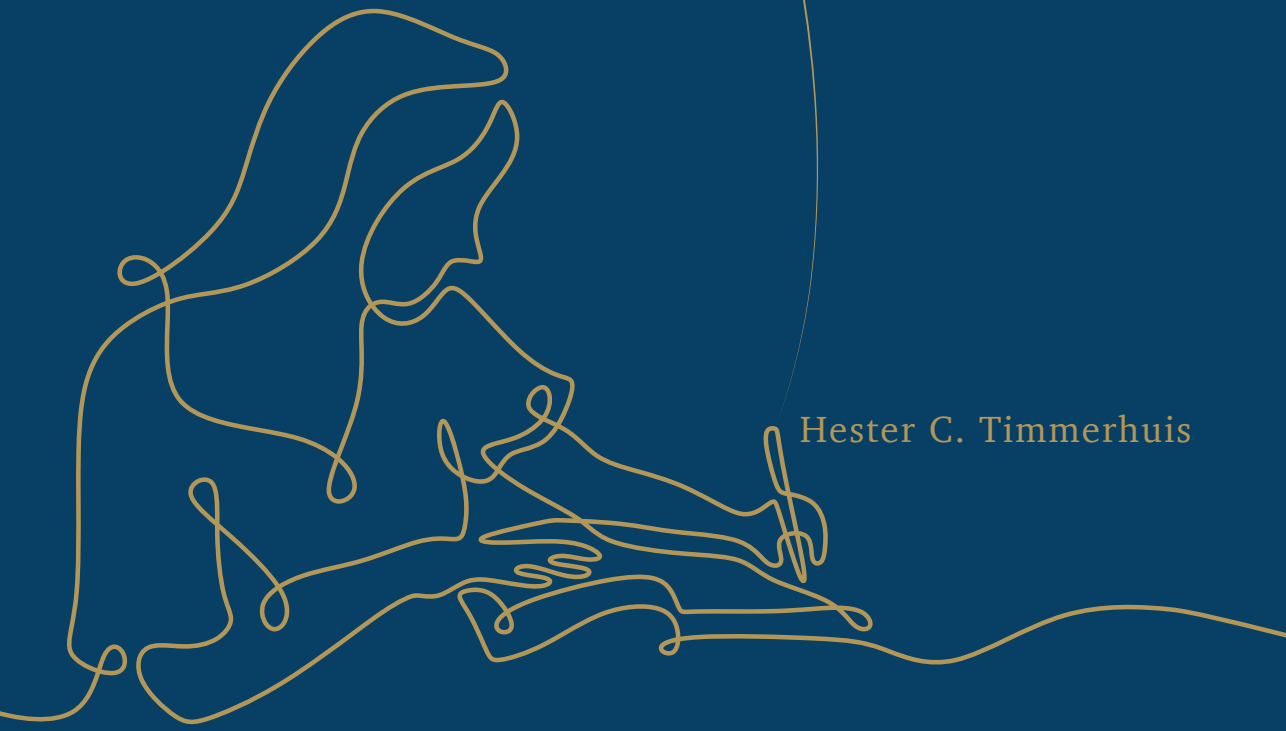
NECROTIZING PANCREATITIS

OFF THE BEATEN PATH



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OFF THE BEATEN PATH

Necrotiserende Pancreatitis
van het gebaande pad
(met een samenvatting in het Nederlands)

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Voor mijn ouders

CONTENTS

CHAPTER I

General introduction

When the pancreas was first described anatomically, it was described as 'unusual', given that it had no cartilage or bone. This is reflected in the name of the organ: in Greek *pan* = 'all' and *kreas* = 'flesh or meat'.[1,2] For a long time, the pancreas was believed to be a non-vital organ. It was the Dutch anatomist Nicholaes Tulp (1953-1674) that published a first clinical description of acute pancreatitis in 1652.[2,3]

Acute pancreatitis is an – initially sterile – inflammatory disorder of the pancreas, which clinically presents as severe abdominal pain. Nowadays, acute pancreatitis is one of the most common gastro-intestinal diseases requiring acute hospitalization.[4,5] In fact, the number of patients admitted for acute pancreatitis every year is rising,[6,7] with an increase from 4665 to 7150 hospital admissions in the Netherlands from 2013 to 2019.[6] The etiology most frequently found in most high-income countries is biliary (i.e. gallstones and/or biliary sludge), followed by alcohol-induced pancreatitis.[8]

Classification of the disease severity has been based on clinical and radiological parameters, since it remains impossible to make an accurate prediction about the severity of acute pancreatitis at time of admission. The Atlanta classification was proposed at an international symposium in 1992.[9] Despite the fact that the classification has proved useful and is widely used, it also showed its flaws.[10] Improved diagnostic imaging and better understanding of both pathophysiology of organ failure and necrotizing pancreatitis led to revision of the Atlanta classification in 2012.[11] Since then, acute pancreatitis can be divided into three different severity categories: 1) mild; no organ failure and no local or systemic complications, 2) moderately severe; organ failure that resolves within 48 hours and/or local or systemic complications without persistent organ failure, and 3) severe; persistent organ failure (>48 hours).[11] In the majority of patients with acute pancreatitis, the disease course is mild and self-limiting requiring supportive care only. An important determinant for the severity of the disease is the development of a well-known local complication: necrosis of the pancreatic parenchyma or extrapancreatic fat tissue. This can be demonstrated on contrast-enhanced computed tomography (CT) and occurs in approximately 20% of patients with acute pancreatitis.[11–15]

The most feared complication in this patient group is secondary infection of the (peri)pancreatic necrosis.[16] Over the past 10-20 years, many studies have been conducted on infected necrosis. The treatment approach of infected necrosis has evolved from an open surgical approach to a minimally invasive endoscopic and/or surgical approach,[17–22] which has substantially improved the treatment and outcome of patients with necrotizing pancreatitis.[17–22]

More than 370 years have passed since Tulps' clinical description of acute

pancreatitis.[3] The Netherlands – mostly due to the inexhaustible efforts of the Dutch Pancreatitis Study Group – remains at the forefront of research in the field of acute pancreatitis. Although our knowledge has exponentially increased, many questions remain unanswered. Especially questions pertaining the rarer and underreported complications.

This thesis goes *'off the beaten path'* and focuses on those complications, in which three main topics regarding short- and long-term outcomes of severe acute pancreatitis have been addressed:

1. Treatment of necrotizing pancreatitis
2. Local complications of necrotizing pancreatitis
3. Long-term outcome and prevention of recurrence after acute pancreatitis

The main study questions for each topic are summarized in Table 1. The background of the three topics is discussed in the following sections.

Table 1 The 11 main study questions that are addressed in this thesis

Chapter	Study question
PART I – TREATMENT OF NECROTIZING PANCREATITIS	
II	What is the step-up approach in the management of infected necrosis? *Book chapter*
III	How is the current use of antibiotics in necrotizing pancreatitis and what is the clinical consequence? *Multicenter observational cohort study*
PART II – LOCAL COMPLICATIONS OF NECROTIZING PANCREATITIS	
IV	What is the current international clinical practice in diagnosis and treatment of disruption or disconnection of the pancreatic duct in patients with necrotizing pancreatitis? *International expert survey and case vignette study*
V	What is the best diagnostic modality to diagnose disruption or disconnection of the pancreatic duct in patients with necrotizing pancreatitis? *Systematic review*
VI	What is the best treatment for disruption or disconnection of the pancreatic duct in patients with necrotizing pancreatitis? *Systematic review and meta-analysis*
VII	What is the current incidence, diagnostic and therapeutic approach and short- and long-term clinical outcome of disruption or disconnection of the pancreatic duct in patients with necrotizing pancreatitis? *Multicenter observational cohort study*
VIII	What is the current incidence, clinical outcome and management of patients with perforation and fistula of the gastrointestinal tract in patients with necrotizing pancreatitis? *Multicenter observational cohort study*
PART III – LONG-TERM OUTCOME AND PREVENTION OF RECURRENCE AFTER ACUTE PANCREATITIS	
IX	What is the diagnostic and therapeutic approach of pancreatic exocrine insufficiency after acute pancreatitis? *Book chapter*

Table 1 Continued.

Chapter	Study question
X	What are the interventions, complications and quality of life during long-term follow-up of patients with necrotizing pancreatitis? *Multicenter observational cohort study*
XI	Can endoscopic ultrasonography detect etiology in patients with idiopathic acute pancreatitis? *Multicenter observational cohort study*
XII	What is the optimal timing of cholecystectomy after necrotizing biliary pancreatitis? *Multicenter observational cohort study*

PART I – TREATMENT OF NECROTIZING PANCREATITIS

The initial treatment of necrotizing pancreatitis consists of supportive care until complications occur. The aforementioned most feared complication, infected necrosis, generally develops three to four weeks after onset of disease[16,23,24] and is associated with a prolonged hospital and intensive care stay, sepsis, multiple organ failure and a 20-30% mortality rate.[25–27] Antibiotic prophylaxis was found to be ineffective for the prevention of infected necrosis and is therefore not recommended.[13,28,29] Empirical broad-spectrum antibiotics, however, should be started when infected necrosis is suspected based on clinical deterioration[28–32] and in the absence of an alternative source of infection.[33] As soon as patients undergoing antibiotic therapy do not improve or show clinical deterioration, pancreatic intervention is indicated.[13] Open surgical necrosectomy was the standard first step of intervention until publication of the PANTER trial in 2010,[17] which has shown many advantages for the surgical 'step-up' approach compared to the open approach. In the period that followed, the endoscopic techniques evolved, and gastroenterologists became more and more involved. As a result, the TENSION trial was initiated to compare the endoscopic step-up approach to the surgical step-up approach[19] which showed a shorter hospital stay and fewer pancreaticocutaneous fistulas in the endoscopic group.[19] The step-up approach – either endoscopic or percutaneous catheter drainage followed by minimally invasive necrosectomy - is considered standard treatment. Therefore, a summary of the current step-up approach in the management of infected necrosis is presented in *CHAPTER II*.

Although the current guidelines are clear regarding antibiotics, optimal antibiotic use remains challenging. This is partially explained by the difficulty to differentiate between clinical deterioration caused by systemic inflammatory response syndrome (SIRS) and clinical deterioration caused by sepsis due to infected necrosis.[34] In addition, microbiological cultures are not always available at the time of antibiotic initiation, making targeted antibiotic therapy difficult.

This may lead to an overuse and/or misuse of antibiotics.[35–38] An evaluation of the current use of antibiotics and the clinical consequence of potential overuse of antibiotics in necrotizing pancreatitis has not been performed. *CHAPTER III* presents an observational, multicenter, cohort study that investigated the timing and use of antibiotics and the clinical consequences of antibiotic treatment in patients with necrotizing pancreatitis.

PART II – LOCAL COMPLICATIONS OF NECROTIZING PANCREATITIS

Necrosis of the pancreatic parenchyma may lead to loss of integrity of the pancreatic duct. This causes the main pancreatic duct to no longer communicate with the gastrointestinal tract, resulting in pancreatic fluid leakage to the surrounding tissues.[41,42] This is known as pancreatic duct disruption or disconnection,[43] which was first described by Kozarek et al in 1996.[44] One of the main problems with this complication of pancreatitis is the lack of a standardized guidelines on the diagnostic workup and treatment. An evaluation of the current consensus among expert pancreatologists had never been performed. In *CHAPTER IV* we summarize a study among international expert pancreatologists that assesses their current diagnostic and therapeutic approach for disruption or disconnection of the pancreatic duct in necrotizing pancreatitis.

Although disruption or disconnection of the pancreatic duct is an increasingly reported entity, the reported estimates on the incidence vary from 10-50%.[41,43,45–49] This wide range might be explained by the lack of a standardized and evidence-based method and timing of a diagnostic work-up.[13,28,29,50] 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.[43,51–60] While ERCP is still considered as the reference standard, it is an invasive procedure which also carries a relatively high risk of complications.[61,62] *CHAPTER V* presents a systematic review of the accuracy of the various diagnostic modalities to assess a pancreatic duct disruption and disconnection in patients with necrotizing pancreatitis.

Like the diagnostic work-up, 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.[42] *CHAPTER VI* describes a systematic review and meta-analysis to identify different treatment options for pancreatic duct disruption and disconnection in patients with acute necrotizing

pancreatitis, and compares the outcomes of the different treatment strategies.

Once the pancreatic fluid has gone *'off the beaten path'*, a complicated course is likely to follow, which may be characterized by recurrent or persistent peripancreatic fluid collections, pancreatic ascites, or pancreatic fistulas including external fistulas following percutaneous catheter drainage.[42,53,63–67] The exact clinical impact of disruption or disconnection of the pancreatic duct remains unclear. It is generally believed that is has a large impact on the patient's quality of life, and that it is associated with a worse clinical outcome and high health care resource utilization.[41,43,46,52,53,68] Especially data on late presentation of consequences, such as recurrent pancreatitis and chronic pancreatitis, are lacking. In *CHAPTER VII* we summarize the results of an observational pro- and retrospective cohort study on current clinical practice and on short and long-term clinical outcomes in patients with disruption or disconnection of the pancreatic duct.

A less common, but not less important, complication in patients with necrotizing pancreatitis is perforation or a fistula of the gastrointestinal tract. It is defined as discontinuation of the gastrointestinal wall either with or without connection to another organ, which may involve the stomach, duodenum, jejunum, ileum, and colon.[39,40] This causes gastrointestinal contents to no longer follow the natural route, but to go *'off the beaten path'*. Even though perforation and fistulas of the gastrointestinal tract are known to occur in clinical practice, data on this topic remain scarce. Therefore, we performed an observational, multicenter cohort study of patients with necrotizing pancreatitis with the aim to explore the incidence, risk factors, clinical course and treatment of perforation and fistula of the gastrointestinal tract, which is described in *CHAPTER VIII*.

PART III – LONG-TERM OUTCOME AND PREVENTION OF RECCURENCE AFTER ACUTE PANCREATITIS

An often underdiagnosed and undertreated long-term complication of acute pancreatitis is pancreatic exocrine insufficiency, which occurs in around a third of patients after an episode of acute (necrotizing) pancreatitis. *CHAPTER IX* describes the diagnostic and therapeutic approach to pancreatic exocrine insufficiency after acute pancreatitis.

The guidelines withhold on recommendations for the long-term follow-up of patients with acute pancreatitis. Especially when patients are treated conservatively initially, long-term follow-up data are lacking. Most long-term follow-up studies that are conducted, report on results of a mixed group of

patients undergoing different types of treatment (i.e., endoscopic, minimally invasive, and invasive surgery) for (infected) necrosis.[75–80] While one treatment modality may require a standard follow-up, another treatment modality may need a follow-up that goes *'off the beaten path'*. As a result, adequate follow-up based on the individual needs following an initial episode of necrotizing pancreatitis cannot be performed. *CHAPTER X* presents a prospective long-term follow-up study describing interventions, complications, and quality of life over a follow-up period of more than ten years after discharge from the index admission.

An important and dreaded long-term complication of acute pancreatitis is recurrent pancreatitis. When no etiology is found after routine work-up during the initial admission,[69,70] which happens in approximately 25% of patients and is known as idiopathic acute pancreatitis, the risk of recurrent pancreatitis is higher.[71] Endoscopic ultrasound is advised in patients with idiopathic acute pancreatitis.[13] This recommendation is, however, weak and based on evidence of low quality. Until now, endoscopic ultrasound has not been performed routinely, which may lead to under treatment of this patient group. In *CHAPTER XI* we present the results of the Pancreatitis of Idiopathic origin: Clinical added value of endoscopic UltraSound (PICUS), a prospective observational, multicenter cohort study.

If a biliary aetiology is found, international guidelines advise to perform a cholecystectomy in order to avoid recurrent biliary events, such as cholangitis, recurrent acute pancreatitis, and acute cholecystitis.[13,50,72] In patients with mild biliary pancreatitis, same-admission cholecystectomy is safe and reduced recurrent biliary events compared to interval cholecystectomy as shown in a randomized trial.[73] Due to the potentially higher risk of complications, the optimal timing of cholecystectomy in patients with necrotizing pancreatitis remained unknown.[74] In *CHAPTER XII* we summarize an observational study of a prospective cohort to determine the optimal timing of cholecystectomy after necrotizing biliary pancreatitis.

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PART I

TREATMENT OF NECROTIZING PANCREATITIS

PART I

CHAPTER II

Management of infected necrosis: step-up approach

Chapter 28
The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery
Fourth Edition 2023

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INTRODUCTION

In the majority of patients with acute pancreatitis, the disease course is mild and self-limiting requiring supportive care only. Approximately 20% of patients, however, develop necrotizing pancreatitis. This is characterized by necrosis of the pancreatic or peripancreatic tissue, as seen on contrast-enhanced computed tomography (CT).[1,2] Necrosis of the pancreatic or peripancreatic tissue is sterile, therefore initial management remains supportive including fluid resuscitation, pain control, and nutritional support.[2,3]

Secondary infection of pancreatic or extrapancreatic necrotic tissue occurs in one-third of patients with necrotizing pancreatitis.[1] Infected necrosis is associated with a prolonged hospital and intensive care stay, sepsis, multiple organ failure, and a 20–30% mortality rate.[4-6] Although infection can occur in the early phase of pancreatitis, it usually develops 3 to 4 weeks after onset of disease.[7-9] Infected necrosis is suspected when the patients show clinical deterioration, in the absence of an alternative source of infection, despite maximal conservative support[10] or when gas configurations are present in the necrotic collections or necrosis as demonstrated on abdominal imaging.[3] Fine-needle aspiration of peripancreatic or pancreatic collections is not indicated because of the considerable number of false negative (20–29%) and false positive (4–10%) results.[10-12]

THE HISTORY OF PANCREATIC INTERVENTIONS

The benefit of surgical treatment in acute pancreatitis has been an ongoing debate since the late nineteenth century. It was in 1886 that Nicholas Senn considered surgery in the early phase of pancreatitis as ineffective and risky.[13] Despite a mortality rate of more than 50%, laparotomies with drainage of the lesser sac and placement of gauze to achieve optimal drainage and to prevent wound closure, were considered the best treatment for acute pancreatitis until the 1930s.[14] Around this time, it became possible to diagnose acute pancreatitis without needing laparotomy by determination of serum amylase levels. This contributed to the use of conservative treatment for acute pancreatitis, which was reinforced in 1948 by a publication highlighting the poor survival rates after early surgery.[15] However, since conservative treatment was not giving satisfactory results, in the 1960s surgical procedures were reconsidered and surgical treatment was again indicated in the initial stages of acute pancreatitis. It was in the 1980s that the therapeutic approach of acute pancreatitis changed again, when a series of prospective studies showed superior results of conservative treatment compared

with surgical treatment in patients with sterile necrosis.[16-18]

The value of abdominal abscess drainage under ultrasound or CT was discovered in 1979, while it was not until 1987 when the possibility of aspiration of pancreatic or peripancreatic fluid ultrasound or CT-guided aspiration was used for early diagnosis of infected necrosis.[19,20] At the beginning of the twenty-first century, the first study was published on laparoscopic necrosectomie followed by a study involving endoscopic necrosectomy in 2009.[21,22] The necessity of surgical debridement for infected necrosis was subsequently questioned when Runzi et al. showed that initial conservative therapy, including antibiotic therapy, could be instituted.[23] Mortality in patients managed with surgery was identical to those managed conservatively.[23] Surgical therapy, when required, was often delayed to a later stage of disease, when the systemic inflammatory response has been stabilized and necrotic pancreas had become demarcated. In other patients, surgical therapy was avoided altogether. Subsequent studies have confirmed this strategy, Garg et al. describe a 10-year series of 80 patients with infected pancreatic necrosis in whom 47 were treated with antibiotics alone.[24] The urge for surgical debridement for all patients with infected pancreatic necrosis is therefore no longer considered valid.[25] Although laparoscopic direct necrosectomy was already described in the 1990s, it failed to gain popularity due to technical difficulty. Therefore, until publication of the PANTER trial in 2010, necrosectomy by laparotomy was the standard intervention.[26] In the PANTER trial, 88 patients were randomly assigned to the "step-up" approach or to immediate open necrosectomy. A step-up approach consisted of percutaneous catheter drainage, followed, if needed, by minimally invasive necrosectomy. Major short-term complications such as new onset multiorgan failure and long-term complications such as endocrine insufficiency, and costs, were decreased in the patients who were assigned to the "step-up" approach. The effect of the step-up approach was beneficial in patients with and without organ failure.[26] In addition, necrosectomy was avoided in 23–50% of the patients treated with percutaneous catheter drainage.[26-29] Since then, the step-up approach is considered to be the standard treatment. Several new minimally invasive strategies have been introduced and compared in randomized controlled trials with the goal of improving survival and decreasing complications and comorbidities. In the most recent study, 19 out of the 49 (39%) patients with infected necrosis did not require intervention at all and could be treated with antibiotics alone.[30]

STEP-UP APPROACH

Antimicrobial management of infected necrosis

When infected necrosis is clinically or radiologically suspected, antibiotic therapy

can be initiated without fine-needle aspiration or pancreatic culture.[11,31] Since it is hypothesized that translocation of bacteria from the gut is the major source for infection of necrosis, antibiotics that are effective on gut-derived bacteria with the potential to penetrate into the pancreas (carbapenems, quinolone, metronidazole, third-generation cephalosporins) should be considered as empirical treatment.[7,32,33] Antibiotic therapy should be adjusted accordingly once pancreatic culture results have been obtained. Since there are no data on the adequate duration of antibiotic therapy, it remains unknown when to stop antibiotic administration or when to proceed to pancreatic intervention. Current guidelines recommend that antibiotics are discontinued once the last percutaneous catheter drain has been removed for more than 48 hours and/or pancreatic cultures remain negative.[11] In addition, improvement of clinical, biochemical, and radiological signs aids in the decision to stop antibiotics. This is especially important in patients undergoing endoscopic treatment of the infected necrosis, as no drains are removed, and no new pancreatic cultures are available.

Percutaneous or endoscopic drainage of infected necrosis

Pancreatic intervention is indicated in patients who fail to improve or who show clinical deterioration under antibiotic therapy.[11] Invasive intervention should preferably be delayed until collections have become walled-off, typically 3–4 weeks after the onset of disease.[11] In the recent multicenter randomized POINTER trial, no difference in the rate of complications or mortality was found between patients randomly assigned to immediate drainage (<24 hours after suspected or proven infected necrosis, 55 patients) or postponed drainage (when the collections were walled-off, 49 patients). The mean number of pancreatic interventions was higher in the group of patients who underwent immediate drainage.[30]

Radiologically guided percutaneous catheter or endoscopic transluminal drainage is the first step in the step-up approach. The choice of one approach over another is based on multiple factors including characteristics of the collection (i.e., location, extent, integrity of the pancreatic duct) and clinical (i.e., hemodynamic) status of the patient. The randomized TENSION trial assigned 98 patients to either the endoscopic step-up approach (51 patients) or the surgical step-up approach (47 patients). No difference was found in major complications or death during a 6-month follow-up between the two groups. The rate of pancreatic fistulas and length of hospital stay were lower in the group assigned to the endoscopic step-up approach.[34] Therefore, the endoscopic approach is preferred.

Endoscopy

There are several endoscopic techniques to treat (infected) walled-off necrosis. The similarity between these techniques is the transmural access route. Since the superiority of endoscopic ultrasound (EUS)-guided drainage in patients with pseudocysts using an echo-endoscope has been shown in two randomized trials, conventional transmural drainage using a standard endoscope (blind access) has nowadays been replaced by EUS-guided drainage.[35,36]

During endoscope drainage a transmural drain is inserted into the cavity through either a single or several access sites (multiple transluminal gateway technique).[37] The multiple transluminal gateway technique led to more frequently reported clinical success compared with single-access endoscopic drainage in two retrospective series.[37,38] In both methods, balloon dilatation is performed to create a fistula between the gastrointestinal tract and the collection after the collection is accessed.[39] This fistula must be maintained to allow the evacuation of pus, debris, and necrotic tissue. This can be done by inserting multiple plastic double-pigtail stents or a self-expandable metal stent (e.g., lumen-apposing metal stents [LAMS]). Due to the larger lumen of the LAMS, expectations were high, and this was confirmed in one small retrospective study.[40] An interim analysis of an ongoing single-center randomized trial, however, has revealed an important rate of delayed stent-related adverse events, consisting of bleeding and embedded LAMS. This led to the need to perform imaging to exclude vascular complications and the retrieval of the LAMS within 4 weeks.[41] A prospective observational cohort study, conducted by the Dutch Pancreatitis Study Group, has shown no increased risk of complications, including bleeding, in patients treated with LAMS.[42]

With regard to removal of the endoscopic drains, plastic double-pigtails stents can be left in situ indefinitely, unlike LAMS, which it is advised to remove within 6 weeks due to worrisome long-term adverse events.[41,42] Subsequently, in the presence of a disruption of the pancreatic duct, LAMS should be replaced by plastic double-pigtail stents. The use of LAMS did not reduce the need for endoscopic transluminal necrosectomy compared with plastic double-pigtail stents (34 [64%] patients vs. 27 [53%], respectively). In the TENSION trial, 57% of the patients who underwent endoscopic drainage required a necrosectomy.[34]

Radiology

As shown in the PANTER trial, percutaneous catheter drainage is feasible in >95% of the patients.[26] According to the Seldinger or the tandem trocar technique regular silicone pigtail drains are used.[29] The percutaneous catheter drain is preferably inserted in the retroperitoneal cavity to facilitate minimally invasive retroperitoneal necrosectomy if necessary as the next step. During the initial percutaneous procedure (real-time) ultrasound guidance in combination with

fluoroscopy is often preferred to prevent puncture of organs of the gastrointestinal tract. If the collection contains limited liquid content, visualization with ultrasound can be difficult. In these patients, CT-guided drainage can be performed. Drain diameter may vary and there is no comparative data regarding the influence of different sizes of the drain; however, large-bore catheters of more than 14 French seem to obstruct less frequently.[29] In half of the patients, drains are required to be replaced or upsized.[26] Successful percutaneous catheter drainage can be predicted when the collection shows a decrease in size of at least 75% after the first 10–14 days following percutaneous catheter drainage.[28,43] No data is available on the optimal timing of removal of percutaneous catheter drains. In about half of the patients surgical necrosectomy was required following primary percutaneous catheter drainage as the primary treatment.[29,35]

Pancreatic debridement of infected necrosis

If no further clinical improvement is seen or when patients show clinical deterioration after endoscopic drainage or percutaneous catheter drainage without options for further percutaneous drainage, debridement of pancreatic necrosis is indicated. The optimal timing for repeat intervention, however, remains unclear. If clinically possible, the collection should be walled-off before necrosectomy is performed since early necrosectomy is associated with poor outcomes.[44] As with the choice for the first step, the subsequent approach (either endoscopic or surgical) for necrosectomy should be based on patient characteristics and location of the peripancreatic or pancreatic necrosis and should be performed as minimally invasive as possible.[11,26,34]

Especially in high-risk, critically ill patients minimally invasive surgery and endoscopic necrosectomy were associated with reduced death rates as compared to open necrosectomy.[45] Regardless of the benefits of minimally invasive intervention, patients with intra-abdominal hemorrhage, perforation and/or abdominal compartment syndrome may require immediate intervention using either a minimally invasive or more invasive method.[11]

The TENSION trial did not show superiority of endoscopy necrosectomy in outcomes such as major complications and death. Length of hospital stay, rate of pancreatic fistulas, and costs were significantly reduced in the patients undergoing the endoscopic step-up approach.[34]

Endoscopy

Endoscopic transluminal necrosectomy is performed to remove solid necrotic debris by a combination of sucking debris through the working channel of the endoscope directly inserted into the necrotic collection (direct transluminal endoscopic necrosectomy), removing necrotic material with a removal device,

and applying irrigation.[37,46] Although not well studied, the anatomical position of the initial puncture is also important for direct transluminal endoscopic necrosectomy.[42] Due to the lack of specifically designed endoscopic accessories, pre-existing tools are used during necrosectomy, such as different types of stone removal baskets (i.e., Dormia), polypectomy snares, balloons, nets, and different types of forceps.[42] These devices often lack sufficient grip, however, making the procedure time-consuming and often marginally effective requiring more than one procedure. Preliminary results suggests that the EndoRotor device (i.e., an automated mechanical endoscopic resection system designed for tissue dissection and resection with a single device) can safely, rapidly, and defectively remove necrotic tissue in patients with (infected) walled-off necrosis.[47]

Surgery

There is a large variance in the used and personal favor of the various techniques. Surgical debridement can be performed with open or minimally invasive (laparoscopic) techniques.[44,48] Open debridement with external drainage is performed through a laparotomy followed by entry in the retroperitoneum to remove necrotic tissue. Subsequently, two to four large, closed suction drains are left to facilitate drainage of the cavity. However, this procedure is only appropriate in patients with walled-off necrosis. There are various minimally invasive approaches described, including percutaneous necrosectomy (MIRP), video-assisted retroperitoneal debridement, laparoscopic transgastric necrosectomy, laparoscopic cystgastrostomy, and personal variations on the aforementioned techniques.[49-53] In general, minimally invasive surgery continues to be the preferred technique; however, open necrosectomy remains a possibility for some patient groups.

