Minimally invasive strategies for the surgical treatment of colonic peritonitis
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General introduction and thesis outline
**GENERAL INTRODUCTION**

**Colonic peritonitis**
Peritonitis as a sign of intra-abdominal infection can be caused by a variety of clinical conditions. Common causes include abdominal organ infections and subsequent perforations, complicated abdominal surgery and abdominal trauma. The spillage of gastrointestinal or genitourinary contents or microorganisms, by either direct perforation or breach of the inflamed organ wall is usually the source of this secondary peritonitis. Hence, the most common pathogens reflect those in the gastrointestinal tract, with enterobacteriaceae (E coli, Proteus mirabilis, Klebsiella pneumonia), streptococci, enterococci, and anaerobic organisms such as Bacteroides fragilis.

**Classification of colonic peritonitis**
The severity of peritonitis from colonic origin largely depends on the extent of peritoneal contamination. In general, a closed infected compartment such as an abscess causes less severe symptoms than a general peritonitis, and cloudy or purulent peritonitis might cause a less severe sepsis than faecal peritonitis. Available classification systems are the Mannheim peritonitis index (MPI), the left colonic Peritonitis Severity Score (PSS) and the Hinchey classification for perforated diverticulitis. All these classifications discriminate patients with faecal peritonitis from those with purulent or less severe forms of peritonitis.

There is an important difference in aetiology of purulent and faecal peritonitis, where the first can be caused by bacterial translocation, ruptured abscess or sealed perforation with minimal fluid leakage, while the latter can only be explained by an overt perforation from the bowel lumen into the free peritoneal cavity. (figure 1)

**Presentation**
Peritonitis can result in a variety of symptoms from local tenderness to an acute abdomen with general abdominal pain and rigidity. These symptoms can be accompanied by symptoms of systemic sepsis such as fever, sinus tachycardia, hypotension, organ failure, systemic inflammatory response syndrome (SIRS) and could lead to multi organ failure and even death.

Treatment is based on two pillars, one is the management of the sepsis (and septic shock) with antibiotics and fluid resuscitation, the other is controlling the source of peritonitis and usually requires surgical therapy. The urgency of treatment depends on the affected organ, progression of clinical symptoms and physiological stability of the patient.

The common principle is that an inflammatory mass can be treated without surgical or radiological intervention, contained abscesses with percutaneous drainage, while peritoneal contamination with purulent and faecal peritonitis require surgical management. When surgery is indicated, the physiological condition of the patient might determine the choice
between short and simple damage-control surgery or a more complex one-stage procedure as a permanent solution.

Figure 1. Hinchey classification scheme. Reproduced with permission from Jacobs, NEJM 2007, Copyright Massachusetts Medical Society
Diverticular disease and perforated diverticulitis

Colonic diverticular disease compromised a spectrum of different conditions, ranging from the presence of asymptomatic uninflamed diverticula to perforated diverticulitis with associated systemic sepsis.

Colonic diverticula are actually pseudo-diverticula with herniation of the mucosal and submucosal layers of the colonic wall. This usually occurs at the weaker areas where the vasa recta penetrate the smooth muscle layer. Diverticulitis occurs when a diverticula becomes inflamed, which occurs in only a minority of the patients with diverticular disease. And even in case of an episode of acute diverticulitis, only about 25% of patients present with complicated disease including abscesses, fistula, obstruction and perforated disease with peritonitis. If perforated diverticulitis is present urgent surgical treatment is required, with an associated high morbidity and mortality rates.

Perforated diverticulitis can be classified according to the Hinchey classification and several other similar classification systems based on the degree of peritoneal contamination. The Hinchey classification is developed to grade intraoperative findings, but as in current practise only grade III and IV require surgical treatment, it is usually used to classify the clinical and radiological diagnosis.

Current trends in treatment of acute diverticulitis involve less aggressive treatment for all stages. Conservative treatment without antibiotics, diet restriction or hospitalisation for uncomplicated disease, only antibiotic treatment or percutaneous drainage for abscesses and surgical treatment limited to Hinchey III and IV perforated diverticulitis. Somewhere between the 1960s to ‘80s, the surgical treatment of choice for perforated diverticulitis became the open Hartmann’s procedure. Before, patients would usually undergo a three stage procedure, with faecal diversion and drainage followed by resection and in the third stage re-anastomosis. Patients with severe sepsis and peritonitis would often undergo several planned relaparotomies for peritoneal lavage until the systemic sepsis was controlled. Later, the less invasive on-demand relaparotomy strategy was shown to have similar outcomes in a randomised trial, while reducing the need for relaparotomy to 40% of the included patients.

