a course of antibiotics) than to refrain. The medical file review disclosed that occasionally antibiotic therapy was started before the CT was conducted and even when the result confirmed AUD, most doctors would continue the initiated antibiotic treatment. Reasons for incompliance to follow protocol should be studied more in-depth. Qualitative studies using interviews are one possible strategy. Patients preference can also play a role here, since they may feel they're not receiving any treatment if they don't get antibiotics. Especially discontinuation after initiation might be difficult to accept, particularly if the symptoms have been reduced. Patients with recurrent AUD might also be accustomed to antibiotic treatment and may have difficulties in accepting a change in management.

Both studies showed that the patients receiving antibiotics had a higher CRP at admission (paper I median 117 mg/L vs. 52, p=.008 and paper II median 90 vs. 60mg/L p=.016) and it is likely that higher CRP lowers the threshold to prescribe antibiotics. This is reasonable since a high CRP can be a predictor of complicated course of diverticulitis(119, 120). A meta-analysis evaluating treatment failure with or without antibiotics including nine studies and over 2500 patients, presented no differences in rates of failure, recurrence, readmission, need for surgery and complications between the groups(121). The only factor associated with failure was more comorbidities. Therefore, current guidelines emphasise that antibiotic-free management is for immunocompetent and otherwise healthy patients, for others, individualised decisions should be made(43, 44). Concerns have been raised that the patients seen in the real world are more ill, then the study population in antibiotic-free management studies. The study subjects might normally be treated as out-patients, or by their general practitioner (GP) but were hospitalised due to the study setting. Therefore, it is claimed that antibiotic treatment is required to a higher degree when admitting patients from the emergency department. Unfortunately, the exact management of AUD at GP-clinics is to a large degree unknown. All trials studying the outpatient management of AUD, have been conducted at hospital emergency departments(36, 122, 123). A systematic review covering this topic, including 10 studies, showed that out-patient management was reasonable in selected patients but in all studies, antibiotics were given(124). Two other systematic reviews, which included a few studies without antibiotic treatment, have come to the same conclusion (59, 60). In all compared trials, there is only one RCT on this topic and it included antibiotic treatment(122). With most guidelines recommending an episode of acute diverticulitis to be CT-verified, it is reasonable to believe that the patients seen at the emergency departments are the majority of patients presenting with suspicion of acute diverticulitis. As noted in both paper I and II, CT was used for diagnosis in the majority of cases at both hospitals, so this change in management has been easier to adapt to. Previous studies have shown that the risk for a complicated course (mainly perforation) of acute diverticulitis is most common in the first episode(34, 88, 89, 125-127) and this strengthens the recommendation that patients with recurrent AUD can be managed without antibiotics and most likely in the out-patient setting.

Different methodologies have been used to assess the risk for misdiagnosing CRC as acute diverticulitis. Most studies have compared the CRC rate in patients with acute diverticulitis to the rate of CRC in screening populations which is reported to be between 0.5% and 0.78% in meta-analyses(128, 129) while some only account for the incidence in their studied cohorts(100, 130-132). The conclusion in most studies has been that the CRC risk is not higher after an episode of AUD(96, 98, 100, 111, 133). Referencing to screening populations can be misleading, since the prevalence is dependent on participation rates, which can be affected by many reasons (geography, symptoms, screening method). Participation varies between 20-60% of invited individuals (128, 134, 135). A recent meta-analysis showed that the pooled prevalence of CRC was 1.9% in all patients. AUD and ACD patients had a prevalence of 1.3% and 7.9% respectively, without including pre-malignant lesions(103). This is higher than the estimated prevalence in both screening populations and the age-adjusted incidence rate in the general population (0.78% and 0.046% respectively)(129, 136). Our results support the increased risk in all acute diverticulitis patients (SMR 6.23 for

AUD and 16.34 for ACD overall), but it was higher in ACD patients and in younger age-groups (<60 years), although the latter group was small, which is a limitation. A recent Spanish study has also confirmed elevated risks of missing CRC after both AUD and ACD(137). It has been claimed that asymptomatic post-AUD patients, have a low risk of having a misdiagnosed CRC, but this could not be evaluated in our study since on-going symptoms at follow-up was missing in 60%.