II

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PART I

CHAPTER III

Overuse and misuse of antibiotics and the clinical consequence in necrotizing pancreatitis *an observational multicenter study*

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ABSTRACT

Objective
The use and impact of antibiotics and the impact of causative pathogens on clinical outcomes in a large real-world cohort covering the entire clinical spectrum of necrotizing pancreatitis remain unknown.

Background
International guidelines recommend broad-spectrum antibiotics in patients with suspected infected necrotizing pancreatitis. This recommendation is not based on high-level evidence and clinical effects are unknown.

Methods
This study is a post-hoc analysis of a nationwide prospective cohort of 401 patients with necrotizing pancreatitis in 15 Dutch centers (2010-2019). Across the patient population from the time of admission to 6 months post admission, multivariable regression analyses were used to analyze (1) microbiological cultures and (2) antibiotic use.

Results
Antibiotics were started in 321/401 patients (80%), administered at a median of 5 days (P25-P75: 1-13) after admission. The median duration of antibiotics was 27 days (P25-P75: 15-48). In 221/321 patients (69%) infection was not proven by cultures at the time of initiation of antibiotics. Empirical antibiotics for infected necrosis provided insufficient coverage in 64/128 patients (50%) with a pancreatic culture. Prolonged antibiotic therapy was associated with Enterococcus infection (OR 1.08 [95% CI 1.03-1.16], P=0.01). Enterococcus infection was associated with new/persistent organ failure (OR3.08 [95% CI 1.35-7.29], P< 0.01) and mortality (OR 5.78 [95% CI 1.46-38.73], P=0.03). Yeast was found in 30/147 cultures (20%).

Discussion
In this nationwide study of patients with necrotizing pancreatitis, the vast majority received antibiotics, typically administered early in the disease course and without a proven infection. Empirical antibiotics were inappropriate based on pancreatic cultures in half the patients. Future clinical research and practice must consider antibiotic selective pressure due to prolonged therapy and coverage of Enterococcus and yeast. Improved guidelines on antimicrobial diagnostics and therapy could reduce inappropriate antibiotic use and improve clinical outcomes.

INTRODUCTION

Antibiotic treatment remains the cornerstone of disease management when infected necrosis occurs in patients with necrotizing pancreatitis. However, optimal antibiotic use is challenging. Firstly, it remains difficult to differentiate between clinical deterioration caused by systemic inflammatory response syndrome (SIRS) or by sepsis due to infected necrosis.[1] Secondly, for targeted antibiotic therapy, microbiological cultures are required, but fine needle aspiration (FNA) is currently not routinely recommended, given the possibility of possible false-negative results and iatrogenic infection.[2]

While international guidelines do not recommend antibiotic prophylaxis,[2–4] empirical broad-spectrum antibiotics are recommended when infected necrosis is suspected based on clinical deterioration.[2–7] However, the worldwide use of broad-spectrum antibiotics may lead to antibiotic resistance.[8] Antimicrobial resistance is reported to be a leading cause of death around the world, indicating a health problem whose magnitude is at least as large as major diseases such as the human immunodeficiency virus.[9] Previous studies have concluded that there is an overuse and misuse of antibiotic regimens in patients with necrotizing pancreatitis.[10–13] However, the studies are either small and retrospective[11,13] or based only on questionnaires rather than clinical data[10,12] (the most recent data dates from 2013[12]). Since 2013, the treatment approach for infected necrosis has changed from invasive to less invasive interventions, with antibiotics playing a larger role. In the current era, there is limited understanding on the clinical impact of cultured microbes, antibiotic resistance, and antibiotic use. As a result, patients may keep receiving unnecessary or untargeted, broad-spectrum antibiotic therapy. To address this efficiency in clinical research, we evaluated the clinical impact of different pathogens and antibiotic use on clinical outcomes in the current era in a large prospective cohort of unselected patients with necrotizing pancreatitis.

METHODS

Study design and population

This study was a post-hoc analysis of patients included in the nationwide prospective registry of acute pancreatitis (PWNCORE) of the Dutch Pancreatitis Study Group. A subset of these patients was also randomized in the TENSION study.[14] For the current study, all patients with necrotizing pancreatitis over 18 years of age, treated between January 1, 2010, and December 31, 2019, were selected, spanning 15 hospitals. Patients were excluded for which electronic

medical records were unavailable, who exhibited signs of chronic pancreatitis according to the M-ANNHEIM criteria[15] or who were diagnosed with pancreatic carcinoma at admission. Approval was obtained for PWN-CORE by a central medical ethics committee and by the institutional review board of each participating hospital. For the current study, the medical ethics committee waived the need for additional ethical approval. This study was reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines[16] and conducted in accordance with the principles of the Declaration of Helsinki. All patients or their legal representatives gave written informed consent for the PWN-CORE registry.

Definitions

Acute pancreatitis was diagnosed according to the revised Atlanta classification.[17] Necrotizing pancreatitis was defined as either necrosis of pancreatic tissue or/and peripancreatic tissue demonstrated on a contrast-enhanced computed tomography (CT) or by a computed tomography severity index (CTSI)-score of 3 or higher.[17] An expert pancreatic radiologist (TLB) reviewed all abdominal radiologic images to determine the computed tomography severity index-score and to assess the presence and location of peripancreatic fluid collections and (peri)pancreatic necrosis.

Antibiotic use information was collected from the time of admission until 6 months postadmission. We included both antibacterial and antifungal therapy but excluded selective decontamination of the digestive tract. Broad-spectrum antibiotics included carbapenems, quinolones, metronidazole, and third-generation or higher-generation cephalosporins.

For the current study, we made a distinction between a proven and nonproven infection according to predefined criteria and following a standard diagnostic work-up (i.e.,, blood cultures, urine cultures, chest x-ray). This distinction was based on the notes of the treating clinician. Proven infections included pneumonia, cholangitis, cholecystitis, urinary tract infection, infected (peri-)pancreatic necrosis, and other less prevalent infections. All definitions are provided in Supplementary Table S1. Nonproven infections were defined as instances of clinical suspicion for one of the aforementioned infections or fever of unknown origin but without meeting the criteria for proven infections. Infected necrosis was considered proven when (1) gas configurations were present on contrast-enhanced CT before the first pancreatic intervention or (2) either FNA or the first drainage procedure from pancreatic of peripancreatic fluid resulted in a positive culture. If infection of the pancreatic necrosis could not be proven according to our criteria, but there was a clinical suspicion according to the treating clinician, we defined this as suspected infected necrosis (nonproven infection).

We only included cultures that were directly obtained from percutaneous catheter drains within 24 hours after the intervention or during radiologic, endoscopic or surgical intervention (including FNA) to describe the microbiological pathogens in infected pancreatic necrosis and to distinguish relevant cultures from drain colonization. Antimicrobial therapy consisted of both antibiotics and antifungals but did not include selective decontamination of the digestive tract. Antibiotic susceptibility was defined as reported by the local microbiology laboratories. When a susceptibility report was missing, the susceptibility was additionally interpreted by a clinical microbiologist (ES) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines[18] (Supplementary Text S2). Multidrugresistant bacteria are described in Supplementary Text S3.

Data collection

Using a standardized case-record form, clinical data were collected prospectively during the initial hospital admission, and follow-up data was collected retrospectively. Data regarding (indications for) antibiotics, clinical outcomes (ie, interventions, organ failure, mortality, readmissions and length of hospital stay) was collected from the date of admission until the last date of data collection (January 2020) or death. If, at any time before or during follow-up, a patient was transferred to another hospital, all the required follow-up data was retrieved from that institution. All data were collected by 1 author (HCT) and subsequently verified by a second author (FvdB). Discrepancies were resolved by consensus during research meetings of the Dutch Pancreatitis Study Group. All authors had access to the study data and reviewed and approved the final manuscript.

Statistical analysis

The timing and indication of all antimicrobial therapies were reported as descriptive data. We separately assessed antibiotic use early in the disease (< 7 and <14 d after admission), when it was less likely that patients had already developed infected necrosis. Antibiotics and their susceptibility were reported for patients in whom a pancreatic culture was obtained. Microbiological pathogens and their characteristics obtained from pancreatic cultures were described and compared. Descriptive data was reported as a mean with SD when normally distributed and as a median with interquartile ranges (P25-P75) when not normally distributed. Categorical data was shown as frequencies and percentages. When multivariate analyses were not deemed possible, predefined as less than 40 events of the outcome, univariate analyses were performed using Fisher exact test or χ^2 test for categorical data and the Student t-test or the Mann-Whitney U test for continuous data. To adjust for potential confounding factors, generalized

linear models were constructed to explore the effect and duration of antibiotics on microbiological findings and clinical outcomes. We also constructed generalized linear models to explore the association between microbiological pathogens and clinical outcomes. The variables included as covariates varied by the clinical outcome, including variables that were considered to be associated with a poor clinical course. The selection was based on clinical reasoning and was reported for each variable in Supplementary Table S4. If applicable, we calculated odds ratios (OR) with their respective 95% confidence intervals (CI). A P value <0.05 was considered statistically significant. Statistical analysis was performed using R (R version 3.6.1 (2019-07-05)).

RESULTS

Between 2010 and 2019, 1593 patients with acute pancreatitis across the 15 participating hospitals were registered in the PWN-CORE registry and screened for eligibility. In total, 401 patients with necrotizing pancreatitis were included in the present study (Fig. 1). Clinical characteristics are provided in Table 1, and clinical outcomes and interventions are provided in Table 2. The median follow-up was 46 months (P25-P75: 28-66).

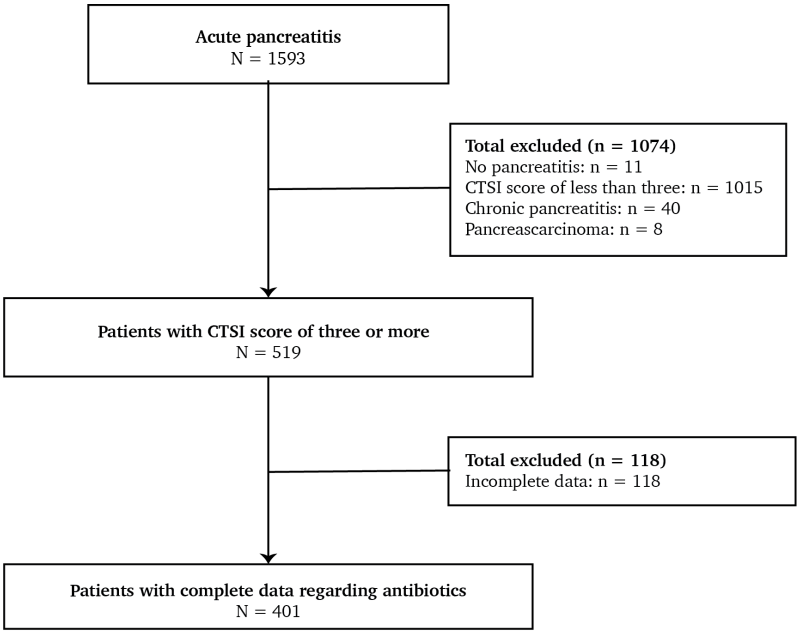

Figure 1 Inclusion flowchart
CTSI indicates *computed tomography severity index*

Table 1 Clinical characteristics in 401 patients with necrotizing pancreatitis

	Overall, N = 401
Age (y)	59 (48 – 69)
Male sex	244 (61)
Etiology	
Biliary	187 (47)
Alcohol	61 (15)
Post-ERCP	43 (11)
Idiopathic	64 (16)
Other	46 (11)
Medical history	
Cardiovascular	174 (43)
Pulmonary	53 (13)
Chronic renal	17 (4)
Diabetes mellitus	47 (12)
ASA[a]	
I	133 (33)
II	176 (44)
III	78 (20)
IV	4 (1)
Smoking, yes[b]	83 (21)
Alcohol use[c]	192 (65)
BMI[d]	28.3 (24.8 – 31.6)
Laboratory values*	
Leucocytes[e] (10^9/l)	17.8 (13.9 – 22.2)
CRP[f] (mg/l)	288 (191 – 352)
Imaging severity	
CT severity index[g]	6 (4 – 8)
Parenchymal necrosis	172 (67)
Pattern parenchymal necrosis[h]	
Right	4 (2)
Left	14 (8)
Central	78 (45)
Subtotal	27 (16)
Diffuse	47 (27)
Extent of necrosis[i]	
<30%	91 (23)
30-50%	37 (9)
>50%	43 (11)
Follow-up (m)	46 (28 – 66)

Data are presented as n (%) or median (interquartile range: P25-P75).
*Highest value within 48 hours after admission.
Missing patients: a=10, b=148, c=107, d=263, e=39, f=37, g=146, h=144, i=144.
ERCP *indicates endoscopic retrograde cholangiopancreatography;* ASA, *American Society of Anesthesiologists;* BMI, *body mass index;* CRP, *c-reactive protein;* CT, *computed tomography*

Table 2 Pancreatic interventions and clinical outcomes in 401 patients with necrotizing pancreatitis

	Overall, N = 401
Clinical outcomes	
Death pancreatitis related	28 (7%)
Hospital stay length, overall	44 (20 – 79)
Initial	23 (13 – 51)
Readmission	259 (65%)
Length hospital stay readmission	20 (7 – 43)
Infected necrosis	198 (49%)
Timing infected necrosis after admission	29 (19 – 47)
Gas configurations on CT	34 (14%)
Positive pancreatic culture	111 (46%)
Both gas configurations and positive pancreatic culture	53 (22%)
ICU-admission	157 (39%)
Length of ICU-stay	12 (4 – 35)
Organ failure	124 (31%)
Transient SOF	24 (21%)
Persistent SOF	84 (72%)
Transient MOF	14 (12%)
Persistent MOF	63 (54%)
Extra pancreatic infections before IPN or pancreatic intervention	
Pneumonia	74 (18%)
Urinary tract infection	73 (18%)
Interventions	
Pancreatic intervention or FNA	204 (51%)
Percutaneous catheter drainage	119 (60%)
No. of PCD	3 (1 – 5)
Endoscopic transluminal drainage	121 (61%)
No. of ETD	1 (1 – 1)
Necrosectomy	93 (47%)
ETN	58 (29%)
No. of ETN	2 (1 – 4)
Surgical necrosectomy	41 (21%)
No. of SN	1 (1 – 2)
Need for additional intervention	150 (75%)
Total number of pancreatic interventions for IPN	3 (2 – 5)

Data are presented as n (%) or median (interquartile range: P25-P75).
CT indicates *computed tomography*; ICU, *intensive care unit;* SOF, *single organ failure;* MOF, *multiple organ failure;* IPN, *infected pancreatic necrosis;* FNA, *fine needle aspiration;* PCD, *percutaneous catheter drainage;* ETD, *endoscopic transluminal drainage,* ETN, *endoscopic transluminal necrosectomy;* SN, *surgical necrosectomy*

Antibiotics were started in 321 patients (80%), after a median of 5 days (P25-P75: 1-13) following admission. At the start of antibiotic treatment (ie, for all indications), 221 of the 321 patients (69%) did not have a proven infection. Of these patients, 154/221 (70%) eventually developed an infection after a median of 10 (IQR 3–29) days following the start of antibiotics. Infected necrosis was the most common first proven infection following initiation of antibiotics (n=92, 60%). In 251 of 321 patients (63%), antibiotics were started within 14 days following admission, with no proven infection in 178 (71%) patients. In those first 14 days, pneumonia was the most common proven infection (n=21, 30%). The median duration of antibiotic use was 27 days (P25-P75: 15-48). Indications at the different time points for starting antibiotics in the disease course are given in Table 3.

Antifungals were started in 74 of 401 patients (23%) after a median of 33 days (P25-P75: 19-51), 8 of the 74 (11%) had no proven fungal infection. In the 66 (89%) patients with a proven fungal infection, antifungals were most often started for a yeast-positive pancreatic culture (n=47, 71%). The median duration of antifungals was 15 days (P25-P75: 7-24). Information on Clostridioides difficile is provided in Supplementary Text S5.

Infected necrosis and antimicrobial therapy

Overall, in 260 of 401 patients (65%), antimicrobial therapy was administered for either suspected or proven infected necrosis after a median of 17 days (P25-P75: 8-29) following admission. Meropenem was the most prescribed antibiotic (n= 76, 29%), followed by cefuroxime (n=43, 17%) (Table S6). Infected necrosis was proven in 198 of 401 patients (49%) after a median of 29 days (P25-P75: 19-47). In 179 of the 198 (90%) patients, antibiotics were started for a median duration of 11 days (P25-P75: 6-19) at a median of 20 days (P25-P75: 9-39) before confirmation of infected necrosis; 125 of the 179 (70%) patients received broad-spectrum antibiotics. A total of 29 of 198 patients (15%) with proven infected necrosis were treated with antibiotics alone and did not undergo an invasive intervention.

An FNA or pancreatic intervention was performed in 204 patients (51%). A pancreatic culture was obtained in 176 of these 204 patients (86%). In 165 of the 204 patients (66%), the pancreatic culture was obtained during the initial intervention. Of these, 128 (78%) received empirical antibiotics at the time of culturing, and 102 of the 128 (80%) received antibiotics for more than 24 hours before culturing (Supplementary Table S7). In 62 of the 128 patients (48%), the micro-organisms were either partially (n=24, 39%) or completely unsusceptible (n= 38, 61%) to the antibiotics that were started empirically. Broad-spectrum antibiotics, as recommended in the current guidelines, were administered in 55

Table 3 Indications for antimicrobial therapy in 401 patients with necrotizing pancreatitis

	Antibiotics				Antifungal
	First N = 321 (80%)	First <7 days after admission N = 197 (62%)	First <14 days after admission N = 251 (78%)	Before diagnosis IPN N = 179 (91%)	First N = 74 (23%)
No proven infection	*221 (69)*	*148 (75)*	*178 (71)*	*129 (72)*	*8 (11%)*
Fever e.c.i.	68 (30)	61 (41)	64 (36)	41 (32)	-
Suspected infected pancreatic necrosis	108 (48)	46 (31)	70 (39)	70 (54)	-
Suspected pneumonia	29 (13)	23 (16)	27 (15)	9 (7)	-
Suspected cholangitis	16 (7)	14 (9)	15 (8)	6 (5)	-
Suspected cholecystitis	1 (0.4)	1 (1)	1 (1)	1 (1)	-
Suspected urinary tract infection	1 (0.4)	1 (1)	1 (1)	-	-
Prophylactic during procedure	2 (1)	2 (1)	2 (1)	2 (2)	-
Broad coverage of potential yeast	NA	NA	NA	NA	8 (100)
Proven infection	*100 (31)*	*49 (25)*	*73 (29)*	*50 (28)*	*66 (89)*
Infected pancreatic necrosis	24 (24)	4 (8)	9 (13)	11 (22)	47 (75)
Pneumonia	24 (25)	16 (33)	21 (30)	16 (32)	5 (8)
Cholangitis	13 (14)	12 (25)	12 (17)	4 (8)	-
Cholecystitis	3 (3)	3 (6)	3 (4)	2 (4)	-
Urinary tract infection	17 (18)	6 (12)	13 (18)	8 (16)	-
Other	19 (19)[a]	8 (8)[b]	8 (11)[c]	3 (6)[d]	14 (17)[e]

Data are presented as n (%).
[a]Other: phlebitis n=4, parotitis n=3, line infection n=3, spleen abscess n=1, clostridium difficile infection n=1, secondary peritonitis due to duodenal perforation n=2, gastric perforation n=1, infected ascites n=1, bacteremia e.c.i. n=3.
[b]Other: phlebitis n = 2, parotitis n = 2, line infection n=1, spleen abscess n=1, secondary peritonitis due to duodenal perforation n=1, gastric perforation n=1.
[c]Other: phlebitis n = 4, parotitis n = 3, line infection n=2, spleen abscess n=1, secondary peritonitis due to duodenal perforation n=2, gastric perforation n=1, bacteremia e.c.i. n=2.
[d]Other: phlebitis n=3, parotitis n=3, line infection n=2, Clostridioides difficile n=1
[e]Other: bacteremia n=5, candida esophagitis n=7, candida in sputum n=5, line infection n=2
IPN indicates *infected pancreatic necrosis;* NA, *not applicable*

of the 62 patients (89%). This was comparable to the group of patients in which the micro-organisms were susceptible to the antibiotics (n= 55 (78%); P= 0.96). Enterococcus spp, specifically Enterococcus Faecium, was more often found in patients in whom the micro-organisms were (partially) unsusceptible (P=0.03) (Table S8). In these patients, antibiotics were adjusted according to the antibiotic susceptibility profile for 53 patients (85%), with no adjustments made for the remaining 9 patients (15%).

Micro-organisms identified in pancreatic samples

An FNA was performed in 41 of 401 patients (10%), with positive results in 31 of 41 patients (76%). A follow-up culture was obtained from the first pancreatic intervention in 23 of 31 patients (74%), with similar micro-organisms identified as in the FNA in 11 cultures (48%). Between FNA and the first pancreatic intervention, 17 of the 23 patients (74%) received antimicrobial therapy for a median of 13 days (P25-P75: 4 -17).

Overall, the culture was positive at least one time during the study period in 164 of the 176 patients (93%) in whom a pancreatic sample was obtained. In 147 of 176 patients (80%), cultures were obtained within 24 hours after invasive pancreatic intervention (Supplementary Table S9). Cultures were polymicrobial in 75 of 146 patients (51%). Gram-negative bacteria were isolated in 91 of 146 patients (62%), with Escherichia coli most often reported (n= 48, 33%). Gram-positive bacteria were isolated in 100 patients (68%), with E faecium (n=47, 32%) most often reported. Yeast were found in 30 patients (20%), with Candida albicans (n=22) most often reported. In 3 patients (2%), multidrug- resistant bacteria were found: ESBL-E (n= 2) and tobramycin and ciprofloxacin-resistant Morganella spp (n= 1).

Additional pancreatic intervention was performed in 150 of the 204 patients (74%) after a median of 11 days (P25-P75: 6-18) following the first intervention. In 130 of these 150 patients (87%), antimicrobial therapy was administered between the first and second intervention for a median of 6 days (P25-P75: 3-10). The reported micro-organisms in the cultures of the repeated intervention are described in Supplementary Table S10. A substantial increase in the presence of multidrug-resistant bacteria [most often ESBL (n= 5, 56%) and yeast was identified (n= 9, 14%) and n=17 (27%), respectively].

Clinical associations of antibiotics and micro-organisms

Univariate comparisons of clinical outcomes and interventions are provided in Supplementary Table S11.

The duration of antibiotic therapy overall and before a pancreatic culture was associated with the finding of Enterococcus spp (adjusted OR 1.08 (95%

CI 1.03-1.16; P= 0.01 and adjusted OR 1.01 (95% CI 1.00-1.02; P=0.04)). The finding of Enterococcus spp in the first pancreatic culture was associated with a higher rate of new or persistent organ failure (adjusted OR 3.68 (95% CI 1.61-8.79; P<0.01). Higher mortality rates were associated with pancreatic infections with Enterococcus spp, isolated in either the initial or repeat pancreatic culture (adjusted OR 5.78 (95% CI 1.46-38.73; P= 0.03) and adjusted OR 4.47 (95% CI 1.40 – 1.724; P=0.02)). Covariates included in the generalized linear models are provided in Supplementary Table S4.

DISCUSSION

We found that antibiotics are started in a large proportion of patients with necrotizing pancreatitis, often without a proven infection. In patients with infected necrosis, half of the identified micro-organisms were partially or not at all susceptible to the empirically started antibiotics. The prolonged duration of antibiotics was associated with more Enterococcus spp as a cultured pathogen, while the presence of Enterococcus spp in pancreatic tissue was associated with increased organ failure and mortality.

In line with previous studies,[10–13] antibiotics are still widely and inconsistently administered early in the disease course (80%) in contradiction to current guidelines.[2–4] The drawback of these studies is that they are either small and retrospective[11,13] or based solely on questionnaires rather than clinical data.[10,12] In addition, all the studies suffer from a lack of current data, with the most recent data dating from 2013.[12] Nevertheless, our findings show that clinical practices regarding the administration of antibiotics have not been improved since the early 2000s. This continues overuse and misuse of antibiotics and the associated avoidable, negative patient outcomes and underlines the importance of bringing these findings to the forefront.

In a similar vein, antimicrobial therapy is not indicated for SIRS without a proven infection (generally <14 d after the onset of disease)[1]; however, three-quarters of the patients received antimicrobial therapy within this time frame. This is presumably influenced by the challenges to clinically distinguish between SIRS and sepsis and the lack of knowledge regarding the timing of infections in necrotizing pancreatitis. These challenges further highlight the need for more accurate tools to accurately distinguish between inflammation and infection, which will inform when to withhold antibiotic treatment.

In line with previous research, our study shows gastrointestinal microbiota, particularly E. faecium and E. coli,[19] dominate the pancreatic cultures. Although carbapenems, specifically meropenem, were most frequently used as the empirical

antibiotic when infected necrosis was suspected, E. faecium – which is intrinsically not susceptible to carbapenems – was 1 of the most frequently isolated micro-organisms. Since Enterococcus spp and fungi are generally not susceptible to the recommended empirical broad-spectrum antibiotics, it is likely that there is ongoing migration of gastrointestinal micro-organisms during antibiotic treatment. As a result, empirical therapy is likely insufficient to treat those patients and therefore cannot be treated with antibiotics alone. We also found an increased rate of organ failure and mortality in patients infected with Enterococcus spp, further underlining the potential benefit of targeted antibiotic treatment. In comparative literature, enterococcal bacteraemia was also associated with increased mortality rates.[20,21] One study found inappropriate antibiotic therapy to be an independent risk factor for mortality in enterococcal bacteraemia.[22] However, these findings should be interpreted with caution. Despite performing multivariate analyses, it remains unclear whether prolonged antibiotic usage and subsequently potential organ failure and mortality, can be prevented in these complex patients. Furthermore, antibiotic selective pressure may explain these results: prolonged treatment leads to the selection of opportunistic pathogens such as Enterococcus spp. Nevertheless, our findings suggest that for patients with suspected infected necrosis, obtaining early, multiple, and repeat cultures from pancreatic necrosis to adjust empirical antimicrobial therapy should be considered instead of treating the blind with a wide range of antibiotics. Furthermore, empirical coverage of Enterococcus could play a potential role in antibiotic stewardship and future research.

Based on the first culture, only half (50%) of patients received adequate antimicrobial therapy. The lack of adequate therapy can be explained by previous treatment with antibiotics that treat the sensitive pathogens. Furthermore, it remains unknown if every identified micro-organism is clinically relevant. Since all patients underwent pancreatic intervention due to clinical stagnation or clinical deterioration, it seems plausible that the untreated pathogens are clinically relevant and therefore should be treated.

Culture-based antimicrobial therapy could potentially increase the number of patients who can be treated without invasive interventions and reduce the severity of clinical outcomes due to suboptimally treated micro-organisms. While we found that 15% of the patients could be treated with antibiotics alone, the POINTER trial showed that 35% of the patients in the postponed drainage group could be treated with antibiotics alone, without drainage.[23] This difference could be explained by the design and focus of the POINTER trial, in which all patients with infected necrosis were closely prospectively monitored on a daily basis and randomized when possible, compared with prospectively monitoring once or twice a week in our cohort. In daily clinical practice, however, it is common and

according to the guidelines to immediately schedule a drainage procedure in case of infected necrosis. However, in the POINTER trial, the effect of antibiotics was awaited, given the patients a chance to recover before the drainage procedure. Furthermore, targeted antibiotic therapy was started in a subset of patients based on FNA. Routine FNA could be a potential solution to prevent 'blind' antibiotic treatment, an approach currently discouraged by the guidelines.[2] In our study, half of the patients' FNA culture results differed from the subsequent culture following the pancreatic intervention; this result may be explained either by the growth of new micro-organisms under antimicrobial therapy or by only a limited part of the collection sampled through FNA. This emphasizes the importance of FNAs in multiple locations of the collection and the importance of obtaining cultures during each pancreatic intervention.