In the 1990s, laparoscopic peritoneal lavage emerged as a promising alternative for sigmoidectomy in patients with purulent peritonitis due to perforated diverticulitis. This technique became increasingly popular since the 2008 study by Myers and colleagues reporting a 95% success rate in a series of 92 patients. Two years later a systematic review of case series showed a mortality rate under 5% and a colostomy was avoided in the vast majority of patients. Four different European research groups, including our own, developed a randomised trial to confirm these success rates in a randomised trial, as all case series appeared to suffer from a severe selection bias.
Anastomotic leakage following colorectal surgery

The second major cause of colonic peritonitis discussed in this thesis is anastomotic leakage following colorectal surgery. Benign and malignant disease of the colon such as diverticulitis, inflammatory bowel disease and colorectal cancer require surgical treatment by segmental colectomy followed by anastomosis of the bowel ends. Despite all efforts, every anastomosis has a risk of leakage. Anastomotic leakage can be caused by either technical problems or failure of the anastomotic healing process. Most research focusses on these risk factors for anastomotic leak such as suture techniques, patient factors such as age and comorbidity, and perioperative factors such as perfusion and oxygenation.22

Aetiology and risk factors

The many factors that have been found to increase the risk of anastomotic leakage, suggesting it is most likely a multifactorial process. Early leakage within the first days following surgery is most likely due to iatrogenic factors such as technical failure of the anastomosis. During these first days, the strength of the anastomosis largely depends on the strength of the used biomaterials as collagenolysis exceeds production of the collagen matrix.23 During the following days, leakage is most likely caused by impaired healing due to insufficient perfusion and subsequent ischemia, local inflammation, and patient factors (age, diabetes, smoking, alcohol abuse, obesity, NSAID use, steroid use, chemotherapy, radiation).24 Not surprisingly, those risk factors for anastomotic leakage are similar to those for impaired wound healing.25-27

Prevention

The only way to fully prevent anastomotic leakage is to abstain from restorative surgery and perform a Hartmann’s procedure with permanent end colostomy in all patients. However, methods to prevent leakage would be preferred to maintain quality of life for these patients.28 Other than appropriate patient selection, several technical interventions have been introduced to reduce the risk of leakage. Examples are double sutured anastomosis, stapled anastomosis, omentumplasty, reinforcement with tissue adhesives, and endoluminal covering of the anastomosis with products like the C-seal or intraluminal stents.29-33 Unfortunately, none of these methods has resulted in a significant reduction of the leakage rate in clinical studies so far.

Treatment

In case that leakage does occur with subsequent peritonitis and sepsis, surgical treatment is required. The gold standard is the most radical option with laparotomy, resection of the anastomosis, closure of the distal segment and end colostomy of the proximal segment. Although effective, less invasive options might be an alternative. In some patients the anastomotic leak might be salvageable by suture, glue or resection and re-anastomosis.34,35
Laparoscopy in colorectal surgery

The first laparoscopic procedure was a laparoscopy performed by a gynaecological patient back in 1901 in Russia. In these early days, laparoscopic was mainly used to diagnose diseases of the female reproductive organs. During the 20th century, laparoscopic surgery developed rapidly and nowadays a wide range of surgical procedures can be performed using the laparoscopic technique. Either within the abdominal cavity as in other spaces such as in the thorax, joints and soft tissue spaces.

![Diagram showing surgical procedures]

**Figure 2.** Adapted from Phitayakorn et al.34

(figure 2) Or as investigated in part II of this thesis, all these options might be carried out by laparoscopy.
In general, the benefits of laparoscopic surgery rely on the reduction of inflicted trauma due to the reduced incision length and more delicate tissue handling facilitated by the instruments and magnified camera view. This results in less blood loss, less postoperative pain, and faster gastrointestinal and functional recovery. Although laparoscopic procedures usually took longer and the disposable instruments increased the procedure related costs, the reduction in hospital stay could compensate for these increased costs. The reduced length of incisions resulted in better cosmetic results and reduced the risk of wound infections and incisional hernia.

Due to the lack of knowledge and expertise in the early years of laparoscopy, the application of this new minimal invasive approach has long been limited to elective and non-complex indications in low risk patients. However as expertise grows and the functionality and quality of the cameras and instruments improve, more patients can benefit from laparoscopic treatment.

