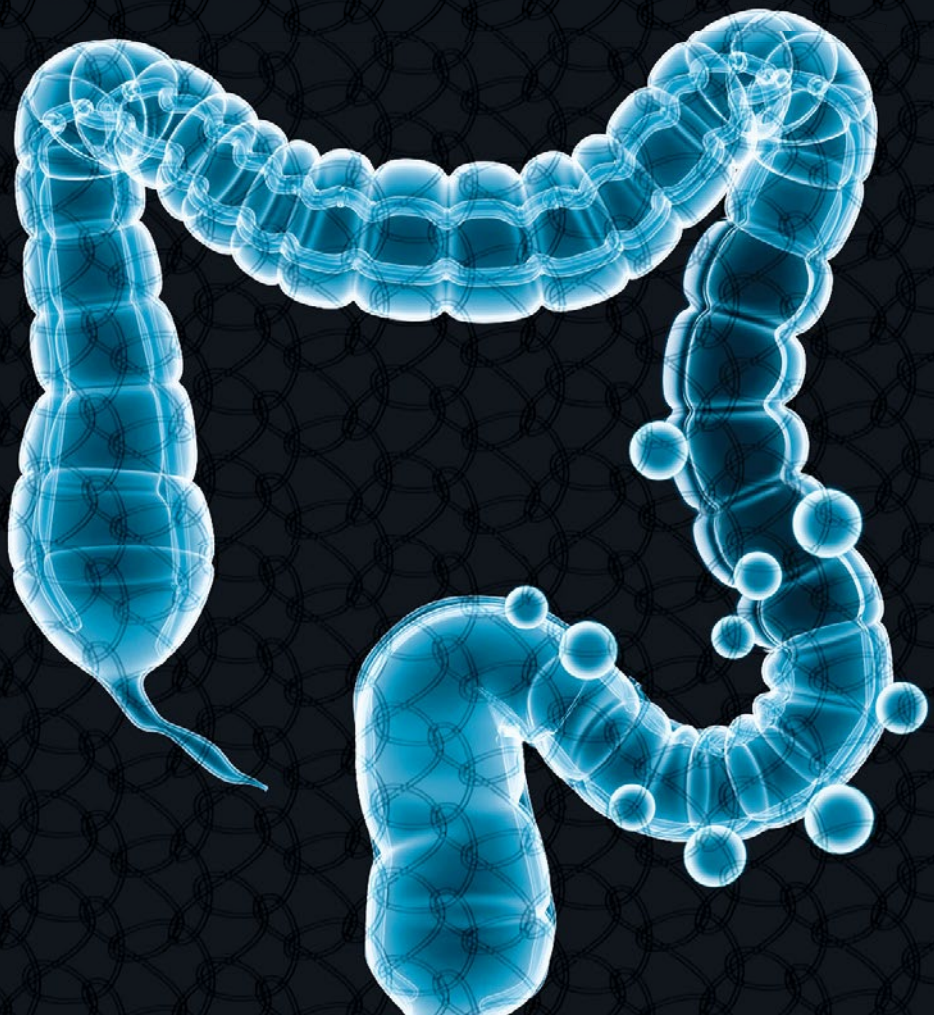
NEW APPROACHES TO THE SURGICAL TREATMENT OF INTRA-ABDOMINAL INFECTION

IRENE MULDER



New Approaches to the Surgical Treatment of Intra-abdominal Infection

Irene M. Mulder

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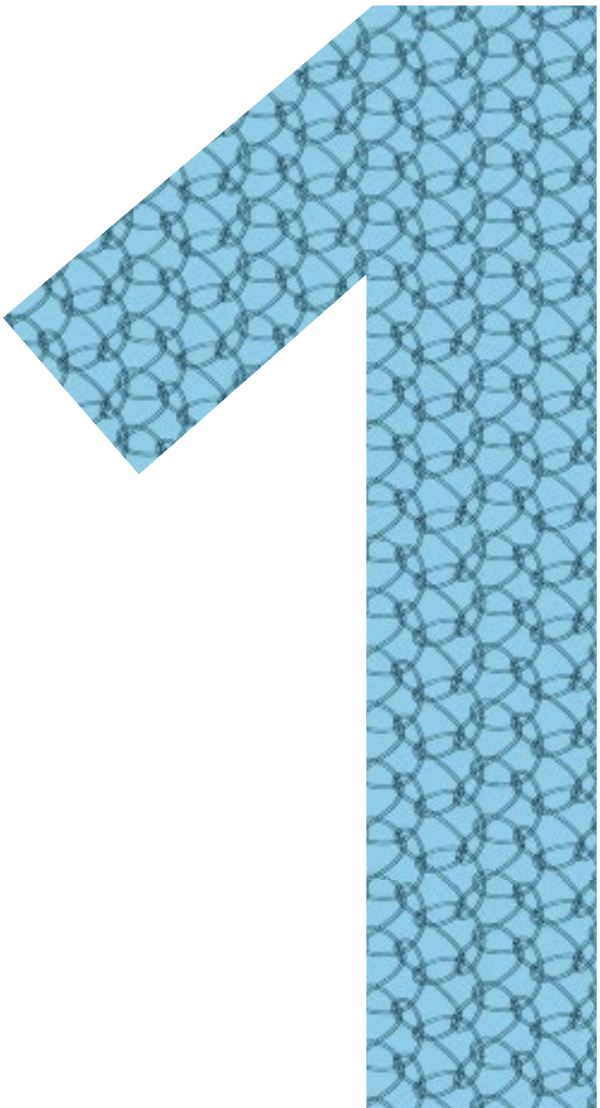
CHAPTER



General introduction and outline of the thesis

INTRA-ABDOMINAL INFECTION

Abdominal pain

Of all visits to the emergency department 10-15% of patients present with acute abdominal pain[1,2]. A large proportion (38-72%) of patients with acute abdominal pain are admitted to the hospital[3-5]. The cause of abdominal pain can range from self-limiting to life threatening disease. Other complaints in the presence of abdominal pain are usually anorexia, vomiting, diarrhoea and constipation. Clinical findings include fever or hypothermia, tachycardia, tachypnea, decreased bowel sounds, abdominal tenderness or guarding. Diffuse abdominal pain and generalised tenderness are often symptoms of intra-abdominal infection. Approximately in half of patients abdominal pain, as presented in the emergency department, is caused by infection[4].

Peritonitis

The abdominal cavity is a sterile compartment which is covered by a mesothelial membrane surrounding the abdominal viscera: the peritoneum. Intra-abdominal infection refers to the inflammatory responses of the body in response to inflammation (without bacteria) or infection (with bacteria) within the abdomen. Whether bacterial contamination will transform to intra-abdominal infection depends on bacterial pathogenicity and host defence mechanisms[6]. Many different diseases can cause the activation of the immune system leading to inflammation of the peritoneum (peritonitis).

Primary peritonitis describes infection of the peritoneum caused by bacteria from a source outside the abdomen, usually bacteria from the bloodstream entering the peritoneal cavity.

More common is secondary peritonitis which results from an infection inside the abdominal compartment. Common causes of secondary peritonitis are perforation of the gastrointestinal tract (58%), postoperative anastomotic leakage (27%), ischemia (6%) and inflammation (4%). Perforation is localised in the lower gastrointestinal tract (64%), upper gastrointestinal tract (25%), or appendix (2%)[7]. When anatomical disruption of an organ is present it is considered a complicated intra-abdominal infection.

Classification of peritonitis

Peritonitis is mainly classified depending on the extent of contamination of the peritoneal cavity. A unique defence mechanism is present in the peritoneal cavity designed to confine the infection which can lead to intra-abdominal abscess formation. When only a part of the peritoneum is affected due to nearby inflammation of an organ or abscess this will cause mild symptoms. In cases of inflammation of the total abdominal cavity (generalised peritonitis), as a rule patients will experience more complaints. In most

classifications purulent peritonitis is discriminated from faecal peritonitis. This because the latter can only be explained by perforation of the bowel with accessory high bacterial load. Available classification systems are the Mannheim Peritonitis Index, the left colonic Peritonitis Severity Score (PSS) and the Hinchey classification for perforated diverticulitis[8-10]. Classification of peritonitis can be useful because it may guide treatment and enables research.

Abdominal sepsis

The immune response to invasion of the abdominal cavity by micro-organisms is a complex network of pro-and anti-inflammatory cascades. When the immune system does not resolve the infection progression of the infection to the systemic circulation can progress to sepsis. Common signs are fever, tachycardia, tachypnea, decreased urine production and confusion. Due to decreased systemic vascular resistance hypotension and subsequent shock can occur. When shock is not treated adequately this can lead to multi organ failure and even death.

Primary treatment of sepsis consists of intravenous fluids and antibiotics followed by elimination of the source of infection. In case of abdominal sepsis contained abscesses can be drained percutaneously. When peritoneal contamination has lead to purulent or faecal peritonitis surgical treatment is warranted. Depending on the condition of the patient surgery can comprise short damage-control surgery or lengthy complex surgery with anastomosis of the bowel after resection. Despite considerable improvement in antibiotic treatment, intensive care capacity and treatment options mortality is still between 9% and 30% in patients with abdominal sepsis[11,12].

DIVERTICULITIS

Apart from appendicitis, one of the most frequent causes of abdominal infection is represented by diverticulitis. In the Netherlands colonic diverticular disease leads to over 18.000 hospital admissions per year[13]. This disease comprises many different conditions: from asymptomatic diverticulosis to perforated diverticulitis with systemic sepsis.

Pathogenesis of diverticular disease

Diverticula arise at the point where the vasa recta penetrate the colonic wall to supply blood to the mucosa of the colon[14]. This weak point is where the mucosa and submucosa protrude through the muscle layer of the colonic wall. Pathogenesis of diverticulosis has not been conclusively established. Many theories on the development of diverticulosis have been proposed, including dietary habits, medicine use, motility disorders of the colon and collagen abnormalities of the colonic wall[15]. The prevalence of diverticulosis is estimated at 5% by the age of fourty years and increases with age up to 50-70% in

octogenarians[16,17]. Most people with diverticulosis remain asymptomatic[18,19]. Symptoms of diverticular disease include change of bowel habit, abdominal pain, symptoms of inflammation, diverticular bleeding and fistula formation.

Diverticulitis is the result of diverticular inflammation. There are several theories about the pathogenesis. It was believed that fecalith obstruction leads to an increased pressure of the diverticular sac with bacterial overgrowth, resulting in necrosis and perforation of the diverticulum. More recent studies suggest low-grade inflammation as a form of inflammatory bowel disorder and possible changes in colon flora in patients with diverticulitis[20]. Of all patients with an episode of acute diverticulitis only 25% present with complicated disease including abscess formation, fistula, obstruction or perforated disease with peritonitis.

Classification and diagnosis of diverticulitis

Several grading systems exist for acute diverticulitis of which the Hinchey Classification is still mostly used. Edward Hinchey proposed to differentiate according to the intra-operative degree of abdominal contamination[8]. In current practice clinical evaluation alone seems inadequate to make a diagnosis of diverticulitis and adequately grade diverticulitis therefore radiological investigation is performed in most cases[21-23]. Based on radiological finding patients may be selected for conservative treatment of complicated diverticulitis. It is of great importance to differentiate between uncomplicated and complicated diverticulitis in patients because of the high morbidity and mortality in case of perforation[24,25].

In **Chapter 2** the accuracy of preoperative staging of perforated diverticulitis by CT scanning is investigated.

Operative treatment of diverticulitis

The treatment of diverticular disease depends on the severity of the disease. In case of complicated diverticular disease operative treatment is mostly the treatment of choice. Since the beginning of the previous century, a three-stage operation strategy was common practice. A preliminary transverse colostomy was advised with a period of three to six months delay before resection of the inflamed sigmoid. The rationale for this strategy was that primary resection was too difficult and hazardous during the acute stage of the disease. After several months, the second stage - resection of the involved bowel - could be performed to treat and prevent relapse. The third stage involved reconstruction of the bowel with reversal of the colostomy after several months of recovery. Mortality rates were high when using this complex treatment strategy. The conviction arose that the colonic segment with the perforation had to be resected immediately eliminating the remaining source of infection in the peritoneal cavity. Subsequently a two-stage operation

i.e. Hartmann's procedure, became the preferred surgical strategy, although Henri Hartmann had only developed his operation for rectal carcinoma originally. During the Hartmann's procedure sigmoid colectomy with subsequent colostomy is considered the first step, the second stage being represented by the colostomy closure. This treatment strategy remained the treatment of choice for decades.

Improvement in surgical and radiological intervention techniques and progress in the management of peritoneal sepsis have resulted in increasing interest in colonic resection with direct construction of bowel continuity since the 1990s. However, fear of anastomotic leakage often deters many surgeons from performing a one-stage procedure with primary anastomosis under conditions of generalised peritonitis.

In 1996, a new nonresectional laparoscopic approach was described[26]. In patients with purulent peritonitis without gross fecal contamination (Hinchey III), only laparoscopic peritoneal lavage, inspection of the colon, and the placement of abdominal drains appeared to diminish morbidity and improve outcome[26-28].

In **Chapter 3** a narrative review on treatment options for perforated diverticulitis is presented.

In 2008 the results of a first large series was published on patients treated by laparoscopic lavage and drainage of the abdominal cavity without colonic resection in case of purulent peritonitis[29].

In **Chapter 4** the early experience of Dutch surgeons with laparoscopic peritoneal lavage for complicated diverticulitis in a historical series is investigated.

To confirm the published success rates of laparoscopic lavage a multicentre randomised controlled trial on operative treatment strategies for perforated diverticulitis was initiated. The LADIES-trial is a joint initiative between the LOLA-trial, which compares laparoscopic lavage and drainage with resectional surgery in purulent peritonitis, and the DIVA-trial, which compares Hartmann's procedure with sigmoid resection with primary anastomosis in purulent or faecal peritonitis.

In **Chapter 5** the study protocol of the LADIES-trial is described.

In **Chapter 6** the clinical results of the surgical treatment with laparoscopic lavage of this randomised trial are reported.

Guidelines on treatment of diverticulitis

The diagnosis and treatment of diverticulitis are marked by many speculatives and dogmas. In recent years research on diverticulitis is extensively performed and published.

In **Chapter 7** the Dutch National Guidelines for diagnosis and treatment of acute colonic diverticulitis is summarised. The guidelines are based on an evidence-based review of the literature by a multidisciplinary workgroup initiated by the Dutch Society of Surgery.

TREATMENT OF COMPLICATIONS FOLLOWING INTRA-ABDOMINAL INFECTION

Abdominal surgery

If patients require surgical treatment for perforated diverticulitis they are mainly operated via open surgery, although experience with laparoscopic surgery is increasing. Open surgery is mostly performed by opening the midline of the abdominal wall through the linea alba. Following surgery the wound edges of this avascular plane of the abdominal wall are sutured back together.

Incisional hernia

When healing of this incision fails an incisional hernia will develop. This is defined as an abdominal wall gap with or without a bulge in the area of a postoperative scar[30]. Incisional hernia is one of the most frequent complications following abdominal surgery with an incidence of 10-20% after a ten year follow-up[31-34]. Perforated diverticulitis leads to purulent or faecal peritonitis with high bacterial load with increased risk of surgical site infection and compromised wound healing[35].

Incisional hernia repair

Due to the experienced pain or discomfort, risk of strangulation of herniated bowel and negative impact on quality of life, repair of incisional hernia is often performed[36,37]. Primary suture repair of large abdominal defects resulted in a recurrence rate of up to 63%[38].When a mesh is used during hernia repair to reinforce the abdominal wall recurrence rates of herniation is reduced by 50%[39]. Mesh repair is considered the gold standard, however the performed technique and mesh material are far from standardised until now.

Complications following incisional hernia repair

Implantation of meshes can be complicated by mesh infection, erosion, shrinkage and adhesion formation. Mesh infection is a feared complication and reported in up to 16% of patients after hernia repair[40]. Failure of the hernia repair is influenced by many factors such as mesh material. Therefore many modifications to the mesh have been made to optimize biocompatibility and reduce complications.

Currently non-resorbable synthetic materials are the most commonly used prosthesis for reinforcement of ventral hernias. Advantages of synthetic meshes are low recurrence rates, ease of use and relatively low costs. Infection of the mesh might be reduced in macroporous meshes because large pores permit infiltration of macrophages and allow rapid fibroplasia and angiogenesis, with reduced infiltration and growth of bacteria[41,42]. The drawback of macroporous meshes is the increased risk of visceral adhesions to the site of the repair[41,43,44]. To reduce adhesion formation antiadhesive coatings have been added to synthetic meshes with positive results[44-46]. Mesh infection often necessitates removal of the mesh, which leaves the patient with a contaminated field and an abdominal wall deficit that is often larger than the original hernia which makes the use of synthetic mesh debatable[47,48].

In case of high risk of infection at the surgical site a biological mesh is recommended for ventral hernia repair[49]. The risk is significantly increased in incisional hernias type III and IV (Working Group Incisional Hernia of the European Hernia Society) as often is the case after operations for perforated diverticulitis of the colon. Biological meshes are extracellular scaffolds, processed from animal (bovine or porcine) small intestine submucosa, pericardium, or dermis. The donor tissue is said to be cleared of cells and immunogenic particles, after which a scaffold of extracellular matrix (ECM) remains. After implantation the scaffold is gradually vascularized and remodeled into the host tissue while degradation of the ECM takes place[50,51]. To increase biomechanical strength chemical crosslinking of the biological mesh can be conducted. Crosslinking stabilizes the 3-dimensional structure of the ECM. This improves withstanding of the ECM's enzymatic degradation, which can be accelerated by inflammation or infection at the implantation site[52-54].

In **Chapter 8** infection rate, adhesion formation, incorporation and shrinkage of synthetic and biological meshes after implantation in a contaminated environment are compared.

In **Chapters 9** and **10** the infectious complications and functional outcome of crosslinked and non-crosslinked biological meshes in a contaminated environment and clean environment are investigated, respectively.

Adhesion formation

Intraperitoneal adhesion formation remains a major clinical problem with an incidence up to 93% after abdominal surgery[55]. Adhesions are considered a physiologic response to surgical trauma or infection like perforated diverticulitis[56,57]. However postoperative adhesions result in an increased risk of small bowel obstruction, chronic abdominal pain, infertility and inadvertent bowel injuries at future operations[58]. To prevent formation of adhesions surgical techniques are adjusted to reduce tissue injury, such as the introduction

of laparoscopic surgery. Furthermore intra-abdominally positioning of various barriers have been studied.

In **Chapter 11** the influence of a new adhesion barrier on the formation of adhesions in a peritonitis rat model is evaluated.

In **Chapter 12** the results of the studies in this thesis are discussed and future perspectives are described.

In **Chapter 13 and 14** the results of the studies are summarised in the English and Dutch language, respectively.

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PART ONE

Treatment of perforated diverticulitis

CHAPTER

Preoperative staging of perforated diverticulitis by computed tomography scanning

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ABSTRACT

Background

Treatment of perforated diverticulitis depends on disease severity classified according to Hinchey's preoperative classification. This study assessed the accuracy of preoperative staging of perforated diverticulitis by computerized tomography (CT) scanning.

Methods

All patients were included who presented with perforated diverticulitis between 1999 and 2009 in two teaching hospitals of Rotterdam, the Netherlands, and in addition had a preoperative CT scan within 24 h before emergency surgery. Two radiologists reviewed all CT scans and were asked to classify the severity of the disease according to the Hinchey classification. The CT classification was compared to Hinchey's classification at surgery.

Results

Seventy-five patients were included, 48 of whom (64%) were classified Hinchey 3 or 4 perforated diverticulitis during surgery. The positive predictive value of preoperative CT scanning for different stages of perforated diverticulitis ranged from 45 to 89%, and accuracy was between 71 and 92%. The combination of a large amount of free intra-abdominal air and fluid was strongly associated with Hinchey 3 or 4 and therefore represented a reliable indicator for required surgical treatment.

Conclusions

The accuracy of predicting Hinchey's classification by preoperative CT scanning is not very high. Nonetheless, free intra-abdominal air in combination with diffuse fluid is a reliable indication for surgery as it is strongly associated with perforated diverticulitis with generalized peritonitis. In 42% of cases, Hinchey 3 perforated diverticulitis is falsely classified as Hinchey 1 or 2 by CT scanning.

INTRODUCTION

Diverticular disease has become more prevalent in Western countries[1]. About 10–25% of individuals with diverticulosis will develop symptomatic diverticulitis, and of these, 15% will develop significant complications, such as perforation[2]. Although the absolute prevalence of perforated diverticulitis complicated by generalized peritonitis is low, its importance lies in the significant postoperative mortality, ranging from 4 to 26% regardless of the surgical strategy selected[3,4]. The optimal treatment for perforated diverticulitis is still a matter of debate[5].

Optimal treatment strategies are based on disease severity as classified by Hinchey (Table 1)[6]. Today, a conservative treatment with antibiotics (and abscess drainage) is advocated for Hinchey 1 and 2 perforated diverticulitis[7]. Patients presenting with perforated diverticulitis with generalized peritonitis (Hinchey 3 and 4) should undergo emergency surgical treatment. Laparoscopic peritoneal lavage without resection of the affected bowel segment in patients with purulent peritonitis (Hinchey 3) appears to diminish the morbidity and improve outcome[8-10], whereas acute resection should be performed in patients with gross fecal peritonitis (Hinchey stage 4)[9].

Unfortunately, (the modified) Hinchey's classification is based on clinical findings during surgery. Ideally, one should be informed about the severity of the disease to optimize treatment strategy. Today, computed tomography (CT) scanning is the modality of choice in the assessment and management of diverticulitis with its high sensitivity and specificity[11-15]. With CT-guided percutaneous abscess drainage (PCD), it has also become an important therapeutic modality[11-16]. The CT-based classification by Hansen– Stock can be used as a classification system and accounts for asymptomatic diverticulosis as well as complicated diverticulitis in different stages, including perforation[17]. Nevertheless, the degree of peritonitis—and hence the severity of disease—in perforated diverticulitis can be represented best by the modified Hinchey's classification.

The aim of this study was to assess the accuracy of preoperative CT scanning in predicting the stage of severity of perforated diverticulitis. The CT findings are compared with the clinical findings during surgery classified according to the Hinchey classification[6].

Table 1. The modified Hinchey classification of perforated diverticulitis.

Hinchey classification	Clinical features
0	Mild clinical diverticulitis
1 a	Confined pericolic inflammation or phlegmon
b	Confined pericolic abscess
2	Pelvic, intra-abdominal, or retrocolic abscess
3	Generalized purulent peritonitis
4	Generalized fecal peritonitis

In the original Hinchey classification, Hinchey 1a and 1b were combined

MATERIALS AND METHODS

All patients who underwent emergency surgery for perforated diverticulitis between January 1999 and January 2009 at the Erasmus University Medical Centre and Maasstad Hospital in Rotterdam, the Netherlands, were selected from computerized surgery registration databases. After patient selection was completed, predetermined parameters were extracted from medical records and the computerized patient's registration databases. The indication for surgery was based on clinical and radiological findings. Only patients who underwent preoperative CT scanning within 24 h before emergency surgery were included in this study, because clinical evolution could disturb comparability between radiologic and surgical findings, when the interval is longer. Patient characteristics, preoperative findings, for example, Hinchey classification, Mannheim Peritonitis Index, specific findings on CT scan, and postoperative outcome were registered and analyzed.

A total of 158 consecutive patients underwent emergency surgery for perforated diverticulitis during the study period. Forty-six patients were excluded from analysis because they underwent emergency surgery without the performance of a preoperative CT. These patients were operated on based on clinical assessment only (n=24), free intraperitoneal air on plain radiography (n=16), or specific findings during ultrasound (n=6). Another 37 patients were excluded because time of scanning was more than 24 h before surgery (median 3 days, range 2–50 days). The remaining 75 patients were included in the study, and the characteristics of these patients are listed in Table 2.

All preoperative CT scans were independently reviewed by a consultant radiologist and a senior radiology resident. Both were asked to classify disease severity according to the Hinchey classification (Table 1). Features recorded by the radiologist were, among others, thickness of bowel wall, number of diverticula, pericolic inflammation, stenosis, amount and location of free intraperitoneal air, fluid, and/or abscesses. Based on these features,

Table 2. Patient characteristics.

Characteristics	
Gender (male/female)	30/45 (40/60%)
Hospital (Erasmus/ Maasstad)	38/37 (51/49%)
Age	Median 63 years (range 23-89)
ASA I	13 (17%)
II	25 (33%)
III	27 (36%)
IV	10 (13%)
MPI	Median 19 (range 5-39)

Values in parentheses are percentages unless indicated otherwise.
ASA American Society of Anaesthesiologist classification, *MPI* Mannheim Peritonitis Index

they were asked to grade the severity of disease subjectively according to Hinchey's classification. Both radiologists were blinded to the patients' surgical and pathological findings at the time of CT review. If there was any discrepancy in the radiologists' evaluations, a consultation between them took place so that they could come to a final agreement. Different types of CT scanners were used ranging from single-slice to 64-slice dual-source scanners. CT-examinations performed after 2001 at the Erasmus University and after 2006 at the Maasstad Hospital could be digitally analyzed. Different imaging protocols were used, and slice thickness varied between 3 and 8 mm. The contrast agent used was intravenous, oral, and/or rectal.

RESULTS

Sixty-six patients (88%) received intravenous contrast, and 15 of them (20%) received rectal contrast at the same time. Nine patients (12%) underwent CT scanning without contrast. The location of the diverticular diseases was located in the sigmoid colon in 72 patients (96%), in the descending colon in 16 patients (21%), and in the transverse colon in 2 patients (3%). Extra luminal air was found in 47 patients (64%), and abscesses were found in 41 (55%) patients. CT scanning showed bowel obstruction in one patient. No fistula formation was observed. Median colonic thickness was 9 mm (range 2–20 mm).

Comparison of findings during surgery (gold standard) and CT findings regarding Hinchey classification is shown in Table 3. The inter-observer agreement for scoring Hinchey was high with a discrepancy rate of 7% (5/75). Final agreement was reached in the 5 cases that initially were differently scored by the radiologists. In all cases, the initial conclusion of the consultant radiologist was chosen.

Forty-eight of the 75 patients (64%) were correctly staged by CT scanning in accordance with the Hinchey classification. Based on the results, sensitivity, specificity, positive predictive values (=precision of CT), and accuracy of CT were calculated for all stages of disease (Table 3). The use of rectal contrast did not significantly increase the accuracy of CT scanning (correctly staged with rectal contrast: 62%, without rectal contrast: 73%; P=0.55). Stratifying the patients according to time intervals (within 12 h and between 12 and 24 h before surgery) did not change the result (correctly staged with 12 h: 62%, between 12 and 24 h: 66%: P=0.81). In Table 4, distribution of specific CT features is listed for the different Hinchey stages found during surgery. Signs of diffuse intraperitoneal fluid on CT scans are not seen in Hinchey 1 and 2 patients (both 0%). Nevertheless, free intraperitoneal fluid is not pathogmonomic for Hinchey 3 or 4 perforated diverticulitis, as it is only seen on CT scans in 38 and 56% of cases, respectively. Intraperitoneal air in different amounts is found in almost all stages of perforated diverticulitis (75–100%). The combination of diffuse free air and intra-abdominal fluid is strongly associated with Hinchey 3 and 4 (positive predictive value: 80 percent). The positive predictive value of CT scanning for perforated diverticulitis that requires surgical treatment (e.g., Hinchey 3 and 4) is 94%. Unfortunately, the negative predictive value is only 61%.

Table 3. Hinchey classification according to CT imaging compared to the true findings during surgery for perforated diverticulitis.

Hinchey classification according to CT-scan	**Hinchey classification at surgery**			
	1	2	3	4
1	13	***1***[b]	***7***[b]	--
2	***2***[a]	9	***9***[b]	--
3	***2***[a]	--	16	--
4	--	--	***6***[a]	10
Performance of CT-scan				
Sensitivity (%)	76	90	42	100
Specificity (%)	86	83	95	91
Positive predictive value (%)	62	45	89	63
Negative predictive value (%)	93	98	61	100
Accuracy (%)	84	85	71	92

[a] overstaged | [b] understaged | The numbers that are underlined refer to the patients that are correctly classified by preoperative CT | The numbers that are italicized refer to the patient that are incorrectly classified by preoperatieve CT | *CT* computed tomography

Table 4. Specific computed tomography findings compared to true findings during surgery (Hinchey classification) in patients with perforated diverticulitis.

Hinchey classification at surgery	Free intraperitoneal air (%)	Loculated gas bubbles (%)	Diffuse intraperitoneal fluid (%)	Abscess (%)	Pericolic fluid collection (%)
1	25	50	0	30	15
2	35	65	0	100	50
3	66	33	38	47	56
4	100	0	53	30	29

DISCUSSION

The optimal treatment strategy for perforated diverticulitis depends on the severity of disease classified according to Hinchey's classification[18]. Ideally, perforated diverticulitis is adequately staged before surgery in order that the optimal treatment strategy (antibiotics, abscess drainage, surgery) can be chosen. In recent years, CT scanning has become the imaging modality of choice to determine the extent of the disease and surgeons tend to rely more frequently on the CT findings to decide upon further treatment.

The present study shows that CT scanning has a high specificity for Hinchey 3 and 4 perforated diverticulitis (95 and 91%, respectively). This means that when the radiologist diagnoses Hinchey 3 or 4 diverticulitis, this compares well with the true findings, and hence, emergency surgery is indicated. The positive predictive value for surgery is 94%, which is excellent. Nevertheless, sensitivity for Hinchey 3 is low (42%), meaning that a significant number of patients with Hinchey 3 diverticulitis are understaged (as Hinchey 1 or 2) by retrospective assessment of the CT scan. The main reason for this discrepancy was the relatively small amount of free intra-abdominal pus found during surgery. This can easily be missed on an emergency CT scan (Figure 1). Another reason for the relatively high number of misclassifications of Hinchey 3 perforated diverticulitis by preoperative CT scanning could be rupture of a diverticular abscess, in which Hinchey 2 perforated diverticulitis found on the CT scan has proceeded toward Hinchey 3 at the time of surgery[19]. It is therefore possible that future patients who undergo CT scanning are classified as Hinchey 1 or 2 perforated diverticulitis and are treated according to these CT findings (that is conservatively), are in reality Hinchey 3 patients (n=16/41; 39% of Hinchey 1 and 2 cases; Table 3), and should have been treated surgically. It seems that only Hinchey 4 perforated diverticulitis is excellently staged by CT scanning. The conclusion after the radiologists' report will always be that emergency surgery is indicated in these patients. Due to the low sensitivity of CT scanning in Hinchey 3 patients, the predictive value of CT for conservative treatment is only 61%.

The inter-observer agreement for scoring Hinchey was high. In 5 cases, the consultant radiologist convinced the resident to revise her conclusion. In daily practice, and especially during night shifts, the CT scan is first read by the radiology resident. If necessary, the original reading is changed by the consultant radiologist, who will see the CT only the day after. The relative inexperience by the residents could lead to over- or undertreating a patient with perforated diverticulitis who undergoes a CT scan. Although in this study overtreatment or undertreatment was not caused by this phenomenon, we recommend a dedicated consultant radiologist to read all CT scans performed on patients in this category.

Lohrmann et al. previously investigated the value of CT scanning in diverticular disease[14]. They stated that CT scanning correctly determined Hinchey stage in 93% of patients. Unfortunately, only 7 patients were found to have Hinchey 3 or 4 perforated diverticulitis (CT sensitivity of 71% in this subgroup). This suggests that the study was based on a heterogeneous group of patients, only a few of whom had perforated diverticulitis with peritonitis.

Ritz et al. conclude in their study on 204 patients who had undergone surgery for diverticular disease that CT scanning is an accurate modality for staging this disease[15]. The positive predictive value of CT scanning compares well with the results of this present study, especially the positive predictive value of perforated diverticulitis Hinchey 3 and 4 (100 and 94%). Unfortunately, surgery was performed within 24 h after CT scanning in only 42 patients (21%). In all other patients, elective surgery was performed after a mean of almost 7 days of initial conservative therapy with antibiotics or percutaneous abscess drainage. No new CT scan was performed prior to elective surgery; hence, clinical evolution could have disturbed comparability between radiologic and surgical findings.

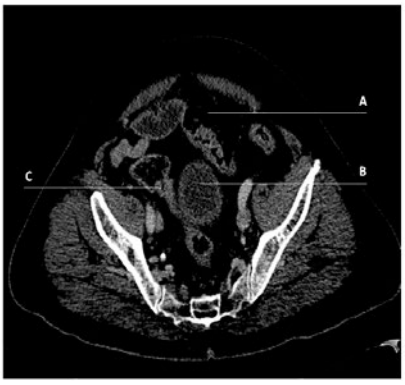

Figure 1. Preoperative CT image without evident signs of free fluid or generalized peritonitis of a patient who appeared to have Hinchey 3 perforated diverticulitis during surgery. *A* free air; *B* bladder; *C* colonic diverticulum

The present study exclusively covers patients with perforated diverticulitis. Nevertheless, 36% of the patients studied who underwent surgery appeared to have Hinchey 1 or 2 during surgery (Table 4; n=27). Twenty-five of these patients were 'proven' Hinchey 1 or 2 by preoperative CT scanning, but the indication for emergency surgical treatment was set by the surgeon on call who probably doubted the CT report in combination with the clinical symptoms (sepsis, acute abdomen). These patients could conceivably be treated conservatively instead if preoperative (CT) assessment had 100% accuracy. Even if subjective 'clinical' signs of acute abdomen are present or objective findings of small amounts of free air are present on CT (75% of Hinchey 1 patients and 90% of Hinchey 2 patients; Table 3), true Hinchey 1 and 2 patients can be treated conservatively with antibiotics and analgesics[18]. If this conservative treatment fails, surgical intervention is indicated.

The combination of free air and intra-abdominal fluid seen on the CT scan correlated well with Hinchey 3 and 4 perforated diverticulitis as found during surgery, and these are the main findings the radiologists used to for the CTbased diagnosis of Hinchey 3 or 4. Only very few patients with a CT scan diagnosis of Hinchey 3 or 4 diverticulitis appear to have a stage of disease during surgery that might have been treated successfully without surgery. In other words, large amounts of free air and free fluid are indications for emergency surgery.

Preoperative differentiation between Hinchey stage 3 and 4 is not very important, as both need emergency surgical treatment. Nevertheless, it could be useful in deciding on the surgical approach[5]. In case of purulent peritonitis (Hinchey 3), laparoscopic peritoneal lavage and drainage without resection of the affected bowel segment has shown excellent results[10]. In case of fecal peritonitis, laparotomy is recommended for resection of the affected bowel segment[5]. Unfortunately, the present study shows that preoperative differentiation between Hinchey 3 and Hinchey 4 is not possible with CT scanning. It is therefore advisable to perform diagnostic laparoscopy, when the CT scan shows large amounts of free air and fluid (CT Hinchey 3/4). When purulent peritonitis is found, laparoscopic treatment could be performed. In case of fecal spill, conversion toward laparotomy is indicated.

CT technology has evolved rapidly in the past decades and will continue to do so in the future. In previous studies, CT scanning could only visualize bowel wall discontinuity in a minority of patients with proven bowel perforation[14]. Thanks to advances in technology, multidetector row CT scanners are able to visualize the site and size of the perforation more accurately[20-22]. This additional information would be helpful in deciding on the appropriate surgical technique. In Hinchey 3 perforated diverticulitis, most of times the perforation has been sealed by omentum. In case of Hinchey 4 diverticulitis, an overt perforation is found, causing a fecal spillage.

CONCLUSIONS

Current CT scanning does not seem to suffice to accurately predict the severity of perforated diverticulitis according to Hinchey's classification[21]. Nevertheless, specific findings on CT like the combination of a large amount of free intraperitoneal air and diffuse intraperitoneal fluid are a good predictor for Hinchey 3 or 4 diverticulitis and mandate surgical intervention. Diagnostic laparoscopy is advised in these patients to distinguish between purulent or fecal peritonitis. To date, distinction between Hinchey 3 and 4 with preoperative CT scanning is not possible. Diagnosis of Hinchey 1 or 2 perforated diverticulitis after CT assessment is not reliable, as 39% of these patients are in fact Hinchey 3 patients for whom surgery is indicated. In the absence of free intraperitoneal air, conservative treatment is justifiable. A prospective study is warranted to confirm our statements.

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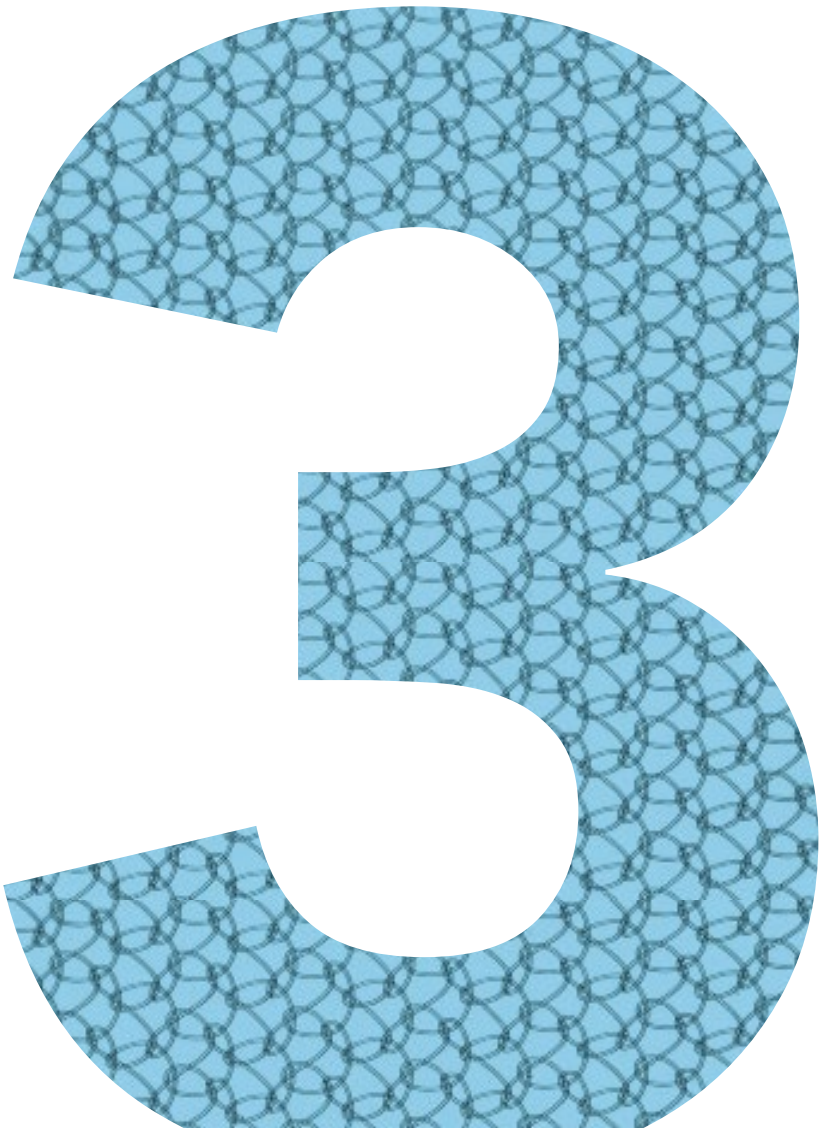
CHAPTER



Treatment options for perforated colonic diverticular disease

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INTRODUCTION

Diverticular disease is one of the most common diseases of the gastrointestinal (GI) tract requiring in-hospital treatment in Western countries. Despite its high incidence, controversies remain about the optimal treatment of the different stages of this disease.

