Diagnosis of intra-abdominal infections and management of catastrophic outcomes
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General introduction and outline of thesis
GENERAL INTRODUCTION

Intra-abdominal infections

The term ‘intra-abdominal infection’ refers to inflammatory responses of the abdominal cavity due to activation of the (native) immune system usually in response to microorganism. It represents a wide spectrum of diseases with a variety in causes and severity. When inflammation (without bacteria) or infection (with bacteria) is isolated to a single organ or component, and no anatomical disruption is present, the process is usually described as an ‘uncomplicated intra-abdominal infection’. A ‘complicated intra-abdominal infection’ occurs when the infection extends into the peritoneal cavity, the space formed by a mesothelial membrane covering the abdominal viscera, the peritoneum. The resulting infection of the peritoneum is also referred to as ‘secondary peritonitis’. In contrast, ‘primary peritonitis’ describes infection of the peritoneum without a source within the abdomen, in general due to bacteria from the bloodstream entering the abdomen. ‘Tertiary peritonitis’ entails an ill-defined entity and usually describes persistent or recurrent secondary peritonitis after initial adequate treatment. The term tertiary peritonitis should be avoided. As secondary peritonitis is the most frequent form of peritonitis, this term is used interchangeably with (complicated) intra-abdominal infection. When an intra-abdominal infection is confined (walled-off) within a limited area of the abdominal cavity as result of the unique defence mechanisms of the peritoneal cavity in particular the peritoneal layer and the omentum, an intra-abdominal abscess may form.

Diagnosis of intra-abdominal infections

Diagnosis of an intra-abdominal infection is based on symptoms and clinical findings, by laboratory investigations and diagnostic imaging. Typically, a patient with an intra-abdominal infection presents with abdominal pain and symptoms of gastro-intestinal dysfunction such as anorexia, vomiting, diarrhoea, or obstipation. Of all patients presenting with acute abdominal pain at the Emergency Department, approximately one in two has some form of an intra-abdominal infection. Especially complicated cases of intra-abdominal infections can cause concomitant sings of systemic inflammatory responses, characterized by fever or hypothermia, tachycardia, tachypnoea, and vital organ failure. On clinical examination, there may be tenderness on palpitation of the abdomen. Diffuse abdominal pain and generalised tenderness are often symptoms of a complicated infection. Although physical examination can provide valuable information, findings are notoriously nonspecific and clinical evaluation alone has been shown to have limited diagnostic value.

The usual first step after mere clinical evaluation in the diagnostic work-up of a patients with a suspected intra-abdominal infection is laboratory testing of blood. Commonly used markers of inflammation are white blood cell (WBC) count and serum C-reactive protein (CRP) level. Measurement of these inflammatory markers is widely available and well
established in routine clinical practice. Although both markers rise rapidly in response to an inflammatory or infectious process, they are non-specific and are therefore limited in their ability to discriminate between different types and causes of infections. Combined with information from medical history and physical examination, these inflammatory markers may aid in a distinction between non-urgent and urgent conditions, the latter including most intra-abdominal infections.

Diagnostic imaging studies may serve as the definitive diagnostic approach in patients with a suspected intra-abdominal infection. The role of imaging is to define the cause before a treatment strategy is chosen. The most widely used imaging modalities for suspected abdominal infections are ultrasound and computed tomography (CT). Ultrasound imaging has the advantage of being non-invasive and widely available. Intra-abdominal abscesses, free intra-abdominal fluid or air, and certain specific diagnosis can well be made on ultrasound. However, its diagnostic accuracy is operator dependent and certain patient characteristics such as obesity or the presence of a paralytic ileus hamper performance. Computed tomography, preferably enhanced with oral and intravenous contrast, is superior in terms of diagnostic performance for most intra-abdominal infections. Drawbacks of CT include exposing the patient to ionizing radiation, the risk of contrast-induced nephropathy, costs and availability out of office hours.

**Acute appendicitis**

One of the most common intra-abdominal infections is acute appendicitis. It is the most frequent underlying condition in patients presenting with acute abdominal pain in the Emergency Department. Approximately 16,000 appendectomies are performed in the Netherlands each year, more than any other emergency operation. Despite its high incidence the underlying cause for infection of the *appendix vermiformis* remains unclear. The classical symptoms of acute appendicitis include diffuse abdominal pain, which progresses and migrates to the right lower quadrant of the abdomen with localized rigidity. However, this classical presentation is not frequently encountered, and the clinical diagnosis of appendicitis is therefore not straightforward. To enhance diagnostic accuracy, imaging is now widely applied in the diagnostic work-up of patients with suspected appendicitis. Both ultrasound and CT are commonly used, but the optimal diagnostic strategy is still under debate. Furthermore, surgical resection of the appendix as the only appropriate treatment is being questioned. During the last decades, conservative management with antibiotics of uncomplicated cases of appendicitis is suggested to be a safe and effective alternative. This new approach does entail the new diagnostic dilemma of the need to preoperatively distinguish between uncomplicated and complicated (gangrenous or perforated) appendicitis.
Postoperative intra-abdominal infections