Effects of the pneumoperitoneum and CO₂ insufflation

Surgical trauma is known to negatively influence the local and systemic inflammatory response as shown by elevated levels of CRP, interleukins and TNF-α during and up to days after surgery. While a less severe increase in these markers of the inflammatory response have been shown after laparoscopic surgery. The preserved immune competence is suggested to protect against tumour cell seeding and infectious complications. However, it is uncertain whether it is only the reduced surgical trauma, or the pneumoperitoneum and the CO₂ insufflation that contribute to these effects.

Insufflation with CO₂ causes relative acidosis and increases the end-tidal CO₂ levels if not compensated with mechanical hyperventilation. These effects are related to the used pressure and duration of the pneumoperitoneum. In healthy patients, these effects are non-significant, but their effects have been feared in patients with cardiac and pulmonary comorbidity and those with sepsis. However, these feared negative influence have not been seen in the clinical practise. In contrast, in the Dutch Surgical Colorectal Audit (DSCA) laparoscopic surgery compared to open surgery was most beneficial in high risk patients with regard to postoperative mortality (>70 years, 3% vs 5.2%; ASA III+, 5% vs 8.4% for laparoscopic and open surgery respectively).

In case of generalised peritonitis and sepsis, the immunologic effects are highly important to determine the safety of laparoscopic procedures in these patients. Concentrations of peritoneal cytokines such as TNF-α and IL-6 are shown to be lower after pneumoperitoneum compared to laparotomy in a septic animal model and CO₂ is believed to have bacteriostatic properties. No bacterial translocation due to the increased pressure was seen in three animal studies in groups with CO₂ laparoscopy, air laparoscopy and laparotomy, while others did show an increase in bacteraemia in septic animals after laparoscopy. Despite the contrasting results of animal studies, no signs of increased bacteraemia following
laparoscopic treatment of peritonitis have been shown in clinical studies in perforated appendicitis, cholecystitis and perforated diverticulitis.\textsuperscript{48}

Additional difficulties and risks of the laparoscopic technique in peritonitis can be the presence of distended and vulnerable bowel, dense inflammatory masses and adhesions. All these factors can cause difficult visualisation of the focus and poor overview and therefore increase the risk of bowel injury with instruments used. However, laparoscopic treatment in small-bowel obstruction has already been shown to be safe and feasible in large patient series,\textsuperscript{49} as was laparoscopic surgery for peritonitis of several causes.\textsuperscript{50}
AIM AND OUTLINE OF THIS THESIS

As laparoscopic surgery has proven to be superior with regard to short term recovery following colorectal surgery, we expect similar benefits in patients with acute peritonitis. These benefits might even be larger in the presence of peritonitis and distended bowel, as the abdominal wall can be preserved in laparoscopic surgery and less additional trauma is inflicted. The hypothesized reduction of the inflammatory response can reduce septic complications, especially those related to SIRS. The aim of this thesis is to investigate minimally invasive strategies for the surgical treatment of colonic peritonitis, focusing on the laparoscopic treatment options for perforated diverticulitis (part I) and colorectal anastomotic leakage (part II).

In chapter 2 we present the clinical results of the LOLA arm of the randomised Ladies trial comparing laparoscopic lavage to sigmoidectomy for purulent perforated diverticulitis. And chapter 3 describes the cost analysis of laparoscopic lavage in the same randomised trial. Chapter 4 describes the patients with purulent perforated diverticulitis within and outside of the LOLA-arm of the Ladies trial and compares predictors for postoperative outcomes such as surgical procedure and surgeon’s specialisation. Chapter 5 is a systematic review of the sparse evidence available on acute laparoscopic sigmoidectomy for the treatment of perforated diverticulitis. Laparoscopic sigmoid resection might be a valid alternative between laparoscopic lavage and open sigmoidectomy for perforated diverticulitis. Therefore, in chapter 6, we present a propensity matched cohort of patients with laparoscopic and open sigmoidectomy for perforated diverticulitis. Chapter 7 provides an overview of the available evidence and guidelines on all aspects of diverticulitis, including laparoscopic lavage and laparoscopic sigmoidectomy for the treatment of perforated diverticulitis.

The second part of the thesis addresses the laparoscopic treatment of anastomotic leakage following laparoscopic colorectal surgery. In chapter 8 we present our own cohort of patients with either laparoscopic or open reintervention following laparoscopic colorectal surgery. In chapter 9, we present a similar but larger series of patients from the Dutch Surgical Colorectal Audit.
REFERENCES