Our findings are supported by a recent American study, including 932 860 persons with a first episode of acute diverticulitis where the post-diverticulitis CRC rate was found to be 0.57%, whereas the prevalence of CRC without a history of diverticulitis was 0.31% giving an OR 1.8 hence, making the risk almost double(138). Just as in our study the risk was even higher in younger patients <50 years.

The attempt in paper III was to assess the risk of misdiagnosing CRC as diverticulitis and by that, evaluating the need for colon examination. This, by comparing the incidence within one year with data for CRC incidence in the population using data from Cancer Registry. By doing this a reliable estimation of the CRC prevalence could be made, instead of comparison to the incidence in screening populations which can be affected by several confounders. To assess the number of patients at risk, i.e. patients with diverticulitis in the whole country numbers were extrapolated from a local registry. By doing this we believe that the risk ratio gives a more accurate picture of misdiagnosis, rather than just the incidence in diverticulitis patients. The limitations of register-based studied have been mentioned earlier. The Norwegian Cancer Registry has a high validity, but the Norwegian Patient Registry is unvalidated. As in the first two studies, out-patients were not included and therefore some diverticulitis patients might be missing out of which a few might have been diagnosed with cancer within a year.

In the last study we looked at the long-term (5 year) consequences and differences between laparoscopic lavage and sigmoid resection for patients with Hinchey <IV perforated diverticulitis. In the last years, two similar RCTs on this topic, the DILALA and LOLA trial have published their results and there have been several systematic reviews and meta-analyses analysing the short-term results with diverging conclusions(79, 80, 139-149). Besides shorter operating time and lower costs in the laparoscopic lavage arm, the only clear conclusion has been a higher stoma rate in the resection arm. The long-term results show that after five years there is no difference in the rate of secondary operations (including stoma reversal). In the laparoscopic lavage group 30% needed a sigmoid resection while 33% of alive patients still had a stoma in the resection group, compared to only 8 % in the lavage group. The most important reason for the high stoma prevalence in the resection group is that some stomas were never reversed. This reflects the frailty of some patients where reversal wasn't recommended and the wish of some other patients who did not want a reversal. Most

stomas in this group were colostomies and reversal would therefore require a larger surgical procedure with considerable morbidity(150) with complication rates around 40% in some studies(151, 152). Observational studies disclose that the reversal rate after Hartmann's operation is usually around 50-60%(153, 154). The higher stoma-reversal rate in the SCANDIV trial is most likely attributable to the study setting. The stoma reversal rate in the DILALA trial was also high(79). Surprisingly, there were no differences in functional outcomes or QoL between the two groups, so the importance of stoma prevalence might be overstated, although stoma prevalence has shown to affect QoL negatively in a previous study(153).

Cost-analysis performed for both the LOLA arm of the LADIES trial and for the DILALA trial demonstrated much lower costs with laparoscopic lavage compared to resection surgery(155, 156) and stoma equipment accounted for a substantial part after resection. The recurrence rate in the laparoscopic lavage group is consistent with the only other long-term (46 months median) follow-up done on laparoscopic lavage for perforated diverticulitis, which was done retrospectively in the Netherlands(157).