Another frequently encountered class of intra-abdominal infections are postoperative infections after primary surgery. Of all severe cases of secondary peritonitis, approximately one in four develops postoperatively. Furthermore, up to 19 per cent of patients undergoing elective abdominal surgery have been reported to develop postoperative peritonitis, either by leakage of a constructed anastomosis or as an abscess arising from residual intraperitoneal bacteria. Especially patients initially surgically treated for an intra-abdominal infection have a high risk of postoperative recurrent or ongoing abdominal infection. Postoperative peritonitis may also be the result of inadvertent and undetected injury to the bowel during surgery. Prognosis of postoperative intra-abdominal infection is worse compared to other forms of secondary peritonitis. The high mortality rate is explained by the pre-existing activation of an inflammatory response due to previous surgery, followed by a second hit due to the subsequent infection of the peritoneal cavity. Diagnosis of postoperative intra-abdominal infections is complex as symptoms are difficult to distinguish from the normal postoperative inflammatory responses. The classical symptoms of abdominal pain, fever and a rigid abdomen are often lacking or already present after surgery, and presentation is more insidious. Furthermore, inflammatory markers are increased even during an uneventful postoperative period because of ‘normal’ surgical tissue damage. Diagnostic imaging is usually required to diagnose postoperative intra-abdominal infections, but even then, the diagnosis may be difficult or at least uncertain.

Catastrophic outcomes of intra-abdominal infections

The surgical conditions affecting the abdomen “which can assume catastrophic proportions” are many. The end results of these situations have been referred to as ‘abdominal catastrophes’, although this term is not well defined. Some have used the term to describe abdominal conditions that, if not surgically treated, lead to an inevitable death, the most ‘catastrophic’ outcome of all. The majority of reports on abdominal catastrophes, however, describe the devastating complications of intra-abdominal infections, and the surgical decisions they may require.

Among the frequently described ‘abdominal catastrophes’ are situations following surgery for intra-abdominal sepsis, when primary closure of the abdomen is impossible due to visceral oedema resulting in an open abdomen or ‘laparostoma’. In approximately 10 per cent of patients undergoing surgery for secondary peritonitis primary closure is not possible. In other treatment strategies the abdomen is sometimes deliberately left open in fear of intra-abdominal hypertension or abdominal compartment syndrome. An open abdomen with temporary abdominal closure has also been used in situations where a one or multiples reoperations are needed to get the abdominal disease under control. A surgical strategy with planned relaparotomies for secondary peritonitis has been shown inferior to an on-demand
relaparotomy strategy. However, in recent years some surgeons use a strategy of damage control surgery and leaving the abdomen open, thus far practised in trauma patients, in peritonitis patients with dubious results and lacking solid data.

To protect the viscera in an open abdomen some form of ‘temporary abdominal closure’ is applied, for instance by sowing an absorbable synthetic mesh to the medial edges of the abdominal fascia. Other temporary closure devices such as a Bogota (plastic) bag or negative pressure wound therapy have also been applied. Ideally, delayed fascial closure is obtained during one of the subsequent reoperations, but in the majority of peritonitis patients this cannot be achieved. Early mortality rate in patients with an open abdomen and abdominal sepsis is high, with reported rates of approximately 25 per cent. The long-term consequence of an open abdomen, in case delayed fascial closure is not achieved, is a complete disruption of the normal anatomy of the abdominal wall. The resulting large abdominal defect (abdominal wall hernia or ventral hernia) can be severely invalidating. Surgery to reconstruct this defect, after a prolonged period during which a neo-peritoneal cavity forms, is challenging and not without risks.

Other catastrophic outcomes of severe peritonitis include conditions resulting in the necessity to divert into a proximal stoma. The potential consequence is excessive secretory losses of bowel contents, with malabsorption of macronutrients, water and electrolytes. The corrosive output may irritate surrounding skin, and stoma care is usually complex and challenging. Nutritional support may be necessary to meet metabolic requirements. Another feared postoperative complication of an abdominal infection is the formation of an enterocutaneous fistula. This abnormal connection between a bowel segment and the skin typically arises as a result of abdominal surgery with intra-abdominal infectious complications. Associated morbidity is high, and loss of bowel contents through the fistula frequently leads to malabsorption, comparable to a proximal stoma. An open abdomen is particularly prone to fistula formation. These fistula are referred to as ‘entero-atmospheric fistula’, and are associated with severe wound management problems and refractory forms of intestinal malabsorption.

**Acute intestinal failure**

With improvements of peri-operative care, patients more frequently survive the initial period of abdominal sepsis associated with abdominal catastrophes. As a result, the need for long-term management is more frequently encountered. Loss of bowel contents from a fistula or proximal stoma may ultimately lead to the necessity of intravenous supplementation, a state called ‘acute intestinal failure’. Whereas historically intestinal failure was associated with chronic or congenital digestive diseases, interest and awareness for temporary and reversible intestinal failure has increased. Patients with acute intestinal failure are severely ill and are at risks of developing septic, metabolic and nutritional complications. Care for
these patients is complex and characterized by challenging skin, wound and stoma care. In addition, management requires provision of complex home (nutritional) care, which entails its own unique associated difficulties. After several months, when the patients’ status permits, surgery to restore intestinal continuity and function, and reconstruction of the abdominal wall, can be considered.

