COMPLICATED ACUTE PANCREATITIS

INTERVENTIONS AND TIMING OF TREATMENT

Sven M. van Dijk



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COMPLICATED ACUTE PANCREATITIS – INTERVENTIONS AND TIMING OF TREATMENT

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CHAPTER 1

General introduction and thesis outline

This chapter is partly based on '*Managing infected pancreatic necrosis*'
Chirurgia 2018 May-Jun;113(3):291-299

BACKGROUND

Acute pancreatitis (AP) is an inflammatory process of the pancreas involving a varying local and systemic inflammatory response. The rising incidence of AP in both the United States and Europe has placed an increasing burden on healthcare services(1,2). The majority of cases of AP are mild and thus self-limiting, with an associated mortality rate below 1%(3). The remaining 20% of patients will develop severe acute pancreatitis (SAP), with an associated mortality rate of 10-40%(3).

The predominant aetiological factors of AP are gallstones, biliary sludge and alcohol. Irrespective of the aetiology of AP, intra-pancreatic activation of digestive enzymes, coupled with persistently elevated cytosolic calcium, triggers activation of trypsinogen(4,5) resulting in pancreatic autodigestion. Alterations in the microcirculation of the pancreas as a result of hypovolaemia, increased capillary permeability, possible localised vasoconstriction as well as hypercoagulability all contribute to pancreatic ischaemia (6). In combination with the release of various inflammatory mediators, cellular apoptosis and necrosis, either peripancreatic or pancreatic necrosis or both can result. Necrosis is directly related to disease severity and secondary infection of this necrosis is responsible for between 66-80% of late mortality in patients with SAP (7–9). Thus, the formation of necrosis and subsequent infection thereof carries significant prognostic implications. Inhibition of the cascade of events that lead to development and progression of AP has been subject of much investigation. Strategies to prevent the formation of pancreatic necrosis would be clearly beneficial in AP. To date, therapy remains largely supportive in the early phase of AP. Adequate fluid resuscitation is essential to improve patient outcomes (10), but does not prevent the formation of pancreatic necrosis per se (11). Furthermore, modulation of pro-inflammatory, anti-inflammatory and/or cellular responses have shown promise in experimental models, but were not beneficial in the clinical setting (5). Thus, efforts need to be concentrated on optimal prevention of infected pancreatic necrosis as well as improving management strategies.
This thesis focusses on the treatment strategies in patients with pancreatic necrosis.

TIMING OF INTERVENTION

In patients with infected (peri-)pancreatic necrosis, the timing of intervention is not well established. There are numerous reasons for delaying surgical intervention. First, encapsulation of the collections evolves over time towards walled off necrosis (WON) as the necrosis liquefies, facilitating interventional procedures. Current guidelines recommend delaying intervention until around 3-4 weeks to allow this process to occur (3,10,12). Second, extrapolated data from patients undergoing open necrosectomy demonstrated worse outcome after early necrosectomy (10). Finally,

the risk of bowel perforation and bleeding during necrosectomy decreases as the collection matures towards WON. It is recognised, however, that in certain patients delaying drainage for up to 4 weeks is not always possible due to deteriorating sepsis. It is believed that by releasing the pressure of the infected (peri-)pancreatic fluid, systemic sepsis is halted. This in turn allows for further antibiotic therapy to take place and continued maturation of the WON (13). In such cases, percutaneous drainage should be performed and if required, the necrosectomy delayed. The POINTER trial (ISCRTN33682933), a multicenter randomized controlled trial of which the protocol is presented in this thesis, compares the outcomes of immediate (< 24 hrs) versus delayed drainage after diagnosing infected (peri-)pancreatic necrosis. With the hypothesis that earlier intervention may prevent clinical deterioration and ultimately improve outcome.

INVASIVE INTERVENTION

Acute necrotic collections (ANC) and WON carry a 32% risk of becoming infected (14). Although some studies have reported successful antibiotic treatment for these infected collections, most patients will progress to an invasive intervention (15–17). Sterile necrosis can be treated conservatively in the vast majority of patients(14). Interventions in patients with symptomatic sterile necrosis may actually introduce infection into the (peri-)pancreatic necrosis. Infected (peri-)pancreatic necrosis was historically treated with early laparotomy and debridement of the necrotic material. This approach was however associated with significant morbidity, mortality as well as long-term pancreatic insufficiency (17). The landmark PANTER trial publication in 2010 revolutionized the surgical invention of infected (peri-) pancreatic necrosis, demonstrating the superiority of the minimally invasive step-up approach (17). As a result, initial percutaneous catheter drainage, followed by, if necessary, necrosectomy, the so called 'step-up approach', has become the standard of care. Catheter drainage will successfully treat infected (peri-)pancreatic necrosis in 35-70% of cases (17–20), without the need for an additional necrosectomy.

The approach to necrosectomy has also shifted from open surgery to minimally invasive techniques. Minimally invasive retroperitoneal, endoscopic and laparoscopic necrosectomies have all been performed. Video-assisted retroperitoneal debridement (VARD) is a relatively straightforward strategy for patients in whom left or right sided retroperitoneal collections with infected necrosis are drained (12). Using a small (i.e. 5 cm) incision, with a zero-degree camera and long graspers, a minimally invasive necrosectomy can be performed safely. A recent analysis of 1980 patients favoured endoscopic and minimally invasive surgical necrosectomy in very high risk patients, demonstrating a lower risk of mortality when compared to patients who underwent open necrosectomy

(21). A small multicenter randomized controlled trial (RCT) compared endoscopic transluminal necrosectomy with minimally invasive necrosectomy and concluded that the endoscopic approach reduces the pro-inflammatory response and the rates of major complications, pancreatic fistulae and death (22). The more recent, large multicenter TENSION RCT compared endoscopic transluminal drainage with endoscopic necrosectomy (if necessary) with percutaneous catheter drainage followed by VARD (if required) (18). Although the endoscopic step-up approach failed to demonstrate superiority when compared to the surgical step-up approach with regard to reducing major complications or death it did reduce the rate of pancreatic fistulae as well as hospital stay.

Many variables have been introduced in the era of managing infected (peri-) pancreatic necrosis through minimally invasive techniques that require further investigation. The initial sizes of drains and stents, the number as well as the role/timing of upsizing these drains or stents, the ideal types of drains and stents as well as the route, method and type of lavage all still need to be established. Additionally, the combination of both endoscopic and minimally invasive techniques are possible, but the benefit thereof is untested. Currently, the evidence is clearly in favour of a step-up approach in the management of infected (peri-)pancreatic necrosis with a preference to minimally invasive necrosectomy. Furthermore, initial data indicates that the endoscopic route may potentially be more beneficial when compared to the percutaneous minimally invasive route.

OUTLINE OF THE THESIS

With the paradigm shift from direct open necrosectomy to a delayed minimally invasive step-up approach, mortality of SAP has been drastically reduced. However, even with the current minimally invasive techniques, mortality rates remain between 15-19% (17–20). The aim of the studies in this thesis is to investigate several aspects of the (minimally invasive) treatment of (infected) necrotizing pancreatitis. Furthermore, the diagnosis and treatment of disruption or disconnection of the pancreatic duct, as a result of the parenchymal necrosis, is explored.

This thesis aimed to answer the following questions:

- What is the evidence in the diagnosis, classification and treatment of acute pancreatitis, emphasizing the evidence obtained through randomized controlled trials? (Chapter 2)
- What are the outcomes of Video-assisted Retroperitoneal Debridement (VARD) in a large multicentre cohort, and how have the use and outcomes of VARD evolved in time? (Chapter 3)
- What are the treatment strategies used in patients with a disrupted or disconnected pancreatic duct, as a result of acute necrotizing pancreatitis, and what are the outcomes of these different treatment strategies? (Chapter 4)

- What are the imaging modalities for diagnosing a disrupted pancreatic duct in patients with acute pancreatitis, and what is the diagnostic accuracy? (Chapter 5)
- What is the study design of the multicenter randomized controlled POINTER trial; comparing immediate catheter drainage to postponed catheter drainage in patients with infected necrotizing pancreatitis? (Chapter 6)

With the improved outcomes since the introduction of the minimally invasive step-up approach, new studies will most-likely have smaller impact. Recently the Comprehensive Complication Index (CCI) was developed to be more sensitive than existing morbidity endpoints and may serve as a primary endpoint (23).

- What is the value of the Comprehensive Complication Index as an outcome measure in patients with infected necrotizing pancreatitis? (Chapter 7)

Finally, in clinical research the importance of patients' opinions in has grown significantly, with an increased involvement and participation of patients in nearly all stages of the research process. Therefore, we investigated the opinion pancreatitis patients on clinical research.

- What are, according to patients with acute and chronic pancreatitis, the major clinical symptoms, what is their experience with participating in research, and what is their advice about topics for future clinical research? (Chapter 8)

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2

CHAPTER 2

Acute pancreatitis: recent advances through randomised trials

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Gut 2017 Nov;66(11):2024-2032

ABSTRACT

Acute pancreatitis is one of the most common gastrointestinal conditions requiring acute hospitalisation and has a rising incidence. In recent years, important insights on the management of acute pancreatitis have been obtained through numerous randomised controlled trials. Based on this evidence, the treatment of acute pancreatitis has gradually developed towards a tailored, multidisciplinary effort, with distinctive roles for gastroenterologists, radiologists and surgeons. This review summarises how to diagnose, classify and manage patients with acute pancreatitis, emphasizing the evidence obtained through randomised controlled trials.

BACKGROUND

With over 26.000 hospital admissions in the United Kingdom each year, acute pancreatitis is among the most common gastrointestinal conditions requiring acute hospitalisation.[1] The worldwide incidence of acute pancreatitis is rising, thus further increasing its burden on health care services.[2] Acute pancreatitis is an inflammatory process which causes a local and systemic inflammatory response syndrome (SIRS). Although the majority of patients have a mild disease course, around 20% will develop moderate or severe pancreatitis, with necrosis of the (peri)pancreatic tissue and/or (multiple-)organ failure (Figure 1).[3]

Over the last decades, the treatment of acute pancreatitis has gradually developed towards a tailored, multidisciplinary approach, with a distinctive role for endoscopic, radiological and surgical treatment strategies. Much of the new evidence on the treatment of acute pancreatitis arises from randomised controlled trials (RCT's), which are universally considered as the reference standard for comparing treatment strategies in medicine. Random allocation of patients, if possible blinded, keeps all known and unknown variables constant except for the allocated treatment, thereby measuring the 'true' effect of the investigated treatment. In the past decade, numerous RCT's have had a great impact on the treatment of acute pancreatitis. This review provides an overview of current clinical practice concerning the diagnosis, classification and treatment of acute pancreatitis, while focussing on the outcomes of these RCT's.

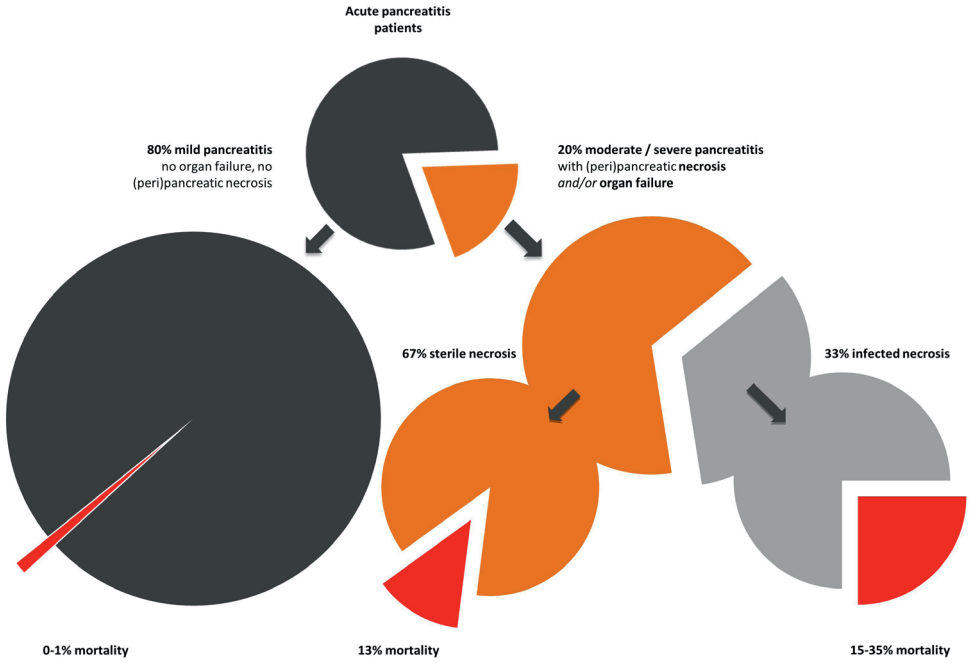


Figure 1 – Mortality rates of acute pancreatitis

METHODS

For this review the most recent international evidenced-based guidelines on acute pancreatitis, the 2012 International Association of Pancreatology / American Pancreatic Association (IAP/APA) guidelines,[4] were used as the starting point. PubMed was searched for studies, specifically RCT's, published after the IAP/APA guideline using the following terms: Pancreatitis (MeSH Terms) OR (acute pancreatitis (Title)). All articles regarding chronic pancreatitis and malignant disease were excluded. Two authors (SvD and NH) assessed all English articles concerning RCT's on adults published between June 2012 and February 2017. In total 490 articles were found of which all potential 'practice changing' RCT's were incorporated within this review. Additionally, relevant articles from the reference list of the included articles were reviewed as well as new, evidence-based guidelines on acute pancreatitis published after the IAP/APA guideline.

EARLY PHASE OF ACUTE PANCREATITIS

Diagnosis

According to the 2012 Revised Atlanta Classification, the diagnosis acute pancreatitis requires at least two of the three following criteria: (1) abdominal pain consistent with pancreatitis, (2) serum amylase and/or lipase of at least 3 times the upper limit of the normal value or (3) findings consistent with acute pancreatitis on imaging (contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) or ultrasound).[5] In case of typical clinical and laboratory findings, an additional CECT or other cross sectional imaging is not required to confirm the diagnosis. The severity of acute pancreatitis is classified as mild, moderate or severe. Mild when there are no local or systemic complications present; moderate in case of local (e.g. peripancreatic fluid collections) or systemic complications (e.g. exacerbation of chronic disease) or transient organ failure (<48h) and severe in case of persistent organ failure (>48h).[5]

Aetiology

In Western countries, gallstones and/or biliary sludge are the most prevalent (approximately 40-50%) cause of acute pancreatitis.[6,7] With approximately 20% of cases, alcohol is the second most frequent cause of acute pancreatitis in most countries.[6–8] Less frequent causes of acute pancreatitis include medication, endoscopic retrograde cholangiopancreatography (ERCP), hypercalcemia, hypertriglyceridemia, surgery and trauma.

Determining the aetiology of acute pancreatitis is of importance, as it partly drives early management as well as the follow-up strategy. Standard work-up of acute pancreatitis includes medical history, physical examination, laboratory tests (liver

enzymes, triglycerides, calcium) and transabdominal ultrasound. In 10-25% of cases the aetiology of the pancreatitis remains unclear. Idiopathic pancreatitis requires additional diagnostic work-up in the form of a repeat transabdominal ultrasound and ultimately an endoscopic ultrasound (EUS).[4] Meta-analyses show that in around 61% of cases an aetiology can be established by EUS. This includes the detection of microlithiasis or biliary sludge (41%), for which cholecystectomy is required to prevent recurrences (Figure 2), but also other causes such as chronic pancreatitis or pancreatic tumours.[9]

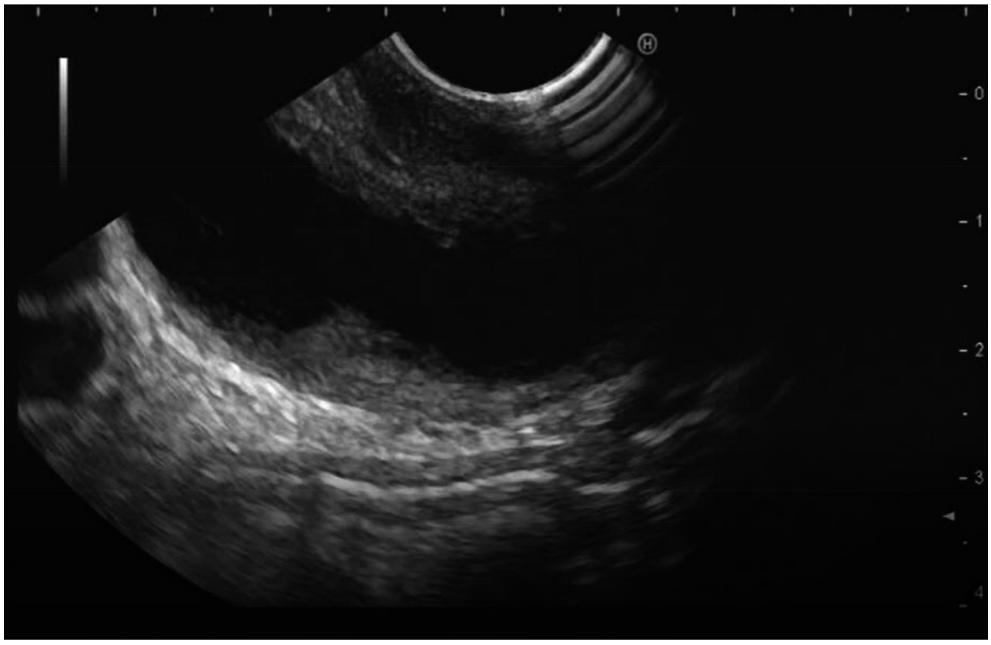


Figure 2 - Linear endoscopic ultrasound image of sludge in the gallbladder

Prediction of severity

Prediction of severity of acute pancreatitis is used to identify patients at low or high risk of developing complications. This is useful both for triaging patients for the proper level of monitoring and for stratification of patients for inclusion in RCT's. Multiple scoring systems are available that combine clinical and laboratory findings to determine the likelihood of a severe disease course: the acute physiology and chronic health evaluation II (APACHE-II), Ranson score, modified Glasgow/Imrie score, SIRS criteria, bedside index for the severity in acute pancreatitis (BISAP) and harmless acute pancreatitis score (HAPS), while single laboratory parameters such as C-reactive protein (CRP) can also be used.

Approximately 50% of all patients have predicted severe pancreatitis. Although only half of these will ultimately develop (moderately) severe pancreatitis, virtually none of the patients with predicted mild pancreatitis will do so. Mortality of predicted severe pancreatitis is approximately 10%, as compared to <1% in patients with predicted mild pancreatitis. The scoring systems are therefore primarily used to exclude the possibility of developing severe pancreatitis. Since the accuracy of the various predictive scoring systems is comparable,[10] the IAP/APA guideline advises to use persistent (>48h) SIRS because of its relative simplicity.[4]

Treatment in the acute phase

As no curative therapy is currently available for acute pancreatitis, early treatment consists of supportive care which includes adequate fluid resuscitation and pain management.

Fluid resuscitation

Inflammation of the pancreas and the accompanying systemic inflammatory response leads to extravasation of fluid to the third space. In severe cases this may cause hypovolemia, hypoperfusion and ultimately organ failure. To counteract this cascade, adequate fluid resuscitation is needed. Few RCT's studied the type of fluids. In critically ill patients in general, colloids are discouraged since there is no evidence to support their effectiveness whereas hydroxyethyl starch (HES) might even increase mortality.[11] The IAP/APA guideline therefore proposes crystalloids in the form of Ringer's lactate. This is based on one multicentre RCT in 40 patients with acute pancreatitis that showed beneficial effects on CRP levels and SIRS with Ringer's lactate as compared to normal saline.[4,12] This advantage of Ringer's lactate or other balanced fluids (e.g. Plasma-lyte) over normal saline in pancreatitis patients has however not been confirmed by larger RCT's. Further studies are needed as multiple RCT's in the general intensive care setting have so far failed to find better outcomes when using balanced fluids.[13–16]

Five RCT's using different fluid resuscitation protocols have been conducted.[12,17–20] Two of these RCT's in 76 and 115 patients with severe acute pancreatitis show that rapid, uncontrolled fluid resuscitation (10-15/ml per kg per hour or a until a haematocrit <35% within 48h) significantly worsened the rates of infections, abdominal compartment syndrome, the need for mechanical ventilation and even mortality.[17,18]

One RCT in 60 patients with predicted mild pancreatitis demonstrated that aggressive fluid hydration with Ringer's lactate (20ml/kg bolus followed by 3ml/kg/h) compared to standard hydration with Ringer's lactate (10 mL/kg bolus followed by 1,5 ml/kg/h) improved a composite endpoint (i.e. 'clinical improvement

within 36h').[19] So, both too little as well as too much fluid administration in the acute phase of pancreatitis can be harmful, possibly dependent on the severity of the pancreatitis. As advised by the IAP/APA guideline, early goal directed therapy with adequate monitoring might therefore remain the preferred solution.[4]

Early goal-directed therapy was the subject of one multicentre RCT in 40 acute pancreatitis patients and one RCT in 200 patients with severe acute pancreatitis.[12,20] The first RCT could not confirm superiority of early goal-directed therapy, but the incidence of SIRS in the entire RCT was very low, suggesting less severe pancreatitis patients. The second RCT showed reductions in the duration of mechanical ventilation and in the rates of multiple organ failure and mortality in the early goal-directed therapy group, especially if fresh frozen plasma was added as a resuscitation fluid. However, as baseline APACHE-II scores were significantly worse in the control group, suggesting non-balanced randomization, further RCT's are needed.

It is difficult to draw conclusions based on these RCT's as multiple of the three main parameters of interest (fluid type, fluid protocol and resuscitation goals) differ between trials. Since no single parameter adequately reflects hydration status, it is therefore advised to observe trends in multiple parameters. On the nursing ward, target measures include a heart rate <120/min, a mean arterial pressure between 64 and 85 mmHg and a urinary output of at least 0.5 ml/kg/h. Relevant laboratory findings include blood urea nitrogen (BUN), creatinine levels and especially haematocrit, which should stay between 35% and 44%.[4]

Pain management

Pain is the predominant symptom of acute pancreatitis and should be treated promptly and adequately. Frequent reassessment of pain scores and, if indicated, adjustment of analgesic types and/or dosages is needed to assure proper pain management. Several RCT's compared different types of analgesia in acute pancreatitis.[21–28] A systematic review on opioid use in acute pancreatitis and a recent meta-analysis reported that the quality of the majority of these RCT's is low and no particular analgesic strategy is superior.[29,30] As current evidence is limited, pain can be managed according to general state-of-the-art pain protocols.

Antibiotics and probiotics as prophylaxis

One of the most lethal complications of acute pancreatitis is secondary infection of pancreatic or peripancreatic necrosis.[31] This is thought to occur as a result of bacterial translocation from the gut.[32] Several double-blind RCT's failed to show a reduction of infection of (peri)pancreatic necrosis through the prophylactic use of

antibiotics,[33–35] as confirmed by meta-analyses.[36,37] Antibiotics are therefore only indicated when infection is either proven or clinically suspected. In order to prevent bacterial translocation, attempts were made to influence the intestinal microbiome using probiotic bacteria. Two RCT's compared probiotic bacteria with placebo in 62 and 45 patients with severe acute pancreatitis and reported promising results.[38,39] A subsequent multicentre RCT* in 296 patients with predicted severe pancreatitis, however, showed increased rates of mortality and non-occlusive mesenteric ischemia in patients receiving probiotics.[40] Therefore, administration of probiotics is currently considered contraindicated in the treatment of (predicted) severe pancreatitis.

Nutrition

Enteral nutrition does not only provide adequate caloric intake, it may also improve clinical outcomes. It has been hypothesized that the combination of disturbed intestinal motility, bacterial overgrowth, and increased permeability of the gut, can lead to bacterial translocation thus causing infection of pancreatic necrosis.[32,41–45] Enteral nutrition may reduce translocation by stimulating intestinal motility, reducing bacterial overgrowth and thereby maintaining mucosal gut integrity.[46,47] A Cochrane review involving 8 RCT's confirmed this, showing reduced rates of infection, organ failure and mortality in 348 patients with acute pancreatitis receiving routine enteral nutrition as compared to routine total parenteral nutrition.[48]

Furthermore, the timing of initiation of enteral nutrition could also be relevant. Some retrospective studies suggested that an early start of naso-enteric feeding significantly reduced infection rates.[49–51] A multicentre RCT* in 208 patients with predicted severe pancreatitis, comparing very early nasojejunal feeding (<24h) with introduction of an oral diet after 72 hours (with on-demand nasojejunal feeding) showed no beneficial effects on infection rates or mortality. Importantly, in the control group, 69% of patients did not require a naso-enteral tube, thus avoiding potential patient discomfort.[52] A second recent RCT, comparing early nasojejunal feeding (<24h) with no nutritional support in 214 patients, also failed to show benefits from early nutritional support.[53] Based on these RCT's, tube feeding in predicted severe pancreatitis can be limited to those patients who have insufficient oral caloric intake after 3-5 days.

It was previously believed that nasogastric feeding in acute pancreatitis would increase the risk of aspiration, and increase inflammation and pain as a result of stimulation of the pancreatic excretion. However, as 3 RCT's found nasogastric feeding non-inferior to nasojejunal feeding.[54–56] Consequently, both routes of enteral feeding are now considered feasible and safe.[57] In patients with

(predicted) mild pancreatitis, 3 RCT's have shown that a normal oral diet can be resumed once the pain is decreasing.[58–60]

ERC in biliary pancreatitis

In patients with acute biliary pancreatitis, (transient) obstruction at the level of Vaters ampulla is thought to initiate pancreatic inflammation. Persisting biliary obstruction may aggravate the disease course. Early biliary decompression and stone removal using endoscopic retrograde cholangiography (ERC) with endoscopic sphincterotomy (ES) has therefore been extensively studied as a potential intervention to improve clinical outcomes in biliary pancreatitis. Common bile duct (CBD) stones may however, pass into the duodenum spontaneously, in which case ERC with ES might be redundant and even harmful. Several RCT's have shown that early ERC is not effective in patients with predicted mild pancreatitis,[61–63] as the potential benefits do not outweigh the procedural risks.

Emergency ERC with ES is indicated within 24 hours after diagnosing acute biliary pancreatitis with concomitant cholangitis.[4,64] Importantly, diagnosing cholangitis in patients also suffering from SIRS, as is commonly seen in the early phase of (predicted severe) biliary pancreatitis can be challenging. The definition of cholangitis differs between trials and includes Charcot's triad,[61] expert opinion[65] and the updated Tokyo guidelines (TG13) for acute cholangitis.[66] These definitions do not take into account the underlying cause, namely acute pancreatitis, and have low thresholds regarding the presence of inflammation and cholestasis. This may lead to overdiagnosing of acute cholangitis in acute pancreatitis, potentially exposing patients to unnecessary ERC procedures[66]. Further research is needed to establish appropriate diagnostic criteria for cholangitis in acute biliary pancreatitis patients.

The use of routine (early) ERC with ES in predicted severe biliary disease course is controversial. Several RCT's,[61–63,65,67,68] subsequent meta-analyses and guidelines provide conflicting advice on this issue.[69] A possible explanation for these discrepancies are the differences in the definitions used for biliary pancreatitis and cholangitis, as well as differences in patient populations and in timing and quality of the ERC. For example, in some studies ERC was performed in non-biliary pancreatitis, in other studies patients with cholangitis were randomised while these patients should always undergo ERC and sphincterotomy was not performed routinely. Recently, a multicentre RCT* comparing routine early ERC plus ES with conservative treatment in 232 patients with predicted severe acute biliary pancreatitis but without cholangitis, was completed and results are awaited (the APEC-trial, ISRCTN97372133).[70]

The use of EUS for the detection of CBD stones is emerging in biliary pancreatitis. The sensitivity and specificity of EUS for CBD stone detection are superior to both transabdominal ultrasound and serum markers. As ERC with ES is presumably most effective in patients with persisting CBD stones, an EUS-first strategy to establish the indication for ERC with ES in acute biliary pancreatitis patients could improve outcomes. A meta-analysis comparing an EUS-first strategy with ERC including one RCT in 140 patients showed promising results. Around 71% of ERC procedures could be avoided without a negative effect on the clinical course of the pancreatitis.[71,72] A recent prospective cohort study supports these observations.[73] Furthermore, a decision tree analysis on cost effectiveness demonstrated that, especially in patients with severe acute biliary pancreatitis, an EUS-first method is less costly than ERC only.[74] Further research is needed to confirm the effectiveness and feasibility of this relatively new strategy.

BEYOND THE EARLY PHASE

Imaging

The 1992 Atlanta Classification was a global consensus on how to define acute pancreatitis and how to classify the severity and local pancreatic complications.[31] In 2012, the Atlanta classification was revised to better define the morphology of acute pancreatitis and (peri)pancreatic collections as seen on CECT.[5] The revised Atlanta classification distinguishes interstitial oedematous pancreatitis from necrotising pancreatitis, wherein the latter is subdivided in parenchymal and peripancreatic necrosis (Figure 3). In most cases a combination of parenchymal and peripancreatic necrosis is seen.[5] In the first 3-4 days of acute pancreatitis, CECT is unreliable for determining the extent of necrosis and the presence of collections.[75,76] Only patients suspected of having abdominal catastrophes, such as perforation, bleeding or ischaemia, should have an urgent CECT.[76,77] If patients fail to improve after 5-7 days of initial treatment, a CECT can determine the presence and extent of necrosis and (peri)pancreatic collections.[4,64]

The terminology of (peri)pancreatic collections has changed in the revised Atlanta classification.[5] In case of interstitial pancreatitis these collections are referred to as 'acute pancreatic fluid collections' (APFC), and in case of necrotising pancreatitis as 'acute necrotic collections' (ANC). Over time, acute collections either resolve spontaneously or mature with encapsulation of fluid and/or necrotic tissue. In ANC this leads to walled-off necrosis (WON) (Figure 4).[5,78] The process of encapsulation mostly takes around 4-6 weeks. If the necrotic collections remain sterile, patients can be treated conservatively. Intervention is only indicated in case of infection. In sterile collections interventions should only be considered in case of mechanical obstruction and/or failure to thrive which persists for 6-8 weeks.

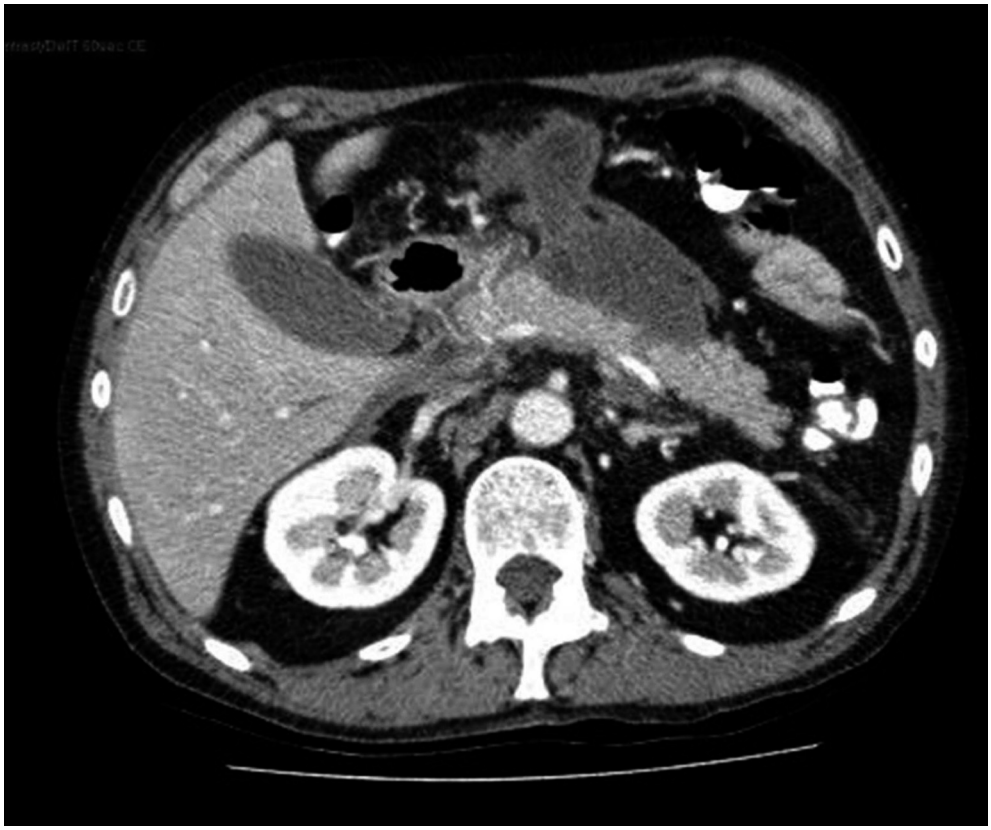


Figure 3 - Peripancreatic necrosis—a form of necrotising pancreatitis

INFECTED NECROTISING PANCREATITIS

Collections with necrosis (i.e. ANC, WON) become infected in about one-third of patients.[79] Infected necrotising pancreatitis has a mortality of 15%.[3] Infection can be diagnosed in three ways: 1) by gas configurations in the necrotic collection on imaging (figure 5),[5] 2) by a positive gram stain or culture from a (percutaneous) fine-needle aspiration of the necrotic collection[80] or 3) suspected by clinical diagnosis. Clinical suspicion of infection is based on signs of infection (temperature >38.5 degrees Celsius, rising serum inflammatory markers) or when new/persistent organ failure occurs, which is typically most reliable after the initial phase of SIRS. [4,81,82]

If infection of a necrotic collection is proven or clinically highly suspected, antibiotic treatment is indicated. The preferred antibiotics are broad-spectrum, with the capability of penetrating the necrotic pancreatic tissue, according to local antibiotics protocol. A positive culture may be used to switch to targeted antibiotics. Although there are some series with high success rates of solely antibiotic treatment, most

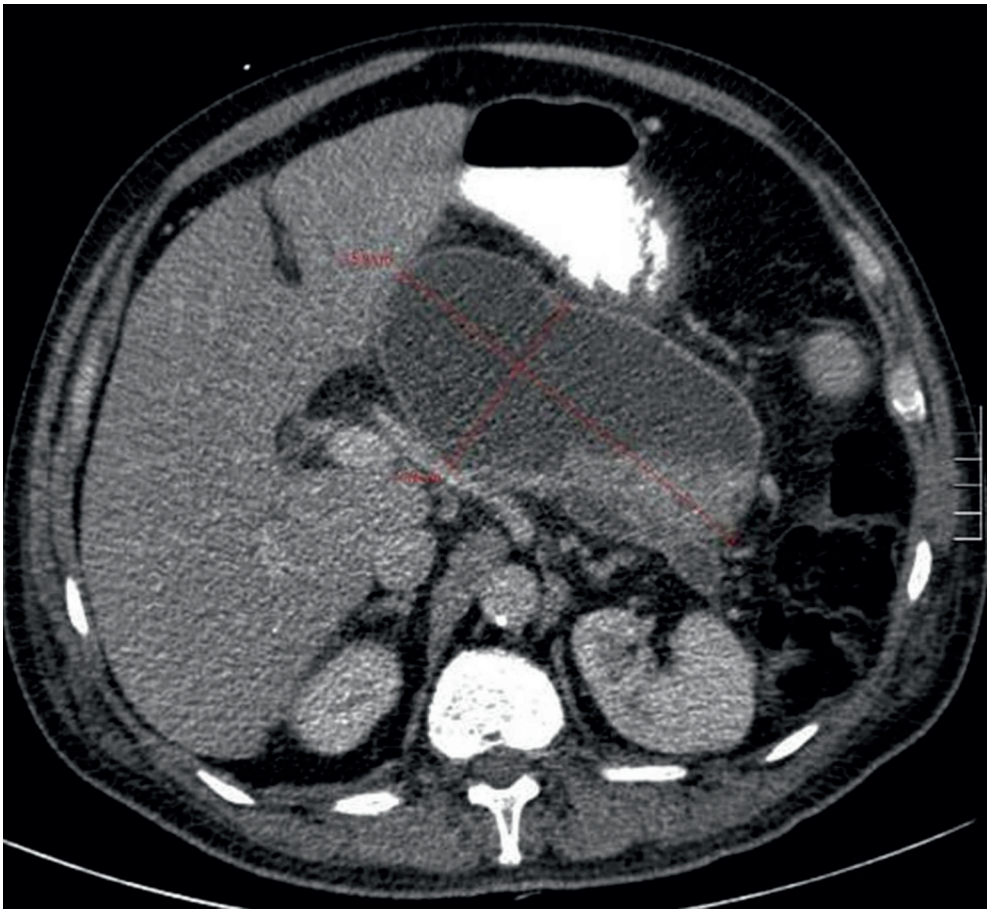


Figure 4 - Walled-off necrosis—a form of necrotising pancreatitis

patients will eventually need an intervention (i.e. catheter drainage, necrosectomy) to treat infected necrosis (Figure 1).[82–84] Antibiotics are therefore mostly used to support patients until collections become encapsulated (WON). This is presumed to facilitate safer interventions with a lower risk of bleeding and less re-interventions. Some experts, however, question this delay in treatment and suggest immediate catheter drainage.[85] A multicentre RCT* is currently comparing immediate vs postponed drainage in 104 patients with infected necrotising pancreatitis (POINTER trial; ISCRTN33682933).