Most people with diverticular disease remain asymptomatic; however, approximately 15% develop symptoms, and of these, 15% will develop significant complications such as perforation[1]. Although the absolute prevalence of perforated diverticulitis (PD) complicated by generalized peritonitis is low, its importance lies in the significant postoperative mortality rate, ranging from 4–26%[2-4]. Owing to the low prevalence of generalized peritonitis due to perforated diverticulitis (GPPD), strategies for the treatment of this stage of diverticulitis are even less thoroughly investigated. There are two major reasons for this.

Firstly, in the pathogenesis of diverticular disease, diverticulitis and perforation seem to have multifactorial origins, including lifelong dietary habits, medicine use, coexistence of other bowel or collagen-related diseases, and genetic influences. This complex interaction of factors makes it very difficult to investigate. Nevertheless, fundamental epidemiological research is warranted to assess the etiology of this disease and subsequently to develop prevention strategies.

Secondly, although uncomplicated diverticulitis is a common GI disease, the incidence of PD is relatively low (fewer than four cases per 100 000)[3]. Owing to this low incidence, it is difficult to design and successfully complete randomized controlled trials to assess optimal treatment strategies. Operations for PD are classified as emergency and may be performed outside office hours, rendering it even more difficult to start such trials.

Nevertheless, the consequences of this disease for general healthcare and for the patients in particular are enormous, as it is accompanied by high morbidity and mortality rates and poor quality of life having survived the event. Healthcare costs are significant owing to long periods of intensive care and overall hospital stay, the high rate of additional interventions or operations to treat complications, and outpatient stoma care[5].

ETIOLOGY

The prevalence of diverticulosis is estimated at 5% by the age of 40 years and up to 50–70% at 80 years of age[1,6]. Its exact prevalence is difficult to assess because most people remain asymptomatic[1]. Only about 15% of patients with diverticulosis will manifest any related clinical symptoms[1,7]. Approximately 80% of patients presenting with PD do not have a previous history of diverticular disease[8].

The pathogenesis of this disease process is probably multifactorial involving dietary habits (low fiber), changes in colonic pressure, motility, and wall structure associated with ageing, along with other factors[9]. The reason why a subgroup of individuals with diverticulosis progresses from asymptomatic to symptomatic or even to complicated PD remains poorly understood. Dietary shifts during the past century have likely not only influenced colonic motility and intraluminal pressure, but also altered colonic flora[10]. The change in the colonic microbial environment may be an important element in the transformation of asymptomatic diverticular disease into diverticulitis, but its exact role has not been adequately defined[11].

Like the pathophysiology of diverticula, the etiology of diverticular inflammation is also speculative. The development of diverticulitis has been described as similar to that of appendicitis. Perforation of variable extent may result, accounting for a range of symptoms[12,13].

In general, patients with diverticular disease show raised intracolonic pressures, especially in the sigmoid colon[14]. As almost all diverticular perforations occur in the sigmoid colon, these pressure changes must be an important etiological factor. Furthermore, the properties of the colonic wall are likely important because diverticula consist predominantly of mucosa lacking a smooth muscle layer. The mucosal barrier is vulnerable and may be impaired by various exogenous factors, such as the use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids or opiate analgesics, smoking, and alcohol consumption[15].

The etiology of perforation remains unknown, but it is thought to be a result of an excessive increase in intradiverticular pressure and focal necrosis[16]. This local perforation may form pericolic phlegmones and pus collections (Hinchey I)[17]. If this process progresses further, localized abscesses may form between loops of the small bowel or in the pelvic peritoneum (Hinchey II). If the pus cannot be contained, the abdominal peritoneum becomes contaminated, producing generalized purulent peritonitis (Hinchey III). The same is found when a large intraperitoneal diverticular abscess ruptures into the abdominal cavity[18]. If the initial perforation is large, fecal contamination of the abdominal cavity can occur (Hinchey IV)[17].

Since the incidence of diverticulosis increases with age, the majority of patients presenting with symptoms are elderly. Complicated diverticulitis is also observed predominantly in older patients. This problem is caused by an obscure presentation of diverticular complications in the elderly patient, with a consequent delay in diagnosis. Polypharmacy (e.g. with NSAIDs or corticosteroids) may further exacerbate this problem and may even increase the risk of developing complications[19].

PREVENTION

The possible role of diet and lifestyle offers strategies for prevention. Large, prospective studies have identified a preventive effect of both vegetable and high fiber intake and physical exercise in the development of diverticular disease, as well as diverticulitis[20-22]. Fiber as a dietary supplement may be beneficial in prevention. Nevertheless, it is remarkable that the incidence of diverticular disease has not been reduced, given the fact that several studies have shown an increased intake of fiber in Western populations over the last three decades[23]. The exact role of fiber in the pathophysiology of diverticulosis and its prevention remains unclear. Furthermore, when symptoms have developed, evidence of a benefit of fiber intake is even less convincing[23].

One of the latest therapies for the prevention of recurrent diverticulitis is the use of mesalazine, rifaximin, or a combination of the two[24,25]. The rationale for mesalazine use is that it inhibits some key factors of the inflammatory cascade[26]. Another very recent therapeutic strategy is the use of probiotics[27]. Probiotics diminish changes in the spectrum of intestinal microflora and the adherence and translocation of pathogens. They also regulate the production of antimicrobials and interact as competitive metabolites with pro-inflammatory organisms. Importantly, the combination of the *Lactobacillus* spp. with rifaximin seems effective in reducing severe forms of diverticulitis and preventing recurrences, hence reducing surgical treatment significantly[28,29].

The role of surgery in the prevention of complicated diverticular disease is unclear. Advances in diagnostic modalities, medical therapy, and surgical techniques over the past two decades have changed both the management and outcomes of diverticulitis[30]. Patients treated nonoperatively would be expected to do well without elective colectomy since most patients will not have further episodes of diverticulitis[31,32]. Recurrent episodes of diverticulitis do not lead to more complications or failure of conservative treatment[3,33]. At present, it is thought that elective resection for uncomplicated diverticulitis does not alter outcome, nor does it decrease mortality or prevent severe complications of the disease (e.g. perforation)[32,33]. Moreover, the prevalence of persistent symptoms after surgery for diverticular disease (up to 25%) may be an additional reason to discuss the indication for prophylactic surgery[34].

PERFORATED DIVERTICULITIS WITH LOCALIZED PERITONITIS: TREATMENT STRATEGIES

The optimal treatment strategy for PD depends on the degree of peritonitis. The introduction of computed tomography (CT) has improved preoperative assessment of diverticular disease. The CT-based classification by Hansen–Stock is the primary

classification system and accounts for asymptomatic diverticulosis as well as complicated diverticulitis in different stages, including perforation[35]. Nevertheless, the degree of peritonitis – and hence the severity of disease – in PD can be represented best by Hinchey's classification (Figure 1). Hinchey I and II represent localized peritonitis with phlegmon or abscess near the affected sigmoid and abscess elsewhere, respectively. Even localized PD can present as acute abdominal pain, frequently resulting in emergency surgery when a preoperative CT scan for diagnosis is not performed.

The high specificity of CT has allowed this modality to become a surrogate for the perioperative assessment made by the Hinchey classification[36]. Furthermore, CT has become an important therapeutic aid. It is now recognized that patients with small, contained perforations, who are not systemically ill, can be treated initially with antibiotics alone or by CT-guided percutaneous drainage[36,37]. Although mechanical control of the source of infection remains important, several studies have found that abscesses up to 4 cm seem to respond better to antibiotics alone[37,38].

Therefore, in general, Hinchey I and II PD can be treated conservatively with fluids, analgesics, and antibiotics, with or without percutaneous drainage of abscesses. It must also be noted that in Hinchey I and II, small amounts of free air are shown on CT scan, but this does not imply the need for surgical treatment *per se*. If conservative treatment fails, surgical intervention is indicated, in which resection with primary anastomosis (PA) is preferred above sigmoid colectomy with subsequent colostomy, also referred to as Hartmann's procedure (HP). The performance of a diverting loop-ileostomy to "protect" the anastomosis should be considered, especially in patients with a number of comorbidity factors[39].

PERFORATED DIVERTICULITIS WITH GENERALIZED PERITONITIS: TREATMENT STRATEGIES

Hinchey III and IV (GPPD) are characterized by generalized purulent and fecal peritonitis, espectively. Both represent indications for emergency surgery. Since the beginning of the previous century, a three-stage operation strategy was common practice for the treatment of complicated diverticular disease. A preliminary transverse colostomy was advised with a period of 3–6 months delay before resection[40,41]. The rationale for this strategy was that primary resection is too difficult in the acute stage of the disease. After several months, the second stage – resection of the involved bowel – could be performed to treat and prevent relapse of the disease.

Since the 1960s, combinations of antibiotics were used for the treatment of Gram-negative bacteria and anaerobic bacteria, and these resulted in improved survival in

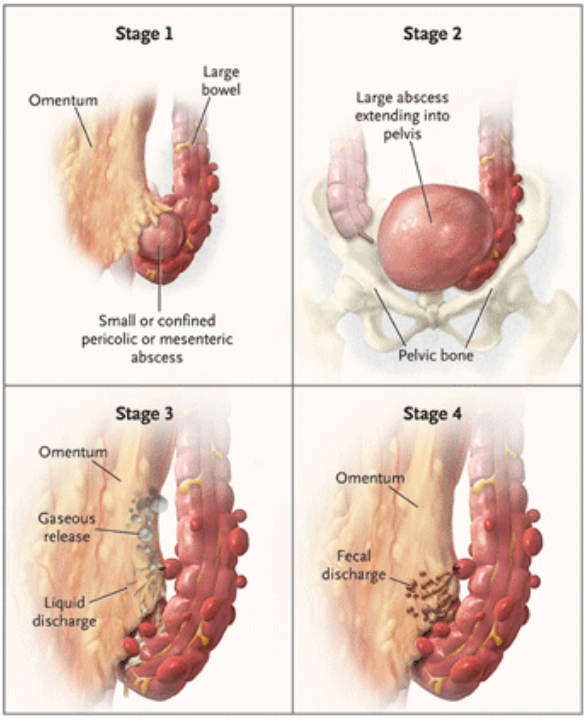

Figure 1. The Hinchey Classification of perforated diverticulitis.
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septic patients[42]. Unfortunately, mortality rates in patients with GPPD remained high. It was thought that the basic cause of this high mortality was the remaining source of infection in the peritoneal cavity. Based on this "expert opinion evidence", the conviction arose that the colonic perforation had to be removed immediately[42,43].

A two-stage operation (e.g. HP) subsequently became the preferred surgical strategy in these patients[44]. The second stage was represented by the colostomy closure. This change in strategy was mainly based on the results of two reviews published in 1980 and 1984 by Greif et al.[45] and Krukowski and Matheson[46], respectively. Unfortunately, these reviews were not systematic, containing a wide range of different surgical techniques and covering more than 25 years during which substantial improvements in antibiotic and other perioperative supportive therapies had taken place. Furthermore, it is not known whether the patients were comparable for a number of essential variables, such as age, American Society of Anesthesiologists (ASA) classification, and Hinchey scores.

Between 1993 and 2000, two randomized controlled trials assessing primary versus secondary resection were published[47,48]. These randomized controlled trials drew opposing conclusions. Kronborg[47] concluded that three-stage nonresectional surgery (suture and transverse colostomy) in PD was still superior to primary resection because of a lower postoperative mortality rate; however, mortality was not different in Hinchey IV who underwent primary resection or patients who were treated according to the three-staged surgical strategy. Unfortunately, the study was stopped early because of low recruitment (an average of four patients each year) and hence underpowered. A total of 62 patients were included and operated on by 27 different surgeons over a period of 14 years. Zeitoun et al. concluded that primary resection was superior to nonresectional surgery because of less postoperative peritonitis and fewer reoperations[48]. However, postoperative mortality after primary resection was higher compared with nonresectional surgery (24% vs. 19%). Nontheless, HP became the advocated surgical strategy.

Improvements in surgical and radiological intervention techniques and progress in the management of peritoneal sepsis has resulted in increasing interest in colonic resection with PA since the 1990s. Several systematic reviews have concluded PA to have a better clinical outcome than HP for patients with GPPD[22]. However, fear of anastomotic leakage often deters many surgeons from performing a one-stage procedure (e.g. PA) in GPPD, although it is becoming more widely accepted that anastomotic leakage does not seem to be related to the grade of contamination of the abdomen.

Restoration of bowel continuity after HP is a technically challenging operation and is associated with significant morbidity and mortality[49]. These rates can be as high as 25% and 14%, respectively, after colostomy reversal in patients who have undergone HP for PD[2,4]. The performance of a diverting loop-ileostomy has been reported to decrease the rate of symptomatic anastomotic leakage in patients operated on for diverticular peritonitis. The risk of a permanent ileostomy is recognizably less than that of HP, with fewer complications[50,51].

In 1996, a new nonresectional laparoscopic approach was described[52]. In patients with peritonitis without gross fecal contamination, laparoscopic peritoneal lavage, inspection of the colon, and the placement of abdominal drains appeared to diminish morbidity and improve outcome[52-54]. In a series of 100 patients with GPPD, Myers et al. showed excellent results after laparoscopic lavage and drainage of the peritoneal cavity, with morbidity and mortality rates <5%[55].

In a second elective stage, definitive surgery can take place (e.g. laparoscopic resection and PA)[53,54], although subsequent elective resection is probably unnecessary[55,56]. Nevertheless, the number of studies are rather limited and mostly based on small groups

of patients. Furthermore, the rates of additional radiological interventions and conversion to an open procedure are high[57]. Finally, for many hospitals, it will not be possible to have a surgical team with expertise in colorectal laparoscopic surgery present at all times.

Some authors have expressed their concerns regarding laparoscopic nonresectional treatment of GPPD. They state that the decision to perform nonresectional surgery is influenced by the surgical access to the abdomen (i.e. laparoscopy), rather than based on evidence in literature[58]. Unfortunately, the evidence to which these investigators refer (primary resection favoring three-stage procedures) is equivocal or contradictory, as stated above[46-48].

The major criticism of the nonresectional laparoscopic lavage technique is the continued presence of the perforated colon as a septic focus and the column of feces in the colon as potential ongoing sources of contamination. This was also the main criticism towards the three-stage procedure that was used to treat GPPD until the 1970s. However, GPPD is accompanied by ileus, hence it is not likely that the fecal column is propelled towards the perforation. Moreover, a patent communication between the colonic lumen and the peritoneal cavity usually cannot be found during laparoscopy because the site of the original perforation has become sealed by the inflammatory process and omentum, and seems efficient to control the source of contamination. In patients who are found to have fecal peritonitis or who fail to improve after lavage, acute resection should still be performed[57,59].

The suggestion that nonresectional surgery in combination with more advanced antibiotics has never been proven to be an inferior strategy could explain the excellent results after laparoscopic lavage in combination with modern management of peritoneal sepsis with improved antibiotics and intensive care medicine.

In the case of Hinchey III peritonitis, laparoscopic treatment by lavage and drainage without resection has shown such excellent results that this new approach cannot be ignored[53-55,57]. The problem is that Hinchey's classification represents the severity of disease during surgery. Preoperative CT scanning is essential to differentiate between Hinchey I, II, and generalized peritonitis (Hinchey III and IV), but exact differentiation between purulent of fecal peritonitis is not possible with today's radiological modalities. It is therefore advised that all patients with GPPD on CT scan undergo diagnostic laparoscopy. In cases of purulent peritonitis, laparoscopic lavage and drainage can then be performed. Alternatively, resectional surgery can be considered, for which PA is preferred. In cases of fecal peritonitis, conversion to laparotomy is advised to perform sigmoid resection with PA (or HP), as laparoscopic lavage and drainage have shown not to be successful in Hinchey IV PD.

The abovementioned statements still need to be confirmed in randomized, controlled trials. Currently, a nationwide randomized trial (Ladies [Laparoscopic Peritoneal Lavage or Resection for Generalized Peritonitis for PD] trial) is running in The Netherlands under the auspices of the Dutch Diverticular Disease (3D) Collaborative Study Group[60]. While awaiting the results of randomized trials assessing laparoscopic lavage, the open approach (PA or HP) presently remains the standard procedure in patients with generalized (purulent of fecal) peritonitis from a free macroperforation in diverticulitis.

FUTURE STRATEGIES

Currently, the only patients who require surgery (laparoscopically or open) are those who fail conservative treatment and those with generalized peritonitis who require emergency surgery[38,61]. It seems that a more minimally invasive surgical treatment could be a safe and feasible option in GPPD. To ensure good results, it is essential that these procedures are performed by dedicated colorectal surgeons who have laparoscopic lavage in their armamentarium of procedures. Minimally invasive nonresectional treatment of GPPD has the highest probability of success[53].

If nonresectional laparoscopic lavage and drainage to treat GPPD is found to be a safe and better alternative for resectional surgery in the future, why should this be different from nonresectional nonsurgical (e.g. CTguided) percutaneous lavage and drainage? As yet, the literature does not report this treatment strategy. Is it possible that this will be the next step in the ever more conservative management of different stages in diverticular disease?

Fluid resuscitation and modern antibiotic strategies will not be different from laparoscopically lavage procedures. In order to gain control of the septic focus using percutaneous techniques, it is important that large size catheters are used for adequate drainage of thick and viscous purulent contents[62]. The main problem is the inability for inspection of the abdominal cavity to localize the site and size of the perforation. Such a careful inspection of the abdominal cavity, to look for or exclude other causes of generalized purulent peritonitis, is not possible using today's radiographic modalities. Furthermore, in cases of a large perforation causing fecal peritonitis, source control by percutaneous lavage and drainage is impossible; hence, surgical treatment will be necessary to achieve source control and restore premorbid anatomy and function. It is, therefore, not likely that percutaneous (nonsurgical) nonresectional lavage and drainage will play a prominent role in the treatment of GPPD in the near future, because it cannot yet meet the principles of abdominal infection treatment.

PROPOSAL FOR A TREATMENT STRATEGY FOR PERFORATED DIVERTICULITIS

Further basic and clinical investigations need to be performed in order to fill the several gaps in our knowledge of the pathophysiology of diverticulitis, as well as its treatment and prevention. For the same reason, there is a need for further good quality epidemiological research to identify risk factors in diverticular perforation. Whether new insights into the etiology will lead to new surgical strategies for prevention and treatment of PD remains to be seen.

Abdominal CT scanning is essential in patients suspected of having PD, because only patients with generalized peritonitis (free fluid and large amount of peritoneal free air) need to undergo emergency surgery. Unfortunately, CT scans cannot presently differentiate between Hinchey III or IV PD. The differentiation between the two is essential because the treatment strategy is different. It is therefore advised that patients who have GPPD on CT scan will undergo diagnostic laparoscopy, followed by definitive surgery. Hinchey III patients should undergo laparoscopic lavage and drainage, while Hinchey IV patients need to undergo conversion towards laparotomy for resection of the affected colon segment. Future randomized controlled trials must assess whether laparoscopic lavage for Hinchey III, and PA with ileostomy for Hinchey IV, are indeed the preferred surgical strategies. In cases of Hinchey I and II, a conservative treatment is advocated.

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CHAPTER

Early experience with laparoscopic lavage for perforated diverticulitis

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ABSTRACT

Background

Laparoscopic lavage has recently emerged as a promising alternative to sigmoid resection in the treatment of perforated diverticulitis. This study examined an early experience with this technique.

Methods

The files of all patients with complicated diverticulitis were searched in 34 teaching hospitals of the Netherlands. Patients with perforated diverticulitis treated with laparoscopic lavage between 1 January 2008 and 31 December 2010 were included.

Results

Treatment with laparoscopic lavage was performed in only 38 patients in ten hospitals. Lavage was successful in controlling sepsis in 31 of the 38 included patients, with 32% morbidity (10 of 31 patients) and fast recovery. Overall, 17 of 38 patients developed complications, of whom two had a missed overt sigmoid perforation. Two patients died from multiple organ failure and one from aspiration pneumonia; one other patient died after palliative management of inoperable lung carcinoma. Three patients in whom lavage was successful underwent subsequent sigmoid resection for recurrent diverticulitis. Patients in whom lavage was unsuccessful tended to have more co-morbidities, a higher preoperative C-reactive protein concentration and a higher Mannheim Peritonitis Index.

Conclusion

Laparoscopic lavage for perforated diverticulitis was feasible in the majority of patients, but identification of an overt sigmoid perforation and patient selection are of critical importance.

INTRODUCTION

Perforated diverticulitis is a serious condition that can present as either purulent (Hinchey III) or faeculent (Hinchey IV) peritonitis[1]. Regardless of this classification, sigmoid resection with either end colostomy or primary anastomosis has been the standard treatment. However, these operations are associated with high morbidity and mortality rates, the latter being 27% in a national study of patients with both purulent and faecal peritonitis[2,3]. In addition, the stoma is never reversed in many patients[2,3].

Laparoscopic lavage, originally described in Ireland in 1996, has emerged as a promising alternative to sigmoid resection[4]. A systematic review has shown that, for Hinchey III diverticulitis, lavage leads to low morbidity and mortality rates, while avoiding the creation of a stoma[5]. However, the available data are derived from small nonrandomized studies.

Hinchey II diverticulitis is defined as diverticulitis with a pelvic abscess of at least 5 cm in diameter. Percutaneous drainage is recommended for this condition; surgery is required only when the abdominal abscess is not amenable to percutaneous treatment and signs of sepsis are present[6-9]. Lavage does not seem to be sufficient for Hinchey IV diverticulitis (faeculent peritonitis). As there is overt communication between the intestinal lumen and the peritoneal cavity, sigmoid resection is recommended to prevent further dispersion contamination[5].

Laparoscopic treatment, as promoted by the Irish group, has been received with both enthusiasm and scepticism in the Netherlands[10]. Convinced by the existing evidence, some hospitals have implemented lavage as a new standard for Hinchey III diverticulitis; others have been more reluctant, fearing failure of the new strategy. Before the start of the Ladies trial (a large randomized trial investigating the safety and efficacy of laparoscopic lavage for perforated diverticulitis), some surgical units had already started to apply this novel strategy[11]. The aim of the present study was to report on the results of laparoscopic lavage performed in these centres before the start of the Ladies trial.

METHODS

Eligible for this study were patients treated with laparoscopic lavage for perforated diverticulitis in Dutch teaching hospitals before the start of the Ladies trial in the interval from 1 January 2008 to 31 December 2010. Medical records in the 34 hospitals were screened for the diagnosis 'diverticulitis' or 'acute abdomen'. The medical files of these patients were checked for the type of surgery they had undergone. Patients were included if they underwent laparoscopic lavage as the primary treatment for diverticulitis with either free air (Hinchey II or III) and/or with purulent peritonitis (Hinchey III). Demographic data,

co-morbidity, American Society of Anesthesiologists (ASA) grade, preoperative white blood cell count, Creactive protein (CRP) concentration, and results of plain abdominal X-ray and computed tomography (CT) were recorded. The following information was obtained from the operation records: presence of abdominal pus and its location, presence of faeces, presence of overt sigmoid perforation, closure of overt perforation, amount of saline used for lavage and placement of drains. Survival, length of time in the intensive care unit (ICU), antibiotic regimen, and number of complications, diagnostic measures, reinterventions, reoperations and readmissions were recorded. Treatment failure was defined as ongoing abdominal sepsis.

The Mannheim Peritonitis Index (MPI) was used as a predictor of the mortality risk (Table 1). The Hinchey classification was used to stratify the patients according to the intraoperative findings: Hinchey II for a large pelvic abscess, and Hinchey III when purulent peritonitis was present.

Data on the following co-morbidities were extracted from the patient's history: cardiovascular morbidity (myocardial infarction, ischaemic attack, aneurysm, atrial fibrillation, thrombosis), pulmonary morbidity (chronic obstructive pulmonary disease), malignancies, organ failure (renal insufficiency, pulmonary insufficiency) and other morbidities (hypertension, diabetes, hypercholesterolaemia).

RESULTS

Thirty-eight patients treated with laparoscopic lavage were identified in ten hospitals. All had clinical evidence of diverticulitis with obvious signs of local or generalized peritonitis. Patient characteristics are shown in Table 2. A total of 24 men and 14 women were included, of median age 59 (range 23–79) years. Eighteen patients had one or more co-morbidities. Stratified by the most severe co-morbidity, eight patients had cardiovascular disease (myocardial infarction, stroke, atrial fibrillation and thrombosis), five were previously diagnosed with malignancy, two had pulmonary disease (chronic obstructive pulmonary disease) and three had hypertension. One patient had respiratory insufficiency before surgery. Four patients had undergone previous abdominal surgery not related to diverticular disease. None of the patients had had a previous episode of diverticulitis, although one had been admitted for uncomplicated diverticulitis 7 days before surgery. None of the patients used systemic corticosteroids.

Twenty-eight of the 38 patients had surgery on the day of arrival at the emergency department (Table 2). Preoperative imaging revealed free intra-abdominal air in 32 of 35 patients who had CT. At operation a pelvic or retroperitoneal abscess was found in five patients; local or generalized purulent peritonitis was present in 33 patients, of whom two had overt sigmoid perforation.

Table 1. Mannheim Peritonitis Index.

Risk factor		Weight
Age (years)	<50	0
	>50	5
Sex	M	0
	F	5
Organ failure*	No	0
	Yes	7
Malignancy	No	0
	Yes	4
Preoperative duration of peritonitis (h)	≤24	0
	>24	4
Diffuse generalised peritonitis	No	0
	Yes	6
Exudate	Clear	0
	Cloudy, purulent	6
	Faeculent	12

The origin of sepsis was always colonic: 0 of 4 points.*Includes kidney failure (creatinine over 177 µmol/L, urea more than 167 µmol/L, oliguria less than 20 ml/h), lung failure (partial pressure of oxygen less than 50mmHg, partial pressure of carbon dioxide greater than 50mmHg), shock (hypodynamic or hyperdynamic) and profound intestinal obstruction (paralysis for more than 24 h or complete mechanical ileus).

The amount of irrigation fluid was reported in 14 patients, in whom a median of 4 (range 3–6) litres of saline was used. The placement of drains was reported in 36 patients: no drains were placed in three, one drain was used in 17 patients, and two in 16. One of the patients required conversion to an open procedure because the left lower quadrant could not be visualized. In both patients with overt sigmoid perforation, the perforation was closed primarily.

Table 2. Risk factors for treatment failure.

	Overall (n=38)	Sepsis controlled (n=31)	Sepsis not controlled (n=7)
Sex ratio (M:F)	24:14	20:11	4:3
Age (years)*	59 (23-79)	58 (23-79)	66 (39-77)
ASA fitness grade			
I	12	11	1
II	11	9	2
III	12	10	2
IV	3	1	2
Comorbidities			
none	20	18	2
1	6	4	2
2	6	5	1
≥2	6	4	2
Mannheim Peritonitis Index†	13.3 (5.0)	12.6 (5.1)	15.0 (4.3)
Preoperative CRP (mmol/l)†	203 (143)	180 (123)	322 (187)
Preoperative WBC count ($x10^3/mm^3$)†	15.4 (5.3)	15.8 (4.8)	13.5 (7.4)
Preoperative hospital stay			
0	28	21	7
1	5	5	0
2	2	2	0
>2	3	3	0
Free air			
No imaging	3	3	0
No	3	2	1
Pericolic	4	4	0
Distant	28	22	6
Operative findings			
Pelvic abscess, diffuse free air on CT (Hinchey II)	5	3	2
Localised cloudy or purulent exudate (Hinchey III)	29	25	4
Generalised cloudy or purulent exudate (Hinchey III)	4	3	1
Overt perforation			
Yes	2	2	0
No	36	29	7

Values are *median (range) and †means (s.d.). *ASA*, American Society of Anesthesiologists; *CRP*, C-reactive protein; *WBC*, white blood cell; *CT*, computed tomography

The median duration of operation was 68 (range 30–220) min. There were no intraoperative complications. A postoperative antibiotic regimen of cefuroxime and metronidazole was reported in 12 patients. The regimen used in the other patients was unclear or not specified.

Postoperative outcomes are summarized in Table 3 and Figure 1. The median length of postoperative hospital stay was 10 (range 4–77) days. Six patients required admission to the ICU, with a median stay of 6 (range 2–46) days. Four patients required readmission to the surgical ward after discharge.

Laparoscopic lavage failed to control sepsis in seven of the 38 patients. Two patients died from multiple organ failure after operation. A laparotomy was performed in five other patients: sigmoid resection and end colostomy in three, a diverting stoma in one and closure of the sigmoid perforation in one. At laparotomy, faeculent peritonitis was found in two patients and purulent peritonitis in one. Intraoperative data were lacking for the other two patients. Abdominal sepsis was controlled in all five patients after the second operation. Nonetheless, one patient died from aspiration during the postoperative course. All patients in whom lavage was unsuccessful developed complications within 30 days (Table 3). No carcinoma was found on histopathological examination of specimens of resected sigmoid.

Lavage was successful in controlling the abdominal sepsis in 31 patients, including two who had an overt sigmoid perforation closed primarily. One patient with a pre-existing bronchial carcinoma developed persistent small bowel obstruction after surgery; because of the poor prognosis, parenteral feeding was stopped and the patient died. Ten of 31 patients developed complications within 30 days (Table 3).

Follow-up visits were reported in 28 patients, a median of 69 (range 12–529) days after surgery. Follow-up was carried out for more than 3 months only when late complications occurred. Two patients underwent elective sigmoid resection for recurrent symptomatic diverticulitis at 6 and 9 months after operation, and one patient required emergency sigmoid resection for recurrent perforated diverticulitis at 12 months.

In 17 of 30 patients who were treated successfully and recovered, follow-up colonoscopy was performed to exclude colonic malignancy; in none of these malignancy was found.

Patient characteristics were analysed to determine predisposing factors for uncontrolled abdominal sepsis (Table 2). Patients in whom lavage was unsuccessful were more likely to have co-morbidities, had a higher mean CRP concentration and a higher MPI.

Table 3. Outcomes of surgery.

	Overall (n=38)	Sepsis controlled (n=31)	Sepsis not controlled (n=7)
Laparotomy	**5**		Hartmann's procedure 3 Diverting stoma 1 Closure of perforation 1
Hospital stay (days)*	10 (4-77)	10 (4-42)	16 (6-77)
ICU admission	6	2	4
Readmission	4	3	1
In-hospital death	4	1	3
Multi organ failure	2		2
Aspiration	1		1
Persistent bowel obstruction	1	1	
30 day morbidity†	**17**	**10**	**7**
Bowel obstruction	5	3	2
Abdominal abscess	4	2	2
Enterocutaneous fistula	3	1	2
Wound infection	2	1	1
Incisional hernia	2	0	2
Pneumonia	2	1	1
Pulmonary embolism	1	1	0
Burst abdomen	1	0	1
Atrial fibrillation	1	1	0
Recurrent diverticulitis	**3**	**3**	
Elective sigmoid resection	2	2	
Emergency sigmoid resection	1	1	

*Values are median (range). †Number of patients with complications. The breakdown describes all complications; some patients had more than one complication. *ICU*, intensive care unit.

DISCUSSION

Treatment with laparoscopic lavage in the Netherlands was less successful than in the Irish experience; the Irish group reported very promising results with a mortality rate of 4% in a series of 92 patients[10]. The present study analysed a retrospective series of patients from ten hospitals. It suffers from all the limitations of retrospective research, especially the risk of patient selection bias. Because of this and the small study size, the results should be interpreted with caution. In this series, two patients (5%) treated with lavage died after

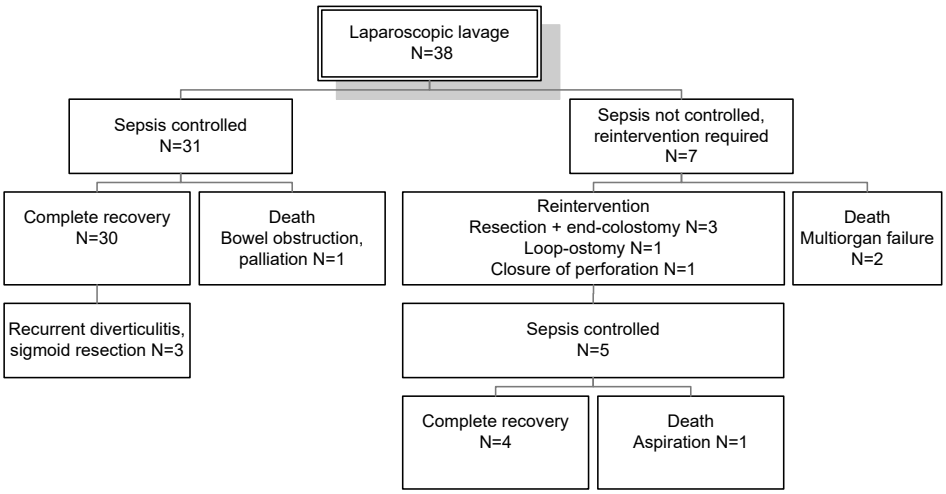

Figure 1. Flow chart of clinical outcome.

surgery and five other patients required further surgery because of ongoing abdominal sepsis. The 31 patients in whom lavage was successful had low mortality and morbidity rates, and a quick recovery.

Selection of patients who would benefit from laparoscopic lavage is probably of utmost importance, with faeculent peritonitis and the presence of overt perforation being absolute contraindications to lavage. The extent of peritonitis could not be analysed in the present study as this was not reported consistently in the operation records. Unsuccessful treatment was associated with higher ASA grade and co-morbidities. Although the MPI has been designed as a predictor of postoperative death in patients with peritonitis, certain elements of the index (higher age, organ failure, concomitant disease, generalized peritonitis, faeculent peritonitis) have been reported to predict reintervention for secondary peritonitis, as was found here[12,13]. The preoperative CRP concentration was higher in the group in whom sepsis was not controlled. This is a known predictor of perforated appendicitis and perforated diverticulitis[14,15]; however, it remains unclear whether CRP can predict the success of laparoscopic lavage for perforated diverticulitis.

No randomized studies have been published on this topic. The available evidence is therefore limited to uncontrolled studies with a high risk of selection and publication bias. Most studies have analysed patients with both Hinchey II and Hinchey III and have considered Hinchey II patients as candidates for lavage treatment, without discrimination within this group of patients based on the presence of free abdominal air. This might make the results appear considerably better because Hinchey II diverticulitis is known to be associated with fewer complications than true perforated diverticulitis[16]. The present

study included patients with purulent peritonitis and/or distant free air only. Laparoscopic treatment does not seem to be appropriate for patients with Hinchey II diverticulitis without free air. These patients can be treated either conservatively or by percutaneous drainage of the pelvic abscess[6]. Laparoscopic lavage is considered to be unsafe for faeculent peritonitis or when an overt perforation is present.

Laparoscopic lavage is a promising novel treatment for perforated purulent diverticulitis. The high morbidity and stoma rates associated with sigmoid resection can be avoided. However, in the present series, mortality and morbidity were high among patients in whom the abdominal sepsis was not controlled. When no clinical improvement is observed within 48 h, (laparoscopic) reintervention is indicated for additional lavage or resection. The study suggests that laparoscopic lavage might not benefit all patients with Hinchey III diverticulitis. It appears that patients with multiple co-morbidities, a high CRP concentration and a high MPI are at risk of failure of lavage. Sigmoid resection as a first step might be the best intervention for these patients, but the mortality rate is high anyway. It remains unproven which risk factors predispose to failure of lavage; the results of four randomized trials addressing this topic are eagerly awaited[11,17-19].

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CHAPTER

The ladies trial: 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

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HA Prins
HBAC Stockmann
RAEM. Tollenaar
BA van Wagensveld
PPLO Coene
GD Slooter
ECJ Consten
EB van Duijn
MF Gerhards
AGM Hoofwijk
TM Karsten
PA Neijenhuis
CFJ Blanken-Peeters
HA Cense
GHH Mannaerts
SC Bruin
QAJ Eijsbouts
MJ Wiezer
EJ Hazebroek
AAW van Geloven
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ABSTRACT

Background

Recently, excellent results are reported on laparoscopic lavage in patients with purulent perforated diverticulitis as an alternative for sigmoidectomy and ostomy.

The objective of this study is to determine whether LaparOscopic LAvage and drainage is a safe and effective treatment for patients with purulent peritonitis (LOLA-arm) and to determine the optimal resectional strategy in patients with a purulent or faecal peritonitis (DIVA-arm: perforated DIVerticulitis: sigmoid resection with or without Anastomosis).

Methods

In this multicentre randomised trial all patients with perforated diverticulitis are included. Upon laparoscopy, patients with purulent peritonitis are treated with laparoscopic lavage and drainage, Hartmann's procedure or sigmoidectomy with primary anastomosis in a ratio of 2:1:1 (LOLA-arm). Patients with faecal peritonitis will be randomised 1:1 between Hartmann's procedure and resection with primary anastomosis (DIVA-arm). The primary combined endpoint of the LOLA-arm is major morbidity and mortality. A sample size of 132:66:66 patients will be able to detect a difference in the primary endpoint from 25% in resectional groups compared to 10% in the laparoscopic lavage group (two sided alpha = 5%, power = 90%). Endpoint of the DIVA-arm is stoma free survival one year after initial surgery. In this arm 212 patients are needed to significantly demonstrate a difference of 30% (log rank test two sided alpha = 5% and power = 90%) in favour of the patients with resection with primary anastomosis. Secondary endpoints for both arms are the number of days alive and outside the hospital, health related quality of life, health care utilisation and associated costs.

Discussion

The Ladies trial is a nationwide multicentre randomised trial on perforated diverticulitis that will provide evidence on the merits of laparoscopic lavage and drainage for purulent generalised peritonitis and on the optimal resectional strategy for both purulent and faecal generalised peritonitis.

Trial registration

Nederlands Trial Register NTR2037

BACKGROUND

Diverticular disease is an important condition in terms of healthcare utilisation and it is one of the five most costly gastrointestinal disorders in westernised countries[1]. Despite this high prevalence, treatment of all different stages of diverticular disease is still hardly evidence based, hence containing a lot of controversies.

Perforated diverticulitis is a perforation of an inflamed diverticulum of the large bowel, mostly the sigmoid, resulting in either purulent or faecal peritonitis (Hinchey stadia III or IV). Both conditions require emergency surgery[2,3]. Regardless of selected strategy emergency operations for acute perforated diverticulitis are associated with substantial morbidity (up to 50%) and mortality (15 to 25%)[3-8]. Primary sigmoidectomy with or without anastomosis has become the standard practice for patients with generalised peritonitis complicating diverticulitis and for many surgeons the Hartmann's procedure remains the favoured option[6-10]. Restoration of bowel continuity after this procedure is a technically difficult operation, with high morbidity and mortality rates[11,12]. Therefore stoma reversal after HP is only performed in 50 to 60% of the patients, thereby compromising quality of life and increasing costs[13,14].

