Diagnosis of intra-abdominal infections and management of catastrophic outcomes
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SUMMARY

Intra-abdominal infections are a diverse group of frequently encountered conditions of varying severity with various underlying pathologies. The first part of this thesis focused on the diagnostic work-up of suspected intra-abdominal infections in the diverse patient population presenting with abdominal pain (the predominant symptom of an intra-abdominal infection), in patients clinically suspected of acute appendicitis (the most common intra-abdominal infection), and in patients suspected of a postoperative intra-abdominal infection (a separate entity within intra-abdominal infections). The second part of this thesis explored different aspects of management of the potential catastrophic outcomes of intra-abdominal infections, including the open abdomen, complex abdominal wall defects and acute intestinal failure.

PART I - Diagnosis of intra-abdominal infections

In Chapter 1 the potential of the commonly used inflammatory markers white blood cell (WBC) count and C-reactive protein (CRP) level to distinguish non-urgent from urgent conditions, the latter including most intra-abdominal infections, was evaluated. Included were 2961 patients presenting with acute abdominal pain. Although accurate discrimination between non-urgent and urgent conditions based only on these markers seems unrealistic, they could guide management in terms of selecting patients for immediate additional diagnostic imaging. The results showed that the combination of a WBC count greater than $15 \times 10^9/L$ and a CRP level greater than 50 mg/L resulted in the highest probability of an urgent condition; 85.5 per cent. However, only few patients presented with these levels and most patients with an underlying urgent condition had lower inflammatory marker levels. Furthermore, a low WBC count and a low CRP level did not sufficiently exclude the presence of an urgent condition. Indications for imaging and management decisions based exclusively on these inflammatory markers in patients with acute abdominal pain therefore seem imprudent.

Of the available imaging modalities for suspected intra-abdominal infections, computed tomography (CT) is known to be the most accurate. Whether or not contrast enhancement, and which route of contrast enhancement, influences the diagnostic accuracy is unclear. In Chapter 2 the available evidence was systematically reviewed and meta-analysed. A total of 18 studies were included of which 11 investigated CT in unselected patients with acute abdominal pain. The remaining 7 studies made a head-to-head comparison in patients with suspected appendicitis (5 studies), acute diverticulitis (1 study) or acute abdominal pain (1 study). In 4580 patients with acute abdominal pain (originating from 11 studies), intravenous contrast enhancement resulted in the highest diagnostic accuracy (90.6 per cent) when compared to unenhanced (73.4 per cent), although this difference was not significant. In patients suspected of appendicitis or diverticulitis available evidence suggests lack of benefit of intravenous
contrast enhancement over no contrast administration. Studies on the additional value of rectal contrast were lacking.

Several aspects of the diagnosis of acute appendicitis, the most common intra-abdominal infection, were evaluated in the next three chapters. Chapter 3 assessed the diagnostic value of WBC count and CRP level, related to the duration of symptoms, in 1024 patients clinically suspected of acute appendicitis. Symptoms for more than 48 hours and a WBC count greater than $20 \times 10^9$/L seemed to prove appendicitis with 100 per cent accuracy. However, only less than 1 per cent of patients presented with this profile. Levels of the inflammatory markers within normal range did not exclude appendicitis. Ten per cent of patients with symptoms for more than 48 hours and normal inflammatory markers levels still had acute appendicitis.

In Chapter 4 a scoring system was developed to distinguish uncomplicated from complicated appendicitis based on clinical and imaging features. This distinction is nowadays even more important, as conservative management has been suggested to offer a safe and effective alternative to appendectomy for uncomplicated cases of appendicitis. Prospective data from 395 patients with suspected appendicitis was used to construct two separate scores for ultrasound and CT. With use of the scoring systems, a substantial group of patients deemed to have uncomplicated appendicitis could be identified of whom 95 per cent were correctly labelled as such.

The two most frequently applied imaging strategies for suspected acute appendicitis, a conditional CT strategy (CT after inconclusive or negative ultrasound only) and an immediate CT strategy, were directly compared in Chapter 5. In a prospective cohort the conditional CT strategy enabled the correct identification of as many patients with appendicitis as the immediate CT strategy: approximately 95 per cent. However, conditional CT imaging resulted in more false positives compared to immediate CT imaging (14 versus 8 per cent).

In Chapter 6 the value of CRP for the diagnosis of postoperative intra-abdominal infections after (predominantly elective) major abdominal surgery was evaluated. A systematic review was conducted and 16 studies comprising 2215 patients were included. Meta-analysis showed that CRP has a negative predictive value of more than 90 per cent from postoperative day 3 onwards. The results suggest that CRP can be used as marker that permits safe and early hospital discharge of patients. The moderate positive predictive value of CRP (64 per cent) for the diagnosis of postoperative intra-abdominal infections cannot justify performing imaging or making treatment decisions based on high levels of CRP alone.