The question of what the optimal treatment strategy is for acute perforated purulent diverticulitis is a recurrent issue. Our belief is that shared decision-making with the patient, where both short- and long-term consequences are considered should guide in the decision-making process. It is important however, to keep in mind that for now, it is impossible to differentiate Hinchey grade III (purulent diverticulitis) and IV (faecal peritonitis) pre-operatively, which needs to be considered when discussing treatment strategies. It is possible that the lavage itself may not add much of healing properties, but that the main benefit is the diagnosing of correct Hinchey grade (specifically ruling out faecal peritonitis). For faecal peritonitis the treatment recommendation is still resection surgery. This is based mostly on empirical knowledge and this was practised in the SCANDIV and in LADIES trials and is still recommended in recent guidelines(43, 44, 78, 80). Therefore, patients with perforated diverticulitis should be prepared for this outcome. Previously the surgical strategy has been Hartmann's operation and not restorative surgery with primary anastomosis, but this has become subject to much interest lately. Two RCT's from 2012 which were both discontinued prematurely (one due to a higher rate of serious complications in the Hartmann arm after stoma reversal at interim analysis, and one due to poor patient accrual) showed no differences in the number of overall complications or morbidity between treatment groups(158, 159). The French DIVERTI trial concluded similar results but couldn't reach the acquired sample size either(160). The DIVA arm of the LADIES trial which enrolled patients with both purulent or faecal peritonitis (Hinchey III &IV) is the most recent multicentre RCT comparing Hartmann's operation to primary anastomosis and was also closed prematurely due to poor patient accrual. It is, however, the largest study to date on this topic and the results revealed that stoma-free survival was significantly higher in patients with primary anastomosis compared with Hartmann's operation (which was their primary endpoint) and no significant differences in morbidity and mortality at one-year follow-up(161). Outcomes were slightly better for Hinchey III patients. These results are interesting but may require advanced surgical technical skills, since a primary anastomosis in the acute setting can be difficult to perform. As not all emergency surgeons are colorectal surgeons, this procedure might be out of reach for some, as has been one proposed explanation to the poor patient accrual in the trials comparing Hartmann's operation to primary anastomosis(159, 160). A recent study comparing colorectal surgeons to non-colorectal surgeons when performing primary anastomosis in acute diverticulitis surgery has revealed a 1.4 times higher mortality rate if the anastomosis was performed by a non-colorectal surgeon(162). Laparoscopic lavage may therefore serve as a bridge to convert an acute situation to an elective one, ensuring patients receiving a later resection under better circumstances and more likely with a primary anastomosis.

Conclusions

The studies in this thesis show that

- Management of AUD without antibiotics is difficult to implement, despite high quality evidence demonstrating the safety. A treatment protocol can facilitate adoption to new knowledge, but continuous efforts are required to change and maintain change of treatment practices over time.
- The use of CT in diagnosing acute diverticulitis has not made follow-up colonoscopy obsolete, demonstrated by the CRC incidence being higher after acute diverticulitis than in the general population. This difference is accentuated in ACD patients.
- The use of laparoscopic lavage for patients with Hinchey<IV perforated purulent diverticulitis has similar long-term outcomes as resection surgery. A third of patients in the laparoscopic lavage group will eventually be subjected to a sigmoid resection. They have a much lower stoma prevalence compared to patients in the resection group. There is no difference in functional outcomes or QoL. Shared-decision making should be encouraged taking both short and long-term consequences into account.

Future perspectives

Clinical treatment and management are constantly changing and hopefully evolving to better practices. With the enormous amount of research being made and papers being published on acute diverticulitis, there is no reason to believe that this development will stop now. The results from paper I & II need further attention, with first implementing a protocol at SUS and then educational measures to facilitate implementation. At HH, reasons for not following the protocol should be further investigated, maybe with interviews. It is important to adapt to new knowledge and accepting new guidelines. Changes to clinical practice should be evaluated with a follow-up of risks, as was done in the first study. The follow-up after acute diverticulitis will probably keep being debated. There is a need to optimise resource utilisation, especially considering the increasing incidence of diverticulitis in younger age groups. It can be claimed that with the increasing use of colonoscopy screening, the need for follow-up colonoscopy decreases, but the screening in most countries is executed from 50 years of age. Since our study and others show an increased relative risk of CRC in younger patients post diverticulitis (probably due to the low incidence of CRC in the general population in this group) for now the recommendation of follow-up with colon examination still avails. Future studies on AUD should consider the out-patient management by GPs for a more accurate picture of the whole acute diverticulitis spectrum. The use of laparoscopic lavage should be an accepted tool in the on-call surgeons' arsenal for treating acute purulent perforated diverticulitis. Continuous evaluation in a real-world clinical setting is warranted. Presently, it is impossible to differentiate between purulent and faecal peritonitis preoperatively. Future studies should concentrate on methods to do so. Coming RCTs may compare laparoscopy with and without lavage to antibiotic treatment only. Risk factors for failure of laparoscopic lavage should also be explored, in order to better guide patients between different treatment options. So far, the only study evaluating this, was done retrospectively and showed immunosuppression as the only risk factor for failure(163).