As compared with the current literature, the incidence of multidrug-resistant bacteria in the first pancreatic tissue sample was relatively low.[24] This may be explained by the restrictive antibiotic policies in the Netherlands. However, an increase in the presence of multidrug-resistant bacteria and yeast was found in repeat pancreatic cultures. This result is worrisome, particularly for countries with less restrictive antibiotic policies, as (1) multidrug-resistant bacteria and yeast infections are associated with prolonged hospitalization and poor prognosis[25–31] and (2) antibiotic resistance, the most commonly used antibiotics for infected necrosis are gradually losing their effectiveness.[8] If found in the cultures, empirical fungal therapy and treatment of the yeast should be potentially considered. Notably, the current national guidelines only recommend consideration of empirical fungal therapy in selected individual cases.[32]

The results of his study should be interpreted in light of some limitations. Firstly, this is a post-hoc analysis of prospectively collected data. Although all data has been carefully collected and evaluated, a part of the data regarding antimicrobial therapy was retrospectively collected from electronic records. Secondly, the percentage of patients with infected necrosis in our cohort was relatively high as compared with the literature.[33,34] This could be explained by our focus on several prospective studies on invasive intervention in patients with infected necrosis during the study period.[14] Thirdly, data from the Netherlands, a country with low antibiotic resistance may not be fully generalizable to countries with higher levels of antibiotic resistance.[35] Strengths of this study include the fact that this is the first multicenter study on the whole spectrum of antimicrobial therapy and its clinical impact in a large sample size of patients with acute necrotizing pancreatitis in recent real-world clinical practice. Nevertheless, even in the Netherlands, where care for pancreatitis patients is to a great extent centrally organized within the Dutch Pancreatitis Study Group, there remains meaningful opportunity to improve in the use of antibiotics. We can extrapolate

that there is probably significant potential to improve the use of antibiotics in many other countries with similar healthcare organizations. As mentioned earlier, this magnitude of the opportunity underlines the importance to make the current guidelines and recommendations regarding antibiotic use known to all of those who treat patients with acute pancreatitis. This can be achieved via presentations at national and international conferences and by implementing stricter antibiotic policy regulations in hospitals (e.g., establish one responsible department).

In conclusion, this study shows the current extensive use of antibiotics in patients with acute necrotizing pancreatitis early in the disease course, when infected necrosis rarely occurs. Half of the patients with infected necrosis received inappropriate empiric antimicrobial treatment. Our findings emphasize the need for clear guidelines the use of antimicrobial resources and diagnostic testing (i.e., FNA), with a potential role for empirical coverage of Enterococcus and yeast infections guided by antibiotic stewardships. Furthermore, prospective observational studies and large, pragmatic randomized trials are needed to define more clear indications, timing, and duration of antibiotic treatment in patients with both sterile and infected acute necrotizing pancreatitis.

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SUPPLEMENTARY APPENDIX

Table S1 Definitions

Acute pancreatitis	According to the revised Atlanta classification. At least two out of three of the following criteria: 1) clinical presentation with abdominal pain, 2) serum amylase or lipase levels exceeding three times the upper limit of normal and/or 3) abdominal imaging confirmed diagnosis of acute pancreatitis
Pancreatic parenchymal necrosis	Diffuse or focal area(s) of non-enhancing pancreatic parenchyma as detected on contrast enhanced CT (CECT)
Extrapancreatic necrosis	Persistent peripancreatic fluid collections on CECT in the absence of pancreatic parenchymal non-enhancement
Documented infections	
Pneumonia	Clinical signs of pneumonia with a positive sputum culture
Urinary tract infection	Clinical signs of urinary tract infection with either a positive urine culture or a positive sediment
Cholecystitis	According to the 2018 Tokyo classification for acute cholecystitis (definite diagnosis: one item in A + one item in B+C): A. Local signs of inflammation: Murphys' sign or right upper quadrant mass, pain or tenderness B. Systemic signs of inflammation: – (1) fever, (2) elevated C reactive protein, (3) elevated white blood cell count C. Imaging findings characteristic of acute cholecystitis Cited from Yokoe et al.[1]
Cholangitis	Acute abdominal pain, serum bilirubin level greater than 40 μmol/L and/or a dilated CBD and/or choledocholithiasis on ultrasound, CT, endoscopic ultrasound or MRCP/MRI in combination with a body temperature greater than 38·5°C with chills of 39·0°C or higher regardless of chills and without an obvious other cause for fever, with or without a positive blood culture.
Phlebitis	A tender red area, which may feel hard, swollen and warm, around the intravenous insertion or injection site as seen by the treating clinician.
Parotitis	Inflammation of one or both parotid glands as seen by the treating clinician.
Infected necrosis	One of the following: a) gasconfigurations on contrast-enhanced CT or b) positive culture from either a fine needle aspiration or from a drainage procedure from the (peri)pancreatic collection/walled-off necrosis
Primary infected necrosis	The initial culture of the peripancreatic or pancreatic collection or necrosis was positive and no previous abdominal intervention (e.g. abdominal surgery with opening of the bursa omentalis)
Pancreas intervention	All interventions for (peri)pancreatic collections and/or necrosis (e.g. percutaneous catheter drainage, endoscopic transluminal drainage, surgical or endoscopic necrosectomy), without ascites drainage or decompression laparotomies
Repeat intervention	All pancreatic interventions after the initial pancreatic intervention
Organ failure	No organ failure is assumed in the absence of lab and/or information in the discharge letter and/or notes. Definitions are adapted from the Atlanta classification and the same as previously used in the PANTER[2] and TENSION[3] trial.
Cardiovascular	Systolic blood pressure < 90 mmHg despite adequate fluid resuscitation or need for vasopressor support
Pulmonary	PaO2 < 60 mmHg despite FiO2 30%, or the need for mechanical ventilation
Renal	Serum creatinine > 177 mmol/L after rehydration or need for hemofiltration or hemodialysis
Early organ failure	Occurrence of organ failure within the first seven days after admission

Table S1 Continued.

Multiple organ failure	Failure of 2 or more organ systems on the same day
Chronic pancreatitis	Defined according to the M-ANNHEIM[4] criteria

References:

1 Yokoe M, Hata J, Takada T, et al. Tokyo guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2018;25:41–54.

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Supplementary Text S2

For example, when for an *Enterobacter* species (spp) no beta-lactam antibiotics and no multi-drug resistance was reported that could indicate carbapenem resistance, we categorised it as susceptible to carbapenems.

Supplementary Text S3

Multidrug-resistant bacteria were defined as either *Enterobacterales* producing extended-spectrum beta-lactamases (ESBL-E), *Enterobacterales* producing carbapenemase, methicillin-resistant Staphylococcus aureus (MRSA), tobramycin and ciprofloxacin-resistant *Morganella* spp, multidrug-resistant *Pseudomonas aeruginosa,* multidrug-resistant *Acinetobacter baumanii* and VRE were collected from the medical records.

Table S4 Covariates included in the generalized linear model

Outcome	Covariates
Finding of *Enterococcus* spp in the first pancreatic culture	Age + male sex + duration of antibiotics prior to pancreatic culture + highest C-reactive protein in the first 48 hours after admission + presence of peri- and/or pancreatic necrosis + extent of parenchymal necrosis + occurrence of early organ failure
Finding of *Enterococcus* spp in all pancreatic cultures	Age + male sex + duration of all antibiotics given in the 6 months included in this study + highest C-reactive protein in the first 48 hours after admission + presence of peri- and/or pancreatic necrosis + extent of parenchymal necrosis + occurrence of early organ failure
New or persistent organ failure after the first positive culture	Age + male sex + presence of *Enterococcus* spp in pancreatic culture + presence of *Staphylococcus* spp in pancreatic culture + presence of *Streptococcus* spp in pancreatic culture + presence of *Enterobacterales* spp in pancreatic culture + presence of yeast in pancreatic culture + presence of peri- and/or pancreatic necrosis + ASA status of three
Mortality	Age + highest C-reactive protein in the first 48 hours after admission + presence of *Enterococcus* spp in either the first or repeat pancreatic culture

Supplementary Text S5

In 19 of 401 patients (5%), an infection with *Clostridioides difficile* occurred after a median of 62 days (P25-P75: 23-99) since admission. Except for one patient, all patients received antibiotics before diagnosis of *Clostridioides difficile* for a median of 24 days (P25-P75: 7-43) days.

Table S6 Type of antibiotics

	First antibiotic for the following indication	
	Overall, N = 321	**(Suspected) IPN[a], N = 260[b]**
Carbapenem		
Meronem	45 (14)	76 (29)
Imipenem	4 (1)	9 (3)
Imipenem/cilastatine	7 (2)	12 (5)
Cephalosporin		
Cefuroxime	66 (21)	43 (17)
3thrd generation cephalosporin		
Ceftriaxon	56 (18)	31 (12)
Cefotaxim	19 (6)	12 (5)
Penicillin		
Penicillin	-	1 (0.4)
Amoxicillin	13 (4)	7 (3)
Amoxicillin/Clavulanic acid	58 (18)	24 (9)
Piperacillin/Tazobactam	33 (10)	29 (11)
Flucloxacillin	10 (3)	7 (3)
Quinolone		
Ciprofloxacin	14 (4)	11 (4)
Norfloxacin	1 (0.3)	-
Glycopeptide		
Vancomycin	2 (0.6)	8 (3)
Teicoplanin	1 (0.3)	1 (0.4)
Aminoglycoside		
Gentamicin	20 (6)[c]	23 (9)[f]
Tobramycin	2 (0.6)	-
Sulfonamide		
Trimethoprim/sulfamethoxazole	1 (0.3)	1 (0.4)
Metronidazole	85 (27)[d]	69 (27)[g]
Other	7 (2)[e]	-

Data are presented as n (%). The percentages do not add up to 100% given that patients may have received multiple types of antibiotics. They may have also received multiple antibiotics from the same type of antibiotic treatment.

[a]Either clinically suspected or proven

[b]Missing in 1 patient.

[c]Gentamycin was always combined with another antibiotic: cefuroxime (n=4), ceftriaxone (n=2), amoxicillin/clavulanic acid (n=5), cefuroxime and metronidazole (n=5), cefotaxim and gentamycin (n=1), amoxicillin and gentamycin (n=1)

[d]Except for one patient, metronidazole was always combined with another antibiotic: cefuroxim (n=36), ceftriaxone (n=23), cefotaxim (n=6), cefuroxime and gentamycin (n=6), cefuroxime and other (n=1), ceftriaxone and flucloxacillin (n=1), amoxicillin (n=1), amoxicillin and gentamycin (n=1), ciprofloxacin (n=1), cefotaxim and ciprofloxacin (n=1), cefotaxim and gentamycin (n=1), flucloxacillin and ciprofloxacin (n=1), cefotaxim and ciprofloxacin (n=1), meronem and ceftriaxon (n=1), cefotaxim and amoxicillin/clavulanic acid (n=1)

[e]Other: nitrofurantoin n=6, erythromycin n=1.

[f]Except for two patients, gentamycin was always combined with another antibiotic: cefuroxime (n=3), ceftriaxone (n=4), amoxicillin/clavulanic acid (n=7), cefuroxime and metronidazole (n=5), cefotaxim and metronidazol (n=5), cefuroxime, amoxicillin, ciprofloxacin and metronidazole (n=1)

[g]Except for two patients, metronidazole was always combined with another antibiotic: cefuroxime (n=27), cefuroxime and gentamycin (n=5), ceftriaxone (n=18), ceftriaxone and penicillin (n=1), cefotaxim (n=5), cefotaxim and gentamycin (n=1), amoxicillin (n=1), amoxicillin/clavulanic acid (n=1), ciprofloxacin (n=1), vancomycin (n=1), cefotaxim and vancomycin (n=1), amoxicillin and ciprofloxacin (n=2)

IPN indicates *infected pancreatic necrosis*

Table S7 Antibiotics administered at time of culture in 126 patients

	Susceptible antibiotic			
	No, N = 62	**Yes, N = 64**	**Risk ratio (95% CI)**	***P***
Carbapenem	27 (44)	32 (52)	RR 1.19 (0.82 – 1.72)	0.47
Meronem	23	27		
Imipenem	2	1		
Imipenem/cilastatine	2	4		
Cephalosporin	18 (29)	16 (26)	RR 0.89 (0.50 – 1.58)	0.84
Cefuroxime	9	9		
3thrd generation cephalosporin	9 (15)	7 (11)	RR 0.78 (0.31 – 1.96)	0.79
Ceftriaxon	4	4		
Cefotaxim	5	3		
Penicillin	16 (26)	13 (21)	RR 0.81 (0.43 – 1.54)	0.67
Penicillin	1	-		
Amoxicillin	2	-		
Amoxicilline/Clavulanic acid	6	7		
Piperacillin/Tazobactam	6	6		
Flucloxacillin	1	-		
Quinolone	2 (3)	2 (3)	RR 1.00 (0.15 – 6.88)	1.00
Ciprofloxacin	2	2		
Glycopeptide	3 (5)	8 (13)	RR 2.67 (0.74 – 9.58)	0.21
Vancomycin	3	7		
Teicoplanin	-	1		
Aminoglycoside	4 (6)	10 (16)	RR 2.50 (0.83 – 7.55)	0.15
Gentamicin*	4[a]	9[d]		
Sulfonamide	-	2 (3)	NA	0.50
Trimethoprim/sulfamethoxazole	-	2		
Clindamycin*	1 (2)[b]	-	NA	1.00
Other	-	2		
Metronidazole*	12 (19)[c]	10 (16)[e]	RR 0.83 (0.39 – 1.79)	0.81
Combination of antibiotics	18 (29)	21 (34)	RR 1.17 (0.69 – 1.97)	0.70

Data are presented as n (%). Risk ratios are reported as relative risks.
*Clindamycin, gentamycin and metronidazole were always administered in combination with another antibiotic:
[a]Amoxicilline/clavulanic acid (n = 1), cefotaxim and metronidazole (n=1), cefuroxime and metronidazole (n=2).
[b]Ciprofloxacine (n=1)
[c]Flucloxacilline (n=1), amoxicilline (n=1), cefotaxim and gentamycin (n=1), ceftriaxone (n=2), cefuroxime and gentamycin (n=2), cefuroxime (n=5)
[d]Cefuroxime and ciprofloxacin (n=1), piperacillin/tazobactam and trimethoprim/sulfamethoxazole (n=1), amoxicilline/clavulanic acid (n=1), ceftriaxon (n=1), cefuroxime (n=1), cefuroxime and metronidazole (n=2), cefuroxime and vancomycin (n=1), meronem and vancomycine (n=1)
[e]Cefotaxim (n=1), ceftriaxone (n=1), ceftriaxone and vancomycin (n=1), cefuroxime (n=4), cefuroxime and gentamycin (n=2), meronem and ceftriaxone (n=1)
CI indicates *confidence interval*

Table S8 Frequency micro-organisms identified in 126 pancreatic tissue samples obtained under antibiotics

	Antibiotic sensitivity		
	No, N = 62	Yes, N = 64	*P*
Multi drug resistant bacteria	**3 (5)[a]**	**1 (2)[b]**	0.552
Polymicrobial	**40 (65)**	**28 (44)**	0.141
Gram-positive bacteria	**46 (74)**	**39 (61)**	0.151
Gram-positive bacteria only	**16 (26)**	**21 (33)**	0.841
Enterococcaceae	42	18	**0.002**
Enterococcus species (undefined)	*2*	*1*	
E. faecium	*32*	*14*	***0.029***
E. faecalis	*10*	*4*	*0.084*
E. avium	*1*	*1*	
E. hirae	*1*	*0*	
Staphylococcaceae	12	14	0.958
Staphylococcus species (undefined)	*8*	*7*	
S. aureus	*2*	*6*	
S. Hominis	*1*	*2*	
Coagulase-negative staphylococci	*8*	*0*	
Streptococcaceae	4	10	0.523
Streptococcus species (undefined)		*2*	
S. milleri	*1*	*4*	
S. oralis	*1*	*1*	
S. anginosus	*1*	*1*	
S. parasanguinis	*1*	*1*	
S. salivarius	*1*	*0*	
Group B streptococcus	*0*	*2*	
Lactobacillaceae	0	4	0.161
Lactobacillus species (undefined)	*0*	*3*	
Lactobacillus rhamnosus	*0*	*1*	
Gram-negative bacteria	**42 (68)**	**40 (63)**	0.711
Gram-negative bacteria only	**12 (19)**	**21 (33)**	0.098
Enterobacterales	32	30	0.959
Citrobacter species	*2*	*0*	
C. freundii	*1*	*3*	
Escherichia coli	*21*	*21*	*0.685*
Enterobacter cloacae	*4*	*2*	
E. aerogenes	*1*	*1*	
Klebsiella pneumoniae	*5*	*1*	
K. oxytoca	*2*	*2*	
Raoultella ornithinolytica	*0*	*2*	
Pseudomonadaceae	4	1	0.370
Pseudomonas aeruginosa	*3*	*1*	
P. oryzihabitans	*1*	*0*	

Table S8 Continued.

	Antibiotic sensitivity		
	No, N = 62	**Yes, N = 64**	***P***
Bacteroidaceae	2	1	0.554
Bacteroides species (undefined)	*1*	*0*	
B. fragilis	*1*	*1*	
Aeromonadaceae	2	0	0.253
Aeromonas species	*1*	*0*	
A. sobria	*1*	*0*	
Pasteurellaceae	1	3	0.842
Aggregatibacter aphrophilus	*1*	*0*	
Haemophilus parainfluenzae	*0*	*3*	
Xanthomonadaceae	3	0	0.160
Stenotrophomonas maltophilia	*3*	*0*	
Neisseriaceae	0	1	0.212
Eikenella corrodens	*1*	*0*	
Morganellaceae	6	4	0.961
Morganella morganii	*2*	*1*	
Proteus mirabilis	*3*	*3*	
P. vulgaris	*1*	*0*	
Prevotellaceae	0	2	0.327
Prevotella oris	*0*	*1*	
P. buccae	*0*	*2*	
P. melaninogenica	*1*	*0*	
Sphingomonadaceae	1	0	0.420
Sphingomonas paucimobilis	1	0	
Yeast	**15 (24)**	**12 (19)**	0.702
Yeast only	**4 (6)**	**2 (3)**	0.397
Yeast (undefined)	*3*	*1*	
Candida albicans	*8*	*12*	
C. glabrata	*5*	*5*	
C. Guilliemondii	*0*	*1*	

Data are presented as n (%). The percentages do not add up to 100% given that patients may have multiple microorganisms in one pancreatic tissue sample.
[a]Extended-spectrum beta-lactamases n=2, tobramycin and ciprofloxacin resistant *Morganella* species n=1
[b]Extended-spectrum beta-lactamases n=1

Table S9 Frequency micro-organisms identified in 147[a] pancreatic tissue samples

Multi drug resistant bacteria	**3 (2)[b]**
Polymicrobial	**75 (51)**
Gram-positive bacteria	**100 (68)**
Gram-positive bacteria only	**46 (31)**
Enterococcaceae	
Enterococcus species (undefined)	*2*
E. faecium	*47*
E. faecalis	*17*
E. avium	*2*
E. hirae	*1*
Staphylococcaceae	
Staphylococcus species (undefined)	*1*
S. aureus	*12*
Coagulase-negative staphylococci	*19[c]*
Streptococcaceae	
Streptococcus species (undefined)	*4*
S. mitis	*1*
S. milleri	*5*
S. oralis	*2*
S. anginosus	*5*
S. parasanguinis	*2*
S. salivarius	*3*
S. gordonii	*1*
Group B streptococcus	*2*
Lactobacillaceae	
Lactobacillus species (undefined)	*3*
Lactobacillus rhamnosus	*3*
Actinomyces species	1
Gram-negative bacteria	**91 (62)**
Gram-negative bacteria only	**38 (26)**
Enterobacterales	
Citrobacter species	*1*
C. freundii	*4*
Escherichia coli	*48*
Enterobacter cloacae	*8*
E. aerogenes	*2*
Klebsiella pneumoniae	*5*
K. oxytoca	*7*
Raoultella ornithinolytica	*2*
Pseudomonadaceae	
Pseudomonas aeruginosa	*4*
P. oryzihabitans	*1*

Table S9 Continued.

Bacteroidaceae	
Bacteroides species (undefined)	*2*
B. fragilis	*3*
B. thetaiotaomicron	*1*
Aeromonadaceae	
Aeromonas species	*1*
A. sobria	*1*
Pasteurellaceae	
Aggregatibacter aphrophilus	*1*
Haemophilus parainfluenzae	*3*
Xanthomonadaceae	
Stenotrophomonas maltophilia	*3*
Neisseriaceae	
Eikenella corrodens	*1*
Morganellaceae	
Morganella morganii	*3*
Proteus mirabilis	*6*
P. vulgaris	*1*
Prevotellaceae	
Prevotella oris	*1*
P. buccae	*3*
P. melaninogenica	*1*
Sphingomonadaceae	
Sphingomonas paucimobilis	1
Yeast	**30 (20)**
Yeast only	**7 (5)**
Yeast (undefined)	*3*
Candida albicans	*22*
C. glabrata	*9*

Data are presented as n (%). The percentages do not add up to 100% given that patients may have multiple microorganisms in one pancreatic tissue sample.
[a]Samples obtained from: fine needle aspiration (n=29, 20%), the first percutaneous catheter drain (n=60, 41%), a repeat percutaneous catheter drain (n=6, 4%), an endoscopic intervention (n = 48, 33%), surgical intervention (n=4, 3%).
[b]Extended-spectrum beta-lactamases n = 2, tobramycin and ciprofloxacin resistant *Morganella* species n = 1.
[c]S. Epidermidis (n=13), S. Haemolyticus (n=2), S. Hominis (n=3).

Table S10 Frequency new micro-organisms identified in 65 repeat pancreatic tissue samples obtained within 24 hours after intervention

Multi drug resistant bacteria	**9 (14)[a]**
Gram-positive bacteria	**48 (74)**
Enterococcaceae	
Enterococcus spp (undefined)	*1*
E. faecium	*17*
E. faecalis	*14*
E. avium	*1*
Staphylococcaceae	
Staphylococcus epidermidis	*8*
S. aureus	*5*
S. haemolyticus	*1*
Coagulase-negative staphylococci	*1*
Streptococcaceae	
Streptococcus spp (undefined)	*4*
S. constellatus	*2*
S. mitis	*1*
S. milleri	*4*
S. intermedius	*1*
S. anginosus	*3*
Group F streptococcus	*1*
Group G streptococcus	*1*
Lactobacillaceae	
Lactobacillus spp (undefined)	*4*
L. rhamnosus	*4*
Actinomycetaceae	
Actinomyces spp	1
A. odontolyticus	1
Veillonellaceae	
Veilonella parvula	1
V. atypica	1
Gram-positive bacteria undefined	2
Gram-negative bacteria	**47 (72)**
Enterobacteriaceae	
Citrobacter spp	*1*
C. freundii	*6*
C. kaarri	*1*
C. koseri	*1*
Escherichia coli	*16*
Enterobacter cloacae	*4*
Klebsiella pneumoniae	*5*
K. oxytoca	*7*
K. variicola	*1*

Table S10 Continued.

Pseudomonadaceae	
Pseudomonas aeruginosa	*6*
P. putida	*1*
Bacteroidaceae	
Bacteroides fragilis	*4*
B. vulgatus	*2*
B. uniformis	*1*
Parabacteroides distasonis	*1*
Pasteurellaceae	
Haemophilus parainfluenzae	*1*
Xanthomonadaceae	
Stenotrophomonas maltophilia	*1*
Morganellaceae	
Morganella morganii	*1*
Proteus mirabilis	*3*
Prevotellaceae	
Prevotella spp	*2*
P. oris	*1*
P. buccae	*2*
Fusobacteriaceae	
Fusobacterium	1
Alcaligenaceae	
Achromobacter species	1
Burkholderiaceae	
Burkholderia multivorans	1
Gram-negative bacteria undefined	1
Yeast	**17 (27)**
Candida albicans	*12*
C. glabrata	*5*
C. kruseri	*1*
C. parapsilosi	*1*
C. pelliculosa	*1*
C. tropicalis	*1*

Data are presented as n (%). The percentages do not add up to 100% given that patients may have multiple microorganisms in one pancreatic tissue sample.
[a]Extended-spectrum beta-lactamases n=5, *Enterobacterales* producing carbapenemase n=1, multidrug-resistant *Pseudomonas aeruginosa* n=3.
spp indicates *species*

Table S11 Comparison of clinical outcomes and interventions in 152 patients with different types of microorganisms in positive pancreatic cultures from initial and repeat interventions

	Enterococcae		P	Streptococcae		P
	No N = 71	Yes N = 81		No N = 121	Yes N = 31	
Clinical outcomes						
Death pancreatitis related	2 (3)	14 (17)	0.01	12 (10)	3 (10)	1.00
Readmission	56 (81)	56 (69)	0.13	86 (74)	25 (81)	0.49
LOS, readmission (d)	33 (21-56)	26 (10-63)	0.06	28 (14-58)	40 (22-73)	0.26
LOS, overall (d)	72 (52-119)	99 (71-148)	<0.01	87 (59-132)	75 (50-118)	0.12
LOS, initial (d)	37 (22-70)	80 (41-118)	<0.01	68 (35-112)	33 (17-65)	<0.01
ICU-admission	39 (57)	60 (74)	0.03	80 (68)	17 (55)	0.20
Length ICU-stay (d)	11 (7-31)	30 (7-66)	<0.01	25 (7-48)	11 (8-30)	0.08
Organ failure	28 (72)	51 (85)	0.01	64 (80)	12 (71)	0.11
Transient SOF	8 (29)	6 (12)	0.59	11 (17)	3 (25)	1.00
Persistent SOF	17 (61)	43 (84)	<0.01	50 (78)	8 (67)	0.10
Transient MOF	3 (11)	5 (10)	0.73	6 (9)	1 (8)	1.00
Persistent MOF	14 (50)	33 (65)	0.01	38 (59)	7 (58)	0.38
Extra pancreatic infections before IPN or pancreatic intervention						
Pneumonia	12 (17)	23 (28)	0.13	26 (22)	8 (26)	0.64
Urinary tract infection	11 (16)	19 (23)	0.31	24 (21)	7 (23)	0.81
Interventions						
PCD	44 (64)	54 (67)	0.73	79 (68)	17 (55)	0.21
No. of PCD	3 (2-4)	3 (2-5)	0.28	3 (2-5)	2 (2-3)	0.04
ETD	33 (48)	48 (59)	0.19	55 (47)	25 (81)	<0.01
No. of ETD	1 (1-1)	1 (1-1)	0.29	1 (1-2)	1 (1-1)	0.04
Necrosectomy	28 (41)	41 (51)	0.25	54 (46)	14 (45)	1.00
ETN	15 (54)	21 (51)	0.57	24 (44)	11 (79)	0.10
No. of ETN	2 (1-3)	3 (1-4)	0.45	2 (1-4)	2 (2-4)	0.09
SN	17 (61)	21 (51)	0.85	33 (61)	5 (36)	0.17
No. of SN	1 (1-1)	1 (1-2)	0.52	1 (1-2)	1 (1-2)	0.19
Need for add. intervention	49 (71)	70 (86)	0.03	95 (81)	22 (71)	0.22
No. pancreas interventions	3 (1-5)	4 (2-6)	0.02	3 (2-6)	3 (1-4)	0.29
Long-term complications						
Endocrine PI	19 (28)	36 (44)	0.04	46 (39)	8 (26)	0.21
Exocrine PI	20 (29)	40 (49)	0.01	46 (39)	13 (42)	0.84

Data are presented as n (%) or median (interquartile range: P25-P75).
ICU *indicates intensive care unit;* SOF, *single organ failure;* MOF, *multiple organ failure;* IPN, *infected pancreatic necrosis;* PCD, *percutaneous catheter drainage;* ETD, *endoscopic transgastric drainage;* ETN, *endoscopic transgastric necrosectomy;* SN, *surgical necrosectomy;* PI, *pancreatic insufficiency*

Staphylococcae			Enterobacteriaceae			Yeast		
No N = 109	Yes N = 43	P	No N = 60	Yes N = 92	*P*	No N = 106	Yes N = 46	*P*
12 (11)	3 (7)	0.55	8 (13)	7 (8)	0.26	11 (10)	5 (11)	1.00
77 (73)	34 (79)	0.53	41 (72)	71 (77)	0.56	78 (74)	36 (78)	0.68
24 (13-56)	44 (25-68)	0.09	25 (14-44)	37 (16-71)	0.22	32 (16-58)	27 (12-60)	0.77
81 (54-124)	94 (64-153)	0.24	75 (48-99)	102 (64-156)	<0.01	88 (55-131)	84 (59-124)	0.87
62 (34-104)	51 (24-112)	0.75	42 (28-76)	71 (33-119)	0.02	57 (30-100)	62 (31-114)	0.81
69 (65)	29 (67)	0.85	32 (56)	66 (72)	0.08	71 (67)	30 (65)	0.85
19 (7-45)	30 (8-73)	0.43	11 (7-39)	26 (7-51)	0.05	25 (8-50)	13 (5-43)	0.50
52 (76)	25 (86)	0.47	26 (81)	51 (77)	0.40	56 (79)	24 (80)	0.86
11 (21)	3 (12)	0.55	4 (15)	10 (20)	0.78	9 (16)	5 (21)	0.77
38 (73)	21 (84)	0.20	22 (85)	37 (73)	0.86	42 (75)	19 (79)	0.86
5 (10)	2 (8)	1.00	3 (12)	4 (8)	1.00	6 (11)	3 (13)	1.00
29 (56)	17 (68)	0.17	14 (54)	32 (63)	0.21	34 (61)	13 (54)	0.71
24 (23)	10 (23)	1.00	9 (16)	26 (28)	0.11	28 (26)	9 (20)	0.42
25 (24)	5 (12)	0.12	12 (21)	19 (21)	1.00	21 (20)	10 (22)	0.83
63 (60)	33 (77)	0.06	32 (56)	65 (71)	0.08	74 (70)	26 (57)	0.14
3 (2-5)	3 (2-5)	0.03	3 (1-5)	3 (2-5)	0.03	3 (2-5)	3 (2-5)	0.27
60 (57)	20 (47)	0.28	42 (74)	38 (41)	<0.01	48 (45)	33 (72)	<0.01
1 (1-1)	1 (1-1)	0.45	1 (1-1)	1 (1-1)	<0.01	1 (1-1)	1 (1-1)	0.01
50 (48)	17 (40)	0.47	25 (44)	43 (47)	0.74	47 (44)	23 (50)	0.60
25 (50)	10 (59)	1.00	17 (68)	18 (42)	0.17	20 (43)	16 (70)	0.04
3 (2-4)	2 (1-2)	0.79	2 (1-4)	2 (1-4)	0.16	2 (2-3)	2 (1-4)	0.04
27 (54)	10 (59)	1.00	11 (44)	27 (63)	0.18	32 (68)	7 (30)	0.046
1 (1-1)	1 (1-2)	0.93	1 (1-2)	1 (1-1)	0.21	1 (1-2)	1 (1-3)	0.07
80 (76)	37 (86)	0.27	43 (75)	75 (82)	0.41	81 (76)	40 (87)	0.19
3 (2-5)	4 (2-6)	0.12	2 (2-5)	4 (2-6)	0.16	3 (2-5)	3 (2-6)	0.42
36 (34)	19 (44)	0.27	19 (33)	36 (39)	0.49	38 (36)	18 (39)	0.72
40 (38)	20 (47)	0.36	21 (37)	39 (42)	0.61	36 (34)	24 (52)	0.046

PART II

LOCAL COMPLICATIONS OF NECROTIZING PANCREATITIS

PART II

CHAPTER IV

Diagnosis and treatment of pancreatic duct disruption or disconnection: *an international expert survey and case vignette study*

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ABSTRACT

Background
Pancreatic duct disruption or disconnection is a potentially severe complication of necrotizing pancreatitis. With no existing treatment guidelines, it is unclear whether there is any consensus among experts in clinical practice. We evaluated current expert opinion regarding the diagnosis and treatment of pancreatic duct disruption and disconnection in an international case vignette study.