Recently laparoscopic lavage (LL) emerged as an effective alternative for patients with perforated diverticulitis with purulent peritonitis[15]. This nonresectional procedure has first been described by O'Sullivan in 1996[16]. In 2009, a systematic review on all studies on laparoscopic lavage with a total number of 231 patients was performed. Mortality was less than 2% and a (permanent) colostoma was avoided in the majority of these patients[15-22]. So laparoscopic lavage for perforated purulent diverticulitis has a great potential in improving health and reducing costs.

Nevertheless, since sigmoidectomy is still considered the standard of care for perforated diverticulitis, implementation of LL might be variable. Some surgeons will embrace lavage because of its technical simplicity; other might be reluctant fearing failure of this novel strategy. Only a head to head comparison of both surgical strategies will provide an evidence based surgical approach of patients with perforated diverticulitis with purulent peritonitis (LOLA-arm).

In case of faecal peritonitis there is no evidence that LL is a valid alternative for a resectional strategy. But again, the optimal surgical treatment is still a matter of debate. The available literature suggests equality of Hartmann's procedure (HP) and resection with primary anastomosis (PA) regarding postoperative mortality and morbidity[5,8,9,23,24]. The likelihood of stoma closure seems higher after PA with ileostomy (85%) compared to HP (60%), but robust evidence is lacking[13,25]. Therefore, HP and PA are compared to

determine the optimal resectional treatment for perforated diverticulitis with generalised purulent or faecal peritonitis, regarding stoma free survival (DIVA-arm).

Study objectives

For this two-armed randomised trial two objectives can be defined to determine the optimal strategy for the treatment of perforated diverticulitis. First, is laparoscopic lavage for patients with purulent peritonitis superior compared to sigmoidectomy, in terms of mortality, morbidity, quality of life, health care utilisation and associated costs (LOLA-arm)? Secondly, is HP or PA the superior approach for patients with purulent or faecal generalised peritonitis in terms of stoma free survival, quality of life and cost-effectiveness (DIVA-arm)?

METHODS/DESIGN

The Ladies trial is designed as a nationwide multicentre randomised trial in which patients with generalised peritonitis caused by perforated diverticulitis are randomised to undergo either laparoscopic lavage and drainage or resectional surgery by laparotomy.

Patients presenting with clinical signs of diverticulitis with diffuse peritonitis can be included upon the finding of free gas on plain abdominal radiography, upon the finding of free gas on CT, or upon the finding of peritonitis with diffuse fluid or gas on CT. Exclusion criteria include dementia, pelvic irradiation, steroid treatment, prior sigmoidectomy and preoperative shock with inotropic requirement. All patients need to fulfil the selection criteria and will need to give written informed consent.

Eligible patients undergo diagnostic laparoscopy to exclude other causes of generalised peritonitis. If the diagnosis perforated diverticulitis is confirmed, the patient can be enrolled and randomised. Block-randomisation is performed during laparoscopy via the trial website according to Figure 1. In case of purulent peritonitis (Hinchey III) patients are randomised to LL, HP or PA (LOLA-arm). The best evidence indicates that the latter two resectional strategies are equal in terms of postoperative morbidity and mortality in case of generalised peritonitis[8]. For this reason a three way 2:1:1 randomisation is performed.

In case of an overt perforation with faecal peritonitis (Hinchey IV) patients will undergo laparotomy and are randomised 1:1 to either undergo HP or PA.

Patients who are either ineligible for trial entry, who show other causes of peritonitis than diverticulitis at laparoscopy or who do not wish to take part in the study are treated at the discretion of the surgeon on call. These patients will be registrated by the trial coordinator.

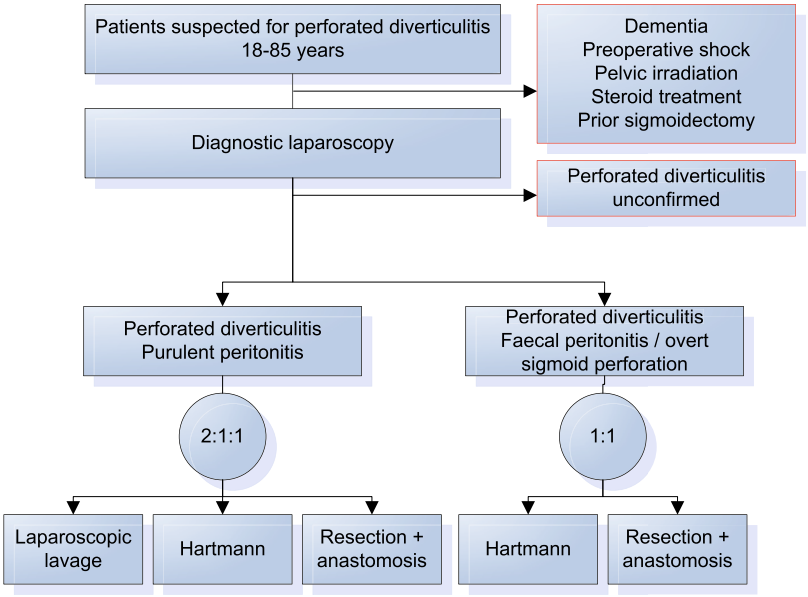

Figure 1. Flow chart of the trial.

Endpoints

Primary endpoint of the LOLA-arm is the combined number of mortality and major morbidity, twelve months after initial surgery. Secondary endpoints of the LOLA-arm are quality of life, health care utilisation and associated costs. Mayor morbidity includes reintervention, fascial dehiscence, incisional hernia, myocardial infarction, urosepsis, respiratory failure and renal failure. Respiratory failure is defined as a SOFA score of less than 300. Renal failure is defined as a threefold creatinine increase or a GFR decrease over 75% or a urinary output of less than 0.3/kg/h for 24 hours or anuria for twelve hours.

Primary endpoint of the DIVA-arm is the stoma free survival within twelve months after initial surgery. Secondary endpoints are quality of life and cost-effectiveness.

Participating centres

More than thirty-five teaching hospitals in the Netherlands are participating in this trial, including six academic centres.

Study population

This study consists of patients eligible for surgical treatment of perforated diverticulitis. Inclusion criteria are age between 18 and 85 years, a clinical suspicion for perforated diverticulitis and free gas on plain abdominal radiography, free gas on CT, or peritonitis with diffuse fluid or gas on CT.

Ethics

This study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Medical ethics approval has been obtained by the medical ethics committee from the Academic Medical Centre in Amsterdam, dated September 30th, 2009. Prior to randomisation, written informed consent must be obtained from all patients.

Study outline

Diagnostic laparoscopy: a careful inspection of the stomach, duodenum and sigmoid is performed to localise the site of perforation. In case of peritonitis due to a perforated diverticulum it must be attempted gently to locate the site of perforation. Careful removal of adherent omentum or bowel is tried. If clearly adherent, it should be left in place.

If no obvious perforation is apparent and faecal content is absent, the patient is randomised online between treatment with LL, HP or PA in a ratio 2:1:1.

In case of an overt perforation or intra-abdominal contamination with faeces, the patient is not eligible for LL and is randomised between HP and PA.

LL: the abdominal cavity is irrigated with six litres of warm saline. At the end of the procedure a Douglas drain is inserted via the right lateral port.

HP: The perforated diseased part must be resected. There is no need of having the distal transsection line on the proximal rectum. An end-colostomy is performed according to the preference of the operating surgeon, the same accounts for closing the rectal stump.

PA: Sigmoidectomy is done according to the guidelines of the American Society of Colon and Rectal Surgeons[26,27]. The distal transsection margin has to be on the proximal rectum, the proximal margin is determined by the absence of wall thickening due to diverticulitis. The type of anastomosis and the decision to perform a defunctioning loop-ileostomy are to the discretion of the surgeon on call.

Leaving a Douglas drain after resectional surgery is at the discretion of the operating surgeon. The resected tissue is sent for histological investigation to exclude malignancy.

Antibiotics are administered for seven days in both groups. Postoperatively, oral diet and mobilisation are advanced as soon as possible. Within four to six weeks after surgery a sigmoidoscopy is performed to exclude malignancy as the underlying cause of the perforation.

After the sigmoidoscopy is performed, the patient will be offered reversal of the stoma, when he or she is found eligible for surgery by the surgeon and anaesthesiologist.

Statistical analysis

The analysis will be performed in accordance with the intention to treat principle.

In the LOLA-arm of the study, the assumpted difference in the combined number of mortality and major morbidity between laparoscopic lavage and resection is 15%. With a two sided likelihood ratio test and a significance level of 0.05, a sample size of 132:66:66 will be necessary to detect this difference. With a group size of a hundred patients per arm it is also possible to find a significant difference (alpha = 0.05, beta = 0.1) of at least 10% in subscales of the SF-36, a validated quality of life questionnaire, at two, four, thirteen, 26 and 52 weeks after initial surgery.

In the DIVA-arm 212 patients are needed to significantly demonstrate a difference in stoma free survival between both treatment arms, using log rank statistics with a power of 90% and a type I error of 5%. The suspected postoperative mortality for HP and PA is equally high (+ 15%)[8]. About 60% of the patients that underwent HP have their stoma reversed[11,12]. When corrected for the expected mortality before reversal, the reversal rate will be 50%. Patients with a protective loop-ileostomy after PA will have their enterostomy reversed in over 85%[12]. After correction for expected mortality before reversal, this will result in a 72% stoma reversal rate in the initial patient population.

Economic evaluation

Comparisons of the different surgical strategies in the economic evaluation will be analogous to the analyses of the clinical endpoints. The economic evaluation will be performed from a societal perspective, with the costs per unit improvement on the primary clinical endpoints, defined as combined mortality and morbidity for the LOLA-arm, and stoma free survival for the DIVA-arm.

We hypothesise that a more effective intervention will be associated with less health care utilisation as well as absence from paid work (productivity costs). Therefore, the primary analysis will be a cost-effectiveness analysis that evaluates costs associated with an improved surgical outcome.

In addition, a secondary analysis will evaluate cost differences in relation to differences in quality-adjusted life-years (QALYs). This cost-utility analysis, resulting in an incremental cost-effectiveness ratio expressed in costs per QALY, will be included to allow comparison with other health-related interventions or programs. With a study horizon of twelve months, no discounting will be applied. We will differentiate between direct medical, direct non-medical and indirect costs.

Data collection and monitoring

An electronic Case Report Form (CRF) will include general patients data: sex, age, medical history, POSSUMscore, preoperative APACHE-score, surgical parameters, Hinchey score, data concerning type of intervention, complications, mortality, duration of hospital and intensive care stay and the patients response to the questionnaires.

Patients will be followed for a period of twelve months. During this follow-up period patients will complete a set of questionnaires (SF-36, EQ-5D and GIQLI) two, four, thirteen, 26 and 52 weeks after the initial surgery. The questionnaires will be sent to the patients by mail accompanied by a stamped return envelope. Collection of the questionnaires will be safeguarded by the trial coordinator.

At four, thirteen, 26, 39 and 52 weeks after initial surgery, the patients will be asked to complete questionnaires to assess complications, additional interventions, readmissions, duration of hospital and intensive care stay, visits to the outpatient clinic, number of days of sick leave and to ensure completions of the questionnaires.

Patient safety

An independent data monitoring and safety committee has been established to interpret the data from the current trial, to monitor any early significant differences between the groups of treatment and to make interim analyses to decide on continuation of the study after every 25 included patients.

An independent trial monitor will monitor the study procedure and the data of included patients.

A data management agency created the online database of the study to guard the entry of data by the local investigators. The same organisation has trained all trial coordinators, all local investigators and some local coinvestigators on the guidelines of Good Clinical Practice.

The trial coordinators have trained all other personnel on the protocol, on asking informed consent, on reporting Serious Adverse Events and on data entry.

According to the Good Clinical Practice guidelines, a list of Serious Adverse Events is defined. All events on this list have to be reported by the local investigators to the trial coordinators within 24 hours after the event. These events will be reported to the central Medical Ethics Committee (CCMO) within 24 hours afterwards. With this measure, the central Medical Ethics Committee compares the incidence of complications between the arms of the trial and can decide on continuation of the trial.

DISCUSSION

Since the introduction of laparoscopic lavage and drainage for purulent peritonitis for perforated diverticulitis in 1996, the number of patients treated with this new method had gradually inclined. However, there have been no publications of high methodological quality on this topic[28]. Therefore we do not know whether laparoscopic lavage is in fact a safe and effective treatment. Since the existing publications do promise a significant reduction in mortality and major morbidity, a randomised trial is appropriately warranted. A data monitoring committee will guard the methodological quality of the study, the safety of the patients, and monitor any early significant differences between the different surgical strategies.

We have not found any evidence that laparoscopic lavage is a safe treatment for perforated faecal peritonitis. Therefore in this group of patients randomisation will only take place between the two resectional strategies.

In the presented study all patients suspected for perforated diverticulitis are included, and a midline laparotomy can be avoided in selected patients with other pathology.

We do not know whether the lavage itself is important for the treatment of the peritonitis, since there are no publications on the treatment of purulent perforated diverticulitis with diagnostic laparoscopy and antibiotic treatment alone. Laparoscopic lavage in combination with antibiotic treatment however, has been examined in a systematic review with very promising results[28].

The stoma reversal rate is the primary endpoint for the DIVA-arm of the trial. Questions could be raised about the benefits of this reversal for a patient that is incontinent for faeces. A definitive colostoma for this specific group of patients might be preferable considering daily care. However this group of patients will be small and no studies have compared quality of life for incontinent patients with or without a stoma. The colostoma and ileostoma show equal impact on the patients quality of life, and quantification of incontinence problems is unpractical in the emergency setting[29]. Therefore incontinence is not established as an exclusion criterion. All resections will be performed with the intention of stoma reversal.

In the Netherlands the standard of care for perforated diverticulitis is either HP or PA. Resection with primary anastomosis is a type of treatment not mastered by every gastrointestinal surgeon. In the emergency setting, some surgeons might prefer HP, fearing anastomotic leakage. However, there is no clear evidence available showing a difference in mortality and major morbidity between HP and PA. Therefore we decided to

include treatment with PA in the randomisation process of the LOLA-arm as well.

Our hypothesis is that PA leads to a 22% higher stoma free survival, and that this procedure might be advocated as the new standard of care in selected patients with generalised peritonitis caused by perforated diverticulitis.

LIST OF ABBREVIATIONS

LOLA-arm: Laparoscopic lavage and drainage or sigmoidectomy with HP or PA for purulent peritonitis for perforated diverticulitis; DIVA-arm: Sigmoidectomy with HP or PA for generalised peritonitis for perforated diverticulitis; SF-36: Quality of Life Questionnaire Short Form 36; GIQLI: Gastro Intestinal Quality of Life Index; EQ-5D: Euro Quality of Life Questionnaire; LL: Laparoscopic lavage; HP: Hartmann's procedure; PA: Sigmoidectomy with primary anastomosis.

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5

CHAPTER

Laparoscopic peritoneal lavage or sigmoidectomy for perforated diverticulitis with purulent peritonitis: a multicentre, parallel-group, randomised, open-label trial

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ABSTRACT

Background

Case series suggest that laparoscopic peritoneal lavage might be a promising alternative to sigmoidectomy in patients with perforated diverticulitis. We aimed to assess the superiority of laparoscopic lavage compared with sigmoidectomy in patients with purulent perforated diverticulitis, with respect to overall long-term morbidity and mortality.

Methods

We did a multicentre, parallel-group, randomised, open-label trial in 34 teaching hospitals and eight academic hospitals in Belgium, Italy, and the Netherlands (the Ladies trial). The Ladies trial is split into two groups: the LOLA group comparing laparoscopic lavage with sigmoidectomy and the DIVA group comparing Hartmann's procedure with sigmoidectomy plus primary anastomosis. The DIVA section of this trial is still underway but here we report the results of the LOLA section. Patients with purulent perforated diverticulitis were enrolled for LOLA, excluding patients with faecal peritonitis, aged older than 85 years, with high-dose steroid use (≥20 mg daily), and haemodynamic instability. Patients were randomly assigned (2:1:1; stratified by age [<60 years *vs* ≥60 years]) using secure online computer randomisation to laparoscopic lavage, Hartmann's procedure, or primary anastomosis in a parallel design after diagnostic laparoscopy. Patients were analysed according to a modified intention-to-treat principle and were followed up after the index operation at least once in the outpatient setting and after sigmoidoscopy and stoma reversal, according to local protocols. The primary endpoint was a composite endpoint of major morbidity and mortality within 12 months. This trial is registered with ClinicalTrials.gov, number NCT01317485.

Findings

Between July 1, 2010, and Feb 22, 2013, 90 patients were randomly assigned in the LOLA section of the Ladies trial when the study was terminated by the data and safety monitoring board because of an increased event rate in the lavage group. Two patients were excluded for protocol violations. The primary endpoint occurred in 30 (67%) of 45 patients in the lavage group and 25 (60%) of 42 patients in the sigmoidectomy group (odds ratio 1.28, 95% CI 0.54–3.03, P=0.58). By 12 months, four patients had died after lavage and six patients had died after sigmoidectomy (P=0.43).

Interpretation

Laparoscopic lavage is not superior to sigmoidectomy for the treatment of purulent perforated diverticulitis.

INTRODUCTION

Diverticular disease is the fourth most costly gastrointestinal disorder in developed countries with an estimated annual hospital admission rate of 209 per 100 000 adults in Europe[1,2]. The prevalence of this disorder increases with age and is estimated at 5% of people in their forties and can be as high as 80% in those aged older than 80 years[2,3]. Of patients with acute diverticulitis, 8–35% presented with perforated disease with abscesses or peritonitis[2,4]. Perforated diverticulitis is graded according to the Hinchey classification, with abscess formation scored as Hinchey I or II, purulent peritonitis as Hinchey III, and faecal peritonitis as Hinchey IV[5]. Laparoscopic peritoneal lavage has emerged as a promising alternative to sigmoidectomy in patients with purulent peritonitis owing to perforated diverticulitis. This non-resectional strategy was first described in 1996[6,7]. In 2008, Myers and colleagues reported a 95% success rate of laparoscopic peritoneal lavage in 92 patients[8]. 2 years later a systematic review of case series showed a mortality rate of less than 5% and a colostomy was avoided in most patients[9]. Since these publications, laparoscopic lavage for purulent perforated diverticulitis has gained popularity because of its great potential to improve outcomes and reduce costs. Despite the absence of robust evidence from randomised trials, laparoscopic lavage has been embraced by many surgeons. Even some national and international guidelines state that it is a safe approach in purulent perforated diverticulitis[10,11]. The laparoscopic lavage (LOLA) group of the Ladies trial postulated that laparoscopic lavage compared with sigmoidectomy for purulent perforated diverticulitis would lead to a reduction in composite outcome of major morbidity and mortality in a randomised multicentre trial[12].

METHODS

Study design and participants

The Ladies trial is a multicentre, parallel-group, randomised, open-label superiority trial done in 34 teaching hospitals and eight academic hospitals in Belgium, Italy, and the Netherlands. It was designed to compare laparoscopic lavage and sigmoidectomy for purulent perforated diverticulitis in the LOLA group and to compare Hartmann's procedure versus sigmoidectomy with primary anastomosis in both purulent and faecal perforated diverticulitis in the DIVA group. Patients with signs of general peritonitis and suspected perforated diverticulitis were eligible for inclusion. Radiological examination by radiography or a CT scan had to show diff use-free intraperitoneal air or fluid for patients to be classified as having perforated diverticulitis. Exclusion criteria were dementia, previous sigmoidectomy, pelvic irradiation, chronic treatment with high-dose steroids (>20 mg daily), being aged younger than 18 years or older than 85 years, and having preoperative shock needing inotropic support. Patients with Hinchey I and II perforated diverticulitis were excluded from the study and patients with Hinchey IV peritonitis or

overt perforation could only be included in the DIVA group. The study protocol12 was approved by the ethical review board and written informed consent was obtained from all patients before randomisation. This study was investigator initiated and designed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Randomisation and masking

After preoperative informed consent was obtained by the surgeon or surgical resident, diagnostic laparoscopy was done to confirm the diagnosis of perforated diverticulitis and to distinguish between purulent and faecal peritonitis or overt perforation. Only patients with purulent perforated diverticulitis without overt perforation were randomly assigned within the LOLA group with secure online computer randomisation, either directly in the operating room or by the trial coordinator on the phone. Patients were randomly assigned (2:1:1) to receive either laparoscopic lavage, sigmoidectomy without primary anastomosis, or sigmoidectomy with primary anastomosis (with or without defunctioning ileostomy), allowing for a 1:1 comparison between lavage and sigmoidectomy in the LOLA group (figure, Appendix). Patients with an overt perforation or faecal peritonitis were included in the DIVA group of the study and not analysed within the LOLA group. We used a random and concealed block size of 2, 4, or 6 for randomisation and stratified for age (younger or older than 60 years). Treatment allocation was not masked to patients, physicians, or researchers at any timepoint.

Procedures

The procedures for surgery, reintervention, and stoma reversal have previously been described[12]. To determine the presence of a sigmoid perforation, adherent tissues were carefully removed, but when firmly adherent, they were left in place. Laparoscopic lavage was done by irrigation with up to 6 L of warm saline throughout the abdominal cavity. A Douglas drain was inserted in the right lateral port site. Sigmoidectomy with primary anastomosis was done according to the guidelines of the American Society of Colon and Rectal Surgeons and the creation of a defunctioning ileostomy was at the discretion of the surgeon[13]. 4–6 weeks after laparoscopic lavage, sigmoidoscopy was done to exclude malignancy as the underlying cause of perforation. In the sigmoidectomy group, patients were offered stoma reversal if they were fit enough and willing to undergo surgery. Routine sigmoidectomy was not recommended for patients after laparoscopic lavage. Patients were followed up after the index operation at least once in the outpatient setting and after sigmoidoscopy and stoma reversal, according to local protocols. If the patient was not in active follow-up by the surgeon at 12 months, the patient was contacted to verify the remaining follow-up.

Outcomes

The primary endpoint of the LOLA group was a composite endpoint including major

morbidity and mortality within 12 months. Major morbidity was defined as the occurrence of the following events or conditions: surgical reintervention, abdominal wall dehiscence, abscesses needing percutaneous drainage during the full period and urosepsis, myocardial infarction, renal failure, and respiratory insufficiency within 30 days after operation or in hospital[12]. Elective stoma reversal surgery was not defined as morbidity or reintervention for either group, whereas elective sigmoidectomy after lavage was scored accordingly. Secondary outcomes were operating time, length of hospital stay, days alive and outside the hospital, shortterm morbidity and mortality, incisional hernia, reinterventions within 12 months, and health-related quality of life (measured with Short Form-36 version 2 [SF-36v2], Gastrointestinal Quality of Life Index [GIQLI], and EuroQol 5D 3 level [EQ-5D-3L] questionnaires at 2, 4, 13, and 26 weeks)[14]. These timepoints were chosen to address both short-term and long-term postoperative recovery. Short-term morbidity and mortality were defined as within 30 days after operation or until discharge, if the patient was still admitted at that time. We did a post-hoc analysis of the incidence of recurrent diverticulitis and the incidence of underlying perforated colorectal carcinoma diagnosed during follow-up. Failure of treatment was defined as persisting abdominal sepsis, resulting in surgical reintervention or death[15].

Statistical analysis

We calculated that a sample size of 264 patients for the LOLA group was needed to detect a 15% difference in the composite endpoint of major morbidity and mortality, with an expected rate of 25% in the sigmoidectomy group and 10% in the laparoscopic lavage group at 12 months. We used a two-sided likelihood ratio test and a power of 90%[12]. The assumption of 10% major morbidity and mortality is based on the reported morbidity and mortality by Toorenvliet and colleagues, whereas 25% major morbidity and mortality was based on adjusted data from the scientific literature because we only included patients with a Hinchey III score and excluded those with Hinchey IV or other risk factors for postoperative morbidity and mortality according to our set exclusion criteria[9,16,17]. We designed a monitoring plan for source data verification on the basis of the assumption that the trial was a moderate-risk study. The first three participating patients in each centre, followed by a 50% sample control of the following included patients, were verified by an independent clinical research associate. The clinical research associate verified informed consent, inclusion criteria, adverse events, and adherence to Good Clinical Practice guidelines, with the resources available (eg, patient charts at the participating hospital). In regular interim analyses, an independent data and safety monitoring board (DSMB) assessed the progress of the trial and examined safety variables after inclusion of every 25 patients. Although no stopping rules were defined in the protocol, a formal DSMB charter was developed and approved by the central ethical committee. This charter allowed the DSMB to stop the study for safety or early superiority without any prespecified definitions. According to this charter, the DSMB assessed the

progress and analysed outcomes on the basis of the data supplied by the researchers—eg, for early morbidity (<30 days) and major morbidity as defined in the study protocol. The DSMB was granted access to individual data for those patients with study-related severe morbidity and mortality. We analysed patients according to a modified intention to- treat principle. We tested the primary endpoint using binary logistic regression analysis with post-hoc correction for the planned stratified age groups (<60 years and ≥60 years) with a two-sided significance level of 5%. We tested secondary outcomes with linear and binary logistic regression analysis with post-hoc correction for the planned stratified age groups (<60 years and ≥60 years) to compare groups. For categorical data and binary data with no events in one of the groups, we calculated numbers and percentages and compared these between groups with unadjusted Fisher's exact test. We reported data with effect sizes, mean differences (MD), odds ratios (OR) and 95% CI, or with 1000 samples bias corrected and accelerated bootstrapped 95% CIs in the case of non-parametric data. We tested continuous variables for normality using the Shapiro-Wilk test and Q-Q plots. We summarised data as either means with SDs or medians (IQRs), depending on normality. We did post-hoc subgroup analysis for the American Society Anesthesiologists physical status classification (ASA) grade because ASA grade differed significantly between the two treatment groups at baseline. Subgroup analyses have been done with logistic regression analysis. We used a complete case analysis approach apart from the quality of life questionnaires (SF-36v2, GIQLI, and EQ5D), assuming random missing data. All questionnaires were scored according to the relevant manuals and presented as domains and summarised scores. In cases of missing items within domains of the SF-36 and GIQLI, missing items were substituted with the mean value if at least half of the items in the subscale were known. When questionnaires were not returned for any of the four timepoints, missing data were imputed by linear interpolation if the borderline timepoints (eg, 2 weeks and 6 months) were available. Missing observations in the first or last timepoint were imputed with the first observation carried backward and last observation carried forward method. At least one returned questionnaire was needed for imputation of the missing timepoints. Questionnaire outcome comparisons were corrected for multiple testing with the Benjamini-Hochberg method, although this correction was not prespecified in the protocol. The trial was registered with the trialregister.nl, number NTR2037 and ClinicalTrials.gov, number NCT01317485.

Role of the funding source

The funder of the study critically reviewed and adjusted the study design, but had no role in data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had full responsibility for the decision to submit for publication.

RESULTS

Between July 1, 2010, and the early termination of the trial on Feb 22, 2013, we randomly assigned 90 patients in the LOLA group; 47 patients were assigned to laparoscopic lavage and 43 to the sigmoidectomy. Patients were followed up for 12 months (figure 1). Two patients were excluded because of protocol violations of the inclusion criteria; one used high-dose steroids and the other was randomly assigned despite a known diagnosis of perforated rectal carcinoma at the time of surgery. One patient in the lavage group was lost to follow-up at 12 months because he could not be located after he moved house. Patients in this trial were included from 30 hospitals (28 from the Netherlands, one Belgian, and one Italian). Because the registration of non-included patients seemed to be incomplete, a chart review was done in all participating hospitals in the Netherlands to verify the number of excluded and missed patients within the study period. In these hospitals, 563 patients with acute surgery for perforated diverticulitis were identified of whom 186 were eligible and underwent diagnostic laparoscopy, 77 were excluded with Hinchey I or II diverticulitis. Of 247 eligible patients with Hinchey III perforated diverticulitis, 84 were included in the LOLA group. Another six patients were included from foreign participating hospitals (Appendix, Table 1). The baseline characteristic of patients included in this trial (Table 1) did not differ from the eligible but not included patients (Appendix). The mean age in the 88 analysed patients was 63 years (SD 12.5) and 51 (58%) were men. The proportion of patients with ASA grade III or IV was lower in the lavage group. The physiological score and operative severity score (POSSUM-OS) reported in the sigmoidectomy group was higher than that in the lavage group, but can be attributed to the two point higher procedure score for sigmoidectomy (Appendix). Within the sigmoidectomy group, 20 patients were allocated to sigmoidectomy with end colostomy and 22 to sigmoidectomy with primary anastomosis, of whom one was converted to a Hartmann's procedure and one crossed over to laparoscopic lavage (because this patient could not be placed in the stirrups, needed to use the circular stapler because of recent knee surgery). 14 patients were diverted with an ileostomy. One patient in the lavage group was converted to open Hartmann's because of faecal contamination of the pelvis identified during lavage. Seven sigmoidectomies were completed by laparoscopy, all others were converted to open surgery after randomisation. The LOLA group of the Ladies trial was terminated early for safety reasons after the third planned interim analysis after 75 patients were enrolled, the data were reported to the DSMB on Nov 14, 2012. As the DSMB requested additional data, the final data on which the decision was taken included 46 lavage and 40 sigmoidectomy patients from the LOLA group. During the first two analyses, the DSMB raised concerns about the safety of the patients in the lavage group because of the high short-term morbidity and reintervention rate, but the numbers were too small to form a conclusion. At the third analysis, the interim data for in-hospital major morbidity or mortality was 16 (35%) of 46 in the lavage group versus seven (18%) of

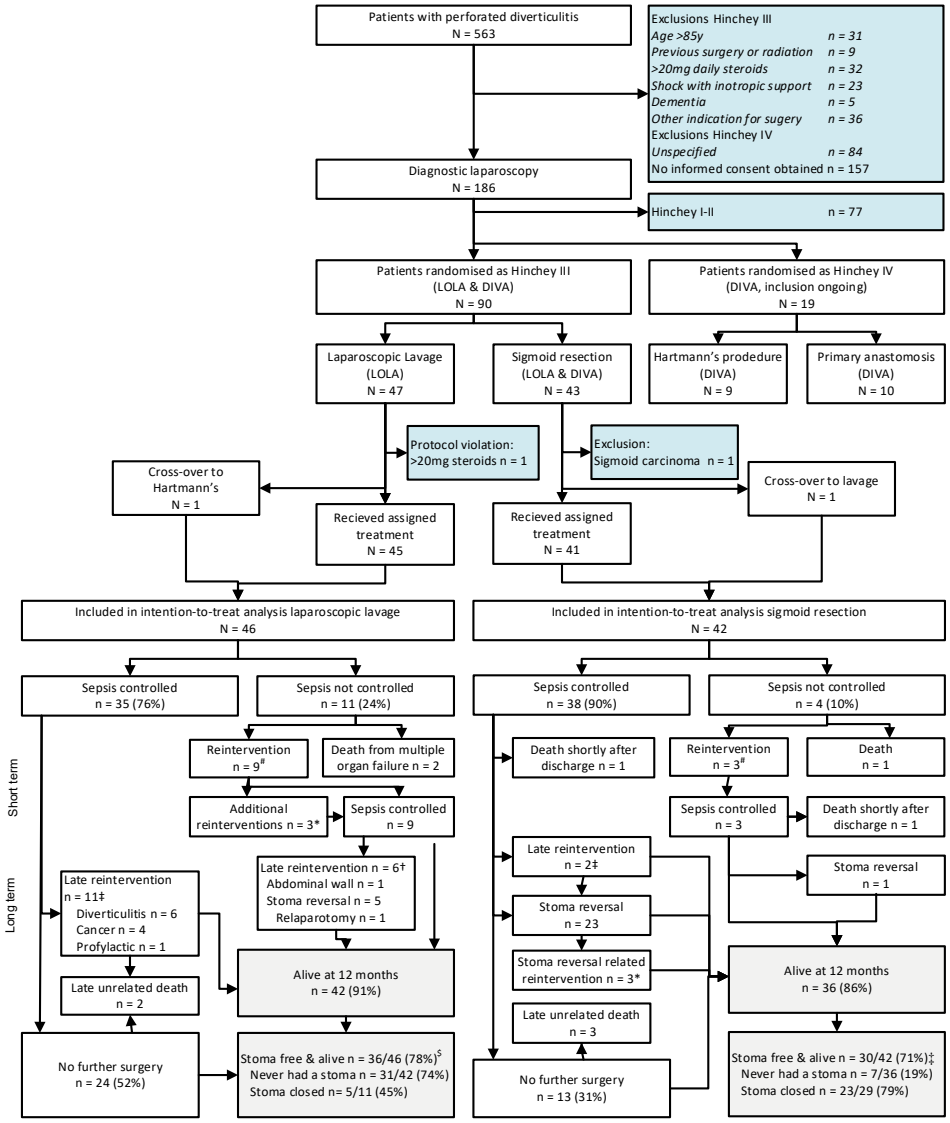

Figure 1. Trial profile of included patients and additional treatment received. | Lavage group: # Laparoscopic Hartmann's procedure (HP), laparoscopic primary anastomosis (PA) with ileostomy, 4 open HP, 3 with multiple procedures. | *1 patient with four open lavages (OL) resulting in a laparostoma, 1 patient with redo laparoscopic lavage followed by open HP, 1 patient open HP followed by OL and open rectal stump reresection due to persistent leakage. | † 1 sigmoidectomy with primary anastomosis, abdominal wall and fistula correction following laparostoma, 1 relaparotomy for haematoma after Hartmann's reversal, 4 uncomplicated stoma reversals. | ‡ 4 laparoscopic and 2 converted PA without ileostomy for persistent or recurrent diverticulitis or abscesses, 1 prophylactic single port PA without stoma. 2 open HP, 1 open PA for cancer, 1 liver

Figure 1. Continued
metastasectomy plus diagnostic laparoscopy with peritoneal metastases followed by acute fascial dehiscence correction.| $ 36 of total 46 lavages were alive and stoma free at 12 months, 31 of 42 patient alive never had a stoma, 5 of 11 patients alive with stoma were reversed. | Sigmoidectomy group: # 1 relaparotomy for acute fascial dehiscence, 1 suspected but unconfirmed anastomotic leak, 1 second look laparotomy in a patient with an open abdomen, who died shortly after discharge due to pneumosepsis. | * 1 revision of the obstructed anastomosis before the ileostomy reversal, 1 splenectomy and video assisted thoracoscopic surgery (VATS) for a splenic abscess and thoracic empyema | † 1 relaparoscopy for bleeding, 1 open lavage for haematoma 1 relaparotomy with end colostomy for anastomotic leakage. All following Hartmann's reversal. | ‡ 30 of 42 total sigmoidectomies stoma free and alive at 12 months, 7 of 36 patients alive never had a stoma, 23 of 29 patients alive with stoma were reversed.

40 (complete data were not available for 2 patients) in the sigmoidectomy group (P=0.12), with 37 events in the lavage group and ten events in the sigmoidectomy group (P=0.0005). Surgical reinterventions accounted for most of these adverse events with 18 (lavage) versus two (sigmoidectomy) in-hospital reinterventions (P=0.0011) and 28 (lavage) versus 11 (sigmoidectomy) overall surgical reinterventions (P=0.0219). Therefore, the DSMB advised to us to end the LOLA group of the trial as the safety of the participants in the lavage group was at risk. As the safety concerns were limited to the laparoscopic lavage group, the DIVA group was continued as planned after the ethical committee approved the amended protocol. Therefore, data about the comparison between sigmoidectomy with and without primary anastomosis will not be presented until the remaining DIVA group is closed. During the 12-month follow-up, no difference was reported in the incidence of the composite primary endpoint (30 patients in the lavage group *vs* 25 patients in the sigmoidectomy group; OR 1.28, 95% CI 0.54–3.03, P=0.5804). This rate includes four (9%) and six (14%) patients who had died either postoperatively or during the follow-up in the lavage and sigmoidectomy group (OR 0.53, 95% CI 0.13–2.15, P=0.3772). Five patients died during their primary hospital stay or shortly thereafter, whereas the remaining five late deaths (two in the lavage group, three in the sigmoidectomy group) were unrelated to the study procedures (Appendix). The mean operating time was shorter for the lavage group with 60 min compared with 120 min in the sigmoidectomy group (mean difference [MD] –54.53, 95% BCa CI –68.04 to –40.26, P=0.0010). The length of postoperative hospital stay did not differ between the two groups, 8 days (IQR 6–15) after lavage and 10 days (7–14) after sigmoidectomy (MD –0.62, 95% BCa CI –8.34 to 6.38, P=0.8751). The combined major morbidity and mortality rate within 30 days after operation or in hospital was higher after laparoscopic lavage (18 [39%] patients in the laparoscopic lavage group compared with eight [19%] in the sigmoidectomy group [OR 2.74, 95% CI 1.03–7.27, P=0.0427]), most of which could be explained with the higher rate of reinterventions in the lavage group (16 and three patients, OR 6.93, 95% CI 1.85–

26.00, P=0.0041). Short-term adverse events are summarised in Table 2 and the Appendix. Sepsis was controlled successfully in the short term, defined as not needing surgical reintervention and being alive, in 35 (76%) of the patients in the lavage group and 38 (90%) of the patients in the sigmoidectomy group (Appendix). Persistent sepsis in the lavage group needed surgical reintervention in nine patients and was caused by faecal peritonitis or overt perforation in six patients. One patient was diagnosed with an underlying carcinoma during pathological assessment. Seven patients had a Hartmann's procedure, one a primary anastomosis with ileostomy, and one patient had four relaparotomies after laparoscopic lavage, followed by delayed elective sigmoidectomy. Two other patients died from multiorgan failure. Three patients in the sigmoidectomy group needed reintervention because of an acute fascial dehiscence, an unconfirmed anastomotic leakage, and a negative second look laparotomy in a patient with an abdomen left open. One patient died because of massive arterial embolism and another two patients died shortly after extended hospital stay because of renal or respiratory failure. Routine pathological assessment revealed two patients with underlying carcinoma in the sigmoidectomy group, both treated with adjuvant chemotherapy. Stoma reversal surgery was done in five of 11 patients (one ileostomy, four of ten colostomies) in the lavage group and 24 of 35 in the sigmoidectomy group (12 of 14 ileostomies, 12 of 21 colostomies). Morbidity occurred in one patient in the lavage group and six patients in the sigmoidectomy group after stoma reversal, including one patient (lavage) and three patients (sigmoidectomy) with a surgical reintervention, after Hartmann's reversal. No reversal-related mortality occurred (Appendix). Laparoscopic lavage was successful in 24 (52%) patients in the long term, defined as no acute or elective surgical reintervention or related mortality, and 31 (74%) of the 42 patients alive never had a stoma (Appendix). Seven patients had elective laparoscopic sigmoidectomy, of whom two were converted to laparotomy. Four had open surgery for colorectal cancer, of whom three were diagnosed during follow-up colonoscopy. The other patient presented with a colovesical fistula after 8 months. Two of these four patients developed metastases. Two patients that had acute reoperation after laparoscopic lavage needed additional surgical reintervention, including one haematoma after Hartmann's reversal. In the sigmoidectomy group, no further surgery was done in 13 (31%) patients, of whom 6 never had a stoma (Appendix). During follow-up, two patients needed surgical reintervention; one for revision of the obstructed anastomosis before the ileostomy could be reversed and the other patient needed splenectomy and video-assisted thoracoscopic surgery for a splenic abscess and thoracic empyema. Three more patients had surgical reintervention after Hartmann's reversal, two postoperative haematomas, and one anastomotic leakage. 36 (78%) patients in the lavage group and 30 (71%) in the sigmoidectomy group were alive and stoma free after 12 months (OR 1.53, 95% CI 0.55–4.30, P=0.4193). In each group, another six patients were alive but not stoma free at 12 months. Incisional hernia occurred in five patients each in both groups. Four of five hernias in the laparoscopic group occurred after conversion or relaparotomy, three had surgical repair. Of the five patients who had hernias

in the sigmoidectomy group, only one parastomal hernia was corrected during colostomy reversal. Long-term adverse events are summarised in Table 2 and the Appendix. The number of days alive and outside the hospital during the 12-month period did not differ between both groups (Appendix). The response rate of the quality of life questionnaires varied between 56 (64%) of 88 at 2 weeks and 52 (59%) of 88 at 6 months. 69 (78%) patients completed at least one of the questionnaires. No differences were identified in the main scores of the SF-36, GIQLI, and EQ5D questionnaires, and no subscale remained significant after the p values were corrected post hoc for multiple testing (Appendix). In a post-hoc subgroup analysis for patients aged younger than 60 years or 60 years and above, the primary endpoint did not differ between the two treatment groups. Post-hoc stratified analysis for patients with a low ASA grade (I or II) or high ASA grade (III or IV) did not show a significant between-group difference in the primary outcome (OR 1.36, 95% CI 0.51–3.62, P=0.5337; Appendix; article online).