Lastly, the quest for improved treatment and management of this multifaceted disease continues with clinical practices being questioned and changes in new guidelines. Amidst this, the implementation and follow-up of changes should not be forgotten.

Populärvetenskaplig sammanfattning

Inflammation av tarmfickor lokaliserade i tjocktarmen s.k. divertikulit är en mycket vanlig åkomma i Sverige och i de flesta västländer. Frekvensen stiger med ökande ålder, i övrigt är det oklart vad som föranleder denna fickbildning och särskilt vad som orsakar inflammation i dessa. Vissa livsstilsfaktorer kan öka risken såsom övervikt, rökning och viss kost. Även ärftlighet och andra sjukdomar tros spela viss roll. Tarmfickorna bildas oftast i slutet av tjocktarmen och symptom vid inflammation är smärta, ofta i nedre delen av buken till vänster, feber och förhöjda inflammatoriska markörer vid blodprovstagning. Om inflammationen begränsas till tarmfickorna i tjocktarmen, kallas det akut ***okomplicerad*** divertikulit. Behandlingen har tidigare varit antibiotika och tarmvila. Om inflammationen sträcker sig utanför tarmväggen och t.ex. orsakar ett hål i tarmfickan, kallas detta akut ***komplicerad*** divertikulit. Medan okomplicerad divertikulit oftast är mild och kan läka ut spontant, har den traditionellt behandlats med antibiotika. Komplicerad divertikulit däremot är ett allvarligt tillstånd med både ökad sjuklighet och i vissa fall dödlighet. Behandling vid komplicerad akut divertikulit har varit antibiotika och akut kirurgi, oftast med en operation där man tar bort tarmavsnittet som är sjukt samt anlägger en s.k. stomi (påse på magen som avföringen kommer ut i). På senare tid har man ifrågasatt denna stora operation, eftersom studier visat att tillståndet kanske kan lösas med en titthålsoperation. Finner man då endast var i bukhålan och ingen avföring kan tillståndet botas genom att utföra en sköljning av bukhålan.

Vid akut okomplicerad divertikulit har man på senare tid också ändrat behandlingen. Antibiotika verkar inte tillföra något mervärde och påverkar varken sjukdomsförlopp, komplikationsrisk, vårdtid eller återfallsrisk. Efter tillfrisknande brukar patienter med akut divertikulit följas upp med en kolonutredning (koloskopi eller kolonröntgen) för att säkerställa att det inte gömmer sig någon cancer i tarmen, som misstolkats som divertikulit. På senare tid har frågan om kolonutredning diskuterats flitigt, eftersom majoriteten av patienter med akut divertikulit numera genomgår en röntgenundersökning när de söker akut för att säkerställa diagnos (till skillnad från tidigare då diagnosen sattes på typiska kliniska tecken) och därför skulle kolonutredning kanske kunna avvaras.

Syftet med denna avhandling är att undersöka förändrade handläggningar vid akut divertikulit, både okomplicerad och komplicerad samt vid uppföljning.