Methods
An online case vignette survey was sent to 110 international expert pancreatologists. Expert selection was based on publications in the last 5 years and/or participation in development of IAP/APA and ESGE guidelines on acute pancreatitis. Consensus was defined as agreement by at least 75% of the experts.

Results
The response rate was 51% (n = 56). Forty-four experts (79%) obtained a MRI/MRCP and 52 experts (93%) measured amylase levels in percutaneous drain fluid to evaluate pancreatic duct integrity. The majority of experts favored endoscopic transluminal drainage for infected (peri)pancreatic necrosis and pancreatic duct disruption (84%, n = 45) or disconnection (88%, n = 43). Consensus was lacking regarding the treatment of patients with persistent percutaneous drain production, and with persistent sterile necrosis.

Conclusion
This international survey of experts demonstrates that there are many areas for which no consensus existed, providing clear focus for future investigation.

INTRODUCTION

Approximately 20% of patients with acute pancreatitis develop necrosis of the pancreatic parenchyma or extrapancreatic fat tissue.[1-3] Necrosis of the pancreatic parenchyma is frequently accompanied by loss of pancreatic duct integrity. As a result, the main pancreatic duct no longer communicates with the gastrointestinal tract, leading to leakage of pancreatic fluid in the surrounding tissues.[4,5] This phenomenon is also referred to as a disrupted or disconnected pancreatic duct and is thought to persist in approximately 10%–30% of patients with necrotizing pancreatitis.[4,6,7] Leakage of pancreatic fluid due to a disrupted or disconnected pancreatic duct causes several problems, such as persistent pancreatic fistulas, recurrent pancreatic fluid collections, and pancreatic ascites, which generally impedes the patient's recovery. Despite the complexity of this condition, there are currently no standardized guidelines on the diagnostic workup and treatment. It is also unclear whether there is consensus among expert pancreatologists in daily clinical practice. The aim of this study was to evaluate current expert opinion regarding the diagnosis and treatment of pancreatic duct disruption and disconnection following necrotizing pancreatitis to aid clinical decision making and to identify areas of future research.

METHODS

Study design

An international case vignette survey study among a multidisciplinary expert group of pancreatologists was performed. Experts were selected based on publications on pancreatic duct disruption and disconnection following necrotizing pancreatitis in the last five years, and/or participation in the development of the International Association of Pancreatology/American Pancreatic Association (IAP/APA) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines on acute pancreatitis.[2,8] Invitations were sent through e-mail in August 2019, followed by four weekly reminders. Additionally, targeted email reminders were sent in December 2019. The survey was administered via Research Electronic Data Capture (REDCap) and data was collected anonymously.

Survey design

The survey consisted of several demographical questions, including the experts' specialty, type of hospital, and working experience. Moreover, 6 general questions and 3 case vignettes with regards to diagnosis and treatment of disrupted or disconnected pancreatic duct were included in the survey (Supplementary

Appendix). The case vignettes addressed several clinical scenarios, but all concerned a 65-year old female patient, without significant co-morbidity, admitted with biliary necrotizing pancreatitis (Fig. 1). For each vignette, the experts were questioned on their preferred diagnostic modality and treatment strategy. The survey questions were developed by an international multidisciplinary writing committee, including gastroenterologists, surgeons and a radiologist. Questions were based on the results of two systematic reviews and the preliminary results of an (unpublished) prospective observational cohort study of the Dutch Pancreatitis Study Group.[9-11]

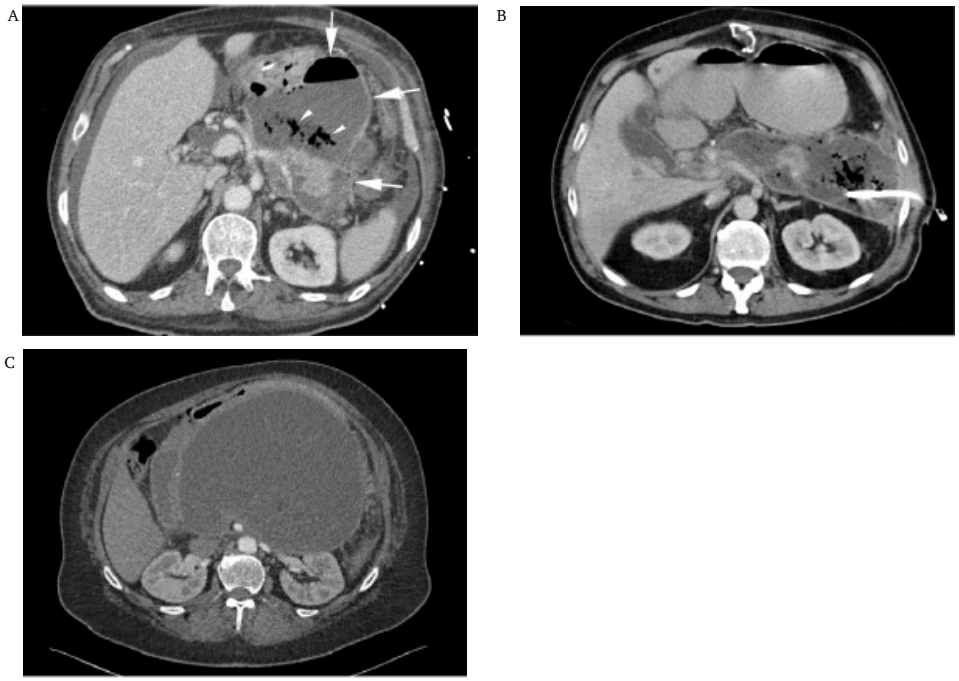

Figure 1 The case vignettes: clinical scenarios and imaging findings

Study definitions

Disruption of the pancreatic duct was predefined as a partial interruption of the pancreatic duct. Disconnection of the pancreatic duct was defined as a complete (circumferential) interruption of the pancreatic duct. Consensus was defined as agreement by at least 75% of the experts. Consensus statements were evaluated based on the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (Table 4).[12,13] Quality of evidence was categorized as high (level A), moderate (level B), low (level C), or very low (level D).

Statistical analysis

Descriptive data are presented as frequencies with percentages for categorical data. Continuous variables are summarized as mean with standard deviation (SD) or median with interquartile range (IQR) depending on normality of distribution. Subgroup analyses using Fisher's exact test for categorical variables were performed to compare treatment strategies of expert pancreatologists from different specialties. P-values <0.05 were considered statistically significant and all tests were two-sided. Statistical analysis was conducted using R version 3.5.1.

RESULTS

Expert profile

A total of 124 international expert pancreatologists were invited to participate in the survey (Fig. 2). Twelve experts were excluded because of incorrect contact details and 2 declined participation. A total of 56 international expert pancreatologists completed the survey. The response rate was 56/110 (51%): 27 surgeons (48%), 25 gastroenterologists (45%) and 4 radiologists (7%) participated (Table 1). Thirty-two (57%) were from Europe, 17 (30%) from North America, 3 (5%) from Asia, 3 (5%) from Oceania, and 1 (2%) from South America. The majority of experts (n = 49, 88%) worked in academic centers and 51 experts (91%) had over 10 years of experience in treating patients with necrotizing pancreatitis. Surgical experts had significantly longer experience treating patients with necrotizing pancreatitis (median > 20 years), as compared to the gastroenterologists (median 15–20 years) and radiologists (median 10–15 years; p = 0.047) (Supplementary Appendix Table 1).

Diagnosis

No consensus was reached on whether, in general, routine imaging should be performed to evaluate pancreatic duct integrity in patients with necrotizing pancreatitis. Imaging was obtained always by 20 (36%), usually by 15 (27%), sometimes by 17 (30%), and never by 4 experts (7%) (Table 2). There was also no agreement regarding the indication and best timing to assess a potential disrupted or disconnected pancreatic duct: 14 experts (25%) would evaluate pancreatic duct integrity before drainage of infected (peri)pancreatic necrosis; 36 experts (64%) in case of persistent percutaneous drain production; and 33 (59%) in case of persistent sterile (peri)pancreatic necrosis during follow-up. Once the decision was made to evaluate pancreatic duct integrity, 44 of 56 experts (79%) preferred magnetic resonance imaging (MRI) and/or magnetic resonance cholangiopancreatography (MRCP) (consensus statement 1, GRADE C; Table 4).

Moreover, 26 of these 44 experts (59%) considered a secretin-enhanced MRI/MRCP (always n = 1, usually n = 9, or sometimes n = 16). Seventeen experts (30%) preferred to evaluate pancreatic duct integrity by contrast-enhanced CT (CECT), 11 (20%) by endoscopic retrograde cholangiopancreatography (ERCP), and 3 (5%) by endoscopic ultrasound (EUS). Differences in approach between specialties are outlined in Supplementary Appendix Table 1.

Fifty-two experts (93%) indicated that they measure amylase levels in percutaneous drain fluid to evaluate pancreatic duct integrity (consensus statement 2, GRADE C): 26 always (46%), 12 usually (21%), and 14 sometimes (25%). There was no consensus on the most appropriate timing of amylase measurements: 15 experts preferred measurement during admission after drainage (29%), 13 during follow-up (25%), and 24 preferred both (46%).

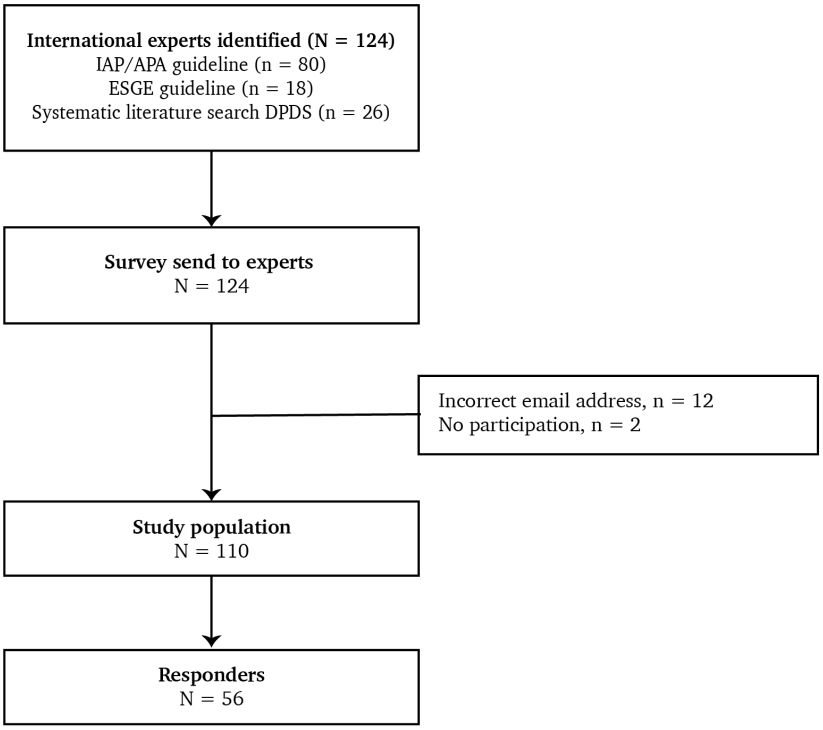

Figure 2 Identification and selection of international expert pancreatologists.
ESGE indicates *European Society of Gastrointestinal Endoscopy*; IAP/APA, *International Association of Pancreatology/American Pancreatic Association*

Table 1 Details of experts

Demographics	**N = 56**
Specialty	
Surgeon	27 (48)
Gastroenterologist	25 (45)
Radiologist	4 (7)
Continent	
Europe	32 (57)
North America	17 (30)
Asia	3 (5)
Oceania	3 (5)
South America	1 (2)
Type of hospital	
Academic	49 (88)
Non-academic	7 (12)
Experience in treating patients with necrotizing pancreatitis	
5-10 years	5 (9)
10-15 years	12 (21)
15-20 years	14 (25)
>20 years	25 (45)

Data are presented as n (%).

Table 2 Survey results: diagnostic approach

	N = 56
Do you evaluate pancreatic duct integrity in patients with necrotizing pancreatitis?	
Always	20 (36)
Usually	15 (27)
Sometimes	17 (30
Never	4 (7)
Which diagnostic modality do you perform to evaluate disrupted or disconnected pancreatic duct in patients with necrotizing pancreatitis?	
CT	17 (30)
MRI/MRCP	44 (79)
EUS	3 (5)
ERCP	11 (20)
Do you perform a secretin-enhanced MRI? (*n* = 44)	
Always	1 (2)
Usually	9 (21)
Sometimes	16 (36)
Never	18 (41)
Do you measure amylase levels in percutaneous drain fluid in patients with necrotizing pancreatitis?	
Always	26 (26)
Usually	12 (21)
Sometimes	14 (25)
Never	4 (7)

Table 2 Continued.

	N = 56
When do you perform amylase measurements in percutaneous drain fluid? (*n* = 52)	
During the initial admission	15 (29)
After the initial admission	13 (25)
Both	24 (46)

Data are presented as n (%).
CT indicates *computed tomography*; MRI, *magnetic resonance imaging*; MRCP, *magnetic resonance cholangiopancreatography*; EUS, *endoscopic ultrasound*; ERCP, *endoscopic retrograde cholangiopancreatography*

Treatment

Thirty experts (54%) pointed out that the presence of a (suspected) disrupted or disconnected pancreatic duct influences their preferred method of intervention for necrotizing pancreatitis, especially regarding the type of intervention, transluminal stent type and duration of stenting.

The results of the case vignettes are summarized in Table 3. For the first case vignette (patient A: infected necrosis and indication for drainage), the majority of experts preferred endoscopic transluminal drainage if duct disruption (84%, n = 47) or duct disconnection (88%, n = 49) is confirmed on imaging (consensus statement 3, GRADE C). The minority of experts simultaneously administered somatostatin analogues (5% in case of duct disruption, and 7% in case of disconnection). Only a few experts would combine endoscopic transluminal drainage with endoscopic transpapillary drainage for duct disruption (13%, n = 7) or duct disconnection (4%, n = 2).

There was no consensus on the preferred type of transluminal stent used for endoscopic transluminal drainage among the gastroenterologists: 56% of the gastroenterologists (n = 14) favored double pigtail plastic stents and 44% (n = 11) lumenapposing metal stents (LAMS). Most gastroenterologists (84%, n = 21) would retrieve transluminal stent(s) during follow-up, but 16 (76%) of them would first perform imaging to rule out a disrupted or disconnected pancreatic duct (consensus statement 4, GRADE D). Ten of 14 gastroenterologists (71%) that opted for double pigtail plastic stents would retrieve the stents during follow-up, in contrast to 4 gastroenterologists (29%) who would leave the stents in place. The gastroenterologists that preferred LAMS (44%, n = 11), would all remove the LAMS within 8 weeks after initial drainage.

For the second case vignette (patient B: infected necrosis with persistent drain output), 42 experts (75%) would perform an intervention if pancreatic duct disruption was located in the pancreatic head. Fourteen experts (25%) would treat such patient conservatively. There was also no consensus on the type of intervention: 20 experts (36%) preferred endoscopic transpapillary drainage,

19 experts (34%) preferred endoscopic transluminal drainage to internalize the external drain, and 3 experts (5%) surgical resection. If duct disruption was located in the pancreatic tail, 19 experts (34%) would treat the patient conservatively, and 37 experts (66%) would proceed to intervention. Nine experts (16%) favored endoscopic transpapillary drainage, 25 experts (45%) endoscopic transluminal drainage to internalize the external drain, and 3 experts (5%) distal pancreatectomy. Additionally, 5 experts (9%) would consider surgery at an earlier stage in younger and surgical fit patients, whereas 25 experts (45%) would consider surgery later in the disease course.

There was no consensus on the therapeutic approach presented in the third case vignette (patient C: asymptomatic patient with persistent sterile (peri) pancreatic necrosis during follow-up): 19 experts (34%) preferred conservative treatment whereas 37 experts (66%) would perform an intervention. Thirty-three experts (59%) preferred endoscopic transluminal drainage over other therapeutic options, for both pancreatic duct disruption and disconnection. Six of these experts (11%) would combine the procedure with endoscopic transpapillary stenting for pancreatic duct disruption and 3 experts (5%) for pancreatic duct disconnection.

Table 3 Case vignettes results: treatment approach

	Conservative treatment	*Somatostatin analogue*	*Endoscopic transpapillary drainage*	*Endoscopic transluminal drainage*	*Percutaneous catheter drainage*	*Surgical cystogastro- or jejunostomy*	*Surgical resection*
Infected (peri)pancreatic necrosis and need for drainage							
Disrupted pancreatic duct	-	3 (5)	9 (16)	47 (84)	10 (18)	1 (2)	-
Disconnected pancreatic duct	-	4 (7)	3 (5)	49 (88)	9 (16)	2 (5)	-
Infected (peri)pancreatic necrosis and persistent drain production							
Duct disruption in pancreatic head	14 (25)	-	20 (36)	*19 (43)*	-	-	3 (5)
Duct disruption in pancreatic tail	19 (34)	-	9 (16)	*25 (45)*	-	-	3 (5)
Persistent sterile (peri)pancreatic necrosis during follow-up*							
Disrupted pancreatic duct	*19 (34)*	1 (2)	8 (14)	33 (59)	2 (4)	1 (2)	-
Disconnected pancreatic duct	*19 (34)*	1 (2)	4 (11)	33 (59)	3 (5)	2 (4)	-

Data are presented as n (%).
*Combined treatment was possible, % percentage of experts (n = 56)

DISCUSSION

This international expert survey identifies a lack of expert consensus regarding the optimal diagnostic and treatment approach for patients with disrupted or disconnected pancreatic duct following necrotizing pancreatitis. The experts reached agreement in two important areas: 1) MRI/MRCP as the preferred diagnostic modality to evaluate pancreatic duct integrity; and 2) endoscopic transluminal drainage as the preferred intervention for patients with infected (peri)pancreatic necrosis and pancreatic duct disruption or disconnection.

In line with the survey results, (secretin-enhanced) MRI/MRCP is advised in current guidelines (Table 4).[8] The sensitivity of MRI/MRCP to evaluate pancreatic duct integrity is lower than the current reference standard ERCP, but with less risks of procedure-related complications.[14-17] Secretin stimulates the secretion of pancreatic juice, which dilates the pancreatic duct, and improves the diagnostic capabilities of MRCP.[14-16] Interestingly, in this survey, almost half of experts who preferred MRI/MRCP, never performed secretin-enhanced MRI/MRCP. Presumably, limited access to secretin and/or high(er) costs compared with 'standard' MRI/MRCP could have contributed to the experts' responses.

CECT and EUS were chosen by the minority of experts. Disrupted or disconnected pancreatic duct can be suspected on CECT, but has a wide reported sensitivity range (0–80%).[18,19] The role of EUS as diagnostic modality is unclear, and only evaluated in one prospective study in which pancreatic duct integrity was assessed during initial endoscopic transluminal drainage of walled-off necrosis.[20] Nevertheless, adequate visualization of the pancreatic duct by EUS depends on the endoscopists experience.

Table 4 Consensus statements on diagnosis and treatment

STATEMENT		AGREEMENT	GRADE
Diagnostics			
1.	MRI/MRCP for evaluation of pancreatic duct integrity in patients with necrotizing pancreatitis.	79%	C
2.	Amylase measurements in percutaneous drain fluid for evaluation of pancreatic duct integrity.	93%	C
Treatment			
1.	Endoscopic transluminal drainage for infected (peri)pancreatic necrosis and (suspicion of) disrupted or disconnection pancreatic duct.	88%	C
2.	Evaluation of pancreatic duct integrity prior transluminal stent removal.	76%	D

GRADE indicates *Grades of Recommendations, Assessment, Development, and Evaluation;* MRI, *magnetic resonance imaging;* MRCP, *magnetic resonance cholangiopancreatography.*

The majority of experts considered measuring amylase levels in percutaneous drain fluid for evaluation of pancreatic duct integrity. Overall, diagnostic accuracy of amylase-measurement in drain fluids is 65% (Table 4).[18,21-25] The combination of drain output and amylase level contributes to early recognition and treatment of pancreaticocutaneous fistula. Based on the volume of amylase in percutaneous drain fluid, one cannot differentiate between partial disruption or complete disconnection of the pancreatic duct. In this survey, the most appropriate time of measuring amylase levels remained unclear. Also, there is no clearly defined cutoff level of drain output. A recent retrospective study, however, demonstrated that patients with 'low output' pancreaticocutaneous fistula (<200 ml/day) were successfully treated conservatively, with spontaneous closure of the fistula within 3 months.[26]

According to the survey, endoscopic transluminal drainage was the experts' first preferred treatment strategy for patients with infected (peri)pancreatic necrosis and a confirmed disrupted or disconnected pancreatic duct. A consistency in preference over disease stage, as presented in the different cases in the survey, was nevertheless not found. To the extent that expert preference is aligned with treatment success, the survey results are in line with a recent systematic review, which reported that endoscopic transluminal drainage had the highest pooled success rate of 92%.[9,20,27-29] In these studies, double plastic pigtails were used and left in situ for a long or even indefinite period of time.[20,28,29] Previous research demonstrated a decreased recurrence rate of pancreatic fluid collections when double plastic pigtails are either left in situ, or exchanged in case of LAMS.[30] Surprisingly, the majority of experts indicated to remove transluminal stents, but only after they evaluated pancreatic duct integrity on imaging.

Based on the available literature and the survey results, several steps for patient care and topics for future research were identified (Fig. 3). Because the presence of a disrupted or disconnected pancreatic could influence the route of drainage and type of stent, evaluation of pancreatic duct integrity before drainage may be considered. MRI/MRCP, if CECT cannot provide a definite answer, seems justified as the first step. Regarding interventions, endoscopic transluminal drainage in the case of (suspected) pancreatic duct disruption or disconnection in a patient with infected (peri)pancreatic necrosis seems to be preferred. If (peri) pancreatic necrosis cannot be reached endoscopically, or already has been drained percutaneously, it is recommended to measure drain output and amylase levels to monitor the development of pancreaticocutaneous fistula. Conservative treatment of patients with low output pancreaticocuteanous fistula seems indicated. Long-term indwelling or transluminal double pigtails stents is suggested in the case of a proven disrupted or disconnected pancreatic duct.

This study has several limitations. First, the 51% response rate is limited,

compared to previous similar expert surveys.[31,32] The topic of this survey represents a niche and limited studied aspect of acute pancreatitis, which might explain the lower response rate.

Second, while we could assert the experts' preferences over the different disease stages as presented in the case vignettes, our survey design did not allow us to evaluate the experts' preference for cases without documented pancreatic duct disruption or disconnection. The survey findings only allowed us to draw conclusions on treatment preferences for (peri)pancreatic necrosis in the presence of documented pancreatic duct disruption or disconnection. Therefore, it is unknown whether experts would have adjusted initial treatment for (peri) pancreatic necrosis based on pancreatic duct integrity. Because endoscopic transluminal drainage has become increasingly popular in recent years as the first step for (peri)pancreatic necrosis, it may be possible that endoscopic transluminal drainage is also the preferred choice regardless of pancreatic duct integrity.[33,34]

Additionally, it was difficult to address all clinical scenarios concerning a disrupted or disconnected pancreatic duct in a short survey and the case vignettes. It is a heterogeneous disease, clinically characterized by different manifestations (e.g., recurrent pancreatic fluid collections, pancreaticocutaneous, gastrointestinal or pleural fistula). As a result, the clinical situations that were considered most relevant, in particular pancreatic duct disruption or disconnection in the presence of (peri)pancreatic necrosis, were evaluated in the survey. Also, the survey results did not indicate a clear difference in treatment approach between management for a partial disrupted and complete disconnected pancreatic duct. Moreover, the survey did not evaluate the treatment of patients with persistent, treatment refractory disrupted or disconnected pancreatic duct and the role of surgery in such cases. Last, treatment of patients with gastro-intestinal or pleural fistulas was not addressed in the survey.

Consequently, expert opinion on less common, but not less important, clinical manifestations of a disrupted or disconnected pancreatic duct remained unclear. To investigate the incidence and clinical consequences of disrupted or disconnected pancreatic duct and pancreatic fistula, the POLAR study, a prospective multicenter study (Netherlands Trial Register, NL8123), was recently initiated. In the study, patients with parenchymal necrosis will undergo a standardized diagnostic work-up according to the current guidelines, including a secretin-enhanced MRCP. The aim of the POLAR study is to develop a personalized best practice algorithm for patients with pancreatic disruption or disconnection following necrotizing pancreatitis. Other areas of future research should include the optimal management of patients with persistent drain production or with persistent sterile necrosis, the choice of transluminal stent (metal or plastic) in cases of a

disrupted or disconnected pancreatic duct, and less common complications such as gastro-intestinal or pleural fistulas.

In conclusion, this international survey identified a clinically relevant lack of expert consensus on diagnosing and treating pancreatic duct disruption or disconnection in patients with necrotizing pancreatitis. Nonetheless, MRI/MRCP was the preferred diagnostic, and endoscopic transluminal drainage the preferred intervention for patients with infected necrotizing pancreatitis and pancreatic duct disruption or disconnection.