Another aspect of the diagnosis of postoperative intra-abdominal infectious was evaluated in Chapter 7. A decision tool to determine the probability of ongoing sepsis from an abdominal infectious focus in patients operated for secondary peritonitis was externally validated. A
total of 161 assessments with use of the decision tool were performed in 69 patients. The discriminative capacity of the decision tool score was fair (area under the receiving operator curve of 0.79). The incidence rate of ongoing sepsis differed significantly between three score-categories. The negative predictive value of a decision tool score categorized as ‘low’ was 89 per cent. In clinical practice this negative predictive value can aid postoperative decision-making.

PART II - Management of catastrophic outcomes of intra-abdominal infections

Chapter 8 explored current literature on intra-abdominal hypertension and the abdominal compartment syndrome. The number of yearly published articles on these topics showed an exponentially increase during the last six decades, suggesting increased awareness and interest. However, the quality of the available evidence was low, as most studies were case-reports and expert opinions. The majority of studies described the abdominal compartment syndrome in surgical intensive care patients. The most frequently described specific subgroups were trauma patients and patients with severe pancreatitis.

In Chapter 9, the result of a systematic review and meta-analysis of the literature on the open abdomen and temporary abdominal closure techniques in patients with peritonitis is described. Included were 74 studies comprising 4358 patients. The most frequently described temporary abdominal closure technique was negative pressure wound therapy. When combined with continuous mesh or suture mediated fascial traction, negative pressure wound therapy showed the best results in terms of achieving delayed fascial closure and risk of enteroatmospheric fistula. However, the overall quality of the evidence was very poor.

Outcome of management of acute intestinal failure by a specialised team was presented in Chapter 10. An observational study on 89 patients with acute intestinal failure, the majority caused by enteric fistula, was conducted. Approximately half of the patients presented with an ‘open abdomen’ (laparostomy). Overall mortality including deaths from underlying diseases was 16 per cent, postoperative hospital mortality was 5 per cent. Most patients needed to undergo reconstructive surgery and almost all (94 per cent) could spend the preoperative period of rehabilitation at home. The vast majority of patients had successful restoration of enteral autonomy: 73 per cent of all patients, 87 per cent of surviving patients, and 83 per cent of patients who underwent reconstructive surgery.

An overview of outcomes of the repair of (clean-) contaminated abdominal wall defects is described in Chapter 11. The systematic review of the literature resulted in 32 studies that were included. Available low-level evidence shows no benefit of biologic over synthetic mesh for repair of potentially contaminated hernias, but as head-to-head comparison are lacking all studies are likely influenced by selection bias. Lack of evidence hampers surgical decision-making in the approach of contaminated abdominal wall defects since all but one study
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used biologic meshes in the presence of contamination. Without head-to-head comparison differences in patient characteristics and likely selection bias in single-type intervention studies make definite conclusions hazardous.

In Chapter 12 outcome of major complex abdominal wall repair in contaminated circumstance was described. All patients operated in two established acute intestinal failure centres in Europe with use of a porcine-derived non-cross-linked biologic mesh were analysed. Bridging repairs were necessary in only a quarter of the patients despite high overall complexity. Approximately 44 per cent of the 80 included patients developed a wound infection but removal of the mesh was never necessary. After median clinical follow-up of 7 months, hernia recurrences were found in 10 patients (13 per cent), of whom 3 initially underwent bridged repairs because of the inability to achieve fascial closure despite component separation. Repair of challenging abdominal wall defect can be done effectively with non-cross-linked biologic mesh and component separation technique without the need for mesh removal despite wound infections.

FUTURE PERSPECTIVES

The aim of this thesis was to evaluate different aspects of the diagnosis of intra-abdominal infections and to elaborate on the management of the potential catastrophic complications. The findings described in this thesis contribute to the evolving care for patients with intra-abdominal infections but also raise new questions. This section of the thesis contemplates on the future perspectives for intra-abdominal infections.

Studies on the diagnosis of intra-abdominal infections generally lack evaluation of clinical outcomes. The majority of studies solely evaluate pure diagnostic accuracy. Even important, however, is the influence of an inflammatory marker, imaging modality or imaging strategy on patient-related outcomes, management decisions, and cost-effectiveness. Future research in the field of the diagnosis of intra-abdominal infections should therefore additionally focus on the impact on clinical outcomes.

One of the limitations of the available evidence on the diagnostic value of CRP level and WBC count for intra-abdominal infections is the lack of studies on its additional value to clinical evaluation alone. In practice, the inflammatory markers are always interpreted with knowledge of the findings of medical history and physical examination. In most diagnostic studies however, the value of these markers as independent predictors is evaluated. Due to short-sighted conclusions from diagnostic research, unjust assumptions of the clinical value are made. In clinical practice for instance, CRP is being used increasingly as a single marker to predict the presence of a postoperative infection although CRP has a limited positive
predictive value and is only useful as a negative predictive test. To address this knowledge gap, future studies should compare clinical diagnoses with and without inflammatory markers, enabling proper evaluation of their true additional value.

In addition to the absolute level of inflammatory markers, their change over time may also have diagnostic value. Especially during the postoperative course following abdominal surgery, with elevated inflammatory markers being normal as result of surgical trauma, the difference between early postoperative levels and levels found at postoperative day 3 to 5 may be more informative than the absolute value on any given moment. For selected patients presenting with acute abdominal pain with a suspected (uncomplicated) intra-abdominal infection who are considered for outpatient re-evaluation, the course of inflammatory markers could also be relevant.