Table 1. Baseline demographic and clinical characteristics in randomly assigned patients with perforated diverticulitis.

	Laparoscopic lavage N=46	**Sigmoidectomy N=42**
Age, years	62.3 (12.7)	64.0 (12.3)
Gender		
Male	26 (56.5)	25 (59.5)
Female	20 (43.5)	17 (40.5)
BMI, kg/m^2 *	27.6 (6.2)	27.0 (4.4)
ASA I	10 (21.7)	8 (19.0)
II	21 (45.7)	13 (31.0)
III	5 (10.9)	13 (31.0)
IV	3 (6.5)	2 (4.8)
missing	7 (15.2)	6 (14.3)
History of diverticulitis†	12 (31.6)	10 (26.3)
Previous laparotomy‡	4 (8.9)	3 (7.3)
Disease severity pre-operative		
APACHE II	7.3 (4.2)	9.0 (4.8)
POSSUM PS	20.8 (6.2)	22.8 (6.2)
POSSUM OS	17.1 (0.5)	20.0 (2.2)
Interval from ER to surgery	13 (8-32)	13 (6-42)
Gastrointestinal surgeon	37 (80.4)	36 (85.7)

Data are mean (SD) median (IQR) or number (%). BMI=Body-mass index. ASA=American Society of Anesthesiologists classification. APACHE II=Acute Physiology and Chronic Health Evaluation II. POSSUM PS= Physiology and Operative Severity Score for the enumeration of Mortality and Morbidity – Physiology Score. POSSUM OS= POSSUM Operative Score. ER=moment of presentation at the emergency department. Data provided for *n=40, n=39 †n=38, n=38 ‡n=45, n=41 patients in the laparoscopic lavage group and sigmoidectomy group respectively.

Table 2. Serious adverse events as defined as major morbidity.

	Laparoscopic lavage N=46		Sigmoidectomy N=42		P-Value
	N patients	*N events*	*N patients*	*N events*	
Short term serious adverse events	18 (39%)	39	8 (19%)	14	**0.0427**
Death	2 (4%)	2	1 (2%)	1	0.6237
Surgical reintervention	9 (20%)	15	3 (7%)	3	0.1230
Abscess with percutaneous drainage	9 (20%)	12	0	0	**0.0027**
Fascial dehiscence	0	0	3 (7%)	3	0.1046
Myocardial infarction	0	0	1 (2%)	1	0.4773
Respiratory failure	6 (13%)	6	2 (5%)	2	0.1955
Renal failure	2 (4%)	2	3 (7%)	2	0.9207
Long term serious adverse events	17 (37%)	30	17 (40%)	20	0.1156
Death	2 (4%)	2	5 (12%)	5	0.1875
Surgical reintervention	13 (28%)	16	5 (12%)	6	0.1156
Abscess with percutaneous drainage	2 (4%)	4	2 (5%)	2	0.9207
Fascial dehiscence	5 (11%)	5	5 (12%)	5	0.4359
Sigmoid carcinoma	5 (11%)	5	2 (5%)	2	0.3047
Recurrent diverticulitis	9 (20%)	9	1 (2%)	1	**0.0315**
Composite primary outcome (major morbidity or mortality at 12 months)	30 (67%)	-	25 (60%)	-	0.5804

Data are number (%) unless otherwise stated. Short term is defined as within 30-days or in-hospital, long term is defined as after 30-days or discharge and within 12 months.

DISCUSSION

In this study, which was terminated early, laparoscopic peritoneal lavage for purulent perforated diverticulitis did not result in a reduction in the composite endpoint of major morbidity and mortality compared with sigmoidectomy at 12 months. Although laparoscopic lavage did result in a higher acute reintervention rate, 76% of patients were discharged without further surgery. The higher morbidity rates did not result in excess mortality, suggesting that patients that fail lavage can be salvaged when reintervention is timely. The 24% failure to control sepsis with lavage could be attributed to misdiagnosis of faecal peritonitis in most cases. As the phlegmon is often located at the pelvic entrance, occluding the view on Douglas pouch, the limited exploration as described in our study protocol might have resulted in these misdiagnoses. A third of the pathological specimens from the sigmoidectomy group showed a perforation, similar to the 37% perforations identified in the pathological specimens of a previous study. These rates suggest a similar rate of sealed or missed perforations in the lavage group[18]. A CT scan with rectal contrast might be able to discriminate faecal from purulent peritonitis by showing

contrast extravasation. However, the use of rectal contrast for acute abdominal CT scans is not routine practice and is barely discussed in guidelines[19]. The use of rectal contrast might also help to diagnose underlying colorectal carcinoma. Seven (8%) patients were diagnosed with a sigmoid carcinoma, which is not unusual compared with the 3% and 7% reported in two previous trials on perforated diverticulitis[20,21]. These carcinomas have been responsible for a third of the elective sigmoidectomies in the lavage group. At the time we initiated the Ladies trial, the evidence for laparoscopic lavage consisted of limited and low quality evidence from case series. A success rate of 96% for laparoscopic lavage with low mortality (2%) and morbidity (10%) was reported in a systematic review including 231 patients from 13 papers[9]. More recently published case series show higher failure rates of up to 34% and a morbidity rates up to 56% for laparoscopic lavage (panel and Appendix)[15,22]. The favourable results of the largest series by Myers and colleagues[8] and several other series might have a selection bias because the complete population from which these patients were selected was not described and a large proportion of patients without perforation (Hinchey II) were included. The excellent results of the early case series are unlikely to be reproduced in large randomised controlled trials because selection bias is usually stronger in the series and the patient's condition is a major predictor of postoperative outcomes[17]. Although the results of laparoscopic lavage were not as good as expected, the 30-day mortality rate of 2% in the sigmoidectomy group of this study was low compared with previous studies. However, these previously reported rates of 10–22% include patients with faecal peritonitis, with a reported odds ratio for increased mortality of 3.9 in patients with faecal peritonitis[17,23,24]. While designing the study, we assumed that taking the short-term morbidity and mortality as the primary endpoint would underappreciate the benefits of lavage. We expected that in the sigmoidectomy group more late surgeries—eg, abdominal wall repairs, and morbidity associated with stoma closure—would occur. Stoma closure was part of the sigmoidectomy strategy and therefore not counted as an adverse event. Our power calculation was done on the basis of a 15% difference in the composite endpoint. Both the 10% and 25% for lavage and sigmoidectomy were conservative estimates, allowing for a clinically relevant difference and sufficient group size to avoid an underpowered study. Traditionally, surgical studies focused on morbidity and mortality and used these as primary outcomes. Similar outcomes are used in the other trials on perforated diverticulitis[25-27]. Other definitions of success can be used provided that no excess mortality exists in one of the study groups—eg, no further surgery, never having had a stoma, and enabling delayed laparoscopic surgery. Because of the design of the study, it had insufficient power to conclude on non-inferiority. A non-inferiority trial with mortality as the primary endpoint would need a very large sample size, while patient accrual in emergency trials has been shown to be difficult[28]. Two earlier randomised trials of perforated diverticulitis were terminated at less than half of the calculated sample size because of a declining accrual rate[20,21]. Because of the parallel randomisation in the DIVA group, the ostomy reversal rate in the sigmoidectomy group

was affected by the allocation to Hartmann's or primary anastomosis. However, this was not expected to affect the 12-month morbidity and mortality rate in our study because no differences were shown in recent randomised trials[20,21]. Although no differences between groups could be identified in the quality of life questionnaires, we did not collect data for patients' satisfaction with the long-term result of the treatment. A higher satisfaction might be expected in those patients who never had a stoma and never needed additional surgery, even if an interventional drain had been necessary. Strengths of this study include conduct according to Good Clinical Practice principles and source verification of the data by an independent monitor. Running investigator driven trials according the Good Clinical Practice principles is uncommon in surgery, but was demanded by the Dutch Inspectorate of Health Care after irregularities reported in the conduct of the Dutch PROPATRIA study[29]. Another important strength of the study is that we were able to account for the eligible but not included patients. In this way, we have been able to assess and rule out a patient selection bias despite the low accrual rate of 34%. The participation of a large number of hospitals strengthens the external validity and applicability of the study results. At the same time, the low number of included patients per hospital can be seen as a weakness because of heterogeneity. We conclude that laparoscopic lavage is not superior to sigmoidectomy for the treatment of purulent perforated diverticulitis in terms of major morbidity and mortality at 12 months. Although the acute reintervention rate was higher after lavage, in more than three-quarters of these patients, the sepsis was controlled. No excess mortality was present in patients who failed lavage. Optimisation of preoperative imaging is warranted to identify those patients who are likely to fail lavage because of the presence of a persistent perforation or a perforated carcinoma. Pooling of the forthcoming data of the other perforated diverticulitis trials (DILALA, LapLAND, and SCANDIV)[24–26] with our data might identify additional factors that contribute to an improved selection of patients that either need lavage or sigmoidectomy in the acute setting.

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CHAPTER

Guidelines of diagnostics and treatment of acute left-sided colonic diverticulitis

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ABSTRACT

Background

The incidence of acute left-sided colonic diverticulitis (ACD) is increasing in the Western world. To improve the quality of patient care, a guideline for diagnosis and treatment of diverticulitis is needed.

Methods

A multidisciplinary working group, representing experts of relevant specialties, was involved in the guideline development. A systematic literature search was conducted to collect scientific evidence on epidemiology, classification, diagnostics and treatment of diverticulitis. Literature was assessed using the classification system according to an evidence-based guideline development method, and levels of evidence of the conclusions were assigned to each topic. Final recommendations were given, taking into account the level of evidence of the conclusions and other relevant considerations such as patient preferences, costs and availability of facilities.

Results

The natural history of diverticulitis is usually mild and treatment is mostly conservative. Although younger patients have a higher risk of recurrent disease, a higher risk of complications compared to older patients was not found. In general, the clinical diagnosis of ACD is not accurate enough and therefore imaging is indicated. The triad of pain in the lower left abdomen on physical examination, the absence of vomiting and a C-reactive protein >50 mg/l has a high predictive value to diagnose ACD. If this triad is present and there are no signs of complicated disease, patients may be withheld from further imaging. If imaging is indicated, conditional computed tomography, only after a negative or inconclusive ultrasound, gives the best results. There is no indication for routine endoscopic examination after an episode of diverticulitis. There is no evidence for the routine administration of antibiotics in patients with clinically mild uncomplicated diverticulitis. Treatment of pericolic or pelvic abscesses can initially be treated with antibiotic therapy or combined with percutaneous drainage. If this treatment fails, surgical drainage is required. Patients with a perforated ACD resulting in peritonitis should undergo an emergency operation. There is an ongoing debate about the optimal surgical strategy.

Conclusion

Scientific evidence is scarce for some aspects of ACD treatment (e.g. natural history of ACD, ACD in special patient groups, prevention of ACD, treatment of uncomplicated ACD and medical treatment of recurrent ACD), leading to treatment being guided by the surgeon's personal preference. Other aspects of the management of patients with ACD have been more thoroughly researched (e.g. imaging techniques, treatment of complicated ACD and elective surgery of ACD). This guideline of the diagnostics and treatment of ACD can be used as a reference for clinicians who treat patients with ACD.

INTRODUCTION

Left-sided diverticulosis of the colon is a common condition in Western society. The prevalence of diverticulosis coli depends on age and increases from about 5% around 40 years of age to 65% at the age of 85 years or older[1,2]. It is estimated that approximately 25% of the patients with diverticulosis will develop an episode of acute left-sided colonic diverticulitis (ACD)[3]. Patients with acute abdominal pain due to ACD impose an impressive burden to healthcare[4] . In the past years, a dramatic rise in the number of hospitalizations for ACD has been noted in the Netherlands. In 2009, 18,355 patients were hospitalized with ACD as compared to 13,655 patients in 2006. Meanwhile, expenditures for these hospital admissions in the Netherlands exceed EUR 80 million per year[5,6]. This rise in hospital admissions is also notable in other countries. A recent study from the United States showed an increase in hospital admissions during the period 1998–2005 of 26%, with the greatest rise in patients between 18 and 44 years of age[4]. In the Netherlands, women make up 60% of hospital admissions for ACD[6]. This difference in incidence of ACD between men and women has been noticed in other countries as well. Patients younger than 50 years of age with ACD are predominantly men, whereas in the age group of 50–70 years there seems to be a preference for women[7-11]. Patients with mild (recurrent) diverticulitis are usually treated by a general practitioner or on an outpatient basis, which makes it difficult to accurately determine the true incidence and recurrence rates of diverticulitis.

Although ACD is a very common disease, the clinical diagnosis remains a challenge for clinicians and health care researchers. Diagnostics and treatment of diverticulitis are mostly characterized by doctors' personal preferences rather than standardized evidence-based protocols. This is mainly due to the fact that there is a large amount of conflicting and low-quality evidence in publications regarding diverticulitis. To provide doctors and other health care providers support in clinical decision-making, practice guidelines can be developed. Guidelines are applicable nationwide, but if based on international literature can be applicable to developed countries. Therefore, a multidisciplinary working group developed national guidelines including the epidemiology, classification, diagnostics and treatment of ACD in all its aspects based on an evidence-based review of the international literature.

METHODS

The guideline was written under the auspices of the Netherlands Society of Surgery, in collaboration with the Netherlands Societies of Internal Medicine, Gastroenterologists, Radiology, Health Technology Assessment and Dieticians. The working group consisted of four surgeons, a gastroenterologist, a radiologist, an internist specialized in infectious

diseases, a dietician and an epidemiologist and statistician. Participation of a patients' representative in the working group was not possible because a patient association for patients with ACD does not exist in the Netherlands. The working group defined the following sections of relevance: terminology and classification, epidemiology, special patient groups with ACD, prevention of recurrent ACD, clinical diagnosis and radiological imaging, colonoscopy, treatment of uncomplicated and complicated ACD, and elective surgery and medical treatment in patients with ACD.

Search Strategy

Systematic searches of the Medline and Embase databases were performed using the keywords relevant to each section. Terms relevant to each section of the guideline were mapped to Medline Subjects Headings (MeSH) terms, as well as searched for as text items. Relevant keywords and search strategies can be found in Appendix 1. Articles describing randomized controlled trials and systematic reviews were searched for using the methodological filters of the Scottish Intercollegiate Guidelines Network (https://www.sign.ac.uk/methodology/filters.html). Different date censoring and limitations were applied according to the relevance of each keyword. Only publications in English, French, German and Dutch were retrieved and read in full. The bibliographies of included articles were subsequently hand-searched for other relevant references, and experts in the field were asked if they found any relevant reports missing.

Critical Appraisal

Articles selected to support recommendations were assessed using the national classification system for evidence-based guideline development (http://www.cbo.nl), which is equivalent to the levels of evidence as published by the Centre for Evidence-Based Medicine of the University of Oxford (www.cebm.net; Table 1). Articles were classified according to the type of article and individually assessed for methodological quality using the GRADE method as proposed by the GRADE working group. That working group has developed a common, sensible and transparent approach to grading the quality of evidence and strength of recommendations (http://www.gradeworkinggroup.org).

The main literature on which the conclusion for each relevant topic is based is stated with the conclusion, accompanied by the level of evidence (Table 2). The final recommendations are based on the available evidence from the literature, also taking into account 'soft' factors such as patient preferences, costs and availability of facilities. Recommendations can be strong ('we can be confident about the recommendation', level 1) to weak ('we cannot be confident', level 4). A concept guideline was sent to all involved societies for comment and approval after which internal consensus was reached between the members of the working group. Amendments were made based upon these comments, leading to the final version of the guideline 'Diagnostics and Treatment of Acute Colonic Diverticulitis', as approved by all societies.

Table 1. Classification of evidence.

Level of Evidence	Interventional research	Studies concerning diagnostic accuracy	Studies on complications or side-effects, etiology, prognosis
A1	Systematic review/ meta-analysis of at least 2 independently performed level A2 studies		
A2	Double blind controlled randomised comparative clinical trial of good study quality with an adequate number of study participants	Diagnostic test compared to reference test; criteria and outcomes defined in advance; assessment of test results by independent observers; independent interpretation of test results; adequate number of consecutive patients enrolled; all patients subjected to both tests	Prospective cohort with sufficient amount of study participants and follow-up, adequately controlled for confounders; selection in follow-up has been successfully excluded
B	Comparative studies, but without all the features mentioned for level A2 (including patient-control studies, cohort studies)	Diagnostic test compared to reference test, but without all the features mentioned in A2	Prospective cohort study, but without all the features mentioned for level A2 or retrospective cohort study or case-control study
C	Non-comparative studies		
D	Expert opinion		

Table 2. Grading of the conclusions according to the level of evidence.

Level	Conclusion based on
1	Systematic review (A1) or at least 2 independent studies with evidence level A2 (*There is evidence that…)*
2	One study with evidence level A2 or at least 2 independent studies with evidence level B (*It is likely that …*)
3	One study with evidence level B or level C (*There are indications that…*)
4	Expert opinion (*The working group recommends….*)

RESULTS

Terminology and Classification

The term 'diverticular disease' used in Anglo-Saxon literature is made up of a spectrum of conditions all related to diverticulosis of the colon. Some use the term 'diverticular disease' for patients with symptoms associated with diverticulosis and distinguish diverticulitis as a different entity, whereas others include diverticulitis and diverticular bleeding in the term 'diverticular disease'. The lack of uniformity in terminology results in difficulties interpreting and comparing findings between studies. It seems best to use the term 'diverticulosis coli' and to distinguish between uncomplicated (asymptomatic) and complicated (symptomatic) diverticulosis. Patients with uncomplicated diverticulosis have no symptoms, and therefore the term asymptomatic diverticulosis is also used. Complicated diverticulosis coli, or symptomatic diverticulosis coli, is the complete spectrum of symptoms that can arise in patients with diverticulosis coli. This includes patients with (chronic) persistent abdominal pain, acute colonic diverticulitis and diverticular bleeding. ACD refers to inflammation of diverticula. Uncomplicated ACD is referred to when inflammation of one or more diverticula leads to an inflammatory process without perforation or abscess formation. Complicated diverticulitis is associated with abscess formation, perforation or fistula formation. Recurrent episodes of ACD may result in stenosis and obstruction or fistula to nearby organs (mostly bladder) or the skin; these late complications are also referred to as complicated diverticulitis.

To classify acute diverticulitis, Hinchey et al.[12] proposed a classification system, which is currently used in clinical practice in a modified version[13] (Table 3). The Hinchey classification has traditionally been used to distinguish four stages of complicated diverticulitis. Wasvary et al.[13] introduced stage 0, clinically mild diverticulitis, and differentiation in stage I between limited pericolic inflammation (stage Ia) and abscess formation smaller than 5 cm in the proximity of the primary inflammatory process (stage Ib). This broadened the original Hinchey classification by not only addressing perforated disease, but also by including mild clinical disease[13,14]. After the introduction of computed tomography (CT) for diagnosing acute diverticulitis, several radiologic classification systems were proposed additionally[15,16]. CT findings were correlated with the modified Hinchey scores to come to uniform reporting of CT findings (Table 3).

Conclusion and Recommendations

Uniform terminology is needed in patients with diverticulosis coli. A distinction is made between uncomplicated (asymptomatic) diverticulosis and complicated (symptomatic) diverticulosis. The latter term is used for the complete spectrum of symptoms that can arise in patients with diverticulosis coli (level 4).

Table 3. CT findings according to Kaiser et al 2005[15].

Modified Hinchey classification		Accompanying CT findings
Stage 0	Clinically mild diverticulitis	Diverticula with or without wall thickening of the colon
Stage Ia	Confined pericolic inflammation and phlegmonous inflammation	Colonic wall thickening with inflammatory reaction in pericolic fatty tissue
Stage Ib	Abscess formation (<5cm) in the proximity of the primary inflammatory process	Alterations as stage Ia + pericolic or mesocolic abscess formation
Stage II	Intra-abdominal abscess, pelvic or retroperitoneal abscess, abscess distant from the primary inflammatory process	Alteration as stage Ia + distant abscess formation (mostly pelvic or interloop abscesses)
Stage III	Generalised purulent peritonitis	Free air with local or generalised free fluid and possible thickening of the peritoneum
Stage IV	Fecal peritonitis	Similar findings to stage III

Epidemiology

Researching the natural history of ACD is hampered by a number of factors. There is no registry of patients regarding the natural course of the disease. Most patients with recurrent episodes of ACD have had elective surgery after two episodes of ACD, which makes it difficult to determine true recurrence rates in patients with ACD[17]. Recurrence rates of ACD, in which a recurrence is based on the clinical diagnosis without imaging, varies between 9 and 29% (level C[9,18-23]). The accuracy of the diagnosis in these studies is questionable because of the lack of a good reference test. There are two studies with adequate reference testing that give information on the natural disease history, and they report an estimated chance of recurrence of 9% (level C[24]) and 23% (level C[25]). The highest risk of recurrence seems to be in the first year (10%) and drops to approximately 3% in the years thereafter (level C[21]). The real risk of recurrence is underestimated in these studies; recurrence rates apply invariably to a selected group of patients, namely patients with symptoms severe enough for hospital admittance. The majority of recurrences tend to be mild recurrences that can be managed by conservative treatment (level C[9,18,19,21-25]). Based on recent studies, most perforations do not occur after recurrences, but after the first attack of ACD (level C[26-33]). Multiple recurrences were not associated with a higher chance of mortality, nor did they lead to a higher chance of complicated disease (level C[26-33]).

Conclusions and Recommendations

The natural history of diverticulitis is usually mild and most patients are treated successfully

by conservative means (level 3). Multiple recurrences do not lead to a higher risk of complicated diverticulitis (level 3). Patients should be informed of an approximately 25% risk of recurrence after an initial episode of ACD (level 3).

Special Patient Groups

Young Patients

The definition of young age in patients with ACD is either below 40 or 50 years. Of all patients hospitalized for ACD, 18–34% are younger than 50 years[34,35]. Some authors have reported that young patients have an increased risk of complications and recommend early resection[8,36-38]. This assumption is based on outdated studies in which 48–88% of the patients who had surgery for suspected diverticulitis appeared to have another diagnosis at surgery. Recent studies, using CT to diagnose ACD, did not find a higher risk of complications in young patients (level C[7,18-20,25,34,35,39,40]). In young patients, the reported high risk of recurrent disease is caused by a higher accumulated risk due to higher life expectancy rather than absolute risk (level C[18-20,40]). There is no evidence that younger patients should be treated differently than older patients (level C[20,25,34,35,39,40]).

Immunocompromised Patients

In patients with a compromised immune system, an increased incidence of ACD has been reported compared to healthy individuals, especially in patients with kidney failure, organ transplant patients and patients using corticosteroids (level C[41,42]). These patients were significantly more often diagnosed with complicated diverticulitis (level C[28,42-45]). Screening and prophylactic sigmoid resection is not routine for patients waiting for organ transplantation (level C[42,46]). Patients with immune deficiency caused by HIV infection, diabetes, malignancy or chemotherapy do not have an increased risk of complicated diverticulitis (level C[47,48]). Some reports indicate an increased risk of ACD in obese patients, but evidence is inconsistent (level B[49] and level C[50,51]).

Conclusions and Recommendations

Young patients do not have a more aggressive course of ACD than older patients (level 3). Young patients have a higher risk of recurrent disease, but the absolute risk difference is relatively small (level 3). Screening for diverticulosis in immunocompromised patients or patients awaiting organ transplantation in order to perform a prophylactic colonic resection is not effective (level 3).

Prevention of Diverticulitis

There are indications that people with a healthy lifestyle, characterized by physical exercise, a fiber-rich diet, limited intake of red meat, low alcohol consumption and nonsmoking, have a decreased risk of diverticulitis (level B[52] and level C[53]).

Conclusions and Recommendations

Counseling patients on risk factors for developing diverticulosis should be included in treatment protocols (level 3).

Clinical Diagnosis and Radiological Imaging

Clinical Diagnosis

The clinical diagnosis of ACD, based on reported complaints, physical examination and laboratory results, is correct in 43–68% of patients (level B[54,55] and level C[56,57]). To improve diagnostic reliability, a clinical decision rule and a clinical scoring system for diagnosing ACD using logistic regression have been published[54,55]. Reliable independent individual risk factors for ACD in both studies were pain only in the left lower abdominal quadrant, the absence of vomiting and a C-reactive protein level >50 mg/l. If all three criteria were met, 97% of the patients had ACD (level B[54,55]).

Radiological Imaging

Radiological imaging techniques that are used for the diagnosis of ACD are soluble contrast enemas, ultrasound (US), CT and magnetic resonance imaging (MRI). Soluble contrast enemas are obsolete for diagnosing ACD due to low accuracy and the inability to determine the extent and complications of the disease (level A2[58] and level B[59]). The most used US technique to examine patients with suspected ACD is the graded compression procedure. With this technique, interposing fat and bowel can be displaced or compressed by means of gradual compression to show underlying structures[60]. US is a real-time dynamic examination with wide availability and easy accessibility. The use of CT in evaluation of patients with ACD has increased to a large extent. CT has the advantage of delineating the extent of the extraluminal disease process, has an unlimited view and may also direct therapeutic intervention in case of complicated disease, e.g. US-guided percutaneous drainage of intra-abdominal abscesses. CT criteria are also used as a prognostic tool to determine the risk of complications during conservative treatment[16,61]. The most used diagnostic criteria to diagnose ACD with US and CT are increased thickness of the colonic wall, pericolic fat stranding and presence of inflamed diverticula. To optimally depict diverticulitis, the use of intravenous, oral and/or rectal contrast agents are advised[62]. Studies report high diagnostic sensitivity and specificity for both US (92 and 90%, respectively) and CT after negative or inconclusive US (94 and 99%, respectively; level A1[63,64]). More recently, in a large prospective series of unselected patients with acute abdominal pain at the emergency department, for which imaging was indicated by the treating physician, a much lower sensitivity of 61% (52–70%) was found for US, whereas the sensitivity of CT for the diagnosis of ACD was 81% (74–88%). Sensitivity can be increased up to 94% by performing US first, and CT only in case of a negative or inconclusive US. This step-up approach lowered the exposure to ionizing radiation for the study population (level A2[65,66]). Besides the known differences between

the techniques (availability, costs, reproducibility and interobserver differences), exposure to radiation during CT and contrast-induced nephropathy are a concern[60]. MRI has the advantage that no ionizing radiation and intravenous contrast medium are needed to reach a higher soft tissue contrast than CT. MRI is increasingly used in the acute setting for patients with acute abdominal pain, but accuracy data are still limited. Based on studies with small numbers of patients, sensitivity and specificity of MRI for diagnosing ACD vary between 86 and 100% and 88 and 100% (level B[67,68] and level C[69,70]).

Conclusions and Recommendations
In general, the clinical diagnosis of ACD is not sufficiently accurate and therefore radiological imaging is indicated in these patients (level 2). Patients with mild symptoms and no signs of complicated ACD, and the combination of pain in the lower left abdomen on physical examination, the absence of vomiting and a C-reactive protein >50 mg/l may be withheld from initial imaging for diagnosing ACD (level 2). If imaging is indicated, a conditional CT after negative or inconclusive US is the most appropriate approach in diagnosing ACD (level 2).

Colonoscopy
Colonoscopy is not recommended in the acute phase to diagnose ACD (level B[71] and level C[72]). Although proven feasible in one prospective study, it is rarely needed in the acute phase (level C). Possible difficulties of colonoscopy in the acute phase are incomplete examination due to pain, stenosis and incomplete bowel preparation. Discouragements to perform colonoscopy in the acute phase are based on the hypothesis that insufflation of air is associated with the risk of converting a sealed perforation to a free perforation[73-75].

Colonoscopy is usually done 6 weeks after an episode of ACD, so as to exclude a colonic malignancy. The lifetime risk of developing colonic cancer is approximately 5%. After an episode of ACD, it is unlikely that patients have an increased risk of developing colonic cancer (level B[76,77] and level C[78]). Although safe, routine performance of a colonoscopy in asymptomatic patients after an episode of ACD to exclude other diagnoses was not found to be helpful (level B[71,79,80]).

Conclusions and Recommendations
Colonoscopy in the acute phase of diverticulitis is not recommended for diagnostic purposes (level 3). There is no place for routine endoscopic examination after an episode of ACD (level 2).

Treatment of Uncomplicated Diverticulitis

Most patients with uncomplicated diverticulitis (Hinchey 0 or Ia) can be treated conservatively with success rate of 93–100% (level C[15,81-86]). Conservative treatment includes antibiotics, starvation and bed rest in almost all studies. There is no evidence that bed rest, dietary restrictions or laxatives positively influence the treatment outcome of ACD. In patients who do not tolerate oral feeding, it is recommended to start parenteral feeding when oral feeding is not to be expected within 3 days (level D[87]). Almost all international guidelines advise the use of antibiotics for the treatment of diverticulitis[17,88-91]. However, there is no evidence that routine administration of antibiotics influences the course of uncomplicated diverticulitis (level A2[92] and level B[79]). Oral administration of antibiotics seems equally effective to intravenous administration (level B[93]). Intravenous administration over 4 days is equally effective as 7 days (level B[84]). A recent prospective randomized clinical trial did not find a reduction of abscess formation, perforation and recurrence rates with the use of antibiotics[92]. The use of antibiotics seems appropriate in patients presenting with signs of generalized infection (temperature >38.5° C), affected general condition or signs of bacteremia or septicemia and in immunocompromised patients.

Analgesia is part of the treatment of patients with ACD. There is no evidence that acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) or morphinomimtics have a negative effect on the course of an episode of ACD. Multiple studies found that patients on home NSAID medication present more often with complicated diverticulitis, i.e. perforation (level C[48,94-97]). The (adverse) effect of NSAIDs started as an analgesic in patients with uncomplicated ACD has not been studied. Morphinomimetics can be safely administered to patients with acute abdominal pain without negatively affecting the diagnostic accuracy of clinical evaluation (level A2[98,99]).

Conclusions and Recommendations

There is no evidence that bed rest, dietary restrictions or laxatives influence the treatment of ACD (no evidence). There is no evidence that antibiotics should be routinely administered to patients with uncomplicated diverticulitis (level 2). Antibiotic treatment is recommended when signs of generalized infection (temperature >38.5° C) and affected general condition or signs of bacteremia or septicemia are present (level 4). Antibiotic treatment is recommended in immunocompromised patients (level 4).

Treatment of Complicated Diverticulitis

Hinchey Ib and II

There are no high-quality reports on the management of patients with ACD and abscess formation (HincheyIb and II); therefore, no consensus has been reached about the most optimal treatment strategy. Since the introduction of broad-spectrum antibiotics and improvement in US- and CT-guided percutaneous drainage techniques, alternatives to

surgery have become available. Conservative treatment with antibiotics is successful in up to 73% (95% CI: 66.3–78.9) of patients presenting with an abscess of less than 4–5 cm in diameter (level C[16,18,100-104]). When conservative treatment fails, percutaneous drainage should be performed, which is successful in up to 81% (95% CI: 73.7–89.1) of patients (level C[15,16,100-104]). The risk of failure of conservative treatment is higher in patients with abscesses larger than 4–5 cm than in patients with smaller abscesses (level C[15,16,100-104]).

Hinchey III and IV

Peritonitis is the most life-threatening complication of ACD, with a mortality of 14%[105,106]. Perforation of the colon to the intra-abdominal cavity results in a purulent or fecal peritonitis. Perforation is a relatively rare complication with an incidence of 3.5 per 100,000 individuals per year[107]. In a large population-based study from the United States, only 1.5% of patients with ACD were found to have a perforation, and 9.6% were found to have an abscess[108]. Peritonitis is a progressive disease leading to general signs of illness expressed in organ dysfunction or organ failure caused by bacteremia and septicemia. Prevention of these events by early intervention, i.e. aggressive resuscitation preventing inadequate tissue perfusion and oxygenation, the administration of broad spectrum antibiotics, and elimination of the source of infection, is the keystone of sepsis treatment[109]. Early treatment in patients with peritonitis significantly improves outcome[109-111]. No evidence-based advice can be provided for the indications for surgery in patients with perforated diverticulitis, but the indication seems self-evident.

Operative Therapy

There are different surgical options for patients with Hinchey III and IV peritonitis: diverting colostomy, Hartmann's procedure or primary resection with anastomosis, and laparoscopic lavage with drainage of the abdominal cavity. Hartmann's procedure is the most performed, which is a two-stage procedure involving resection of the diseased colon, closure of the distal rectal stump and construction of an end colostomy. In the secondstage the colostomy is reversed; however, restoration of the bowel continuity is not performed in up to 55% of patients due to operative risks[112]. Alternatively, resection with primary anastomosis, with or without a protective ileostomy or colostomy, can be performed. A diverting ileostomy or colostomy combined with intraoperative irrigation of the afferent colon can be performed to reduce the rate of symptomatic complications in case of anastomotic leakage (level B[113,114]). Studies comparing mortality, morbidity, wound complications, operation time and antibiotic treatment of Hartmann's procedure and primary anastomosis did not show any significant differences. However, most studies were prone to selection bias: patients were not randomized for Hartmann's procedure or primary anastomosis and patient groups were not comparable on patient characteristics and disease severity. It is likely that the choice of operation is influenced by patient conditions and perioperative findings. Nevertheless, there are indications that Hartmann's

procedure and primary anastomosis have comparable outcomes (level B[113,115,116]). However, in critically ill patients, hemodynamic instability is a relative contraindication for a primary anastomosis. Due to administration of inotropes to maintain sufficient blood pressure, splanchnic perfusion can be reduced, leading to increased risk of anastomotic leakage. This hypothesis has been confirmed (mainly in animal experiments) in studies on anastomotic healing in general surgery, although not after resection for diverticulitis. Fecal contamination of the abdominal cavity is not thought to be a contraindication for construction of a primary anastomosis[117]. Another treatment option in patients with purulent peritonitis is laparoscopic lavage and drainage of the abdominal cavity in which the colon is not resected. In nonrandomized series, hampered by patient selection, laparoscopic treatment accompanied by intravenous antibiotics seems to be an effective and safe treatment in Hinchey III patients (level C[57,118]). However, the results of the first randomized trial need to be reviewed for a definite conclusion[119].

Conclusions and Recommendations

Smaller abscesses (<4–5 cm) can be treated with antibiotics alone, whereas larger abscesses can best be treated with percutaneous drainage combined with antibiotic treatment (level 3). Operative treatment is considered standard therapy for patients with Hinchey III and IV diverticulitis (no evidence). In hemodynamically stable patients with acute diverticulitis and an indication for operative treatment, primary anastomosis with or without a diverting ileostomy or colostomy is preferred over Hartmann's procedure (level 2). In patients with Hinchey III diverticulitis, the safety and efficacy of treatment with laparoscopic peritoneal lavage is uncertain and will remain so until the results of the first randomized trial on the subject become available (level 3).

Elective Surgery

The American Society of Colon and Rectal Surgeons (ASCRS) state in their most recent guideline that elective sigmoid resection after recovery from ACD should be made on a case-by-case basis[90]. This advice differs significantly from the previous advice, given 6 years earlier, in which a plea for elective surgery after two episodes of diverticulitis was proposed[120]. Recent data on the natural history of diverticulitis has shown that recurrent episodes of diverticulitis mostly run a benign course and only 5.5% of the patients with recurrent hospitalizations for diverticulitis are subjected to emergency surgery[20]. Moreover, most patients who present with complicated diverticulitis do so at the time of their first attack (level C[26,121,122]). Recurrent diverticulitis even seems to reduce the risk of perforation, possibly due to adhesion formation caused by inflammation. Therefore, a policy of elective sigmoid resection after recovery from uncomplicated ACD does not decrease the likelihood of later emergency surgery, and the number of previous episodes itself is no longer an indication for elective sigmoid resection (level C[18,26,33,121-123]). Persistent colonic symptoms, particularly abdominal pain, have been reported in patients

after episodes of diverticulitis. It has been suggested that this pain represents increased visceral sensitivity[124]. These patients might benefit from early colonic resection.

After elective sigmoid resection, there is a risk of anastomotic leakage, stoma formation, morbidity and mortality. Despite resection, even recurrent diverticulitis and continuing complaints have been described. Patients with immune deficiencies might benefit from early resection since they have a greater risk of perforations and a complicated course of recurrent episodes of diverticulitis (level C[18,33,121,122]).

Elective sigmoid resection for complicated diverticulosis can be performed either with an open or laparoscopic approach. Two randomized trials favored laparoscopic surgery over open surgery. In the 'Sigma trial', significantly more complications, higher pain scores and longer hospital stay were found among patients with open surgery. Operating time was significantly longer in the laparoscopic group, with a conversion rate of 19%. Quality of life was significantly better after 6 weeks, but did not differ after 6 months (level A2[125]). The study by Gervaz et al.[126] also had equal long-term results, except for the cosmetic outcome, which was better in the laparoscopic group. No difference was found considering ventral hernia, patient satisfaction, quality of life or total costs (level A2). Laparoscopic surgery provides a faster functional recovery than open sigmoid resection and possibly less chance of complications, but the long-term advantages of laparoscopic sigmoid resection are not yet evident (level A2[125,126] and level B[127-131]). Both the Sigma trial and the Gervaz study did not use the Enhanced Recovery after Surgery (ERAS) principles, which are now widely adopted in the perioperative care of patients with abdominal surgery. The ERAS program reduced the risk of complications and hospital stay of open surgery to a large extent[130]. In addition, laparoscopic surgery is often done by dedicated surgeons, while open surgery is usually performed by a much larger group of surgeons, possibly influencing the results.