De två första studierna undersöker hur många patienter med okomplicerad divertikulit som behandlas utan antibiotika vid Helsingborgs lasarett, och om införandet av ett behandlingsprotokoll för handläggning av akut okomplicerad divertikulit utan antibiotika, påverkade antibiotikaanvändning. Därefter jämfördes resultaten med uppföljande studie några år senare där också andelen patienter som behandlades utan antibiotika på Skånes Universitets Sjukhus (SUS), där man inte infört ett behandlingsprotokoll, inkluderades. I Helsingborg handlades 60% av patienterna utan antibiotika det första halvåret efter att protokollet hade införts, jämfört med 4% innan protokollet. Två år senare hade siffran sjunkit till 48%. På SUS däremot var det endast 11% som behandlades utan antibiotika under samma tidsperiod. Orsakerna till den höga antibiotikaanvändningen behöver studeras närmare i framtiden.

Den tredje studien analyserade hur många patienter med akut divertikulit som fick en koloncancerdiagnos inom ett år efter genomgången divertikulit som ett mått på feldiagnostisering. Alla patienter i Norge med akut divertikulit under en tre-årsperiod matchades mot det norska cancerregistret och journalerna granskades. En kvot beräknades avseende hur stor ökad risk som förelåg att erhålla en koloncancerdiagnos inom ett år om en individ haft akut divertikulit, vilken jämfördes med den generella koloncancerförekomsten i befolkningen. Både efter akut okomplicerad men särskilt efter komplicerad divertikulit förelåg en ökad koloncancerrisk, som var mer uttalad i yngre åldersgrupper (<60 år). Rekommendationen är att fortsätta följa upp patienterna med en kolonundersökning.

Den sista studien undersökte långtidsresultat hos patienter med akut komplicerad divertikulit, i form av de som drabbades av ett hål i tarmfickorna. En grupp behandlades med titthålskirurgi och sköljning av bukhålan och jämfördes med dem som opererades med borttagande av tarm. Korttidsuppföljningen hade inte visat någon skillnad i dödlighet mellan grupperna, men bland de som genomgick buksköljning hade fler patienter genomgått ytterligare en operation och de hade lägre andel stomier. Långtidsuppföljningen visade fortsatt ingen skillnad i dödlighet eller andelen totala operationer mellan grupperna och fortsatt färre stomier hos de som genomgått buksköljning. Det var ingen skillnad i livskvalitet mellan de båda grupperna. Slutsatsen var att buksköljning är lika bra som tarmoperation, på kort sikt kan det innebära risk för ytterligare operationer, men stomiförekomsten är lägre. Om möjligt bör man därför diskutera val av operationsmetod med patienten innan operation och då ta med både kort-och långtidskonsekvenser i beräkningen.

Errata

Paper I

Abstract: C-reactive protein was significantly higher in patients treated with antibiotics vs non-antibiotics, should be (median 117 mg/L vs. 52, p=.008), instead of (median 117 mg/L vs. 70, p=.005).

In **Table 2b**. should be Total n=47, without antibiotics n=28 instead of Total n=50, without antibiotics n=31 and also in text under results (page 65). After the introduction of the protocol, 60% (28/47) of the patients were managed without antibiotics instead of, After the introduction of the protocol, 60% (31/50) of the patients were managed without antibiotics.

In **Table 4.** should be any complication total n=21 (16) instead of n=18 (14) and total antibiotics should be n=19 (19) instead of n=16 (16) and p=.10 instead of p=.18.

In the last paragraph in **Results** should be "Among patients treated
with antibiotics, 19% had a recurrence instead of 16% had a recurrence".

Paper III

In Figure 1. "Study flowchart" in the second box to the right should be "Estimate CT-verified ACD whole population n = 1206" instead of "Estimate CT-verified AUD whole population n = 1206" and likewise in the last box to the right should be "Estimated rate of CRC the year after CT-verified ACD 39/1206 = 3.2%" instead of "Estimated rate of CRC the year after CT-verified AUD 39/1206 = 3.2%"

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New Treatment Aspects of Acute Diverticulitis

Najia Azhar is a colorectal surgeon at the Department of Surgery, Skåne University Hospital in Malmö. Her thesis examines the changing clinical aspects of treatment and management of acute diverticulitis.

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