Intervention

Historically, patients with necrotising pancreatitis underwent early laparotomy to debride the necrotic tissue. This was associated with high mortality rates, probably because these often severely ill patients could not endure the extra 'hit' of the surgical trauma.[86,87] Current guidelines therefore advocate to delay interventions until

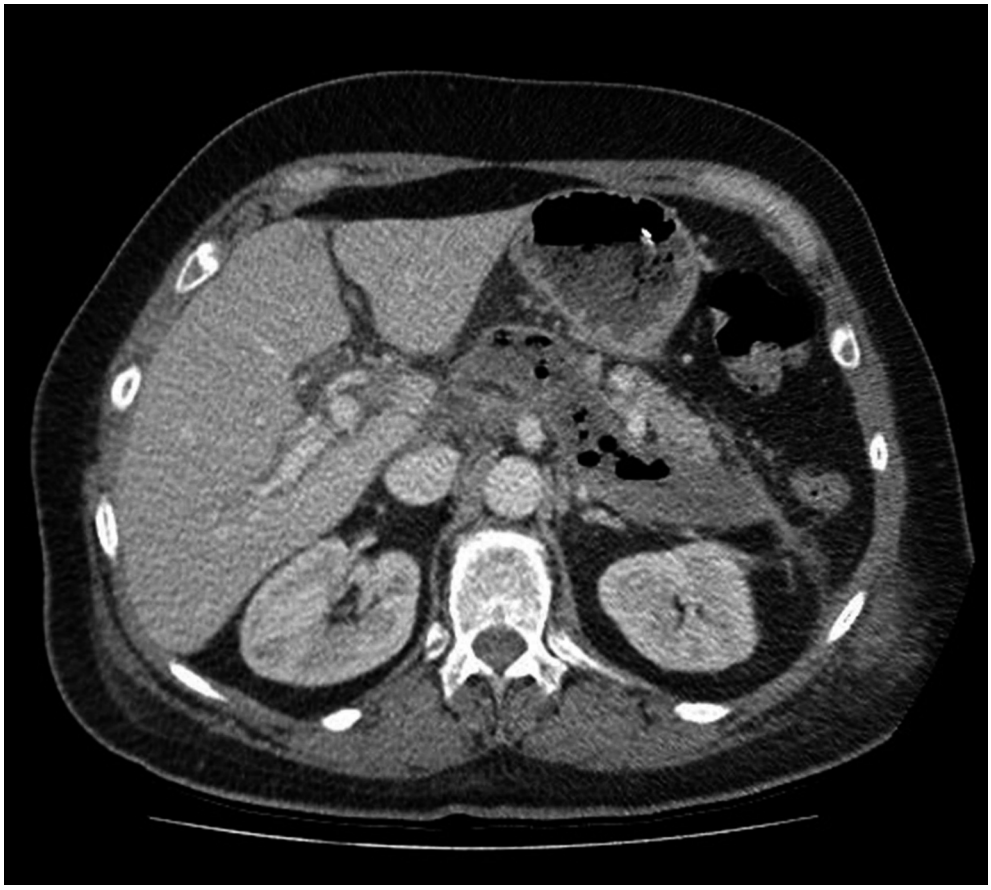


Figure 5 - Infected necrotic collection, with gas configurations, on day 20 after onset of disease. Not fully encapsulated

the stage of WON[4,64]. In a multicentre RCT*, 88 patients with infected necrotising pancreatitis were randomised between necrosectomy via laparotomy or a step-up approach. This approach consisted of percutaneous catheter drainage followed, in case of lack of clinical improvement, by video-assisted retroperitoneal debridement (VARD).[82] The step-up approach reduced the composite endpoint (i.e. death or major complications) from 69% to 40% (risk ratio 0.57; 95% CI 0.38–0.87; p=0.006). Another finding was that 35% of patients in the step-up arm could be treated with catheter drainage only, and did not require a necrosectomy.[82]

The step-up approach is now considered the standard practice of care for patients with infected pancreatic necrosis and has been implemented in all major guidelines.[4,64] Catheter drainage is only followed by necrosectomy when clinically indicated. Several methods of surgical necrosectomy are available; either open or minimally invasive techniques. As RCT's comparing these methods 'head-to-head' are lacking,

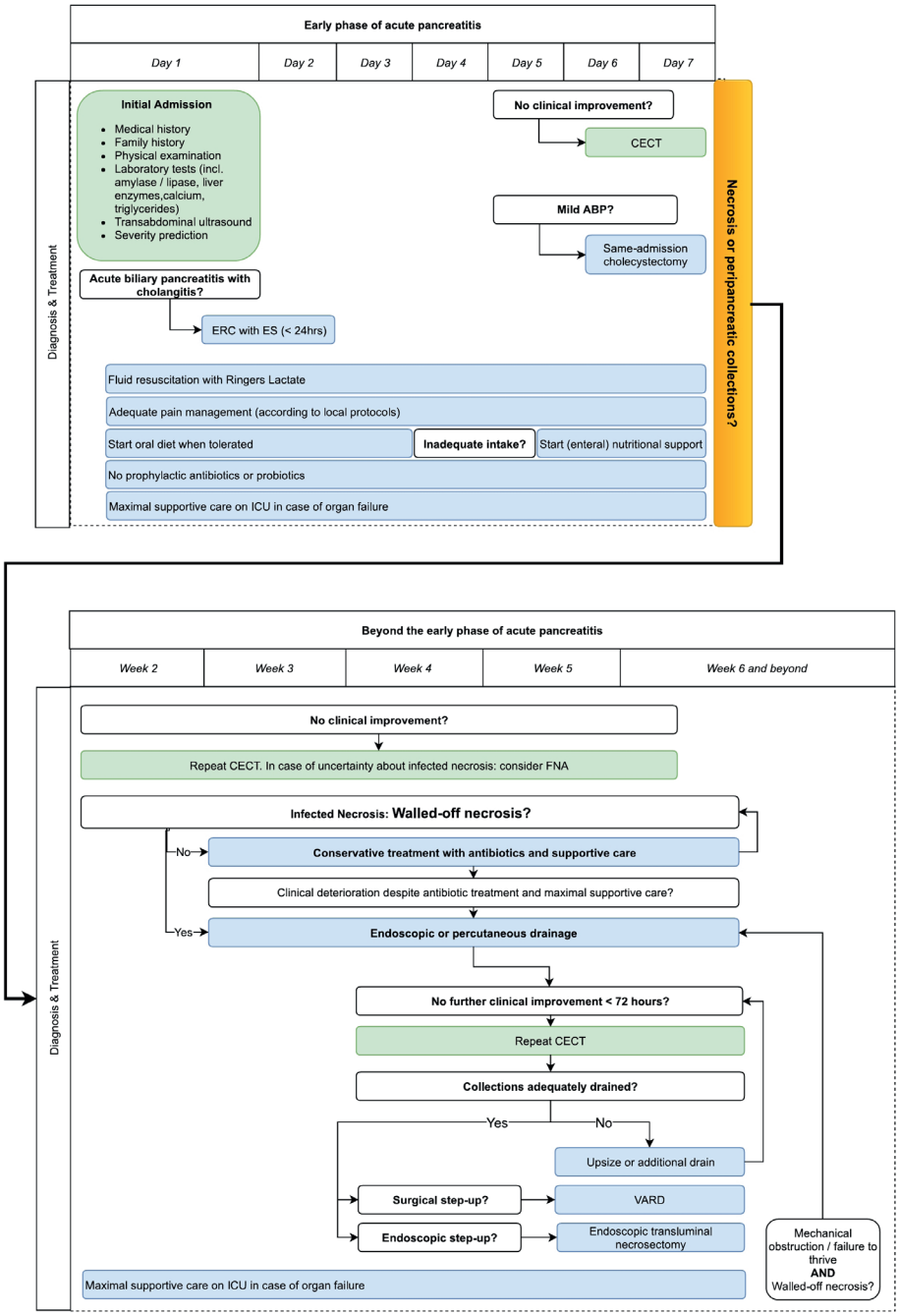


Figure 6 - Flowchart acute pancreatitis. CECT, contrast-enhanced CT; ERC, endoscopic retrograde cholangiography; ES, endoscopic sphincterotomy; VARD, video-assisted retroperitoneal debridement

the optimal method of necrosectomy remains unclear. Retrospective studies suggest a decreased risk of complications using minimally invasive techniques. [88,89]

The step-up approach can also be performed endoscopically. In 2000, endosonography-guided transgastric necrosectomy was first described. It avoids general anaesthesia and may further reduce the surgical stress and complications. [90] The technique has since been reported in several retrospective cohort studies. [91,92] A multicentre pilot RCT* in 20 patients found a reduction in the primary endpoint of pro-inflammatory response and in the combined secondary endpoint of major complications in patients undergoing endoscopic necrosectomy, compared to minimal invasive surgical necrosectomy.[93] Although promising, this was a pilot RCT and did not include a step-up approach. A subsequent multicentre RCT*, including 98 patients, comparing an endoscopic step-up approach with a surgical step-up approach has recently been completed and results are awaited (TENSION trial, ISRCTN09186711).[81]

AFTERCARE

Prevention of recurrence

Some 17-22% of patients will have a recurrent pancreatitis and 8-16% of patients will develop chronic pancreatitis.[94–96] Several studies have attempted to reduce recurrence rates, most of them addressing the underlying cause of the disease. In patients with alcoholic pancreatitis, supervised alcohol abstinence should be advised, as continuation of alcohol-consumption increases the risk of recurrence and ultimately of chronic pancreatitis.[97–99] Smoking is an additional, but poorly recognized, risk-factor for recurrent acute and chronic pancreatitis.[94] One RCT in 120 patients showed that repeated outpatient-clinic visits with an intervention against alcohol consumption reduces the recurrence of pancreatitis, compared to a single intervention.[100] However, adherence to these abstinence-programs remains poor.[101]

In patients with biliary pancreatitis, cholecystectomy will reduce the risk of recurrence but its optimal timing has been debated. In severe biliary pancreatitis it is common practice to delay cholecystectomy until the patient has recovered and local signs of inflammation have resolved or until at least 6 weeks after discharge.[102] In mild biliary pancreatitis, current guidelines recommend cholecystectomy during the same hospital admission. Several clinical audits have shown that guideline adherence is poor, cholecystectomy is often delayed.[99,103–107] Concerns about the perceived increased difficulty of surgical dissection after pancreatitis, resulting in higher surgical complication rates,[108,109] and logistical challenges with busy

emergency theatre lists[104,110] have probably contributed to these delays. A recent multicentre RCT* in 266 patients with mild biliary pancreatitis demonstrated that same-admission cholecystectomy reduced the recurrence rate of gallstone-related complications from 17% to 5% as compared to interval cholecystectomy after 4 weeks (RR 0.28, 95% CI 0.12–0.66; p=0.002).[111] This included a reduction of recurrent biliary pancreatitis from 9% to 2% (RR 0.27; CI 0.08–0.92, p=0.03). Same-admission cholecystectomy was not associated with increased technical difficulty or complications and decreased overall costs.[111,112]

The value of cholecystectomy has also been investigated in acute idiopathic pancreatitis. A multicentre RCT in 85 patients showed that routine elective laparoscopic cholecystectomy reduced the rate of recurrent pancreatitis from 30% to 10% (p=0.016) as compared to conservative management. However, since routine EUS was not included in the work-up of (presumed) idiopathic pancreatitis, the treatment effect of cholecystectomy may have been overestimated in this trial. Many patients with presumed idiopathic pancreatitis patients may in fact have had acute biliary pancreatitis. This was also reflected in the large percentage (59%) of gallbladders in which biliary stones or sludge were found at pathological examination in this RCT.[113]

Exocrine and endocrine insufficiency

Due to extensive loss of pancreatic tissue in necrotising pancreatitis, there is a reduction of both endocrine and/or exocrine pancreatic function in 19-80% of all patients.[114–117] Awareness on these conditions may support timely treatment in order to prevent complications from diabetes or malnutrition from malabsorption.

Future

This review summarised the best available evidence in acute pancreatitis, mostly based on RCT's. Although many clinical questions have been addressed by RCT's, many questions remain, for instance regarding fluid and pain management but also on the use and timing of interventions such as ERC and the 'step-up approach'. Besides these important questions no single RCT has reported on an effective treatment to halt the early sequence of severe systemic inflammation, ultimately leading to multiple organ failure and death in acute pancreatitis. Further innovative studies and RCT's are needed to find such a treatment and to improve outcomes in acute pancreatitis.

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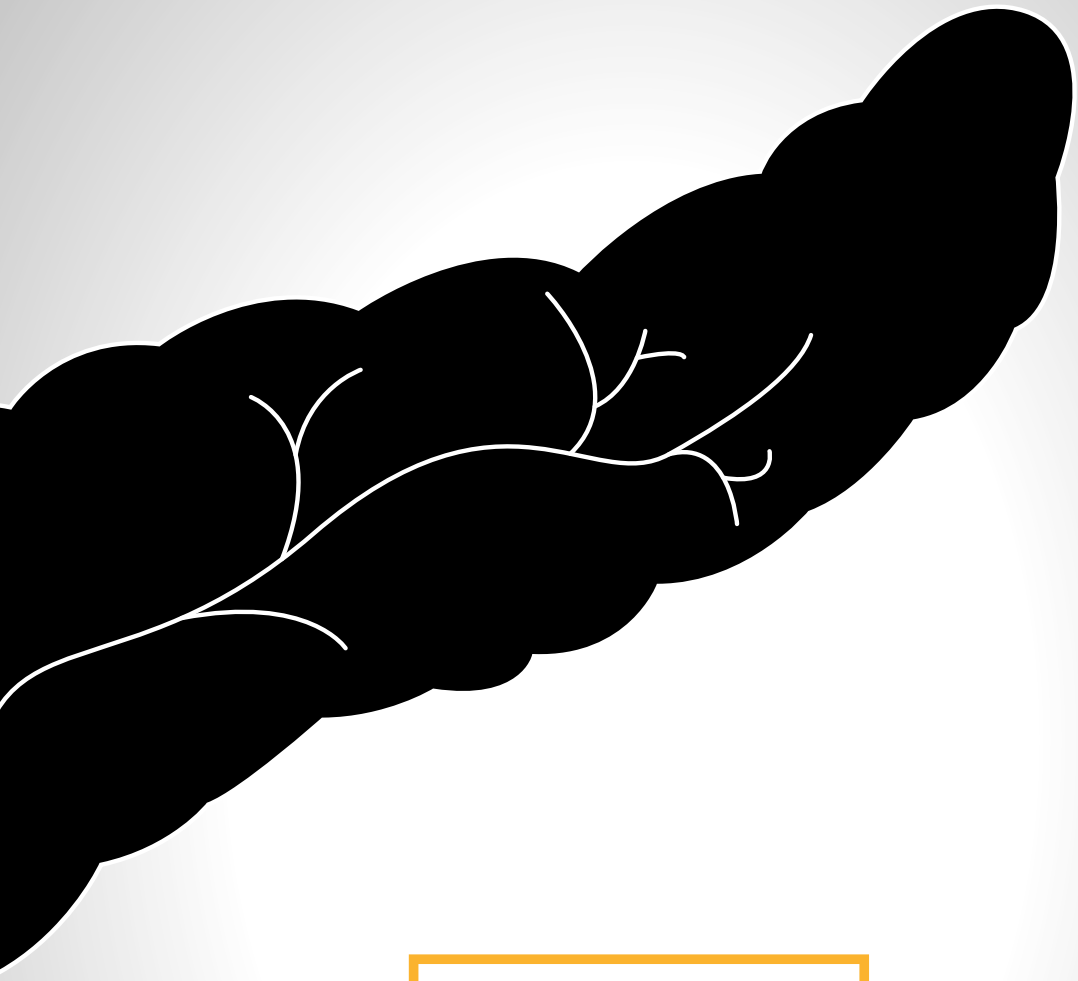
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3

CHAPTER 3

Outcome and timing of video-assisted retroperitoneal debridement (VARD) following catheter drainage in the step-up approach for infected necrotizing pancreatitis

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ABSTRACT

Introduction: Video-assisted retroperitoneal debridement (VARD) is the preferred surgical treatment in patients with infected necrotizing pancreatitis in whom percutaneous catheter drainage (PCD) alone does not suffice. Since the introduction of this step-up approach in 2009, the use of PCD has increased and it is unclear how this has influenced the use, timing and outcome of VARD.

Methods: A retrospective analysis of a nationwide cohort (2004-2015) of patients undergoing VARD after PCD for infected necrotizing pancreatitis in 21 hospitals in the Netherlands. Patients were prospectively followed during their initial admission, follow-up data were collected retrospectively. Primary endpoint was in-hospital death. Trends in time were analyzed, using 2009 as cut-off.

Results: In 108 patients in whom PCD did not suffice, a VARD was performed, with 15.7% (n=17) in-hospital mortality. The majority of patients (69%) was treated with one VARD procedure. After 2009, the number of pre-operative PCD procedures per patient increased (from median 1 [IQR 1-2] to 3 [IQR 1-3], $p<0.001$) and VARD was increasingly postponed (from 45.9 to 65.3 days, $p<0.001$). Meanwhile, the mortality after VARD did not improve (14.3% vs 16.9%, $p=0.705$).

Discussion: VARD is a safe and effective procedure in patients with infected necrotizing pancreatitis in whom PCD does not suffice. VARD is increasingly being postponed because of increased use of repeat PCD without improvement in clinical outcomes. Future research will have to investigate the optimal number of pre-necrosectomy PCD's and timing of PCD and subsequent VARD.

INTRODUCTION

The step-up approach (i.e. delay-drain-debride) is the treatment of choice for infected necrotizing pancreatitis.[1,2] The step-up approach can be performed either endoscopically or surgically.[3–5] During the last decade there has been a shift towards endoscopic transluminal procedures. Since not all necrotic collections are suitable for endoscopy, and endoscopic expertise is not always present, there clearly remains a role for the surgical step-up approach. In the surgical step-up approach, the first step is a percutaneous catheter drainage (PCD) of the collection with infected necrosis, preferably through the retroperitoneum.[6–8] Because 35-50% of patients can be successfully treated with PCD alone,[9,10] PCD has since become increasingly popular in recent years and many patients undergo repeat PCD procedures.

Many patients, however, will eventually need a necrosectomy after PCD.[6,11,12] Several techniques for necrosectomy have been described.[6,8,21,13–20] In the most severely ill patients, minimally invasive procedures are associated with better outcomes than open necrosectomy.[11,22] In the Netherlands, the video-assisted retroperitoneal debridement (VARD) is the preferred minimally-invasive surgical technique if PCD does not suffice.[23] VARD has previously been described in several series and was investigated in randomized trials.[5,6,11,24]

Large, long-term, prospective series on the implementation of VARD (i.e. IDEAL stage 4[25]), however, are lacking. Therefore, the aim of this multicenter study is to present outcomes of all consecutive VARD procedures that have been performed in the last 12 years in hospitals of the Dutch Pancreatitis Study Group. We evaluate the use, timing and outcomes of the VARD, with a focus on postoperative mortality and major complications.

METHODS

A post-hoc analysis of a multicenter prospective cohort (2004-2015) was performed in 21 hospitals comprising both academic hospitals and large teaching hospitals of the Dutch Pancreatitis Study Group (DPSG) in the Netherlands. In hospitals that participated in the previous randomized trials of the DPSG, all consecutive adult patients with acute pancreatitis (also patients who were non-eligible for the trials) were asked informed consent for registration between 2004 and 2015 (during enrollment of the PANTER[11] and TENSION[5] trials). Patients were prospectively followed during their initial admission, follow-up data were retrospectively collected, verified by two independent researchers (SMvD and NDH) and analyzed.

All patients who underwent a VARD procedure for infected necrotizing pancreatitis were included in this analysis. Patient who had undergone an emergency laparotomy for pancreatitis prior to VARD (e.g. abdominal compartment syndrome, bleeding or colonic ischemia) and patients with chronic pancreatitis were excluded.

Baseline characteristics were age, sex, ASA-classification, BMI, etiology, and ICU admission at time of VARD. The primary endpoint was in-hospital mortality, defined as death during index admission in which the VARD was performed. If a patient was readmitted within 7 days after discharge, this admission was considered as the same index admission. Secondary endpoints included new-onset organ failure after, bleeding requiring invasive intervention, pancreatic fistula, enteric fistula, number of drainages before necrosectomy, time between admission and necrosectomy, number of reinterventions, number of VARD procedures, length of postoperative hospital stay and length of postoperative stay on the Intensive Care Unit (ICU). New onset (post VARD) organ failure was defined as new onset circulatory (systolic blood pressure less than 90 mm hg or need for catecholamine support), pulmonary (PaO2 60 mmHg or less or need for mechanical ventilation) or renal failure (creatinine level greater than 177 umol/L after rehydration or need for hemofiltration or hemodialysis). Multiple organ failure was defined as failure of 2 or more organ systems, occurring at the same time. Pancreatic fistula was defined as prolonged fluid flow with increased (>3x the upper limit of normal serum levels) fluid amylase levels. Gastrointestinal fistula or perforation was defined as fecal production from the drains or perforation of a hollow organ on computed tomography.

Statistical analysis

In order to assess differences in time patients were divided in two groups: patients who were admitted from 2004 to 2008 and patients admitted during 2009 and thereafter. This cut-off was chosen because of the publication of the results of the PANTER trial, and the consequently implementation of the step-up approach, including VARD, in clinical practice. After 2009, primary open necrosectomy was essentially abandoned in the Netherlands.

Data were analysed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Outcomes were reported as counts and percentages for categorical variables. Continuous variables were summarized as either means with corresponding standard deviations (SD) or medians with interquartile ranges (IQR) depending on normality distribution. For analysing the differences between the two groups, a chi-square test was used for categorical variables, a Mann-Whitney U test was used for continuous not normally distributed variables and student's

T-test was used for continuous normally distributed variables. A p-value below 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Between 2004 and 2015 we identified 527 patients who underwent an intervention (either percutaneous or endoscopic drainage and/or necrosectomy) because of infected necrotizing pancreatitis. In the entire cohort, hospital mortality was 16.9% (89/527 patients). In total, 113 patients underwent a VARD-procedure. Five patients were excluded because of a prior laparotomy to treat abdominal compartment syndrome. Finally, 108 patients (80 male, 28 female, mean age 57.6) after VARD were included in our analysis of which the baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics

Sex, n(%)	
Male	80 (74.1)
Female	28 (25.9)
Age, mean(sd)	57.6 (12.1)
ASA classification, n(%)	
I	26 (24.1)
II	70 (64.8)
III	12 (11.1)
BMI, mean (sd)	29.1 (6.1)
Etiology, n(%)	
Biliary	54 (50.0)
Alcohol	20 (18.5)
Other	15 (13.9)
Unknown	19 (17.6)
Referral from other hospital, n(%)	70 (64.8)
Admitted on ICU at the time of VARD, n(%)	33 (30.6)
Timing of necrosectomy, days from diagnosis, mean(sd)	56.5 (26.9)
Number of catheter drainage procedures before VARD, median (IQR)	2 (1-3)
Type of drainage procedures before VARD, n(%)	
Percutaneous	97 (93.3)
Endoscopic	1 (1.0)
Percutaneous and endoscopic (and vice versa)	6 (5.8)

VARD characteristics

Nearly all patients (97%, 105/108 patients) had a PCD before they underwent VARD. Patients underwent a median of 2 (IQR 1-3) drainage procedures before VARD. Mean time from diagnosis to VARD was 56.5 (SD 26.9) days.

VARD outcome

In-hospital mortality was 15.7% (17/108 patients). All patients died due to progressive or refractory (multiple) organ failure, mostly (12/17 patients) within the first 30 days after the VARD. One patient died in the postoperative phase because of respiratory failure as a result of massive aspiration at the induction of general anesthesia before VARD.

Fifteen (13.9%) patients developed new-onset multiple organ failure after VARD. Pancreatic fistula occurred in 19 (17.6%) patients, gastrointestinal fistula or perforation in 17 (15.7%) and bleeding requiring re-intervention in 18 (16.7%) patients. (Table 2)

Table 2. Outcomes of 108 VARD procedures

In-hospital mortality, n(%)	17 (15.7)
30-days mortality, n(%)	12 (11.1)
New ICU admission, n(%)	31 (28.7)
Only 1-2 days postoperative ICU surveillance, n(%)	9 (8.3)
Length of postoperative hospital stay, days, mean (sd)	58.1 (45.9)
Length of postoperative ICU stay (all patients), days, mean (sd)	22.0 (40.4)
New-onset single organ failure, n(%)	23 (21.3)
New-onset multiple organ failure, n(%)	15 (13.9)
Gastrointestinal fistula or perforation, n(%)	17 (15.7)
Bleeding, n(%)	18 (16.7)
Pancreatic fistula, n(%)	19 (17.6)
Re-interventions for infected necrosis following VARD	
Number of re-drainages, median (IQR)	0 (0-1)
Number of re-necrosectomies, median (IQR)	0 (0-1)
Patients requiring no re-necrosectomie, n(%)	75 (69.4)
Patients requiring no re-interventions (PCD or re-necrosectomy) for necrosis, n(%)	56 (51.9)

Trends in time

Patient baseline characteristics did not differ before and after 2009, except for the timing of the VARD and the number of pre-operative PCD procedures. Before 2009, VARD was performed after mean 45.9 days after admission, following median 1 (IQR1-2) pre-operative drainage procedures, where after 2009, VARD was performed after 65.3 days, following median 3 (IQR1-4) pre-operative drainage procedures (p-value timing VARD =<0.001, p-value number of pre-VARD drainage procedures = <0.001). Timing of primary drainage did not differ. Trend in time between primary drainage and VARD is presented in figure 1. Trend in number of pre-operative drainage procedures is presented in figure 2. Length of post-operative hospital stay (60.8 vs 55.9 days, p=0.586), length of total hospital stay (105.4 vs

120.9 days, p=0.064), in-hospital mortality after VARD (14.3% vs 16.9%, p=0.705 and other post-operative complications did not improve after 2009 (table 3).

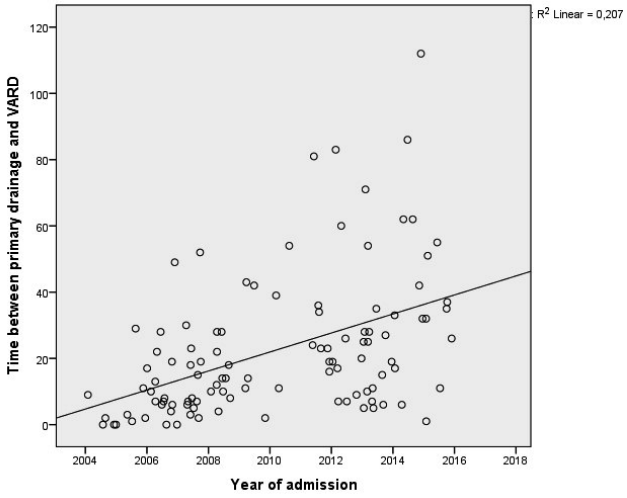


Figure 1 – Timing VARD

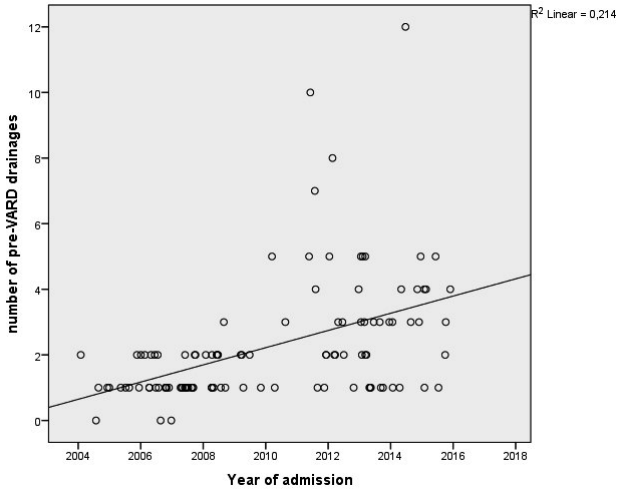


Figure 2 – number of drainage procedures prior to VARD

Table 3. Trends in time

BASELINE	**2004-2008** N = 49	**2009-2015** N= 59	**p-value**
Male sex, n(%)	38 (77.6)	42 (71.2)	0.452
Age, mean (sd)	57.7 (12.2)	57.4 (12.2)	0.896
BMI, mean (sd)	30.1 (7.1)	27.9 (4.3)	0.179
ASA, n(%)			0.405
I	10 (20.4)	16 (27.1)	
II	35 (71.4)	35 (59.3)	
III	4 (8.2)	8 (13.6)	
Etiology, n (%)			0.274
Biliary	27 (55.1)	27 (45.8)	
Alcohol	11 (22.4)	9 (15.3)	
Other	4 (8.2)	11 (18.6)	
Unknown	7 (14.3)	12 (20.3)	
Referral from other hospital, n(%)	31 (63.3)	39 (66.1)	0.759
Admitted on ICU at time of VARD	18 (36.7)	15 (25.4)	0.221
Time (days) between diagnosis and primary drainage, mean (sd)	33.1 (16.4)	33.6 (20.0)	0.885
Time (days) between diagnosis and VARD, mean (sd)	45.9 (21.4)	65.3 (28.0)	**<0.001**
Number of drainages before VARD, median (IQR)	1 (1-2)	3 (1-4)	**<0.001**
OUTCOME			
In-hospital mortality, n(%)	7 (14.3)	10 (16.9)	0.705
New ICU admission, n(%)	15 (30.6)	16 (27.1)	0.689
Only 1-2 days postoperative surveillance, n(%)	3 (6.1)	6 (10.2)	
Length of hospital stay, days, mean (sd)	105.4(48.6)	120.9(46.4)	0.064
Length of postoperative hospital stay, days, mean (sd)	60.8 (45.7)	55.9 (46.4)	0.586
Length of postoperative ICU stay (all patients), days, mean (sd)	15.8 (39.3)	22 (36.1)	0.525
New-onset single organ failure, n(%)	11 (22.4)	12 (20.3)	0.790
New-onset multiple organ failure, n(%)	9 (18.4)	6 (10.4)	0.220
Gastrointestinal fistula or perforation, n(%)	6 (12.2)	11 (18.6)	0.363
Bleeding, n(%)	11 (22.4)	7 (11.9)	0.142
Pancreatic fistula, n(%)	9 (18.4)	10 (16.9)	0.847
Re-interventions for infected necrosis, after VARD			
Number of re-drainages, median (IQR)	0 (0-0)	0 (0-2)	0.079
Number of re-necrosectomies, median (IQR)	0 (0-0)	0 (0-1)	0.261
Patients requiring no re-interventions for necrosis, n(%)	29 (59.2)	27 (45.8)	0.165

DISCUSSION

Minimally invasive necrosectomy is the treatment of choice in infected necrotizing pancreatitis, when (percutaneous or endoscopic) catheter drainage only does not suffice.[3,11,26] In this largest multicenter series on the outcomes of VARD in the step-up approach to infected necrotizing pancreatitis, in-hospital mortality was 15.7% which is similar to earlier studies.[11,12,26,27]

Minimally invasive necrosectomy has shown to reduce mortality, as compared to open necrosectomy.[26] The current series shows the VARD is a good option in the minimally invasive treatment of infected necrotizing pancreatitis. Several other minimally invasive techniques have been described, like minimal access retroperitoneal pancreatic necrosectomy (MARPN), laparoscopic transgastric necrosectomy or endoscopic necrosectomies.[13,27,28] Benefits of the VARD approach include the good visualization of the necrotic cavity and the possibility of removing large pieces of necrotic tissue in one procedure.[6,21,29,30] This is reflected by the finding that VARD is a final solution in the majority (69%) of patients. This is comparable to previous studies on VARD, showing that 71-80% of patients require only one operation.[5,6,11,31] In other minimally invasive, especially endoscopic, procedures for infected pancreatic necrosis, multiple re-necrosectomies are required. In a recent randomized controlled trial comparing the surgical with endoscopic step-up approach, of 29 patients that required an endoscopic transluminal necrosectomy, 20 patients (69%) required one or more re-necrosectomies[5]. A large series on MARPN showed a median of 3 (IQR 2-4) procedures required to achieve an optimal debridement.[13,14]

Postoperative bleeding may complicate VARD. With the damaged tissues due to infected necrosis and the potential presence of pseudoaneurysms, the postoperative 16.7% bleeding rate in this cohort may come as no surprise, and is comparable to previous series.[5,6,11] In the current study, none of the bleedings ultimately led to death, confirming the safety of VARD. Furthermore, with the current advances in the interventional radiology, a laparotomy is rarely required[32–36] and bleeding can mostly be managed by angiographic embolization.[37–40]

For many complications it may be questioned whether they are caused by the procedure or by the disease. The abovementioned bleeding can both be a result of pseudoaneurysms or the VARD. Gastrointestinal fistula or perforations can also be a result of the damaged tissues due to infected necrosis. Many, fistula are not clinically relevant as they are only radiologically detectable and cause no symptoms. In general, radiographically confirmed intestinal fistula without fecal production from drains do not require a deviating ileostomy. Pancreatic fistula

could also be caused by the disease or the procedure. As a result of pancreatic necrosis, the integrity of the pancreatic duct may be lost, resulting in disrupted or disconnected pancreatic duct.[41–45] As there is currently no standard work-up for the diagnosis of duct disruption or disconnection, this diagnosis is often made late in the disease course and could possibly be underreported. However, the reported fistula rates are comparable to other surgical treatment strategies. This confirms VARD is a safe procedure to use in the treatment of infected pancreatic necrosis.