To reduce the risk of recurrent diverticulitis, the sigmoid should be resected up to the proximal rectum (level C[131,132]). There is no evidence for the optimal proximal resection margin; however, a resection as limited as possible in soft compliant bowel is recommended[90].

Conclusions and Recommendations

Patient-related factors, not so much the number of previous episodes of diverticulitis, should play the most important role in selecting patients who might benefit from elective sigmoid resection (level 3). If appropriate laparoscopic expertise is present, laparoscopic surgery for recurrent episodes of diverticulitis might be favored over open sigmoid resection in terms of short-term outcome, but no long-term benefits have been reported (level 1). During elective sigmoid resection, the part of the colon resected proximally to

the inflammatory process should be as limited as possible with the proximal rectum as the distal margin (level 3).

Medical Treatment of Recurrent Diverticulitis

Traditionally, fiber-enriched diets in patients with diverticulitis have been considered to prevent recurrent episodes of ACD. However, randomized clinical trials on fiber-enriched diets in patients with ACD have had inconsistent results[133]. A recently published systematic review of high-fiber dietary therapy could not include any studies concerning prevention of diverticulitis with a high-fiber diet[134]. Despite the lack of evidence, high daily fiber intake is recommended as treatment in various guidelines[17,88,90,91]. Since obesity and smoking are associated with an increased risk of complications of diverticulitis, weight reduction and cessation of smoking can have a favorable influence on prevention of recurrent diverticulitis (level B[51,135]). Although evidence on lifestyle advice to prevent recurrent episodes of ACD is missing, it is likely that the same measures to prevent ACD also apply to patients after an episode of ACD. Hence, a healthy lifestyle, characterized by physical exercise, a fiber-rich diet, little intake of red meat, low alcohol consumption and nonsmoking are advised in patients after an episode of ACD (level B[52] and level C[53]).

Recently, new theories about similarities between ACD and inflammatory bowel disease have been proposed, leading to new treatment possibilities, such as probiotics, antibiotics and anti-inflammatory agents[136]. Regarding drug treatment, intermittent administration of a nonabsorbable antibiotic (rifaximin) after an episode of acute diverticulitis decreased the chance of readmission by 50% and of recurrent diverticulitis by 73% (level B[137]). Prevention of recurrent disease is more effective when 5-aminosalicylic acid (mesalazine) is combined with rifaximin, compared to rifaximin alone (level A2[138] and level B[139]). Furthermore, a combination of probiotics and anti-inflammatory medication is preferred over treatment with probiotics alone (level A2[140]).

Residual complaints after an episode of diverticulitis occur often and medical treatment can reduce symptoms. In these patients a trial period of intermittent administration of a nonabsorbable antibiotic with mesalazine or probiotics should be considered. This is especially so since there is little risk from treatment by nonresorbable antibiotics or mesalazine combined with probiotics, while mortality and morbidity of operative treatment are substantial.

Conclusions and Recommendations

The working group advises to give lifestyle advice to patients following an attack of diverticulitis, focusing on increasing daily fiber intake, weight reduction, cessation of smoking and increasing physical activity (level 4). Nonabsorbable antibiotics seem to reduce the risk of recurrent episodes of diverticulitis (level 3). The combination of

5-aminosalicylic acid and rifaximin is more effective than rifaximin alone in the prevention of recurrent episodes of diverticulitis (level 2). The working group opinion is that in patients with recurrent diverticulitis or patients with residual complaints following an episode of diverticulitis, in which other pathologies have been excluded, a trial period of intermittent mesalazine, with or without a combination of an oral nonresorbable antibiotic or probiotic, should be considered (level 4).

CONCLUSION

This review of guidelines for diverticulitis summarizes the extensive literature available on epidemiology, prevention, diagnosing and treatment of patients with acute diverticulitis in all its aspects. The guideline was developed in order to standardize the treatment of patients with acute diverticulitis and to provide clinicians who deal with patients with diverticulitis on a daily basis, with an evidence-based medical approach in treating and counseling patients. Despite a large amount of literature, not all topics were equally well addressed. Nevertheless, this review is the best evidence-based approach currently available. The results of well-designed randomized studies will become available in the near future and give more insight into the optimal treatment of patients with acute diverticulitis of the colon.

APPENDIX 1

Search Strategies for the Relevant Key Words
Last search update: February 2012

Subject: natural course of ACD
Date censoring: none

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Natural history" [MeSH] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Natural history" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "uncomplicated"

Subject: natural course in young and immunocompromised patients
Date censoring: from 1960
Restrictions: none

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Young" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Recurrence" [MeSH] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "diabetes mellitus" [MeSH] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "transplantation" [MeSH] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "immunosuppression" [MeSH] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "AIDS or HIV" [MeSH] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "neoplasms" [MeSH]

Subject: colonoscopy
Date censoring: from 1970
Restrictions: none

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "colonoscopy" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] ("Diverticulitis" OR "Diverticular disease") AND ("Colon carcinoma" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields]) AND "colon cancer" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic"[MeSH] OR "diverticulitis" [All Fields] AND "IBD"

Subject: clinical diagnosis
Date censoring: from 1980
Restrictions: none

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "clinical parameters" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "sensitivity" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic"[MeSH] AND "diagnosis"

Subject: radiological imaging
Date censoring: from 1980
Restrictions: none

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "contrast enema" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Ultrasonography" [MeSH] OR "ultrasonography" [subheading] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Tomography, Spiral Computed" [MeSH] OR "Tomography, XRay Computed" [MeSH] OR "Tomography Scanners, X-Ray Computed" [MeSH] OR "Computed Tomographic" [MeSH] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Magnetic Resonance Imaging" [MeSH] OR "Colonography"

Subject: uncomplicated diverticulitis
Date censoring: from 1975
Restrictions: none

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "uncomplicated diverticulitis" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Anti-Bacterial Agents" [MeSH] OR "Anti-Bacterial Agents" [Pharmacological Action] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("intestines" [MeSH Terms] OR "intestines" [All Fields] OR "bowel" [All Fields]) AND ("rest" [MeSH Terms] OR "rest" [All Fields])) OR (("diverticulitis" [MeSH] OR "diverticulitis" [All Fields]) AND ("bed rest" [MeSH] OR ("bed" [All Fields] AND "rest" [All Fields]) OR "bed rest" [All Fields] OR "bedrest" [All Fields])) OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND (("diverticulitis" [MeSH] OR "diverticulitis" [All Fields]) AND ("overweight" [MeSH] OR "overweight" [All Fields])) OR (("diverticulitis" [MeSH] OR "diverticulitis" [All Fields]) AND "BMI" [All Fields])

OR (("diverticulitis" [MeSH] OR "diverticulitis" [All Fields]) AND "adipositas" [All Fields]) OR (("diverticulum" [MeSH] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND "adipositas" [All Fields]) OR (("diverticulum" [MeSH] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND "BMI" [All Fields]) OR (("diverticulum" [MeSH] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND ("overweight" [MeSH] OR "overweight" [All Fields]))

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND [Diet Therapy] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Vegetables" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Fruit" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Starvation" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Laxatives"

Subject: complicated diverticulitis
Date censoring: from 1990
Restrictions: Adults 19+, series >50 patients

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Abscess" [MeSH:NoExp] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Hinchey III" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Hinchey IV" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Diverticulitis, Colonic/mortality" [MeSH] OR "Diverticulitis, Colonic" [MeSH] AND "Intestinal Perforation" [MeSH] OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "laparoscopy" ("diverticulitis"/exp OR "diverticulitis":ab,ti OR "diverticular disease":ab,ti) AND ("laparoscopy"/exp OR "laparoscopic surgery"/ exp OR "laparoscope"/exp OR "minimally invasive surgery"/ exp OR laparoscop * :ab,ti OR laparascop * :ab,ti OR (minimal * :ab,ti AND adj:ab,ti AND invasive:ab,ti)) AND ("acute disease"/exp OR "emergency"/exp OR acute:ab,ti OR emergenc * :ab,ti OR "colon perforation"/exp OR (perforat * :ab,ti AND [1970–2011]/py)) "Diverticulitis, Colonic" [MeSH] AND "Recurrence" [MeSH] AND "Therapeutics" [MeSH] database

Subject: prevention of recurrence and antibiotics
Date censoring: from 1966
Restrictions: none

("Diverticulitis" AND "Recurrence" AND "Therapy") OR ("Diverticulum, Colon" [MeSH]) AND (("Diet Therapy" [MeSH]) OR ("Dietary Fiber" [MeSH])) (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("overweight" [MeSH Terms] OR "overweight" [All Fields])) OR (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND "BMI" [All Fields]) OR (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND "adipositas" [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND "adipositas" [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND "BMI" [All Fields]) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND ("overweight" [MeSH Terms] OR "overweight" [All Fields])) (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("smoking" [MeSH Terms] OR "smoking" [All Fields])) ("diverticular disease" [MeSH Terms] OR "diverticular disease" [All Fields]) AND ("smoking" [MeSH Terms] OR "smoking" [All Fields]) (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("exercise" [MeSH Terms] OR "exercise" [All Fields] OR ("physical" [All Fields] AND "exercise" [All Fields]) OR "physical exercise" [All Fields])) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND ("exercise" [MeSH Terms] OR "exercise" [All Fields] OR ("physical" [All Fields] AND "exercise" [All Fields]) OR "physical exercise" [All Fields])) OR (("diverticulitis" [MeSH Terms] OR "diverticulitis" [All Fields]) AND ("physical therapy modalities" [MeSH Terms] OR ("physical" [All Fields] AND "therapy" [All Fields] AND "modalities" [All Fields]) OR "physical therapy modalities" [All Fields] OR "physiotherapy" [All Fields])) OR (("diverticulum" [MeSH Terms] OR "diverticulum" [All Fields] OR ("diverticular" [All Fields] AND "disease" [All Fields]) OR "diverticular disease" [All Fields]) AND ("physical therapy modalities" [MeSH Terms] OR ("physical" [All Fields] AND "therapy" [All Fields] AND "modalities" [All Fields]) OR "physical therapy modalities" [All Fields] OR "physiotherapy" [All Fields]))

Subject: Elective surgery
Date censoring: 1970
Restrictions: none

"Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Elective sigmoid resection" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "Elective colectomy" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] OR "Surgery" AND "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "laparoscopic colectomy" OR "Diverticulitis" [MeSH] OR "Diverticulitis, Colonic" [MeSH] OR "diverticulitis" [All Fields] AND "laparosc * ".

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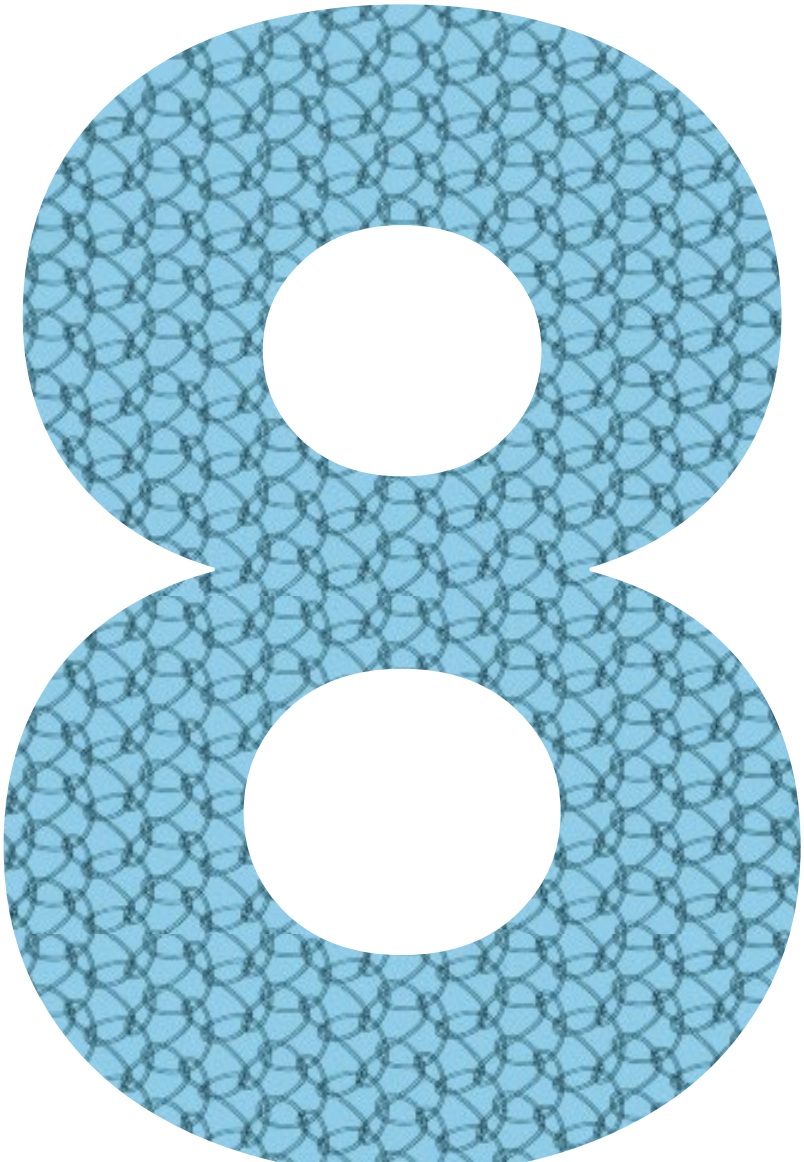
PART TWO

Treatment of complications following intra-abdominal infection

CHAPTER



Experimental study on synthetic and biologic mesh implantation in a contaminated environment

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ABSTRACT

Background

Implantation of meshes in a contaminated environment can be complicated by mesh infection and adhesion formation.

Methods

The caecal ligation and puncture model was used to induce peritonitis in 144 rats. Seven commercially available meshes were implanted intraperitoneally: six non-absorbable meshes, of which three had an absorbable coating, and one biological mesh. Mesh infection, intra-abdominal abscess formation, adhesion formation, incorporation and shrinkage were evaluated after 28 and 90 days. Histological examination with haematoxylin and eosin and picrosirius red staining was performed.

Results

No mesh infections occurred in Sepramesh, Omyramesh and Strattice . One mesh infection occurred in Parietene and Parietene Composite. Significantly more mesh infections were found in C-Qur (15 of 16; P≤0.006) and Dualmesh (7 of 15; P≤0.035). Sepramesh showed a significant increase in adhesion coverage from 12.5% at 28 days to 60.0% at 90 days (P=0.010). At 90 days there was no significant difference between median adhesion coverage of Parietene Composite (35.0%), Omyramesh (42.5%), Sepramesh (60.0%) and Parietene (72.5%). After 90 days the adhesion coverage of Strattice was 5.0%, and incorporation (13.4%) was significantly poorer than for other non-infected meshes (P≤0.009). Dualmesh showed shrinkage of 63% after 90 days.

Conclusion

Parietene Composite and Omyramesh performed well in a contaminated environment. Strattice had little adhesion formation and no mesh infection, but poor incorporation. Some synthetic meshes can be as resistant to infection as biological meshes.

SURGICAL RELEVANCE

Surgeons are reluctant to use synthetic materials in contaminated environments owing to the risk of mesh infection. Mesh infection often necessitates removal of the mesh, leaving an abdominal wall deficit larger than the original hernia. Recently developed biological meshes are suggested to allow implantation in a contaminated environment.

This experiment shows promising results regarding infection rate, incorporation and adhesion formation of certain synthetic meshes in a contaminated environment. Biological meshes showed no mesh infection and little adhesion formation. However, incorporation of biological meshes was poor, making the biomechanical strength of the repair questionable. In contaminated abdominal wall surgery one-stage repair might be performed with implantation of certain types of synthetic mesh.

INTRODUCTION

Mesh reinforcement during ventral hernia repair drastically reduces 10-year recurrence rates[1,2]. Non-absorbable synthetic materials are currently the most commonly used prosthesis for reinforcement of ventral hernias. Advantages of synthetic meshes are low recurrence rates, ease of use and relatively low costs. However, implantation of synthetic meshes can be complicated by mesh infection and adhesion formation. Mesh infection is a feared complication and reported in up to 16% of patients after abdominal wall repair[3]. The risk of mesh infection is increased in a contaminated environment, which makes the use of synthetic mesh debatable[4]. Mesh infection after implantation often necessitates its removal, which leaves the patient with a contaminated field and an abdominal wall deficit that is often larger than the original hernia. Macroporous meshes have been preferred because large pores permit infiltration of macrophages and allow rapid fibroplasia and angiogenesis, with reduced infiltration and growth of bacteria[5,6]. The drawback of macroporous meshes is the increased risk of visceral adhesions to the site of the repair, with associated small bowel obstruction, pain, infertility and enterocutaneous fistula formation[5,7,8]. These adhesions arise as a result of fibrin deposition in the abdominal cavity, with subsequent formation of adhesions. The presence of contamination increases fibrin deposition, leading to an increased amount and tenacity of adhesions intra-abdominally and to the mesh[9]. In a clean environment antiadhesive coatings have proved to reduce adhesion formation to macroporous meshes[8,10,11]. The aim of the study was to compare commercially available synthetic and biological meshes in terms of infection rate, adhesion formation, incorporation and shrinkage after implantation in a contaminated environment.

METHODS

One hundred and forty-four male Wistar rats weighing 250–350 g were obtained from a licensed breeder (Harlan Laboratories, Boxmeer, The Netherlands). They were bred under specific pathogen-free conditions, kept under standard laboratory conditions in individually ventilated cages, and fed freely with standard rat chow and water throughout the experiment. The protocol of the experiment was approved by the Ethical Committee on Animal Experimentation of Erasmus University Rotterdam.

Peritonitis model

Rats were anaesthetized by isoflurane/oxygen inhalation and received buprenorphine analgesia (0.05 mg/kg subcutaneously). The abdomen was shaved and the skin disinfected with 70% alcohol, after which the abdominal cavity was opened through a 3-cm midline incision. To induce peritonitis, a caecal ligation and puncture (CLP) model was used[12]. The caecum was carefully manipulated outside the abdominal cavity and ligated just distal to the ileocaecal valve with a monofilament nonabsorbable suture (4-0 Ethilon; Ethicon, Johnson & Johnson, Somerville, New Jersey, USA), maintaining the continuity of the bowel. The caecum was punctured distally to the ligation with an 18-G needle. The fascia and skin were closed with a running absorbable suture (5-0 Safil; B. Braun, Melsungen, Germany). After 24 h the abdomen was reopened, a culture swab was taken to confirm peritonitis, the necrotic caecum was resected and the abdominal cavity was rinsed with at least 20 ml phosphate-buffered saline at 37°C. A sterile mesh, measuring 2.5 × 3 cm, was implanted intraperitoneally with three transmuscular nonabsorbable sutures (5-0 Ethilon) on both sides of the incision in all mesh groups. No mesh was implanted in the control group. After administration of gentamicin (6 mg/kg intramuscularly) the abdominal wall and skin were closed separately with a running absorbable suture (5-0 Safil).

Implanted meshes

The rats were divided into eight groups, a control group that received no mesh and groups in which one of the following seven meshes was implanted intraperitoneally: non-cross-linked collagen (Strattice; LifeCell, Branchburg, New Jersey, USA), polypropylene (Parietene; Sofradim, Trevoux, France; part of Covidien, North Haven, Connecticut, USA), collagen–polyethyleneglycol–glycerol-coated polypropylene (Parietene Composite; Sofradim), omega-3-fatty acid coated polypropylene (C-Qur; Atrium, Hudson, New York,USA), carboxymethylcellulose–sodium hyaluronate coated polypropylene (Sepramesh; Bard, New Providence, New Jersey, USA), expanded polytetrafluoroethylene (PTFE) (Dualmesh; Gore, Flagstaff, Arizona, USA) and condensed PTFE (Omyramesh; B. Braun).

Measurements

Half of the surviving animals were killed after 28 days and half after 90 days. The abdomen was shaved, disinfected and opened through a U-shaped incision extending laterally and caudally to the mesh. Directly after opening the abdomen, a swab of the abdominal cavity was taken for culture. Mesh infection was defined as the presence of abscesses of the mesh, and parts of the mesh were cultured for microbiological evaluation. Adhesions were scored using a grid placed over the mesh, dividing it into 30 equal squares. The tenacity of the adhesions was graded using the Zühlke score, a four-degree classification of adhesions based on histological and morphological criteria[13]. Pictures of the abdominal wall with mesh and any adhesions were taken with a 5.0-megapixel digital camera. The abdominal cavity was inspected for abscesses; when present, these were scored and cultured at four sites: the liver, abdominal wall, bowel and omentum[14]. Mesh incorporation was defined as the percentage of the mesh edge incorporated into the abdominal wall, taking into account any shrinkage. Shrinkage was defined as the relative loss of surface compared with the original size of the mesh, measured with a caliper. The animals were killed by cardiac cut. All measurements were carried out by two independent observers and disagreements reconciled by discussion.

Histological evaluation

At least two representative samples of macroscopically non infected meshes with adjacent abdominal wall were excised by full-thickness (mesh and abdominal wall muscle) biopsy punches of 5 mm diameter. The samples were embedded in Tissue-Tek (Sakura, Alphen, Rijn, The Netherlands) and immediately frozen in liquid nitrogen. Frozen sections of 6 µm were made using a cryostat (Leica; Davis Instruments, Vernon Hills, Illinois, USA). Sections were stained with either haematoxylin and eosin or picrosirius red (Direct Red 80; Fluka Chemie, Zwijndrecht, The Netherlands)[15]. Samples were assigned a random number before evaluation and scored by two observers blinded to the specific type of mesh. Fibrosis, lymphocyte infiltration and angiogenesis were scored macroscopically at 200× magnification using a light microscope (Olympus, Center Valley, Pennsylvania, USA). The following grading scale was used: 0, none present; 1, little; 2, moderate; and 3, extensive. The picrosirius red-stained sections were analysed for collagen and scored by means of the same scale for the presence of collagen around the mesh and abdominal wall.

Statistical analysis

Results are presented as median (interquartile range). Mesh infection, tenacity and percentage of adhesions, histological score, abscess formation, survival and weight were compared using Kruskal–Wallis, Mann–Whitney *U*, $\chi 2$ and Fisher's exact tests as the data did not show a normal distribution. If the overall test showed differences, pairwise tests were done to determine the groups causing the overall significance. Exact methods for significance were used when computational limits allowed these. All reported P values are

two-sided and P<0.050 was considered statistically significant. In view of the numbers, it was not possible to adjust the P values using Bonferroni's correction. Statistical analysis was performed using PSAW statistical software package version 17 (IBM, Armonk, New York, USA).

RESULTS

During the first 2 days of the experiment 22 (15.3%) of the 144 rats died. Necropsy was performed and septicaemia was found to be the cause of death in all rats (Table 1). On day 13 one rat in the C-Qur group died from intestinal obstruction due to severe adherence of the bowel to the infected mesh. Abdominal cultures on day 1 confirmed bacterial contamination in all animals with Gram-positive (*Enterococcus, Staphylococcus, Streptococcus*) and Gram-negative (*Escherichia coli* and *Proteus*) microorganisms. All animals exhibited symptoms of sepsis including apathetic behaviour, ocular exudates, piloerection, diarrhoea and weight loss. The maximum percentage weight loss varied between 11.1 and 14.2%, and was more pronounced in the C-Qur group (P≤0.048 compared with other groups).

Table 1. Postoperative mortality and number of animals at 28 and 90 days after surgery.

Group	Mesh material	No. of animals	Postoperative death	No. analysed	
				28 days	90 days
Control	No mesh	18	2	8	8
Strattice	Non-cross-linked collagen	18	4	7	7
Parietene	Polypropylene	18	2	8	8
Parietene Composite	Collagen-polyethyleneglycol-glycerol-coated polypropylene	18	4	7	7
Sepramesh	Carboxymethylcellulose-dodium hyaluronate-coated polypropylene	18	2	8	8
C-Qur	Omega-3-fatty acid-coated polypropylene	18	2	8*	8
Dualmesh	Expanded polytetrafluoroethylene	18	3	7	8
Omyramesh	Condensed polytetrafluoroethylene	18	3	7	8
Total		144	22	60	62

*One rat in the C-Qur group died after 13 days. The results of this rat were analysed together with the rats killed after 28 days in the C-Qur group.

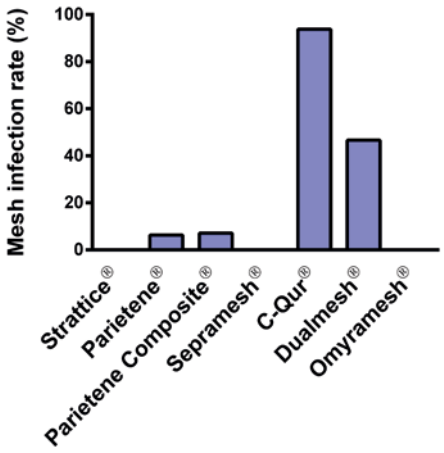

Figure 1. Comparison of mesh infection rates (combined 28 and 90 days). Values are percentage of macroscopically infected meshes among surviving animals.

Mesh infection

At the time of death macroscopic infection of the mesh was present in 24 (22.6%) of 106 animals. The infection rate among C-Qur meshes was high (15 of 16 rats) compared with all other meshes (P≤0.006) (Figure 1). Dualmesh also showed a high infection rate (7 of 15 rats), significantly higher than all other groups apart from C-Qur (P≤0.035). All infected meshes became large fibrotic pseudotumours. No additional mesh infection was discovered by microbiological culture of the meshes.

Abscesses

Intra-abdominal abscesses were found in 37 rats (62%) after 28 days and 27 (44%) after 90 days (P=0.049).The majority of abscesses were located at the caecum or abdominal wall. There was no significant difference between groups in intra-abdominal abscesses (P=0.482).

Adhesions

After 28 and 90 days the surfaces of all infected meshes were completely covered with adhesions. Owing to the high infection rate in C-Qur and Dualmesh the median adhesion coverage was 90–100% (Figure 2). After 28 days significantly less adhesion to the mesh surface was found for Strattice (median 10.0% (5.0–10.0)) and Sepramesh (12.5% (6.3–22.5)) compared with all other meshes (P≤0.004 and P≤0.017 respectively). Median adhesion coverage was 45.0% for Parietene Composite, 52.5% for Parietene and 55.0% for Omyramesh. Sepramesh showed an increase in adhesion formation from a median of 12.5% at 28 days to 60.0% at 90 days (P=0.010). After 90 days Strattice (5.0 %(5.0–10.0))

had significantly less adhesion coverage than the other meshes (P≤0.003). At 90 days there was no significant difference between median adhesion coverage of Parietene Composite (35.0%), Omyramesh (42.5%), Sepramesh (60.0%) and Parietene (72.5%).

Incorporation

After 28 and 90 days C-Qur showed no or very little incorporation into the abdominal wall owing to the high rate of mesh infection (Figure 3). Strattice showed a poor incorporation of 22.7% at 28 days, which was lower than for Omyramesh (47.1%; P=0.004), Parietene Composite (42.5%; P=0.004) and Sepramesh (35.6%; P=0.004). The incorporation of Strattice was not improved after 90 days (median 13.4%). This was significantly worse than the incorporation of Parietene Composite (54.5%; P=0.003), Omyramesh (50.4%; P<0.001), Parietene (48.4%; P=0.009) and Sepramesh (40.9%; P=0.002). At 90 days, Dualmesh (29.4%) was incorporated more poorly than Parietene (P=0.020), Parietene Composite (P=0.009) and Omyramesh (P=0.002).

Shrinkage

The shrinkage of C-Qur could not be determined owing to the formation of large fibrotic pseudotumours in all but one of the meshes. The non-infected Dualmesh showed the

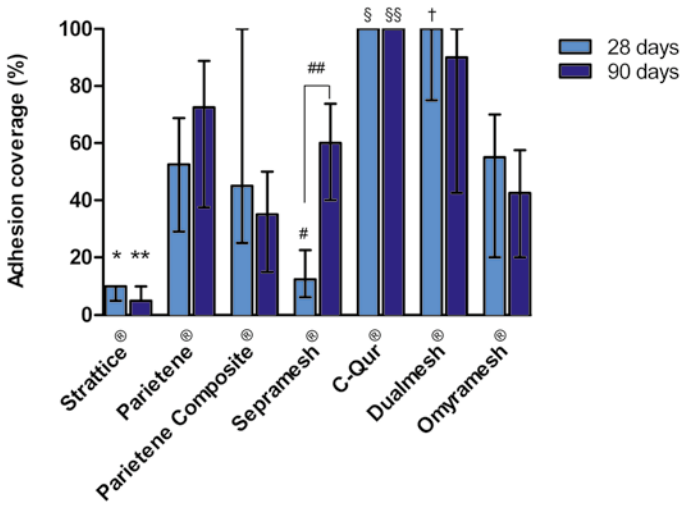

Figure 2. Comparison of percentage of mesh adhesions at 28 and 90 days follow-up. Values are median (interquartile range). *28 days Strattice vs Parietene P<0.001, vs Parietene Composite P=0.004, vs C-Qur P<0.001, vs Dualmesh P=0.001, vs Omyramesh P=0.003. **90 days Strattice vs all other meshes P≤0.003. #28 days Sepramesh vs Parietene P=0.001, vs Parietene Composite P=0.009, vs C-Qur P<0.001, vs Dualmesh P<0.001, vs Omyramesh P=0.017. ##Sepramesh 28 vs 90 days P=0.010. §28 days C-Qur vs Parietene P=0.006, vs Omyramesh P=0.005. §§90 days C-Qur vs Parietene P<0.001, vs Parietene Composite P=0.001, vs Sepramesh P<0.001, vs Omyramesh P=0.001. † 28 days Dualmesh vs Parietene P=0.004, vs Omyramesh P=0.008 (Mann-Whitney U test).

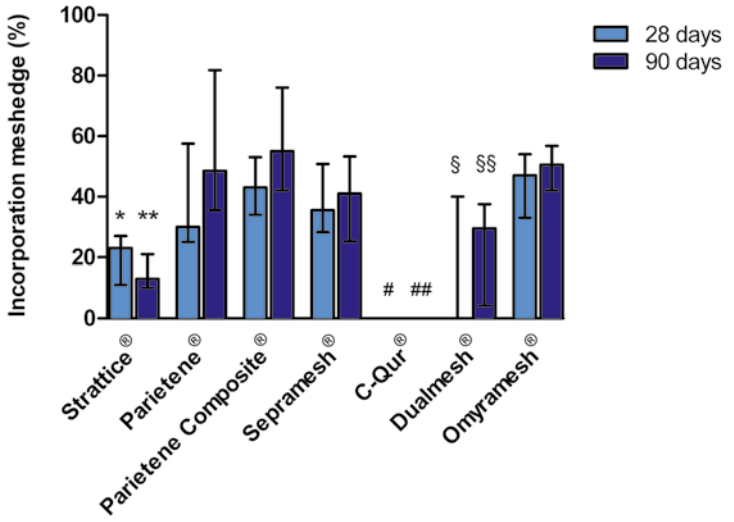

Figure 3. Comparison of percentage of mesh edge incorporation at 28 and 90 days follow-up. Values are median (interquartile range). *28 days Strattice vs Parietene Composite P=0.004, vs Sepramesh P=0.004, vs C-Qur P=0.010, vs Omyramesh P=0.004. **90 days Strattice vs Parietene P=0.009, vs Parietene Composite P=0.003, vs Sepramesh P=0.002, vs C-Qur P<0.001, vs Omyramesh P<0.001. #28 days C-Qur vs Parietene P=0.002, vs Parietene Composite P=0.001, vs Sepramesh P=0.002, vs Omyramesh P=0.001. ## 90 days C-Qur vs all other meshes P≤0.007. §28 days Dualmesh vs Parietene Composite P=0.023, vs Omyramesh P=0.023. §§90 days Dualmesh vs Parietene P=0.020, vs Parietene Composite P=0.009, vs C-Qur P=0.007, vs Omyramesh P=0.002. (Mann-Whitney U test).

highest percentage loss of mesh surface, of 63% after 90 days (P≤0.012 compared with other meshes). All other meshes had a median loss of mesh surface of between 0 and 10% after 28 days. Strattice showed a progressive median loss of surface from 0% at 28 days to 23% at 90 days (P=0.003). After 90 days the purely synthetic Dualmesh, Omyramesh and Parietene showed shrinkage of between 0 and 15%. Parietene Composite and Sepramesh did not shrink after 90 days (P≤0.026 and P≤0.014 respectively compared with all other meshes).

Histology

Fibrosis was observed in all mesh-surrounding tissues. This was especially pronounced for the four polypropylene based meshes and Omyramesh (Figure S1, supporting information). Dualmesh showed a clear encapsulation of the mesh, almost without cellular infiltration into it. A large number of vessels could be seen in the tissue surrounding Parietene Composite and Omyramesh. Because of wide intra-animal variation, no statistically difference was found for fibrosis, influx of lymphocytes, angiogenesis and collagen deposition (data not shown).

DISCUSSION

In this experimental contaminated environment, the collagen-coated polypropylene mesh Parietene Composite and the condensed PTFE Omyramesh had a low risk of infection, moderate adhesion formation and good incorporation. The biological Strattice mesh did not become infected and showed remarkably little adhesion formation, but poor incorporation. If a mesh is used in a contaminated environment, consensus exists that a biological collagen mesh or a synthetic macroporous, monofilament mesh may be advantageous[5,16-18]. Biological collagen meshes have been developed specifically for a contaminated environment and Strattice did not show any mesh infection in this experiment. Biological meshes, particularly Strattice, have shown improved clearance of bacteria, which decreases the possibility of infection and formation of adhesions[19]. A prospective multicentre study of contaminated ventral hernia repair with Strattice reported a similar low infection rate with little need to remove the mesh[20]. The macroporous Parietene, Parietene Composite, Sepramesh and Omyramesh had a low risk of infection. Large pores allow admission of macrophages, fibroplasia and angiogenesis, which improves the ability to clear infection[5,6]. In this study, however, the macroporous C-Qur mesh showed a high infection rate. This polypropylene mesh is coated with anti-inflammatory omega-3 fatty acids. In an experimental clean environment macrophages were scarcely present in the mesh after implantation[11,21]. It might be hypothesized that the anti-inflammatory properties of the omega-3 fatty acid coating have prevented macrophage penetration, although no clinical or experimental literature on the characteristics of omega-3 fatty acids in the presence of bacteria has yet been published. Dualmesh showed a high infection rate, probably because of its partially microporous structure (smaller than 10 µm). The increased risk of infection after surgery with Dualmesh, and the need to remove the prosthesis in case of infection, is notorious in the clinical situation[22-24]. Mesh infection is caused by infiltration and proliferation of bacteria within the pores and interstices of synthetic materials. Small pores prevent infiltration of immune cells and make microporous meshes more susceptible to infection[5,25].Additionally, the hydrophobic visceral surface of Dualmesh decreases adhesion of tissue cells, allowing bacteria a free passage to the implant surface[16]. Intra-abdominal adhesion and abscess formation are important causes of morbidity and mortality following contaminated abdominal surgery. During peritonitis fibrin is deposited in the abdominal cavity, inducing adhesion formation and providing possible niduses for abscess formation[9]. Biological Strattice mesh showed low adhesion formation after 90 days, confirming previous experimental results[26-28]. Sepramesh showed a significant increase in adhesion formation between 28 and 90 days, implying that the cellulose–hyaluronate coating is absorbed before a neoperitoneal layer is formed. These results confirm that adhesion formation in the presence of mesh is not complete after 7 days[8,11]. The surface of Parietene Composite and Omyramesh were least covered with adhesions after 90 days. Low adhesion formation on the collagen-coated

Parietene Composite has been described in a clean environment[8,11]. The present results suggest that the collagen coating remains present until a neoperitoneum has formed, even in a contaminated environment. The low adhesion formation on Omyramesh confirms experimental findings with this relatively new mesh in a clean environment[29,30]. The low adhesion formation might be explained by its smooth, monolayer, non-fibrous, macroporous structure. The plain polypropylene Parietene mesh was largely covered with adhesions. Clinically, uncoated polypropylene meshes are known to induce severe adhesion formation with attachment of intestine to the mesh when implanted intraperitoneally[7,31]. In 21% of patients with an intraperitoneal uncoated polypropylene mesh, adhesions made bowel resection necessary during re-exploration in one study[7]. The non-infected, partially microporous, expanded PTFE Dualmesh had an alarmingly high shrinkage rate (median 63% after 90 days). Such shrinkage has frequently been reported experimentally, but this does not seem to be correlated with a higher recurrence rate clinically[8,23,32]. A fibrous capsule surrounding the mesh was observed, almost without cellular infiltration into the mesh. Contraction of this capsule was probably the cause of shrinkage, which might have been more pronounced in the small meshes used in the present experiment compared with the much larger meshes used clinically. Of the macroporous meshes, the plain polypropylene Parietene showed the most shrinkage (15% after 90 days), confirming experimental results[32,33]. The biological Strattice mesh had a 23% loss of surface after 90 days, probably caused by collagenase activity. Premature weakening of the biomechanical properties of the scaffold combined with insufficient incorporation can possibly result in loss of the prosthesis and hernia recurrence[34]. Until evidence of biomechanical strength after hernia repair with biological meshes has been provided, synthetic meshes are preferred for primary repair.

Translation of experimental results to the clinical situation should be done with caution. However, the CLP model is suitable for studying the behaviour of synthetic and biological meshes experimentally in a contaminated environment. In this model, as in clinical infections, peritonitis arises from a complex interaction of the immune system with inflammatory, haemodynamic and biochemical alterations similar to human sepsis, with a consistent increase in cytokine levels[35-38]. Another advantage of this experimental model is the use of rats of the same age and sex, and specified pathogen-free bacterial status. This minimizes biological and microbiological variability, and makes it suitable for comparing characteristics of different meshes in a similar contaminated environment[38]. A limitation of the model is the size of the mesh and mesh pores in relation to the abdominal wall, which is different between rats and humans. This might lead to an overestimation of shrinkage. The meshes in this experiment were fixated with six sutures. In humans the number of fixation points in relation to the mesh size would be much higher. This might have influenced incorporation, as described in previous experimental mesh studies[8,11]. Finally, the concentration of the antiadhesive coatings and its systemic effects during breakdown

in this model might be different from the human situation. The experimental results of synthetic mesh implantation in a contaminated environment make strict contraindication in humans questionable. Although there are no meshes without disadvantages, certain permanent synthetic meshes might be somewhat infection-resistant and therefore useful for permanent hernia repair in a contaminated environment.

