Diagnosis in acute abdominal pain and ongoing abdominal sepsis
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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
General introduction

Diagnosis in acute abdominal pain

Acute abdominal pain is a common complaint in patients presenting to the emergency department accounting for up to 5-10% of all visits to the emergency department.\textsuperscript{1,2} It is not only a common condition seen at the emergency department but many of these patients are admitted to the hospital. The proportion of patients admitted differed among cohort studies, although in all studies being a large proportion ranging from 38% up to 72%.\textsuperscript{3,5} The underlying conditions causing acute abdominal pain represent a wide variety of diagnoses ranging from self-limiting to life threatening. Therefore, rapid work-up to assigning a timely and accurate diagnosis is essential to detect urgent conditions and initiate adequate treatment. The physician evaluating patients with acute abdominal pain in the emergency department is presented with a twofold challenge. First the distinction between urgent and non-urgent diagnoses has to be made. Secondly, the right condition has to be diagnosed since different diagnoses frequently warrant different treatment strategies. In most developed countries where additional diagnostic modalities are available at the emergency department the work-up of patients with acute abdominal pain follows a similar pattern as shown in figure 1. Although the prevalence of acute abdominal pain has remained stable since the 1970’s there has been a considerable change in diagnostic work-up over the last four decades.\textsuperscript{1,6,7} Introduction of new diagnostic modalities expanded the chain of routinely taken steps. In 1972 laboratory tests were used in almost all patients evaluated with acute abdominal pain where 95% of patients had a total blood count on top of history taking and physical examination. Until now total blood count is done in almost all patients, but additional laboratory tests are also routinely performed such as C-reactive protein.\textsuperscript{4,5} In the study that described the diagnostic work-up pattern in 1972 the only imaging modality available was the plain abdominal X-ray which was used in 42% of patients in the cohort evaluated.\textsuperscript{6} With the introduction of abdominal ultrasound and computed tomography the use of imaging changed substantially. There has been a six-fold increase in the use of these modalities from 7% in 1992 to 42% in 2007.\textsuperscript{1,7}

Since acute abdominal pain is a common complaint, having all the patients complete all the steps in the work-up would put a large burden on logistical resources and costs. Therefore, the extent to which patients should undergo additional diagnostic work-up remains subject of much debate. History taking and physical examination are used as key diagnostics to identify those patients actually needing additional work-up. Studies evaluating elements of
history taking and physical examination however suggested that there is room for improvement of the accuracy of the clinical diagnosis.\textsuperscript{8,9} A more recent study suggests that this statement is still up to date. In this cohort study, the missed urgent cases was 12\% and the false positive rate for urgent diagnosis was 27\% when the clinical diagnosis is based on history taking, physical examination and laboratory findings.\textsuperscript{4} In addition, there is debate which physician is best to evaluate patients with acute abdominal pain and select patients in need of additional work-up as history taking and physical examination are highly examiner dependent. Emergency department physicians, surgical resident and surgeons predominantly evaluate patients with acute abdominal pain. To our knowledge no papers have been published studying the inter-examiner differences between these physicians in their assessment...
of the clinical diagnosis. A limited amount of studies describe individual entities of the diagnostic pathway, for instance the inter-examiner reliability of different components of history taking and physical examination.\textsuperscript{10-12}

For the most frequent of urgent diagnosis, acute appendicitis, scoring tools were introduced in an attempt to enhance the accuracy of the clinical diagnosis.\textsuperscript{13,14} Before scoring tools are to be used in daily practice they need to be tested in other data sets than they were developed in, which is known as external validation. Unfortunately, in case of external validation of the scoring tools for acute appendicitis the accuracy was judged to be insufficient.\textsuperscript{15} Despite these findings effort is still being made to improve the accuracy of the clinical diagnosis with comparable scoring tools.\textsuperscript{16,17} Results in external validation from these newer scoring tools show that these efforts did result in higher diagnostic accuracy than earlier scoring tools.\textsuperscript{18,19} Similar scoring tools were introduced more recently for acute diverticulitis.\textsuperscript{20,21} These scoring tools have not yet been externally validated.

Accuracy of imaging modalities for specific diagnosis that occur frequently, such as acute appendicitis and diverticulitis have been studied quite extensively.\textsuperscript{22-25} For some less frequent diagnoses such as acute cholecystitis or acute intestinal ischemia reports on diagnostic accuracy are less frequent if reported at all.