When comparing the periods before and after 2009, a rather large difference in the number of pre-operative drainages can be seen. Previous studies have shown that a proportion of patients can be treated with drainages only.[5,11] This is compatible with the idea that a pro-active drainage strategy can reduce the necessity for necrosectomy.[46,47] However, these repeated drainage procedures may also result in a large delay to necrosectomy. At the same time, the length of hospital stay after the necrosectomy has not been reduced, ultimately leading to a prolonged hospitalization. How many drainages are justified to prevent one necrosectomy? Is this an intentional delay or procrastination? This study shows that in more than half of the patients, VARD is the final procedure, requiring no additional drainages or necrosectomy. If a patient requires a VARD, this may be beneficial to perform earlier after the primary drainage, reducing the number of pre-necrosectomy PCD's. However, we cannot predict which patient ultimately requires a necrosectomy, and which patient does not. Unfortunately, with the data of the current study we cannot report how many patients are treated with drainages only, without a necrosectomy. Future studies should investigate the optimum in number of PCD and timing of PCD and necrosectomy.

This study has several limitations. First, we only included patients who gave informed consent which could have introduced some selection bias. The majority of patients in this cohort are referred by other hospitals to tertiary centers. If patients were only transferred for the VARD, and not for the whole treatment sequence, we cannot rule out that patients were missed for giving informed consent, and therefore not included in the analysis, due to their limited hospital stay in the participating hospital. Second, patients were only prospectively followed during the initial admission. Patients who were initially discharged, before they were re-admitted and underwent VARD, were only scored retrospectively, which could have caused selection bias. However, due to multicenter aspect, the size of the cohort and with a large proportion of patients admitted at ICU during their VARD, we still believe this is a representative cohort. Third, the number of patients who were treated with PCD alone in both time periods is lacking.

In conclusion, the step-up approach (i.e. delay-drain-debride) is the treatment of choice in patients with infected necrotizing pancreatitis. The increased popularity of PCD has caused delays in the use of VARD. It is currently unclear whether these delays have harmed patients. VARD remains a good option in those patients in whom PCD does not suffice and should be in the surgeon's armamentarium. Future research should investigate the optimum in number of pre-necrosectomy drainage procedures and timing of PCD and subsequent VARD.

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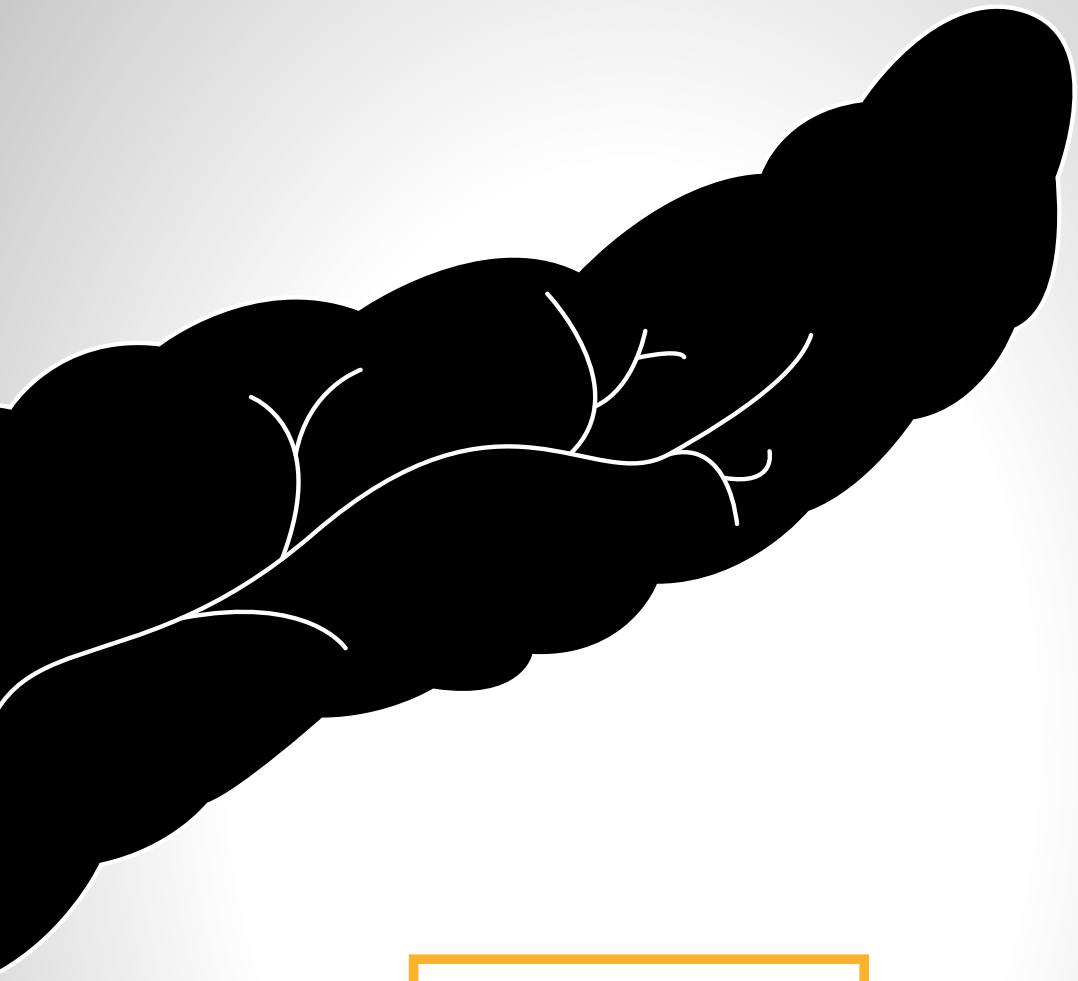
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4

CHAPTER 4

Treatment of disrupted and disconnected pancreatic duct in necrotizing pancreatitis: a systematic review and meta-analysis

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ABSTRACT

Background: Necrotizing pancreatitis may lead to loss of integrity of the pancreatic duct, resulting in leakage of pancreatic fluid. Pancreatic duct disruption or disconnection is associated with a prolonged disease course and particular complications. Since a standard treatment for this condition is currently lacking, we performed a systematic review of the literature to compare outcomes of various treatment strategies.

Methods: A systematic review was performed according to the PRISMA guidelines in the PubMed, EMBASE and Cochrane databases. Included were articles considering the treatment of patients with disrupted or disconnected pancreatic duct resulting from acute necrotizing pancreatitis.

Results: Overall, 21 observational cohort studies were included comprising a total of 583 relevant patients. The most frequently used treatment strategies included endoscopic transpapillary drainage, endoscopic transluminal drainage, surgical drainage or resection, or combined procedures. Pooled analysis showed success rates of 81% (95%-CI: 60-92%) for transpapillary and 92% (95%-CI: 77-98%) for transluminal drainage, 80% (95%-CI: 67-89%) for distal pancreatectomy and 84% (95%-CI: 73-91%) for cyst-jejunostomy. Success rates did not differ between surgical procedures (cyst-jejunostomy and distal pancreatectomy (risk ratio = 1.06, p=0.26)) but distal pancreatectomy was associated with a higher incidence of endocrine pancreatic insufficiency (risk ratio = 3.06, p=0.01). The success rate of conservative treatment is unknown.

Discussion: Different treatment strategies for pancreatic duct disruption and duct disconnection after necrotizing pancreatitis show high success rates but various sources of bias in the available studies are likely. High-quality prospective , studies, including unselected patients, are needed to establish the most effective treatment in specific subgroups of patients, including timing of treatment and long-term follow-up.

INTRODUCTION

Acute pancreatitis is one of the most common gastro-intestinal diseases requiring acute hospitalization.[1,2] Although most patients have a mild disease course, nearly 20% developfs necrosis of the pancreas or peripancreatic tissue.[3–6] Necrosis of the pancreatic parenchyma may lead to loss of integrity of the pancreatic duct, consequently leading to duct disruption or disconnection.[7] This causes extraductal and extrapancreatic leakage of pancreatic fluids, which may result in several complications such as (recurrent) peripancreatic fluid collections with secondary infection, pancreatic ascites or, in case of leakage of pancreatic fluids towards other organs, pancreatic fistulas.[8,9]

A disrupted duct is defined as a partial interruption of the duct intregrity, whereas a disconnected duct is defined as a circumferential interruption of the pancreatic duct.[10] The treatment of this complication is not standardized, and includes conservative, medical, endoscopic, or surgical treatment. As there is no guideline available for this condition, treatment is currently at the judgement of the treating clinicians.[11]

The aim of this systematic review is to identify different treatment options for pancreatic duct disruption and disconnection in patients with acute necrotizing pancreatitis, and to compare the outcomes of the different treatment strategies.

METHODS

Study selection

The study was conducted according to the Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[12] A systematic literature search was performed in the PubMed, EMBASE and Cochrane databases for studies published up to December 7th 2017. Search terms were based on the disease ("pancreatitis") and the morphological/ anatomical changes (e.g. disrupted or disconnected duct), with search field for the disease restricted to title and abstracts. Studies were restricted to English language. A detailed overview of the search and syntax is presented in the ***Appendix.***

Eligibility criteria

After removal of duplicates, studies were screened by title and abstract by two independent authors (SMvD, ER). Inclusion criteria were all studies considering acute necrotizing pancreatitis and disrupted or disconnected duct. Studies considering duct disruption as a result of chronic pancreatitis, or did not report on outcomes of these patients separately, were not included. Reviews, case reports, animal studies, editorials, opinion statements, studies with only patients under 18 years old, studies with fewer than 5 relevant patients and studies not describing

visualization of the pancreatic duct anomalies were excluded. Of all remaining studies, full-text was assessed for eligibility. Final decision on eligibility was reached by consensus.

Critical appraisal

Methodological quality of the studies was independently assessed by two authors (SMvD, HCT), using the Newcastle-Ottawa Scale.[13] Using this grading system, one point is awarded for each segment if the study meets the criteria of the Newcastle-Ottawa Scale. For Comparability, two points could be assigned. The scoring algorithm indicates a poor quality study scoring up to 2 points, a fair quality study scoring 3-6 points and a good quality study scoring ≥7 points.

Data extraction

The following characteristics were extracted from all included studies: author, title, year of publication, country, type of study, number of patients in the study and number of relevant patients. All adult patients with a disconnection or disruption of the pancreatic duct as a result of acute pancreatitis were considered as relevant patients. Data concerning treatment of disconnected/disrupted duct syndrome were extracted separately. We extracted data on treatment strategies (including conservative treatment) and techniques and outcomes such as complications, mortality and re-interventions.

Statistical analysis

The procedural outcomes are reported success rates, with success being defined as resolution of the peripancreatic collection or pancreatic fistula-closure. Data from studies comparing two different treatments were pooled using meta-analysis software RefMan version 5.3 using a random-effects model. Outcomes of studies reporting only one procedure were pooled using a single-proportion meta-analysis STATA-module Metaprop in RStudio, version 3.4.3. Studies reporting on multiple modalities were not included in meta-analysis. Outcomes are presented as (pooled) proportion of success, risk ratio of success or standardized mean difference, all with 95% confidence intervals (CI). Statistical heterogeneity between the included studies was determined by forest plots and by calculating the I^2-index. A high I^2-index represents a high suspicion of heterogeneity. In case of high hetereogeneity, sensitivity analysis was performed, exploring data using different effect models (both a random effect model and fixed effect model). All pooled event rates were shown in forest plots, regardless the level of heterogeneity.

RESULTS

Search results

The search identified 2068 potentially relevant studies, 926 results returned from the EMBASE search, 1047 results from PubMed and 131 from the Cochrane database. After removing 819 duplicates 1249 studies remained. Based on screening the title and abstract, 1187 studies were excluded. After full-text assessment of the remaining 62 studies, 34 studies were additionally excluded: 8 reviews, 13 case-reports or series with fewer than 5 relevant patients, 4 editorials, 3 studies with a different cause of the duct disruption (e.g. chronic pancreatitis or trauma), 5 studies did not report the diagnosis of duct disruption or disconnection or a specific treatment. Furthermore, 2 studies were excluded because they reported on overlapping series.[10,14–16] For these studies we included the largest cohort.[14,15] Six studies only reported diagnosis and no therapy of duct anomalies.[9,17–21] Ultimately, 21 studies were included in this systematic review (figure 1).[7,14,29–38,15,39,22–28] The total number of patients in the studies was 1181, of whom 583 were relevant for this review (i.e. patients with acute pancreatitis, and disconnected or disrupted pancreatic duct in whom outcomes were reported).

Study characteristics

All studies were observational cohort studies, published between 1991 and 2017 and originating from 7 different countries in 3 different continents. All but one study were retrospective cohort studies, three studies were designed as a retrospective analysis of a prospectively maintained database *(table 1)*. Randomized controlled trials are lacking. Reported treatments can roughly be divided in 3 types of interventions: (1) endoscopic transpapillary drainage procedures, (2) endoscopic transluminal drainage of pancreatic fluid collections and (3) surgical procedures (drainage and/or resection). Conservative treatment was not reported, although some studies reported that patients had conservative treatment before they underwent intervention *(table 2, 3, 4 and 5)*. Six studies report on the use of somatostatine analogs (e.g. octreotide), of which 2 reported it was not used,[34,39] and the other 4 studies reported percentages of patients that used it prior to intervention (34%, 92%, 50% and 33% respectively).[23,24,29,37]

In all but one studies, success was defined as a resolution of peripancreatic collections or fistula closure, one study did not mention how treatment success was defined.[7] In all studies duct disruption or disconnection was confirmed with one or more diagnostic modality. Twenty of 21 studies used ERCP and/or MRCP to diagnose this, whether or not in combination with another diagnostic modality. Details of the success definitions and diagnosis of the duct disruption per study are presented in S*upplementary table 1*.

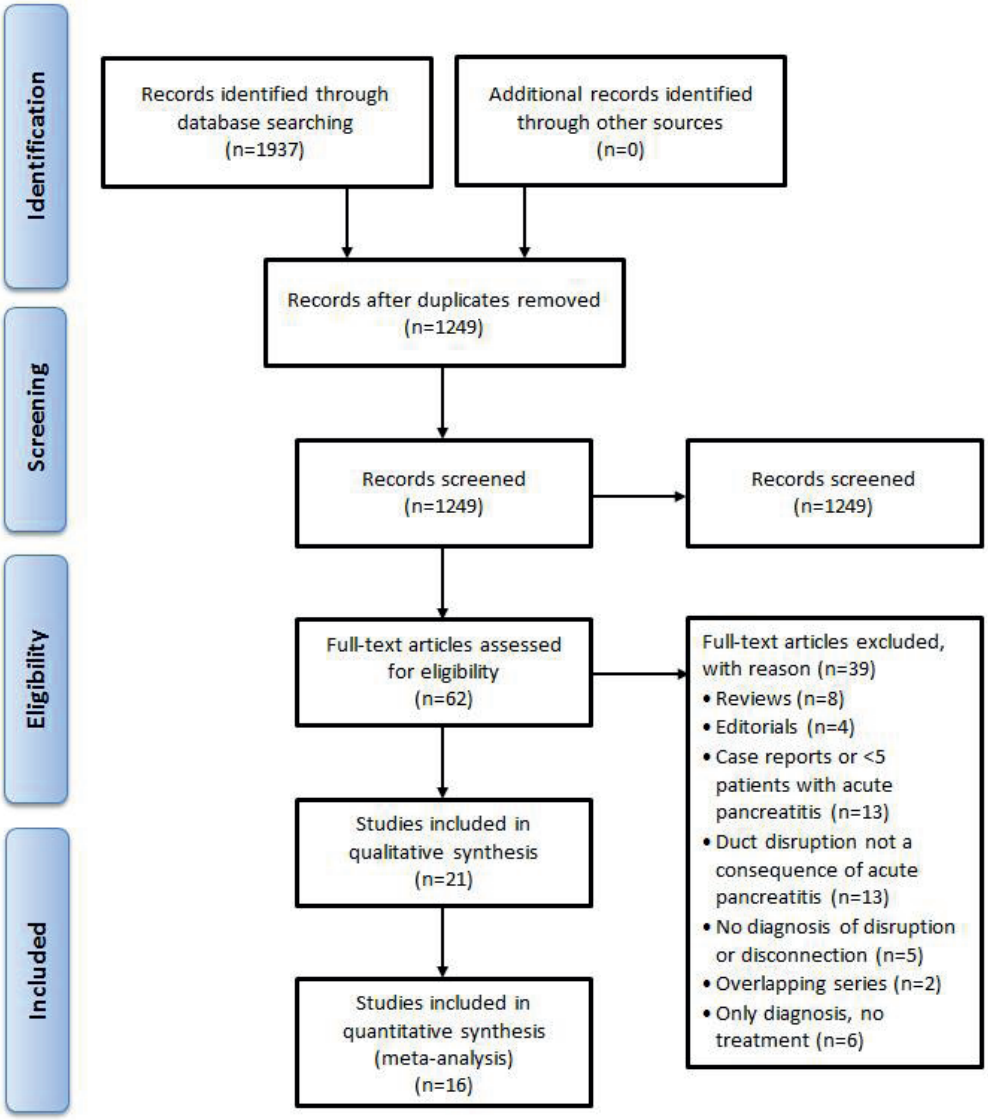


Figure 1 – Flow diagram

Quality assessment

Quality assessment scores according to the Newcastle-Ottawa Scale are presented in *Supplementary table 2.* One study scored as poor quality,[32] all other studies scored fair quality.[7,14,29–31,33–39,15,22–28]

Table 1 - Study characteristics

Author	Year of publication	Country	Inclusion period	Number of patients	Relevant patients#	Study design
Bang et al.	2016	USA	May 2014 - Nov 2015	42	21	Prospective cohort study
Beck et al.	2011	USA	1993 - 2010	197	82	Cohort study, retrospective analysis of prospectively collected database
Das et al.	2016	USA	2008 - 2013	107	39	Retrospective cohort study
Devière et al.	1995	Belgium	Jun 1986 - Jul 1993	13	9	Retrospective cohort study
Dhar et al.	2017	USA	2002 - 2014	42	42	Retrospective cohort study
Fischer et al.	2014	USA	July 2005 - Jun 2011	50	43	Retrospective cohort study
Howard et al.	2001	USA	Jun 1995 - Jun 2000	27	27	Cohort study*
Irani et al.	2012	USA	Oct 2002 - Oct 2011	15	12	Cohort study, retrospective analysis of prospectively collected database
Jang et al.	2016	South Korea	2005 - 2013	84	32	Retrospective cohort study
Kozarek et al.	1991	USA	3 year period	18	10	Cohort study*
Lawrence et al.	2008	USA	Mar 1997 - Jun 2003	189	30	Cohort study, retrospective analysis of prospectively collected database
Murage et al.	2010	USA	Nov 1995 - Sept 2008	76	59	Retrospective cohort study
Pearson et al.	2011	USA	2002 - 2011	7	7	Retrospective cohort study
Pelaez-Luna et al.	2008	USA	Jan 1999 - Jul 2006	31	31	Retrospective cohort study
Rana et al.	2010	India	*"last 12 years"*	23	15	Cohort study*
Rana et al.	2015	India	*"last 4 years"*	35	35	Retrospective cohort study
Sharaiha et al.	2016	USA	Jan 2014 - May 2015	124	19	Retrospective cohort study
Smoczynski et al.	2015	Poland	2001 - 2013	22	22	Retrospective cohort study
Telford et al.	2002	USA	1993 - 2001	43	24	Retrospective cohort study
Téllez-Aviña et al.	2016	Mexico	2008 - 2015	21	18	Cohort study, retrospective analysis of prospectively collected database
Yokoi et al.	2016	Japan	Jan 2005 - Feb 2014	15	6	Retrospective cohort study

*Unclear if prospective or retrospective study design

#patients with disrupted or disconnected pancreatic duct as a result of acute pancreatitis

Table 2 - Endoscopic treatment – Transpapillary procedures

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time untill succes	Procedure-related Complication	Follow-up (median)
Das et al.	2016	107#	39	35 endoscopic transpapillary drainage with transpapillary stent* Sphincterotomy, pancreatic duct stone extraction and -duct stricture dilatation was based upon discretion of endoscopist	Conservative management (including percutaneous drainage and pancreatic rest, not specified for acute pancreatitis patients)	Mean 33 days from diagnosis of duct disruption	24/35	NR	Not specified for subgroup of acute pancreatitis patients	Overall 21 months (range 1-84)
Kozarek et al.	1991	18	10	Transpapillary stent (n=9) and/or transpapillary drain (n=4)	7/10 had previous percutaneous or surgical pancreatic drainage	Median 6 weeks (range 1-18 months)	9/10 resolution of fluid collection 9/10 resolution of symptoms	6 weeks	Infection (n=1); Stent occlusion (n=1). 3 patients required subsequent surgery: tail resection (n=2); Head resection (n=1)	Median 16 months (range 3 – 36 months)
Rana et al.	2010	23	17	Transpapillary nasopancreatic drain Bridging of the disruption (n=15) As near as possible to the disruption (n=6) Unsuccessful (n=2)	Percutaneous drainage	NR (At least 6 weeks after prior percutaneous drainage)	Bridging: no recurrence of external fistula Not-bridging: 2 successful	mean 5.37 (range 2–8) weeks	1 stent occlusion *Long term complications:* Bridging: 1 pseudocyst Non-bridging: 1 pseudocyst 1 bleeding pseudoaneurysm	Mean 38 (range 2-102 months)
Smoczynski et al.	2015	22	22	First active drainage: -Transpapilary nasopancreatic drain In the walled-off necrosis (n=18) Bridging the disruption (n=4) After active drainage: transpapillary stent in pancreatic duct. Proximal to the PD leak (n=10) Bridging the PD leak (n=12)	None	Mean 16 (range 5-50) , weeks	Therapeutic success in 20/22 patients. 2/22 patients clinical symptoms of WOPN disappeared, but the size of the collection remained >3cm	NR	3/22 gastrointestinal bleeding, conservatively treated *At 1 year follow up:* 4/22 recurrent fluid collection (all with disconnected duct); 2 treated with transluminal drainage, 2 surgically treated	1 year

Telford et al.	2002	43	24	41 Transpapillary stent placement Short stent (n=16) Into the disruption (n=13) Bridging the disruption (n=14) 2 nasopancreatic drain	24/43 total parenteral nutrition and somatostatin analogue; 16/43 percu-taneous drain; 1 endoscopic cystduodenostomy; 5 surgical cyst drainage or pancreatic debridement	NR	Resolution of PD disruption in 25/43 patients. AP patients : Successful 11, 12 unsuccessful	NR	4/43 clinical deterioration	Median 24 months
Yokoi et al.	2016	15	6	Transpapillary bridging stent (n=3) If bridging not possible: Transpapillary drain into collection (n=3)	Standard treatment for acute pancreatitis, including step-up approach for infected necrotizing pancreatitis: All patients had one or more percutaneous drain(s)	Median 16.5 days (range 1-300 days)**	All successful fistula closure	Median time to fistula closure after transpapillary treatment 45 (16-330) days. **	No procedure related complications. 2 patients eventually died of infectious complications	NR

 # Patients with necrotizing pancreatitis were excluded from this study
* 5/35 patients underwent concurrent transluminal drainage for large peripancreatic fluid collections.

** not specified for only patients with duct disruption

NR = not reported

Table 3 - Endoscopic treatment – (mainly)Transluminal drainages / cysto-ostomies

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time untill succes	Procedure-related Complication	Follow-up (median)
Bang et al.	2016	42	21	Endoscopic ultrasound-guided transluminal drainage, with plastic stents indefinitely left in situ	NR	NR	20/21 no recurrence	8 weeks	-	272 days (range 68-501)
Devière et al.	1995	13	9	(1 transpapillary drainage), *3 cystogastrostomy**, *2 cystoduodenostomy**, 2 combined procedures (1 surgical pancreatojejunostomy)	-Total parenteral nutrition and somatostatin -4 previous drainage attempts	NR	*Long term:* 8/8 endoscopically treated 0/1 surgically treated	4-8 weeks	1 infected pseudocyst. Furthermore uncomplicated	mean 30.6 months (range 12-72)
Rana et al.	2015	35	35	Transluminal drainage with stents left in place long term	NR	NR	All successful resolution of walled-off necrosis	NR	Spontaneous stent-migration in 8/35 patients, causing recurrent fluid collection in 3 patients.	Mean 28.2 (±14.0) months, range 6-50
Téllez-Aviña et al.	2016	21	18	Endoscopic transluminal drainage with plastic pigtail stents	NR	NR	Clinical success in 17/21 (80.9%) patients 3 required repeat endoscopy 1 required surgery	NR	1 post-ERC P pancreatitis. 2 (9%) prosthesis migrations; 1(4.7%) infection after drainage, 1 (4.7%) prosthesis migration with suspicion of perforation not confirmed by surgery and 1 (4.7%) patient who developed an infection after prosthesis migration. Diabetes mellitus n=11	Median 28 (range 7-76) months

* transluminal drainage with sphincterotomy (n=3), transluminal drainage without sphincterotomy (n=2)

NR = Not Reported

Table 4 - Surgical procedures

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time untill succes	Procedure-related Complication	Follow-up (median)
Beck et al.	2011	197	82	42 surgery: 30 Roux-en-Y drainage, dependent on anatomy →19x jejunum to walled-off necrosis →2x jejunum to drain traject →9x jejunum on pancreatic duct 12 resection pancreatic remnant	10/82 patients had percutaneous drainage, unsuccessful	> 8 weeks Mean time until operation = 3.2 ± 0.8 months	Overall success rate surgery = 96% Patients without intervention NR	8 weeks	1% mortality Persistent fever and leukocytosis in 13/19 patients with Roux-en-Y jejunum to WOPN	47 months
Dhar et al.	2017	42	42	21 fistulojejunostomy 21 distal pancreatectomy	None	NR	17/21 Fistulojejunostomy 20/21 distal pancreatectomy	NR	Significantly more blood loss (p<.01)and blood transfusion in DP (p<.01); worsening of endocrine insufficiency in 52.4% vs 19.1% in FJ-group(p=.02)	12 months (range 3-69 months)
Fischer et al.	2014	50	43	cDPSD Necrosectomy with tail resection (n=28)* dDPSD: Distal pancreatectomy with splenectomy(n=15)**	Endoscopic procedures: cDPSD (n=10) dDPSD (n=15) Percutaneous procedure cDPSD (n=9) dDPSD (n=3)	cDPSD: median(range): 60 (26-4793) dDPSD: median(range): 440 (69-5235)	25% recurrent pseudocyst	NR	cDPDS: 10(36%) Clavien Dindo class II, 0 Class III, 2(8%) Class IVa; 10(36%) exocrine and 16(57%) endocrine insufficiency dDPDS: 4(27%) Clavien-Dindo Class II; 0 Class III, 0 Class IV; 9 (60%) exocrine and 11(73%) endocrine insufficiency	Mean 17.6 months

Howard et al. 2001	27	27	Roux-en-Y internal drainage (n=13) 9 pancreaticojejunostomy 4 cystojejunostomy Distal pancreatectomy-splenectomy (n=14)	Prior surgery , unspecified, in 8 patients in the roux-en-y-group, 7 in de distal pancreactectomy group	6.1 (±2.3) vs 4.9(±2.0) months	Roux-en-Y 100% Distal pancreatectomy 93%	NR	Death 1(8%) vs 1(7%); Bleeding 1(8%) vs 1(8%); Wound infection 2(15%) vs 0(0%); Postoperative Diabetes 2(15%) vs 0(0%); wound infection 2(15%) vs 0(0%); pneumonia 1(8%) vs 0(0%); Significant more intraoperative blood loss in distal pancreatectomy (P<.0001)	Median 17 (±8) vs 18 (±9) months
Murage et al. 2010	76	59	Distal pancreatectomy (n=42) Roux-en-Y internal drainage (n=34) Pancreatojejunostomy (n=18) Cystojejunostomy (n=10) Fistulojejunostomy (n=6)	55% pancreatic debridement and external drainage		DP: 74% success rate: 11(26%) symptomatic recurrences; ID 82% success rate: 6(18%) symptomatic recurrence	NR	More intraoperative blood-loss in DP (P = .001); no differences in major perioperative morbidity rates (≥IIIa; 14% vs 6%; P=.103), 90-day mortality rates (0 vs 0; P≥ .05), or in-hospital duration of stay (11 days vs 9 days; P = .080), DM (12% vs 3% p=.063) or steatorrhea (p=.408 between DP vs ID	Median 22 months
Pearson et al. 2011	7	7	Roux-en-Y internal drainage	Conservative medical treatment or endoscopic intervention, not specified	Median 270 days (range 164-365)	100% successful resolution, no recurrences during follow-up	NR	1 delayed bleeding of splenic artery requiring distal pancreatectomy and splenectomy	Median 264 days (range 29-740)

*CDPSD = Concurrent diagnosis of DPSD with AP
**DDPSD= Delayed diagnosis of DPSD
NR = Not reported

Table 5 - Other /combined procedures

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time untill succes	Procedure-related Complication	Follow-up (median)
Irani et al.	2012	15	12	Outside-in interventional radiologist–guided transgastric/-duodenal puncture (n=10); Inside-out endoscopic ultrasound-guided fistula puncture (n=3); Reconnecting the disconnected duct: Interventional radiologist–guided transpapillary access and internalization (n=2)	NR	NR	100%, no recurrences	Median 7 days (range 1-73 days	No mortality; Adverse events in 4/15(27%): 1 fever requiring oral antibiotics, 5 new PFC (2 asymptomatic): 4 spontaneous migration of transluminal stents, of which 3 developed a new symptomatic PFC.	Median 25 months (range 6-113)
Jang et al.	2016	84	32	Disconnection: percutaneous drain (n=10); Endoscopic ultrasound-guided transluminal drain(n=5); Attempted transpapillary drainage (n=5, successful in 1); Endoscopic necrosectomy (n=5); surgical resection (n=2) Partial disruption: attempted transpapillary drainage (n=12, successful in 11); Endoscopic ultrasound-guided transluminal drainage (n=6); Endoscopic necrosectomy (n=3); Percutaneous drain (n=2)	NR	Median 39 days (range 21-178 days)	Disconnection: 29%, not specified per treatment Partial disruption: 67%, not specified per treatment	NR	NR	Median 512 days (35-3500)

Lawrence et al.	2008189	30	Transluminal drain (n=15); Transpapillary drain (n=7); surgical drainage(cystenterostomy or cystgastrostomy) (n=5); percutaneous drain (n=2).	NR	NR	Initial success / recurrence rate (rec):Transluminal drain 11/15 (73%), rec 5/11(45%); transpapillary drain 5/7 (71%), rec 2/5(40%); surgical drainage 5/5 (100%), rec 3/5(60%); percutaneous drain 1/2 (50%), rec 1/1 (100%)	NR	1 mild post-sphincterotomy bleeding.	Median 38 months (range 3-94)
Pelaez-Luna et al.	200831	31	Endoscopic treatment (n=26) Transgastric (n=12) Transduodenal (n=10) Transpapillary (n=4) Surgical treatment (n=12) *(Primary surgery (n=5); After endoscopic treatment (n=7))* Cystenterostomy (n=3) Distal pancreatectomy (n=5) Necrosectomy, debridement end/or external drainage (n=2) Necrosectomy, followed by pancreatectomy in second surgery (n=1) Necrosectomy followed by external cyst drainage (n=1)	NR	Median 56 (range 3-251) days between initial AP event and diagnosis of DPDS. Time to first intervention not reported	Endoscopic improvement: 19 (61%); Pancreatic-duct integrity reestablished 3/19; Endoscopic failure that required surgery 7 (23%)	NR	Deaths 0%; CP/pancreas atrophy 8 (26%); Chronic abdominal pain 1 (3%); Persistent pancreatic fistula (duodena, gastric, cutaneous) 1(3%); Complete resolution 3 (10%) Persistent but smaller collections 13 (42%); DM 5 (16%); Lost immediately after last intervention 8 (26%)	Median 6.5 (range 0.5-90) months
Sharaiha al.	2016 124	19	Transluminal (lumen-apposing metal) stent with concurrent ERCP with pancreatic stenting	None	NR (At least 4-6 weeks after onset of pancreatitis)	Not specified for patients with duct disconnection/ disruption	Not specified for patients with duct disconnection/ disruption	Not specified for patients with duct disconnection/ disruption	Not specified for patients with duct disconnection/ disruption

NR = Not reported

Endoscopic transpapillary drainage

Six studies reported on endoscopic transpapillary drainage for disrupted or disconnected duct.[23,29,34,36,37,39] Procedures vary from transpapillary placement of a nasopancreatic drain or a stent, either to bridge the disruption of the pancreatic duct, placing a stent only across the ampulla, or placing a drain through the duct disruption into the fluid collection. Success rates range from 48 to 100%. Meta-analysis showed a pooled success rate of 81% (95%-CI: 60-92%), with a I^2 = 68% (Figure 2A). Differences within the studies in the presence of complete disconnection or partial disruption of the pancreatic duct are presented in *Supplementary table 3*.

Endoscopic transluminal drainage

Four studies reported on endoscopic transluminal drainages as treatment of duct disruption.[15,22,24,38] All studies used plastic stents for transgastric or transduodenal drainage of the fluid collection caused by the duct disruption. Time from the start of the disease until intervention was not reported. Three out of four studies reported to use plastic pigtail stents, which were left indefinitely or 'long-term'.[15,22,38] One study did not report specifications on the type of drain or stent.[24] Success rates range from 81-100%. Meta-analysis showed a pooled success rate of 92% [95%-CI: 77-98%] with a I^2 = 32% (figure 2B).

Surgical treatment

Six studies reported on surgical procedures.[7,14,25,26,31,32] The procedures described are either distal pancreatectomy or a Roux-and-Y internal drainage of the cyst or fistula tract. The choice of procedure was at the discretion of the surgeon in all studies. Meta-analysis of the success rates of the two procedures showed a pooled success rate of 80% [95%-CI: 67-89%] for distal pancreatectomy and 84% [95%-CI: 73-91%] for Roux-and-Y internal drainage (figures 2C and 2D). There were no differences (risk ratio = 1.06, p=0.26) between both strategies. Distal pancreatectomy was associated with more intraoperative blood loss (std. mean difference = 2.30, p=0.02) and a higher incidence of pancreatic endocrine insufficiency (risk ratio = 3.06, p=0.01). No differences were found regarding exocrine insufficiency (risk ratio = 1.17, p=0.68) (supplementary figures).

Other

Five studies reported on different procedures than described above, or combined treatments.[27,28,30,33,35] All procedures and related success rates and complications are reported in *table 5*. Due to the heterogeneity of treatment a meta-analysis was deemed not possible.