The increase in use of diagnostic imaging for suspected intra-abdominal infections is likely to continue. Imaging has become more widely available and has proven to enhance diagnostic performance. Nonetheless, the drawbacks of imaging deserve further attention. The increase in use of CT, for instance during the acute postoperative phase, has led to an rise in costs in spite of the fact that we do not known whether clinical outcomes improve and associated downstream costs are being saved. With respect to CT, exposing patients to ionizing radiation and the associated lifetime radiation-induced cancer risk is a big concern. New techniques have made reductions in radiation dose without decreasing image quality possible, and promising results of low-dose CTs for diagnosing intra-abdominal infections, predominantly appendicitis, have been reported. Future studies should further evaluate the technical possibilities of reducing radiation dose, not only for appendicitis but for all intra-abdominal infections.

Another disadvantage of CT is the need for contrast enhancement. Intravenous contrast is associated with the risk of contrast induced nephropathy while oral and rectal contrast administration can lead to considerable patient discomfort and may effect emergency department throughput. Furthermore, repeat CT studies performed because the original contrast protocol was deemed inadequate to answer the clinical question contribute to excess ionizing radiation, risk of contrast nephropathy and increased costs. As demonstrated in Chapter 2, it is yet unclear whether the administration of contrast agents is indeed needed for the diagnosis of several intra-abdominal infections.

With the increase in use of CT, it is questionable whether ultrasound imaging will continue to play a role in the diagnosis of intra-abdominal infections. For most intra-abdominal infections, CT is superior in terms of pure diagnostic accuracy. As aforementioned, the disadvantages of CT are being addressed and may become less relevant in the (near) future. Nevertheless, especially as part of a conditional CT strategy ultrasound offers a non-invasive alternative and can reduce the number of needed CT scans while maintaining
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diagnostic accuracy, as demonstrated for acute appendicitis in Chapter 5. Exemplary are recent studies on ultrasound for suspected appendicitis from the United States where CT imaging was considered standard during the last decade but concerns regarding the drawbacks of CT have led to renewed interest in ultrasound. An advantage of CT is the fact that, with current telemedicine possibilities, a supervisor or specialised radiologist such as an abdominal radiologist is quickly and easily consulted. Ultrasound, a hands-on and dynamic examination, lacks these possibilities.

Advancements in diagnosis and management of intra-abdominal infections ideally result in fewer catastrophic outcomes. However, despite improvements in technique, anastomotic devices and perioperative care, an intestinal anastomosis remains associated with a considerable risk of leakage, leading to one of the most severe forms of an intra-abdominal infection. Furthermore, regarding the most common intra-abdominal infection, appendicitis, rates of complicated disease have steadily increased over the last 25 years. Catastrophic outcomes of intra-abdominal infections are therefore likely to continue to challenge both patients and doctors.

Although a repeated relaparotomy strategy with temporary abdominal closure for severe peritonitis has been shown to offer no advantage over an on-demand approach, open abdomens are still encountered since primary closure is sometimes frankly not possible. As described in Chapter 9, outcome of an open abdomen in patients with peritonitis is worse than previously claimed based on results in trauma patients. Delayed fascial closure is not as frequently achieved, enteric fistula rates remain significant and the most widely applied closure techniques require multiple dressing changes and OR visits. A potential alternative abdominal closure technique is the use of a biologic mesh. Early closure of the abdomen during the initial operation or shortly thereafter in these contaminated fields with a non-cross-linked biologic mesh may form an immediate solution and can theoretically reduce the rate of fistula formation and hernia recurrence. The potential of a non-cross-linked biologic mesh as closure technique of the open abdomen is currently investigated in the ongoing CLOSE-UP study.

Repair of complex abdominal wall defects has evolved considerably over the last few decades. Prevention of large defects is being pursued by means of laparoscopic abdominal surgery and minimal invasive interventions for infectious complications. The introduction of component separation techniques and the development of lightweight and composite synthetic materials and biologic meshes have expanded surgical options for treatment of abdominal wall defects. In addition, new so-called bioabsorbable synthetic materials have been developed, which are gradually resorbed and have scaffold-like properties enabling tissue-ingrowth, mimicking biologic material. The possibilities of these techniques and materials are still being explored and well-founded indications for their use need to be formulated, as underlined in Chapter 11.
Management of acute intestinal failure and all other catastrophic outcomes of intra-abdominal infections is ideally based on high quality evidence consisting of randomised clinical trials. However, the rarity and complexity of these conditions limits the opportunities to undertake rigorous research, and prospective trials therefore seem impracticable. Other types of research can nevertheless provide us with valuable information. It is vital for these future studies to provide clear patients characteristics, use accepted definitions and report on standard outcomes. Realisation of uniformity across studies may ultimately enable evidence-based improvements of care for patients with catastrophic outcomes of intra-abdominal infections.
REFERENCES