**Diagnosis of ongoing abdominal sepsis**

Part two of this thesis focusses on the surgical strategies in abdominal sepsis, which can develop as a consequence of an urgent condition in a patient presenting with acute abdominal pain. Abdominal sepsis is also known as peritonitis. Based on etiological ground distinction is made between primary peritonitis where the infectious route is commonly unknown and the gastrointestinal tract is intact, and secondary peritonitis where there is a breach in the continuity of the gastrointestinal tract.\textsuperscript{26,27} Tertiary peritonitis is a term that is used to describe ongoing abdominal sepsis, but its use should be avoided being vague and not based on etiological ground.\textsuperscript{27,28} Whenever abdominal sepsis is mentioned in this thesis it should be interpreted as secondary peritonitis, whereas primary peritonitis is a distinct condition where surgical intervention plays a limited role.\textsuperscript{29}

Abdominal sepsis is associated with high mortality (20%-30%), morbidity (40%-50%) and extensive use of hospital resources with only a slight decrease over the past few decades.\textsuperscript{30-34} Among patients with acute abdominal pain sepsis is frequently encountered in surgical practice. A study in the United States estimates that one out of nine emergency admissions was
due to abdominal sepsis, not even including those cases that developed after elective surgery (e.g. anastomotic leakage). Surgery is the cornerstone of treatment of abdominal sepsis besides resuscitation and antimicrobial therapy. Surgery focuses on source control and prevention of ongoing infection. Source control is defined as surgical elimination of the infectious focus by direct repair, resection or exteriorization, but also additional measures such as radiological intervention or removal of an infected catheter. Despite adequate source control during the initial operation, a relaparotomy may sometimes be necessary. It is generally accepted that the clinical course in patients presenting with less severely illness (Acute physiology and chronic health evaluation' (APACHE-II) score ≤ 10) dictates whether a relaparotomy is necessary. Only in case of clinical deterioration or insufficient improvement in the first few days a relaparotomy is performed. This is called the ‘on-demand’ strategy. Until recently, more severely ill patients (APACHE-II score >10) were submitted to more aggressive surgical strategies, such as planned ‘open abdomen’ treatment and planned relaparotomies. In radical peritoneal debridement fibrin deposition is removed from the entire abdominal cavity, but high mortality and morbidity rates has made this treatment obsolete in current practice. In the open abdomen strategy the abdominal wall is not closed after the initial operation. This approach is not advised, as a randomised trial was aborted because of a significantly higher mortality in the open abdomen strategy group compared to a closed abdomen group (55% versus 30%). Nevertheless, more aggressive treatment similar to planned open abdomen is still advocated by some as part of a damage control surgery strategy, originally performed only in trauma patients but getting more popular despite lack of evidence. In a planned relaparotomy strategy a relaparotomy is performed every two to three days after the initial operation until there is no macroscopic sign of residual abdominal infection.

On-demand and planned relaparotomy are commonly used strategies in current practice of peritonitis treatment. The last decade there have been several reasons to prefer the on-demand strategy instead of planned relaparotomy strategy. A meta-analysis of observational studies has shown a non-significant lower mortality in the on-demand strategy (combined odds ratio: 0.70, 95% CI 0.27 to 1.80), in a retrospective cohort study mortality is significantly lower in the on-demand strategy compared with the planned relaparotomy strategy (22% versus 36%, p = 0.016), although severity of disease is comparable for both strategies, illustrated by a mean APACHE-II score of 10.8 versus 11.7, respectively. In 2007 the only randomised trial comparing on-demand and planned relaparotomy strategies has been
published (RELAP trial). For this trial 510 patients with secondary peritonitis were registered, of which more than half were excluded from randomisation because of an APACHE-II score ≤ 10. Two hundred and thirty two patients were included (116 on-demand and 116 planned relaparotomy). A non-significant lower mortality was found in the on-demand group compared with the planned relaparotomy group (29% versus 36%, p = 0.22). Even for the most severely ill patients with an APACHE-II score > 20 this pattern was observed. This important finding argues against the often-stated opinion that the most severely ill patient in particular benefit from the planned relaparotomy strategy. Another dogma is that a planned relaparotomy is needed in case of faecal contamination. Data from the randomised trial and a cohort study dispute this dogma, as mortality increases when using a planned relaparotomy strategy in patients with faecal peritonitis. The on-demand strategy significantly decreases healthcare utilisation resulting in a cost reduction of USD 23,000 per patient.