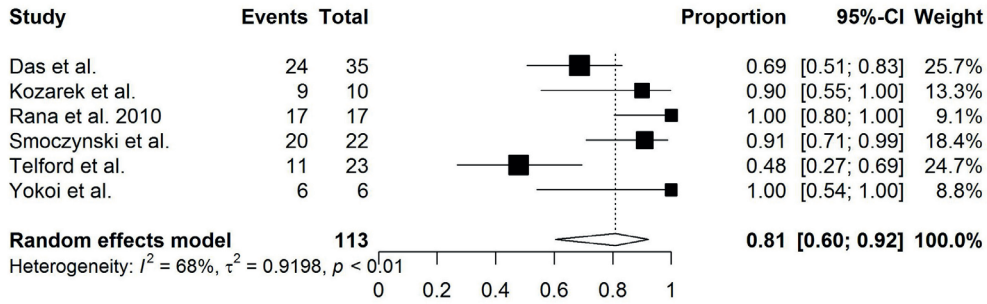


Figure 2A – Pooled success rate of endoscopic transpapillary drainage

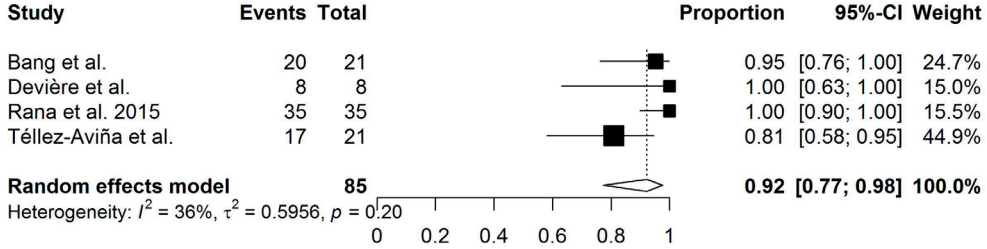


Figure 2B - Pooled success rate of endoscopic transluminal drainage

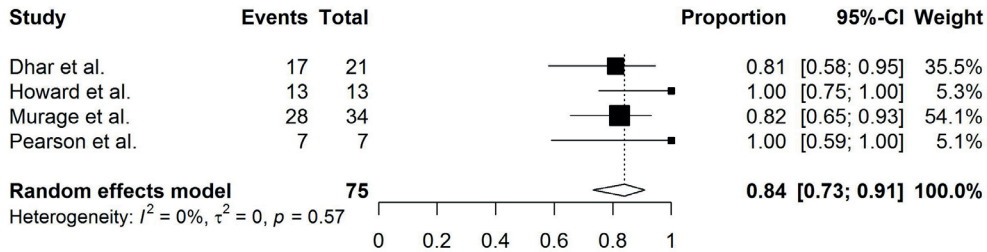


Figure 2C – Pooled success rate of Roux-en-Y internal drainage

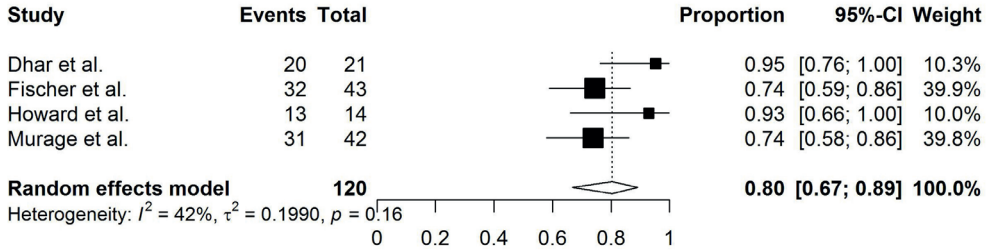


Figure 2D – Pooled success rate of distal pancreatectomy

DISCUSSION

Disruption or disconnection of the pancreatic duct is a severe complication of necrotizing pancreatitis for which no standardized treatment is defined. Which treatment is currently chosen is based on the discretion of the treating clinician and not on evidence-based guidelines. This study is the first systematic review reporting on the potential merits and outcomes of the various treatment strategies available for disrupted or disconnected pancreatic duct syndrome including conservative treatment, endoscopic transpapillary drainage, endoscopic transluminal drainage, surgical drainage, distal pancreatectomy, and combinations of the aforementioned procedures. The pooled success rates of these treatment strategies are all high, over >80%. The success rate of conservative treatment, however, remains unknown.

In all studies the disconnection or disruption of the pancreatic duct was radiologically proven. However, it was not always clear if the reported treatment was the initial treatment performed in the analyzed patients. It cannot be ruled out that some patients had already undergone other types of treatment that failed. This may have introduced bias. There was a great variability in the timing of the different interventions within and between studies. Endoscopic procedures were usually performed in a relatively early stage of the disease and the surgical procedures later in the course of pancreatitis, i.e. up to several months after the onset of the disease, probably after failed conservative or failed endoscopic treatment. This brings into question how reliable the reported success rates are in relation to timing and preceding treatments and whether the success of a treatment can be predicted. This, however, cannot be answered with the current data. Because ofthe high hetereogeneity in the included studies, we used a random effects model for our meta-analysis. We performed a sensitivity analysis, using different models, showing that results remain similar (success rates did not differ >10% between different analysis, data not shown). Because of the heterogeneity, and the fact that the majority of studies only included small numbers of patients, results should be interpreted with caution. A high risk of publication bias remains.

Partly due to uncertainties about the indication and timing of the reported treatments, a scientifically sound and valid comparison between different treatments cannot be made. Confounding by indication likely occurred. For instance, an attempt to endoscopically bridge the pancreatic duct defect will not always be possible and may end up in doing a different procedure such as a the placement of a non-bridging stent.[23,29,34,36,37,39] Having a complete disruption (i.e. disconnection) makes placing a bridging stent almost impossible. Therefore certain conditions influence the likelihood of success and thereby the outcome of a specific procedure. Otherwise, in studies on surgical procedures, the treatment of choice is

often decided during operation, based on peroperative findings, and the preference and skill of the surgeon.[7,14,25,26,31]

The long-term success of each treatment strategy also remains unclear. Because of this and the aforementioned issues it cannot be concluded form the current data which treatment is superior. A suggestion would be to introduce a 'step-up' treatment algorithm, starting with conservative treatment, gradually progressing from minimally-invasive to more invasive surgical procedures. These step-up approaches have already successfully been practiced in other pancreatic conditions.[40–44] Although distal pancreatectomy is associated with a high success rate, it has the highest risk of long-term endocrine and exocrine insufficiency. Conversely, with the current evolution of advanced endoscopy, it can be questioned whether there will still be a prominent role for surgery in the treatment of this condition. Surgical cyst-jejunostomy, for example, has essentially been replaced by transluminal cyst-gastrostomy.[45,46] However, rigorous surgery may provide a definite solution for patients, withholding them from the burden of multiple less invasive procedures and prolonged morbidity, as seen in chronic pancreatitis patients.[42,47,48]

Conservative management, usually, is the first step of treatment. Some clinicians nowadays actively search for the presence of duct disruptions in necrotizing pancreatitis, in order to start treatment in a relative early phase of the disease. It is unclear, however, which patient category will benefit from conservative treatment and therefore a too active approach may cause overtreatment. On the other hand, early diagnosis and treatment may reduce the delay in treatment, which may be beneficial in patients who often already suffered from a prolonged disease course.

This study has some limitations. First, data on the conservative and medical treatment of disconnected/disrupted duct are lacking. This is relevant since probably not all patients require endoscopic or surgical treatment. Second, the majority of included studies are retrospective by design and only present results of a single treatment strategy, while in all probability some patients may have already failed preceding treatments. Moreover, retrospective identification of patients might have introduced selection bias, since patients with the target condition not receiving a diagnostic ERCP or MRCP could not be identified. There is no systematic diagnostic work-up to identify duct disruption, possibly leaving many patients with a duct disruption out of the study cohorts, again, not reporting the conservatively treated patients. Third, most studies lack a comparator making it impossible to analyze the potential superiority of a particular treatment.

A strength of this study is that it is the first systematic review on this subject, and that we were able to perform a meta-analysis of the success rates of the different treatments. Since many of the treatment decisions are based on the site and extent of morphological changes due to necrosis, this systematic review has focused on the studies in which a duct anomaly was proven. Previous studies focused on the treatment of only the complications of disconnected pancreatic duct syndrome (e.g. pseudocysts and pancreatocutaneous fistula),[49] without paying attention to the anatomical substrate as the cause of this complication. The strength of this review is our focus on the cause of the complications: the disruption or disconnection of the pancreatic duct. This duct anomaly instantly provides the possibilities for the different treatment strategies.

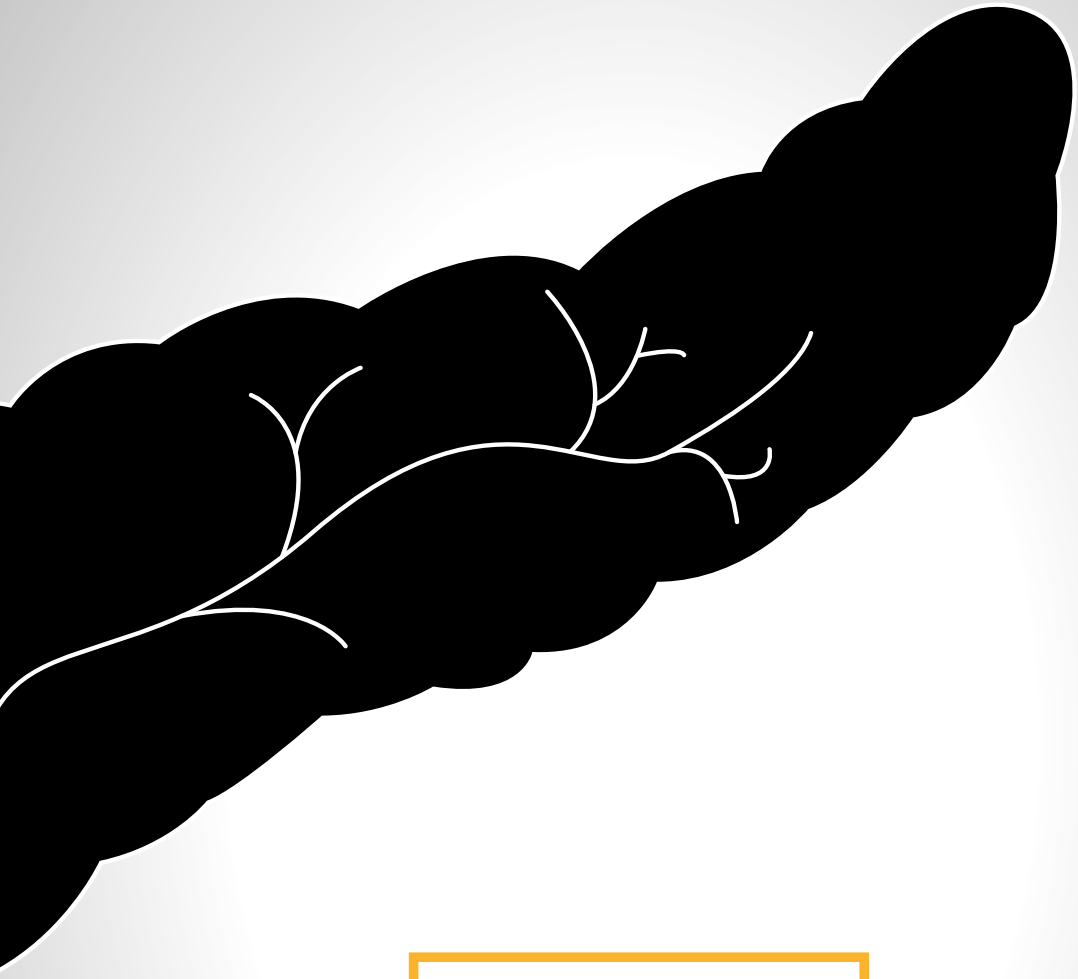
In conclusion, this study provides an overview of the treatment options for patients with a disruption or disconnection of the pancreatic duct after acute necrotizing pancreatitis. The current literature lacks in quality with only one prospective cohort study available and no randomized controlled studies. It is therefore inconclusive about the best treatment of choice. Indication for invasive procedures in the treatment of disrupted and disconnect pancreatic duct remains unclear, due to the lack of a systematic diagnostic work-up, the lack of risk analysis to predict the treatment outcome of the various treatment modalities and the absence of studies reporting on conservative treatment. Future research should address the indication, timing and long-term success of all different treatment strategies in order to devise an evidence-based treatment algorithm.

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CHAPTER 5

Diagnosis of a disrupted or disconnected pancreatic duct in acute pancreatitis: a systematic review

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ABSTRACT

Background: Severe pancreatitis may result in a disrupted pancreatic duct, which is associated with a complicated clinical course. Diagnosis of a disrupted pancreatic duct is not standardized in clinical practice or international guidelines. We performed a systematic review of the literature on imaging modalities for diagnosing a disrupted pancreatic duct in patients with acute pancreatitis.

Methods: A systematic search was performed in PubMed, Embase and Cochrane library databases to identify all studies evaluating diagnostic modalities for the diagnosis of a disrupted pancreatic duct in acute pancreatitis. All data regarding diagnostic accuracy were extracted.

Results: We included 8 studies, evaluating five different diagnostic modalities in 142 patients with severe acute pancreatitis. A sensitivity of 100% was reported for endoscopic ultrasound and endoscopic retrograde cholangiopancreatography. The sensitivity of magnetic resonance cholangiopancreatography with or without secretin was 83%. A sensitivity of 92% was demonstrated for a combined cohort of secretin- magnetic resonance cholangiopancreatography and magnetic resonance cholangiopancreatography. A sensitivity of 100% and specificity of 50% was found for amylase-measurements in drain fluid compared with ERCP.

Conclusions: This review suggests that various diagnostic modalities are accurate in diagnosing a disrupted pancreatic duct in patients with acute pancreatitis. Amylase-measurement in drain fluid should be standardized. Given the invasive nature of other modalities, secretin- magnetic resonance cholangiopancreatography or magnetic resonance cholangiopancreatography would be recommended as first diagnostic modality. Further prospective studies, however, are needed.

INTRODUCTION

Acute pancreatitis is one of the most common gastrointestinal diseases for acute hospital admission (1). The disease course is generally mild. Around 20% of patients, however, develop necrosis of the pancreatic or peripancreatic tissue. This necrosis of the pancreatic parenchyma results in loss of viable pancreatic tissue and potentially loss of integrity of the pancreatic duct. This may cause either a disruption or disconnection of the pancreatic duct, causing leakage of pancreatic fluids in the surrounding tissue or to other organs. A complicated course often follows, which may be characterized by (recurrent) or persistent peripancreatic fluid collections, pancreatic ascites, pancreatic fistula including external fistulas following percutaneous catheter drainage (2–7). This causes a major burden on the patient's quality of life and is associated with high health care resource utilization (8–11).

The diagnosis of a disrupted or disconnected pancreatic duct syndrome is not standardized (12,13). Diagnostic modalities currently used are computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP) with or without secretin, or pancreatography during surgery (6,9,11,14–16). Nowadays, ERCP is still considered as the reference of standard, but this is an invasive procedure with a risk of complications such as secondary infection of pancreatic necrosis, flare of pancreatitis, bleeding and perforation (17,18).

Because treatment success is related to the degree and location of the disruption (19–21), a timely and accurate diagnosis of a pancreatic duct disconnection and disruption is expected to facilitate treatment decisions. Guidelines regarding the preferred method and timing diagnosing a disrupted or disconnected pancreatic duct syndrome in acute necrotizing pancreatitis are, however, lacking.

We performed a systematic review to determine the accuracy of the various diagnostic modalities to assess a pancreatic duct disruption and disconnection in patients with severe acute pancreatitis.

METHODS

Search and study selection

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (22). A systematic search was performed in PubMed, Embase and Cochrane Library from database inception until August 27, 2019. The Embase search was limited to Embase sources and restricted to publication types (inclusion of articles and systematic reviews). Search terms included severe pancreatitis (study population), disconnected duct, pancreatic fistula (outcome) and all synonyms. A manual cross-reference check

was performed on all studies reviewed during full-text article assessment. Detailed search details are presented in the Appendix table 1.

Eligibility criteria

Eligibility assessment was independently performed by two reviewers (HCT, SMvD) in a standardized manner. Discrepancies were resolved by consensus. After removal of duplicates the remaining articles were screened on relevance by title/abstract. Reviews, letters, case reports and book chapters were excluded. Selection was restricted to Dutch, German or English human studies with full-text availability. No other restrictions were imposed. Subsequently, full text was assessed for eligibility. Studies were considered eligible if they were cross-sectional studies, cohort studies (with a minimum number of 5 patients) or randomized trials including patients over 18 years of age with acute pancreatitis who underwent any diagnostic modality for a suspected disrupted or disconnected pancreatic duct.

In this systematic review no distinction will be made between a disrupted (partial) and disconnected (complete) pancreatic duct disruption.

Data extraction and critical appraisal

Relevant study characteristics were extracted using a data extraction template based on the Standards of Reporting of Diagnostic Accuracy (STARD) studies checklist (23). The following information was extracted: (1) country of origin, year of publication, design, setting, inclusion criteria; (2) the performed index test and reference standards; (3) total number of patients included and number of relevant patients; (4) accuracy measurements calculated by constructing 2 x 2 tables derived from each index test and its corresponding reference standard.

Data were extracted regarding the imaging characteristics: type of imaging modality, scoring criteria, technical features for each modality and reported observer experience.

The methodological quality of included study was assessed by two reviewers independently (HCT, SMvD) using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (24). Differences in assessment were resolved by consensus between the two reviewers.

Statistical analysis

For each included study, a 2 x 2 contingency table was constructed for each imaging modality. If data were available, sensitivity, specificity and overall accuracy were calculated from the reconstructed tables. Pooled estimates were considered but were assumed trivial owing to heterogeneous index tests and the limited number of studies covering this subject.

RESULTS

Search

The initial search yielded 3171 articles; 1506 articles returned from MEDLINE and 1665 results from Embase. After removal of duplicates 2283 articles remained. Based on title and abstract screening, 76 articles remained for full-text review. Full-text assessment excluded 68 articles. No additional articles were identified after cross-reference check. Four articles evaluated diagnostic modalities, however, they did not provide sufficient data to reconstruct 2 x 2 tables and calculate the diagnostic accuracy values or even the sensitivity or specificity and were therefore excluded (4,25–27). Finally, 8 articles met the predetermined eligibility criteria (2,6,14,19,28–31) (Figure 1. Flowchart). The excluded-by-reason articles are reported in Appendix table 2.

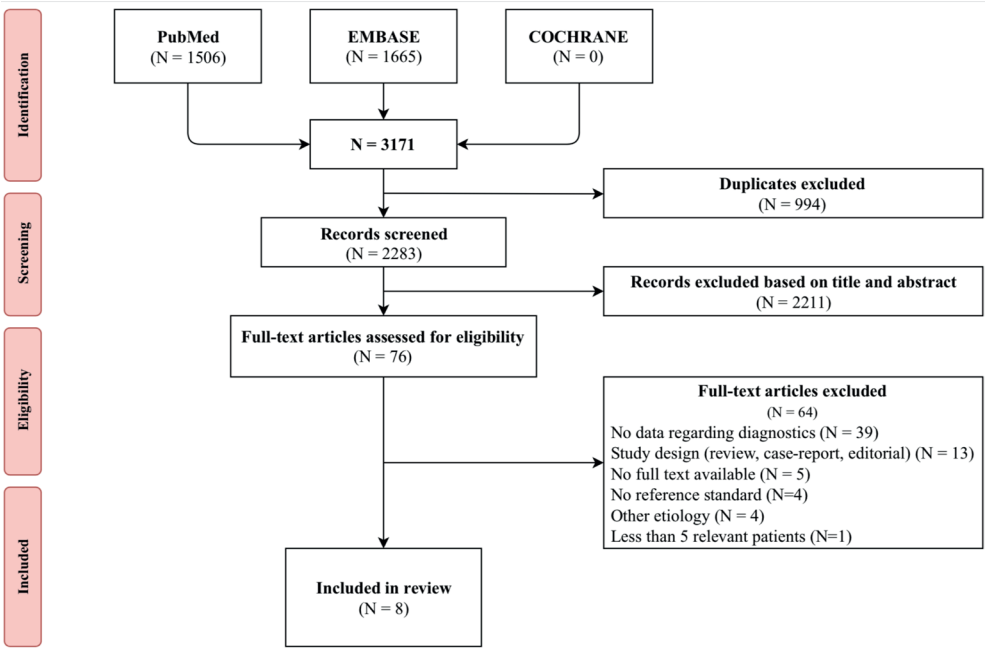


Figure 1. Flowchart

Study characteristics

Study characteristics, including the reference standard for the diagnosis of a disrupted or disconnected pancreatic duct syndrome are presented in Table 1. Data extracted regarding the imaging characteristics are presented in Appendix Table 3. The 8 included studies were observational cohort studies published between 2003 and 2016. Two studies collected data in a prospective manner (29,31), one study did not report the study design (30). A total of 237 patients with moderate to severe

Table 1. Study characteristics of included studies

Study	Year	Country	P/R	Inclusion period	Nr of patients	Relevant patients	Study population	Index test	Reference standard	OE
Bakker et al.	2011	NL	R	2004 - 2007	34	19	Infected necrotizing pancreatitis with pancreatic fistula	Amylase-measurments	ERCP	No
Bang et al.	2016	USA	P	2014 – 2015	42	21	Walled-off necrosis >6cm who underwent EUS guided drainage	EUS	Surgical/ ERCP	No
Drake et al.	2012	USA	R	2000 – 2008	31	31	Acute pancreatitis who underwent ERCP + MRI/MRCP	(Secretin)-MRCP	ERCP	No
Gillams et al.	2005	UK	NR	NR	17	6	Duct disruption e.c.i.: relevant acute pancreatitis	Secretin-MRCP	Surgical	No
Jang et al.	2016	South-Korea	R	2005 – 2013	84	18	Moderate to severe acute pancreatitis who underwent ERCP and/or MRCP	MRCP	ERCP	No
Smoczynski et al.	2015	Poland	R	2001 – 2013	22	8	Walled-off necrosis who underwent endoscopic transpapillary drainage	CECT	ERCP	No
Tann et al.	2003	USA	R	1995 – 2000	26	26	Acute pancreatitis with surgically confirmed duct disruption	ERCP/CECT	Surgical	No
Yokoi et al.	2016	Japan	P	2005 – 2014	15	13	Severe acute pancreatitis who underwent percutaneous drainage of fluidcollection	Amylase-measurements	ERCP	No

P prospective, R retrospective, OE observer experience reported, NR not reported, MRCP magnetic resonance cholangiopancreatography, EUS endoscopic ultrasound, MRI magnetic resonance imaging, ERCP endoscopic retrograde cholangiopancreaticography, CECT contrast-enhanced computed tomography

acute pancreatitis, according the revised 2012 Atlanta classification, were included in the studies (32). In 199 of the 271 patients (peri)pancreatic necrosis was reported (2,6,19,28,29). The number of relevant patients included in the study ranged from 6 to 31, with a total of 142 relevant patients. Three studies primarily investigated the diagnostic accuracy of an imaging modality (14,25,29,30), three studies primarily investigated the best therapy for a disrupted or disconnected pancreatic duct syndrome (2,28,31) and in the last study both were performed. (19).

The studies concerning amylase-measurements in drain fluid compared their index test with ERCP as reference standard (2,28). One study compared ERCP with surgical confirmation (6) and another study compared EUS with either ERCP or surgical confirmation (29). Contrast-enhanced CT was evaluated in two studies, as compared with ERCP (2) or surgical confirmation (6). Three studies compared either MRCP, secretin-MRCP, or both, with ERCP or surgical confirmation as reference standard. One study investigated secretin-MRCP with surgical confirmation as reference standard (30). Comparison of standard MRCP, with ERCP as reference standard, was done in one study (19) and in the last of the three studies no distinction could be made between the patients who underwent standard MRCP or secretin-MRCP, as compared with ERCP (14).

Quality assessment

The QUADAS-2 assessment for each domain is depicted in Figure 2. (Figure 2. Summary of study quality (QUADAS-2)). An outline of each individual study is presented in Appendix Table 4. The risk of bias was divided proportionally with a low and high risk of bias in 50% of the studies. Applicability concerns were low in 75%, high in 21% and unclear in 4% of the studies.

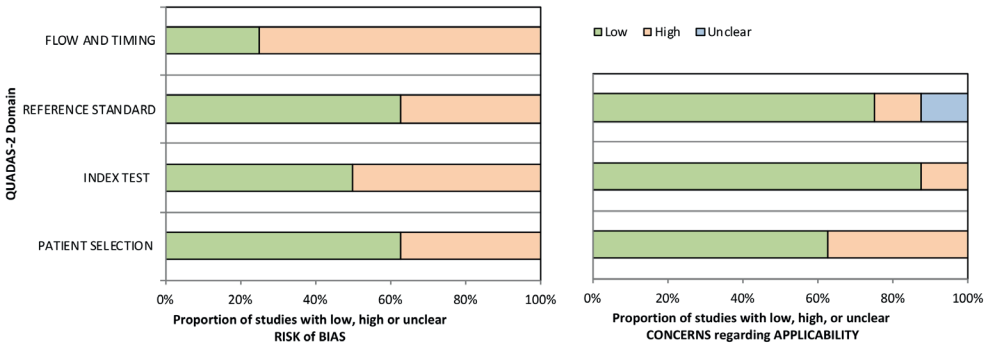


Figure 2. Summary of study quality (QUADAS-2)

Diagnostic accuracy

Results on diagnostic accuracy of the different imaging modalities studies are summarized in Table 2. Additional findings are presented in Appendix Table 5.

Table 2. Results of included studies

Study	Index test	Reference standard	TP	FN	FP	TN	Sensitivity	Specificity	Overall accuracy
Bang et al.	EUS	Surgical	1	0	-	-	100%	-	-
Bang et al.	EUS	Surgical	1	0	-	-	100%	-	-
	EUS	ERCP	20	0	-	-	100%	-	-
Drake et al.	(secretin)-MRCP	ERCP	23	2	0	8	92%	100%	94%
Gillams et al.	Secretin-MRCP	Surgical	5	1	-	-	83.3%	-	-
Jang et al.	MRCP	ERCP	15	3	0	3	83.3%	100%	85.7%
Smoczynski et al.	CT	ERCP	8	2	-	-	80%	-	-
Tann et al.	ERCP	Surgical	26	0	-	-	100%	-	-
	CT	Surgical	26	26			0%		
Yokoi et al.	Amylase-measurements	ERCP	6	0	7	7	100%	50%	65%

TP true positive, FN false negative, FP false positive, TN true negative, - not applicable

Amylase-measurement in drain fluid

Two studies investigated the clinical value of amylase-measurements in drain fluid in detecting pancreatic fistula and a disrupted pancreatic duct in patients with severe acute pancreatitis who underwent percutaneous drainage of a fluidcollection. The presence of pancreatic fistula was, in both studies, defined as output of drain fluid with an amylase content of more than three times the normal serum amylase level. A comparison was made between amylase-measurement and ERCP, with a similar sensitivity found of 100% and also a similar specificity of 50%, resulting in an overall diagnostic accuracy of 65% for amylase measurements in drain fluid (28,31).

ERCP

One study evaluated the diagnostic accuracy of ERCP. A disrupted or disconnected pancreatic duct was confirmed during surgical correction of a disrupted pancreatic duct with a sensitivity of 100%. No data could be extracted to calculate specificity. This study also evaluated prior CT-scans of patients diagnosed with disrupted or disconnected pancreatic duct syndrome by ERCP and none of the prior CT interpretation correctly identified a disrupted or disconnected pancreatic duct (6).

Endoscopic ultrasound

A sensitivity of 100% for detecting a disrupted pancreatic duct with EUS was found in patients with a walled-off necrosis of >6 cm, in whom the pancreatic duct was visible during EUS, as confirmed with histopathological confirmation after distal pancreatectomy or ERCP (29). No specificity was reported or could be calculated.

Contrast-enhanced CT

A sensitivity of 80% was found in the study comparing contrast-enhanced CT with ERCP in patients with walled-off necrosis who underwent endoscopic transpapillary drainage (2). The other study compared contrast-enhanced CT with surgical confirmation during surgical correction for a disrupted pancreatic duct in patients with moderate to severe pancreatitis. A sensitivity of 0% was found (6). For both studies, no specificity was reported or could be calculated from the extracted data.

MRCP

One study investigated the diagnostic yield of MRCP (without secretin) for detecting a pancreatic duct disruption, with ERCP as reference standard (19) in patients with moderate to severe pancreatitis. A sensitivity of 100% was reported. No specificity was reported and could not be calculated from the extracted data.

Secretin-MRCP

Secretin-MRCP, as compared with surgical confirmation of a disrupted pancreatic duct, was evaluated in one study in patients with moderate to severe pancreatitis with a reported sensitivity of 83.3%. Again, specificity was not reported or could not be calculated from the source data (30).

MRCP and secretin-MRCP

In one study, both secretin-MRCP and MRCP were compared with ERCP in patients with moderate to severe pancreatitis, showing a sensitivity of 92%, a specificity of 100% and an overall accuracy of 94%. The diagnostic difference between secretin-MRCP and MRCP was not reported upon (14).

DISCUSSION

This is the first systematic review evaluating the various diagnostic modalities for diagnosing a disrupted pancreatic duct in moderate to severe acute pancreatitis. A sensitivity of 100% was demonstrated for amylase-measurements in drain fluid and ERCP (6,28,31,33). The sensitivity for MRCP and for secretin-MRCP was 83%, both with a specificity of 100% (19,30). For a combined cohort of MRCP and

secretin-MRCP a sensitivity of 92% was found (14). Abdominal contrast-enhanced CT had the lowest sensitivity, ranging from 0-80% (2,6).

In clinical practice, a suspicion on a disrupted or disconnected pancreatic duct is raised if amylase content in drain fluid contains more than three times the normal serum amylase level (6,28,31,33–35). To confirm this suspicion, the current reference standard to diagnose a disrupted or disconnected pancreatic duct is ERCP. This imaging modality is, however, invasive and increases the risk of infected necrosis and other complications in this patient population (17,18). These risks do not occur with EUS or less invasive imaging modalities such as (secretin)-MRCP.

Studies on the accuracy of MRCP or EUS for detecting a disrupted duct in acute pancreatitis are scarce. Only one study evaluated EUS, which demonstrated a sensitivity of 100%. Notably, this study only included patients with a walled-off necrosis of more than 6 cm and a disrupted duct was present in 95% of cases. Moreover, 9 patients were excluded because EUS characterization of the pancreatic upstream gland was suboptimal. If this had been included, the sensitivity would have been considerably lower. Success of visualization was dependent on the size of the walled-off necrosis, which raises the suggestion that EUS is only of added value in a selective patient group (29). In this review, we included two studies that used secretin during MRCP (14,30). One study evaluating secretin-MRCP was excluded due to the limited number of relevant patients (n=3), this study reported a sensitivity of 100% for secretin-MRCP compared with ERCP (16). Secretin-MRCP or MRCP can be performed in nearly all patients (16). Secretin is added for stimulation of pancreatic secretions to facilitate the identification of the pancreatic duct. No complications were reported after administration of secretin (16,30). In one study, only 6 of 31 patients received secretin and in 2 patients, who did not receive secretin, a disruption of the pancreatic duct was missed on MRCP. This raises the question of this may have been avoided with the use of secretin (14). Even though the reported visualization of the pancreatic duct is generally very good, one study reported a poorer visualization by MRCP, as compared with ERCP, in patients with a partial disrupted pancreatic duct, as compared with patients with a completely disrupted pancreatic duct (19). No secretin was used in this study, which may explain the poor visualization of the pancreatic duct. Another advantage of secretin-MRCP, besides accurate visualization of the pancreatic duct for detection of a disruption or disconnection, is an accurate visualization of the biliary duct. This may aid in establishing the cause of pancreatitis or evaluation of complications such as biliary obstruction due to peripancreatic collections or inflammation (16,36).

Besides lack of clear evidence and guidelines for the diagnosis, there is also no consensus on the optimal treatment strategy of disrupted or disconnected duct. Several studies have reported high success rates of various treatment strategies including percutaneous drainage, endoscopic drainage and surgical resection (2,4,6–

8,10,11,14–16,19–21,25–27,29,31,37–52). Yet, many of these studies were retrospective studies comprising selected patient cohorts. There are no large prospective studies of consecutive patients with necrotizing pancreatitis, specifically evaluating the prevalence or treatment outcome of a disrupted or disconnected pancreatic duct. The success rate of conservative treatment also is unknown. Future studies should investigate the optimal timing, method and sequence of invasive interventions in this group of patients. To design these studies, a better understanding of the natural course of a disrupted or disconnected pancreatic duct in several subgroups of patients is needed. For instance, as success rates of different treatment strategies are probably related to the degree and location of the disruption, a distinction must be made between a partial and complete disruption. A partial disruption can often be bridged with a pancreatic duct stent, while it is very difficult to bridge a complete disruption (19–21). Therefore, a timely and accurate diagnosis of a pancreatic duct disruption and disconnection will provide better possibilities to predict which treatment could be successful in a specific patient. The diagnostic criteria for a partial disrupted or complete disrupted or disconnected pancreatic duct syndrome, however, varied in the studies included in this review. There are currently no broadly accepted definitions on a partial disrupted, a complete disrupted, a disconnected or disconnected gland syndrome (6).

This study had some limitations. First, only a few studies could be included and hence number of eligible patients was relatively low. Second, most studies were performed in selected patient cohorts and suffered from high risk of bias. Third, partial verification bias was present in some of the included studies (14,19,31). Also, no standardized definitions for a disrupted pancreatic duct were used. As last, in four studies no specificity could be calculated (2,6,29,30).
This study is the only study comparing different diagnostic modalities in diagnosing a disrupted or disconnected pancreatic duct. Strengths of this review included the use of exhaustive search techniques by two reviewers independently and validated systematic review methods, which strengthens our conclusions.

In conclusion, this systematic review suggests that EUS, ERCP, MRCP and secretin-MRCP appear all accurate in diagnosing a disruption or disconnection of the pancreatic duct in patients with acute pancreatitis. Amylase-measurements in drain fluid should be standardized after percutaneous catheter drainage or surgical drain placement. Given the poor overall visualization of the pancreatic duct in a substantial number of patients with necrotizing pancreatitis on EUS and CT and the invasive nature of ERCP, MRCP or secretin-MRCP is recommended as first diagnostic modality. However, the availability of the different diagnostic modalities, however, varies per hospital and country. Further prospective studies are needed to define

the optimal timing and diagnostic value of secretin-MRCP in different subgroups of patients with necrotizing pancreatitis.