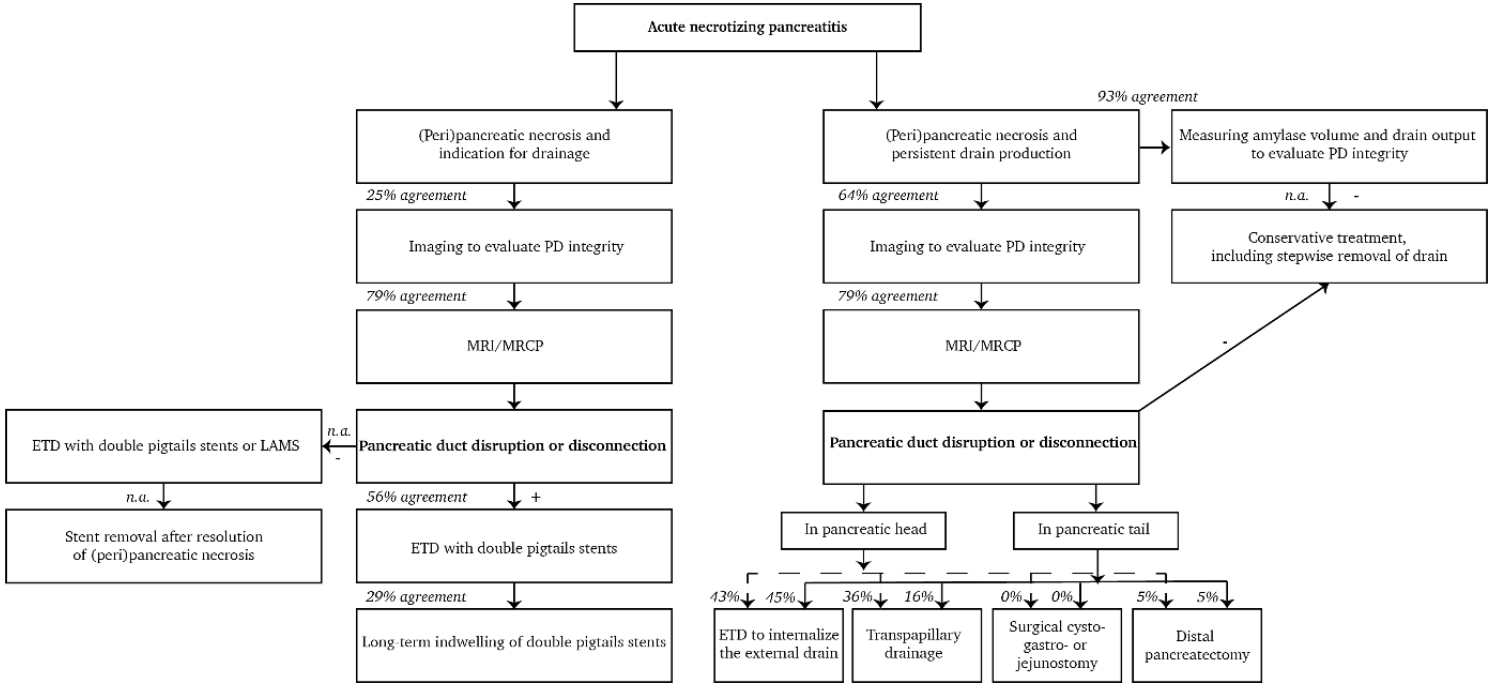

Figure 3 Summary of potential steps for patient care and topics for future research.
ETD indicates *endoscopic transluminal drainage*; LAMS, *lumenapposing metal stents*; n.a. data not analyzed in the survey; % percentage of expert agreement (n = 56)

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PART II

CHAPTER V

Various modalities accurate in diagnosing 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. Study quality was assessed, with proportionally divided high and low risk of bias and low applicability concerns in 75% of the studies. 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.

Conclusion
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.[1-3] The disease course is generally mild. Around 20% of patients, however, develop necrosis of the pancreatic or peripancreatic tissue.[4-7] This necrosis of the pancreatic parenchyma results in loss of viable pancreatic tissue and potentially loss of integrity of the pancreatic duct.[8] 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, or pancreatic fistula including external fistulas following percutaneous catheter drainage.[9-15] This causes a major burden on the patient's quality of life and is associated with high healthcare resource utilization.[8,16-18]

The diagnosis of a disrupted or disconnected pancreatic duct syndrome is not standardized.[19,20] 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.[8,13,17,21-29] 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.[30,31]

Because treatment success is related to the degree and location of the disruption,[28,32,33] a timely and accurate diagnosis of a pancreatic duct disconnection and disruption is expected to facilitate treatment decisions. Evidence-based guidelines are variable regarding the preferred method and timing of diagnosing a disrupted or disconnected pancreatic duct syndrome in acute necrotizing pancreatitis and clear guidelines are missing.[19,20,34,35]

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.[36] A systematic search was performed in PubMed, Embase and Cochrane Library from database inception until April 28, 2020. The Embase search was limited

to Embase sources and restricted to publication types (inclusion of articles and systematic reviews). Grey literature (i.e., conference abstracts, editorials, and dissertations) was excluded. 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 Appendix Table 1–3. The review protocol was not registered online (e.g., PROSPERO) but is available upon request.

Eligibility Criteria

Eligibility assessment was independently performed by two reviewers (HCT, SMvD) in a standardized manner. Discrepancies were resolved by consensus, after discussion in a meeting of the Dutch Pancreatitis Study Group. 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.

Distinction between a disrupted (partial) and disconnected (complete) pancreatic duct disruption was considered but was not deemed possible owing to heterogeneous index test and the limited number of studies covering this subject.

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.[37] 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 × 2 tables derived from each index test and its corresponding reference standard.

Data were extracted regarding the imaging characteristics: type of imaging modality, (quality) scoring criteria, data regarding diagnostic accuracy, technical features for each modality and reported observer experience.

The methodological quality of the included study was assessed by two reviewers independently (HCT, SMvD) using the Quality Assessment of Diagnostic Accuracy Studies- 2 (QUADAS-2) tool.[38] Differences in assessment were resolved by consensus between the two reviewers, or after discussion in a meeting of the

Dutch Pancreatitis Study Group.

Statistical analysis

For each included study, a 2 × 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 4059 articles; 1565 articles returned from MEDLINE, 1718 from Embase, and 776 results from Cochrane library. After removal of duplicates, 2945 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 × 2 tables and calculate the diagnostic accuracy values or even the sensitivity or specificity and were therefore excluded.[11,39-41] Finally, 8 articles met the predetermined eligibility criteria (Fig. 1, Flowchart).[13,21-25,27,28] The excluded-by-reason articles are reported in Appendix Table 2.

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;[22,24] Gillams et al. did not report the study design.[27] A total of 237 patients with moderate to severe acute pancreatitis, according the revised 2012 Atlanta classification, were included in the studies.[4] In 199 of the 271 patients, (peri)pancreatic necrosis was reported.[13,21,24,25,28] The number of relevant patients included in the study ranged from 6 to 31, with a total of 142 relevant patients. Four studies primarily investigated the diagnostic accuracy of an imaging modality,[23,24,27] three studies primarily investigated the best therapy for a disrupted or disconnected pancreatic duct syndrome,[13,21,22,25] and in the last study both were performed.[28]

Table 1 Study characteristics of included studies

Study	Year	Country	Study design	Period (y)	FU	N*	N†	Study population	Index test	Reference standard	OE
Bakker et al.	2011	NL	Retrospective analysis of prospective cohort	2004-2007	NR	34	19	Infected necrotizing pancreatitis with pancreatic fistula	Amylase-measurements	ERCP	No
Bang et al.	2016	USA	Prospective observational cohort study	2014-2015	>90 d	42	21	Walled-off necrosis >6cm who underwent EUS guided drainage	EUS	Surgical/ERCP	No
Drake et al.	2012	USA	Retrospective cohort study	2000-2008	NR	31	31	Acute pancreatitis who underwent ERCP + MRI/MRCP	(Secretin)-MRCP	ERCP	No
Gillams et al.	2005	UK	Cohort study[a]	NR	6 m	17	6	Duct disruption e.c.i.: relevant acute pancreatitis	Secretin-MRCP	Surgical	No
Jang et al.	2016	South-Korea	Retrospective observational cohort study	2005-2013	512 d	84	18	Moderate to severe acute pancreatitis who underwent ERCP and/or MRCP	MRCP	ERCP	No
Smoczynski et al.	2015	Poland	Retrospective observational cohort study	2001-2013	>1 y	22	10	Walled-off necrosis who underwent endoscopic transpapillary drainage	CECT	ERCP	No
Tann et al.	2003	USA	Retrospective observational cohort study	1995-2000	18 m	26	26	Acute pancreatitis with surgically confirmed duct disruption	ERCP/CECT	Surgical	No
Yokoi et al.	2016	Japan	Prospective observational cohort study	2005-2014	NR	15	13	Severe acute pancreatitis who underwent percutaneous drainage of fluidcollection	Amylase-measurements	ERCP	No

*Total number of patients. †Number of relevant patients. [a]Unclear if prospective or retrospective design

FU *indicates follow-up;* OE, *observer experience reported;* NR, *not reported;* NL, *Netherlands;* USA, *United States of America;* UK, *United Kingdom;* MRCP, *magnetic resonance cholangiopancreatography;* EUS, *endoscopic ultrasound;* MRI, *magnetic resonance imaging;* ERCP, *endoscopic retrograde cholangiopancreaticography;* CECT, *contrast-enhanced computed tomography*

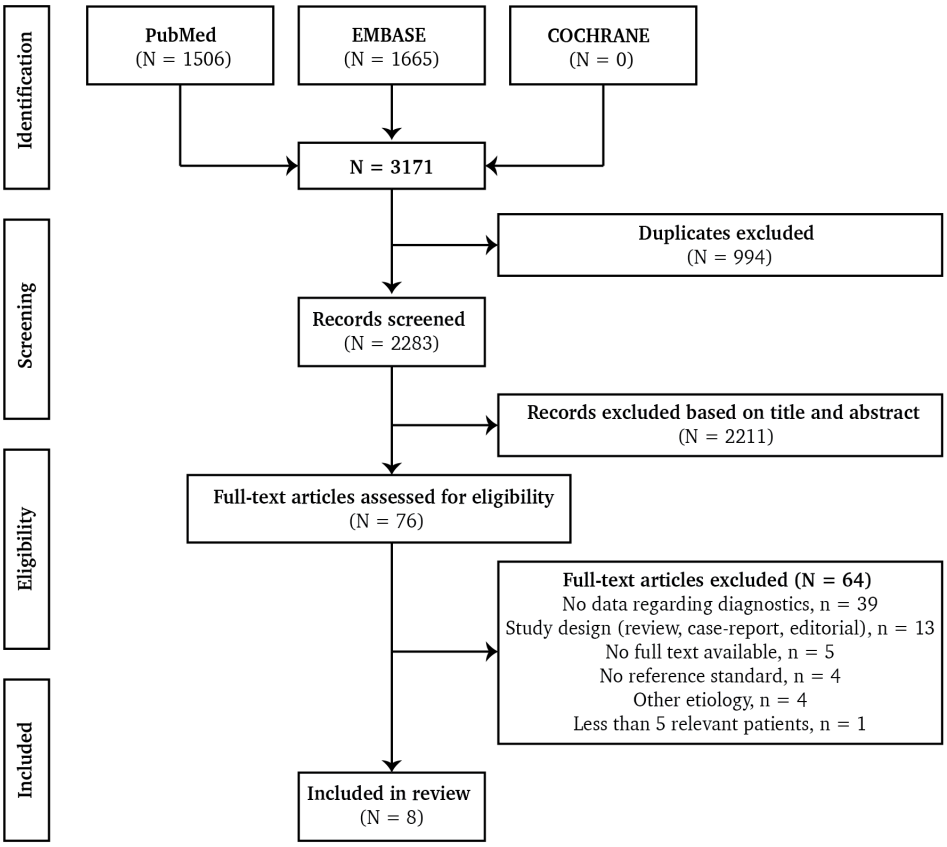

Figure 1 Inclusion flowchart

The studies concerning amylase measurements in drain fluid compared their index test with ERCP as reference standard.[21,25] Tann et al. compared ERCP with surgical confirmation[13] and in the study by Bang et al. EUS was compared with either ERCP or surgical confirmation.[24] Contrast-enhanced CT was evaluated in two studies, as compared with ERCP by Smoczynski et al.[21] or surgical confirmation by Tann et al..[13] Three studies compared either MRCP, secretin-MRCP, or both, with ERCP or surgical confirmation as reference standard. Gillams et al. investigated diagnostic accuracy of secretin-MRCP with surgical confirmation as reference standard,[27] comparison of standard MRCP, with ERCP as reference standard, was done in the study by Jang et al.,[28] and in the study of Drake et al., no distinction could be made between the patients who underwent standard MRCP or secretin-MRCP, as compared with ERCP.[23]

Quality assessment

The QUADAS-2 assessment for each domain is depicted in Figure 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.

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.

ERCP

Tann et al. 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.[13]

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 in the study by Bang et al..[24] No specificity was reported or could be calculated.

Contrast-enhanced CT

A sensitivity of 80% was found by Smoczynski et al. comparing contrast-enhanced CT with ERCP in patients with walled-off necrosis who underwent endoscopic transpapillary drainage.[21] Tann et al. 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.[13] For both studies, no specificity was reported or could be calculated from the extracted data.

MRCP

Jang et al. investigated the diagnostic yield of MRCP (without secretin) for detecting a pancreatic duct disruption, with ERCP as reference standard in patients with moderate to severe pancreatitis.[28] 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 by Gillams et al. 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.[27]

MRCP and secretin-MRCP

In the study by Jang et al., 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.[23]

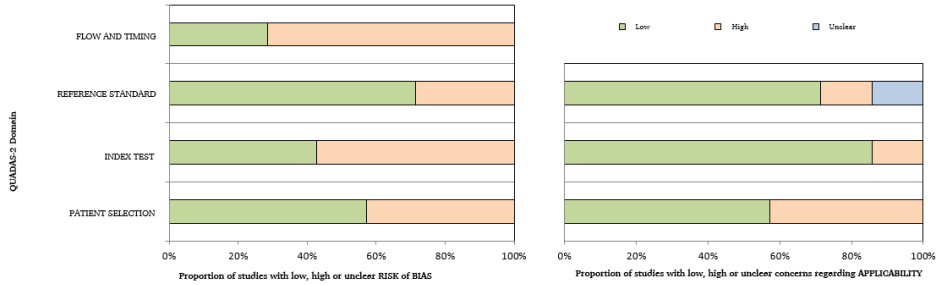

Figure 2 Summary of study quality (QUADAS-2)

Table 2 Results of included studies

Study	Index test	Reference standard	Relevant patients	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)	Overall accuracy (%)
Bakker et al.	Amylase-measurements	ERCP	19	18	0	1	0	100	-	-
Bang et al.	EUS	Surgical	21	1	0	-	-	100	-	-
	EUS	ERCP		20	0	-	-	100	-	-
Drake et al.	(secretin)-MRCP	ERCP	31	23	2	0	8	92	100	94
Gillams et al.	Secretin-MRCP	Surgical	6	5	1	-	-	83.3	-	-
Jang et al.	MRCP	ERCP	18	15	3	0	3	83.3	100	85.7
Smoczynski et al.	CT	ERCP	10	8	2	-	-	80	-	-
Tann et al.	ERCP	Surgical	26	26	0	-	-	100	-	-
	CT	Surgical		26	26	-	-	-	-	-
Yokoi et al.	Amylase-measurements	ERCP	13	6	0	7	7	100	50	65

TP indicates *true positive*; FN, *false negative*; FP, *false positive*; TN, *true negative*; ERCP, *endoscopic retrograde cholangiopancreaticography;* EUS, *endoscopic ultrasound;* MRCP, *magnetic resonance cholangiopancreatography;* CECT, *contrast-enhanced computed tomography*

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.[13,17,22,25] The sensitivity for MRCP and for secretin-MRCP was 83%, both with a specificity of 100%.[27,28] For a combined cohort of MRCP and secretin-MRCP a sensitivity of 92% was found.[23] Abdominal contrast-enhanced CT had the lowest sensitivity, ranging from 0 to 80%.[13,21]

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.[13,17,22,25,42,43] Amylase measurement in drain fluid, however, does not distinguish between a partial and complete disruption. To confirm this suspicion and the degree of disruption, 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.[30,31] 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 Bang et al. 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.[24] Furthermore, complete disconnection may be seen on EUS, but visualization of a partial disruption is not possible on EUS. In this review, we included two studies that used secretin during MRCP.[23,27]

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.[26] Secretin-MRCP or MRCP can be performed in nearly all patients.[26] Secretin is added for stimulation of pancreatic secretions to facilitate the identification of the pancreatic duct. No complications were reported after administration of secretin.[26,27]

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.[23] 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.[28] 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.[26,44]

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.[8,11,13,14,16,18,21-24,26,28,29,32,33,39-41,45-60] 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.[61] 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.[28,32,33] 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. There are currently no broadly accepted definitions on a partial disrupted, a complete disrupted, a disconnected or disconnected gland syndrome.[13] Subsequently, the diagnostic criteria for a partial disrupted or complete disrupted or disconnected pancreatic duct syndrome varied in the studies included in this review. The distinction between a disrupted (partial) and disconnected (complete) pancreatic duct disruption in this systematic review was considered but was not possible owing to heterogeneous index tests and the limited number of studies covering this subject. Therefore, for this systematic review we have consciously chosen to focus on disruption and disconnection together to outline the different diagnostic modalities used to diagnose either disrupted or disconnected pancreatic duct. An important concern, diagnostic accuracy of a modality for a partial disruption may differ from the diagnostic

accuracy for a complete disconnection. This difference could not be made on the extracted data and literature in this systematic review.

This study had some limitations. First, only a few studies could be included and hence number of eligible patients was relatively low. This should be taken into account when considering the calculated sensitivity. Second, most studies were performed in selected patient cohorts and were not designed to answer this question and suffered from high risk of bias. Subsequently, no clear pre-specified index test and clearly defined reference standard were used. Third, partial verification bias was present in some of the included studies[22,23,38] and the flow and timing of these tests may impose bias. Also, no standardized definitions for a disrupted pancreatic duct were used. As last, in four studies no specificity could be calculated.[13,21,24,27] We have not registered our study in the PROSPERO database; however, our study protocol was prospectively designed.

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 technique (in the major databases with small restrictions to publication type and grey literature) 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. These results, however, should be taken with caution due to poor methodological quality of included studies and small sample sizes. Further prospective studies are needed to define the optimal timing and the accurate diagnostic value of (secretin-)MRCP in different subgroups of patients with necrotizing pancreatitis.

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SUPPLEMENTARY APPENDIX

Table S1a Search terms PubMed

	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 fistula		Pancreatic fistul*

Table S1b Search terms Embase

	Emtree terms	All Fields
Acute pancreatitis	'acute pancreatitis'/exp	'acute pancreatitis'/exp
OR		
Acute necrotizing pancreatitis		Acute necrotizing pancreatit*:ti,ab OR severe pancreatit*:ti,ab OR severe acute pancreat*:ti,ab OR complicated pancreat*:ti,ab OR complicated acute pancreat*:ti,ab
OR		
Acute pancreatitis	'pancreatitis'/exp	'pancreatitis'/exp OR pancreatitis:ti,ab
OR		
Pancreas	'pancreas'/exp	'pancreas'/exp OR pancreas:ti,ab
AND		
Necrosis	'necrosis'/exp	'necrosis'/exp OR necrot*:ti,ab OR necros*:ti,ab OR Severe:ti,ab OR Acute:ti,ab OR Serious:ti,ab
AND		
Pancreatic duct	'pancreatic duct'/exp	'pancreatic duct'/exp OR duct*:ti,ab OR tail:ti,ab OR tails:ti,ab OR pd:ti,ab
AND		
Disconnection		Disconnect*:ti,ab OR disrupt*:ti,ab OR leak*:ti,ab OR interrupt*:ti,ab OR ruptured:ti,ab OR abnormalit*:ti,ab
OR		
Disconnected pancreatic duct syndrome	'disconnected pancreatic duct syndrome'/exp	'disconnected pancreatic duct syndrome'/exp

Table S1c Search terms Cochrane library

	MeSH terms	All Fields
Acute necrotizing pancreatitis	Necrotizing pancreatitis, Acute	Acute necrotizing pancreatitis OR severe pancreatitis OR severe acute pancreatitis OR complicated pancreatitis OR complicated acute pancreatitis OR walled off pancreatic necrosis in Title Abstract Keyword
OR		
Pancreatitis	Pancreatitis	(Pancreatitis OR pancreas OR pancreatitis)
OR		
Pancreas	Pancreas	
AND		
Necrosis	Necrosis	(Necrosis OR necrotizing OR necrotizing OR necrosis OR severe OR acute OR serious) in Title Abstract Keyword
AND		
Pancreatic duct	Pancreatic ducts	(Pancreatic duct OR duct OR tail OR tails OR pd)
AND		
Disconnection	NA	(Disconnect OR disrupt OR leak OR inteerupt OR ruptured OR abnormalit) in Title Abstract Keyword
OR		
Pancreatic fistula		Pancreatic fistula in Title Abstract Keyword

Table S2 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

Table S2 Continued.

Author	Year	Journal	Reason for exclusion
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

Table S3 Imaging characteristics of magnetic resonance imaging or cholangiopancreatography

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 indicates *not reported*

Table S4 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/?)

Table S5 Other findings

Study	Year	Study population	N	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 indicates *not reported;* EUS, *endoscopic ultrasound;* ERCP, *endoscopic retrograde cholangiopancreatography;* NA, *not applicable;* CT, *computed tomography*

Table S6 PRISMA 2009[1] checklist

Section/topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. file: 1-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9

Table S6 Continued.

Section/topic	#	Checklist item	Page #
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, 26
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13
DISCUSSION			
Summary of evidence		Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations		Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions		Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

NA indicates *not applicable*

References:

[1]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

PART II

CHAPTER VI

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 = .26)) but distal pancreatectomy was associated with a higher incidence of endocrine pancreatic insufficiency (risk ratio = 3.06, p = .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% develop 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 integrity, 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 heterogeneity, 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 (Fig. 1).[7,14,15,22-39] 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 (Tables 2-5). 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 Supplementary table 1.

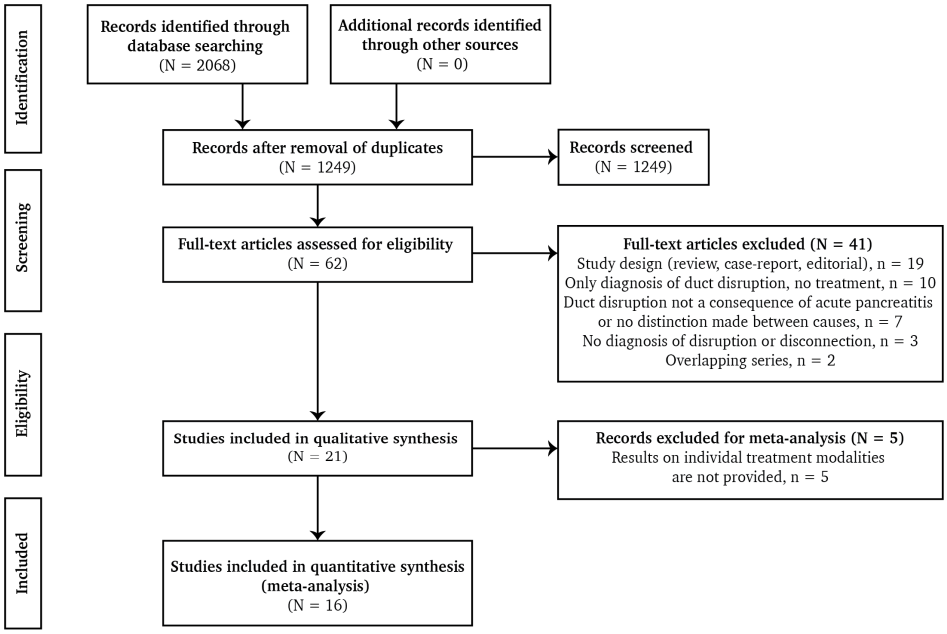

Figure 1 Flow diagram

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.[7,14,15,22-31,33-39]

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 $I^2 = 68\%$ (Fig. 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 to 100%. Meta-analysis showed a pooled success rate of 92% [95%-CI: 77-98%] with a $I^2 = 32\%$ (Fig. 2B).

Table 1 Study characteristics

Author	Year	Country	Inclusion period	N†	N‡	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	Retrospective analysis of prospective cohort
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	Retrospective analysis of prospective cohort
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	Retrospective analysis of prospective cohort
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	Retrospective analysis of prospective cohort
Yokoi et al.	2016	Japan	Jan 2005 - Feb 2014	15	6	Retrospective cohort study

*Unclear if prospective or retrospective study design
†Total number of patients
‡Number of relevant patients
USA indicates *United states of America*

Table 2 Endoscopic treatment – Transpapillary procedures

Study	Year	N†	N‡	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Success rate	Time until success	Procedure-related Complication	FU
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)

Table 2 Continued.

Study	Year	N†	N‡	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Success rate	Time until success	Procedure-related Complication	FU
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

Table 2 Continued.

Study	Year	N†	N‡	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Success rate	Time until success	Procedure-related Complication	FU
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

†Total number of patients
‡Number of relevant patients
⁑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

FU indicates *follow-up*; NR, *not reported;* PD, *pancreatic duct*

Table 3 Endoscopic treatment – Transluminal drainages/cysto-ostomies

Study	Year	N†	N‡	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (d)	Success rate	Time until success	Procedure-related complication	FU
Bang et al.	2016	42	21	Endoscopic ultrasound-guided transluminal drainage, with plastic stents indefinitely left in situ	NR	NR	20/21no 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-ERCP 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

†Total number of patients
‡Number of relevant patients
*Transluminal drainage with sphincterotomy (n=3), transluminal drainage without sphincterotomy (n=2)
FU indicates *follow-up*; NR, *not reported;* ERCP, *endoscopic retrograde cholangiopancreatography*

Surgical treatment

Six studies reported on surgical procedures (Table 4).[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 (Fig. 2C and D). There were no differences (risk ratio = 1.06, p = .26) between both strategies. Distal pancreatectomy was associated with more intraoperative blood loss (std. mean difference = 2.30, p = .02) and a higher incidence of pancreatic endocrine insufficiency (risk ratio = 3.06, p = .01). No differences were found regarding exocrine insufficiency (risk ratio = 1.17, p = .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.

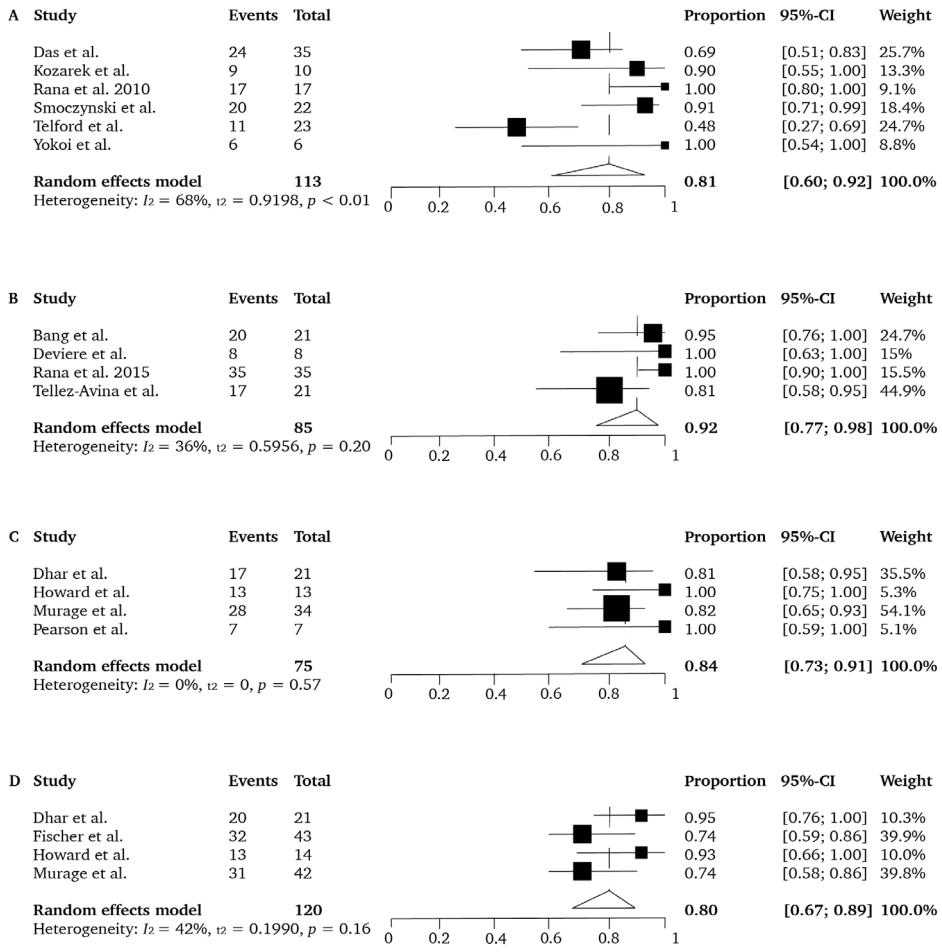

Figure 2 A, pooled success rate of endoscopic transpapillary drainage; B, pooled success rate of endoscopic transluminal drainage; C, pooled success rate of Roux-en-Y internal drainage; D, pooled success rate of distal pancreatectomy.