Patients treated with the on-demand strategy are admitted shorter to the ICU and hospital. Less relaparotomies are performed in the on-demand group compared to the planned group; 42% of patients in the on-demand group had one or more relaparotomies (113 relaparotomies in total) versus 94% of patients in the planned relaparotomy group (233 relaparotomies in total). Furthermore, the rate of unnecessary relaparotomies was significantly lower in the on-demand group compared with the planned relaparotomy group (31% versus 66%, p < 0.001).

With this evidence relaparotomy on demand should be favored over planned relaparotomy. However, the main obstacle for exclusive use of the on-demand strategy lies in the timely and adequate identification of patients with ongoing abdominal sepsis needing a relaparotomy. There is no guideline available to support the decision whether or not to perform a relaparotomy and is currently based on a series of subjective variables. There are no reliable variables that predict which patients will have an ongoing abdominal infection requiring a relaparotomy. The common non-specific parameters of infection such as fever, C-reactive protein and white blood cell count are no good as markers of ongoing infection needing relaparotomy. However, what can be said is that clinical variables after the initial emergency operation have the best predictive value. Therefore, intensive monitoring of the patient is an essential part of the on-demand strategy; round the clock (24/7) logistics to re-evaluate the decision to perform a relaparotomy is required.

Results of two national surveys among Dutch surgeons, performed in 2002 and 2008, have been compared. The percentage of surgeons exclusively using the planned relaparotomy
strategy has declined drastically from 23% in 2002 to 1% in 2008. However, the percentage of surgeons exclusively using the on-demand strategy remained unchanged (39% in 2002 versus 41% in 2008). The majority of surgeons (58%) vary between both strategies despite of substantial evidence that the on-demand strategy should be preferred. It is clear that implementing the safe and more efficient on-demand strategy requires additional effort.

Outline of the thesis
In line with the diagnostic work-up pathway described in the introduction the first chapter of this thesis concerns the clinical assessment. To create more clarity in the debate who can best evaluate patients with acute abdominal pain in the Emergency Department we performed a study described in Chapter 1 in which the diagnostic accuracy of the clinical diagnosis between surgical residents and surgeons is compared. As part of this study we performed an external validation of two clinical scorings tools; one for appendicitis and one for diverticulitis. In addition to merely external validation we studied how these clinical scoring tools influenced diagnostic certainty of its users that is described in Chapter 2. Together with the scoring tool for diverticulitis that was studied in chapter 2 another recently described scoring tool for acute diverticulitis is externally validated in different sets of data in Chapter 3. Imaging is the next step in the diagnostic pathway of acute abdominal pain. In Chapter 4 the diagnostic accuracy of imaging modalities for acute cholecystitis is summarized in a systematic review. Accurate diagnosis of intestinal ischemia is known to be challenging since it is a relatively rare condition and the presentation is accompanied with a wide spectrum of complaints. A comprehensive overview of the complete diagnostic pathway is described in Chapter 5. Literature is systematically reviewed for each of the different steps in the work-up of intestinal ischemia.

In Chapter 6 the current insights in the surgical treatment of abdominal sepsis are discussed in a review. Focus is predominantly on the identification of patients with ongoing abdominal sepsis after their initial surgical treatment. Initial abdominal microbial profiles are evaluated if they are associated with ongoing abdominal sepsis or death in Chapter 7. As in the evaluation of acute abdominal pain there are clinical scoring tools used in abdominal sepsis such as the APACHE-II or SOFA score. These have been designed to predict outcome in terms of morbidity and mortality in critically ill patients. The most commonly used scoring tools were examined in Chapter 8 for their ability to identify patients with an ongoing abdominal
sepsis needing a relaparotomy. In contrast to the scoring tools evaluated in chapter 8 a new scoring tool specifically designed to aid selection of patients with ongoing abdominal sepsis needing a relaparotomy is described in Chapter 9. Although a randomized study has clearly shown that relaparotomy on demand should be the surgical strategy of choice, planned relaparotomy in abdominal sepsis is still practised. In Chapter 10 factors are uncovered that hinder and stimulate the implementation of the on demand strategy.
REFERENCES