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CHAPTER 5

APPENDIX

Supplementary table 1. Search terms

	MeSH terms	All Fields
Acute necrotizing pancreatitis	Necrotizing pancreatitis, Acute	acute necrotizing pancreatit* OR necrotising pancreatit* OR severe pancreatit* OR severe acute pancreat* OR complicated pancreat* OR complicated acute pancreat* OR walled off pancreatic necros*
OR		
Pancreatitis	Pancreatitis	Pancreatitis
OR		
Pancreas	Pancreas	Pancreas
AND		
Necrosis	Necrosis	Necrot* OR Necros* OR Severe OR Acute OR Serious
AND		
(Pancreatic duct	Pancreatic ducts	duct* OR tail OR tails OR pd
AND		
Disconnection	NA	Disconnect* OR Disrupt* OR Leak* OR Interrupt* OR Ruptured OR abnormalit*)
OR		
Pancreatic fistul*		

Supplementary table 2. Excluded articles based on full text

Author	Year	Journal	Reason for exclusion
Alsaad et al.	2016	BMJ Case Reports	Other type of article
Arvantikas et al.	2004	Gastroenterology	<5 number relevant patients
Bang et al.	2018	Annals of Surgery	No diagnostic values reported
Beck et al.	2012	Journal of the American College of Surgeons	No diagnostic values reported
Brennan et al.	2006	Digestive Surgery	No diagnostic values reported
Caperan et al.	2006	Gastroenterolgie Clinique et Biologique	No diagnostic values reported
Chen et al.	2019	BMC Gastroenterology	No diagnostic values reported
Das et al.	2016	Pancreatology	No diagnostic values reported
Deviere et al.	1995	Gastrointestinal Endoscopy	No diagnostic values reported
Dhaka et al.	2015	World Journal of Gastroenterology	No diagnostic values reported
Dhar et al.	2017	Journal of Gastrointestinal Surgery	No diagnostic values reported
Dua et al.	2018	Journal of Surgical Research	No diagnostic values reported
Dua et al.	2018	Journal of Surgical Research	No diagnostic values reported
Fischer et al.	2014	Journal of American College of Surgeons	No diagnostic values reported
Freeny et al.	1988	Journal of Radiology	No diagnostic values reported
Fulcher et al.	2000	The Journal of Trauma	Other etiology of pancreatitis
Gamez-del-Castillo et al.	2016	Revista Espanola de Enfermedades Digestivas	Other type of article
Gupta et al.	2010	Clinical Gastroenterology and Hepatology	Other type of article
Hakime et al.	2007	Journal de Radiologie	No full-text available
Halttunen et al.	2007	European Journal of Trauma and Emergency Surgery	Other etiology of pancreatitis
Howard et al.	2001	Surgery	No diagnostic values reported
Irani et al.	2012	Gastrointestinal Endoscopy	No diagnostic values reported
Jagielski et al.	2018	Przeglad Gastroenterologiczny	No diagnostic values reported
Jagielski et al.	2017	Digestive Endoscopy	Other type of article
Jagielski et al.	2018	Surgical Endoscopy	No diagnostic values reported
Jimenez-Fuertes et al.	2016	Cirugia Espanola	No full-text available
Jin et al.	2017	World Journal of Gastroenterology	No diagnostic values reported
Kamal et al.	2015	Abdominal Imaging	No diagnostic accuracy

Karjula et al.	2019	Endoscopy	No diagnostic values reported
Kozarek et al.	1991	Gastroenterology	No diagnostic values reported
Lau et al.	2001	American Journal of Surgery	No diagnostic accuracy
Lawrence et al.	2008	Gastrointestinal Endoscopy	No diagnostic values reported
Morgan et al.	2007	Surgical Clinics of North America	Other type of article
Murage et al.	2010	Surgery	No diagnostic values reported
Mutignani et al.	2017	Digestive Diseases and Sciences	No diagnostic values reported
Nabi et al.	2019	Journal of Pediatric Gastroenterology and nutrition	No diagnostic values reported
Nadkarni et al.	2015	Pancreas	No diagnostic values reported
Nealon et al.	2009	Journal of the American College of Surgeons	No diagnostic values reported
Neoptolemos et al.	1993	British Journal of Surgery	No full-text available
Pearson et al.	2012	The Official Journal of the International HPB Association	No diagnostic values reported
Pelaez-Luna et al.	2008	Gastrointestinal Endoscopy	No diagnostic values reported
Peng et al.	2013	PLOS One	No diagnostic accuracy
Pezelli	2014	Nature Reviews Gastroenterology and Hepatology	Other type of article
Pons et al.	2010	Revue du Praticien	No full-text available
Prakesh et al.	2019	ACG Case Reports Journal	Other type of article
Rana et al.	2010	Journal of Gastroenterology and Hepatology (Australia)	No diagnostic values reported
Rana et al.	2013	Pancreatology	No diagnostic values reported
Rana et al.	2015	Journal of Gastrointestinal Surgery	No diagnostic values reported
Rana et al.	2019	Pancreatology	No diagnostic values reported
Rana et al.	2019	JGH Open	No diagnostic values reported
Sandrasegaran et al.	2017	American journal of roentgenology	No diagnostic values reported
Sharaiha et al.	2016	Clinical Gastroenterology and Hepatology	Other type of article
Sherman et al.	2014	Gastroenterology	Other etiology of pancreatitis
Sikora et al.	2005	Digestive Surgery	No diagnostic values reported
Solanki et al.	2011	Journal of the Pancreas	Other type of article
Tajima et al.	2006	Surgery	Other etiology of pancreatitis

Telford et al.	2002	Gastrointestinal Endoscopy	No diagnostic values reported
Tellez-Avina et al.	2018	Journal of Clinical Gastroenterology	No diagnostic values reported
Tirkes et al.	2013	Radiographics	No diagnostic values reported
Trevino et al.	2010	Journal of Gastroenterology and Hepatology (Australia)	No diagnostic values reported
Uomo et al.	1998	American Journal of Surgery	No diagnostic accuracy
Varadarajulu et al.	2005	Gastrointestinal Endoscopy	No diagnostic values reported
Varadarajulu et al.	2013	Gastrointestinal Endoscopy Clinics of North America	Other type of article
Wilechansky et al.	2017	Digestive Endoscopy	Other type of article
Yamada et al.	2019	World Journal of Clinical Cases	Other type of article
Zein et al.	2003	Gastrointestinal Endoscopy	No full-text available
Zhong et al.	2011	Endoscopy	Other type of article

Supplementary table 3. Imaging characteristics

Magnetic resonance imaging or cholangiopancreatography (MRI/MRCP)							
Study	**Year**	**Magnetic field**	**Coil type**	**Contrast**	**Secretin enhancement**	**Sequence**	**Scoring criteria**
Drake et al.	2012	1.5T	Torso phased array coil	Yes	Yes/No	T2	Duct disruption or any increase in fluid outside the confines of the intestinal lumen after secretin administration
Gillams et al.	2006	1.5T	Torso phased array coil	NR	Yes	T1, T2	Any increase outside the confines of the intestinal lumen constitutes an abnormal leakage of pancreatic fluid
Jang et al.	2016	NR	NR	NR	No	NR	Loss of continuity of main pancreatic duct with or without extravasation

NR not reported

Supplementary table 4. QUADAS-2 characteristics for each study

	DOMAIN 1 Patient selection					DOMAIN 2 Index test(s)				DOMAIN 3 Reference standard				DOMAIN 4 Flow and timing				
	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	**Could the selection of patients have introduced bias?***	Is there concern that the included patients do not match the review question?+	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	**Could the conduct or interpretation of the index test have introducing bias? ***	Is there concern that the index test, its conduct, or interpretation differ from the review question?+	Is the reference standard likely to correctly classify the target condition	Were the reference standard results interpreted without knowledge of the results of the index test?	**Could the reference standard, its conduct or its interpretation have introduced bias***	Is there concern that the target condition as defined by the reference standard does not match the review question? +	Was there an appropriate interval between index test and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	**Could the patient flow have introduced bias?***
Arvanatikis et al.	+	+	+	**L**	**L**	+	+	**L**	**L**	+	-	**L**	**L**	+	-	+	+	**H**
Bakker et al.	+	+	+	**L**	**L**	+	+	**L**	**L**	+	-	**H**	**L**	?	-	+	-	**H**
Bang et al.	-	+	-	**H**	**L**	+	+	**H**	**L**	+	?	**L**	**L**	-	+	-	+	**H**
Drake et al.	-	+	+	**L**	**L**	+	+	**L**	**L**	+	+	**L**	**L**	+	+	+	+	**L**
Gillams et al.	?	+	?	**H**	**H**	?	+	**L**	**L**	+	-	**H**	**?**	-	-	-	+	**H**
Jang et al.	-	+	+	**L**	**L**	?	+	**H**	**L**	+	?	**L**	**L**	?	-	+	+	**H**
Kamal et al.	-	+	+	**L**	**L**	+	?	**L**	**L**	-	+	**H**	**H**	+	+	+	+	**L**
Lau et al.	-	+	+	**L**	**L**	?	-	**H**	**H**	-	-	**H**	**H**	-	-	-	+	**H**
Peng et al.	-	-	+	**H**	**L**	+	+	**L**	**L**	-	-	**H**	**H**	-	-	-	+	**H**
Smoczynski et al.	-	+	?	**H**	**H**	?	?	**H**	**H**	-	-	**H**	**H**	-	-	-	+	**H**
Tann et al.	-	+	+	**L**	**H**	?	?	**H**	**L**	+	?	**L**	**L**	-	+	+	+	**L**
Uomo et al.	-	+	+	**H**	**H**	?	?	**H**	**L**	-	-	**H**	**H**	-	-	-	+	**H**
Yokoi et al.	+	+	+	**L**	**L**	+	+	**L**	**L**	+	-	**L**	**L**	+	-	+	-	**H**

* Risk: Low/High/Unclear (L/H/?)

+ Concern: Low/High/Unclear (L/H/?)

Supplementary table 5. Other findings

Study	Year	Study population	Nr of patients	Incidence disruption	Location disruption	Other findings
Bang et al.	2016	Walled-off necrosis who underwent EUS guided drainage	21	100%	Complete disconnection of the duct was identified in the pancreatic body (n=10), neck (n=9) and body-tail junction (n=2)	Pancreatogram at ERCP was succesfull in 17/20 patients and failed in 3; EUS-guided pancreatogram was succesfull in all 3 patients in whom ERCP failed
Drake et al.	2012	Acute pancreatitis who underwent ERCP + MRI/MRCP	31	74%	The site of the disruption was localized on MRCP in 57% (13/23): the pancreatic head (n=5) and in the pancreatic body (n=5)	NR
Gillams et al.	2005	Duct disruption e.c.i.: relevant acute pancreatitis	6	NA	NR	Of the five patients who underwent ERCP, duct obstruction prevented depiction of the disruption in two (40%), in both whom the disruption was shown by secretin-MRCP
Jang et al.	2016	Moderate to severe acute pancreatitis who underwent ERCP and/or MRCP	84	38%	NR	18 patients underwent both MRCP and ERCP. Complete duct disruption: 88% (7/8) were suspected as having disruption on MRCP, 71% (5/7) with partial disruption were suspected on MRCP
Smoczynski et al.	2015	Walled-off necrosis who underwent endoscopic transpapillary drainage	22	100%	NR	Partial disruption was observed in 14 patients and complete disruption in 8
Tann et al.	2003	Acute pancreatitis with surgically confirmed duct disruption	26	NA	Located in pancreatic neck (n=15), in midbody (n=5) and in body/tail segments (n=6	NR

Yokoi et al.	2016	Severe acute pancreatitis who underwent percutaneous drainage of fluid collection	13	46.2%	The disruptions were found in the pancreatic body (n=4), in the tail (n=2) and in both. (n=1)	Of the 15 patients with a percutaneous drainage, 13 patients developed a pancreatic fistula. No complete disruptions were found.

NR not reported, *EUS* endoscopic ultrasound, *ERCP* endoscopic retrograde cholangiopancreatography, *NA* not applicable, *CT* computed tomography



6

CHAPTER 6

Postponed or immediate drainage of infected necrotizing pancreatitis (POINTER trial): study protocol for a randomized controlled trial

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ABSTRACT

Background: Infected necrosis complicates 10% of all acute pancreatitis episodes and is associated with 15-20% mortality. The current standard treatment for infected necrotizing pancreatitis is the step-up approach (catheter drainage, if necessary followed by minimally invasive necrosectomy). Catheter drainage is preferably postponed until the stage of walled-off necrosis, which usually takes 4 weeks. This delay stems from the time when open necrosectomy was the standard. It is unclear whether such delay is needed for catheter drainage or whether earlier intervention could actually be beneficial in the current step-up approach. The POINTER trial investigates if immediate catheter drainage in patients with infected necrotizing pancreatitis is superior to the current practice of postponed intervention.

Methods: POINTER is a randomized controlled multicenter superiority trial. All patients with necrotizing pancreatitis are screened for eligibility. In total, 104 adult patients with (suspected) infected necrotizing pancreatitis are randomized between immediate (within 24 hours) catheter drainage and current standard care involving postponed catheter drainage. Necrosectomy, if necessary, is preferably postponed until the stage of walled-off necrosis in both treatment arms. Primary outcome is the Comprehensive Complication Index (CCI), which includes all complications between randomization and 6 months follow-up. Secondary outcomes include mortality, complications, number of (re-)interventions, hospital and Intensive Care Unit (ICU) lengths of stay, quality adjusted life years (QALYs) and (in)direct costs. Standard follow-up is at 3 and 6 months after randomization.

Discussion: The POINTER trial investigates if immediate catheter drainage in infected necrotizing pancreatitis reduces the composite endpoint of complications, as compared with the current standard treatment strategy involving a delay of intervention until the stage of walled-off necrosis.

Trial registration: Current controlled trials ISRCTN33682933 (date registration: 6 August 2015).

BACKGROUND

Acute pancreatitis is one of the most common gastrointestinal conditions requiring acute hospital admission [1]. Around 20-30% of these patients develop necrotizing pancreatitis [2]. Infected necrotizing pancreatitis occurs in a third of these patients and is associated with a mortality of 15-20% [3, 4], despite radiological, endoscopic or surgical interventions [3-6]. The current, 2013 international treatment guidelines [7, 8] recommend a step-up approach, based on results of the Dutch PANTER trial [3]. The first step of this step-up approach is catheter drainage, preferably once the (extra)pancreatic collection has organized and has become fully encapsulated (walled-off necrosis). This process usually is complete after 4 weeks after onset of disease. During this time, intravenous antibiotic treatment is used which may obviate the need for any intervention in a small subset of patients [4]. If catheter drainage does not resolve the clinical signs of infection and sepsis, surgical [3] or endoscopic [9] necrosectomy is performed as the next step.

Postponing all interventions for infected necrosis until the stage of walled-off necrosis has been standard practice for many years. The rationale for this delay lies in the prevention of the 'extra hit' (i.e. a pro-inflammatory reaction) of open surgery in these already critically ill patients, as well as the relation between early open necrosectomy and mortality [10]. In line with this practice, catheter drainage in the current step-up approach has also been postponed until the stage of walled-off necrosis. Meanwhile, intravenous antibiotics are administered to reduce systemic illness from the infected necrosis, which may lead to increased incidence of Candida infections and antibiotic-resistance [10]. Notably, several observational studies have suggested that encapsulation is not mandatory for safe and successful catheter drainage [3, 11-15]. In other conditions, such as pancreatic fistula after pancreatic resection, early (percutaneous) catheter drainage has also proven to be safe and successful [16]. Furthermore, an international survey among expert pancreatologists demonstrated 'equipoise' between immediate and postponed catheter drainage of infected necrotizing pancreatitis [17]. The aim of immediate catheter drainage is to prevent further clinical deterioration.

METHODS

The trial protocol is written in accordance with the SPIRIT guidelines (see figure 1 and for the SPIRIT checklist additional file 1) [18].

Study aim

The POINTER trial aims to determine whether immediate catheter drainage in patients with (suspected) infected necrotizing pancreatitis is superior to the current standard of postponed catheter drainage with regard to clinical outcome

Figure 1. SPIRIT schedule of enrolment, interventions, and assessments.

	STUDY PERIOD						
	Enrolment	Allocation	Primary study period			Follow-up	
TIMEPOINT	Screening for infected necrosis	Diagnosing infected necrosis	<24h After randomization	No clinical improvement	Walled-off necrosis	3 months	6 months
	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5
ENROLMENT	X						
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS							
Direct drainage (A)			X				
Drain revision (A)*				X			
Necrosectomy (A)*					X		
Postponed drainage (B)*					X		
Drain revision (B)*					X		
Necrosectomy (B)*					X		
ASSESSMENTS							
Baseline variables		X					
Primary outcome^							X
Secondary outcomes#						X	X

*In case of no clinical improvement. Baseline variables: age, sex, center, body mass index, etiology of pancreatitis, American Society of Anesthesiologist's classification, co-morbidity, disease severity, suspected or proven infected necrosis, time from admission to randomization, time from admission to tertiary referral. ^Primary outcome: Comprehensive Complications Index. #Secondary outcomes: mortality, complications, number of (re-)interventions, hospital and Intensive Care Unit lengths of stay, quality adjusted life years and (in)direct costs.

and cost-effectiveness. The hypothesis is that pro-active diagnosis of infected necrosis and immediate catheter drainage prevents further clinical deterioration of these patients, reducing complications and possibly death, and reduces length of hospital stay and costs, as compared to postponed catheter drainage using antibiotics, preferably until the stage of walled-off necrosis.

Study design and setting

POINTER is a randomized controlled multicenter superiority trial, including hospitalized adult patients with proven or suspected infected necrotizing pancreatitis. In total, 25 centers are participating in the trial, including all 8 Dutch university medical centers. Endpoints are assessed by an adjudication committee, blinded for assigned treatment arm, based on clinical case descriptions and endpoint definitions. A Data and Safety Monitoring Committee (DSMC) monitors patient safety.

Inclusion criteria (see additional file 2; table S1 and additional file 3; table S2)

- Proven infected necrotizing pancreatitis or, if >14 days after onset of disease, clinical suspicion of infected necrosis
- Catheter drainage of the necrotic collection is technically feasible
- Age ≥18 years

Exclusion criteria

- Onset of acute pancreatitis >35 days ago
- Indication for emergency laparotomy because of an abdominal catastrophe
- Previous retroperitoneal intervention for necrotizing pancreatitis
- Documented chronic pancreatitis

Treatment groups

All patients with signs of infected necrotizing pancreatitis are pro-actively assessed for the presence of infected necrosis, either by imaging (gas configurations), fine-needle aspiration (FNA), or clinical signs of infection which may include persistent organ failure. See additional file 4; figure S1 for the inclusion flowchart. FNA is only used on indication and not as a screening tool. Patients who fulfill the eligibility criteria are randomly assigned to group A or B. Since diagnosing infected necrosis and decision-making for invasive intervention in these patients are both challenging, the Dutch pancreatitis expert panel [19] is 24/7 available to assess indication for intervention and eligibility for randomization as was done in the PANTER [3] and TENSION [9] trials.

Intervention group (A)

Group A: immediate catheter drainage, within 24 hours after randomization, while starting (or continuing) antibiotic treatment. In case of no clinical improvement within 72 hours thereafter, the possibility of additional drainage is evaluated, including drain revision or drain upsizing. In case of no clinical improvement thereafter and no possibilities for additional catheter drainage, a necrosectomy is performed, once the (extra)pancreatic collection has developed into walled-off necrosis. No clinical improvement is defined as new organ failure or 2/3 parameters that failure to decrease (temperature, CRP and leukocyte count). See flowchart in additional file 4; figure S1.

Control group (B)

Group B: postponed catheter drainage, using antibiotics, preferably until the (extra) pancreatic necrotic collection has reached the stage of walled-off necrosis. In case of no clinical improvement within 72 hours after drainage, the possibility of additional drainage is evaluated, including drain revision or drain upsizing. In case of no clinical improvement thereafter and no possibilities for additional catheter drainage, a minimally-invasive necrosectomy is performed. No clinical improvement is defined as new organ failure or 2/3 parameters that failure to decrease (temperature, CRP and leukocyte count). See flowchart in additional file 4; figure S1.

Diagnosing infected necrosis

All patients with signs of infected necrotizing pancreatitis are screened for eligibility (additional file 4; figure S1). We distinguish diagnosing infected necrosis in patients in the first 14 days after onset of disease versus thereafter. In the first 14 days a proven infection is mandatory, as in this early course of the disease it is impossible to distinguish systemic inflammatory response syndrome (SIRS) from sepsis. This proof requires either a positive gram stain or culture from FNA or gas configurations in the (peri)pancreatic collection with necrosis on imaging (Contrast Enhanced Computed Tomography (CECT) or Magnetic Resonance Imaging (MRI)). In case of unclear signs of infection, percutaneous FNA is performed in patients with necrotizing pancreatitis within 14 days after onset of disease with 2 consecutive days of clinical signs of infection (i.e. new (multiple) organ failure or 2/3 parameters raised: temperature, CRP or leukocyte count). After the first 14 days, clinical signs of infection suffice for diagnosing infected necrosis (having no other focus for infection, e.g. pneumonia), based on our experiences in previous trials [3, 9]. Obviously, in case of clinical doubt, FNA is still allowed after the first 14 days. The presence of gas in the (extra)pancreatic necrosis on CECT is considered

proven infected necrosis in all patients, regardless of the disease stage (i.e. before or after 14 days).

Supportive treatment

Current standard management of acute (necrotizing) pancreatitis is extensively described in the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines in 2013 [7]. These international guidelines have been adopted by the Dutch Pancreatitis Study Group (DPSG) and the national professional organizations involved. In accordance with these guidelines, patients receive fluid resuscitation, pain management and enteral feeding (oral, if not tolerated enteral). Antibiotic prophylaxis is not given. Patients who deteriorate with clinical signs of infection will undergo infectious focus detection, with cultures of blood, urine, sputum, ascites and diagnostic imaging (e.g. chest X-ray and abdominal CECT). Once an infectious focus is diagnosed, targeted antibiotics are given or, in case of high suspicion of infected necrosis and persistent deterioration, broad spectrum antibiotics with optimal tissue penetration are started empirically. The latter usually consists of meropenem or imipenem, based on the local antibiotics protocol.

Step-up approach

Both a percutaneous-surgical and an endoscopic step-up approach are permitted in the POINTER trial, depending on the location of the necrotic collection(s), the extent of encapsulation and the preference of the treating physician. Catheter drainage can be performed transluminal (transgastric or transduodenal) endoscopically or percutaneous via the retroperitoneal route. In case of no clinical improvement within the first 72 hours after initial catheter drainage, an additional or upsizing drainage procedure is performed (additional file 4; figure S1). In absence of clinical improvement after this second drainage procedure and no further possibilities for optimized or additional drainage, necrosectomy is performed. After percutaneous catheter drainage, additional necrosectomy should be performed surgically (e.g. videoscopic assisted retroperitoneal debridement (VARD)) and after endoscopic transluminal drainage, endoscopic transluminal necrosectomy is performed. Only in case (additional) necrotic collections are not technically approachable via the standard second step, additional catheter drainage or necrosectomy may be performed via the 'other' approach. Both step-up approaches are performed conform the PANTER and TENSION trial protocols [3, 9], see also additional file 5; figure S2 and additional 6; figure S3. The participating centers have documented expertise, defined as having performed at least 10 independent VARD procedures, 10 independent endoscopic transluminal drainage procedures and 10 independent endoscopic transluminal necrosectomies. In case of insufficient local experience

available (e.g. during weekends), the patient is transferred to a tertiary referral center with sufficient experience.

Primary endpoint

Primary endpoint is the Comprehensive Complications Index (CCI) [20-21], including all complications, graded according to the Clavien-Dindo classification, after randomization until 6 months after, other than pre-existent complications, e.g. treatment for infected (extra)pancreatic necrosis. These complications are assessed by an adjudication committee, blinded for assigned treatment arm, based on clinical case descriptions using definitions.

Secondary endpoints

Secondary endpoints are: mortality, new-onset (multiple) organ failure, bleeding requiring intervention, perforation of a visceral organ requiring intervention, enterocutaneous and pancreatic fistula, incisional hernia (including burst abdomen), wound infections, endocrine and exocrine pancreas insufficiency, number of patients with severe complications (Clavien-Dindo III or higher), number of patients per Clavien-Dindo classification, number of surgical, endoscopic and radiological (re-)interventions, length of hospital stay, length of ICU admission, quality adjusted life years (QALYs), and total direct and indirect costs (see additional file 7 for relevant definitions). Also, for mutual comparison, the primary endpoint of the previous PANTER trial will be a secondary endpoint of the POINTER trial (i.e. a composite of major complications; new-onset multiple organ failure, enterocutaneous fistula or perforation of a visceral organ requiring intervention, intra-abdominal bleeding requiring intervention or death during admission or during the 3 months after discharge) [3].

Sample size

The sample size is calculated based on the primary endpoint Comprehensive Complication Index. A mean CCI score of 40 (with a standard deviation of 27) for the postponed catheter drainage is based on the number of complications in the step-up arm of the PANTER trial [3] and TENSION trial [9]. A Student's T-test will have 80% power to detect a clinically relevant reduction of 15 to a CCI score of 25 [21] at a significance level of 0.05, if the sample size equals 2 x 51, is 102 evaluable patients. Assuming a dropout rate of about 2%, 104 patients are included.

Randomization, blinding and treatment allocation

Patients are randomized using a centrally operated computer (ALEA system) with variable block randomization for allocation concealment between group A (immediate catheter drainage) and group B (postponed catheter drainage).

Stratification at randomization is applied for the factors: presence of organ failure (yes vs. no), disease duration (day 0-20 vs. day 21-35) and center (expected high number of included patients vs. other centers). For randomization of a patient, physicians can contact the study coordinator via telephone (www.pancreatitis.nl) 24 hours per day, 7 days per week in order to check the eligibility criteria and to verify whether informed consent has been obtained. Blinding of patients and physicians for treatment strategy is not feasible, since both treatments are highly different timing-wise. Patients are coded by a numeric randomization code (anonymized).

Follow-up

The follow-up duration is 6 months from randomization. Outpatient follow-up visits take place at the discretion of the responsible physician, but in any case 3 and 6 months after randomization that can be considered as standard care. All patients undergo imaging (preferably CECT) at 3 and 6 months post-randomization. Furthermore at these points in time exocrine and endocrine pancreatic function is measured, with respectively blood glucose measurements and fecal elastase tests. No blood or fecal samples are stored at the DPSG datacenter. The treating physician is responsible for the application, interpretation and treatment when needed. Also every patient receives a combined questionnaire at home (SF-36 [22], EQ-5D [23], iMedical Consumption Questionnaire (iMCQ) [24] and iProductivity Cost Questionnaire (iPCQ) [25]) at 3 and 6 months. Data from patient records is collected until 6 months post-randomization.

Baseline values

Baseline criteria (all <24 hours prior to randomization) are: age, sex, center, body mass index, etiology of pancreatitis, American Society of Anesthesiologist's (ASA) classification, co-morbidity, disease severity (SIRS, ICU admission, single or multiple organ failure, Acute Physiology and Chronic Health Evaluation (APACHE) ll score, Multiple Organ Dysfunction Score (MODS) [26], Sequential Organ Failure Assessment (SOFA) score [27], C-reactive protein (CRP)), CT severity index (CTSI), suspected or proven infected necrosis, time from admission to randomization (days), time from admission to tertiary referral (days).

Statistical analysis

All randomized patients are evaluated for primary and secondary endpoints at 6 months after randomization. Using primary source data, a blinded adjudication committee will assess the occurrence of the primary endpoint and/or secondary outcomes after the last patient has completed the predefined follow-up of 6 months after randomization.

The primary analysis is based on intention-to-treat principles. For exploratory reasons also a per-protocol analysis is performed. A tabular listing of all patients excluded from the intention-to-treat populations is provided together with the reasons for exclusion. For the intention-to-treat population the protocol deviations for each randomization arm is listed. Predefined subgroup analyses are performed for patients with and without (multiple) organ failure, disease duration (cut-off 20 days) at time of randomization and per center (high expected number of included patients and other centers).

All analyses are performed in SPSS for Windows or SAS System for Windows. All data handling and analyses are saved in a syntax/program file. Results are presented with all centers combined. A two-tailed p-value <0.05 is considered statistically significant. No corrections for multiple tests are applied.

The primary outcome is a sum of all complications that are weighted for their severity (multiplication of the median reference values from patients and physicians), the Comprehensive Complication Index [20-21]. Comparison of the primary endpoint is expressed in terms of an absolute difference in mean CCI score and standard deviation (SD). Subsequent analyses are directed at secondary endpoints. Data are presented as mean ± SD and in case of skewed distributions as median and range. Values are compared by the Student's t test, Wilcoxon rank sum test, $\chi 2$ test or Fischer exact test as appropriate. In the event of imbalance between groups at baseline, regression analysis is used to correct for the effect of the covariates.

The economic evaluation addresses the question whether or not immediate catheter drainage in patients with infected necrosis is cost-effective compared to the current management of postponed catheter drainage. A cost-effectiveness analysis as well as a cost-utility analysis are performed, both from a societal perspective. The primary outcome parameters in the cost-effectiveness and cost-utility analyses respectively are the costs per unit of the CCI score and the costs per quality adjusted life year (QALY).

Monitoring and quality assurance

Clinical trial monitoring is performed by an independent monitor. The trial monitor checks and verifies documents and reports in every site in the electronic or paper record of the trial patient. The frequency may be changed based on the total enrolment period and enrolment rate. The monitor checks the site files according the Medical Research Involving Human Subjects Act (WMO)/Good Clinical Practice (GCP) standards if and how essential documents are collected/administered and verifies all reported severe adverse events (SAE's). Also, the monitor verifies the

protocol compliance. A monitoring report is made after each monitoring visit in a specific site.

Safety

All physicians who are involved in the trial are asked to report all adverse events to the coordinating investigator. An independent Data Safety Monitoring Committee (DSMC) is assigned to evaluate safety parameters at regular intervals. The DSMC consists of 5 members: 2 surgeons, a gastroenterologist, a radiologist and an epidemiologist. Evaluations are planned after patient number 25, 50 and 75 have completed their 6 months follow-up. Per 25 patients, all deceased patients and every possible trial related serious adverse event are listed and discussed within the DSMC unblinded. During the inclusion period of the study the DSMC performs interim-analyses only on safety. Only in case of safety reasons the POINTER trial will be prematurely terminated, as assessed by the DSMC. There is no interim-analysis for treatment effect. Adverse events are reported using the online module (https://www.toetsingonline.nl) of the Dutch Central Committee on Research involving human subjects.

DISCUSSION

Infected necrosis is a potentially lethal complication of acute pancreatitis, typically requiring invasive intervention. The treatment of infected necrotizing pancreatitis is associated with lengthy hospital stay and high costs. The POINTER trial is the first randomized controlled trial designed to determine the optimal timing catheter drainage in infected necrotizing pancreatitis: i.e. immediate or postponed, once walled-off necrosis has occurred.

According to current evidence-based international guidelines [7, 8], suspected or proven infected necrosis in patients with clinical signs of infection is an indication for invasive intervention. There should be a strong reluctance towards intervening in sterile collections [7, 28]. Currently, an intervention is advised when the infected necrosis has become walled-off, which occurs typically 4 weeks after onset of disease [29]. This practice of postponing interventions until the stage of walled-off necrosis is based on literature from the time where open necrosectomy was the standard intervention [10, 30-31]. It has been recognized that early necrosectomy has major impact on the already critically ill patient, whereas postponed necrosectomy allows the immune system to recover from the pro-inflammatory response due to pancreatitis.

Since the step-up approach is now considered standard of care, the issue regarding the optimal timing of catheter drainage has become highly relevant. Current

literature reports that 35-64% of patients with infected necrotizing pancreatitis can be treated with catheter drainage alone, without the need for invasive necrosectomy [3, 5]. Therefore, several expert pancreatologists have stated that they already practice immediate catheter drainage in patients with infected necrosis. In a recent international survey performed in preparation for this study, 55% of expert pancreatologists stated that they typically postpone catheter drainage using antibiotics, whereas the other 45% proclaimed to drain immediately after diagnosing infected necrosis [17]. Thus, in practice immediate catheter drainage is already performed in individual patients, regardless of the effect of antibiotics alone or the degree of encapsulation. Several retrospective cohorts [32] described (percutaneous) catheter drainage for infected necrosis at a median of 2 weeks (9-15 days) after onset of disease instead of 4 weeks (28 days).
In the step-up approach arm of the PANTER trial, patient outcomes were significantly better compared to the control group (primary open necrosectomy), but mortality (19%) did not differ between both groups [3]. To further reduce mortality and morbidity, the POINTER trial assesses whether early detection of infected necrosis and immediate catheter drainage improve outcomes. Earlier intervention may prevent patients from further deterioration while often waiting several weeks before undergoing an invasive intervention, and thereby reduce complications and length of hospital stay and improve patient quality of life. In the control group, the effect of antibiotics is awaited while letting the (extra)pancreatic necrotic collections become walled-off. In a small minority patients [4], antibiotic treatment alone may suffice, which is another possible benefit for the control group.

Infected necrosis can be diagnosed by the presence of gas in the (extra)pancreatic necrotic collection on imaging (e.g. CECT), irrespective of the source of the gas (i.e. through gas-forming bacteria or loss of integrity of the gastrointestinal tract). Collections with gas are seen in up to 42% of patients with infected necrosis [33] and can occur in every phase of the disease [34-35]. Infected necrosis can also be confirmed by a positive gram stain or culture gathered with FNA. In a recent study, infected necrosis was confirmed by FNA in 86% (of 28 patients) which was similar to the diagnostic performance of clinical symptoms (80% of 92 patients) or gas on imaging (94% of 88 patients) [33]. Until recently, FNA was not routinely used for diagnosing infected necrosis in the Netherlands [17] since its outcome did not change treatment because invasive intervention was postponed until the stage of walled-off necrosis, also in case of a positive culture. In the POINTER trial, however, it is pivotal to detect infected necrosis as early as possible to be able to perform an immediate drainage (group A). Differentiating SIRS from sepsis is, however, very difficult in the first 14 days of the disease. Therefore, in the absence of gas on imaging but with clinical signs of infection in the first 14 days, a positive gram stain

or culture after FNA is obligatory prior to randomization. Since the false-negative rate of FNA is relatively high [33], a second FNA is advised in patients with persistent deterioration and a primary negative FNA. After the first 14 days clinical signs alone are sufficient to diagnose (suspected) infected necrotizing pancreatitis [3].

After the first 14 days, clinical signs of infected necrosis are much more reliable. In the PANTER trial [3] it was possible to reach a 91% accuracy rate of infected necrosis based on clinical criteria. In the POINTER trial, after the first 14 days, randomization can take place based on the clinical diagnosis of infected necrosis as was done in the PANTER trial [3].

Patients are randomized to undergo either immediate (<24 hours) or postponed (in walled-off necrosis) catheter drainage of infected collections. Depending on the location of the necrotic collection(s), the extent of encapsulation and the preference of the treating physician, both the surgical and the endoscopic step-up approach are allowed. It is known that both approaches are effective and safe and that not all (peri)pancreatic collections are approachable via one technique [6, 9].

The Comprehensive Complication Index [20-21] is the primary endpoint of the trial. Patients with infected necrotizing pancreatitis often have a long disease course with multiple complications, and therefore the CCI score is considered a representative tool to take all these complications into account. The individual complications (e.g. organ failure and mortality), number of (re-) interventions, hospital and ICU lengths of stay, QALYs and (in)direct costs are also analyzed as secondary end points.

Patients are stratified based on organ failure at baseline, since it is known that patients with organ failure have poorer outcomes, as compared to patients with no organ failure. Stratification is also performed for disease duration (cut-off 20 days) since this is obviously related to the onset of walled-off necrosis. Finally, stratification takes place for expected high vs. low volumes of patient inclusions.

In conclusion, the POINTER trial is a multicenter randomized controlled trial that investigates whether immediate catheter drainage reduces the Comprehensive Complication Index in patients with infected necrotizing pancreatitis, as compared to postponed catheter drainage.