Table 4 Surgical procedures

Study	Year	N†	N‡	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (d)	Success rate	Time until success	Procedure-related Complication	FU
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 tract-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 FJ 21 DP	None	NR	17/21 FJ 20/21 DP	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	cDPDS necrosectomy with tail resection (n=28)* dDPDS: DP-splenectomy(n=15)**	Endoscopic procedures: cDPDS (n=10)dDPDS (n=15) Percutaneous procedure: cDPDS (n=9)dDPDS (n=3)	cDPDS: median(range): 60 (26-4793) dDPDS: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

Table 4 Continued.

Study	Year	N†	N‡	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (d)	Success rate	Time until success	Procedure-related Complication	FU
Howard et al.	2001	27	27	Roux-en-Y internal drainage (n=13) -9 pancreaticojejunostomy -4 cystojejunostomy DP-splenectomy (n=14)	Prior surgery, unspecified, in 8 patients in the roux-en-y-group, 7 in the DP group	6.1 (±2.3) vs 4.9(±2.0) months	Roux-en-Y 100% DP 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 DP (P<.0001)	Median 17 (±8) vs 18 (±9) months
Murage et al.	2010	76	59	DP (n=42) Roux-en-Y internal drainage (n=34) -Pancreatojejunostomy (n=18) -Cystojejunostomy (n=10) -FJ (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 DP-splenectomy	Median 264 days (range 29-740)

†Total number of patients

‡Number of relevant patientsFU indicates *follow-up*; NR, *not reported*; WOPN, *walled off pancreatic necrosis*; DP, *distal pancreatectomy*; FJ, *fistulojejunostomy*; cDPDS, *concurrent diagnosis of DPDS with acute pancreatitis*; dDPDS, *delayed diagnosis of DPDS*; DPDS, *disconnected pancreatic duct syndrome;* ID, *internal drainage;* DM, *diabetes mellitus*

Table 5 Other or combined procedures

Study	Year	N†	N‡	Intervention	Prior therapy for DPDS	Time until intervention (d)	Success rate	Time until success	Procedure-related complication	FU
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)

Table 5 Continued.

Study	Year	N†	N‡	Intervention	Prior therapy for DPDS	Time until intervention (d)	Success rate	Time until success	Procedure-related complication	FU
Lawrence et al.	2008	189	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.	2008	31	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 acute pancreatitis 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

Table 5 Continued.

Study	Year	N†	N‡	Intervention	Prior therapy for DPDS	Time until intervention (d)	Success rate	Time until success	Procedure-related complication	FU
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

†Total number of patients
‡Number of relevant patients
DPDS, *disconnected pancreatic duct syndrome*; FU indicates *follow-up*; NR, *not reported;* PFC, *pancreatic fluid collection*; CP, *chronic pancreatitis;* ERCP, *endoscopic retrograde cholangiopancreatography;* DM, *diabetes mellitus*

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 of the high heterogeneity 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 perioperative 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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SUPPLEMENTARY APPENDIX

Table S1 Definition of successful treatment and modalities used to diagnose DPDS

	Success definition	Diagnostic modality
Bang et al.	Resolution of WON	EUS
Beck et al.	Fistula/fluid collection resolved	ERCP or MRCP
Das et al.	Resolution of pancreatic duct leak	ERCP
Devière et al.	Cyst resolution	ERCP
Dhar et al.	Resolution of pancreatic fistula or pancreatic fluid collection	Evidence of duct discontinuity on ERCP or MRCP, viable pancreatic parenchyma distal to discontinuity on CT or MRI, or persistent pancreatic fluid collection or fistula with enzyme rich fluid.
Fischer et al.	NA	CT or MRI or ERCP
Howard et al.	Resolution of fistula or pseudocyst	ERCP + CT + (non-healing pancreatic fistula or pseudocyst after conservative treatment)
Irani et al.	Resolution of pancreatic fistula	ERCP
Jang et al.	Resolution of PFC	ERCP or MRCP
Kozarek et al.	Adequate drainage of fluid collection, as determined by CT	ERCP
Lawrence et al.	(radiographic) solution of fluid collection	ERCP + CT
Murage et al.	Long-term resolution of patient's symptoms (eg. No recurrent acute pancreatitis, pancreatic pseudocysts, pancreatic fistulas or chronic pancreatitis)	(ERCP or MRCP) + CT
Pearson et al.	Resolution of fluid collections and internal drainage of a persistent pancreatic fistula	ERCP or MRCP
Pelaez-Luna et al.	Resolution of fluid collections and clinical parameters	ERCP + CT
Rana et al. 2010	Resolution of pancreatic fistula	ERCP
Rana et al. 2015	Resolution of walled-off pancreatic necrosis	ERCP
Sharaiha al.	Resolution of walled-off necrosis, on the basis of image analysis, without need for further intervention via surgery or interventional radiology	Cross-sectional imaging, not specified which modality
Smoczynski et al.	Complete regression of the collection	ERCP
Telford et al.	Resolution of the disruption clinically, on radiologic imaging, and/or at endoscopic retrograde pancreatography	ERCP
Téllez-Aviña et al.	the absence of symptoms and no evidence of collections in a period of time of at least 6 months	ERCP or MRCP
Yokoi et al.	Fistula closure	ERCP

DPDS indicates *disconnected/disrupted pancreatic duct*; WON, *walled of necrosis*; NA, *not assessable*; PFC, *peripancreatic fluid collection*; CT, *computed tomography*; EUS, *endoscopic ultrasound*; ERCP, *endoscopic retrocrade cholangiopancreaticography*; MRCP, *magnetic resonance cholangiopancreaticography*

Table S2 Quality assessment of included studies by the Newcastle-Ottawa Scale

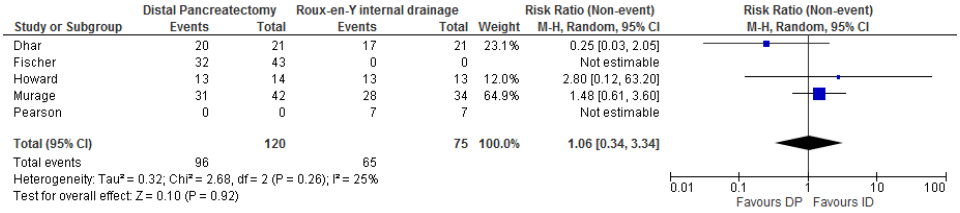
	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Bang et al.	★	-	★	★	-	-	-	-
Beck et al.	★	-	★	★	-	-	★	-
Das et al.	★	-	★	★	-	-	★	★
Devière et al.	★	-	★	★	-	-	★	★
Dhar et al.	✦	-	★	★	★	-	★	★
Fischer et al.		-	★	★	-	-	★	-
Howard et al.	★	-	★	★	★★	-	★	-
Irani et al.	-	-	★	★	-	-	★	-
Jang et al.	★	-	★	★	-	-	★	-
Kozarek et al.	★	-	★	★	-	-	★	-
Lawrence et al.	★	-	★	★	-	-	★	★
Murage et al.	★	-	★	★	-	-	★	★
Pearson et al.	-	-	★	★	-	-	-	-
Pelaez-Luna et al.	★	-	★	★	★★	-	-	-
Rana et al. 2010	-	-	★	★	-	-	★	★
Rana et al. 2015	★	-	★	★	-	-	★	-
Sharaiha al.	-	-	★	★	-	-	-	★
Smoczynski et al.	★	-	★	★	-	-	-	-
Telford et al.	★	-	★	★	-	★	★	-
Téllez-Aviña et al.	★	-	★	★	-	-	★	-
Yokoi et al.	★	-	★	★	-	-	-	-

*A star is awarded if the study meets the criteria of the Newcastle-Ottawa Scale. For comparability, two stars may be assigned. The Newcastle-Ottawa Scale is available online. 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.

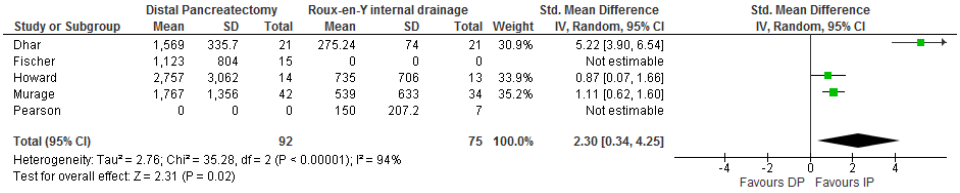
Table S3 Extent of disruption and related success rates

	Partial or complete disruption/ disconnection of pancreatic duct	**Success difference partial/complete**
Bang et al.	21 of 21 complete disconnection	-
Beck et al.	82 of 82 complete disconnection	-
Das et al.	7 of 97 complete disruption, not specified for underlying disease (AP, CP or post-operative)	4 of 7 complete disruptions were unsuccessful
Devière et al.	13 of 13 complete disruption	-
Dhar et al.	42 of 42 complete disconnection	-
Fischer et al.	43 of 43 complete disruption	-
Howard et al.	27 of 27 complete disconnection	-
Irani et al.	15 of 15 complete disconnection	-
Jang et al.	14 of 32 complete disruption; 18 of 32 partial disruption	The success rate of endoscopic transpapillary pancreatic stenting was lower in complete disruption (20% vs. 92%). Patients with complete disruption showed a high rate of recurrence of fluid collections (71% vs. 17%) and required surgery more often (43% vs. 6%)
Kozarek et al.	NR	NR
Lawrence et al.	29 of 29 complete disconnection	-
Murage et al.	NR (most likely not partially disrupted ducts, as the authors state this condition would have been treated by a bridging stent)	-
Pearson et al.	NR	-
Pelaez-Luna et al.	NR	-
Rana et al. 2010	16 of 23 partial disruption; 7 of 23 complete disruption	In 15 of 16 and 6 of 7 patients the disruption was successfully bridged. Fistula resolved in 15 of 15 patients with partially disruption and 2 of 6 with complete disruption
Rana et al. 2015	35 of 35 complete disruption	-
Sharaiha al.	NR	NR
Smoczynski et al.	14 of 22 partial disruption; 8 of 22 complete disruption	12 of 14 bridging stent, all 14 successful treatment; no bridging stents in completely disrupted ducts: 6 of 8 successful treatment
Telford et al.	15 of 41 complete disruption, 26 partial disruption	7 of 15 complete disruptions were unsuccessfully treated
Téllez-Aviña et al.	21 of 21 complete disconnection	-
Yokoi et al.	6 of 6 partial disruption	-

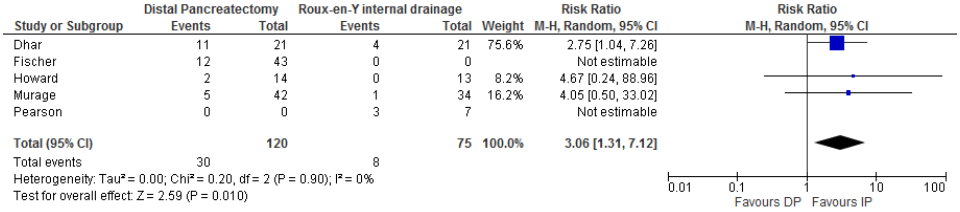
AP indicates *acute pancreatitis*; CP, *chronic pancreatitis*; NR, *not reported*



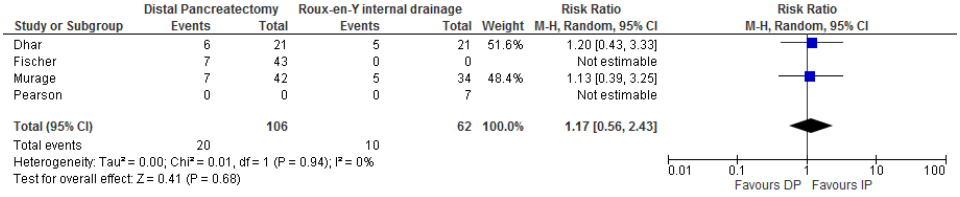
Supplementary Figure 1.1 Forest plot of comparison: Distal pancreatectomy (DP) vs Roux-en-Y internal drainage (ID). Outcome: Success rate



Supplementary Figure 1.2 Forest plot of comparison: Distal pancreatectomy (DP) vs Roux-en-Y internal drainage (ID). Outcome: Intraoperative blood loss.



Supplementary Figure 1.3 Forest plot of comparison: Distal pancreatectomy (DP) vs Roux-en-Y internal drainage (ID). Outcome: new-onset diabetes mellitus.



Supplementary Figure 1.4 Forest plot of comparison: Distal pancreatectomy (DP) vs Roux-en-Y internal drainage (ID). Outcome: new-onset exocrine insufficiency.

Table S4 Search details

Library	Search terms	N
PubMed	((Disconnect* OR disrupt* OR interrupt* OR leak*) AND (duct* OR tail* OR PD)) OR ((pancreas OR pancreatic) AND remnant) AND pancreatitis[Title/Abstract])	1011
Embase	(((Disconnect* or disrupt* or interrupt* or leak*) and (duct* or tail* or PD)) or ((pancreas or pancreatic) and remnant)).af. and pancreatitis.ab.) not "conference abstract".af.	926
Cochrane	((Disconnected OR disrupted OR interrupted OR leakage) AND (duct OR tail OR PD)) OR ((pancreas OR pancreatic) AND remnant) AND pancreatitis	131

Table S5 Checklist PRISMA 2009[1]

Section/topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 Suppl. file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4

Table S5 Continued.

Section/topic	#	Checklist item	Page #
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6 Suppl. file
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6 Suppl. file
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6 Figures
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6 Suppl. file
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

[1]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

PART II

CHAPTER VII

Short-term and long-term outcomes of a disruption and disconnection of the pancreatic duct in necrotizing pancreatitis: *a multicenter cohort study in 896 patients*

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ABSTRACT

Introduction

Necrotizing pancreatitis may result in a disrupted or disconnected pancreatic duct (DPD) with the potential for long-lasting negative impact on a patient's clinical outcome. There is a lack of detailed data on the full clinical spectrum of DPD, which is critical for the development of better diagnostic and treatment strategies.

Methods

We performed a long-term post hoc analysis of a prospectively collected nationwide cohort of 896 patients with necrotizing pancreatitis (2005–2015). The median follow-up after hospital admission was 75 months (P25–P75: 41–151). Clinical outcomes of patients with and without DPD were compared using regression analyses, adjusted for potential confounders. Predictive features for DPD were explored.

Results

DPD was confirmed in 243 (27%) of the 896 patients and resulted in worse clinical outcomes during both the patient's initial admission and follow-up. During hospital admission, DPD was associated with an increased rate of new-onset intensive care unit admission (adjusted odds ratio [aOR] 2.52; 95% confidence interval [CI] 1.62–3.93), new-onset organ failure (aOR 2.26; 95% CI 1.45–3.55), infected necrosis (aOR 4.65; 95% CI 2.87 - 7.64), and pancreatic interventions (aOR 7.55; 95% CI 4.23-13.96). During long-term follow-up, DPD increased the risk of pancreatic intervention (aOR 9.71; 95% CI 5.37–18.30), recurrent pancreatitis (aOR 2.08; 95% CI 1.32–3.29), chronic pancreatitis (aOR 2.73; 95% CI 1.47–5.15), and endocrine pancreatic insufficiency (aOR 1.63; 95% CI 1.05–2.53). Central or subtotal pancreatic necrosis on computed tomography (OR 9.49; 95% CI 6.31-14.29) and a high level of serum C-reactive protein in the first 48 hours after admission (per 10-point increase, OR 1.02; 95% CI 1.00–1.03) were identified as independent predictors for developing DPD.

Conclusion

At least 1 of every 4 patients with necrotizing pancreatitis experience DPD, which is associated with detrimental, short-term and long-term interventions, and complications. Central and subtotal pancreatic necrosis and high levels of serum C-reactive protein in the first 48 hours are independent predictors for DPD.

INTRODUCTION

Necrosis of the pancreatic parenchyma in acute pancreatitis may result in the integrity loss of the pancreatic duct. This can either be a partial disruption or a complete disconnection of the pancreatic duct,[1–3] both resulting in leakage of pancreatic fluid leading to persistent or recurrent peripancreatic collections, pancreatic ascites, or external pancreatic fistulas.[2–14]

A disrupted or disconnected pancreatic duct (DPD) is an increasingly reported entity,[2–17] with estimated incidence rates varying from 10% to 50%.[9,15,16,18] This may be due to a lack of a standardized and evidence-based diagnostic workup.[19–21] Several distinct diagnostic modalities are reported to be used in daily clinical practice to diagnose DPD.[2,6,9,10,13,22–25]

Moreover, the exact clinical impact of DPD remains unclear,[26] with a lack of study into the long-term health implications of DPD in patients with necrotizing pancreatitis. It is generally believed that DPD has a large detrimental impact on a patient's clinical burden and is associated with high healthcare resource utilization.[6,9,10,13,16,27] In particular, DPD has been linked to endocrine pancreatic insufficiency after necrotizing pancreatitis.[28–30] However, studies on this topic do not cover the entire clinical spectrum of patients with necrotizing pancreatitis; primarily focused on reporting specific clinical outcomes, with either small sample sizes or selected study populations (e.g., only patients undergoing a certain invasive intervention). Only a few studies have addressed other long-term consequences of DPD; however, these studies were generally conducted retrospectively in small selected populations.[13,16,27-30] In particular, data on late presentation of consequences of DPD, such as recurrent pancreatitis and chronic pancreatitis, are lacking.

The treatment for DPD range widely from conservative options to invasive radiological, endoscopic, or surgical interventions.[14] International treatment guidelines include conflicting recommendations regarding the choice of treatment plan.[19–21] This is driven by a lack of understanding on the treatment outcomes across the entire DPD population because most studies report only on selected patients undergoing specific treatment modalities.[31] There are currently no tools to predict which patients are at a greater risk of developing DPD. A predictive tool would aid in determining an appropriate treatment plan early in the disease course to prevent further complications and improve patient health outcomes.

Therefore, more data are needed on the full clinical spectrum and predictive indicators of DPD to ultimately improve the timing and choice of diagnostic and treatment strategies. We performed a long-term analysis on a nationwide prospectively collected patient cohort to evaluate the incidence, diagnosis, clinical outcomes, and treatment of DPD in necrotizing pancreatitis. Furthermore, we designed a prediction model for the development of DPD.

METHODS

Study design and population

We performed a post hoc analysis of patients included in the prospective nationwide registry of acute pancreatitis (PWNCORE) of the Dutch Pancreatitis Study Group. A subset of patients in the registry has been included in previously published randomized trials.[32,33] For this study, we selected all patients older than 18 years with necrotizing pancreatitis who were treated between November 1, 2005, and December 31, 2015, in 27 hospitals. Patients were excluded in cases of definite chronic pancreatitis according to the M-ANNHEIM criteria,[34] pancreatic carcinoma during the index hospital admission, or traumatic etiology of pancreatitis. PWN-CORE and each of the trials were approved by a central medical ethics committee and by each participating hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki. We adhered to the Strengthening the Reporting of Observational studies in Epidemiology guidelines.[35] Written informed consent was provided for all patients. Treatment of acute pancreatitis was according to the international guidelines for management of acute pancreatitis.[20,21] The Dutch Association for patients with pancreatic disease, the Alvleesklierevereniging, was actively involved in the design of the abovementioned trials and registration cohort. Their board members were also present during research meetings of the Dutch Pancreatitis Study Group.

Definitions

Acute pancreatitis was diagnosed according to the revised Atlanta classification, that is, at least 2 of 3 of the following criteria: (i) clinical presentation with abdominal pain, (ii) serum amylase or lipase levels exceeding 3 times the upper limit of normal, and/or (iii) abdominal imaging–confirmed diagnosis of acute pancreatitis.[36] All patients underwent computed tomography (CT) during index admission. Necrotizing pancreatitis was defined as a CT severity index score of 3 or higher.[37] An expert pancreatic radiologist (T.L.B.) reviewed all available abdominal radiological images. This review included assessment of the CT severity index (as assessed on the first available CT ≥5 days after onset of disease), the presence and location of peripancreatic collections and (peri) pancreatic necrosis, and the presence of DPD. In daily clinical practice, not all patients who might have had DPD underwent routine evaluation of the pancreatic duct through imaging. Because we wanted to cover the entire spectrum of DPD, we approached the occurrence of DPD pragmatically and made the following distinction: (i) no DPD; (ii) possible DPD, and (iii) confirmed DPD. Patients were classified post hoc by the study team using a standardized approach.

Confirmed DPD was defined by the presence of 1 or more of the

following: (i) (radiological) confirmation by: (A) endoscopic retrograde cholangiopancreaticography (ERCP); (a) extravasation of contrast medium from the ductal system or (b) a cutoff or blowout of the pancreatic duct with inability to demonstrate the upstream pancreatic duct; (B) magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP): an interruption of pancreatic ductal continuity[24,38–40]; or (C) fluoroscopic fistulography: a connection between the pancreatic duct and the external environment[25,41–45] or (ii) functional confirmation: an amylase level in external drain fluid, more than 1 day after placement of the percutaneous catheter drain, exceeding 3 times the upper limit of normal amylase serum level.[46] Based on the available data, no distinction could be made between the presence of a partial disruption or circumferential disconnection with the current data.

Possible DPD was defined as 1 or more of the following criteria and without meeting the criteria for confirmed DPD: (i) morphological signs on imaging, defined as central or subtotal pancreatic necrosis, (ii) amylase or lipase levels exceeding 3 times the upper limit of normal in fluid obtained during endoscopic drainage (not from percutaneous catheter drain fluid), (iii) the presence of other types of internal pancreatic fistula defined as a connection between the pancreas and any other organ depending on the site of the fistula (pleural and common bile duct), and (iv) the need for long-term (≥90 days) percutaneous catheter drainage without an amylase measurement in drain fluid.

Other outcomes included endoscopic and radiological diagnostics for DPD, time to diagnosis, and resolution of DPD (defined as the date of last intervention without the need for a follow-up intervention, when no new interventions are required with an endoscopic drain still in place, or the date of removal of the last percutaneous catheter drain). Clinical outcomes included the following: mortality, early and overall transient and persistent organ failure, abdominal compartment syndrome, gastrointestinal complications, infected necrosis, a number of pancreatic interventions (e.g., radiological/endoscopic/surgical), readmission, long-term complications of endocrine and exocrine pancreatic insufficiency, recurrent pancreatitis, and definite chronic pancreatitis according to the M-ANNHEIM criteria.[34] Clinical outcomes were reported only when occurring more than 7 days after admission; the 7-day cutoff value has been deliberately chosen and was based on the hypothesis that DPD occurs during necrosis. Because necrosis generally develops in the first week, we also expect DPD to develop around that time. Therefore, we included only the clinical outcome that occurred more than 7 days after admission. Detailed definitions for these outcomes were established after a careful review of the current literature in research meetings of the Dutch Pancreatitis Study Group and are summarized in the Supplementary Appendix Table S1.

Data collection

Using a standardized case-record form, clinical data were collected prospectively during the initial hospital admission, and follow-up data were collected retrospectively in January 2020. If at any time before or during follow-up a patient was transferred to a different hospital, all the required follow-up data were retrieved from the relevant hospitals. All data were imported by 1 author (HCT) in Open Clinica and verified by a second author (SMvD). Discrepancies were resolved by consensus during research meetings of the Dutch Pancreatitis Study Group. All authors had access to the study data and reviewed and approved the final manuscript.

Statistical analysis

Patient and disease characteristics and diagnostic modalities were described, for both patients with confirmed DPD and those with possible DPD. Short-term and long-term clinical outcomes and interventions were compared across all categories of patients (confirmed, without DPD, and possible DPD). Multivariate regression analyses were performed to adjust for potential confounders. The clinical outcome was defined as the dependent variable. The covariates varied by clinical outcome and were a combination of the following: presence of confirmed (or in case of the multivariate sensitivity analysis also possible) DPD, age, sex, American Society of Anesthesiologists (ASA) classification, presence of parenchymal necrosis, extent of necrosis, occurrence of infected necrosis, and occurrence of early onset of organ failure after admission (all covariates included per outcome are listed in the supplementary appendix and were based on clinical reasoning, baseline differences, and current literature; see Supplementary Appendix Table S2). Because multiple comparisons (n = 20) were performed, the Bonferroni correction was applied. A corrected P value of <0.0025 was considered significant. Two univariate sensitivity analyses were performed: (i) comparing patients without DPD with patients in whom DPD was confirmed with an amylase level exceeding 3 times the upper limit and (ii) comparing patients with functional DPD with patients with only imaging based DPD. The different treatment strategies for a confirmed DPD were described and visualized using a Sankey diagram. This included radiological/endoscopic/surgical pancreatic interventions for both confirmed DPD and for infected necrosis because, in daily practice, there is often an overlap across both indications in the event of an intervention.

Second, a prediction model was designed to identify predictive indicators for the development of a confirmed DPD. We fitted a multivariable logistic regression model both with and without restricted cubic splines to identify potential nonlinear relationships between predictors and the outcome. Predictors

were identified based on clinical reasoning among members of the study group. The choice of the predictors was further supported by univariate analysis of the patient characteristics (see Supplementary Appendix Table S2) and using a full model strategy using 6 variables: age, sex, ASA classification, leukocyte count at admission, C-reactive protein (CRP) at admission, and pattern of parenchymal necrosis. Owing to the limited number of cases, the ASA classification was categorized into ASA I (reference), ASA II, and ASA ≥III. Likewise, we decided to reduce the patterns of parenchymal necrosis to (i) no necrosis (reference), (ii) central or subtotal, and (iii) right, left, or diffuse, while neglecting the percentage of necrotizing tissue that was involved. Missing values were multiply imputed using the R-package MICE. We generated 50 data sets and pooled the results across the data sets using Rubin rules. Model discrimination was evaluated in the derivation data using the c-statistic (i.e., area under the receiving operator curve). Neither internal nor external validation was attempted because this model was conceived for exploratory purposes only.

Descriptive data were reported as mean with SD when normally distributed and as median with the 25th and 75th percentiles (P25–P75) when not normally distributed. Categorical data were shown as frequencies and percentages. Statistical comparison was performed using the Fisher exact test or X^2 test for categorical data and the Student t test or the Mann-Whitney U test for continuous data. A P value <0.05 (not corrected) or <0.0025 (corrected) was considered statistically significant. We calculated risk ratios and (adjusted) odds ratios (OR) with their respective 95% confidence intervals (CI). Statistical analysis was performed using R, R version 3.6.1 (2019-07-05).

RESULTS

Between November 2005 and December 2015, 2,289 patients with acute pancreatitis were included in the prospective registry. Of this cohort, 896 patients had necrotizing pancreatitis and were included in this study (Figure 1). The median follow-up duration after hospital admission was 75 months (P25–P75: 41–151). Patient and disease characteristics are summarized in Table 1.

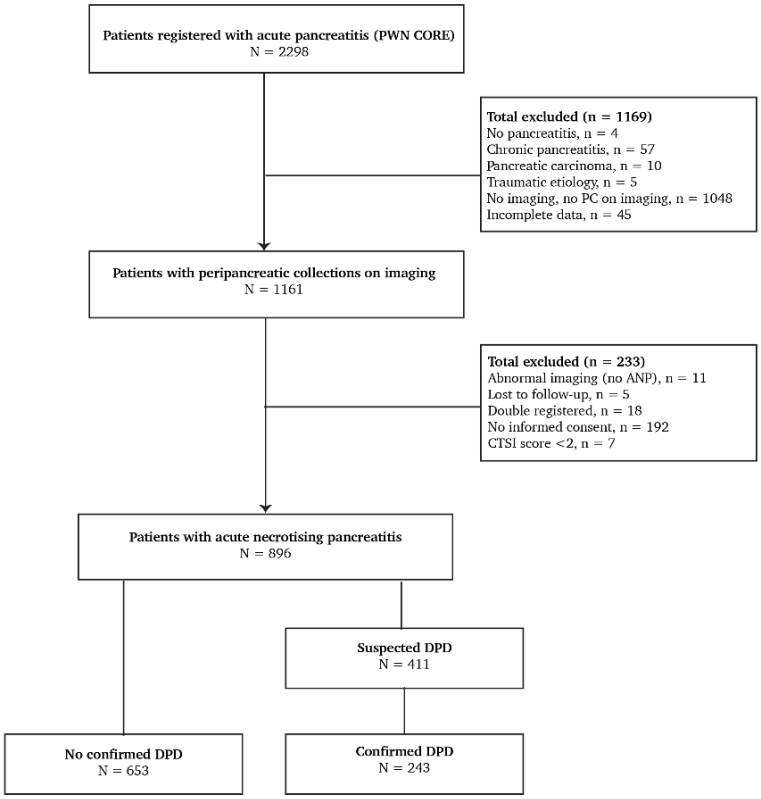

Figure 1 Flowchart of patient inclusion
ANP indicates *acute necrotizing pancreatitis*; CTSI, *computed tomography severity index*; DPD, *disruption or disconnection of the pancreatic duct*; N, *number*; PC, *peripancreatic or pancreatic collection*; PWN CORE *Dutch Acute Pancreatitis Registry*.