SUPPLEMENT

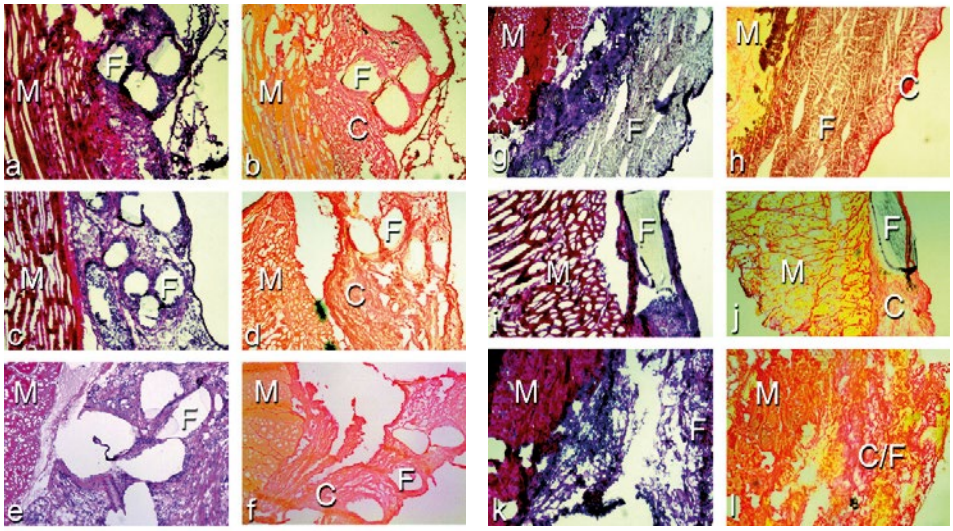

Figure S1 Histological samples after 90 days. **a,c,e,g,i** haematoxylin and eosin staining and **b,d,f,h,j** picrosirius red staining of histological samples after 90 days (original magnification ×40). **a,b** Polypropylene (Parietene; Sofradim, Trevoux, France; part of Covidien, North Haven, Connecticut, USA); **c,d** collagen–polyethyleneglycol–glycerol-coated polypropylene (Parietene Composite; Sofradim); **e,f** carboxymethylcellulose–sodium hyaluronate-coated polypropylene (Sepramesh; Bard, New Providence, New Jersey, USA); **g,h** expanded polytetrafluoroethylene (Dualmesh; Gore, Flagstaff, Arizona, USA); **i,j** condensed polytetrafluoroethylene (Omyramesh; B. Braun, Melsungen, Germany); and **k,l** non-cross-linked collagen mesh (Strattice; LifeCell, Branchburg, New Jersey, USA). The purple and pink cells in the haematoxylin and eosin-stained sections are fibroblasts and lymphocytes. The synthetic fibres of the Parietene (**a,b**), Parietene Composite (**c,d**), Sepramesh (**e,f**) and Omyramesh (**i,j**) are surrounded with fibrotic tissue with newly formed collagen. Around Dualmesh (**g,h**) a cellular layer is observed, forming a capsule; cellular infiltration into the mesh is minimal. In the picrosirius red-stained section of the Strattice mesh (**l**) it is impossible to differentiate between the collagen of the mesh and newly formed collagen (C/F). M, abdominal wall muscle; F, mesh fibres, C, newly formed collagen layer

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CHAPTER

Infection susceptibility of crosslinked and non-crosslinked biological meshes in an experimental contaminated environment

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ABSTRACT

Background

This experimental study investigates infectious complications and functional outcome of biological meshes in a contaminated environment.

Methods

In 90 rats peritonitis was induced, and after 24 hours, a biological mesh was implanted intraperitoneally including 2 non-crosslinked mesh groups (Strattice and Surgisis) and 2 crosslinked mesh groups (CollaMendFM and Permacol). Sacrifice was after 90 and 180 days.

Results

More mesh infections occurred in crosslinked meshes compared with non-crosslinked meshes (70% vs 4%; P<0.001). Mesh infection was the highest in crosslinked CollaMendFM (81.2%) and lowest in non-crosslinked Strattice groups (0%). Incorporation into the abdominal wall was poor in all meshes (0% to 39%). After 180 days no residue of non-crosslinked Surgisis mesh was found. After 180 days, shrinkage was 0.8% in crosslinked Permacol and 20% in Strattice groups. Strattice showed the least adhesion formation (median 5%).

Conclusions

Infection rate of biological meshes in a contaminated field was the highest in crosslinked meshes. All biological meshes showed poor incorporation, which makes long-term abdominal wall repair questionable.

INTRODUCTION

Many factors are of influence on the functional outcome of abdominal wall repair, such as patient characteristics, site of implantation, the presence of contamination, and the chosen mesh material. Especially in the presence of bacterial contamination, repair of abdominal wall defects is a continuing challenge for surgeons. Contamination can be caused by intra-abdominal and surgical site infection, incarcerated and strangulated hernia, concomitant bowel surgery, the presence of a colostomy, acute evisceration, and open abdomen. Introduction of synthetic meshes in abdominal wall repair significantly decreased recurrence rates[1,2]. However, implantation of a synthetic prosthesis into a contaminated environment generates an increased risk for infection[3,4]. Mesh infection often necessitates removal of the mesh, leaving an abdominal wall deficit, sometimes larger than the original hernia, and closure can only be accomplished with contact of the mesh with the intra-abdominal content. Recommendations on mesh selection have been developed by the Ventral Hernia Work Group in 2008[5]. In case of ventral hernia repair with mesh implantation in patients with grade-3 and -4 risk of surgical site infection, biological mesh is recommended.

Biological meshes are extracellular scaffolds, processed from animal (bovine or porcine) small intestine submucosa, pericardium, or dermis. The donor tissue is said to be cleared of cells and immunogenic particles, after which a scaffold of extracellular matrix (ECM) remains. After implantation, the scaffold is gradually vascularized and remodelled into the host tissue while degradation of theECM takes place[6,7]. To increase biomechanical strength, chemical crosslinking of the biological mesh can be conducted. Crosslinking stabilizes the 3- dimensional structure of the ECM. This improves withstanding of enzymatic degradation of the ECM, which can be accelerated because of inflammation or infection at the implantation site[8-10]. Initial animal and clinical data seemed promising; however, compelling evidence is lacking as these data mainly report on clean cases and short follow-up with only a small portion in contaminated cases[11]. Furthermore, recent clinical reports have been published on infectious complications of both non-crosslinked and crosslinked meshes[12-17].

The objective of this experimental study was to investigate the infectious complications and functional outcome of crosslinked and non-crosslinked biological meshes in a contaminated environment in a model of abdominal wall repair in the rat.

METHODS

Animals

Experimental protocols were approved by the Ethical Committee on Animal Experimentation of the Erasmus University Rotterdam. Ninety male rats of the outbred Wistar strain were obtained from a licensed breeder (Harlan, the Netherlands) and accustomed to laboratory conditions 2 weeks before the start of the experiment. The animals were bred under specific pathogen-free conditions, were kept under standard laboratory conditions in individually ventilated cages in pairs, and had free access to standard rat chow and water throughout the experiment.

Peritonitis model

Rats were anaesthetized with isoflurane and O2 inhalation (Pharmachemie, Haarlem, the Netherlands) and received buprenorfin analgesia 0.05 mg/kg subcutaneously (Reckitt Benckiser Healthcare (UK) Limited, Kingston upon Thames, United Kingdom). Procedures were performed under aseptic conditions. The abdomen was shaved and the skin disinfected with 70% alcohol, after which the abdominal cavity was opened through a 3-cm midline incision through the skin and linea alba. To induce peritonitis, the cecal ligation puncture model was performed in all rats[18,19]. The cecum was carefully manipulated outside the abdominal cavity and ligated just distal to the ileocecal valve with a monofilament nonabsorbable nylon suture (Ethilon 4-0; Ethicon, Somerville, NJ), maintaining the continuity of the bowel. Distally, the cecum was punctured once with an 18-ga needle. The fascia and the skin were closed with running absorbable polyglycolic acid sutures (Safil 5-0; B Braun, Melsungen, Germany). After 24 hours of recovery, the animals were re-anesthetized, the abdomen was reopened, a culture swab taken to confirm peritonitis, the necrotic cecum resected, and the abdominal cavity was rinsed with at least 20 mL phosphate-buffered saline at 37°C. A sterile mesh, measuring 2.5 x 3 cm, was implanted intraperitoneally with 6 transmuscular nonabsorbable sutures (Ethilon 5-0) in all mesh groups. In the control group no mesh was implanted. After administration of gentamicin 6 mg/kg intramuscularly (Centrafarm, Etten Leur, the Netherlands), the abdominal wall and skin were separately closed with a running absorbable suture (Safil 5-0). Buprenorfin analgesia 0.05 mg/kg was administrated twice daily on the days animals were operated and the first day after mesh implantation.

Implanted meshes

The control group received no mesh, and in the mesh groups, 1 of 4 biological meshes was implanted within the peritoneal cavity. Four commercially available biological meshes were implanted; non-crosslinked porcine dermis Strattice (LifeCell, Branchburg, NJ), non-crosslinked porcine submucosa Surgisis (Cook, Bloomington, IN), crosslinked

porcine dermis CollaMendFM (C.R. Bard [Davol, Inc],Warwick, RI) and crosslinked porcine dermis Permacol (Covidien, Norwalk, CT). Prostheses were prepared according to the manufacturer's instructions before implantation.

Measurements

Animals were divided in groups according to implanted mesh and intended time of sacrifice, 90 or 180 days after implantation of the mesh. During the experiment, animals were weighed daily and scored for their wellness using an objective 12-point scoring system during the first 14 days of the experiment, thereafter once a week[20]. In case of severe infectious complication, weight loss of 20% or more, or a wellness score of less than 5 out of 12 points, animals were euthanized before the intended end of the experiment and analyzed together with the surviving animals of the group. On all euthanized and deceased animals necropsy was performed.

During sacrifice, the animals were anaesthetized with isoflurane and O2 inhalation; the abdomen was shaved, disinfected, and opened through a U-shaped incision extending laterally and caudally to the mesh. Macroscopically, mesh infection was defined as the presence of abscesses of the mesh. Parts of the mesh were cultured for microbiological evaluation. In all mesh groups, mesh surface and coverage of the mesh surface with adhesions were scored using a grid placed over the mesh, dividing it into 30 equal squares and facilitating accurate estimation of adhesion formation. Tenacity of adhesions was scored using the Zühlke score, a 4-degree classification of adhesions based on histologic and morphologic criteria[21]. Pictures of the abdominal wall with the mesh and the present adhesions were taken (5.0 megapixels digital camera, Sony Cybershot, Tokyo, Japan). The abdominal cavity was inspected for abscesses, and when present, scored and cultured at 4 sites of the peritoneum (liver, abdominal wall, bowel, and omentum) using an objective abscess size scoring system[22]. Mesh incorporation was defined as percentage of the mesh edge incorporated into the abdominal wall, taking into account any surface reduction (Figure 1). If only the sutures secured the mesh to the abdominal wall and no ingrowth of the mesh was seen, ingrowth was scored as 0%. Surface reduction was defined as the relative loss of surface compared with the original size of the implanted mesh measured with a calliper. All measurements were performed by 2 independent observers and disagreements reconciled after discussion. The animals were euthanized by cardiac cut at the end of the experiment during anesthesia.

Statistical analysis

Mesh infection, tenacity, and percentage of adhesions, abscess formation, survival, and weight were compared using nonparametric tests as the data did not show normal distribution (Kruskal-Wallis, Mann-Whitney, chi-square, and the Fisher exact tests).

Therefore, all results are presented using the median and the interquartile range (IQR). In case the overall test showed differences, the pairwise tests were done to determine the groups causing the overall significance.

Exact methods for significance were used when computational limits allowed these. All reported P values are 2-sided and considered significant if less than 0.05. In view of the small sizes of the groups, it was not possible to adjust the P values using the Bonferroni correction. Statistical analysis was performed using PSAW statistical software package, version 17 (IBM SPSS statistics).

RESULTS

During the 2 days after implantation of the mesh, 18 of the 90 rats (20%) were prematurely taken out of the experiment because of a low wellness score. Postoperative mortality was not statistically different between the groups. In all rats necropsy was performed and septicemia was found to be the cause of death. Abdominal cultures at day 1 confirmed bacterial contamination in all animals with gram-positive (Enterococcus, Staphylococcus, Streptococcus) and gram-negative microorganisms (Escherichia coli and Proteus). All animals demonstrated signs of sepsis including apathetic behaviour, ocular exudates, piloerection, diarrhea, and weight loss. Mortality in the groups is depicted in Table 1. Maximum percentage weight loss was significantly higher in CollaMendFM after postoperative day 5 compared with the other groups (median: CollaMendFM, 12%; Strattice, 11%; Surgisis, 9%; Permacol, 9%; $P<0.020$).

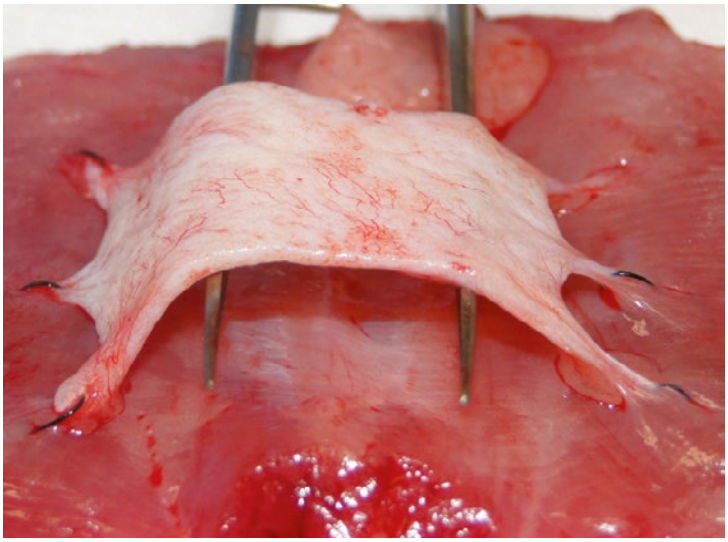

Figure 1. Example of incorporation of the edge of biological mesh in the abdominal wall.

Table 1. Postoperative mortality and animals analyzed at both time points per group.

Group	Material	Animals	Postoperative mortality	90 days	180 days
Control	No mesh	18	2	8	8
Strattice	Non-crosslinked dermis	18	4	7	7
Surgisis	Non-crosslinked submucosa	18	5	6	7
Permacol	Crosslinked dermis	18	5	7*	6
CollamendFM	Crosslinked dermis	18	2	9*	7*
Total		90	18	37	35

*One rat in the Permacol group and 7 rats in the CollamendFM were euthanized before the intended end point. The results of these rats were analyzed together with the rats sacrificed at the intended end point.

Mesh infection and abdominal abscesses

Seven animals (44%) with a CollaMendFM mesh and 1 animal (7%) with a Permacol mesh were euthanized before the intended time point because of clinically evident mesh infection with transcutaneous migration of the prosthesis. At sacrifice, macroscopic infection of the mesh was present in 22 of 57 animals (39%). In Figure 2, the percentage of mesh infections per mesh group is shown. The mesh infection rate was significantly higher for crosslinked meshes compared with non-crosslinked meshes (70% vs 4%; P<0.001). In 16 animals, the mesh was encapsulated by a large abscess, and in 6 animals, abscesses in parts of the mesh were found (Figure 3). No additional mesh infections were discovered by microbiological culture of the meshes performed during sacrifice.

Intra-abdominal or abdominal wall abscesses were found in 42% of all surviving animals at sacrifice. Most abscesses were located at the ligation of the cecal stump. There was no significant difference in amount and size of intra-abdominally (non-mesh related) observed abscesses (P=0.321) between the meshes. Although when differentiated between crosslinked and non-crosslinked meshes, more abscesses were observed in the animals with crosslinked meshes implanted (P=0.011).

Surface reduction

The 22 animals with infected meshes were excluded from this analysis because surface of the mesh could not be accurately measured. The CollaMendFM groups were excluded from analysis because, after excluding the animals with infected meshes, an insufficient number of animals were left to perform statistical testing. Loss of surface of Surgisis was significantly higher at both time points compared with Strattice and Permacol (P<0.036). Both at 90 and 180 days, only in 2 animals a very thin residue of the Surgisis mesh could be found macroscopically. Loss of surface after 90 days was significantly higher in the Strattice compared with the Permacol group (median [IQR], 23% [10-46] vs 3% [0-7];

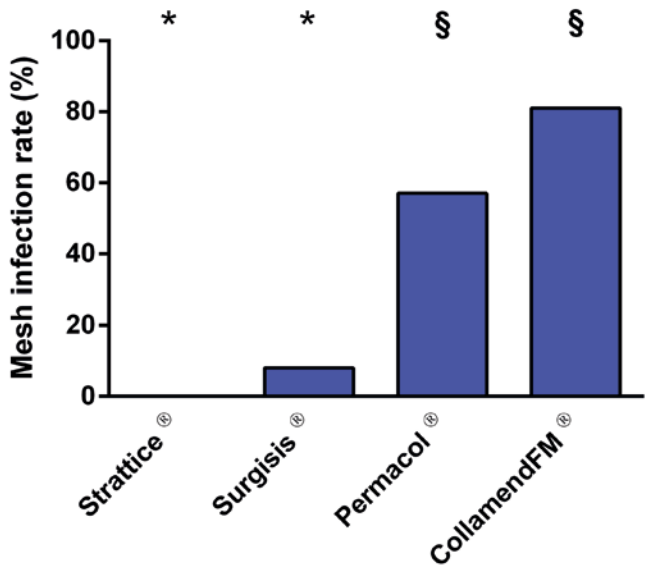

Figure 2. Comparison of combined percentage (90 and 180 days) of mesh infection. Values are percentage of macroscopically infected meshes of surviving animals.
* Non-crosslinked meshes § Crosslinked meshes

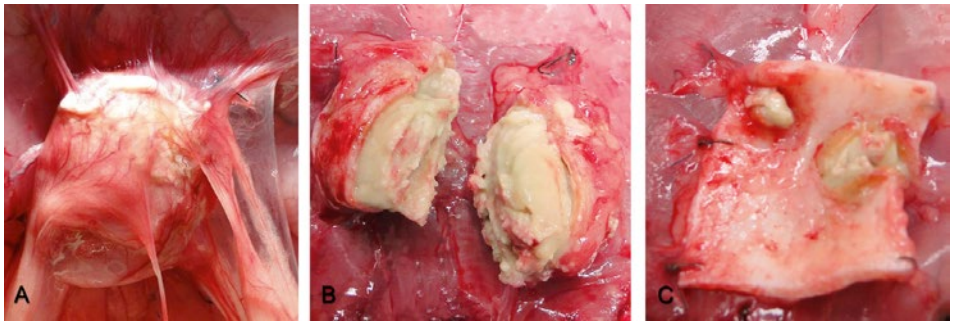

Figure 3. Macroscopic evaluation of mesh infection. Meshoma of a Permacol mesh (A, B) and formation of mesh abscess in a Permacol mesh (C).

P=0.033). In the Strattice group, loss of surface after 180 days was median 20% (IQR, 10-41) and median 1% (IQR, 0-3) for the Permacol group (P=0.075). After grouping the scaffolds by crosslinking, surface reduction of the mesh was lower in the crosslinked group (median [IQR], 2% [0-4]) compared with the noncrosslinked group (23% [10-46]; P<0.001).

Incorporation

Overall incorporation of the biological meshes into the abdominal wall at 90 and 180 days was poor (range, 0%-39%). At 90 days, incorporation of all meshes was median 4% (IQR, 0-21) and at 180 days median 0% (IQR, 0-11). Due to the high infection rate, the CollaMendFM mesh showed incorporation of median 0% at 90 and 180 days (IQR, 0-24; IQR, 0-17, respectively). Most Surgisis meshes could not be identified at 90 and 180 days, leading to an overall incorporation of 0% (IQR, 0-0). Strattice showed incorporation of median 14% (IQR, 10-21) at 90 days, decreasing to median 10% (IQR, 6-12) at 180 days (P=0.128). Permacol was incorporated median 21% (IQR, 3-39) at 90 days, decreasing to 6% (IQR, 0-31) at 180 days (P=0.320). At both time points, incorporation was not different between Strattice and Permacol (P=0.513 and P=0.506). There was no difference in incorporation between crosslinked and non-crosslinked meshes (P=0.537).

Adhesions

In the control group, 6 of 15 rats (40%) showed visceral adhesions to the midline scar with a maximum Zühlke score of 2. Adhesion coverage per mesh group is depicted in Figure 4. At 90 and 180 days, median 100% of the original implantation site of the Surgisis was covered with adhesions (90 days IQR, 76%-100%; 180 days IQR, 100%-100%). CollaMendFM was covered with median 100% adhesions at 90 and 180 days (90 days IQR, 95%-100%; 180 days IQR, 100%-100%). Strattice had little adhesion formation to the mesh at 90 and 180 days (both time points median 5%; IQR, 5%-10%), which was significantly lower than the other meshes (P<0.038). At 90 days, median 68% (IQR, 48%-93%) of mesh surface of Permacol was covered by adhesions and at 180 days, median 42% (IQR 13%-100%). Alteration in adhesion coverage between 90 and 180 days in all mesh groups was not significantly different (P>0.356). Tenacity of adhesions was higher after 90 days for CollaMendFM (median Zühlke score, 4; IQR, 3-4) compared with Permacol (median Zühlke score, 3; 3-3) and Strattice groups (median Zühlke score, 3; IQR, 3-3, respectively; P=0.012 and P=0.031). After 180 days, the tenacity of adhesions decreased and was lowest for Strattice (median Zühlke score, 2; IQR, 2-3), which was significantly lower than that for Permacol (median Zühlke score, 3; IQR, 3-3), CollaMendFM (median Zühlke score, 3; IQR, 3-4) and Surgisis (median Zühlke score, 3; IQR, 3-3, respectively; P=0.013, P=0.007, and P=0.008, respectively).

After grouping the scaffolds by crosslinking, the percentage of the mesh covered with adhesions and the tenacity of the adhesions to the mesh were found to be higher in the crosslinked group (P=0.01 and P=0.024, respectively).

Comments

Crosslinked biological meshes were found to have a significantly higher percentage of mesh infection (70% vs 4%; P<0.001) and intra-abdominal abscesses (P=0.011) than non-

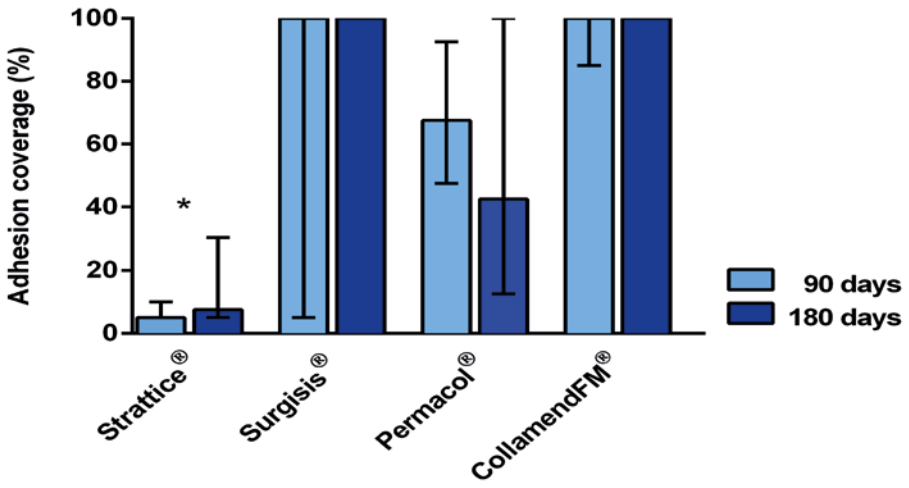

Figure 4. Comparison of percentage of each mesh covered with adhesions after 90 and 180 days follow-up. Values are median (interquartile range). Strattice has significant lower adhesion formation than Surgisis, Permacol and CollaMendFM at 90 and 180 days, * P<0.05.

crosslinked biological meshes. Infectious complications required euthanasia before the intended time point in almost half of animals in the crosslinked CollaMendFM group, as described in previous animal experiments[23-27].These results are in accordance with clinical reports of infectious complications of biological meshes instigating the debate on the indications for their clinical use[12-15,17,28,29]. The development of infection in crosslinked meshes seems comparable to mesh infection in microporous synthetic meshes by preclusion of immune cells[30]. Crosslinking appears to decrease the pore size of biological meshes to a pore size small enough to provide a suitable housing for bacteria while preventing access of macrophages, fibroblasts, blood vessels, and collagen fibers into the pores[31,32]. This may lead to encapsulation rather than remodelling of the mesh[33,34].

However, not all crosslinked meshes have similar densities of crosslinking because of differences in processing. Another interference of mesh integration could be the sterilization technique. CollaMendFM and Surgisis inhibiting tissue integration and reducing tensile strengths[35,36].

However, the influence of sterilization techniques on these parameters is still largely untested. This could be of importance considering the differences found in performance between the crosslinked meshes. In previous studies, the possible effect of crosslinking on the occurrence of infectious complications was not addressed. This experiment is the first step in acquiring more knowledge on the effect of crosslinking on the occurrence of infectious complications after implantation of biological meshes in a contaminated environment.

In abdominal wall repair with a biological mesh, resistance to degradation is critical to prevent recurrence of hernia. During the remodelling process, after implantation a delicate balance exists between ECM degradation and deposition of host collagen. The donor material of the ECM seems to influence the rapidity of degradation of the mesh. High levels of hydroxyproline in collagenase assay suggest low resistance of the submucosa-based mesh to enzymatic degradation[37]. This was illustrated in the present and previous experiments by the complete disappearance of the small intestine submucosa–based Surgisis, which makes long-term hernia repair questionable[34,38]. Meshes derived from dermis were observed to have little surface reduction in the present experiment, with a 20% reduction in noncrosslinked Strattice and 1% in crosslinked Permacol after 6 months. Chemical crosslinking is performed to make biological meshes more resistant to matrix metalloproteases and native and bacterial collagenase. Our experiment also showed decreased surface reduction in the crosslinked group; however, when only dermal meshes were investigated, there was no difference in surface reduction between non-crosslinked and crosslinked meshes. In the present experiment, under contaminated conditions, crosslinked meshes showed poor incorporation in the abdominal wall. The best incorporation was 21% by Permacol after 90 days, which was decreased to only 6% at 180 days. This disappointing incorporation of crosslinked meshes can be explained by delayed collagen degradation, leading to decreased angiogenesis and inflammation due to foreign body reaction resulting in poor tissue integration and adhesion formation[14,24,26,27]. This foreign body reaction can be provoked by exposure of antigenic epitopes known to hinder successful xenotransplantation. For example, galactose-alpha-1,3-galactose (alpha-gal) is proven to be present in the ECM of non-crosslinked Surgisis [39]. Crosslinking can initially mask these antigenic epitopes, but with mesh degradation, epitopes become exposed[40,41]. Exposure of epitopes leads to production of antibodies in humans and primates activating humoral immune and complement response[39,42]. Adhesion formation seems to be related to foreign body reaction to the mesh and sutures and the presence of mesh infection in the present experiment. The amount of adhesions found in this experiment is consistent with earlier experimental reports[19,26,27]. One clinical study evaluated adhesions by laparoscopic re-exploration after ventral hernia repair and found similar surface area and tenacity of adhesions in the biological meshes compared with synthetic meshes[43].

To create a contaminated environment, we used the cecal ligation puncture model, which was originally designed as a sepsis model. In this model, as in clinical infections, peritonitis arises from a complex interaction of the immune system with inflammatory, hemodynamic, and biochemical alterations with a consistent increase of cytokine levels[44-47]. Additionally, in this model genetically identical rats were used of the same age and sex and specified pathogen-free bacterial status. This minimalizes biological and microbiological variability and makes the model suitable for comparing the behaviour of various meshes in a contaminated environment but does not reflect daily practice[46].

A limitation of the model in this experiment is that only a single dose of aminoglycoside is administrated, where this does not reflect the treatment of humans with abdominal sepsis. Administration of antibiotics in rats with fecal peritonitis does reduce bacteremia, bacteria concentration, and mortality rates[48]. But previous experiments proposed a drawback regarding the use of antibiotics because of the possible marked bacterial cell death causing the release of toxic components against the immunologic system and the triggering of uncontrolled activation of this system[49-51]. Previous animal experiments found that when antibiotics were added to the surgical treatment, the inflammatory response is minimized, but there is no difference in survival or amount of intra-abdominal abscesses[52,53]. Therefore, surgical control of the source of infection remains the most important treatment in abdominal sepsis. However, the adjunct of systemic antibiotics to surgical treatment is firmly established in the postoperative period in humans because it reduces the systemic effects of peritonitis and could influence late complications like abscess or fistula formation[54].
Therefore, translation of experimental results to the clinic situation should be done with caution.

In the clinical setting, biological meshes are often implanted in the intraperitoneal or sublay position. A limitation of the present animal study is that thickness and size of the mesh in relation to the abdominal wall is dissimilar between rats and humans. Furthermore, the chosen intraperitoneal placement of the mesh could have influenced incorporation of the mesh in the abdominal wall because the mesothelial layer of the peritoneum is less vascularized than the retromuscular space[55]. On the other hand, closure of the peritoneal layer is often deficient when attempting sublay positioning of the mesh in humans, making the used model clinically relevant.

CONCLUSIONS

In conclusion, this experiment demonstrates a high infection rate and increased adhesion formation of crosslinked biological meshes (Permacol and CollaMendFM). Resistance to infection of non-crosslinked Strattice could allow implantation in the contaminated environment. However, the poor incorporation of all biological meshes and complete degradation of Surgisis makes long-term biomechanical strength of hernia repair questionable. Implantation of biological prostheses could be a valid choice in staged contaminated abdominal wall repair. Prevention of mesh infection associated with high costs for intensive care treatment, reoperation, and prolonged hospital stay might justify the high costs of a biological mesh.

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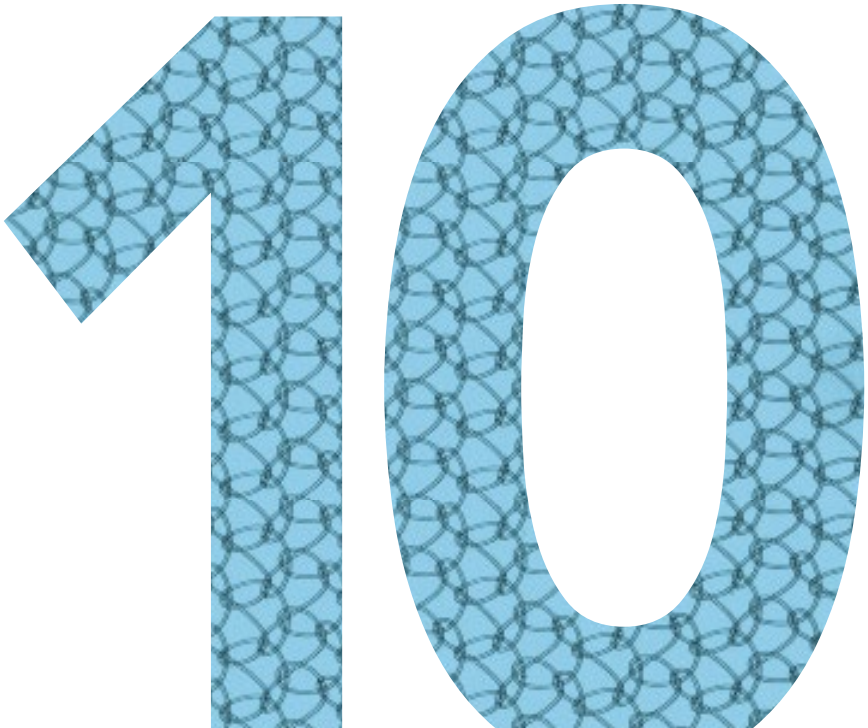
CHAPTER



Problematic incorporation of biological meshes in ventral hernia repair during long-term follow-up

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Submitted

ABSTRACT

Background

This study investigates long-term incorporation, adhesion formation, mesh infection and shrinkage after implantation of biological meshes in non-contaminated environment.

Methods

In 64 rats a mesh-model was used to implant various meshes intraperitoneally: 2 non-crosslinked mesh groups (Strattice and Surgisis) and 2 crosslinked mesh groups (CollaMendFM and Permacol). Sacrifice was after 90 and 180 days.

Results

High numbers of infectious complications were observed (12.5% transcutaneous prosthesis migration and 23.4% macroscopic mesh infection). Incorporation of meshes was poor (0% to 36.8%) on postoperative day (POD) 180. Mesh shrinkage was highest in Surgisis (POD 90 57%, $P<0.01$). On POD 180, shrinkage did not differ between the meshes. Surgisis had the highest adhesion score on POD 90 (90%, $P<0.023$). Adhesions covering the mesh was least in Strattice (5%, $P<0.029$).

Conclusions

Experimental intraperitoneal implantation of biological meshes is accompanied by various infectious complications with little incorporation and will most likely not adequately prevent the formation of recurrent incisional hernia.

INTRODUCTION

The number of patients undergoing elective abdominal wall hernia repair with mesh in the United States was approximately 48,000 in 2010[1]. The subsequent economic burden is justified by the increased quality of life and core physiology after hernia repair[2,3]. Many different mesh types have been introduced on the market with different indications. Synthetic meshes are suggested to be contraindicated in clean-contaminated and contaminated fields following reports on increased susceptibility to infection, fistula formation and adhesion formation. Biological meshes were introduced aiming to reduce infectious complications by complete integration in the host tissue and ingrowth of mononucleair cells. Early short term results after implantation of biological meshes were promising, although mainly investigated in a clean environment. Thereafter reviews concluded that biological meshes should be incorporated in the surgeons armentarium which resulted in widespread implantation of these grafts[4-7].

The Ventral Hernia Working Group of the European Hernia Society recommended use of biological mesh in case of a potentially contaminated or infected wound due to the risk of infectious complications. Consensus on the use of biological meshes has not been reached and surgeons over the world struggle with these recommendations in daily practice[8-10]. In clinical studies with Strattice and Surgisis meshes recurrence of hernia was high which could be due to use of non-crosslinked meshes[11,12]. In a previous animal model infection rate was increased in crosslinked meshes and incorporation of all biological meshes was poor in a contaminated environment[13]. Sustainable hernia repair and low rates of mesh infection when using biological meshes is essential to compete with synthetic meshes in a clean environment.

Long-term follow-up on biological meshes in clinical and animal studies is still scarce. This study aimed to compare two commercially available crosslinked with two non-cross-linked biological meshes in intra-peritoneal position in a rat model. The meshes were tested on infectious complications, adhesion formation, shrinkage and incorporation after a period of 90 and 180 days.

MATERIALS AND METHODS

Animals

Sixty-four male rats of the outbred Wistar strain weighing 288-422 grams were obtained from a licensed breeder (Harlan, the Netherlands) and bred under specific pathogen-free conditions. The animals were accustomed to laboratory conditions one week before the start of the experiment. They were kept under standard laboratory conditions in individually ventilated cages and fed with standard rat chow and water ad libitum throughout the

experiment. Experimental protocols were approved by the Ethical Committee on Animal Experimentation of the Erasmus University Rotterdam.

Implanted meshes

Animals were divided into 8 groups and 4 different commercially available biological meshes were implanted; non crosslinked porcine dermis Strattice (Lifecell, Branchburg, NJ), non crosslinked porcine submucosa Surgisis (Cook, Bloomington, IN), crosslinked porcine dermis Permacol (Covidien, Norwalk, CT) and crosslinked porcine dermis CollamendFM (C.R. Bard/Davol, Inc, Warwick, RI). Prostheses were prepared according to the manufacturer's instructions before implantation.

Mesh model

Rats were anaesthetized with isoflurane/O_2 inhalation (Pharmachemie, Haarlem, the Netherlands) and received buprenorfin analgesia 0.05 mg/kg subcutaneously (Reckitt Benckiser healthcare limited, Kingston upon tames, United Kingdom). Procedures were performed under aseptic conditions. The abdomen was shaved and the skin disinfected with 70% alcohol, after which the abdominal cavity was opened through a 3 cm midline incision through the skin and linea alba. A sterile mesh, measuring 2.5x3cm, was implanted intraperitoneally with three transmuscular non-absorbable sutures (Ethilon 5-0) on both sides of the incision in all mesh groups. Thereafter the abdominal wall and skin were separately closed with a running absorbable suture (Safil 5-0).

Measurements

In case of severe infectious complications animals were euthanized before the intended endpoint. These animals were analysed together with the surviving animals sacrificed at the intended endpoint. Half of the surviving animals were sacrificed after 90 days and half after 180 days. During sacrifice the abdomen was shaved, disinfected and opened through a U-shaped incision extending lateral and caudal to the mesh. Mesh incorporation was defined as percentage of the mesh edge incorporated into the abdominal wall, taking into account any shrinkage (example on page 154 of this thesis). In all mesh groups mesh surface and coverage of the mesh surface with adhesions was scored using a grid placed over the mesh, dividing it into 30 equal squares and facilitating accurate estimation of adhesion formation. Tenacity of adhesions was scored using the Zühlke-score, a 4-degree classification of adhesions based on histological and morphological criteria[14]. Pictures of abdominal wall with mesh and the present adhesions were taken (5.0 megapixels digital camera; Sony Cybershot). Macroscopically mesh infection was defined as the presence of abscesses of the mesh. Shrinkage was defined as the relative loss of surface compared with the original size of the implanted mesh measured with a calliper. All measurements were performed by 2 independent observers and disagreements reconciled after discussion. The animals were euthanized by cardiac cut.

Statistical analysis

Incorporation, mesh infection, tenacity and percentage of adhesions, abscess formation, survival, weight and shrinkage were compared using non-parametric tests (Kruskal Wallis, Mann Witney, Chi-square, Fisher's exact and Spearman's rho) since the data did not show a normal distribution. Therefore all results are presented using the median and the interquartile range (IQR). In case the overall test showed differences, the pairwise tests were done to determine the groups causing the overall significance. Exact methods for significance were used when computational limits allowed these. All reported p-values are two-sided and considered significant if less than 0.05. In view of the small sizes of the groups, it was not possible to adjust the p-values using Bonferroni's correction. Statistical analysis was performed using PSAW statistical software package, version 17 (IBM SPSS statistics).

RESULTS

Mesh infection

During the experiment 8 animals were euthanized due to clinically evident mesh infection with transcutaneous migration of the prosthesis between day 49 and 87. In all euthanized rats, 7 animals of the CollamendFM group and 1 of the Surgisis group, necropsy was performed and large mesh abscesses were found intra abdominally. In total 15 of 64 rats (23.4%) were found to have macroscopic infection of the mesh at time of sacrifice. In Figure 1 the amount of mesh infections per mesh-group is shown. Strattice had a significantly lower number of mesh infections compared to CollamendFM at 90 days (P<0.001). At 180 days CollamendFM showed a significantly higher rate of mesh infection compared to all other meshes (P<0.004). Maximum percentage of weight loss was significantly higher in CollamendFM compared to all other groups (median 6, compared to Strattice 2; Surgisis 3; Permacol 3.5, P=0.001).