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LIST OF ABBREVIATIONS

APA	American Pancreatic Association
APACHE	Acute Physiology and Chronic Health Evaluation
ASA	American Society of Anesthesiologist's classification
CCI	Comprehensive Complication Index
CECT	Contrast Enhanced Computed Tomography
CRP	C-reactive Protein
CTSI	Computer Tomography Severity Index
DPSG	Dutch Pancreatitis Study Group
DSMC	Data Safety Monitoring Committee
FNA	Fine Needle Aspiration
GCP	Good Clinical Practice
IAP	International Association of Pancreatology
ICU	Intensive Care Unit
iMCQ	iMedical Consumption Questionnaire
iPCQ	iProductivity Cost Questionnaire
MODS	Multiple Organ Dysfunction Score
MRI	Magnetic Resonance Imaging
QALY	Quality Adjusted Life Year
SAE	Serious Adverse Event
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SSI	Surgical Site Infection
VARD	Videoscopic Assisted Retroperitoneal Debridement
WMO	Medical research involving human subjects act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met mensen)

CHAPTER 6

APPENDIX

SUPPLEMENTARY MATERIAL

Additional file 1 SPIRIT checklist
Additional file 2 Table S1: in- and exclusion criteria
Additional file 3 Table S2: criteria for infected necrotizing pancreatitis
Additional file 4 Figure S1: inclusion and randomization flowchart
Additional file 5 Figure S2: surgical step-up approach
Additional file 6 Figure S3: endoscopic step-up approach
Additional file 7 Relevant definitions

ADDITIONAL FILE 1 SPIRIT CHECKLIST

Not included in this thesis. Available on https://static-content.springer.com/esm/art%3A10.1186%2Fs13063-019-3315-6/MediaObjects/13063_2019_3315_MOESM1_ESM.docx

ADDITIONAL FILE 2 TABLE S1: IN- AND EXCLUSION CRITERIA

Inclusion	Exclusion
Infected necrotizing pancreatitis[1] Day 0-14: gas on imaging or positive culture Day 15-35: clinical signs alone allowed	Onset of acute pancreatitis >35 days ago
Catheter drainage of the necrotic collection is technically feasible[2]	Indication for emergency laparotomy because of abdominal catastrophe[3]
Age ≥ 18 years	Previous retroperitoneal intervention for necrotizing pancreatitis[4, 5]
	Documented chronic pancreatitis[6]

[1] See criteria in table S2

[2] As deemed by the expert panel and/or treating physician (i.e. enough encapsulation and liquefaction)

[3] For example bleeding, bowel perforation or abdominal compartment syndrome

[4] Ascites drainage is permitted

[5] Emergency laparotomy without opening the bursa is permitted

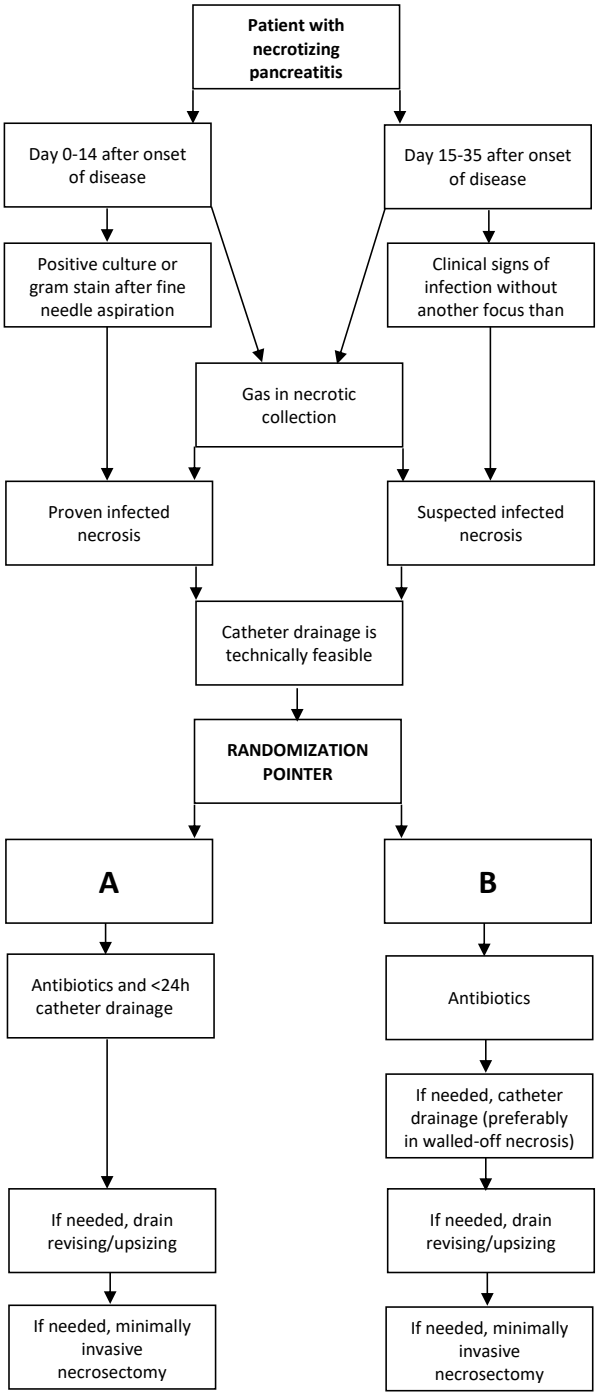
[6] According to the M-ANNHEIM criteria [36]

ADDITIONAL FILE 3 TABLE S2: CRITERIA FOR INFECTED NECROTIZING PANCREATITIS

Day 0-14 after onset of disease: proven infected necrosis	Day 15-35 after onset of disease: proven or suspected infected necrosis
Gas in the necrotic collection on imaging	Gas in the necrotic collection on imaging
Positive gram stain/culture of fine-needle aspiration from the necrotic collection	Positive gram stain/culture of fine-needle aspiration from the necrotic collection
	Clinical signs of infection without obvious another focus than infected necrosis for 3 consecutive days[7]

[7] Either persistent (multiple) organ failure in patients admitted to the Intensive Care Unit. Or 2 of the 3 inflammatory parameters not decreased (temperature (T>38.5 C), C-Reactive Protein or leukocyte count) during 3 consecutive days in patients on regular wards (with no other infection focus). These clinical criteria alone are considered sufficiently reliable only after the initial 14 days of acute pancreatitis.

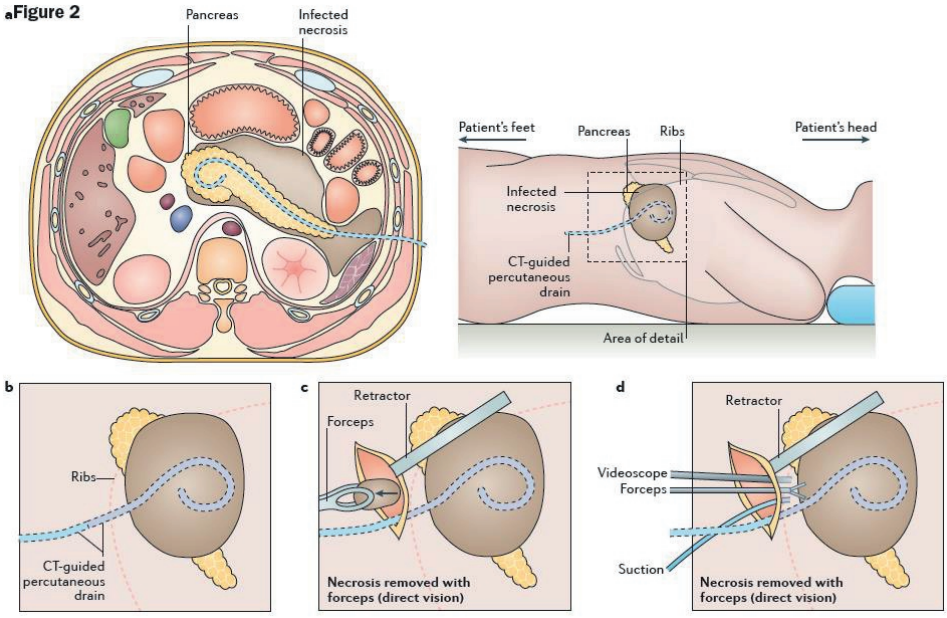
ADDITIONAL FILE 4 FIGURE S1: INCLUSION AND RANDOMIZATION FLOWCHART



ADDITIONAL FILE 5 FIGURE S2: SURGICAL STEP-UP APPROACH [32]

A| Cross-sectional image and torso depicting a peripancreatic collection with fluid and necrosis. The first step of the surgical step-up approach is percutaneous catheter drainage. The preferred access route is through the left retroperitoneal space between the left kidney, dorsal spleen and descending colon. If necessary, percutaneous catheter drainage is followed by a minimally invasive surgical necrosectomy, for example videoscopic-assisted retroperitoneal debridement. B| Enlargement of the area of detail shown in part a of the figure. C| A 5 cm subcostal incision is made, and the previously placed percutaneous drain is used as a guide into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision with a long grasping forceps. D| Further debridement is performed under videoscopic assistance.

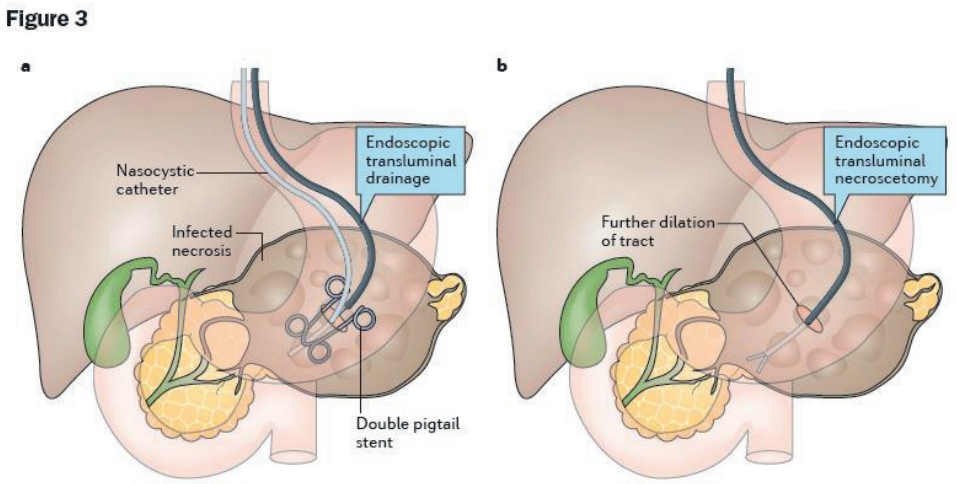
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ADDITIONAL FILE 6 FIGURE S3: ENDOSCOPIC STEP-UP APPROACH [32]

A| The first step of the endoscopic step-up approach is endoscopic transluminal drainage. The preferred access route for endoscopic transluminal treatment is through the posterior wall of the stomach. The necrotic collection often bulges into the stomach, facilitating endoscopic transluminal treatment. The collection is punctured through the gastric wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a nasocystic catheter are placed for continuous postoperative irrigation. B| If necessary, the cystostomy tract is further dilated, the collection is entered by a forward viewing endoscope, and necrosectomy is performed.

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ADDITIONAL FILE 7 RELEVANT DEFINITIONS

Acute pancreatitis
Upper abdominal pain and serum amylase and/ or lipase >3x upper limit of normal, potentially with cross-sectional imaging if first two criteria unclear.

Endocrine pancreatic insufficiency
The need for insulin or oral anti-diabetic drugs; this requirement was not present before onset of pancreatitis.

Enterocutaneous fistula
Secretion of fecal material from a percutaneous drain or drainage canal after drain removal or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery.

Exocrine pancreatic insufficiency
Fecal elastase <0.2 gram and the need for pancreatic enzyme supplementation; this requirement was not present before onset of pancreatitis.

Incisional hernia
Incisional hernia is defined as full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction.

Intra-abdominal bleeding
Bleeding requiring surgical, radiologic, or endoscopic intervention.

M-ANNHEIM criteria
One or more of the following criteria [36]:
1) Pancreatic calcifications
2) Moderate or marked ductal lesions
3) Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation
4) Typical histology of an adequate histological specimen

Multiple Organ Dysfunction Score (MODS)
Scale that ranges from 0 to 24, with higher scores indicating more severe organ dysfunction [26].

Multiple organ failure
Failure of 2 or more organ systems (respiratory, cardiovascular or renal) occurring in the same 24 hours.

Necrotizing pancreatitis
Either pancreatic necrosis or extrapancreatic necrosis. Pancreatic necrosis is defined as diffuse or focal area(s) of non-enhancing pancreatic parenchyma as detected on CECT. Extrapancreatic necrosis is defined as persistent peripancreatic fluid collections on CECT in the absence of pancreatic parenchymal non-enhancement.

New onset (multiple) organ failure
Failure of one (or more) organ systems that was not present prior to randomization or at any time in the 24 hours before intervention.

Organ failure
Failure of one or more of the following organ systems (adapted from the Atlanta classification) and as previously used in the PANTER and TENSION trial [3, 9]:

1) Respiratory: PaO2 <60 mm Hg despite FiO2 30% or the need for mechanical ventilation (pulmonary insufficiency)
2) Cardiovascular: systolic blood pressure <90 mm Hg despite adequate fluid resuscitation or the need for vasopressor support (cardiocirculatory insufficiency)
3) Renal: serum creatinine level >177 umol/L after rehydration or the need for hemofiltration or hemodialysis (renal failure) (in case patients already suffered from renal insufficiency before this episode of AP [creatinine >177 umol/L] this does not count as renal failure)

Pancreaticocutaneous fistula
Output through a percutaneous drain or drainage canal after removal of drains from a surgical wound, or any measurable volume of fluid with an amylase content >3 times the serum amylase level.

Persistent organ failure
Failure of one or more organ systems for at least 48 hours.

Proven infected necrosis
A positive culture or gram stain obtained by fine-needle aspiration from the necrotic collection or gas configurations in the necrotic collection on imaging.

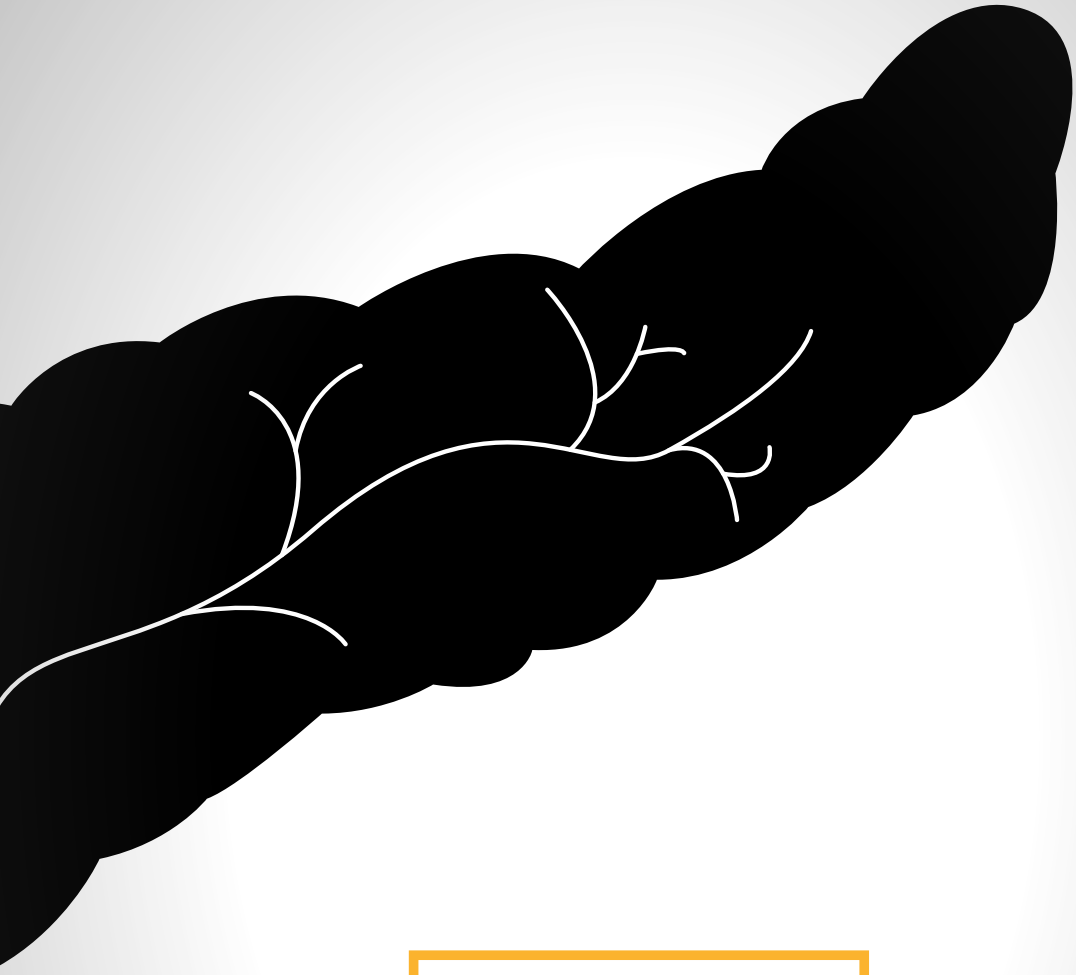
Perforation of visceral organ
Perforation requiring surgical, radiologic, or endoscopic intervention.

Sequential Organ Failure Assessment (SOFA) score
Scale that ranges from 0 to 24, with higher scores indicating more severe organ dysfunction [27].

Suspected infected necrosis
Either persistent (multiple) organ failure in patients admitted to the Intensive Care Unit. Or 2 of the 3 inflammatory parameters not decreased (temperature (>38.5˚C), C-Reactive Protein or leukocyte count) during 3 consecutive days in patients on regular wards (with no other infection focus). These clinical criteria alone are considered sufficiently reliable only after the initial 14 days of acute pancreatitis.

Wound infection
Defined as a superficial incisional surgical site infection (SSI) and must meet the following criterion: infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and the patient has at least 1 of the following:

1) Purulent drainage from the superficial/deep incision but not from the organ/space component of the surgical site
2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
3) At least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.
4) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
5) Diagnosis of superficial/deep incisional SSI by the surgeon or attending physician



7

CHAPTER 7

Validation of the Comprehensive Complication Index in a multicenter randomized trial of infected necrotizing pancreatitis

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ABSTRACT

Introduction: The Comprehensive Complication Index (CCI) is a composite score between 0-100 combining all postoperative complications for individual patients. CCI has shown to be more sensitive than traditional endpoints which may reduce the required sample size in randomized trials of elective surgery. The value of the CCI in a highly complicated disease as infected necrotizing pancreatitis has, however, not been assessed.

Methods: The CCI was calculated for all 88 patients included in the PANTER trial, comparing a minimally-invasive step-up approach with primary open necrosectomy in the treatment of infected necrotizing pancreatitis. The CCI included all major and minor adverse events and subsequent therapeutic actions. The differences in the original composite endpoint (major complications and death) between study groups were compared with the difference in CCI.

Results: The mean CCI was 63.8 (SD 30.5) in the minimally invasive step-up approach, and 72.6 (SD 26.7) in the primary open necrosectomy group. Mean difference of 8.8 points was statistically not significant (p=0.137), where the original primary composited endpoint showed statistical significant differences (69% vs 40%, p=0.006). There were 19/88 patients (7/43 (16%) and 12/45 (26%)) with a CCI above 100, if the formula would not have a cut-off point.

Discussion: High mean scores in CCI reflect the severity and extent of complications in infected necrotizing pancreatitis. In diseases with many complications the CCI may not be more discriminating than traditional (composite) endpoints due to the high mean scores in this logarithmic scale, leading to diminishing yield in scores, when new complications occur.

INTRODUCTION

Necrotizing pancreatitis is a very heterogeneous disease associated with a wide range of complications, including (multiple) organ failure in case of infected necrosis, and high mortality up to 25%(1–3). Several new treatment options have become available in recent years, improving outcome in these patients(4–6). A natural consequence of this improved outcomes is that new randomized trials will struggle to demonstrate incremental benefit as margins become smaller. Therefore, many studies use composite endpoints to increase the studies sensitivity(6–8). In composite endpoints, however, invididual components are weighed equally, for instance, a patient requiring pancreatic enzyme suppletion for exocrine insufficiency has the same score as a patient with multiple-organ failure and months of intensive care admission(9). This may lead to unnoticed differences between techniques or strategies in clinical research. These two problems may be addressed by the Comprehensive Complication Index (CCI).

The CCI was developed as a continuous scale to measure surgical morbidity, combining all postoperative complications, weighed according to their severity. This scale was developed to be more sensitive than existing morbidity endpoints and may serve as a primary endpoint in surgical trials or other clinical research, specifically in the interventional fields of medicine(10–13). The CCI is based on the Clavien-Dindo (CD) classification of surgical complications. The CD classification is an ordinal scale, that does not allow for longitudinal analysis, and only for limited comparisons between groups by comparing incidences complications per CD grade.(14,15) The CCI uses the CD classification to composite all complications into a single continuous variable, which can then be interpreted as a measurement of complete postoperative morbidity. This continuous composited nature of the CCI allows for longitudinal analysis and more extensive comparisons between groups in RCT's.(13)

The CCI has been applied in several medical domains, but not in acute pancreatitis. (10–13,16,17) The CCI may be valuable in acute pancreatitis due to high number and wide variance in severity of complications. Contrary, it might cause problems as the CCI has a maximum score of 100. Diseases potentially leading to such high CCI scores, have not been assessed before. The aim of this study is to assess the value of the CCI after interventions for infected necrotizing pancreatitis. We reassesed the patients who were included in the previously published randomized PANTER trial comparing a minimally invasive step-up approach with primary open necrosectomy in necrotizing pancreatitis(5).

METHODS

Data collection and scoring of complications

The original medical records of all 88 patient from the the previously published PANTER trial(5) were assessed for adverse events and the subsequent therapeutic action(s) during the same follow-up period as the original trial analyses. Complications were independently scored by two authors (SMvD and PDN). Adverse events were defined as "any deviation from the normal postoperative course", as per the CD classification.(18) The 2004 iteration of the CD classification was used to allocate the appropriate CD grade for each individual adverse event.(14) In case of disagreement on the graded CD score, the 'Extended Clavien-Dindo index of complications' was consulted.(19) Furthermore if there was still disagreement on the grading, the complication was discussed in a plenary research meeting and decision made by consensus.

The following additional criteria for scoring of an adverse events were used:

1) The adverse event had to be of new-onset in the timeframe after the first intervention.
2) A therapeutic action had to have been taken to correct the adverse event. E.g. a conservatively treated complication was not scored.
3) If multiple treatments were simultaneously applied for the same complication, the allocated CD grade was the highest possible grade of all applied treatments. For example, a pancreatic fistula that was simultaneously treated with somatostatine-analogue (CD grade 2) and with an endoscopic retrograde cholangiopancreatography (CD grade 3a) was graded a CD grade 3a complication. However, if a subsequent invasive treatment was required, this was considered as failure of treatment, and scored as a new complication.

Aside from the index interventions (percutaneous or endoscopic transluminal drainage or open necrosectomy), all subsequent procedures in both study groups were considered adverse events. To make a fair comparison of complications between groups, the "step-up" procedure (Video Assisted Retroperitoneal Debridement following upfront percutaneous drainage) was not considered as a complication, but as part of the initial treatment. (i.e. this would otherwise allways have caused an additional CD3b complication for the patients in the step-up approach group). All subsequent interventions after the "step-up" (e.g. additional drainages or reoperations) were considered complications, indicated because of inadequate or failure of treatment. An elective cholecystectomy wihin the follow-up period was not considered as a complication, but as regular treatment, however, complications as a result of the cholecystectomy were scored.

The CCI was calculated according to the established formula(20).

All patients who died during the follow-up period were scored as a CCI of 100, in line with the original external validation study of the CCI(13). In patients with a CCI score higher than 100, scores were also capped at 100 points.

Comparison of the CCI with the original primary endpoint

The CCI was compared with the primary outcome of the original study by comparing p-values, to assess whether the CCI was indeed associated with increased sensitivity to treatment effects.(13) Therefore in this study, the mean CCI was calculated in both treatment groups and subsequently the p-values of of the comparison of the CCI between study groups. This p-values resulting from the CCI were compared with the p-value of the original composited endpoint.

Transforming the CCI

Similar to the development of the CCI, in this study a number of transformations of the CCI formula were assessed for their potential to transform non-normally distributed data to a normally distributed data.(20) This would then potentionally allow for application of a more sensitive statistical test. For the calculations, the "Raw CCI" was calculated, as stated in the development of the study:
(CD1*300)+(CD2*1750)+(CD3a*2750)+(CD3b*4550)+(CD4a*7200)+(CD4b*8550).
This is the untransformed sum of complications, multiplied by their impact. Due to the relatively high morbidity rates in the studied patient files, the effect on the distribution of data by setting a various alternative maximum CCI scores for patients who died during the follow-up period was also investigated, e.g. in the original CCI a maximum of 100 is used, we investigated several different other maximums.

Sample size calculation

A sample size calculation was performed to evaluate the sensitivity of the CCI as a primary endpoint compared with the original composite endpoint of the PANTER trial(21). We compared the original sample size of the PANTER trial to a new sample size calculation using the CCI as the outcome measurement, assuming a difference of 10 points for the CCI, in line with the original CCI external validation study.(13) The applied standard deviation was derived from the distribution of the CCI in this study. The sample size calculations were performed assuming two-sided α=0.05 and with 80% power.

Statistical analysis

Statistical analyses were performed using the statistical package SPSS version 22.0 (SPSS Inc, Chicago, IL, USA). Dichotomous variables were compared using Pearson's

χ2-test, continuous variables were compared using the Mann–Whitney-U test. A P-value < 0.05 was considered statistically significant.

RESULTS

All 88 patients of the original study were included in this analysis. Mean CCI was 68.3 (SD 28.8), with a range of 0-100. Overall, 12 surviving patients had a score above 100, and therefore these scores were capped at 100. All 15 patients who died were given a score of 100, without taking their complications in consideration. Distribution of CCI scores is shown in figure 1.

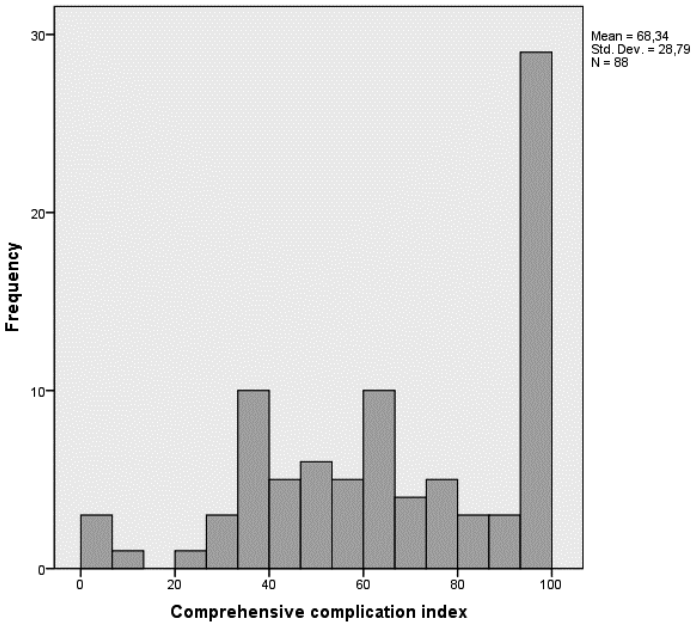


Figure 1 - distribution of CCI-scores

Comparing the CCI with original composite endpoint

In the PANTER trial, the primary endpoint was statistically different between the step-up approach group and open necrosectomy group (40% vs 69%, p=0.006). With the CCI, however, this difference was not statistically significant. In the step-up approach group, the mean CCI was 63.8 (SD 30.5), and in the primary open necrosectomy group, the mean CCI was 72.6 (SD 26.7), p-value = 0.137 (Table 1).

Sample size

The required sample size was recalculated with the numbers presented in table 1. The assumption of a 10 points reduction in CCI was made, with a standard deviation of 28.8. Required sample size would be 132 patients per study group. The calculated

Table 1. Outcomes of the original compoisite endpoint and the CCI

	Minimally Invasive Step-up Approach (n=43)	Primary Open Necrosectomy (n=45)	P-Value
CCI, mean(sd)	63.8 (30.5)	72.6 (26.7)	0.137
Original composite endpoint PANTER: Major complication(s) and/or death – n(%)	17 (40%)	31 (69%)	0.006

sample size with the CCI required a relatively larger sample size when compared to the calculated sample size of the original composited endpoint (table 2).
In line with the external validation study, a sample size of the original composited endpoint was recalculated using a relative risk reduction of 40%. This resulted in a smaller calculated sample size (122 patients per study group), as compared with the sample size that was calculated from using the CCI as the outcome measurement.

Table 2. – Sample size calculations

Endpoint	Assumptions	Required Sample Size
CCI	10 points reduction on CCI, SD = 28.8	132 patients/group
Original composite endpoint POINTER: Major complication(s) and/or death	Reduction from 45 to 16 percent (64% relative risk reduction)	44 patients/group
	40% relative risk reduction	122 patients/group

Transforming the CCI

Several transformations were performed to optimize the CCI for this group of patients with many severe complications. This did not result in functional scores that were better able to differentiate between treatment effects. The current CCI sorted out the largest treatment effect. The different transformations are presented in the Appendix.

DISCUSSION

This post-hoc analysis of a multicenter randomized controlled trial showed very high mean CCI scores in patients with infected necrotizing pancreatitis. The actual outcome of this score which is a summation of all complications and subsequent (re)interventions is very valuable to show the massive impact of this disease on patients. The CCI did not show a siginificant difference between primary open necrosectomy and minimally invasive step-up approach, whereas the original study endpoint did. In this study of patient with infected necrotizing pancreatitis, the CCI did not prove to be more discriminating than the original composite endpoint.

The high mean scores seem an adequate representation of the high morbidity in patients suffering from infected necrotizing pancreatitis, yet it also highlights a limitation of the CCI in regards to its differentiating power in this specific patient category. Because the CCI is a non-linear score, there are diminishing yields in scores in the CCI, when major complications are added to the CCI scores of patients already suffering from high morbidity: For example, a hypothetical patient with a CCI score of 80, will only have a 10 point increase in case of new-onset organ failure (CD grade 4a, representing 7200 points on the "RAW CCI") occurs (Figure 2a), whereas a patient having no adverse events yet (e.i. a CCI of 0) developing new-onset organ failure, will have a 42 point increase of CCI (Figure 2b).

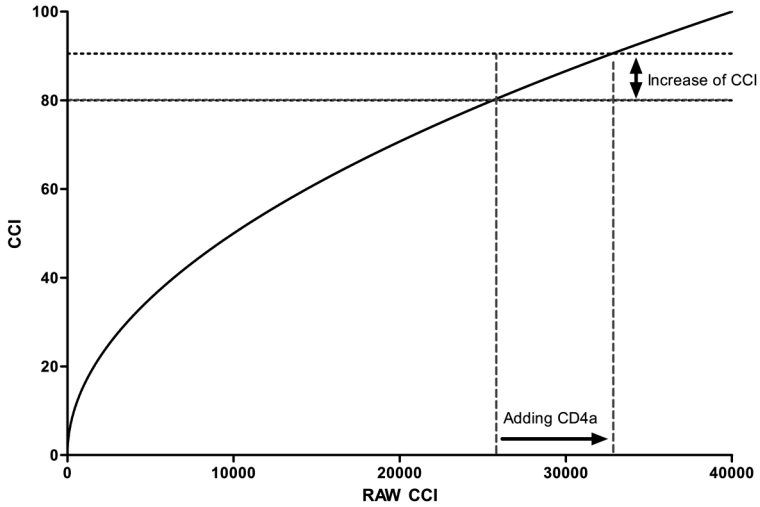


Figure 2a – Impact of adding a Clavien Dindo 4a complication to a CCI of 80

So, the CCI will increase less in case of new complications in patients with already high CCI scores compared to patients with few complications. The original validation studies state that a 10-point difference on the CCI reflects 1-grade on the CD-classification(22). However, given the high mean scores in this population of infected necrotizing pancreatitis, due to the logritmic scale, a 10 point increase may represent more morbidity than a 10 point increase in patients with fewer complications. Differences should therefore be interpreted with care.

The CCI is a novel tool, providing researchers a single continous endpoint for scoring all postoperative morbidity. This is the first study in which the CCI was assessed to measure postprocedural morbidity in infected necrotizing pancreatitis. Infected necrotizing pancreatitis is known for its high rates of morbidity. The CCI scores in

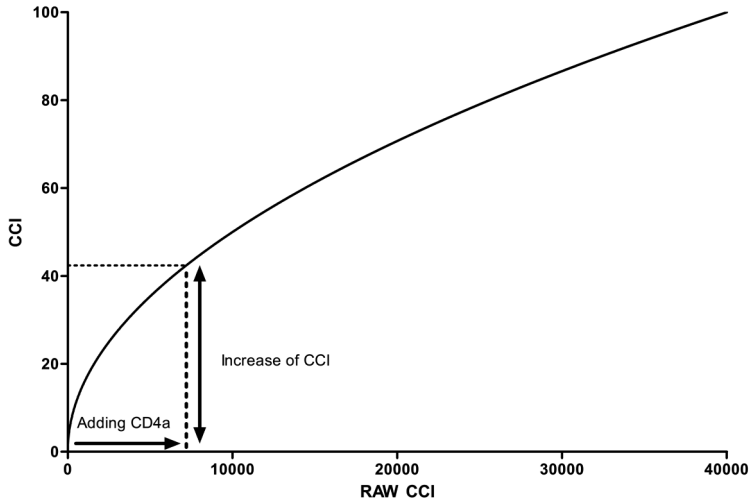


Figure 2b - Impact of adding a Clavien Dindo 4a complication to a CCI of 0,

the present study are much higher than in previous studies (mean scores 0-40.3) (22) For example, in patients undergoing an elective esophagectomy the incidence of anastomotic stricture was investigated comparing an end-to-end anastomosis with an end-to-side anastomosis.(10) The median CCI scores in that validation study were respectively 10.5 and 22.6 at discharge and 26.2 and 26.2 after 1 year. (13) In comparison, in the present study, mean CCI scores in the minimally-invasive and primary necrosectomy groups were nearly three times higher, respectively 63.8 and 72.6 at 6 months after discharge.
Another illustration of the high rate of morbidity in these patients is the 'maximum CCI': When the CCI was developed, using two detailed cohorts of 227 and 1255 patients, only a single patient in both cohorts had a CCI > 100.(20) During development, it was therefore decided that any patient experiencing death, the worst possible adverse event, would arbitrarily receive score of 100 points on the CCI scale.(20) In contrast, of the 88 patients investigated in this study, 12 of the 73 surviving patients (16%) would have a CCI score > 100 if it had not been maximized.

The CCI is based on the Clavien-Dindo classification, grading complications according to the invasiveness of the therapeutic action taken to the adverse event. However, it may happen that a relevant endpoint occurs, for example incisional hernia, but no intervention is undertaken, also not within the follow-up period. These kind of complications are therefore not taken into account with the CCI.
Because of the grading according to invasiveness of the CD-classification, this may also cause some discrepancies in CCI related to the complication. Two examples: 1) a major complication such as a colonic perforation will lead to a single CD3b

complication, when it is surgically treated with an ileostomy; 2) a repeatedly luxating nasojejunal feeding tube, treated with repeat endoscopies will score several 3a complications, and subsequently lead to a higher CCI than the patient with the colon perforation. This brings to question if the CCI truly represents the difference in (the severity of) complications between these two patients.