Diagnosis

A possible DPD occurred in 415 of 896 patients (46%), and DPD was confirmed in 243 of 896 patients (27%). Time to diagnosis for confirmed DPD was 57 (P25–P75: 28–116) days after admission. Univariate comparison of patient characteristics for patients with and without DPD is provided in the supplementary appendix (see Supplementary Appendix Table S2). Of the 243 patients with confirmed DPD, the diagnosis was based on imaging findings in 103 patients (42%). In 55 of the 103 patients (53%), the diagnosis was also confirmed through an amylase level in drain fluid exceeding 3 times the upper limit. In most patients, DPD was confirmed with either MRI/MRCP (n = 37, 36%), ERCP (n = 26, 25%), or on both MRI/MRCP and ERCP (n = 20, 19%). In 204 of 320 (64%) patients who underwent a percutaneous catheter drainage, amylase level was measured with a median of 16,300 U/L (P25–P75: 1,905–63,070). In 140 of 243 patients (58%),

DPD was confirmed only by an amylase level exceeding 3 times the upper limit (median 24,001 U/L; P25–P75: 5,952–65,550) in drain fluid after a median of 22 days (P25–P75: 2–66) after the first intervention. The median number of amylase measurements in these patients was 3 (P25–P75: 1–5). More details on diagnostic modalities used for diagnosing a confirmed DPD are summarized in the supplementary appendix (see Supplementary Appendix Table S3).

Table 1 Patient and disease characteristics in 896 patients with necrotizing pancreatitis

		Confirmed DPD	
	Overall, N = 896	**No, N = 653**	**Yes, N = 243**
Age (y)	58 (47 – 69)	59 (47 – 70)	58 (46 – 68)
Male sex	571 (64)	402 (62)	169 (70)
Etiology			
Biliary	432 (48)	320 (49)	112 (46)
Alcohol	159 (18)	120 (18)	39 (16)
Post-ERCP	31 (4)	26 (4)	5 (2)
Idiopathic	180 (20)	122 (19)	58 (24)
Other	94 (11)	65 (10)	29 (12)
Medical history			
Cardiovascular	377 (42)[a]	281 (43)[cc]	96 (40)[t]
Pulmonary	91 (10)[b]	65 (10)[dd]	26 (11)[u]
Chronic renal	28 (3)[c]	21 (3)[ee]	7 (3)[v]
Diabetes mellitus	108 (12)[d]	81 (12)[ff]	27 (11)[w]
ASA-classification			
I	298 (33)	223 (34)	75 (31)
II	471 (53)	336 (52)	135 (56)
III	123 (14)	91 (14)	32 (13)
IV	4 (0.4)	3 (1)	1 (0.4)
Smoking, yes	130 (15)[e]	87 (13)[gg]	43 (18)[x]
Alcohol use, yes	357 (67)	255 (67)	102 (68)
BMI	27.1 (25 – 30.7)[f]	26.9 (25 – 30.7)[hh]	27.4 (25.1 – 30.8)[y]
Laboratory values			
Leucocytes (10^9/l)	18.2 (14.4 – 22.2)[g]	18 (14.3 – 21.9)[ii]	18.6 (14.8 – 23)[z]
CRP (mg/l)	297 (216 – 377)[h]	289 (201 – 359)[jj]	334 (239 – 425)[aa]
Imaging severity			
CT severity index	6 (4 – 8)[i]	5 (4 – 6)[kk]	8 (6 – 10)
Parenchymal necrosis	542 (60)[j]	330 (51)	212 (87)
Right	15 (2)	11 (2)	4 (2)
Left	52 (6)	43 (7)	9 (4)
Central	233 (26)	104 (16)	129 (53)
Subtotal	76 (8)	34 (5)	42 (17)
Diffuse	161 (18)	136 (21)	25 (10)

Table 1 Continued.

		Confirmed DPD	
	Overall, N = 896	**No, N = 653**	**Yes, N = 243**
Extent of necrosis	[j]		[bb]
<30%	259 (29)	186 (56)	73 (30)
30-50%	132 (15)	76 (23)	56 (23)
>50%	150 (17)	68 (21)	82 (34)
Extrapancreatic necrosis only	354 (40)	323 (49)	31 (13)
Follow-up (m)	75 (41 – 151)	76 (41 – 151)	72 (40 – 150)

Data are presented as n (%) or median (P25-P75).
Missing patients: a=3, b=3, c=3, d=2, e=477, f=494, g=82, h=125, i=8, j=1 missing data on pattern and extent of parenchymal necrosis, k=2, l=2, m=2, n=2, o=167, p=217, q=39, r=52, s=1, t=1, u=1, v=1, w=1, x=126, y=130, z=26, aa=34, bb=1, cc=2, dd=2, ee=2, ff=1, gg=351, hh=364, ii=56, jj=91, kk=1
N indicates *number;* DPD, *disruption or disconnection of the pancreatic duct;* ERCP, *endoscopic retrograde cholangiopancreaticography;* ASA, *American Society of Anaesthesiologists;* BMI, *body mass index;* CRP, *c-reactive protein;* CT, *computed tomography*

Clinical outcome

Infected necrosis occurred in 481 of the 896 patients (54%). Invasive intervention of the pancreas was performed in 465 patients (52%). A total of 223 patients (25%) died during initial admission or follow-up thereafter; cause of death was directly related to pancreatitis in 106 patients (48%). In 245 of 896 patients (27%) a pancreatic fistula was identified, in whom DPD could not always be confirmed. The most frequently reported type of pancreatic fistula was a pancreato-cutaneous fistula (n = 186, 45%). All morphological characteristics and functional findings of DPD are listed in Table 2. Univariate analyses regarding clinical outcomes, pancreatic interventions, and long-term complications in patients with and without confirmed DPD are presented in the supplementary appendix (see Supplementary Appendix Table S4).

The results of the multivariate analyses, fit to quantify the independent effect of confirmed DPD on the different clinical outcomes and need for interventions occurring more than 1 week after admission, are summarized in Table 3. A confirmed DPD was associated with new-onset intensive care unit admission (adjusted OR [aOR] 2.52; 95% CI 1.62–3.93), persistent or new-onset organ failure (aOR 2.80; 95% CI 1.71–4.60 and OR 2.26; 95% CI 1.45–3.55), and with the occurrence of infected necrosis (aOR 4.63; 95% CI 2.87–7.64). Associations were also found between confirmed DPD and pancreatic intervention (aOR 7.55; 95% CI 4.23–13.96), additional pancreatic intervention (aOR 2.62; 95% CI 1.57–4.42), and pancreatic interventions during follow-up (aOR 9.71; 95% CI 5.37–18.30). Patients with a confirmed DPD were more frequently readmitted (aOR 3.40; 95% CI 2.21–5.33), particularly for readmissions related to reintervention (aOR 3.19; 95% CI 1.94–5.36). Furthermore, a confirmed DPD

was associated with a higher risk of recurrent pancreatitis (aOR 2.08; 95% CI 1.32–3.29), chronic pancreatitis (aOR 2.73; 95% CI 1.47–5.15), and endocrine pancreatic insufficiency (aOR 1.63; 95% CI 1.05–2.53). Multivariate sensitivity analyses, fit to quantify the independent effect of possible DPD on the different clinical outcomes and need for interventions occurring more than 1 week after admission, are summarized in Supplementary Appendix Table S5. A univariate sensitivity analysis comparing patients without DPD with patients with DPD confirmed solely by an amylase level exceeding 3 times the upper limit did not show any differences in outcome (see Supplementary Appendix Table S6). In a second univariate analysis, a worse clinical outcome was found for patients with functional DPD compared with patients with only imaging-based DPD (see Supplementary Appendix Table S7).

Table 2 Morphological characteristics and functional findings of a disrupted or disconnected pancreatic duct

	Confirmed DPD N = 243 (27%)	**Possible DPD N = 415 (46%)**
Morphological characteristics*	169 (70)[a]	310 (75)[f]
DPD on imaging	103 (42)	NA
Functional – High amylase in percutaneous drain fluid	194 (84)[b]	NA[g]
Clinical findings		
High amylase during ETD	10 (13)[c]	19 (13)[h]
Pancreatic fistula present†	188 (77)	194 (47)
Long-term drainage	96 (40)[d]	114 (28)[i]
Recurrent collection	93 (38)[e]	120 (29)[j]
Pancreatic fistula, n = 198	190 (78)	197 (47)
Pancreatic cutaneous fistula, n = 186	183 (75)	186 (45)
Pancreatic abdominal fistula, n = 27	27 (11)	27 (7)
Pancreatic pleural fistula, n = 11	10 (4)	11 (3)
Pancreatic CBD fistula, n = 7	5 (2)	7 (2)

Data are presented as n (%).
*central or subtotal necrosis
†excluding fistulas of the gastrointestinal tract
a=3 missing, b=in 11 patients no percutaneous intervention was performed, c=in 166 patients no ETD was performed, in 67 patients ETD was performed with low amylase in drain fluid or no amylase measurement, d=2 missing patients, 29 patients died before removal of drain, e=in 15 patients no follow-up CT was performed, in 13 patients no intervention was performed and therefore not applicable, 34 patients died within 6 months after discharge before recurrent collection could occur, f=3 missing, g=in 48 patients no percutaneous intervention was performed, h=in 270 patient no ETD was performed, in 126 patients ETD was performed with low amylase or no amylase measurement, i=2 missing patients, 48 patients died before removal of drain, j=in 40 patients no follow-up CT was performed, in 36 patients no intervention was performed and therefore not applicable, 65 patients died within 6 months after discharge before recurrent collection could occur.
DPD indicates *disrupted or disconnected pancreatic duct;* ETD, *endoscopic transluminal drainage;* CBD, *common bile duct*

Table 3 Comparison of patients with and without confirmed DPD and its association with clinical outcome, interventions and long-term complications occurring more than 7 days after admission

		Confirmed DPD			
	Overall, N = 896	**No, N = 653**	**Yes, N = 243**	**OR (95% CI)***	***P*†**
Death pancreatitis related					
Death after 7 days	98 (11)	62 (10)	36 (15)	1.26 (0.74 – 2.14)	0.389
ICU-admission					
Ongoing	231 (31)[c]	132 (23)[i]	99 (56)[c]	6.81 (2.83 – 17.02)	**<0.001**
New onset	218 (25)[d]	27 (21)[i]	30 (31)[c]	2.52 (1.62 – 3.93)	**<0.001**
Organ failure					
Ongoing	173 (48)[e]	95 (15)[t]	78 (32)[n]	2.80 (1.71 – 4.60)	**<0.001**
Ongoing MOF	115 (71)[f]	57 (63)	58 (79)	3.11 (1.78 – 5.45)	**<0.001**
New onset	204 (56)[a]	109 (17)[b]	95 (40)[i]	2.26 (1.45 – 3.55)	**0.001**
New onset MOF	142 (71)[e]	74 (69)[i]	68 (74)[bb]	2.32 (1.40 – 3.85)	**0.001**
Infected necrosis	442 (50)[a]	245 (38)[c]	197 (81)[n]	4.63 (2.87 – 7.64)	**<0.001**
Gastrointestinal complications^	123 (14)[a]	51 (8)[i]	72 (30)[b]	3.00 (1.87 – 4.88)	**<0.001**
Interventions					
Pancreatic intervention	459 (52)	238 (99)	221 (98)	7.55 (4.23 – 13.96)	**<0.001**
Percutaneous catheter drainage	319 (36)	141 (22)	178 (73)	6.29 (4.14 – 9.67)	**<0.001**
Need for additional intervention	355 (77)	161 (68)	194 (86)	2.62 (1.57 – 4.42)	**<0.001**
Follow-up intervention	83 (18)	22 (9)	61 (27)	9.71 (5.37 – 18.30)	**<0.001**
Ascites drainage	77 (9)	26 (4)[n]	51 (21)[b]	5.15 (2.93 – 9.30)	**<0.001**
Readmission					
Readmission	601 (68)	403 (62)	198 (81)	3.40 (2.21 – 5.33)	**<0.001**
For re-intervention	118 (20)	38 (9)	80 (40)	3.19 (1.94 – 5.36)	**<0.001**
Long-term complications					
Recurrent pancreatitis	196 (25)[j]	124 (21)[z]	72 (30)[cc]	2.08 (1.32 – 3.29)	**0.002**
Chronic pancreatitis	84 (11)[k]	42 (7)[aa]	42 (17)[dd]	2.73 (1.47 – 5.15)	**0.002**
Endocrine pancreatic insufficiency	241 (30)[l]	130 (23)[aa]	111 (46)[ee]	1.63 (1.05 – 2.53)	0.030
Exocrine pancreatic insufficiency	160 (20)[m]	86 (15)[aa]	74 (34)[ff]	1.35 (0.85 – 2.15)	0.200

Data are presented as n (%) or median (interquartile range).
*Binomial regression (binary data): patients (n=8) who died in the first week after admission were excluded for analysis.
†After the Bonferroni correction was applied, the correct p-value considered statistically significant was <0.0025. The statistically significant p-values are stated in bold.
Missing patients: a=5, b=2, c=4, d=7, e=9, f=17, g=10, h=183, i=3, j=105, k=109, l=102 patients excluded within one year after admission and therefore excluded in case potential outcome was not reached yet, m=103 patients excluded within one year after admission and therefore excluded in case potential outcome was not reached yet, n=1, o=12, p=38, q=40, r=40, s=41, t=8, u=23, v=67, w=69, x=62, y=63, z=73, aa=75, bb=6, cc=32, dd=33, ee=26, ff=28
N indicates *number;* DPD, *disrupted or disconnected pancreatic duct;* OR, *Odds Ratio;* CI, *Confidence Interval;* ICU, *intensive care unit;* MOF, *multiple organ failure*

Treatment

The wide range of treatment strategies for patients with confirmed DPD is shown in the Sankey diagram (Figure 2). Overall, 33 of 243 patients (14%) died before resolution of DPD. DPD was resolved in the remaining 208 patients with 138 of 208 patients (66%) requiring only 1 step of treatment. After the last step of treatment for DPD, 45 of 208 patients (22%) had a recurrent peripancreatic collection that did not require intervention; this condition occurred most frequently after percutaneous catheter drainage as the final step of treatment. The median duration to resolution of DPD was 182 (P25–P75: 103–452) days.

Conservative treatment (i.e., no invasive intervention), was initiated in 14 patients (6%) with a confirmed DPD. No data on drug therapy were available. Four patients (29%) had a recurrent peripancreatic collection. Three of the 4 patients (75%) underwent endoscopic transluminal drainage.

Percutaneous catheter drainage was the first treatment step in 184 patients (76%) with confirmed DPD. Percutaneous catheter drainage during the index admission was sufficient for 108 patients (59%), with the remaining 76 patients (41%) requiring other types of invasive interventions. Of the 108 patients who required only percutaneous catheter drainage, 27 (25%) had recurrent peripancreatic collections during follow-up that were treated conservatively. The median time to resolution of DPD for patients treated only with percutaneous catheter drainage was 131 days (P25–P75: 87–206).

Endoscopic transluminal drainage was performed as a first treatment step in 20 patients (8%), with removal of the plastic pigtails in 15 of the 20 patients (75%). In 9 of the 15 patients (60%), an additional invasive intervention was required after removal of the plastic pigtails. The median time until resolution was 112 days (P25–P75: 55–153). In 76 patients (31%), whose treatment did not initiate with endoscopic transluminal drainage, endoscopic transluminal drainage was performed as part of a follow-up procedure. This resulted in resolution of DPD in 51 patients (76%). In 6 of the patients (9%), peripancreatic collections recurred after removal of the last plastic pigtails.

Endoscopic retrograde cholangiopancreatography was the initial treatment in 5 patients (2%). In 61 patients (25%), an ERCP with stent placement into the pancreatic duct was attempted in conjunction to other treatment modalities with successful stent placement in 42 patients (69%). In 2 patients (5%), the disruption of the pancreatic duct could be bridged, whereas in 19 patients (45%), the disruption could not be bridged and the stent was therefore left either transpapillary or in the necrotic cavity. A follow-up intervention was performed in 34 patients (81%) who underwent ERCP with successful stent placement.

Surgery was performed in none of the patients as initial treatment. A total of 22 patients (9%) eventually underwent surgery, which resulted in resolution of

DPD in 19 patients (86%). The following surgical interventions were performed: surgical cystgastrostomy of a peripancreatic collection (n = 12), distal pancreatectomy (n = 4), pancreatojejunostomy (n = 5), gastrojejunostomy (n = 1), surgery with a splint to bridge the defect in the pancreatic duct (n = 1), and fistulectomy (n = 2). DPD was not resolved after surgery in 2 patients (9%) and still required a percutaneous catheter drain in situ at the last round of follow-up (1 after fistulectomy and 1 after both surgical cystgastrostomy and fistulectomy).

Predictive indicators of DPD

The prediction model for developing confirmed DPD in patients with necrotizing pancreatitis is summarized in Table 4. The following 2 factors were independent predictors of DPD: central or subtotal pancreatic necrosis on CT (OR 9.49; 95% CI 6.31–14.29) and high levels of serum CRP in the first 48 hours of admission (OR 1.02 per 10-point increase; 95% CI 1.00–1.03).

Table 4 Predictive features for developing DPD in patients with necrotizing pancreatitis

	OR (95% CI)	*P*
Age[a,b]	0.93 (0.88 – 1.00)	0.023
Male	1.18 (0.83 – 1.70)	0.357
ASA II	1.39 (0.95 – 2.05)	0.091
ASA ≥III	1.23 (0.70 – 2.15)	0.478
Leucocytes[c]	1.01 (0.95 – 1.07)	0.711
CRP[d,b]	1.02 (1.00 – 1.03)	0.010
Pattern parenchymal necrosis		
Central or subtotal	9.49 (6.31 – 14.29)	<0.001
Right, left or diffuse	1.35 (0.82 – 2.23)	0.243

Missing data were multiply imputed. The discriminative ability of the model to predict confirmed DPD was excellent on the internal dataset, with a c-statistic (i.e. area under the receiver operating curve) of 0.79.
[a]In steps of 5 years, [b]a slightly non-linear association was found with the outcome, [c]highest leucocytes in the first 48 hours after admission in steps of 3, [d]highest CRP in the first 48 hours after admission in steps of 10.
DPD indicates *disrupted or disconnected pancreatic duct;* OR, *adjusted odds ratio;* CI, *confidence interval;* AUC, *area under the curve;* ASA, *American Society of Anesthesiologists;* CRP, *c-reactive protein*

DISCUSSION

In this first long-term analysis of a nationwide prospective cohort, 27% of 896 patients with necrotizing pancreatitis had a confirmed DPD, which was associated with worse short-term and long-term outcomes. Central and subtotal pancreatic necrosis on imaging and high levels of serum CRP in the first 48 hours were independent predictors for DPD.

In accordance with the current guidelines[19–21] and a recent survey,[47] DPD was most frequently diagnosed on MRCP and ERCP. The reported sensitivity of (secretin) MRCP is lower than that of ERCP, but does not carry the risks of procedure-related complications.[24,38–40] Because sensitivity of 100% was demonstrated for amylase measurements in drain fluid,[43,48,49] we have chosen to consider this as a diagnostic tool to confirm DPD. However, each patient in the study did not consistently receive measurement of amylase levels in external drain fluid and standardized imaging leading to delayed or even missed diagnoses of the DPD. Our diagnosis of DPD at a median of 57 days after admission was made post hoc for study purposes. Therefore, during their admission, DPD was probably not recognized as such in all patients and could have been identified more frequently and earlier. These findings, alongside with the apparent negative clinical impact of DPD, clearly indicate that structured diagnostics should be performed in the future in these patients.

Necrosis of the pancreatic parenchyma in acute pancreatitis results in the loss of viable pancreatic tissue and the potential loss of pancreatic duct integrity. Spontaneous resolution may occur in the instances when the pancreatic tail is also affected and/or pancreatic tissue atrophies. If the tail remains intact, patients will experience clinical consequences[19,50] caused by a continuous leakage of pancreatic fluid, which may result in persistent or recurrent peripancreatic collections, pancreatic ascites, or external pancreatic fistula.[2,3,7–12] Based on our findings, DPD leads to extended hospital stays, frequent interventions, and a higher risk of complications. In this study, DPD was clearly associated with an increase, including repeat, interventions during admission, and long-term follow-up, in line with previous studies.[9,10,13,16,27]

Of more importance, our study was the first to demonstrate an association between the presence of DPD and a more severe disease course, such as new intensive care unit admission more than 1 week after admission, persistent and new-onset organ failure, and recurrent and chronic pancreatitis. In line with previous studies, we also found DPD to be associated with a higher risk of endocrine pancreatic insufficiency, probably caused by atrophy of upstream pancreatic tissue during subsequent years because of ductal hypertension.[28–30] A potential shortcoming of our study was the definition used for endocrine pancreatic insufficiency, which was based on the use of antidiabetic medication rather than the results of laboratory test on serum glucose. It is to note we deliberately chose to include only clinical outcome events that arose 7 days after admission because presently there is insufficient data to determine a definite time of development of DPD. Given the data limitation, we hypothesized that DPD develops in line with necrosis, typically occurring in the first week after admission.[51]

In general, persistent peripancreatic collections in the presence of DPD do not

resolve spontaneously without intervention. In this study, percutaneous catheter drainage was still the first choice of treatment for infected necrosis. After this treatment, however, DPD maintains the production of pancreatic fluids, which leads to therapeutic failure. In most of the patients treated only with percutaneous catheter drainage, spontaneous resolution of DPD occurred without follow-up interventions. However, the average duration of drainage was almost 5 months, which may have a negative impact on the patients' quality of life.

At present, endoscopic transluminal drainage is the preferable first step in the treatment for infected necrosis;[6,33,52] the primary benefit of which is a decrease in the number of patients with a pancreatic cutaneous fistula. However, the presence of DPD may, however, guide the choice to initially use a lumen apposing metal stent (LAMS) or plastic double pigtails stent and whether to leave the plastic pigtails in situ. In our study, only a few patients with confirmed DPD underwent endoscopic transluminal drainage as the first step for either infected necrosis or DPD. However, we may have missed patients with proven DPD who underwent endoscopic drainage as an initial treatment. Because the endoscopic drainage route prevents clinical problems such as a pancreato-cutaneous fistula DPD is less often diagnosed because a lack of clinical symptoms, thereby reducing the number of confirmed DPD cases in the patient population in the study. The available literature suggests that endoscopic transluminal drainage is sufficient to prevent DPD's clinical problems at a success rate ranging from 81% to 100%.[7,10,30,31,50] In line with previous studies, after removal of the plastic pigtails, repeat intervention was required in 60% of the patients with DPD in this study. This outcome favors long-term indwelling transmural plastic stents, given this treatment is known to be safe and efficient.[1,30,53,54] Nonetheless, in the clinical setting, LAMS can still be used if preferred. It is, however, recommended that patients are screened for DPD before the LAMS are removed, so that the LAMS can be replaced with plastic pigtails when DPD is present. This emphasizes once more the importance of a standardized diagnostic protocol for patients with a potential DPD.

Today, evidence-based guidelines do not recommend specific treatment for DPD. In this study, the management of DPD varied widely, from conservative to surgical intervention. A previous systematic review by our group extensively compared treatments for DPD and presented high pooled success rates for all the different treatment strategies.[31] Most studies preferred internal drainage with endoscopic management by placing a stent during ERCP.[1,7,11,23,25,31,42,55–58] In 69% of the patients in whom an ERCP was attempted in our study, a pancreatic duct stent was successfully placed; bridging of the disruption occurred in only 2 patients. It should be noted, data on the location of the stent were not available for all patients. Even if ERCP was successful, a follow-up intervention was often

required (81%). This indicates that pancreatic duct stenting is a technically difficult procedure in necrotizing pancreatitis with a relatively low success rate. The low success rate may be because the detached part of the pancreas is often inaccessible and therefore cannot be drained successfully. In addition, the treatment success rate of stent placement may be related to the degree and location of DPD,[39,50,57,59] with a high risk of stent migration and recurrence rate.[1] This again emphasizes the importance of accurate diagnosis of DPD and its degree. Furthermore, new-onset infected necrosis occurred in all 5 patients who underwent pancreatic duct stenting,[59] in line with a previous study in which all patients who underwent prophylactic stenting of the pancreatic duct developed infected necrosis. These results implicate that stenting the pancreatic duct in the presence of sterile necrosis is not recommended, reducing the early treatment options for DPD.

Surgery is widely regarded as the cornerstone of DPD treatment and is considered as standard of care by 1 guideline.[19] In this study, only 3% of patients with DPD underwent pancreatic surgery, contrary to a previous study in which 68% underwent surgery.[60] This may be explained by their relatively rapid switch to surgical intervention (after a median of 128 [P25–P75: 20–2,430] days), while patients in our study had resolution of the DPD with percutaneous catheter drainage only after a median of 131 days. Conversely, the current evolution of advanced endoscopy is expected to increase the use of surgery in patients with DPD. In addition to endoscopic transluminal drainage of recurrent peripancreatic collections with maintenance of long-term transluminal stents, endoscopic ultrasound–guided pancreatogastrostomy is increasingly reported and carries a minimal risk of diabetes.[3,7,61,62] Conversely, adequate surgery may provide a definite solution, safeguarding patients from the burden of multiple procedures and prolonged morbidity, as seen in patients with chronic pancreatitis.[17,63,64] The 2 patients with insufficient result of surgery may suggest that if surgery is performed, a distal pancreatectomy - usually including splenectomy - is the approach with the highest success rate and shelters patients undergoing from multiple procedures. However, distal pancreatectomy results in a significant risk of insulin dependent diabetes. Increasingly, islet auto transplantation from the excised tail is used to avoid the risk of surgically induced or worsened diabetes,[65–68] though this technique may not be possible in patients with an atrophic or damaged tail.

The findings of our study have several implications for clinical practice. Ideally by the end of the first week of admission, implementation of a standardized diagnostic work-up for DPD in patients at high risk for DPD (i.e., subtotal and central necrosis) enables individually curated patient care and a likely reduction in healthcare costs. The wide range of treatment options for DPD paired alongside

the poor clinical outcome in patients with DPD makes it a complex clinical challenge. A potential solution would be to implement a step-up treatment algorithm for patients with DPD, gradually transitioning from minimally invasive to more invasive surgical procedures. Timely intervention in patients with DPD should be considered to prevent potential complications; however, this should be investigated further.

To our knowledge, this study is the first large nationwide multicenter cohort study based on prospectively collected data with a long-term follow-up covering the entire clinical spectrum of DPD in necrotizing pancreatitis. However, this study has some limitations. First, it composes of a post hoc analysis, albeit of prospectively collected data, lacking a standardized diagnostic approach. As a result, the incidence of DPD may be underrepresented, and relevant data may be lacking, such as the relationship between drain output volume and the degree of DPD (i.e., partial or complete DPD). The degree of DPD is a particularly important data point that is lacking because it may influence the treatment success rate.[39,50,57,59] In addition, treatment for infected necrosis and DPD are intertwined and cannot always be specifically assigned to 1 of the 2 entities. More broadly, a specific treatment is not always listed as the starting point of DPD treatment in patients with DPD. To prevent bias, we therefore take the first step of treatment for infected necrosis as the first step in the treatment for DPD. Given the uncertainty of the indication and timing of the reported treatments (i.e., confounding by indication), alongside the range of treatments used, we were unable to make a valid comparison between different treatments or to investigate the impact of the interventions for DPD on clinical outcomes. Separately, there is a high incidence of infected necrosis in our cohort, which is not a completely representative reflection of the clinical practice; this incidence rate could be explained by the fact that patients were registered with the Dutch Pancreatitis Study Group to participate in randomized studies regarding infected necrosis, which may have influenced the incidence rate. Unfortunately, patients did not undergo a predefined diagnostic work-up; therefore, we cannot rule out that the other patients by definition did not have DPD. Second, patients did not follow a predefined treatment protocol, which may have induced bias. On the contrary, this study is a reflection of what happens in current clinical practice. Our study sets out clear points on where future research should focus, starting with a well-designed diagnostic study to identify all patients with DPD, including the degree, and to identify predictive factors for DPD. Subsequently, a prospective clinical intervention study is needed to investigate the best treatment algorithm for patients with clinical consequences of DPD.