Mesh incorporation

Animals with mesh infection were not included in this analysis because no incorporation of the mesh was found in these animals. Incorporation of the meshes was not significantly different between the groups at 90 days (median 13.2%, IQR 0-24.2%). Data per mesh is shown in Figure 2. No Surgisis meshes could be identified at 180 days and incorporation was scored as 0%. Therefore at 180 days the incorporation of Surgisis (0%, 0-0) was significantly lower than Strattice (13.7%, 10.3-22.4; P<0.001) and Permacol (20.7%, 5.7-24.5; P<0.001). For each mesh no difference in incorporation of the mesh was observed between 90 and 180 days.

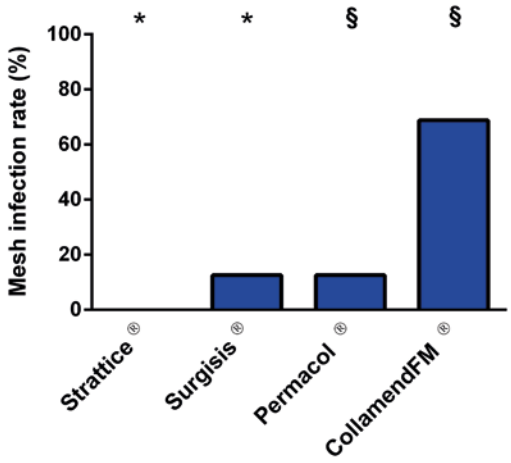

Figure 1. Comparison of combined percentage (90 and 180 days) of mesh infection. Values are percentage of macroscopically infected meshes of surviving animals.
* Non-crosslinked meshes § Crosslinked meshes.

Adhesions

At 90 days Surgisis had the highest percentage of mesh adhesions to the mesh implantation site (90%, 32.5-100) which was significantly more than all other meshes (P<0.023). Data per mesh is shown in Figure 3. Strattice showed a significantly smaller percentage of mesh surface covered with adhesions (5.0%, 5.0-5.0; median Zühlke 2) compared to all other meshes (P<0.029). When only considering non-infected meshes there was no longer a difference in adhesion coverage between Strattice and CollamendFM .

At 180 days CollamendFM had the highest rate of adhesions coverage (median 100, IQR 100-100; median Zuhlke 3) of the mesh due to the high amount of infected meshes. This was significantly more than all other meshes (P<0.029). Adhesions were found at median 40% (IQR 11.2-63.7) of the size of the original implantation site of the Surgisis. Of the non-infected meshes Strattice had the least adhesions (5%, 5.0-5.0) which was significantly less than Surgisis (P<0.001) and Permacol (P<0.001).

Shrinkage

Surface of the mesh could not be accurately measured in infected meshes therefore these were excluded from the analysis. Shrinkage of the mesh was highest in Surgisis at 90 days were a residue of median 43% of the original size was found (shrinkage 57%, IQR 37.0-69.5). Data per mesh is shown in Figure 4. This shrinkage of Surgisis was significantly higher than Strattice (33.0%, 22.5-36.5; P=0.02), Permacol (3.0%, 0.0-7.0; P=0.003) and CollamendFM (0.0%, 0.0-2.2; P=0.016).

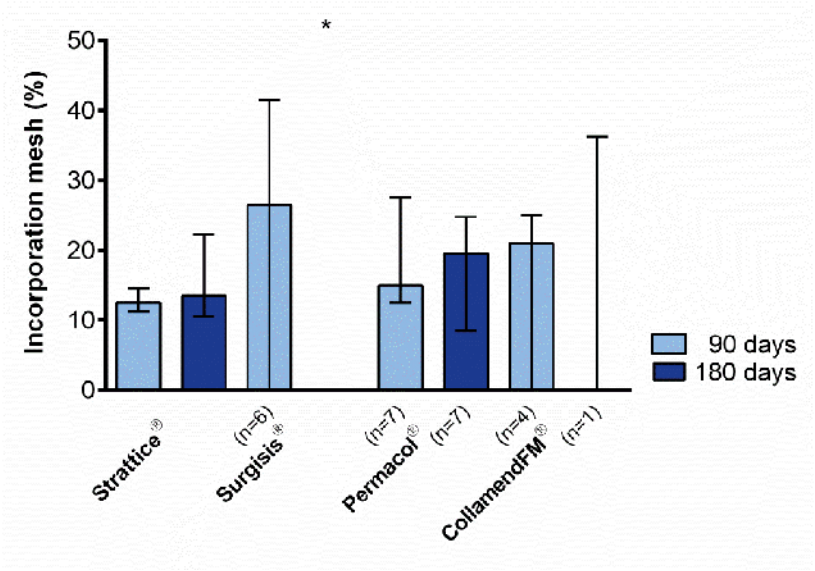

Figure 2. Percentage of the mesh edge incorporated into the abdominal wall, only non-infected meshes included. Values are median (interquartile range). At 180 days: *no Surgisis mesh could be identified and P<0.001 compared to Strattice and Permacol (n=7).

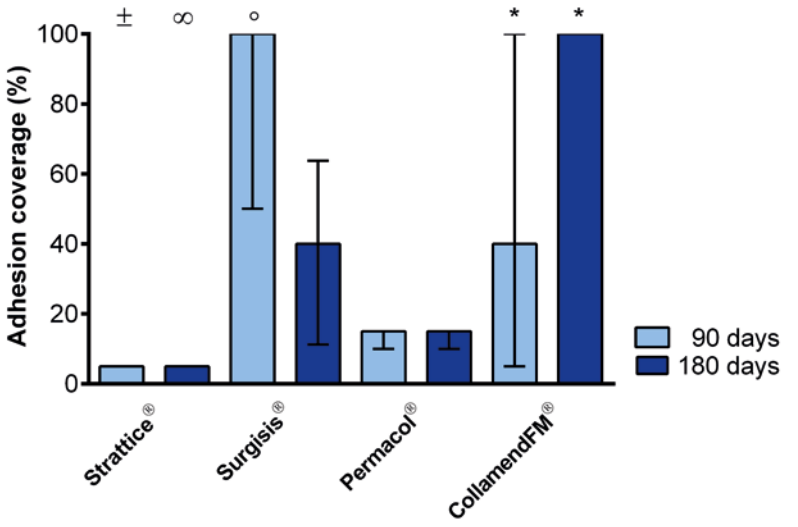

Figure 3. Comparison of percentage of each mesh covered with adhesions at the 90 and 180 days follow-up assessment. Values are median (interquartile range). *n=7. At 90 days: ± P<0.023 compared to all other meshes; ° P<0.029 compared to all other meshes.

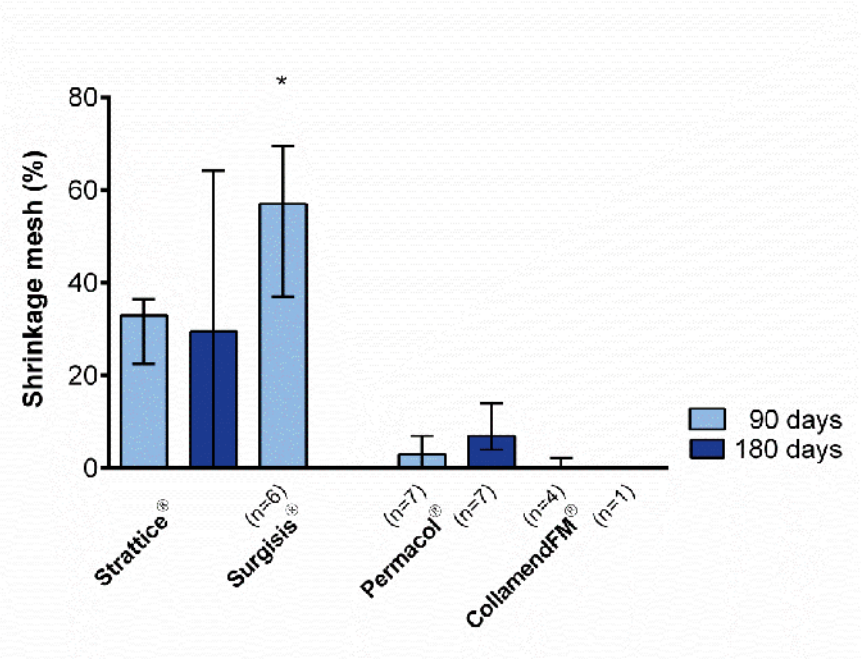

Figure 4. Percentage of shrinkage of the mesh surface, only non-infected meshes included. Values are median (interquartile range). At 90 days: *P<0.016 compared to all other meshes. At 180 days there was no difference between the mesh groups.

Correlation between adhesion formation and incorporation

At 90 days CollamendFM showed a significant correlation between adhesion coverage of the mesh and incorporation of the mesh edge (ρ=-0.973; P=0.01). At 180 days there was no correlation. When the animals in group 90 days and 180 days were combined CollamendFM showed a correlation coefficient of ρ=-0.612; P=0.05. This correlation coefficient indicates that in CollamendFM meshes increase of adhesion formation was correlated with a decrease of incorporation.

DISCUSSION

Based on the results of our long-term animal study we advocate more reluctance on implantation of biological meshes for abdominal wall repair. When biological meshes are implanted in an intraperitoneal position, incorporation in the abdominal wall is poor and adhesion formation and infection susceptibility remain a problem. The best results in our study were found with implantation of non-crosslinked Strattice. Adhesion coverage was low as 5%, but incorporation after 180 days was only 13.7%. Crosslinked Permacol had the better long-term incorporation (20.7%) but adhesion coverage of 15%. Worst results were found with crosslinked CollaMend and non-crosslinked Surgisis.

After implantation of CollaMend infection of the mesh occurred in over 60% leading to a very low incorporation and increased adhesion formation. Non-crosslinked Surgisis dissolved completely within 180 days but induced substantial adhesion formation. These characteristics of biological meshes at long-term follow-up make the strength of the abdominal wall repair questionable. Moreover the adverse effects are comparable to intraperitoneally used (coated) synthetic meshes.

It is a recurrent phenomenon in research where initial studies on new technology describe positive results (whether or not industry driven) and subsequently critical reviews are published only after years of trial and error. The first studies on biological meshes were mainly case series with large variation in sample size, mesh material, implantation technique, follow-up and study endpoints[7,15]. Although the majority of cases were implanted in a non-contaminated environment they have also led to recommendations for the use in contaminated surgical fields. In recent years authors have started to publish their doubts on biological meshes[15,16].

The aim of biological mesh implantation is to create a functional abdominal wall by deposition of native collagen during mesh degradation ('remodelling'). In our current study incorporation of the mesh was highest in Permacol however with only 20.7% incorporation (20.7%, 5.7-24.5), followed by Strattice (13.7%, 10.3-22.4). The steps in this dynamic process include inflammatory response, cellular penetration and neovascularisation of the mesh, fibroblast infiltration and collagen deposition[17]. It appears that all meshes induce varying levels of foreign body reaction and fibrosis. Multiple characteristics of the mesh influence this response: mesh material, weight, pore size, crosslinking and sterilisation technique. More data is becoming available on histopathologic responses to specific synthetic and biological meshes in animal models[16,18,19]. Novitsky et al observed that crosslinked meshes caused extensive foreign body reaction with fibrous encapsulation and no evidence of integration or remodelling of the mesh[16]. Dissimilarities have been found between crosslinked and non-crosslinked meshes suggesting that improved integration into host tissue in non-crosslinked matrix is due to a moderate mononucleair cell reaction[20]. Possible cause of this foreign body reaction is due to presence of nucleair material in the mesh or exposure of antigentic epitopes following implantation[21-25]. It is suggested that some crosslinking processes damage the extracellular matrix and negatively influence the host response leading to encapsulation, decreased fibroblast penetration in the matrix and little collagen synthesis[20,23,26-28]. Similar results have been found in patients who underwent removal of porcine biologic mesh where no to little evidence of neovascularisation or neocellularisation was detected in crosslinked meshes[17]. Non-crosslinked Strattice mesh showed highest degree of new collagen deposition and organization in the study by Novitsky et al. which is comparable to the results in our current study[28].

Clinical studies like the multicentre RICH study showed similar results with a recurrence hernia rate of 19% after 1 year and 28% after 2 years[11]. Likewise, Rosen et al recorded a recurrence rate of 31.3% with a follow-up of 21.7 months after implantation of biological mesh[29]. These results can hardly be called sustainable hernia repairs and are not that dissimilar to synthetic meshes[6,30]. Increasingly synthetic meshes are being implanted in clean-contaminated and contaminated surgical field with quite favorable results[31-34]. Recent studies in grade II contaminated wounds showed lower recurrence rate after implantation of synthetic meshes compared to biological meshes with similar adverse event[35].

Possible factors affecting the collagenesis and consequential recurrence rate of hernias are high rates of postoperative infectious adverse-events. Ambivalent results have been published previously: Basta et al reported a 51.4% incidence of wound complications leading to recurrence hernia rate of 18.9% with postoperative wound infection being the only predictor of recurrence with an odds ratio of 22.1[36]. Increased infection rate of biological meshes could be due to bacterial niches in biomesh pores and bacterial formation of biofilms[37].

Perhaps the advantage of biological meshes over synthetic material is the possibility of performing aggressive salvage procedures with removing parts of an infected mesh in situ to avert removal of all material with subsequently recurrence of hernia.

An important factor when choosing a mesh are the associated costs. Biological meshes are substantially more expensive than synthetic meshes[4,6]. However costs can be reduced when delayed primary closure with implantation of a biological mesh is possible during one hospital admission. In this way the number of admissions and in-hospital days can be reduced compared to staged repair[38]. Additional benefit is earlier restoration of abdominal wall function which may lead to accelerated return to work.

A limitation of our study might be the implantation of the mesh in an intraperitoneal position. After intraperitoneal placement of the mesh there is no close vascular supply to facilitate neovascularisation and fibroblasts have difficulty reaching the mesh[39]. However in previous animal studies intraperitoneal or extraperitoneal implantation of the mesh did not affect host tissue incorporation or mesh degradation[19]. Contact of the mesh with the intraperitoneal compartment can often not be avoided due to the large dimensions of the hernia defect[11,36]. In the retrospective analysis of the RICH study there was no difference in hernia recurrence rate when the retro-rectus plane was compared to intraperitoneal placement. In 2 trials sublay procedures are found to result in less wound complications and seromas compared to onlay procedures[40,41]. It is suggested that further randomized trials on the optimal placement is needed to guide decision-making[17,38].

Another limitation is that this research was performed in animals without any predisposing collagen disease or hernia defect.

CONCLUSIONS

We advocate more caution with implantation of biological meshes for abdominal wall repair. There seems to be no evidence for previously purported hypothesis that biological material enables ingrowth of cells and vessels resulting in a sustainable hernia repair. Implantation of biological mesh does not seem to reduce infection rate which is a significant factor for the recurrence of incisional hernia. Biological meshes might not have the required characteristics for implantation in clean environment with high infection rate and low incorporation of the mesh in the current experiment.

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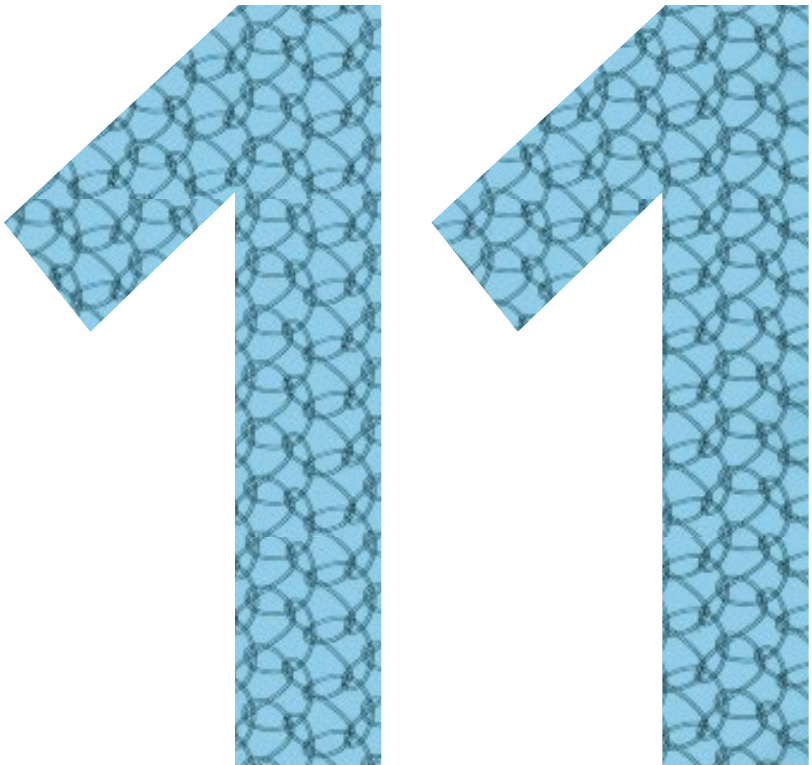
CHAPTER



Polyvinyl alcohol hydrogel decreases formation of adhesions in a rat model of peritonitis

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ABSTRACT

Background

Adhesion formation after surgery for peritonitis-related conditions, with such associated complications as intestinal obstruction, pain, and infertility, remains an important problem. Applying a liquid barrier intra-peritoneally might reduce initial adhesion formation.

Methods

A combination of the cecal ligation and puncture model of peritonitis with the side-wall defect (SWD) model of adhesion formation was performed. Forty rats were assigned randomly to receive no barrier or 1mL or 2mL of the cross-linked polyvinyl alcohol and carboxymethylcellulose (PVA/CMC) hydrogel A-Part Gel (B. Braun Aesculap AG, Tuttlingen, Germany). After 14 days, the animals were sacrificed, and adhesion formation and abscess formation were scored.

Results

Thirty animals survived, distributed equally among the groups. There were significantly fewer adhesions to the SWD in the PVA/CMC groups (median 0) than in the control group (median 26%–50%) ($P<0.05$). The median tenacity of the adhesions was significantly higher in the control group (Zühlke score 2) than in the PVA/CMC groups (Zühlke score 0) ($P<0.05$). The amount and size of intra-abdominal abscesses were not significantly different in the three groups.

Conclusion

In this experiment, PVA/CMC hydrogel reduced the amount of adhesions to the SWD and between viscera significantly with equal risk of abscess formation.

INTRODUCTION

The formation of intra-abdominal adhesions remains a common serious problem in surgical practice. Formation of adhesions is observed after both open and laparoscopic surgery, with a reported incidence as high as 97%[1,2]. Complications of intra-abdominal adhesions include intestinal obstruction, chronic pain, infertility, and troublesome reinterventions. Of all patients undergoing open abdominal surgery, 35% will be readmitted for complications related to adhesions[3]. The cumulative risk of adhesive small-bowel obstruction after colectomy is 11%–25% after one year and 30% after 10 years[4,5]. During reintervention, some extent of adhesiolysis is unavoidable, leading to inadvertent enterotomy in 19% of patients owing to the severity of the adhesions or to iatrogenic bowel injury[6].

Adhesion formation is initiated by the inflammatory response following visceral damage as a result of intra-abdominal surgery and infection[7]. The underlying mechanism is local tissue ischemia and mesothelial injury. The mesothelial and submesothelial cells express proteases and protease inhibitors, disrupting the balance between coagulation and fibrinolysis and creating fibrous bands that form adhesions[7,8]. Furthermore, inflammation intensifies this reaction by attracting and activating fibroblasts and disrupting fibrinolysis[9,10]. Adhesion formation is controlled by macrophages and T lymphocytes and takes place mainly during the first two weeks of healing, before the defect has been covered with mesothelium[11-13]. Adhesion formation can be prevented by a physical barrier that separates the injured tissue from adjacent organs and the peritoneum during the crucial healing period[2,14-16].

Abdominal surgery for intra-abdominal infection with peritonitis is associated with high morbidity and mortality rates and complicated frequently by abscess formation. In peritonitis, severe inflammation of the peritoneum occurs, increasing adhesion formation. Prevention of adhesion formation after peritonitis seems the ultimate challenge for proving the effectiveness of an anti-adhesion barrier. It also is crucial that the barrier does not promote infection or abscess formation[17,18].

Cross-linked biocompatible polyvinyl alcohol (PVA) hydrogels reduce adhesion formation after non-infectious abdominal surgery[16,19-21]. The aim of our experiment was to investigate the effects of PVA hydrogel on adhesion and abscess formation in an experimental bacterial peritonitis and adhesion model in rodents.

MATERIALS AND METHODS

To study the effects of PVA hydrogel on adhesion and abscess formation, a combination of the cecal ligation and puncture (CLP) peritonitis model and the cecal abrasion

sidewall defect (SWD) adhesion model was used. We believe that our combination model resembles adhesion formation in a clinical situation after abdominal surgery in the presence of peritonitis. The protocol of the experiment was approved by the Animal Experiments Committee of the Erasmus University, Rotterdam.

Study design

In 40 male Wistar rats, the CLP model was created by ligation and puncture of the cecum. The following day, the necrotic cecum was resected and the SWD model created. The hydrogel studied in this experiment was A-Part Gel (B. Braun Aesculap AG, Tuttlingen, Germany), which is a crosslinked PVA and carboxymethylcellulose (CMC) formulation. After completion of the SWD model, the rats were assigned randomly to one of three experimental groups: A (control), B (1mL of A-Part Gel), or C (2mL of A-Part Gel). The viscous PVA/CMC gel was administered with a special nozzle to the sites of peritoneal damage; that is, the SWD and around the cecal stump. The abdominal wall and skin were closed separately with continuous, absorbable suture. After 14 days, the animals were sacrificed humanely and scored on adhesion and abscess formation.

Animals

Inbred male rats of the Wistar strain weighing 294–355 g were obtained from a licensed breeder (Harlan, The Netherlands) and accustomed to laboratory conditions two weeks before the start of the experiment. They were bred under specified pathogen-free conditions, kept under standard laboratory conditions in individually ventilated cages (temperature 20–24°C; relative humidity 50%–60%; 12 h light/dark cycles), and fed standard rat chow and water ad libitum during the entire experimental period.

Procedure

Day 0: CLP model. The surgery was performed under aseptic conditions. At the start of the experiment, the animals were anesthetized using isoflurane/O2 by inhalation, and buprenorphine analgesia (0.05mg/kg) was administered subcutaneously. The abdomen was shaved and cleaned with isopropyl alcohol 70%, after which a 3-cm midline incision was made. The cecum was manipulated carefully to the outside of the abdominal cavity and ligated just distal to the ileocecal valve with a monofilament non-absorbable suture (4-0 Ethilon, Ethicon, Inc., Somerville, NJ), maintaining the continuity of the bowel. Distally, the cecum was punctured once with an 18-gauge needle. Some fecal material was expressed through the puncture hole and cultured. The cecum was replaced intra-peritoneally, and the abdominal wall and skin were closed separately with running polyglycolic acid sutures (5-0 Safil, B. Braun Melsungen AG, Melsungen, Germany). For resuscitation, 5mL isotonic sodium chloride solution was administered, and animals were placed under a heating lamp during the immediate post-operative period.

Day 1: CLP and SWD model. The animals were anesthetized using isoflurane/O2 inhalation, and buprenorphine analgesia (0.05 mg/kg) was administered subcutaneously. The abdomen was re-opened through the midline incision, and a culture swab of the abdominal cavity was obtained to confirm fecal peritonitis. The necrotic cecum was resected and the abdominal cavity rinsed with at least 20mL of phosphate buffered saline warmed to 37°C. The remaining cecum was abraded lightly with dry sterile gauze until punctate bleeding was observed. From the left anterior abdominal wall, a tissue strip of 0.5 x 2.0 cm, including peritoneum and muscle, was excised. Before closure of the abdomen, animals were assigned randomly to one of the three experimental groups. All animals received gentamicin (6mg/kg intramuscular), buprenorphine (0.05mg/kg subcutaneously), and isotonic sodium chloride solution (5mL subcutaneously).

Day 1: Application of PVA/CMC hydrogel. Animals in Group A served as the control group and received no additional treatment. Group B received 1mL of PVA/CMC hydrogel, and Group C received 2mL of hydrogel. The hydrogel was applied to the SWD and the abraded cecum. Finally, the abdominal wall and skin were closed separately with running polyglycolic acid sutures (5-0 Safil).

Day 14: Sacrifice. The animals were anesthetized using isoflurane/O2 by inhalation and shaved. After disinfection, the ventral abdominal wall was opened through a U-shaped incision, and a swab of the abdominal cavity was taken. The amount and tenacity of the adhesions was scored, and pictures were taken (5.0-megapixel digital camera; Sony Cybershot , Tokyo, Japan). The abdominal cavity was inspected for abscesses, which were scored and cultured when found. The animal was then euthanized by cardiac cut.

Measurements

Wellness and survival. During the experiment, animals were weighed daily and scored for their wellness using an objective 12-point scoring system[22]. Animals with a weight loss of 20% or more or a wellness score of < 5 were euthanized. A necropsy was performed on all euthanized and deceased animals.

Adhesions. Two independent observers assessed adhesion coverage of the surface of the abdominal wall defect in a blinded manner using a scoring system, dividing the defect into four squares of 0.5 · 0.5 cm (0%, 1%–25%, 26%–50%, 51%–75%, or 76%–100%) and categorized the tenacity of the adhesions using the objective Zühlke score, which is based on histologic and morphologic criteria (Table 1)[23]. In case of inter-observer disagreement, the mean Zühlke score was calculated. The amount of adhesions (between viscera or between viscera and the abdominal wall, including the midline scar) was scored and the severity of the adhesions was graded by the Zühlke score.

Table 1. Zühlke Scoring System for adhesions.

Zühlke Score	Definition
0	No adhesions
1	Minimal, filmy adhesions requiring little blunt dissection
2	Moderate adhesions requiring blunt and partly sharp dissection; beginning of vascularisation
3	Strong adhesions; lysis possible by sharp dissection only; clear vascularisation
4	Very strong adhesions; sharp dissection only; organs attached (damage of organs difficult to prevent)

Translated and reprinted from: Zühlke HV, Lorenz EM, Straub EM, Savvas V: [Pathofysiology and classification of adhesions] (GER). Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir 1990:1009-1016.

Table 2. Abscess Scoring System.

Score	Definition
0	No abscess present at the site
0.5	One small abscess present at the site
1	Several small abscesses present at the site
2	Medium abscess present at the site
3	Large or several medium abscesses present at the site
4	One very large or several large abscesses present at the site

Translated and reprinted from: Rodgers KE, Schwartz HE, Roda N et al. Effect of oxiplex® films (PEO/CMC) on adhesion formation and reformation in rabbit models and on peritoneal infection in a rat model. Fertil Steril 2000;73(4):831-838.

Abscesses. Two independent observers assessed the amount and size of abscesses at four sites in the peritoneum: liver, abdominal wall, bowel, and omentum using an objective size scoring system (Table 2)[24].

Cultures. The fecal sample, intra-abdominal swab, and abscess cultures were evaluated for the strains and amount of bacteria present.

Statistical analysis

Adhesion formation and tenacity, abscess formation, survival, animal weight, and wellness score were compared using non-parametric tests (Kruskal–Wallis, Mann–WhitneyU) because the data did not show a normal distribution. Therefore, all results are presented

using the median and the interquartile range. All reported p values are two-sided and considered significant if P<0.05. Statistical analysis was performed using the PSAW statistical software package (IBM SPSS Statistics, Chicago, IL).

RESULTS

No animals needed to be euthanized because of a weight loss of 20% or more or a wellness score < 5. A total of 30 animals survived; 10/14 (72%) in both experimental groups (B and C) and 10/12 (83%) in the control group (A)(P=0.81). No differences in weight change or wellness score were observed among the three groups. Ten animals died within 24 h after the second operation. All were found to have died of sepsis secondary to fecal peritonitis.

Adhesions

Adhesions to the surface of the SWD were significantly different among the groups (P=0.009) (Table 3). There were significantly more adhesions (median 26%–50%) to the SWD in the control group than in the PVA/CMC groups (median 0)(P=0.02), but no difference in adhesions between the two PVA/CMC groups (P=1.00). The tenacity of the adhesions also was significantly different among the groups (P=0.004) (Table 4). There was a significant difference in adhesion tenacity between the PVA/CMC groups (both having a median Zühlke score of 0) and the control group (median Zühlke score 2)(P=0.01 and P=0.02), but no difference between the PVA/CMC groups (P=0.74). Visceral adhesions between intestinal loops or between intestinal loops and the abdominal wall (including the midline scar) appeared in 70% of the control group, 50% of the PVA/CMC 1-mL group, and 40% of the PVA/CMC 2-mL group (P=0.31). The tenacity was the greatest in the control group (median Zühlke score 3.5) compared with the PVA/CMC 1mL (median Zühlke score 0.5) and PVA/CMC 2mL (median Zühlke score 0), but this difference was not statistically significant. In all surviving animals, adhesions to the cecal stump occurred with comparable tenacity in all groups (median Zühlke score 3–3.5)(P=0.32).

Abscesses

The amount and size of intra-abdominal abscesses were not significantly different among the three groups (P=0.48 and P=0.10). In the control group, four abscesses were found in three animals, with an abscess score ranging from 1 to 4. In the PVA/CMC 1-mL group, seven abscesses were found in six animals, with a score between 0.5 and 2. In the PVA/CMC 2-mL group, five abscesses were found in five animals, with a score of 0.5 and 1.

Cultures

The feces of the rats contained no bacteria other than what was expected in view of their specified pathogen-free status. The culture taken on Day1 proved fecal peritonitis in all 40 rats. During sacrifice, no bacteria were found intra-abdominally. All abscesses contained one or more fecal bacteria.

Table 3. Adhesion coverage of side wall defect by treatment group.

Adhesion coverage (%)	Control	A-Part 1 ml	A-Part 2 ml
0	3	9	8
1-25	2	0	1
26-50	1	0	1
51-75	0	0	0
76-100	4	1	0

Table 4. Zühlke score of adhesions on side wall defect by treatment group.

Zühlke Score	Control	A-Part 1 ml	A-Part 2 ml
0	3	9	8
1	2	0	1
2	0	1	0
3	1	0	1
4	4	0	0

DISCUSSION

The formation of adhesions begins with injury to two opposing layers of the peritoneum, with exudate contributing to the deposit of fibrin. The PVA/CMC hydrogel separates the damaged peritoneal surfaces during the crucial remesothelialisation phase in the first two postoperative weeks and reduces initial adhesion formation[11-13]. This hydrogel is completely biodegradable, and no residues are found after two weeks[25].

A serious concern about barriers is their influence on infection. It was especially interesting that in our experiment, the risk of abscess formation was equal in all groups, with or without PVA/CMC gel. We believe that our experimental model combining peritonitis and adhesions resembles adhesion formation after clinical abdominal surgery in the presence of peritonitis. The CLP model produces generalized peritonitis with an immunologic response secondary to the spill of the animal's own stool into the peritoneal cavity through the devascularized and punctured cecum. This model closely mimics the clinical situation of peritonitis induced by bowel perforation, and subsequent surgical source control followed by post-operative adhesion and abscess formation[26]. In peritonitis models, abscess formation increases until two weeks postoperatively and then decreases in the following weeks[27,28]. The CLP model combines an acceptable mortality rate of 15%–30% with a high incidence of abscess formation[29-31]. The SWD model promotes adhesion formation and mimics peritoneal trauma caused by laparotomy. It is a dependable,

predictable, and readily quantifiable model that allows objective measurement of the extent of adhesion coverage[32,33].

Adhesions are formed predominantly during the first two weeks of healing, before the defect is covered by mesothelium[11-13]. The amount of adhesions does not increase after 14 days, and the situation at that time therefore is representative of the long-term effects. On the other hand, the tenacity of the adhesions is influenced by the chronic inflammatory response and therefore probably will change over time. The combination of the two models promotes a severe inflammatory response with subsequent adhesion formation. An inflammatory reaction occurs, causing an influx of inflammatory cells and activating mesothelial cells, leading to fibrinous exudate. The exudate becomes denser as a result of persisting fibroblasts, and adhesions are formed[7].

In this experiment, the SWD and other visceral adhesions (except to the cecum) were significantly fewer in the groups in which the PVA/CMC hydrogel was used as a barrier. The PVA/CMC probably remained in place on the SWD because of the flat surface of the abdominal wall and the prostrate position of the rodents. There was no reduction of adhesion formation to the cecal stump. This might be the result of the PVA/CMC hydrogel not remaining at the site because of the roundness and gravity making the gel shift from the cecum, losing its barrier function. Also, the non-absorbable suture and possible microscopic fecal leakage from the cecal stump might have given rise to adhesion formation.

In this experiment, the PVA/CMC hydrogel was safe and efficient in reducing adhesion formation in a peritonitis model. Because both concentrations (1mL and 2 mL) of the hydrogel provided the same reduction of adhesion formation and no difference in abscess formation, we conclude that 1mL of A-Part is an adequate dosage to reduce adhesion formation in a Wistar rat weighing 300–350 mg. The promising efficacy demonstrated by the A-Part hydrogel in this experiment stimulated us to investigate this product further, focusing on its safety when applied around an intestinal anastomosis and in the presence of synthetic material such as intra-abdominally placed meshes[33]. The promising experimental results also led to initiation of a clinical trial of the safety and efficacy of the hydrogel[34].

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CHAPTER

General discussion and future perspectives

DIVERTICULITIS

The incidence of acute diverticulitis is rising which is accompanied with many challenges in its diagnosis and treatment. In this thesis we investigated several components of the treatment of patients with diverticular disease to improve patient care in an evidence based manner.

A number of issues in the treatment of diverticular disease remain unresolved. Future research should focus on the etiopathogenesis, prevention and minimally invasive treatment of diverticulitis.

Consensus on the etiopathogenesis of diverticulitis is shifting away from traditional dogmas of fecalith obstruction of a diverticulum. It is now hypothesised that in patients with diverticular disease the changes in colonic flora promote disease and inflammation. The intestine has been shown to harbour a complex bacterial community. This commensal gut flora (intestinal microbiota) protects against epithelial cell injury, regulates fat storage and influences the function of the gut immune system[1-4]. Disease specific variations in the composition of the colonic microbiota have been identified in inflammatory bowel disease and metabolic syndrome[5-9]. Characterization of the colonic microbiota in patients with diverticular disease might clarify its possible role in the pathogenesis of this disease and inflammatory episodes. Additionally, microbiome analysis might offer a new way of diagnosing diverticulitis.

This hypothesis on etiopathogenesis also offers new opportunities to treat diverticulosis with mesalazine, probiotics or intraluminal antibiotics to prevent progression of disease to diverticulitis or recurrence of inflammatory episodes. However current evidence from previous research is not strong enough to recommend medical treatment to prevent relapse[10-12].

Identifying patients with diverticulitis correctly can be difficult because of the great variation in the intensity of symptoms at presentation. A clinical decision model might increase the accuracy of clinical diagnosis and could assist the clinician in omitting unnecessary additional imaging[13-15]. The three strongest clinical features are direct tenderness in the left lower quadrant, the absence of vomiting and a C-reactive protein >50mg/L. In a quarter of patients the diagnosis can be made clinically based on these three features[13]. Such a model can withhold one out of five patients from additional imaging to diagnose diverticular disease[14]. In patients without these features, imaging is required to reach adequate diagnostic accuracy.

Ultrasound and Computed Tomography (CT) scanning are daily practice in patients suspected for diverticulitis to assess alternative diagnosis or confirm the diagnosis and differentiate between complicated and non-complicated diverticular disease.

Ultrasound has an important role in diagnosing diverticulitis due to its wide-spread availability, low cost and possibility to be repeated as often as needed. It is the first choice diagnostic in many patients, in particular patients with renal insufficiency, pregnancy and contrast allergy. The limitations of ultrasound include operator dependency, poor assessment in obese patients and reduced outcome with patients with abdominal tenderness because compression of the transducer probe is too painful. CT scanning has higher accuracy in detection of free air and deeply located or small fluid collections and can help differentiate diverticulitis from colon carcinoma. An important difference between these two imaging modalities is that ultrasound does not require ionizing radiation or the application of oral, rectal or intravenous contrast. Considering that patients with diverticulitis are prone to recurrence they may need multiple CT examinations with increased risk of radiation exposure.

Considering all of the arguments a step-up approach is advised starting with ultrasound and only performing CT scanning when the ultrasound is inconclusive, negative for diverticulitis or suspected for complicated disease.

Currently the most used classification system for diverticular disease is the modified Hinchey classification, which is based on intra-operative findings. This classification is no longer suitable for clinical practice because only a minority of patients with diverticular disease will be treated operatively.

A new classification system for diverticulitis should focus on different types of presentation and radiological findings. Perhaps diagnostic laparoscopy should be more liberally implemented in the diagnostic step-up approach to differentiate between purulent and faecal peritonitis. Such a new grading system can help to tailor treatment in patients with diverticular disease.

Parallel to the reduced invasive diagnostic evaluation of diverticular disease treatment has become less aggressive too. Decades ago peritonitis required explorative laparotomy regardless of cause and severity of the disease. With recent improvement of medical, radiological and surgical treatment the management can be more tailor made and many patients can be treated conservatively.

It is now recommended to omit antibiotics in CT proven diverticulitis with small abscess formation (<5cm)[16,17]. Furthermore patients are encouraged to continue oral intake

when tolerated and ambulatory treatment of these patients seems safe and effective. Avoidance of overtreatment has many benefits: cost reduction, diminished development of antimicrobial resistance and increased quality of life for the patient.

Another dogma has been challenged recently: pneumoperitoneum associated with acute diverticulitis is no longer an indication for emergency surgery in hemodynamically stable patients[18-20]. In carefully selected patients a non-operative treatment (including antibiotics, supportive care and radiological drainage of fluid collections) can be applied without increased complication rate. In these studies distant free air on CT-scan was not associated with poor outcome, and therefore is not per se an indication for surgery. However the evidence on non-surgical management of perforated diverticulitis is scarce and further research is required to demonstrate its safety. Perhaps a next trial should not focus on comparing operative techniques in purulent diverticulitis, but rather computed tomography, antibiotics, and watchful waiting compared with surgical intervention.

Of all patients with an episode of acute diverticulitis 25% present with complicated disease such as abscess formation, fistula, obstruction or perforated disease. In these patients Hartmann's procedure and primary anastomosis with defunctioning stoma are historically the most accepted treatments. Both treatments can safely and effectively be performed laparoscopically[21,22]. Primary anastomosis seems to be preferred over Hartmann's procedure because the last is associated with increased morbidity during the second stage (anastomotic leaks), longer hospital stay and longer follow-up with stoma[23,24]. However no definite conclusions on the preferred treatment can be drawn because previous randomised trials comparing these procedures are characterised by difficult accrual and preliminary termination of the trials[23-25].

With increasing laparoscopic experience a new treatment method has been proposed for patients with perforated purulent diverticulitis: laparoscopic lavage and drainage. Four randomised trial were conducted to investigate the safety and efficacy of laparoscopic lavage[26-29]. Three trials have been published until now with similar results[30-33].