Another limitation of the CCI, especially during a long hospital stay such as in necrotizing pancreatitis, is that duration of the complication is not considered. A patient with three short episodes of organ failure will have a higher CCI than someone having a single episode of six months duration of organ failure. The same is the case for duration of percutaneous drainage: patients can have a percutaneous drain for several months, where patients that had additional drainage may have a shorter drainage-period, but the additional drainages will yield a higher CCI. On the other hand, each separate procedure is painful, cost time and money, and a burden to patients. Therefore the fact that all the procedures are reflected in the CCI are an important quality of this composited score.

The results of this study should be seen in light of several shortcomings. First, although major complications were scored prospectively in the original trial, all other complications were scored retrospectively by assement of the original patient files. The retrospective scoring may have caused underreporting, resulting in lower CCI scores than they would have been when prospectively scored. This is however unlikely to have altered our findings. Second, this study included a relatively small number of patients. Future research should assess the CCI in larger populations to further investigate the discriminating effect and what can be considered as clinically relevant changes in patients with such high CCI scores. Third, in patient with pancreatitis it is nearly impossible to make a distinction if a complication is a result of the intervention, or of the disease itself. This will most likely not create differences in scores between groups, as complications are scored equally in each study arm, however, this consequently leads to these high CCI scores. How relevant is a mild hypopotassaemia in acute pancreatitis? Is there a place for pre-defined 'irrelevant' complications in the CCI? Fourth, complications are scored by the invasiveness of their therapeutic action. This may lead to between-hospital differences, as complication are not treated equally. For example, the placement a nasojejunal feeding tube can be performed radiologically (CD2), endoscopically (CD3a) or by electromagnetic guidance (CD2) This consequently leads to different CCI scores for the same complication, depending on the hospital's expertise.

The CCI is a valuable endpoint, as it reflects the whole spectrum of complications in a post-procedureal period. However, in severe diseases such as infected necrotizing

pancreatitis, in which mean CCI scores are high, the discriminating quality of the CCI decreases, as the yield of score per complication diminishes. Individual complications should therefore allways be considered when the CCI is used as and outcome in severly ill patients.

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CHAPTER 7

APPENDIX

APPENDIX

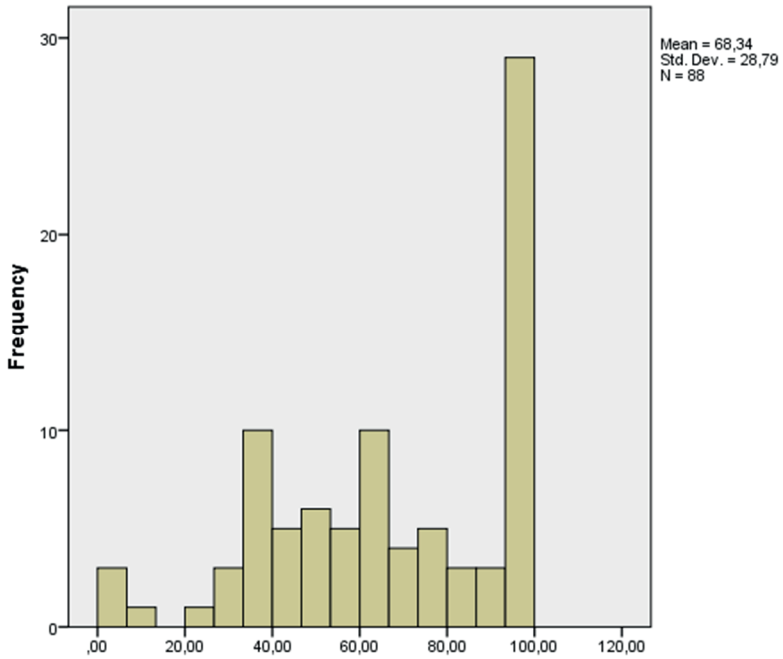
With the CCI not being able to differentiate statistically significant between treatment effects, a number of options for transformation of the CCI were assessed. The transformations of the CCI formula as they were done in the development of the CCI (Slankamenac et al. Ann Surg 2013, Supplemental Digital Content 5a, available at http://links.lww.com/SLA/A405) were repeated in this study and assessed for their effect on the distribution of data.(20) For this, all summarized scores of complications (the "Raw CCI) were used.

SCENARIO 1 – ADJUSTING THE MAXIMUM SCORE

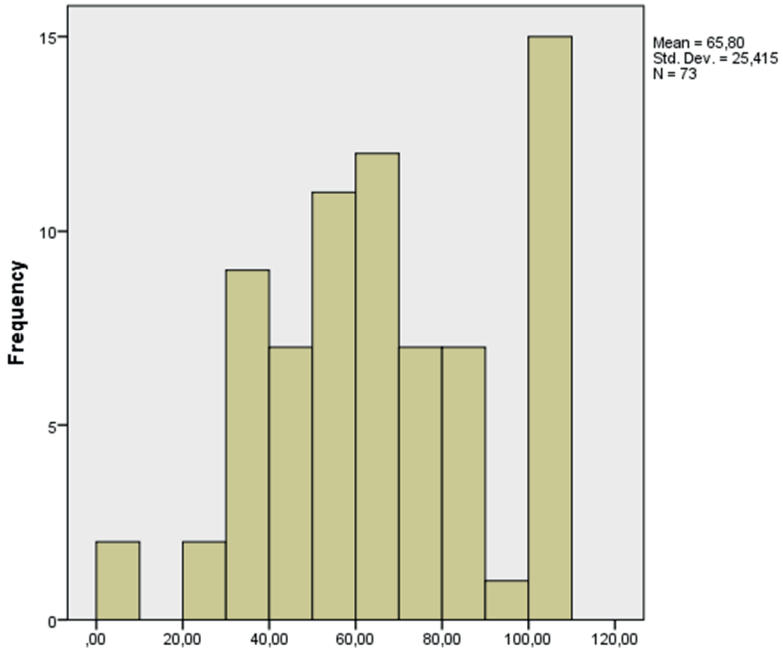
Effect of mortality

Patients that died during the follow-up period of the trial received a set CCI score of 100 points, conform the CCI development study. In the CCI development study this set score of 100 points was chosen because in the original CCI development cohort only 1 patient had a CCI higher than 100. Due to the relatively high mortality rate in our cohort of patients with infected necrotizing pancreatitis, investigated in this study, this skewed the distribution of the CCI to a non-normal distribution, especially in the laparotomy group (*supplementary figures 1a, 2a and 3a*). Due to the high rate of mortality, presentations of distribution of the cohort without the deceased are presented (*supplementary figures 1b, 2b and 3b*)

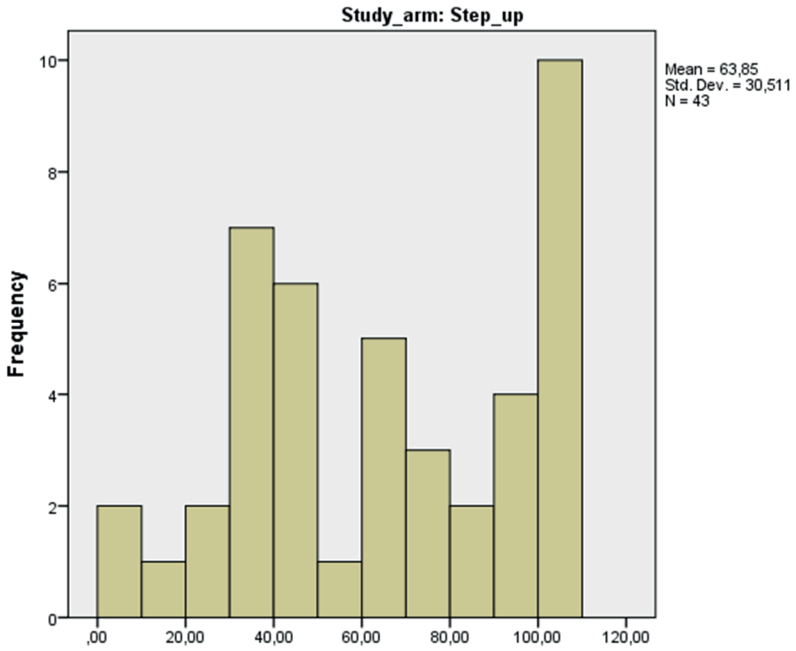
As can be seen in the figures, when leaving out the deceased patients, there still is a overrepresentation patients scoring a CCI of 100, due to the maximization of the score at 100 and the high rate of complications. As an alternative, we assessed the use of a different maximum in the CCI.



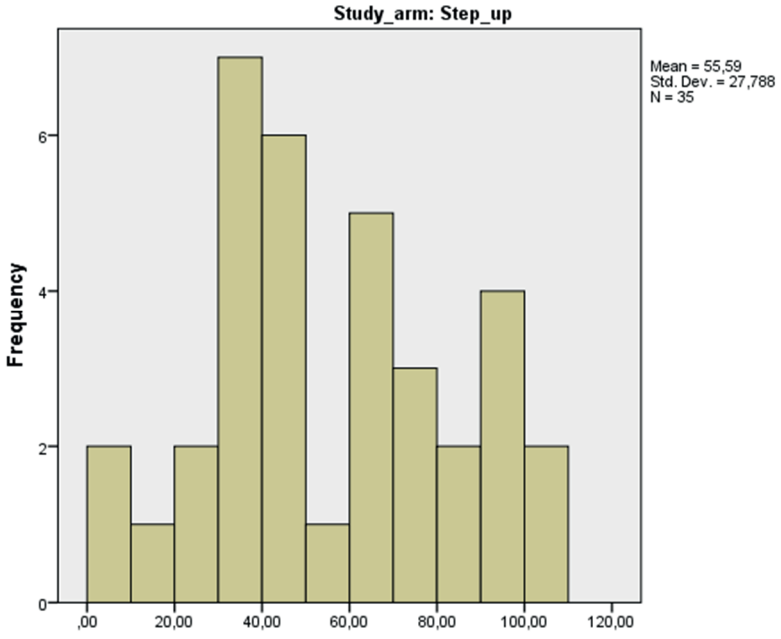
Supplementary figure 1a, distribution CCI – whole cohort



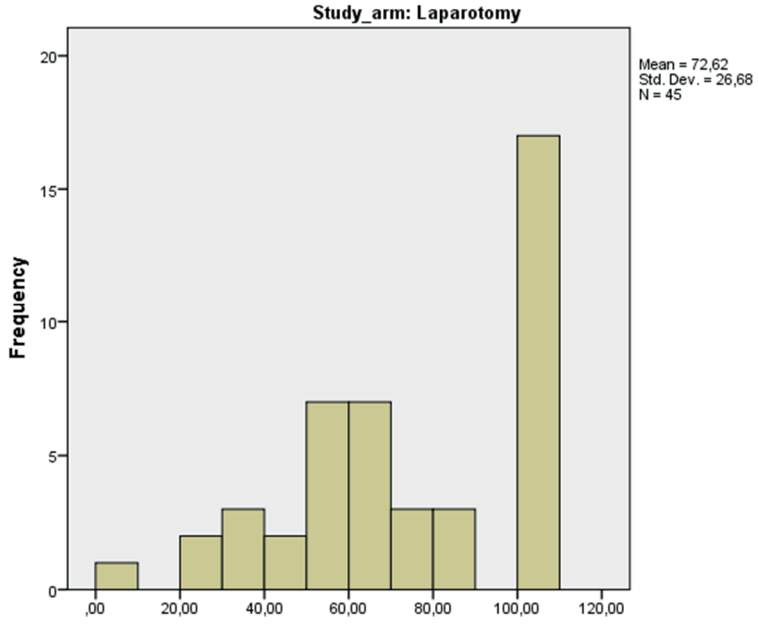
Supplementary figure 1b, distribution CCI – whole cohort, without deceased



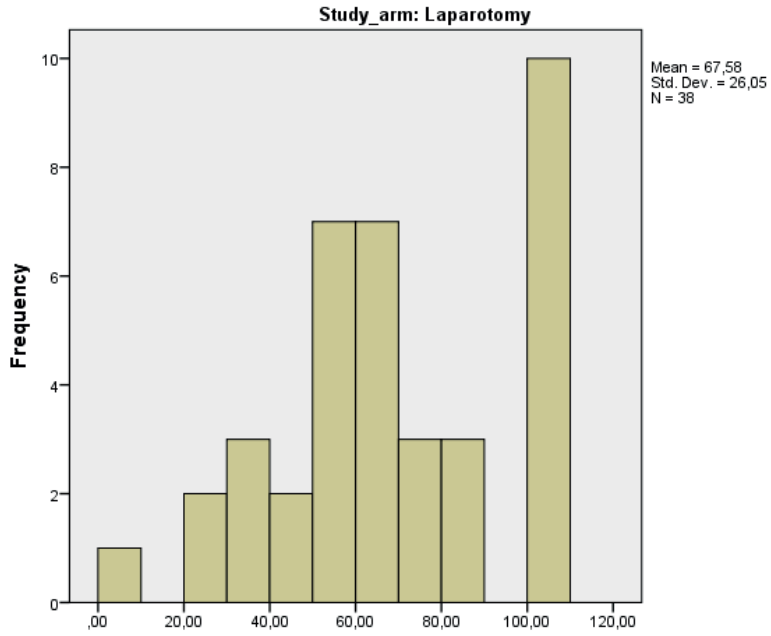
Supplementary figure 2a – distribution CCI - in step-up approach



Supplementary figure 2b – distribution CCI - in step-up approach, excluding deceased patients



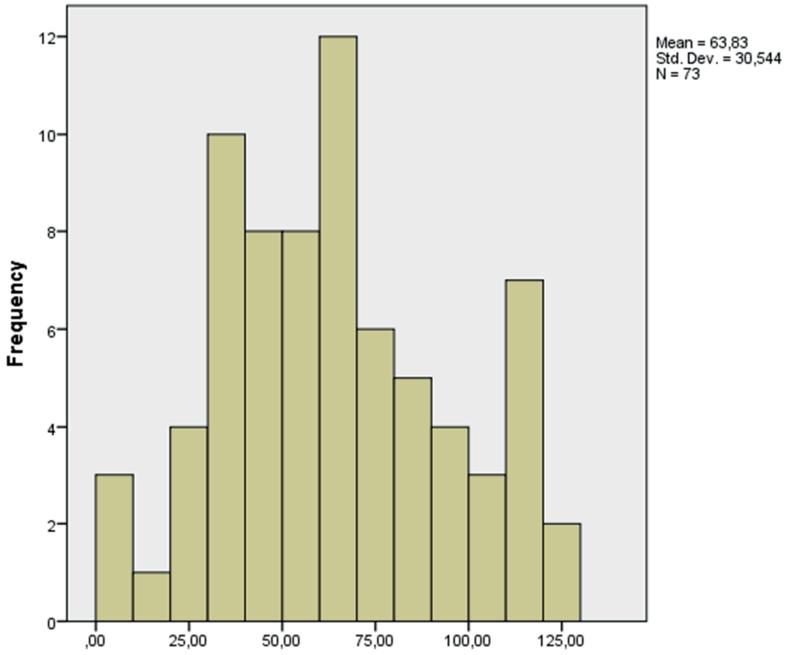
Supplementary figure 3a – Distribution CCI - Laparotomy group



Supplementary figure 3b – Distribution CCI - Laparotomy group, without deceased

Different maximum of CCI

Parallel to the original development, we investigated what our maximum CCI would be in patients that had survived: the maximum score reached in our cohort was 126.6, and a normal distribution can be seen (*supplementary figure 4*).



Supplementary figure 4 – Distritubion of CCI in survivors, without a maximum

In the next step: With the maximum of 126.6, we arbitrarily set our new maximum to 125, and recalculated the CCI with this maximum. Alternatively, different maximum values were assessed, in order to try to give more weight to occurrence of death, compared to complications (*supplementary table 1*).

Supplementary table 1. Outcomes of CCI with different maximums

	Total (n=88)	**Minimally-invasive step-up approach (n=43)**	**Primary open necrosectomy (n=45)**	**P-Value***
Original CCI, mean (SD)	68.3 (28.8)	63.8 (30.5)	72.6 (26.7)	0.137
CCI with 125 as maximum, mean (SD)	74.2 (36.1)	69.1 (37.7)	79.1 (34.3)	0.226
CCI with 150 as maximum, mean (SD)	78.5 (42.8)	73.7 (45.2)	83.1 (40.3)	0.240
CCI with 200 as maximum, mean (SD)	87.0 (58.5)	83.0 (62.3)	90.9 (55.0)	0.240

* mann whitney

The newly set maximums did not increase in-between group differences, but did increase standard deviations. Consequently, the p-values for differences in CCI with a maximum of 125 and above did not improve discriminating effect.

SCENARIO 2 – TRANSFORMING THE FORMULA

The original formula of the CCI is:

$$CCI = \frac{\sqrt{(CD1 * 300) + (CD2 * 1750) + (CD3a * 2750) + (CD3b * 4550) + (CD4a * 7200) + (CD4b * 8550)}}{2}$$

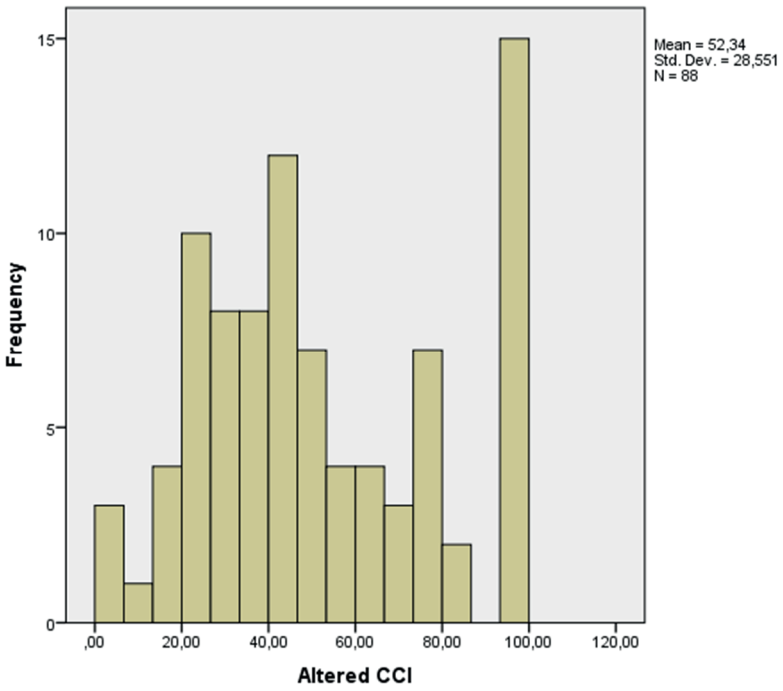
Or

$$CCI = \frac{\sqrt{RAW\ CCI}}{2}$$

As can be seen in *supplementary figure 4*, the distribution of the CCI of the survivors in our cohort reaches over 100. In order to create a score between 0 and 100 (as was done in the original CCI development), the CCI was altered to:

$$Altered\ CCI = \frac{\sqrt{RAW\ CCI}}{3}$$

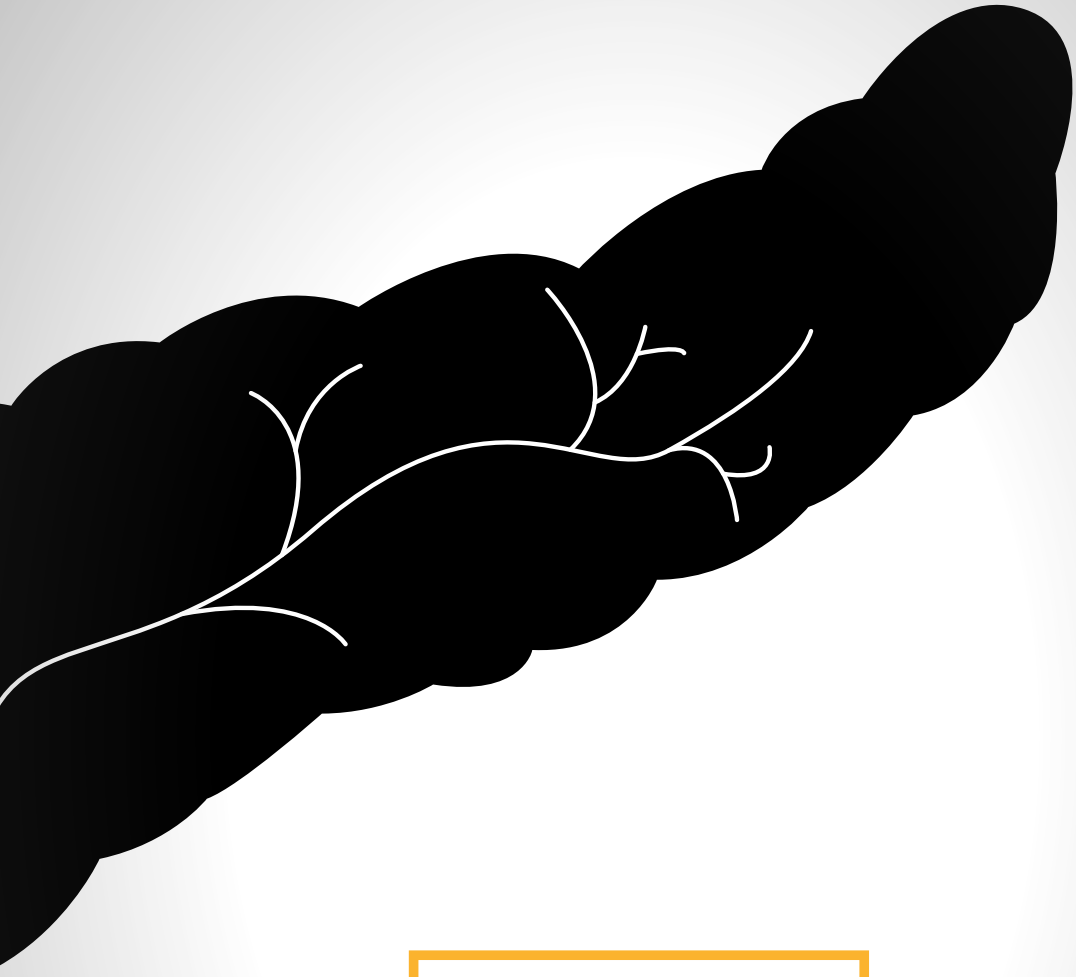
Using this formula, setting a score of 100 for death, this would lead to the following distribution (S*upplementary figure 5*). Results of the in between differences of this altered CCI is presented in *supplementary table 2*. With a p-value of 0.240, this alteration does not show a better discrimination between groups.



Supplementary figure 5 - distribution altered CCI

Supplementary table 2 – outcomes of altered CCI

	Total (n=88)	Minimally-invasive step-up approach (n=43)	Primary open necrosectomy (n=45)	P-Value*
Original CCI, mean (SD)	68.3 (28.8)	63.8 (30.5)	72.6 (26.7)	0.137
Altered CCI, mean (SD)	52.3 (28.6)	49.2 (30.2)	55.4 (26.9)	0.240



8

CHAPTER 8

Patient input into future clinical research in acute and chronic pancreatitis

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PATIENT INPUT INTO FUTURE CLINICAL RESEARCH IN ACUTE AND CHRONIC PANCREATITIS

Topics for future clinical research are typically chosen by principal investigators, research groups, or pharmaceutical companies, driven by their personal, clinical, or economic motives. Patients are rarely involved in these decisions.[1] The importance of patients' opinions in health care research has grown significantly,[2] and patients are increasingly involved in most stages of clinical research, from study design to publication of papers.[2–5] Incorporating patients' opinions could be beneficial in several ways. First, it could increase the legitimacy of clinical research. Because research is often funded by government grants or public organisations, the decision on how to spend these funds should involve all stakeholders, including patients. Second, the quality and relevance of clinical studies could be improved by awareness of patients' experiences of their illness.[6] Patients' opinions on the issues that affect them most or that should be addressed through research might completely differ from the research topics on which clinicians usually focus.[7] Therefore, government organisations and patient advocacy groups are increasingly emphasising the importance of active patient participation in the clinical research process, and mandatory patient participation in funding proposals is becoming more common.

The Dutch Patient Organisation for Pancreatic Diseases (Alvleesklierevereniging) has a longstanding collaboration with the Dutch Pancreatitis Study Group. As a joint effort, we surveyed 252 patients with acute or chronic pancreatitis regarding their symptoms, their experience of participating in research, and their advice about topics for future clinical research, including their opinion on the most relevant reported outcomes and symptoms. More than three-quarters of the patients surveyed reported that pain was a major clinical symptom, and fatigue was reported by more than half of the participants (table). Diet during hospital admission was reported as a major problem by a greater proportion of patients with acute pancreatitis than of those with chronic pancreatitis (table). Nutrition was the most frequently suggested topic for future research (>50% of patients), and disease-related symptoms, such as pain and fatigue, was the second most important topic (table). More than two-thirds of patients said that previous participation in clinical research had been a positive experience, with a similar proportion willing to participate in future clinical trials (appendix). About half of the patients said they were insufficiently informed about ongoing clinical research and the possibility to participate therein. Improving dissemination of information to patients and physicians by patient organisations and study groups could increase awareness of possibilities for clinical research and consequently increase participation.[8] The predominant clinical symptoms and research topics suggested by patients contrast with those focused on by most

current clinical studies, which generally use mortality, morbidity, and survival as primary outcome measures. In both gastrointestinal and non-gastrointestinal diseases, patients' opinions on future research topics have been assessed, eliciting new priorities for researchers.[7,9,10] Patients can have valuable input in steering the direction of clinical research, and should be involved in making decisions about topics and funding for research projects in the future.

Table. Most important reported clinical symptoms and suggested research topics by 252 patients with acute and chronic pancreatitis

	Total N=252 (%)	Acute pancreatitis N= 86 (%)	Chronic pancreatitis N= 94(%)	Acute and Chronic pancreatitis N= 72 (%)	p-value*
Predominant clinical symptoms					
Pain	184 (76·0%)	63 (73·3%)	58 (67·4%)	63 (90·0%)	**0·003**
Fatigue	131 (54·1%)	41 (47·7%)	49 (56·9%)	41 (58·6%)	0·320
Abdominal complaints	101 (41·7%)	31 (36·0%)	41 (47·7%)	29 (41·4%)	0·302
Future uncertainty	88 (36·4%)	33 (38·4%)	26 (30·2%)	29 (41·4%)	0·313
Diet during admission	88 (36·4%)	37 (43·0%)	20 (23·3%)	31 (44·3%)	**0·007**
Pain uncertainty	79 (32·6%)	29 (33·7%)	21 (24·4%)	29 (41·4%)	0·076
Diet after admission	70 (28·9%)	23 (26·7%)	21 (24·4%)	26 (37·1%)	0·188
Diabetes	68 (28·1%)	22 (25·6%)	27 (31·4%)	19 (27·1%)	0·682
Disability	61 (25·2%)	13 (15·1%)	22 (25·6%)	26 (37·1%)	**0·007**
Use of pancreatic enzymes	44 (18·2%)	11 (12·8%)	18 (20·9%)	15 (21·4%)	0·271
Social isolation	33 (13·6%)	5 (5·8%)	14 (16·3%)	14 (20·0%)	**0·025**
Treatment itself	27 (11·2%)	11 (12·8%)	7 (8·1%)	7 (10·0%)	0·326
Insufficient aftercare	25 (10·3%)	11 (12·8%)	9 (10·5%)	5 (7·1%)	0·514
Waiting period until treatment	20 (8·3%)	6 (7·0%)	8 (9·3%)	6 (7·6%)	0·853
None	10 (4·1%)	2 (2·3%)	7 (8·1%)	1 (1·4%)	0·064
Other	35 (14·5%)	17 (19·8%)	7 (8·1%)	11 (15·7%)	0·090
Missing	*10 (3·9%)*	*0 (0%)*	*8 (8·5%)*	*2 (2·8%)*	
Health score in most severe illness (1-10)**	2·3(2-4)	2(1·5-3)	3·5 (2-5)	2(2-3)	**<0·001**
Health score currently (1-10)**	7(6-8)	7(6-8)	7(6-8)	6(5-7)	**0·002**

Future research					
Suggested topics for future research					
Nutrition	132 (53·7%)	49 (57·6%)	55 (59·8%)	28 (40·6%)	**0·035**
Disease related symptoms	122 (49·6%)	40 (47·1%)	48 (52·2%)	34 (49·3%)	0·792
Medication	106 (43·1%)	28 (32·9%)	47 (51·1%)	31 (44·9%)	**0·048**
Quality of life	99 (40·2%)	31 (36·5%)	35 (38·0%)	33 (47·8%)	0·311
Quality of care	75 (30·5%)	30 (35·3%)	26 (28·3%)	19 (27·5%)	0·490
Side effects of treatment	72 (29·3%)	18 (21·2%)	27 (29·3%)	27 (39·1%)	0·052
General health	71 (28·9%)	19 (22·4%)	32 (34·8%)	20 (29·0%)	0·190
Prevention	71 (28·9%)	34 (40·0%)	23 (25·0%)	14 (20·3%)	**0·016**
Results of treatment	65 (26·4%)	16 (18·8%)	26 (28·3%)	23 (33·3%)	0·112
Mental health	58 (23·6%)	19 (22·4%)	22 (23·9%)	17 (24·6%)	
Lifestyle	57 (23·2%)	25 (29·4%)	14 (15·2%)	18 (26·1%)	0·065
Health and labour	37 (15·0%)	7 (8·2%)	15 (16·3%)	15 (21·7%)	0·060
Patient satisfaction	20 (8·1%)	9 (10·6%)	4 (4·3%)	7 (10·1%)	0·244
Other	27 (11·0%)	10 (11·8%)	7 (7·6%)	10 (14·5%)	0·369
*Unknown****	*6 (2·4%)*	*1 (1·2%)*	*2 (2·1%)*	*3 (4·2%)*	
Sufficient information on clinical research					
Yes	92 (37·1%)	24 (27·9%)	37 (39·9%)	31 (44·9%)	0·176
No	130 (52·4%)	50 (58·1%)	49 (52·7%)	31 (44·9%)	
Do not know	26 (10·5%)	12 (14·0%)	7 (7·5%)	7 (10·1%)	
Participated in clinical research	68 (28·6%)	24 (28·2%)	21 (25·0%)	23 (33·3%)	0·523
Experienced participations in research					
Positive	45 (68·2%)	12 (52·2%)	16 (80·0%)	17 (73·9%)	**0·021**
Neutral	13 (19·7%)	9 (39·1%)	3 (15·0%)	1 (4·3%)	
Negative	8 (12·1%)	2 (8·7%)	1 (5·0%)	5 (21·7%)	
Willing to participate in future research					
Yes	165 (67·1%)	60 (70·6%	61 (66·3%)	44 (63·8%)	0·805
No	20 (8·1%)	7 (8·2%)	6 (6·5%)	7 (10·1%)	
Do not know	61 (24·8%)	18 (21·2%)	25 (27·2%)	18 (26·1%)	
Recommend others to participation in future research					
Yes	146 (58·9%)	50 (58·8%)	55 (59·1%)	41 (58·6%)	0·949
No	5 (2·0%)	2 (2·4%)	1 (1·1%)	2 (2·9%)	
Do not know	97 (39·1%)	33 (38·8%)	37 (39·8%)	27 (38·6%)	

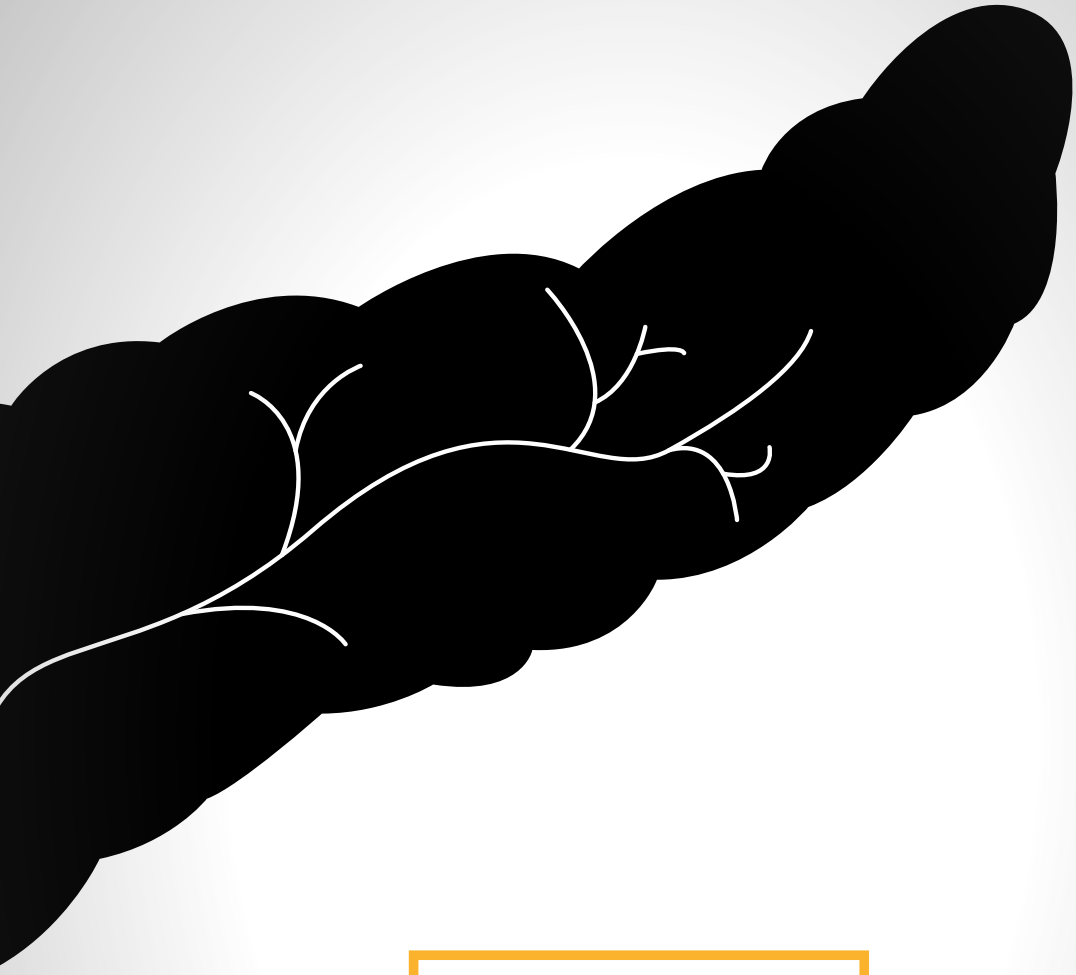
*p values are two-sided. For dichotomous variables χ^2 test was performed, for continuous variables Kruskal-Wallis test

** Values represent the median and interquartile ranges

*** Percentage. All other values represent valid percentages

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9

CHAPTER 9

General discussion and future perspectives

DISCUSSION

Necrotizing pancreatitis is a major disease burden in Western countries[1]. Since the incidence of acute pancreatitis is rising, the incidence of necrotizing pancreatitis is also expected to rise. Optimizing the treatment of this disease with its high risk of major complications is therefore of paramount importance.