OUTLINE OF THE THESIS

This thesis is divided into two parts. The first part focuses on the diagnosis of intra-abdominal infections. The second part explores different aspects of management of the catastrophic outcomes of abdominal infections.

PART I: Diagnosis of intra-abdominal infections

Abdominal pain is one of the key symptoms of an intra-abdominal infection. Of all patients presenting with acute abdominal pain a substantial portion has an intra-abdominal infection, but the variety of underlying diseases in this diverse group of patients makes diagnosis difficult. The inflammatory markers WBC count and CRP are routinely determined. Although the diagnostic value of these markers for most specific diagnosis is low, they could help discriminate between non-urgent conditions and urgent conditions, including most intra-abdominal infections. In Chapter 1 this potential ability of WBC count and CRP is evaluated in 2691 patients presenting with acute abdominal pain at the Emergency Department.

In addition to clinical evaluation and laboratory tests, imaging is usually added to the diagnostic work-up of patients with abdominal pain, with CT being the most accurate modality. Whether or not contrast enhancement of CT provides additional value is under debate. Chapter 2 summarizes and evaluates the available literature on different contrast regimens for CT imaging performed in patients with acute abdominal pain.

Acute appendicitis is the most common intra-abdominal infection, with a life-time risk of developing appendicitis of approximately 7 to 8 per cent. Nevertheless, the diagnosis of appendicitis remains a clinical challenge. Blood test are routinely performed in patients with suspected appendicitis, but the inflammatory markers WBC count and CRP level are known to fall short as independent diagnostic markers. In Chapter 3 the accuracy of the combination of these inflammatory markers related to duration of symptoms for diagnosing appendicitis is evaluated.

Since conservative treatment is now suggested as alternative to appendectomy for uncomplicated appendicitis, it is of great importance to be able to differentiate between complicated and uncomplicated cases before treatment decisions are made. In Chapter 4 a scoring
system based on clinical and imaging features to distinguish uncomplicated from complicated appendicitis is developed.

Although CT is known to be the most accurate diagnostic imaging modality for acute appendicitis, it has several drawbacks. To minimize the number of performed CT scan, while maintaining diagnostic accuracy, a conditional CT strategy can be applied. This strategy entails ultrasound in all patients with acute abdominal pain, with a subsequent CT-scan after inconclusive or negative ultrasound results. This strategy is proven to be the preferred strategy for unselected patients with acute abdominal pain. Whether this also holds for selected patient with clinical suspicion of acute appendicitis is evaluated in Chapter 5.

Postoperative intra-abdominal infections form a special class of abdominal infections given their poor prognosis and diagnostic challenge. Following elective abdominal surgery, abdominal infectious complications have a major influence on outcome. The inflammatory marker CRP has been suggested to be useful as tool to select patients for an early and safe hospital discharge. In Chapter 6 the available literature regarding CRP and its association with infectious complications following abdominal surgery is systemically reviewed.

In particular operations for intra-abdominal infections are associated with postoperative abdominal infectious complications or ongoing infection. Early recognition of these complications is vital, but the diagnosis is complex. In Chapter 7, a decision tool, previously developed to guide postoperative management in patients operated for secondary peritonitis, is externally validated.

PART II: Management of catastrophic outcomes of intra-abdominal infections
The abdominal compartment syndrome is a life-threatening condition characterised by an increase of pressure within the abdominal cavity. It can occur in a wide range of critically ill surgical patients, including patients with abdominal sepsis, and is associated with a high mortality rate. Hypertension of the abdominal compartment was long neglected, but interest and awareness has risen. Chapter 8 sets out to analyse the increasing number of publications on the abdominal compartment syndrome, and discusses the topics and findings of the main clinical studies.

The open abdomen and temporary abdominal closure is seen in a variety of surgical patients. Intra-abdominal infection differs from the other conditions as success rates seem to be lower while the risk of the most feared complication, formation of an entero-atmospheric fistula, is higher. The available literature on the open abdomen, specifically in patients with peritonitis, is systematically reviewed and evaluated in Chapter 9.

Acute intestinal failure may develop as consequence of a constructed proximal stoma for bowel perforation or leakage or due to an enteric fistula. Management is complex, and
specialized care is needed to be able to achieve enteral autonomy. In *Chapter 10*, outcome of patients with acute intestinal failure, managed by a specialised team, is evaluated.

An important aspect of reconstructive surgery for the long-term outcomes of abdominal catastrophes is restoration of the abdominal wall. As these surgical procedures are usually complicated by the presence of contamination, synthetic material to augment the reconstruction is frequently perceived as contra-indicated. New methods and materials, predominantly biologic meshes, have been introduced over the last few decades and have provided alternatives for these complex reconstructions. In *Chapter 11*, all available evidence on techniques for the reconstruction of contaminated abdominal wall defects is evaluated. *Chapter 12* describes the experience of two specialised centres with the reconstruction of contaminated abdominal wall defects with use of a porcine-derived biologic mesh or tissue-enhanced dermal matrix.
REFERENCES