The LOLA part of the Dutch LADIES trial was prematurely terminated after accrual of 90 patients due to increased re-intervention rate in patients treated with laparoscopic lavage[30]. The high re-intervention rate could be because radiological drainage of intra-abdominal abscesses was defined as re-intervention in this trial but not in the other trials. Persistent sepsis in the lavage group demanding surgical intervention was present in nine patients and was caused by faecal peritonitis and overt perforation in six patients. This demonstrates that laparoscopic lavage can only safely be performed in patients with true purulent peritonitis in the absence of visible perforation. After 12 months there was no difference in mortality (lavage 9% versus sigmoidectomy 14%) and morbidity. The number

of patients that were alive and stoma free was higher in those treated by laparoscopic lavage (78%) compared to those in the sigmoidectomy group (71%). The majority of patients in the lavage group never had a stoma. Stoma reversal was not without risks and morbidity occurred in four out of 24 patients.

The study was marked by a slow inclusion and a high number of patients not enrolled in the study although they met the inclusion criteria.

Similar results were found in the SCANDIV trial comparing lavage with primary resection in 172 patients with Hinchey I to IV diverticulitis[31]. Patients with peroperative diagnosis of Hinchey IV were treated with sigmoidectomy. After 90 days there was no difference between the treatment groups in severe morbidity rate (31% lavage versus 22% sigmoidectomy) and mortality rates (13% versus 8%). Re-intervention was performed in more patients following laparoscopic lavage than after primary resection (20% versus 6%). Furthermore abscess formation and secondary peritonitis occurred more frequently in the laparoscopic lavage group.

There are a number of pitfalls in the trial design of the SCANDIV trial. One pitfall is the fact that the technique of primary resection, Hartmann's procedure or primary resection and anastomosis, was determined by the surgeons preference. Furthermore results of the two surgical techniques were not reported separately therefore no conclusions can be made with regard to the preferred technique. Additionally due to randomization prior to diagnostic lavage in this trial a variety of possible biases can be identified. Firstly, due to the high number of alternative diagnosis made during surgical treatment a large amount of patients were excluded. The authors resolved this by increasing sample size during the trial with accompanying possible bias. Secondly, patients with Hinchey grade I and II were included in the trial although laparoscopic lavage has not been designed for these patients. Data on treatment of Hinchey III diverticulitis was taken together with Hinchey I and II and therefore cannot be discriminated. Finally the patients not included in the trial were found to have a higher ASA score and therefore results might not be applicable to very ill patients with acute complicated diverticulitis.

The Scandinavian DILALA trial included 83 patients and randomised between laparoscopic lavage and Hartmann's procedure[32,33]. Results showed no difference in mortality which was 8% in the group treated with laparoscopic lavage and 11% in the patients in the Hartmann's procedure group after 90 days. After 3 months morbidity and re-operation rates were comparable. After a follow-up of 12 months laparoscopic lavage resulted in less reoperations, reduced length of hospital stay (median six versus nine days) and lower incidence of a stoma (7% versus 28%).

However on the eligible but not included patients (52 patients) baseline characteristics are missing therefore selection bias and homogeneity of the groups cannot be assessed. Comparison of the outcome of the different studies is therefore difficult.

Results of the LAPLAND trial are still awaited. This trial will also randomise patients before diagnostic laparoscopy which might result in the inclusion of patients with other diagnosis.

Despite the three finished trial studying laparoscopic lavage as treatment of perforated diverticulitis the available evidence is still not very robust. However this alternative operative strategy seems to control abdominal sepsis with decreased stoma rates and mortality rates comparable to sigmoidectomy.

Important drawback of laparoscopic lavage is the risk that possible undiagnosed colorectal cancer remains in situ. In the three published trials incidence of carcinoma varied between five and eight percent. Delayed diagnosis of colon carcinoma could lead to increased risk of metastasis and decreased survival.

Long term results and pooling of original data of the trials will help us to determine if laparoscopic lavage is a safe and effective treatment for perforated diverticulitis. In addition the dilemma might be solved whether it can be used as a definitive treatment or should be considered a bridge to elective resection of the diseased bowel.

For years it was recommended to perform elective sigmoid resection after two episodes of acute diverticulitis and even after one episode in younger patients. However recurrent diverticulitis rarely progresses to complicated disease and the risk of free perforation decreases with the number of diverticulitis episodes. In papers on laparoscopic lavage only two percent of patients who did not undergo elective colectomy had recurrence of diverticulitis[18,34]. Elective colonic resection after two episodes of diverticulitis is therefore no longer the standard[35]. However elective colectomy might be justified in patients with persisting abdominal complaints following an episode of diverticulitis or high-risk patients for perforated disease, such as patients who use immunosuppression therapy, with chronic renal failure or collagen-vascular diseases.

TREATMENT OF COMPLICATIONS FOLLOWING INTRA-ABDOMINAL INFECTION

Incisional hernia is one of the most frequent postoperative complications following abdominal surgery[36-38]. The incidence is influenced by incision site, closure technique of the abdominal wall, and patient characteristics, such as obesity and collagen disease. Symptoms of incisional hernia vary from low body image, pain, strangulation and

incarceration of intra-abdominal organs to mortality[39-41]. Incisional hernia repair is one of the most performed surgeries for postoperative complications, with associated high costs.

In this thesis we investigated various meshes in a rat model to find the most appropriate mesh to implant intraperitoneally in non-contaminated and contaminated environment.

Many studies on mesh augmentation of the abdominal wall are annually published. Models to investigate hernia repair are mostly performed in animals of the same age and sex, and specified pathogen-free bacterial status. This minimizes biological and microbiological variability, making it suitable for comparing characteristics of different meshes in a similar contaminated environment[42]. To mimic contamination of the peritoneal cavity in humans and study the behaviour of meshes experimentally the caecal ligation puncture (CLP) model can be used. In this model, as in clinical infections, peritonitis arises from a complex interaction of the immune system with inflammatory, haemodynamic and biochemical alterations similar to human sepsis, with a consistent increase in cytokine levels[42-45].

If a mesh is used in a contaminated environment, consensus exists that a biological collagen mesh or a synthetic macroporous, monofilament mesh may be advantageous[46]. The results of the animal experiments in Chapters 8, 9 and 10 of this thesis question this consensus[47,48]. In these experiments incorporation of biological meshes was poor after 180 days. Premature weakening of the biomechanical properties of the scaffold combined with insufficient incorporation can possibly result in loss of the prosthesis and hernia recurrence[49]. However, implantation of biological prostheses could be a valid choice as a temporary measure in staged repair of the abdominal wall.

An advantage of biological meshes over synthetic material might be the possibility of performing aggressive salvage procedures with removing only parts of an infected mesh. As a result removal of all material will subsequently cause recurrence of hernia. Until evidence is provided that biological meshes retain biomechanical strength with acceptable infectious complications synthetic meshes remain the preferred mesh material for (non-contaminated) primary hernia repair.

High costs of a biological mesh might be justified when it prevents mesh infection which is associated with high expenses for intensive care treatment, reoperation, and prolonged hospital stay. However in our experiments with crosslinked biological meshes infectious complications were unacceptably high in contaminated and non-contaminated environment.

Strict contraindication of synthetic mesh implantation in contaminated environment becomes questionable. In accordance with our results in Chapter 8 some synthetic meshes have quite favorable results after implantation in clean-contaminated and contaminated surgical fields[47,50-53]. A recent study in grade II contaminated wounds showed a lower hernia recurrence rate after implantation of synthetic meshes compared to biological meshes[54]. Although there are no meshes without disadvantages certain permanent synthetic meshes might be somewhat more infection-resistant and therefore useful for permanent hernia repair in a contaminated environment.

It is a recurrent phenomenon in research that initial reports (whether or not industry driven) on new technologies describe positive results and subsequently critical reviews are published only after years of trial and error. The perfect mesh is still to be developed. We propose independent laboratories, directed by scientific societies such as the European Hernia Society, in which new mesh-material is tested in standard conditions with respect to flexibility, pore size, adhesion formation, incorporation and infectious complications. Only after obtaining a quality mark by one of these independent laboratories producers should be permitted to implant the new product in patients.

Additionally all patients with an abdominal wall repair should be registered in a prospective database, such as EuraHS and HerniaMed. In these registries data is collected on patient characteristics, comorbidities, surgical techniques, mesh characteristics, short- and long-term postoperative complications, recurrence rates and patients quality of life. This data might help surgeons to choose the right mesh material and surgical techniques to perform sustainable hernia repair with little complications. Another advantage of prospective databases is that surgeons can learn from colleagues who report low recurrence rates and little complications. By comparing surgical techniques and postoperative care excellence can be striven for.

Additionally, quality of care and cost reduction of complex abdominal wall hernia repair can be increased by centralization of care to experienced centres with high volume care.

Intraperitoneal adhesion formation is another common postoperative complication following abdominal surgery. These adhesions cause a continuing risk for bowel obstruction, chronic pain, infertility and inadvertent bowel injuries at future operations. Awareness of adhesion formation is low and the related morbidity underestimated by general surgeons and gynaecologists[55,56]. To increase awareness and change clinical practice, the work of the Dutch Adhesion Group will have to be continued.

Surgical treatment of adhesions induce formation of new adhesions, so prevention is the key to this clinical problem[57,58]. Prevention can be accomplished by systemic acting

pharmacological agents or intraperitoneally applied barriers. Ideally these agents should influence the balance between fibrinogenesis and fibrinolysis without increasing serious adverse events such as gastro-intestinal anastomotic leakage.

Systemically administered agents have been tried extensively but were abandoned due to disappointing results in clinical trials[59]. Promising results have been found in preclinical studies with the use of Cromolyn (publication number EP2638904A1, application number EP20120159348). This drug has been used for decades in the prevention of asthmatic attacks. The suppression of the immune system is thought to limit intraperitoneal adhesion formation. A clinical trial is essential to confirm the preclinical results and monitor for possible complications.

Intraperitoneally applied barriers have demonstrated that their use reduce adhesion formation[59,60]. However, clinicians are still reluctant to use these agents because they fear serious adverse effects and question cost-effectiveness. The results of the study presented in Chapter 11 on cross-linked polyvinyl alcohol and carboxymethylcellulose are promising on the prevention of adhesions in contaminated environment[61]. However more research should be performed to investigate potential infectious complications and negative effects on anastomotic healing.

CONCLUSIONS

New approaches of the surgical treatment of intra-abdominal infection have been addressed in this thesis. New evidence has been delivered with respect to the treatment of diverticulitis, complications following mesh repair of the abdominal wall and prevention of adhesion formation. To improve knowledge on treatment of intra-abdominal infection and its complications we strongly need collaboration of experimental laboratories, standardization of techniques and prospective databases.

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CHAPTER

Summary

This thesis focussed on intra-abdominal infection, its treatment and complications following treatment of intra-abdominal infections.

In **Chapter 2** the accuracy of preoperative staging of perforated diverticulitis with computed tomography (CT) scanning was assessed in a retrospective study. The CT findings were compared with the clinical findings during surgery and classified according to the Hinchey classification. This study showed that the positive predictive value of preoperative CT scanning for different stages of diverticulitis ranged from 45 to 89%. Accuracy was between 71 and 92%. There was a clear understaging of disease in patients with Hinchey 3 diverticulitis, 42% of patients were falsely classified as Hinchey 1 or 2. The presence of a large amount of free intra-abdominal air and fluid was strongly associated with Hinchey 3 and 4.

Therefore, we concluded that current CT scanning does not seem to suffice to accurately predict the severity of perforated diverticulitis according to Hinchey's classification. A new scoring system is needed to guide treatment in patients with diverticulitis.

In **Chapter 3** an overview of treatment options for perforated diverticulitis was given. Historically the most performed surgical treatment is sigmoidectomy with subsequent colostomy, also referred to as Hartmann's procedure. However, this treatment strategy leads to high rates of permanent colostomies. Improvements in intensive care medicine and surgical technique has led to an increased number of patients treated with primary anastomosis instead of colostomy. Due to fear of anastomotic leakage this treatment is reserved mostly for young and healthy patients without faecal peritonitis. In this group of patients with purulent peritonitis, laparoscopic lavage of the abdomen with drainage could be an alternative treatment strategy.

In **Chapter 4** a retrospective study on the early experience with laparoscopic lavage in patients with purulent peritonitis was presented. Laparoscopic treatment was successfully performed in the majority of patients, conversion to laparotomy was performed in 3%. Laparoscopic lavage was associated with 32% morbidity, and a fast recovery if sepsis was successfully controlled which occurred in 81.5% of patients. Patients in whom lavage was unsuccessful tended to have more co-morbidities, a higher preoperative C-reactive protein concentration and a higher Mannheim Peritonitis Index. After successful laparoscopic lavage treatment 10% of patients required subsequent sigmoid resection for recurrent diverticulitis during follow-up. Treatment strategy for perforated diverticulitis with laparoscopic lavage was feasible in the majority of patients, but identification of an overt sigmoid perforation and patient selection are of critical importance for successful treatment.

In **Chapter 5** the protocol of a large randomized multicenter trial on the treatment of perforated diverticulitis was presented, the LADIES trial. This trial investigated the morbidity and mortality in patients with purulent and faecal generalised peritonitis following the three operative strategies; laparoscopic lavage and drainage, sigmoidectomy with primary anastomosis and Hartmann's procedure.

It was a five armed trial: patients with purulent peritonitis were randomised 2:1:1 to laparoscopic lavage, Hartmann's procedure or sigmoid resection with primary anastomosis. The aim of the LOLA trial was to show that laparoscopic lavage would lead to a 15% reduction in major morbidity and mortality compared to sigmoid resection. Patients with faecal peritonitis were to be randomised 1:1 into Hartmann's procedure or sigmoid resection with primary anastomosis. All patients who underwent sigmoid resection (both purulent and faecal peritonitis) were to be analysed in the DIVA trial. This analysis aimed to prove that Hartmann's procedure and sigmoid resection with primary anastomosis would lead to an equal 12 months mortality rate, yet sigmoid resection with primary anastomosis would lead to a 30% higher stoma-free survival.

In **Chapter 6** we discussed the results of the LOLA arm of the LADIES trial. The main conclusion was that laparoscopic peritoneal lavage for purulent perforated diverticulitis does not reduce major morbidity and mortality compared to sigmoidectomy at 12 months follow-up. An increased acute reintervention rate was found in patients after laparoscopic lavage (39%) compared to sigmoidectomy (19%). However 76% of patients did not need further surgery during primary hospital stay. There was no difference between the treatment groups in stoma free rates in surviving patients after 12 months (78% lavage group, 71% sigmoidectomy groups), but in the lavage group 74% never had a stoma.

In **Chapter 7** an overview of the available evidence combined with expert opinion was presented in a guideline for diagnosis and treatment of diverticulitis. The guideline was written under the auspices of the Netherlands Society of Surgery. The working group consisted of four surgeons, a gastroenterologist, a radiologist, an internist, a dietician and an epidemiologist and statistician. The evidence on treatment on some parts of diverticular disease is still scarce, leading to treatment strategies mainly being guided by the doctors personal preference. Although younger patients have a higher risk of recurrent disease there is not an increased risk of complications compared to older patients.

The triad of pain in the lower left abdomen on physical examination, the absence of vomiting and a C-reactive protein >50 mg/l has a high predictive value to diagnose acute colonic diverticulitis. If this triad is present and there are no signs of complicated disease, patients may be withheld from further imaging. If imaging is indicated, ultrasound is the first modality of choice. Only after a negative or inconclusive ultrasound CT scan is advised.

The optimal treatment strategy depends on the degree of peritonitis. In general, patients with Hinchey 1 and 2 diverticulitis can be treated conservatively with fluids, analgesics, and antibiotics, with or without percutaneous drainage of abscesses. There is no indication for routine endoscopic examination after an episode of uncomplicated diverticulitis.

There is no evidence for the routine administration of antibiotics in patients with clinically mild uncomplicated diverticulitis. Pericolic or pelvic abscesses can initially be treated with antibiotic therapy or combined with percutaneous drainage. If conservative treatment fails, emergency surgical intervention is indicated, in which resection with primary anastomosis is preferred above Hartmann's procedure. The performance of a diverting loop-ileostomy to protect the anastomosis should be considered, especially in patients with a number of comorbidity factors.

In the last decades non-resectional treatment with laparoscopic lavage has increased in popularity for treating Hinchey 3 diverticulitis. Initial results showed morbidity and mortality rates <5%. The results of randomised controlled trials comparing laparoscopic lavage with resectional strategies were not included in this guideline because the trials were still recruiting patients.

In **Chapter 8** a rat model in a contaminated environment was presented. In 144 rats we compared seven intraperitoneally placed meshes on infectious complications, adhesion formation, incorporation and shrinkage after a follow-up of 28 or 90 days. Significantly more mesh infections were found after implantation of C-Qur (94%) and Dualmesh (47%). Sepramesh showed a significant increase in adhesion coverage from 12.5% at 28 days to 60% at 90 days. At 90 days there was no difference in adhesion formation between the synthetic meshes (35-73%). After 90 days the adhesion coverage of the biological Strattice mesh was 5%, and incorporation (13%) was significantly poorer than for other meshes. Dualmesh showed shrinkage of 63% after 90 days.

This experimental results of synthetic mesh implantation in a contaminated environment make strict contraindication in humans questionable. Although there are no meshes without disadvantages, certain synthetic meshes might be somewhat more infection-resistant and therefore useful for permanent hernia repair in a contaminated environment.

In **Chapter 9** infectious complications and functional outcome of four biological meshes were investigated in 90 rats. Meshes were implanted in a contaminated environment and outcomes were measured after 90 or 180 days. More mesh infections occurred in crosslinked meshes compared with non-crosslinked meshes (70% vs 4%). Incorporation into the abdominal wall was poor in all meshes ranging from 0% to 39%. After 180 days no residue of non-crosslinked Surgisis mesh was found. After 180 days, shrinkage was

0.8% in crosslinked Permacol and 20% in non-crosslinked Strattice. Strattice showed the least adhesion formation (5%).

In conclusion, this experiment demonstrates a high infection rate and increased adhesion formation of crosslinked biological meshes. Resistance to infection of non-crosslinked Strattice could allow implantation in the contaminated environment. However, the poor incorporation of all biological meshes and complete degradation of Surgisis makes long-term biomechanical strength of hernia repair questionable. Implantation of biological prostheses could be a valid choice in staged contaminated abdominal wall repair. The high costs of a biological mesh can be justified by prevention of mesh infection which is associated with high costs for intensive care treatment, reoperation, and prolonged hospital stay.

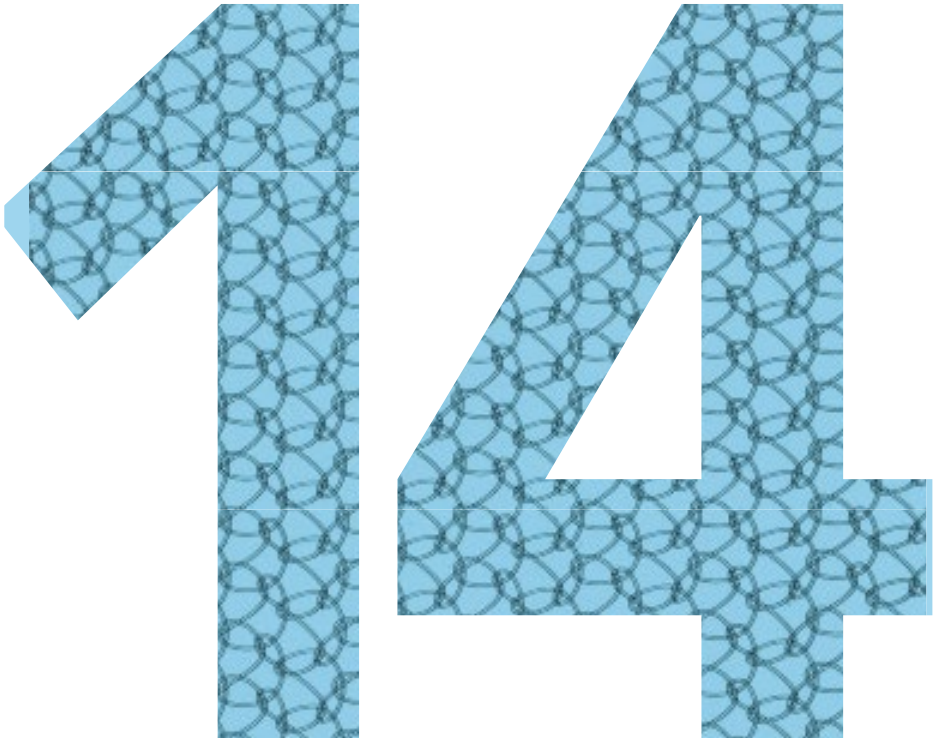
In **Chapter 10** four biological meshes implanted in a non-contaminated environment were compared after 90 or 180 days. In 64 rats infectious complications, incorporation, shrinkage and adhesion formation were investigated. High numbers of infectious complications were observed: 13% transcutaneous prosthesis migration and 23% macroscopic mesh infection. Incorporation of meshes was poor (0% to 37%) after 180 days. Shrinkage did not differ between the meshes after 180 days. After 90 days Surgisis had the highest adhesion score (90%). Adhesions covering the mesh was least in Strattice (5%).

We advocate more caution with implantation of biological meshes for abdominal wall repair. There seems to be no evidence for previously purported hypothesis that biological material enables ingrowth of cells and vessels resulting in a sustainable hernia repair. Implantation of biological mesh does not seem to reduce infection rate which is a significant riskfactor for the recurrence of incisional hernia. Biological meshes might not have the required characteristics for implantation in clean environment with high infection rate and low incorporation of the mesh in the current experiment.

In **Chapter 11** the influence of a new adhesion barrier on adhesion formation was investigated in a peritonitis rat model in 40 rats. Application of the anti-adhesive barrier, polyvinyl alcohol and carboxymethylcellulose hydrogel, resulted in fewer adhesions than in the control group. Additionally the tenacity of the adhesions was lower when the barrier was applied. There was no difference in amount and size of intra-abdominal abscesses between the study groups.

Polyvinyl alcohol and carboxymethylcellulose hydrogel demonstrated promising efficacy in this experiment. Therefore further investigation of this product is needed focusing on its safety when applied around an intestinal anastomosis and in the presence of synthetic material such as intra-abdominally placed meshes.

CHAPTER



Samenvatting

Dit proefschrift richt zich op de behandeling van intra-abdominale infecties en complicaties volgend op de behandeling van intra-abdominale infecties.

In **Hoofdstuk 2** onderzochten wij de waarde van preoperatieve stadiering van geperforeerde diverticultis door middel van Computertomographie (CT) scan in een retrospectieve studie. De CT bevindingen werden vergeleken met de peroperatieve bevindingen en geclassificeerd volgens de Hinchey classificatie. De studie laat zien dat de positief voorspellende waarde van de preoperatieve CT scan varieerde tussen de 45 en 89% voor verschillende stadia van diverticulitis. De diagnostische accuraatheid varieerde tussen de 71 en 92%. Er was een duidelijke onderstadiëring bij patiënten met Hinchey 3 diverticulitis, 42% van de patiënten werden onjuist geclassificeerd als Hinchey 1 of 2. De aanwezigheid van een grote hoeveelheid vrij lucht en vocht intra-abdominaal was sterk geassocieerd met Hinchey 3 en 4.

Daarom concluderen wij dat de huidige CT scans niet voldoen om de ernst van geperforeerde diverticulitis volgens de Hinchey classificatie te voorspellen. Een nieuw gradatie systeem is nodig om richting te geven aan de behandeling van patiënten met diverticulitis.

In **Hoofdstuk 3** werd een overzicht gegeven van behandelopties voor geperforeerde diverticulitis. Historisch gezien is de meest uitgevoerde chirurgische behandeling de sigmoidresectie met aanleg eindstandig colostoma, ook wel de Hartmann procedure genoemd. Echter, deze behandeling leidt tot hoge percentages permanente stoma´s. Verbetering in de intensive care behandeling en chirurgische technieken hebben geleid tot een toenemend aantal patiënten die behandeld worden met primaire anastomose in plaats van een colostoma. Door angst voor lekkage van de anastomose wordt deze behandeling voornamelijk uitgevoerd bij jonge en gezonde patiënten zonder fecale peritonitis. In deze groep patiënten met purulente perionitis zou laparoscopische lavage van het abdomen met drainage een alternatieve behandelstrategie kunnen zijn.

In **Hoofdstuk 4** worden de resultaten van een retrospectieve studie over de eerste resultaten met laparoscopische lavage bij patiënten met purulente diverticulitis gepresenteerd. Laparoscopische behandeling werd succesvol uitgevoerd in de meerderheid van de patiënten, conversie naar laparotomie was in 3% noodzakelijk. Laparoscopische lavage was geassocieerd met een morbiditeit van 32%, en een snel herstel als de sepsis succesvol werd gecontroleerd wat het geval was bij 81,5% van de patiënten. Patiënten bij wie lavage niet succesvol was hadden meer comorbiditeiten, aan hogere preoperatieve C-reactief proteine concentratie en een hogere Mannheim Peritonitis Index. Na succesvolle laparoscopische lavage ondergingen 10% van de patiënten een sigmoid resectie vanwege recidief diverticulitis tijdens de follow-up periode. Operatieve behandeling voor geperforeerde diverticulitis door middel van laparoscopische lavage was mogelijk in de

meerderheid van de patiënten, maar identificatie van duidelijke sigmoid perforatie en patiënt selectie zijn van cruciaal belang voor een succesvolle behandeling.

In **Hoofdstuk 5** werd het protocol gepresenteerd van een grote gerandomiseerde multicenter trial naar de behandeling van geperforeerde diverticulitis, de LADIES trial. Deze trial onderzocht de morbiditeit en mortaliteit in patiënten met purulente en fecale gegeneraliseerde peritonitis na behandeling door 3 operatieve strategiën: laparoscopische lavage en drainage, sigmoidresectie met primaire anastomose en de Hartmann procedure.

Het was een 5-armige trial: patiënten met purulente peritonitis werden 2:1:1 gerandomiseerd voor laparoscopische lavage, Hartmann procedure of sigmoidresectie met primaire anastomose. Het doel van de LOLA trial was aantonen dat laparoscopische lavage zou leiden tot een reductie van 15% in ernstige morbiditeit en mortaliteit vergeleken met sigmoid resectie. Patiënten met fecale peritonitis werden 1:1 gerandomiseerd tusssen Hartmann procedure en sigmoid resectie met primaire anastomose. Alle patiënten die een sigmoid resectie ondergingen (zowel purulente als fecale peritonitis) werden geanalyseerd in de DIVA trial. Deze analyse had als doel bewijzen dat Hartmann procedure en sigmoidresectie met anastomose zouden leiden tot een gelijke mortaliteit na 12 maanden, maar een 30% hogere stoma vrije overleving voor de patiënten behandeld met een sigmoid resectie met primaire anastomose.

In **Hoofdstuk 6** bediscussierden we de resultaten van de LOLA arm van de LADIES trial. De belangrijkste conclusie was dat laparoscopische lavage voor purulente diverticulitis de ernstige morbiditeit en mortaliteit niet verminderde in vergelijking met sigmoidresectie na 12 maanden follow-up. Een hogere re-interventie percentage werd gevonden in patiënten na laparoscopische lavage (39%) vergeleken met sigmoidresectie (19%). Echter, 76% van de patiënten behoefde geen verdere chirurgische interventie tijdens hun primaire ziekenhuisopname. Er was geen verschil in behandel groepen wat betreft stoma vrije overleving in de levende patiënten na 12 maanden (78% lavage groep, 71% sigmoidectomie groepen), maar in de lavage groep had 74% nooit een stoma gehad.

In **Hoofdstuk 7** werd een overzicht gepresenteerd met het beschikbare wetenschappelijke bewijs gecombineerd met expert mening in een richtlijn voor diagnose en behandeling van diverticulitis. De richtlijn werd geschreven onder leiding van de Nederlandse Vereniging voor Heelkunde. De werkgroep bestond uit vier chirurgen, een MDL arts, een radioloog, een internist, een diëtist en een epidemioloog en statitiscus. Het wetenschappelijke bewijs voor behandeling van sommige delen van diverticulitis is nog steeds spaarzaam, hierdoor wordt behandeling vooral beinvloed door de persoonlijke voorkeur van de dokter. Jongere patiënten hebben een hoger risico of terugkeer van klachten, maar geen hoger risico op complicaties dan oudere patiënten.

Aanwezigheid van pijn links onder in de buik bij lichamelijk onderzoek, de afwezigheid van braken en een C-reactive protein > 50 mg/ml heeft een hoge voorspellende waarde bij de diagnose van acute diverticulitis van het colon. Als deze 3 onderdelen samen aanwezig zijn en er zijn geen aanwijzingen voor gecompliceerde ziekte kan bij deze patiënten verder afbeeldend onderzoek achterwegen gelaten worden. Als afbeeldend onderzoek geindiceerd is, is echografie de modaliteit van eerste keus. Alleen na een negatieve of inconclusieve echo wordt een CT-scan geadviseerd.

De optimale behandelstrategie is afhankelijk van de ernst van de peritonitis. In het algemeen kunnen patiënten met Hinchey 1 en 2 diverticulitis conservatief behandeld worden met toediening van intraveneuze vloeistof, pijnstilling en soms antibiotica met of zonder percutane drainage van abcessen. Er is geen indicatie voor routine endoscopisch onderzoek na een episode van ongecompliceerde diverticulitis.

Er is geen bewijs voor routine toediening van antibiotica in patienten met klinisch mild verlopende ongecompliceerde diverticulitis. Abcessen pericolisch of in het kleine bekken kunnen initieel behandeld worden met antibiotische therapie of gecombineerd worden met percutane drainage. Als conservatieve therapie faalt is chirurgische spoed interventie geïndiceerd, waarbij resectie met primaire anastomose te prefereren is boven Hartmann's procedure. De aanleg van een deviërend loop-ileostoma om de anastomose te beschermen moet overwogen worden, met name in patiënten met meerdere comorbiditeiten.

In de laatste decaden is behandeling zonder resectie middels laparoscopische lavage populairder geworden voor behandeling van Hinchey 3 diverticulitis. Initiële resultaten toonden morbiditeit en mortaliteits percentages van minder dan 5%. De resultaten van gerandomiseerde klinische trials waarin laparoscopische lavage wordt vergeleken met resectie waren niet meegenomen in deze richtlijn omdat de trials niet waren afgerond en nog patiënten includeerden.

In **Hoofdstuk 8** werd een diermodel in een gecontamineerde omgeving gepresenteerd. In 144 ratten vergeleken we zeven intraperitoneaal geplaatste meshes op infectieuze complicaties, adhesie vorming, ingroei en krimp na een follow-up van 28 of 90 dagen. Significant meer mesh infecties werden gevonden na implantatie van C-Qur (94%) en Dualmesh (47%). Sepramesh toonde een significante toename in bedekking van de mesh met adhesies van 12.5% na 28 dagen naar 60% na 90 dagen. Na 90 dagen was er geen verschil in adhesie vorming tussen de synthetische meshes (35-73%). Na 90 dagen was de bedekking van de mesh van de biologische Strattice mesh slechts 5%, maar ingroei (13%) was significant slechter dan andere meshes. Dualmesh toonde krimp van 63% na 90 dagen.

Deze experimentele resultaten van synthetische mesh implantatie in gecontamineerde omgeving maken strikte contra-indicatie in mensen discutabel. Ondanks dat er geen meshes bestaan zonder nadelen, zekere synthetische meshes zijn mogelijk meer infectie-resistent dan anderen en daarom nuttig bij gebruik van permanent hernia herstel in gecontamineerde omgeving.

In **Hoofdstuk 9** werden infectieuze complicaties en functionele uitkomsten van vier biologische meshes onderzocht in 90 ratten. Meshes werden geïmplanteerd in gecontamineerde omgeving en uitkomsten werden gemeten na 90 of 180 dagen. Er kwamen meer mesh infecties voor in crosslinked meshes in vergelijking met non-crosslinked meshes (70% vs 4%). Ingroei in de buikwand was slecht in alle meshes variërend van 0% tot 39%. Na 180 dagen kon geen residue worden aangetoond van non-crosslinked Surgisis mesh. Na 180 dagen was krimp 0.8% in crosslinked Permacol en 20% in non-crosslinked Strattice. Strattice had de minste adhesie formatie (5%).

Concluderend heeft dit experiment hoge infectie percentages en toegenomen adhesie vorming aangetoond in crosslinked biologische meshes. Weerstand tegen infectie zou implantatie van non-crosslinked Strattice mogelijk maken in gecontamineerde omgeving. Echter, de slechte ingroei van alle biologische meshes en complete verdwijning van Surgisis maken lange termijn biomechanische kracht van hernia herstel twijfelachtig. Implantatie van biologische protheses kunnen een goede keus zijn bij gecontamineerd buikwandherstel in meerdere fasen. De hoge kosten van een biologische mesh kunnen worden gerechtvaardigd door preventie van mesh infectie wat is geassocieerd met hoge kosten voor intensive care behandeling, reoperatie en verlengde opnameduur.

In **Hoofdstuk 10** werden vier biologische meshes geïmplanteerd in niet-gecontamineerde omgeving en vergeleken na 90 of 180 dagen. In 64 ratten werden infectieuze complicaties, ingroei, krimp en adhesie vorming onderzocht. Er werden veel infectieuze complicaties aangetoond: 13% transcutane migratie van de prothese en 23% macroscopisch mesh infectie. Ingroei van de meshes was slecht (0% tot 37%) na 180 dagen. Krimp was niet verschillend tussen de meshes na 180 dagen. Na 90 dagen had Surgisis de hoogste adhesie score (90%). Strattice had de minste adhesies die de mesh bedekten (5%).

We pleiten voor meer terughoudendheid bij implantatie van biologische meshes voor buikwand herstel. Er lijkt geen bewijs te zijn voor eerder geopperde hypotheses dat biologisch materiaal ingroei van cellen en bloedvaten mogelijk maakt leidend tot een duurzaam hernia herstel. Implantatie van biologische mesh reduceerd het infectie percentage niet wat een significante risicofactor is voor terugkeer van de buikwandbreuk. Biologische meshes bezitten mogelijk niet de benodigde karakteristieken voor implantatie in schone omgeving gezien het hoge infectie percentage en weinig ingroei van de mesh in het huidige experiment.

In **Hoofdstuk 11** onderzochten we de invloed van een nieuwe adhesie barrière op adhesie vorming in een peritonitis rat model in 40 ratten. Aanbrengen van de anti-adhesie barrière, polyvinyl alcohol en carboxymethylcellulose hydrogel, resulteerde in minder adhesies dan in de controle groep. Daarbij was de sterkte van de adhesies minder wanneer de barrière gel was aangebracht. Er was geen verschil in aantal en grootte van intra-abdominale abcessen tussen de studie groepen.

Polyvinyl alcohol en carboxymethylcellulose hydrogel toonde veelbelovende effectiviteit in dit experiment. Daarom is verder onderzoek van dit product nodig met aandacht voor de veiligheid bij aanbrenging rondom een intestinale anastomose en in de aanwezigheid van synthetisch materiaal zoals intra-abdominaal geplaatste meshes.

CHAPTER

List of Publications
Curriculum Vitae
PhD Portfolio
Dankwoord

LIST OF PUBLICATIONS

Ladies Trial: laparoscopic peritoneal lavage or resection for purulent peritonitis and Hartmann's procedure or resection with anastomosis for purulent or faecal peritonitis in perforated diverticulitis.
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*Gastrointestinal bleeding (*2012). Ed. JJY Sung, ISBN 9781405195553, Wiley-Blackwell

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Submitted

Biomaterial-specific inflammatory cell responses in a contaminated environment in vivo in rats.
N Grotenhuis, EB Deerenberg, **IM Mulder**, N Kops, GJVM Van Osch, YM Bastiaansen-Jenniskens, JF Lange.
Submitted

CURRICULUM VITAE

Irene Maria Mulder werd op 14 Augustus 1984 geboren in Nieuwland. In 2002 begon zij met haar studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Tijdens haar studie ging zij 4 weken naar Finland voor keuzeonderwijs (Intensive care geneeskunde) aan de Univeristy Hospital of Turku. Voor haar keuzeonderzoek ging zij 7 maanden naar het Westmead's Childrens Hospital in Sydney, Australië (Pediatric Intensive care). In mei 2009 behaalde zij haar artsdiploma en en begon als arts-assistent chirurgie in het Tweesteden ziekenhuis in Tilburg (opleider dr. S. Kranendonk).

In maart 2010 startte zij als arts-onderzoeker in het Erasmus Medisch Centrum met de coördinatie van de Ladies trial onder begeleiding van professor J.F. Lange en professor W.A. Bemelman. De onderzoeken naar de optimale behandeling van diverticulitis en complicaties na abdominale infectie uitgevoerd tijdens deze periode hebben geleid tot dit proefschrift. Na haar tijd als fulltime onderzoeker heeft zij een jaar als arts-assistent chirurgie gewerkt in het Slotervaart Ziekenhuis in Amsterdam (opleider dr. B.J. Dwars). Daarna is zij januari 2014 begonnen aan haar opleiding tot chirurg in het Rode Kruis ziekenhuis in Beverwijk (opleiders dr. H.A. Cense en professor D.L. van der Peet).

PHD PORTFOLIO

Name PhD student:	I.M. Mulder	PhD period:	2010 – 2016
Erasmus MC Department:	Surgery	Promotors:	Prof. Dr. J.F. Lange
			Prof. Dr. W.A. Bemelman

1. PhD training	**Year**	**Workload**
General courses		**(ECTS)**
Laboratory animal science	2010	3.0
BROK ('Basiscursus Regelgeving Klinisch Onderzoek'	2010	1.0
Seminars and workshops		
Journal club	2010-2012	3.0
Teach the aios	2011	0.2
Ventrale hernia: open en laparoscopisch hernia herstel	2011	0.5
Round table Bard	2011	0.2
Precourse RICH 2012	2012	0.5
Presentations		
Oral presentation Stafdag Heelkunde Erasmus MC	2010	1.0
Poster presentation SEOHS Rotterdam	2010	0.5
Oral presentations ESSR Aachen	2011	2.0
Oral presentation NVGIC dagen	2011	1.0
Oral presentation SEOHS Amsterdam	2011	1.0
Oral presentation RICH Rotterdam	2012	1.0
Oral presentation AHS New York	2012	1.0
Poster presentation AHS New York	2012	0.5
Oral presentations 'voorjaarsvergadering' NvVH Veldhoven	2012	2.0
(Inter)national conferences		
SEOHS	2010-2015	1.5
NVGIC themadag	2010-2011	1.0
Chirurgendagen Veldhoven	2010-2016	3.0
EHS Gent	2011	0.5
ESSR Aachen	2011	1.0
RICH Rotterdam	2012	0.5
AHS New York	2012	1.0

2. Teaching

Lecturing

College Geneeskunde jaar 1: Casus "Dokter, ik ben zo moe…"	2010-2012	1.0
College Ouderdag; anatomie van transplantatieorganen	2011	0.5

Supervising practicals and excursions, Tutoring

Examination of Basic Life Support (EHBO) of medical students	2010-2012	1.0

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