Over the last decades the treatment of acute pancreatitis has changed considerably. As no curative therapy is available, early treatment of acute pancreatitis is restricted to supportive care[2]. In the late phase of (infected) necrotizing pancreatitis, the treatment has shifted from direct open necrosectomy to a step-wise, tailor-made approach of drainage and debridement[3,4]. Since the introduction of the step-up approach, upfront necrosectomy via laparotomy has practically been abandoned in the Netherlands. Currently, treatment of infected necrotizing pancreatitis starts with catheter drainage, and only if unsuccessful this is followed by (minimally invasive) necrosectomy. With the recent technical developments within endoscopy, this step-up approach can also be performed enscopically and transluminal. As has been shown in the TENSION trial, the endoscopic transluminal step-up approach has the same mortality rate as the surgical step-up approach, but reduces the rate of pancreatocutaneous fistula and shortens hospital stay[5]. As a results, there seems to be a shift towards endoscopic procedures for infected necrotizing pancreatitis. As not all infected necrotic collections are suitable for this endoscopic approach, there remains an important role for the surgical step-up approach.

As previous studies have shown, there is proportion of patients that can be treated with drainage procedures only, and do not require a necrosectomy[6,7]. In this thesis, we performed an analysis of 108 consecutive video-assisted retroperitoneal debridement (VARD) procedures. In this study we clearly saw an increased number of preoperative drainage procedures used over time, with a longer period of time between the primary drainage and the necrosectomy than before, indicating that the phase of drainages seems to be more pro-active, before stepping-up to necrosectomy. With the current data, we unfortunately cannot determine how many necrosectomies have been prevented. In a proportion of patients a necrosectomy remains nessecary[7]. This brings to question how many drainages are justified to prevent a single necrosectomy? What is the best timing of each step in the step-up approach? This is an important topic for future research.

Timing of the primary catheter drainage is also of clinical relevance. Current practice is based on the 2012 revised Atlanta Classification[8] which advises to postpone any intervention of the infected necrosis until at least 4 weeks after onset of disease. These 4 weeks of delay allows the collection to become walled-off and liquefy, facilitating easy drainage and debridement. During this period the effect of the antibiotics can be evaluated, as there is a small proportion of patients

in which antibiotic treatment alone suffices[7]. Previous studies, however, have shown that clinically relevant walled-off necrosis (largely or fully encapsulated) is already present in 43% of patients within the first 3 weeks after onset of disease[9]. Furthermore, drainage of the infected collection can be used as a first step to control the sepsis.
So, the question arises whether is it always necessary to postpone catheter drainage until an infected necrotic collection has become fully walled-off? Previous studies have shown that catheter drainage can safely and successfully be performed in the first weeks after onset of disease[10]. Patients may benefit from an earlier drainage, as it may control sepsis and reduce other complications. There seem no specific technical difficulties with an early catheter drainage, as drainage of peripancreatic fluid after, for example, pancreatoduodenectomy is also performed before the collections become walled-off[11,13]. A previous international expert survey showed wide variations in the timing of catheter drainage within the step-up treatment of infected necrosis. Of the expert pancreatologists, 55% postponed catheter drainage of the infected necrosis, whereas 45% immediately drained the infected necrotic collection, as soon as it was diagnosed[13]. In short, there is lack of scientific evidence and expert consensus on the timing of primary catheter drainage in infected necrotizing pancreatitis. The POINTER trial (ISRCTN33682933) was designed to compare an immediate catheter drainage with a postponed catheter drainage in infected necrotizing pancreatitis. Hopefully this trial will give answers for more guidance on the timing of primary catheter drainage, improving the outcome of these severely ill patients[14].

As a result of necrosis of the pancreatic parenchyma, the pancreatic duct may lose its integrity. As a result of this, duct disruption or a disconnected pancreatic duct, may lead to leaks of pancreatic fluid may, which may result in several complications such as (recurrent) peripancreatic fluid collections with secondary infection, pancreatic ascites or, in case of leakage of pancreatic fluids towards other organs, pancreatic fistulas[15,16]. The diagnostic process and treatment of this complication are not well established. We performed a systematic review on the diagnostic modalities used to detect disconnected pancreatic duct, and on the treatments for this condition.
For the diagnosis of disconnected or disrupted pancreatic duct after acute pancreatitis there is a wide variety of diagnostic modalities which are being used. The systematic review suggests that endoscopic ultrasound, endoscopic retrograde cholangiopancreaticography (ERCP), magnetic resonance cholangiopancreatography (MRCP) and secretin-enhanced MRCP are all accurate in diagnosing a disruption or disconnection of the pancreatic duct in patients with acute pancreatitis. ERCP is currently considered as the reference standard,

however because of the invasiveness with potential complications like infection of pancreatic collection, perforation or bleeding, this procedures is less attractive for clinical purposes. The MRCP of secretin-MRCP seems a good option for diagnosis of disrupted or disconnected pancreatic duct because it is non-invasive and has good visualization of the pancreatic duct. Unfortunately, the number of studies on diagnostic accuracy for diagnosing pancreatic duct disruptions are scarce, and studies only report small number of patients.

Our systematic review on the treatment of disrupted or disconnected pancreatic duct also shows a wide variation of treatments. Treatments vary from minimally-invasive percutaneous drainages or endoscopic drainages to surgical resections. Success rates of all reported treatment strategies vary between 80-92%[17]. However, the majority of studies are retrospective studies in very selective patient populations. Furthermore the outcome of conservative treatment is unknown. This could be because diagnosis of duct disruption or disconnection is also not standardized.
Large prospective studies are needed to define the diagnostic value of MCRP or MRCP with secretin in necrotizing pancreatitis. Once diagnosis is accurate, treatment can be investigated. What this treatment should be, or what best-practice treatment algorithm, should be investigated in future.

Infected necrotizing pancreatitis is a disease with severe morbidity and high mortality. Treatment of this infected necrosis has gradually shifted from invasive to minimally invasive techniques, reducing both mortality and morbidity. The studies in this thesis primarily focus on the treatment of complications of the severe acute pancreatitis. However, also on the prevention of pancreatitis and the prevention of the development of complications, a lot of progress can be made. Many questions have been answered, however many remain. The Dutch Pancreatitis Study group has played an important role in answering research questions by working in multicenter and multidisciplinary collaborations. As pancreatitis is a complex disease, requiring multidisciplinary treatment strategies, this collaboration is paramount. The Dutch Pancreatitis Study group will continue its research, and will hopefully find more evidence to improve the treatment of these severely ill patients.

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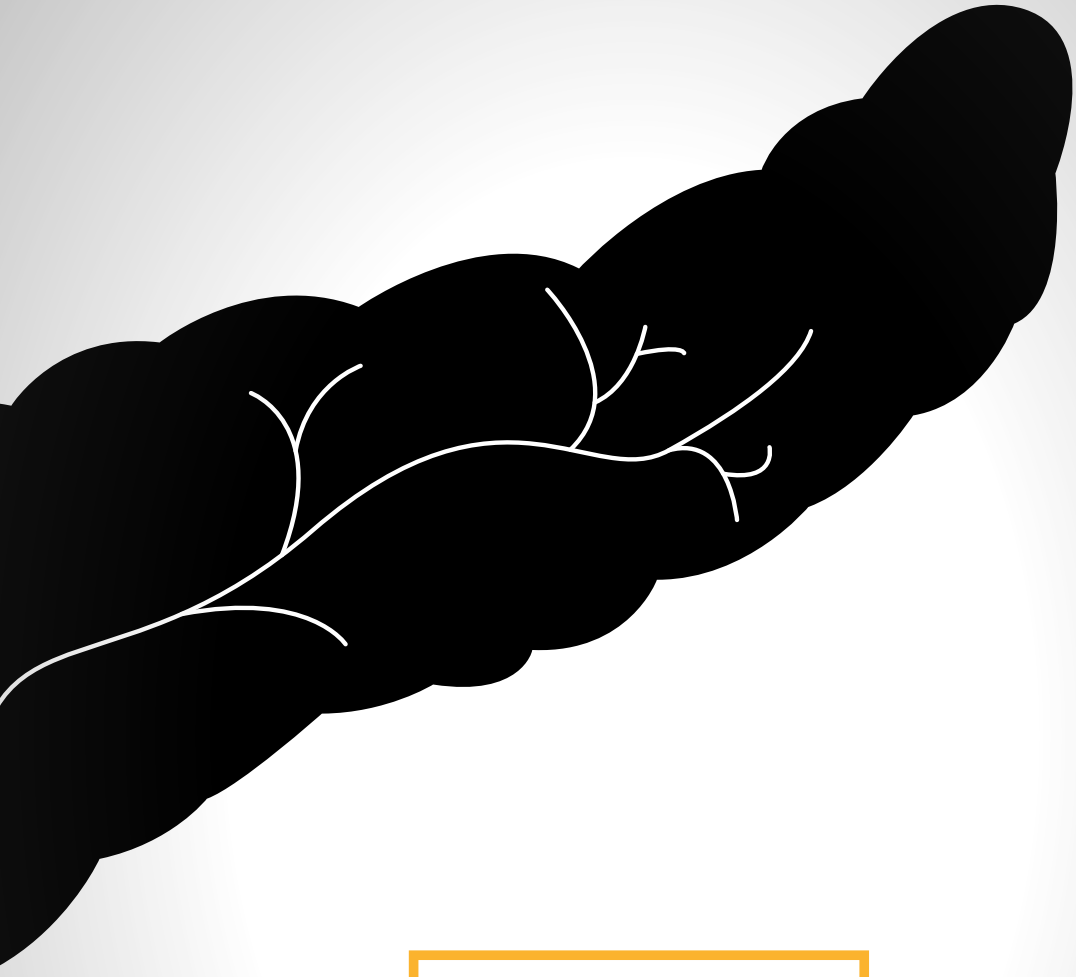
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10

CHAPTER 10

English Summary

ENGLISH SUMMARY

Acute pancreatitis is one of the most common gastrointestinal conditions requiring acute hospitalisation and has a rising incidence. In the most severe form of pancreatitis, patients will develop necrosis of the pancreatic and peripancreatic tissue. In a majority of patients where infection of the necrotic collections occurs, intervention is necessary. Also, as a result of necrosis of the pancreatic tissue, the pancreatic duct may lose its integrity, which may lead to leakage of pancreatic fluids, resulting in complications like recurrent fluid collections or pancreatic fistula. The aim of the studies in this thesis is to optimize the treatment in patients with complicated acute pancreatitis.

Over the last decade, treatment of acute pancreatitis has gradually developed towards a tailored, multidisciplinary effort, with distinctive roles for gastroenterologists, radiologists and surgeons. The review in **chapter 2** summarizes how to diagnose, classify and manage patients with acute pancreatitis, emphasizing the evidence obtained through randomized controlled trials.

Infected necrotizing pancreatitis is treated with the step-up approach, consisting of a primary catheter drainage, followed by a (minimally invasive) necrosectomy, in whom drainage procedures alone do not suffice. In the Netherland, video-assisted retroperitoneal debridement (VARD) is the preferred minimally invasive surgical treatment if a necrosectomy is required. **Chapter 3** presents a cohort of 108 patients that underwent a VARD for infected necrotizing pancreatitis. The in-hospital mortality of these patients was 15.7% (17 patients). When comparing the period before and after 2009, there was a significant increase of the number of pre-necrosectomy drainages procedures (from median 1 [IQR 1-2] to 3 [IQR 1-3], $p<0.001$) and VARD was increasingly postponed (from 45.9 to 65.3 days after onset of disease, $p<0.001$). The majority of patients (69%) required one VARD as final treatment. The VARD is an efficient procedure for a minimally invasive necrosectomy, when drainage procedures alone do not suffice. The optimal number of pre-operative drainages and timing of necrosectomy remain unclear.

Necrotizing pancreatitis may lead to loss of integrity of the pancreatic duct, resulting in leakage of pancreatic fluid. This so-called pancreatic duct disruption or disconnection is associated with a prolonged disease course and particular complications.
Since a standard treatment for this condition is currently lacking, **chapter 4** presents a systematic review of the literature to compare outcomes of various treatment strategies. Twenty-one observational cohort studies were included comprising a total of 583 relevant patients.

Endoscopic transpapillary drainage, endoscopic transluminal drainage, surgical drainage or resection, or combined procedures were the most frequently used treatment strategies. Pooled analysis showed success rates of 81% (95%-CI: 60-92%) for transpapillary and 92% (95%-CI: 77-98%) for transluminal drainage, 80% (95%-CI: 67-89%) for distal pancreatectomy and 84% (95%-CI: 73-91%) for cyst-jejunostomy. However, the success rates of conservative treatment are unknown.

Also the diagnosis of disrupted or disconnected pancreatic duct in acute necrotizing pancreatitis is not standardized. In **chapter 5** we provided an overview of the available literature of the accuracy of the different diagnostic modalities on this condition.
We included 8 studies, evaluating five different diagnostic modalities: endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP), with or without secretin. This review suggests that various diagnostic modalities are accurate in diagnosing a disrupted pancreatic duct in patients with acute pancreatitis (sensitivity EUS and ERCP: 100%, MRCP without secretin: 83%. A combined cohort of MCRP with and without secretin: 92%). Amylase-measurement in drain fluid should be standardized, as it is a non-invasive, cheap and accurate measurement to detect pancreatic fluid leakage. Given the invasive nature of other modalities, secretin-magnetic resonance cholangiopancreatography or magnetic resonance cholangiopancreatography would be recommended as first diagnostic modality. Further prospective studies on this subject, however, are needed.

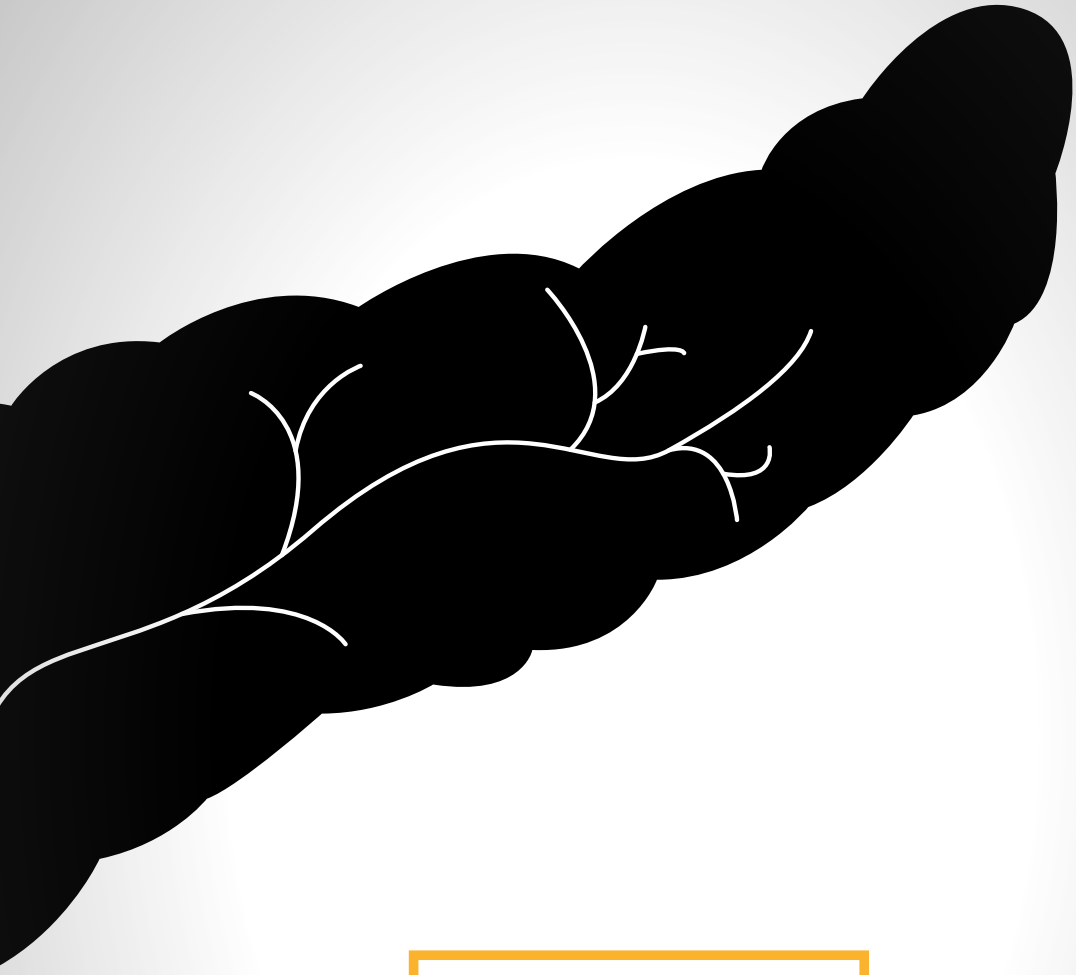
Chapter 6 presents the rationale and design of the randomized controlled multicenter POINTER trial. In the standard treatment of infected pancreatic necrosis, the step-up approach, the primary catheter drainage is preferably postponed until the stage of walled-off necrosis, a process which usually will take around 4 weeks. This delay stems from the time when open necrosectomy was the standard. It is unclear whether such delay is needed for catheter drainage or whether earlier intervention could actually be beneficial in the current step-up approach. The POINTER trial investigates if immediate catheter drainage in patients with infected necrotizing pancreatitis is superior to the current practice of postponed intervention.
In total, 104 adult patients with (suspected) infected necrotizing pancreatitis will be randomized between immediate (within 24 hours) catheter drainage and current standard care of antibiotic treatment and postponed catheter drainage. If a necrosectomy is required, this is preferably postponed until the stage of walled-off necrosis in both treatment arms. Primary outcome is the Comprehensive Complication Index **(chapter 7)**, which is a composite score between 0-100

combining all postoperative complications during follow-up for individual patients. Secondary outcomes include mortality, complications, number of (re-) interventions, hospital and Intensive Care Unit (ICU) lengths of stay, quality adjusted life years (QALYs) and (in)direct costs. Standard follow-up is at 3 and 6 months after randomization.

The abovementioned Comprehensive Complication Index (CCI) has shown to be more sensitive than traditional endpoints which may reduce the required sample size in randomized trials of elective surgery. In **Chapter 7** the value of the CCI in a highly complicated disease as infected necrotizing pancreatitis was assessed. The CCI was calculated for all 88 patients included in the PANTER trial, comparing a minimally-invasive step-up approach with primary open necrosectomy in the treatment of infected necrotizing pancreatitis. The differences in the original composite endpoint (major complications and death) between study groups were compared with the difference in CCI. The mean CCI was 63.8 (SD 30.5) in the minimally invasive step-up approach, and 72.6 (SD 26.7) in the primary open necrosectomy group. Mean difference of 8.8 points was statistically not significant (p=0.137), where the original primary composited endpoint showed statistical significant differences (69% vs 40%, p=0.006). There were 19/88 patients that would actually have a CCI score above 100, if the formula would not have a cut-off point. This high mean scores in CCI reflect the severity and extent of complications in infected necrotizing pancreatitis, and may therefore be useful for research in this severely ill patients. However, in diseases with many complications the CCI may not be more discriminating than traditional (composite) endpoints. Since the logarithmic scale of the CCI and due to the high mean scores in this logarithmic scale, new complications will lead to diminishing yield in scores.

Topics for clinical research are typically determined by clinicians, researchers or pharmaceutical companies, but seldom by patients. In **chapter 8** we aimed to assess patients' dominant clinical symptoms and their opinions regarding the most relevant clinical research topics in pancreatitis. A questionnaire was distributed to 925 members of the Dutch Patient Organization for Pancreatic Diseases. Two-hundred-fifty-two patients with acute or chronic pancreatitis responded. The most reported clinical symptoms were pain by 184 (76%) patients and fatigue by 131(54%) patients. Diet during hospital admission was more often seen as major problem by patients with acute pancreatitis than those with chronic pancreatitis; 43% vs. 23%, p=0.007. Inability to work was more often considered as a major problem by chronic pancreatitis patients; 15% vs. 27%, p=0.007. Sixty-eight(29%) patients participated in clinical research which was valued as a positive

experience by 68%(45/68). In total, 67% of all patients were willing to participate in future clinical research. Nutrition was most often suggested (54%) as a subject for future research. Patients can have valuable input in steering the direction of clinical research, and should be involved in making decisions about topics and funding for research projects in the future.



A

APPENDICES

NEDERLANDSE SAMENVATTING

Acute pancreatitis is een van de meest voorkomende gastro-intestinale aandoeningen waarvoor acute ziekenhuisopname noodzakelijk is, en heeft een stijgende incidentie. In de meest gecompliceerde vorm van pancreatitis, zullen patiënten necrose ontwikkelen van het pancreas- en peripancreatische weefsel. In een meerderheid van de patiënten waarin infectie van deze necrotische collecties is opgetreden, is interventie noodzakelijk. Als gevolg van de necrose van het pancreasweefsel kan ook de integriteit van de ductus pancreaticus verloren raken. Als gevolg daarvan kan lekkage van pancreassappen optreden, wat kan leiden tot terugkerende pancreatische vochtcollecties of pancreasfistels. Het doel van de studies in dit proefschrift is om de behandeling van patiënten met gecompliceerde pancreatitis te verbeteren.

Gedurende het afgelopen decennium heeft de behandeling van acute pancreatitis zich geleidelijk ontwikkeld tot een op maat gemaakte multidisciplinaire aanpak, met onderscheidende rollen voor gastro-enterologen, radiologen en chirurgen. De review in **hoofdstuk 2** vat de diagnose, classificatie en behandeling van acute pancreatitis samen, waarbij een nadruk wordt gelegd op het bewijs dat is verkregen dankzij gerandomiseerde, gecontroleerde studies.

Geïnfecteerde necrotiserende pancreatitis wordt behandeld middels een stapsgewijze benadering ('step-up'-behandeling), bestaande uit een primaire katheterdrainage, gevolgd door een (minimaal-invasieve) necrosectomie in de patiënten waarin katheterdrainages alleen niet afdoende blijken. In Nederland is videoscopisch-geassisteerde retroperitoneaal débridement (VARD) de behandeling van voorkeur, indien een necrosectomie noodzakelijk is. **Hoofdstuk 3** presenteert een cohort van 108 patiënten die een VARD hebben ondergaan in verband met geïnfecteerde necrotiserende pancreatitis. De mortaliteit in het ziekenhuis na VARD van deze patiënten was 15.7% (17 patiënten). Wanneer de periodes van voor en na 2009 werden vergeleken, werd er een significante toename gezien van het aantal preoperatieve drainageprocedures (van mediaan 1 [IQR 1-2] naar 3 [IQR 1-3], $p<0.001$). Daarnaast werd de VARD toenemend uitgesteld (van 45.9 naar 65.3 dagen na start ziekte). De meerderheid van patiënten (69%) had één VARD nodig als definitieve behandeling. De VARD is een efficiënte procedure voor minimaal-invasieve necrosectomie wanneer alleen katheterdraniages niet afdoende blijken. Het optimale aantal preoperatieve drainages en de timing van de necrosectomie blijven onduidelijk.

Necrotiserende pancreatitis kan leiden tot verlies van integriteit van de ductus pancreaticus, hetgeen leidt tot lekkage van pancreassappen. Deze zogenoemde duct-disruptie of duct disconnectie is geassocieerd met een verlengde ziekteduur en specifieke complicaties.
Aangezien er momenteel geen standaardbehandeling is voor deze aandoening, wordt in de systematische review van **hoofdstuk 4** een overzicht gegeven van de literatuur om de uitkomsten van de verschillende behandelstrategieën te vergelijken. Eenentwintig observationele cohortstudies werden geïncludeerd, met een totaal van 583 relevante patiënten. Endoscopische transpapillaire drainage, endoscopische transluminale drainage, chirurgische drainage of resectie of gecombineerde procedures waren de meeste gebruikte behandelmethodes. Gepoolde analyse toonde succespercentages van 81% (95%-betrouwbaarheidsinterval: 60-92%) voor transpapillaire en 92% (95%-BI: 77-98%) voor transluminale drainage, 80% (95%-BI: 67-89%) voor distale pancreatectomie en 84% (95%-BI: 73-91%) cyst-jejunostomie. Echter, de succespercentages van een conservatieve behandeling zijn onbekend.

Ook de diagnose van disruptie of disconnectie van de ductus pancreaticus in acute necrotiserende pancreatitis is niet gestandaardiseerd. In **hoofdstuk 5** wordt een overzicht verschaft van de beschikbare literatuur over de nauwkeurigheid van de verschillende diagnostische modaliteiten voor deze aandoening.
We includeerden 8 studies die 5 verschillende modaliteiten evalueerden: endoscopische echografie (EUS), endoscopische retrograde cholangiopancreatografie (ERCP) en magnetische resonantie cholangiopancreatografie (MRCP), met of zonder gebruik van secretine. Deze review suggereert dat verschillende diagnostische modaliteiten accuraat zijn in het stellen in het diagnosticeren van duct disrupties in patiënten met acute pancreatitis (sensitiviteit EUS en ERCP: 100%, MRCP zonder secretine: 83%. Een gecombineerd cohort van MCRP met en zonder secretine: 92%). Amylasemetingen in drainvocht zouden moeten worden gestandaardiseerd, aangezien dit een niet-invasieve, goedkope en nauwkeurige bepaling is om lekkage van pancreassappen te detecteren. Gezien de invasieve aard van de andere modaliteiten kan een secretine-MRCP of MRCP worden aanbevolen als modaliteit van eerste keus. Aanvullende prospectieve studies op dit onderwerp zijn echter nodig.

Hoofdstuk 6 laat de rationale en het ontwerp zien van de gerandomiseerde, gecontroleerde, multicenter POINTER studie. In de standaardbehandeling van geïnfecteerde pancreasnecrose, de stapsgewijze behandeling, wordt primaire katheterdrainage bij voorkeur uitgesteld tot een stadium van afgekapselde collecties ("walled-off necrosis") is bereikt, een proces dat doorgaans circa 4

weken duurt. Dit uitstellen van behandeling dateert uit de tijd dat een primaire open necrosectomie de standaardbehandeling was. Het is echter onduidelijk of een dergelijk uitstel bij katheterdrainage noodzakelijk is, of dat vroegere interventie zelfs voordelig zou kunnen zijn in de huidige stapsgewijze behandeling. De POINTER-studie onderzoekt of directe katheterdrainage in patiënten met geïnfecteerde necrotiserende pancreatitis superieur is aan de huidige standaardbehandeling van uitgestelde katheterdrainage.
In totaal zullen 104 volwassen patiënten met (verdenking op) geïnfecteerde necrotiserende pancreatitis worden gerandomiseerd tussen directe (binnen 24 uur) katheterdrainage en de huidige standaardbehandeling van antibiotische behandeling met uitgestelde katheterdrainage. Indien er een necrosectomie noodzakelijk is, wordt deze bij voorkeur uitgesteld tot het stadium van volledige afkapseling in beide behandelarmen. Primaire uitkomstmaat is de 'Comperhensive Complication Index' (hoofdstuk 7). Dit is een samengestelde score tussen 0 en 100 die alle postoperatieve complicaties gedurende de follow-up in een patiënt combineert. Secundaire uitkomstmaten zijn mortaliteit, complicaties, aantal (re-) interventies, ziekenhuisopnameduur en opnameduur op de Intensive Care-afdeling, quality adjusted life years (QALYs) en (in)directe kosten. Standaard follow-up is 3 en 6 maanden na randomisatie.

De eerdergenoemde Comprehensive Complication Index (CCI) heeft laten zien sensitiever te zijn dan traditionele eindpunten, hetgeen steekproefgrootte in gerandomiseerde chirurgische studies kan reduceren. In **hoofdstuk 7** onderzoeken wij de waarde van de CCI in patiënten met geïnfecteerde necrotiserende pancreatitis, een ziekte met zeer grote hoeveelheid complicaties. CCI werd berekend in alle 88 patiënten die eerder in de PANTER trial werden geïncludeerd, waarin minimaal-invasive stapsgewijze behandeling werd vergeleken met een directe open necrosectomie in patiënten met geïnfecteerde necrose. De verschillen in het primaire samengestelde eindpunt (majeure complicaties en overlijden) tussen studiegroepen werd vergeleken met het verschil in de CCI. De gemiddelde CCI was 63.8 (standaarddeviatie 30.5) in de minimaal-invasieve stapsgewijze behandeling en 72.6 (SD 26.7) in de groep van primaire open necrosectomie. Het verschil in gemiddelde CCI van 8.8 punten was statistisch niet significant (p=0.137), terwijl het originele primaire samengestelde eindpunt wel statistisch significant verschilde (69% vs 40%, p=0.006). Er waren 19/88 patiënten die een CCI score hoger dan 100 zouden hebben, als de formule geen afkapwaarde zou hebben. Deze hoge gemiddelde scores in de CCI reflecteren de ernst en uitgebreidheid van de complicaties in geïnfecteerde necrotiserende pancreatitis, en de CCI kan daarom bruikbaar zijn in het onderzoek naar deze zeer zieke patiënten. Echter, in ziekten met veel complicaties is de CCI wellicht minder onderscheidend dan traditionele

(samengestelde) eindpunten. Door de hoge gemiddeldes op de logaritmische schaal van de CCI, zullen aanvullende complicaties steeds tot een verminderende meeropbrengst in score leiden.

Onderwerpenvoorklinischwetenschappelijkonderzoekwoordenveelalbepaalddoor artsen, onderzoekersr of de farmaceutische industrie, maar zelden door patiënten. In **hoofdstuk 8** werd als doel gesteld om de voor pancreatitispatiënten meest op de voorgrond staande klinische symptomen te onderzoeken en te onderzoeken wat zij beschouwen als relevante onderwerpen voor toekomstig onderzoek. Er werd een vragenlijst verstuurd naar 925 leden van de Alvleeskliervereniging, waarop 252 patiënten reageerden. De meest gerapporteerde klachten waren pijn, door 184(76%) patiënten, en vermoeidheid, door 131 (54%) patiënten. Dieet gedurende ziekenhuisopname werd vaker als probleem genoemd door patiënten met acute pancreatitis dan door patiënten met chronische pancreatitis; 43% vs. 23%, p=0.007. Arbeidsongeschiktheid werd vaker als probleem genoemd door patiënten met chronische pancreatitis; 15% vs. 27%, p=0.007. Achtenzestig (29%) patiënten hadden eerder aan klinisch wetenschappelijk onderzoek deelgenomen, dit werd door 68% (45/68) als positieve ervaring beschouwd. In totaal stond 67% van alle patiënten welwillend ten opzichte van deelname aan toekomstig wetenschappelijk onderzoek. Voeding werd het meest gesuggereerd (54%) als onderwerp voor toekomstig onderzoek. Patiënten kunnen waardevolle input hebben in het richting geven van klinisch wetenschappelijk onderzoek, en zouden daarom moeten worden betrokken in de besluitvorming omtrent onderzoeksprojecten en subsidieverstrekkingen.

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Year	AMC Graduate School courses	ECTS
2018	Clinical epidemiology: Systematic Review	1.0
2017	Practical Biostatistics	1.1
2016	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	1.0
	Other Courses	
2019	Presenting in English, St Antonius Ziekenhuis	1.0
2018	How to write a clinical paper workshop – British Journal of Surgery, Birmingham	0.5
2017	Randomised Controlled Trials Course: A guide to design, conduct, analysis, interpretation and reporting	2.0
	Seminars and meetings	
2019	Chirurgendagen	0.5
2019	Digestive Disease Days	0.5
2016-2019	Quarterly meetings of the Dutch Pancreatitis Study Group	2.0
2016-2019	Weekly Surgical department seminars, AMC	0.5
2017-2019	Monthly pancreatic research seminars AMC	0.5
2018	Pancreasdag	0.3
2018	IHPBA - Dutch Highlights, Slot Zeist, Zeist	0.15
2018	Chirurgendagen	0.5
2017	IHPBA - Dutch Highlights, Slot Zeist, Zeist	0.15
2017	EAES, Frankfurt	0.7
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2017	Chirurgendagen	0.5
2016	NVGE Najaarscongres	0.5
	Teaching	
2018	Necrotiserende pancreatitis, IC-onderwijs, Zuyderland ziekenhuis, Geleen	0.2
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	Clinical work	
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2015-2016	Surgical resident (ANIOS), Meander Medisch Centrum, Amersfoort	

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Outcome and timing of video-assisted retroperitoneal debridement (VARD) following catheter drainage in the step-up approach for infected necrotizing pancreatitis
Submitted

Van Dijk SM, Van Grinsven J, Domela Nieuwenhuis P, Verdonk RC, Nieuwenhuis VB, Bruno MJ, Van Santvoort HC, Besselink MG
Validation of the Comprehensive Complication Index in a multicenter randomized trial of infected necrotizing pancreatitis
Submitted

Schepers NJ, Hallensleben NDL, Besselink MG, Anten MPGF, Bollen TL, Da Costa DW, Delft F, **Van Dijk SM**, Van Dullemen HM, Dijkgraaf MGW, Van Eijck CHJ, Erkelens GW, Erler NS, Fockens P, Van Geenen EJM, Van Grinsven J, Hollemans RA, Van Hooft JE, Van der Hulst RWM, Jansen JM, Kubben FJGM, Kuiken SD, Laheij R, Quispel R, De Ridder RJJ, Rijk MCM, Romkens TEH, Ruigrok CHM, Schoon EJ, Schwartz MP, Smeets XJNM, Spanier BWM, Tan ACITL, Thijs WJ, Timmer R, Venneman NG, Verdonk RC, Vleggaar FP, Van de Vrie W, Witteman BJ, Van Santvoort HC, Bakker OJ, Bruno MJ,
Urgent ERCP with Sphincterotomy versus Conservative Treatment in Gallstone Pancreatitis
Submitted

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CURRICULUM VITAE



Sven Martijn van Dijk was born on December 1st 1987 in Utrecht, the Netherlands. He was raised in Boxtel, together with his sister and brother. After his graduation from gymnasium at the Jacob Roelands Lyceum, Sven started medical school at the Erasmus University Medical Center in Rotterdam. During his studies, he started working at the department of anatomy, under the supervision of prof. dr. G.J. Kleinrensink. Due to this work, involving dissecting of specimens and giving anatomy lectures and trainings to medical students, he developed a special interest in surgery.

In 2011, Sven paused his studies for a year to become a full time board member of student association C.S. Veritas in Utrecht, where he was the vice president and treasurer. After this year, he continued medical school with a research internship at the department of surgery in the Erasmus University Medical Center, under supervision of prof. dr. J.F. Lange.

Finally, after his medical internships (including internships in the region of Rotterdam, Utrecht and Rwanda), he graduated medical school in 2015. Following his interest in surgery, he started working as a medical doctor (ANIOS) at the department of surgery in the Meander Medical Center in Amersfoort, under supervision of prof. dr. E.C.J. Consten. In 2016 he started as a PhD-student for the Dutch Pancreatitis Study Group, to coordinate the multicenter POINTER trial, under the supervision of prof. dr. M.G.H. Besselink. He designed and started several research projects on acute pancreatitis, and also functioned as the coordinator of the Pancreatitis Expert Panel. The research projects are presented in the current thesis. After 3 years of full-time research, Sven continued working as ANIOS in the surgery department of the St Antonius Hospital in Nieuwegein, under supervision of dr. D. Boerma.

In January 2020, Sven started working as a surgical resident (AIOS) in Tergooi Hospital in Hilversum, under supervision of dr. A.A.W. van Geloven, and hereafter he will continue his surgical training in the Amsterdam UMC, location AMC.

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Collega arts-onderzoekers van de PWN
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