In conclusion, DPD occurs in at least 1 in every 4 patients with necrotizing pancreatitis. Diagnosis of DPD seems to be often missed because of a lack of

standardized diagnostics. Development of standard diagnostic tools and treatment plans is important because DPD seems to be a major factor in determining short-term and long-term complications in the clinical course of necrotizing pancreatitis. High levels of serum CRP in the first 48 hours after admission and central or subtotal pancreatic necrosis on CT were identified as independent predictors for developing DPD. These findings can be leveraged to guide diagnostic and therapeutic strategies in clinical practice and develop future clinical studies.

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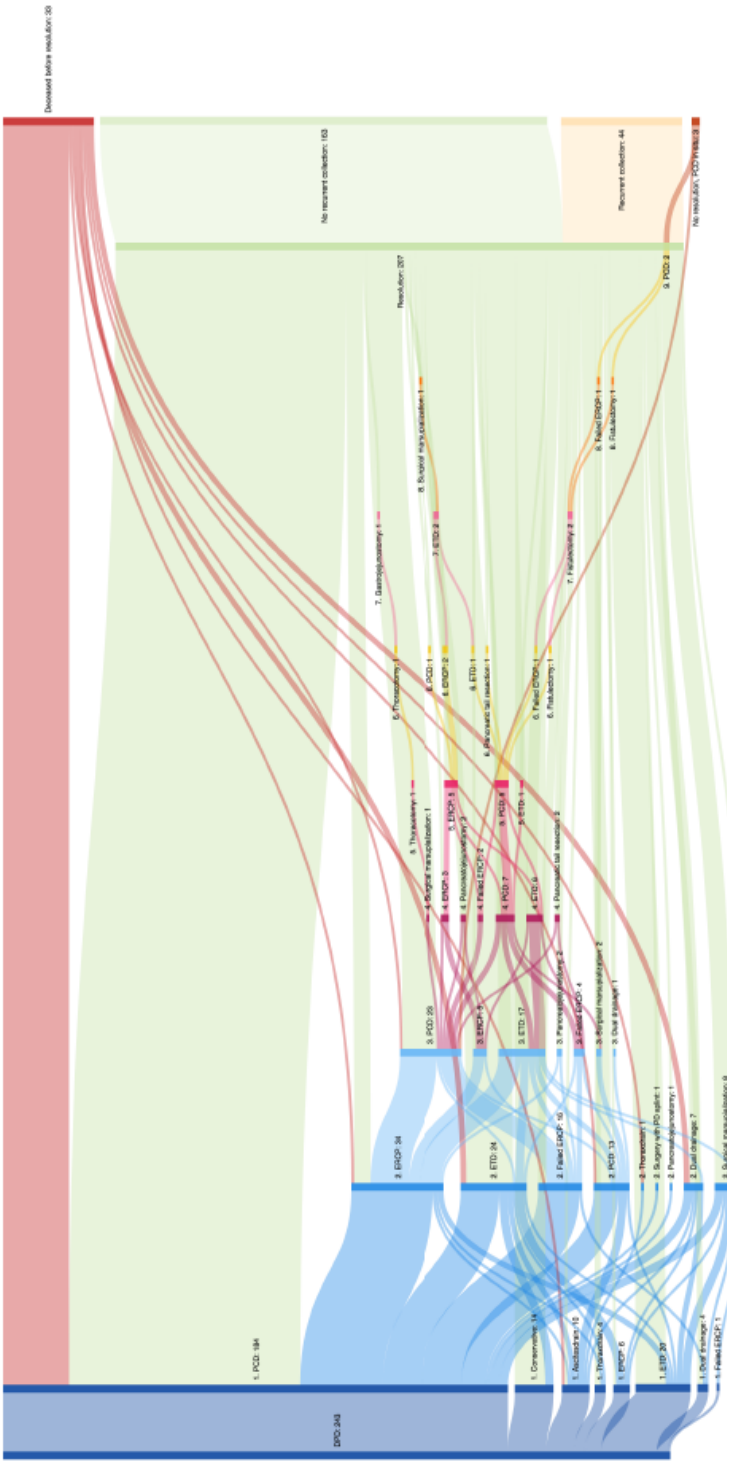

Figure 2 The Sankey diagram of different treatment steps in 243 patients with a confirmed disrupted or disconnected pancreatic duct. Resolution of DPD was defined as the date the patient underwent the last endoscopic or surgical intervention or in case a percutaneous catheter drain was left during the last intervention, the date the last percutaneous catheter drain was removed.
DPD indicates disruption or disconnection of the pancreatic duct; ERCP, endoscopic retrograde cholangiopancreaticography; ETD, endoscopic transluminal drainage; PCD, percutaneous catheter drainage; PD, pancreatic duct.

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SUPPLEMENTARY APPENDIX

Table S1 Definitions

Pancreatic necrosis	Diffuse or focal area(s) of non-enhancing pancreatic parenchyma as detected on contrast enhanced CT (CECT)
Extrapancreatic necrosis	Persistent peripancreatic fluid collections on CECT in the absence of pancreatic parenchymal non-enhancement
Infected necrosis	One of the following: a) gas configurations on contrast-enhanced CT or b) positive culture from either a fine needle aspiration or the first drainage procedure from the (peri)pancreatic collection/walled-off necrosis
Pancreas intervention	All interventions for (peri)pancreatic collections and/or necrosis (e.g. percutaneous catheter drainage, endoscopic transluminal drainage, surgical or endoscopic necrosectomy), without ascites drainage, ERCP or decompression laparotomies
Follow-up intervention	All pancreatic interventions required more than three months after the removal of the last drain removal
Confirmed DPD	Confirmed partial or complete DPD was defined as one or more of the following: 1) (radiological) confirmation by: A) ERCP; i) extravasation of contrast medium from the ductal system; or ii) a cut-off or blowout of the pancreatic duct with inability to demonstrate the upstream pancreatic duct; B) MRI/MRCP: an interruption of pancreatic ductal continuity; or C) fluoroscopic fistulography: a connection between the pancreatic duct and the external environment; or 2) functional confirmation: an amylase level in external drain fluid, more than one day after placement of the percutaneous catheter drain, exceeding three times the upper limit of normal amylase serum level. No distinction could be made between a partial disruption or circumferential disconnection with the current data
Possible DPD	Possible DPD was defined as one or more of the following criteria (i.e. without meeting the criteria for confirmed DPD): 1) morphological signs on imaging, defined as central or subtotal pancreatic necrosis, 2) amylase or lipase levels exceeding three times the upper limit of normal in fluid obtained during endoscopic drainage (i.e. not from percutaneous catheter drain fluid), 3) the presence of other types of internal pancreatic fistula defined as a connection between the pancreas and any other organ depending on the site of the fistula (pleural and common bile duct) and/or 4) need for long-term (≥90 days) percutaneous catheter drainage without an amylase measurement in drain fluid
Resolution of DPD	When no follow-up intervention is required or the percutaneous catheter drain can be removed.
Pancreatic fistula	A connection between the pancreas and any other organ depending on the site of the fistula
Pancreatic cutaneous fistula	A connection between the pancreas and the cutis, confirmed with either an amylase content level in drain fluid exceeding three times the upper limit of normal amylase serum level or confirmed with imaging or during surgery
Pancreatic pleural fistula	A connection between the pancreas and the pleura, confirmed with either an amylase content level in pleural fluid exceeding three times the upper limit of normal amylase serum level or confirmed with imaging or during surgery
Pancreatic common-bile duct fistula	A connection between the pancreas and the common-bile duct confirmed with any (imaging) modality

Table S1 Continued.

Gastrointestinal complication	Perforation, fistula or ischemia/necrosis of the gastrointestinal tract, either spontaneous or iatrogenic
Enterocutaneous fistula	Enterocutaneous fistula is defined as secretion of content from the gastrointestinal tract from a percutaneous drain, drainage canal after removal of drains, or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery
Organ failure	No organ failure is assumed in the absence of lab and/or information in the discharge letter and/or notes.Definitions are adapted from the Atlanta classification and the same as previously used in the PANTER and TENSION trial
Cardiovascular	Systolic blood pressure < 90 mmHg despite adequate fluid resuscitation or need for vasopressor support
Pulmonary	PaO2 < 60 mmHg despite FiO2 30%, or the need for mechanical ventilation
Renal	Serum creatinine >177 mmol/L after rehydration or need for hemofiltration or hemodialysis
Early organ failure	Occurrence of organ failure within the first seven days after admission
Multiple organ failure	Failure of 2 or more organ systems on the same day
Pancreatic exocrine insufficiency	Exocrine insufficiency is defined as an abnormal fecal elastase test (<200 mg/g feces) (not present before onset pancreatitis)
Pancreatic endocrine insufficiency	Endocrine insufficiency is defined as needing insulin or oral antidiabetic drugs (not present before onset pancreatitis)
Recurrent pancreatitis	Recurrent pancreatitis was diagnosed according to the revised Atlanta classification, i.e. at least two out of three of the following criteria: 1) clinical presentation with abdominal pain, 2) serum amylase or lipase levels exceeding three times the upper limit of normal and/or 3) abdominal imaging confirmed diagnosis of acute pancreatitis
Chronic pancreatitis (definite)	Defined according to the M-ANNHEIM criteria for definite chronic pancreatitis

CT indicates *computed tomography;* DPD, *disrupted or disconnected pancreatic duct;* ERCP, *endoscopic retrograde cholangio pancreaticography;* MRI, *magnetic resonance imaging;* MRCP, *magnetic resonance cholangio-pancreatography*

Table S2 Patient and disease characteristics in 896 patients with necrotizing pancreatitis

			Confirmed DPD		
	Overall N = 896	**Possible DPD N = 415**	**Yes N = 243**	**No N = 653**	***P***
Age (y)	58 (47 – 69)	59 (48 – 69)	58 (46 – 68)	59 (47 – 70)	0.12
Male sex	571 (64)	282 (69)	169 (70)	402 (62)	**0.03**
Etiology					
Biliary	432 (48)	196 (47)	112 (46)	320 (49)	0.45
Alcohol	159 (18)	69 (17)	39 (16)	120 (18)	0.43
Post-ERCP	31 (4)	7 (2)	5 (2)	26 (4)	0.22
Idiopathic	180 (20)	98 (24)	58 (24)	122 (19)	0.09
Other	94 (11)	45 (11)	29 (12)	65 (10)	0.39
Medical history					
Cardiovascular	377 (42)[a]	166 (40)[k]	96 (40)[t]	281 (43)[cc]	0.36
Pulmonary	91 (10)[b]	40 (10)[l]	26 (11)[u]	65 (10)[dd]	0.71
Chronic renal	28 (3)[c]	13 (3)[m]	7 (3)[v]	21 (3)[ee]	1.00
Diabetes mellitus	108 (12)[d]	49 (12)[n]	27 (11)[w]	81 (12)[ff]	0.65
ASA					
I	298 (33)	131 (32)	75 (31)	223 (34)	0.38
II	471 (53)	233 (56)	135 (56)	336 (52)	0.29
III	123 (14)	49 (12)	32 (13)	91 (14)	0.83
IV	4 (1)	2 (0.5)	1 (0.4)	3 (1)	1.00
Smoking, yes	130 (15)[e]	64 (15)[o]	43 (18)[x]	87 (13)[gg]	0.13
Alcohol use, yes	357 (67)	167 (67)	102 (68)	255 (67)	0.84
BMI	27.1 (25 – 30.7)[f]	27.7 (25.2 – 30.9)[p]	27.4 (25.1 – 30.8)[y]	26.9 (25 – 30.7)[hh]	0.68
Laboratory values					
Leucocytes (10^9/l)	18.2 (14.4 – 22.2)[g]	18.3 (14.8 – 22.7)[q]	18.6 (14.8 – 23)[z]	18 (14.3 – 21.9)[ii]	0.09
CRP (mg/l)	297 (216 – 377)[h]	321 (237 – 400)[r]	334 (239 – 425)[aa]	289 (201 – 359)[jj]	**<0.01**
Imaging severity					
CT severity index	6 (4 – 8)[i]	8 (6 – 10)	8 (6 – 10)	5 (4 – 6)[kk]	**<0.01**
Parenchymal necrosis[j]	542 (60)	371 (89)	212 (87)	330 (51)	**<0.01**
Right	15 (2)	7 (2)	4 (2)	11 (2)	1.00
Left	52 (6)	15 (4)	9 (4)	43 (7)	0.11
Central	233 (26)	233 (56)	129 (53)	104 (16)	**<0.01**
Subtotal	76 (8)	76 (18)	42 (17)	34 (5)	**<0.01**
Diffuse	161 (18)	36 (9)	25 (10)	136 (21)	**<0.01**
Extent of necrosis[j]		[s]	[bb]		
<30%	259 (29)	122 (29)	73 (34)	186 (56)	0.68
30-50%	132 (15)	105 (25)	56 (26)	76 (23)	**<0.01**
>50%	150 (17)	143 (35)	82 (39)	68 (21)	**<0.01**
Extrapancreatic necrosis only	354 (40)	44 (11)	31 (13)	323 (49)	**<0.01**
Follow-up (m)	75 (41 – 151)	69 (37 – 146)	72 (40 – 150)	76 (41 – 151)	0.62

Data are presented as n (%) or median (interquartile range: P25-P75).
Missing patients: a=3, b=3, c=3, d=2, e=477, f=494, g=82, h=125, i=8, j=1 missing data on pattern and extent of parenchymal necrosis, k=2, l=2, m=2, n=2, o=167, p=217, q=39, r=52, s=1, t=1, u=1, v=1, w=1, x=126, y=130, z=26, aa=34, bb=1, cc=2, dd=2, ee=2, ff=1, gg=351, hh=364, ii=56, jj=91, kk=1
N indicates *number;* DPD, *disruption or disconnection of the pancreatic duct;* ERCP, *endoscopic retrograde cholangiopancreaticography;* ASA, *American Society of Anesthesiologists;* BMI, *body mass index;* CRP, *c-reactive protein;* CT, *computed tomography*

Table S3 Used modalities for diagnosing a confirmed disrupted or disconnected pancreatic duct

	Imaging	Imaging + functional*	Functional	Total
Confirmed DPD	**48**	**55**	**140**	**243**
CT	*NA*	*3 (6)*		3 (1)
MRI/MRCP	*27 (56)*	*10 (18)*		37 (15)
MRCP + CT	2 (4)	NA		2 (0.8)
MRI/MRCP + ERCP	3 (6)	17 (31)		20 (8)
MRI/MRCP + ERCP + CT	1 (2)	NA		1 (0.4)
MRI/MRCP + EUS	2 (4)	1 (2)		3 (1)
ERCP	*9 (19)*	*17 (31)*		26 (25)
ERCP + CT	NA	1 (2)		1 (0.4)
ERCP + EUS	1 (2)	NA		1 (0.4)
ERCP + fistulography	NA	1 (2)		1 (0.4)
Fistulography	*2 (4)*	*1 (2)*		3 (1)
EUS	*1 (2)*	*4 (7)*		5 (2)
Only functional confirmed DPD	NA	NA	140 (100)	140 (58)

Data are presented as n (%).
*DPD is functionally confirmed when amylase level in drain fluids exceeds 3 times the upper limit of normal amylase level
DPD indicates *disrupted or disconnected pancreatic duct;* CT, *computed tomography;* MRI, *magnetic resonance imaging;* MRCP, *magnetic resonance cholangio-pancreatography;* ERCP, *endoscopic retrograde cholangiopancreatography;* EUS, *endoscopic ultrasound*

Table S4 Univariate comparison of clinical outcomes, interventions and long-term complications in patients with and without a possible or confirmed DPD occurring 7 days after admission

		Possible DPD			Confirmed DPD		
	Overall, (N = 896)	No, (N = 481)	Yes, (N = 415)	*P*	No, (N = 653)	Yes, (N = 243)	*P*
Death pancreatitis related	98 (11)	33 (7)	65 (16)	**<0.001**	62 (10)	36 (15)	0.031
Death after 7 days	98 (11)	33 (7)	65 (16)	**<0.001**	62 (10)	36 (15)	0.031
ICU-admission							
Ongoing	231 (31)[c]	72 (17)[b]	159 (51)[a]	**<0.001**	132 (23)[i]	99 (56)[c]	**<0.001**
New onset	218 (25)[d]	11 (16)[b]	46 (29)[a]	**<0.001**	27 (21)[i]	30 (31)[c]	**<0.001**
Organ failure							
New onset	204 (56)[a]	60 (13)[n]	144 (35)[c]	**<0.001**	109 (17)[b]	95 (40)[i]	**<0.001**
Multi-organ failure	142 (71)[e]	37 (63)[b]	105 (74)[d]	**<0.001**	74 (69)[i]	68 (74)[bb]	**<0.001**
Ongoing	173 (48)[e]	50 (11)[d]	123 (30)[b]	**<0.001**	95 (15)[t]	78 (32)[n]	**<0.001**
Multi-organ failure	115 (71)[f]	25 (53)	90 (78)	**<0.001**	57 (63)	58 (79)	**<0.001**
Infected necrosis	442 (50)[a]	125 (27)[n]	317 (78)[c]	**<0.001**	245 (38)[c]	197 (81)[n]	**<0.001**
Abdominal compartment syndrome	24 (3)	5 (1)	19 (5)	**0.001**	10 (2)	14 (6)	**0.002**
Gastrointestinal complications ^	123 (14)[a]	24 (5)[b]	99 (24)[i]	**<0.001**	51 (8)[i]	72 (30)[b]	**<0.001**
Interventions							
Pancreatic intervention	459 (52)	106 (22)	353 (99)	**<0.001**	238 (99)	221 (98)	**<0.001**
Overall drainages, *no.*	2 (1 – 4)	1 (1 – 2)	2 (1 – 4)	**<0.001**	1 (1 – 3)	3 (1 – 5)	**<0.001**
Percutaneous catheter drainage	319 (36)	69 (14)	250 (61)	**<0.001**	141 (22)	178 (73)	**<0.001**
≥4 PCD	100 (31)	11 (16)	89 (36)	**0.002**	31 (22)	69 (39)	**0.002**
Length of PCD	78 (47 – 143)[h]	55 (32 – 75)[o]	92 (55 – 158)[u]	**<0.001**	59 (33 – 83)[u]	109 (66 – 183)[o]	**<0.001**
Endoscopic transluminal drainage	181 (20)	36 (8)	145 (35)	**<0.001**	105 (16)	76 (31)	**<0.001**
Necrosectomy	269 (30)	49 (10)	220 (54)	**<0.001**	131 (20)	138 (57)	**<0.001**
Endoscopic	79 (29)	15 (31)	64 (29)	**<0.001**	55 (42)	24 (17)	0.512
Surgical	198 (74)	34 (69)	164 (75)	**<0.001**	81 (62)	117 (85)	**<0.001**
Need for additional intervention	355 (77)	66 (63)	289 (81)	**<0.001**	161 (68)	194 (86)	**<0.001**

Table S4 Continued.

		Possible DPD			Confirmed DPD		
	Overall, (N = 896)	**No, (N = 481)**	**Yes, (N = 415)**	***P***	**No, (N = 653)**	**Yes, (N = 243)**	***P***
Follow-up intervention	83 (18)	10 (9)	73 (20)	**<0.001**	22 (9)	61 (27)	**<0.001**
Ascites drainages	77 (9)[o]	7 (1)	70 (17)[i]	**<0.001**	26 (4)[n]	51 (21)[b]	**<0.001**
Readmission							
Readmission	601 (68)	289 (61)	312 (76)	**<0.001**	403 (62)	198 (81)	**<0.001**
For re-intervention	118 (20)	12 (4)	106 (34)	**<0.001**	38 (9)	80 (40)	**<0.001**
Hospital stay length, overall	30 (16 – 69)	20 (13 – 37)	89 (55 – 134)	**<0.001**	38 (19 – 71)	107 (75 – 158)	**<0.001**
Initial	53 (24 – 101)	12 (3 – 25)	57 (24 – 100)	**<0.001**	22 (14 – 46)	71 (32 – 112)	**<0.001**
Readmission	21 (7 – 47)	30 (17 – 56)	32 (14 – 66)	**<0.001**	15 (4 – 32)	36 (17 – 75)	**<0.001**
Long-term complications							
Recurrent pancreatitis	196 (25)[j]	95 (21)[p]	101 (29)[v]	**0.016**	124 (21)[z]	72 (30)[cc]	**<0.001**
Chronic pancreatitis	84 (11)[k]	26 (6)[q]	58 (17)[w]	**<0.001**	42 (7)[aa]	42 (17)[dd]	**<0.001**
Endocrine pancreatic insufficiency	241 (30)[l]	75 (17)[r]	166 (47)[x]	**<0.001**	130 (23)[aa]	111 (46)[ee]	**<0.001**
Exocrine pancreatic insufficiency	160 (20)[m]	43 (10)[s]	117 (33)[y]	**<0.001**	86 (15)[aa]	74 (34)[ff]	**<0.001**

Data are presented as n (%) or median (interquartile range: P25-P75). All patients (n=8) who died in the first week were excluded. [$]After the Bonferroni correction was applied, the p-value considered statistically significant was <0.0025. The statistically significant p-values are stated in bold.

Missing patient: a=5, b=2, c=4, d=7, e=9, f=17, g=10, h=183, i=3, j=105, k=109, l=102 patients died within the first year and were therefore excluded, m=103 patients died within the first year and were therefore excluded , n=1, o=12, p=38, q=40, r=40, s=41, t=8, u=23, v=67, w=69, x=62, y=63, z=73, aa=75, bb=6, cc=32, dd=33, ee=26, ff=28

N indicates *number;* DPD, *disrupted or disconnected pancreatic duct;* RR, *Relative Risk;* CI, *Confidence Interval;* ICU, *intensive care unit;* PCD, *percutaneous catheter drainage*

Table S5 Multivariate comparison of clinical outcome, interventions and long-term complications occurring more than 7 days after admission in patients with and without possible or confirmed DPD

		Possible or confirmed DPD			
	Overall, N = 896	**No, N = 481**	**Yes, N = 415**	**OR (95% CI)***	***P***
Death pancreatitis related					
Death after 7 days	98 (11)	33 (7)	65 (16)	2.49 (1.37 – 4.57)	0.003
Death after 21 days	85 (10)	24 (5)	61 (15)	3.90 (2.02 – 7.84)	**<0.001**
ICU-admission					
Ongoing	231 (31)[c]	72 (17)[b]	159 (51)[a]	20.00 (6.46 – 65.32)	**<0.001**
New onset	218 (25)[d]	11 (16)[b]	46 (29)[a]	4.90 (2.67 – 9.01)	**<0.001**
Organ failure					
Ongoing	173 (48)[e]	50 (11)[d]	123 (30)[b]	8.15 (4.23 – 1.59)	**<0.001**
Ongoing multi-organ failure	115 (71)[f]	25 (53)	90 (78)	8.00 (3.75 – 17.04)	**<0.001**
New onset	204 (56)[a]	60 (13)[n]	144 (35)[c]	3.74 (1.96 – 7.11)	**<0.001**
New onset multi-organ failure	142 (71)[e]	37 (63)[b]	105 (74)[d]	6.46 (3.12 – 13.36)	**<0.001**
Infected necrosis	442 (50)[a]	125 (27)[n]	317 (78)[c]	8.10 (4.47 – 15.28)	**<0.001**
Gastrointestinal complications^	123 (14)[a]	24 (5)[b]	99 (24)[i]	4.81 (2.45 – 9.55)	**<0.001**
Interventions					
Pancreatic intervention	459 (52)	106 (22)	353 (99)	12.12 (6.25 – 2.46)	**<0.001**
Percutaneous catheter drainage	319 (36)	69 (14)	250 (61)	9.13 (5.19 – 16.41)	**<0.001**
Need for additional intervention	355 (77)	66 (63)	289 (81)	2.86 (1.41 – 6.09)	0.005
Follow-up intervention	83 (18)	10 (9)	73 (20)	10.92 (5.19 – 24.98)	**<0.001**
Ascites drainage	77 (9)	7 (1)	70 (17)[i]	14.37 (6.16 – 37.94)	**<0.001**
Readmission					
Readmission	601 (68)	289 (61)	312 (76)	4.33 (2.46 – 7.92)	**<0.001**
For re-intervention	118 (20)	12 (4)	106 (34)	3.79 (1.89 – 8.13)	**<0.001**
Long-term complications					
Recurrent pancreatitis	196 (25)[j]	95 (21)[p]	101 (29)[v]	1.72 (0.97 – 3.03)	0.062
Chronic pancreatitis	84 (11)[k]	26 (6)[q]	58 (17)[w]	3.64 (1.67 – 7.90)	**0.001**
Endocrine pancreatic insufficiency	241 (30)[l]	75 (17)[r]	166 (47)[x]	1.11 (0.60 – 2.01)	0.739
Exocrine pancreatic insufficiency	160 (20)[m]	43 (10)[q]	117 (33)[y]	1.33 (0.66 – 2.61)	0.414

Data are presented as n (%) or median (interquartile range).
*Binomial regression (binary data): patients (n=8) who died in the first week after admission were excluded for analysis. $After the Bonferroni correction was applied, the p-value considered statistically significant was <0.0025. The statistically significant p-values are stated in bold.
Missing patient: a=5, b=2, c=4, d=7, e=9, f=17, g=10, h=183, i=3, j=105, k=109, l=102 patients excluded within one year after admission and therefore excluded in case potential outcome was not reached yet, m=103 patients excluded within one year after admission and therefore excluded in case potential outcome was not reached yet, n=1, o=12, p=38, q=40, r=40, s=41, t=8, u=23, v=67, w=69, x=62, y=63, z=73, aa=76, bb=6, cc=32, dd=33, ee=26, ff=28
N indicates number; DPD, *disrupted or disconnected pancreatic duct;* OR, *Odds Ratio;* CI, *Confidence Interval;* ICU, *intensive care unit;* MOF, *multiple organ failure*

Table S6 Univariate comparison of clinical outcome, interventions and long-term complications occurring more than 7 days after admission in patients with and without confirmed DPD and in patients with and without confirmed functional DPD

	Confirmed DPD			Only functional confirmed DPD		
	No, (N = 653)	Yes, (N = 243)	*P*	No, (N = 653)	Yes, (N = 140)	*P*
Death pancreatitis related	62 (10)	36 (15)	**0.031**	62 (10)	30 (21)	**<0.001**
Death after 7 days	62 (10)	36 (15)	**0.031**	62 (10)	30 (21)	**<0.001**
Death after 21 days				49 (8)	30 (21)	**<0.001**
ICU-admission						
Ongoing	132 (23)	99 (56)	**<0.001**	131 (23)	68 (68)	**<0.001**
New onset	27 (21)	30 (31)	**<0.001**	27 (21)	21 (31)	**<0.001**
Organ failure						
Ongoing	95 (15)	78 (32)	**<0.001**	95 (15)	59 (42)	**<0.001**
Ongoing multi-organ failure	57 (63)	58 (79)	**<0.001**	57 (63)	42 (76)	**<0.001**
New onset	109 (17)	95 (40)	**<0.001**	109 (17)	62 (45)	**<0.001**
New onset multi-organ failure	74 (69)	68 (74)	**<0.001**	74 (69)	44 (75)	**<0.001**
Infected necrosis	245 (38)	197 (81)	**<0.001**	245 (38)	125 (90)	**<0.001**
Abdominal compartment syndrome	10 (2)	14 (6)	**0.002**	10 (2)	12 (9)	**<0.001**
Gastrointestinal complications^	51 (8)	72 (30)	**<0.001**	51 (8)	49 (36)	**<0.001**
Interventions						
Pancreatic intervention	238 (99)	221 (98)	**<0.001**	238 (99)	132 (97)	**<0.001**
Percutaneous catheter drainage	141 (22)	178 (73)	**<0.001**	141 (22)	116 (83)	**<0.001**
≥4 PCD	31 (22)	69 (39)	**0.002**	31 (22)	48 (41)	**0.001**
Endoscopic transluminal drainage	105 (16)	76 (31)	**<0.001**	105 (16)	27 (19)	0.385
Necrosectomy	131 (20)	138 (57)	**<0.001**	131 (20)	88 (63)	**<0.001**
Endoscopic	55 (42)	24 (17)	0.512	55 (42)	5 (6)	0.052
Surgical	81 (62)	117 (85)	**<0.001**	81 (62)	85 (97)	**<0.001**
Need for additional intervention	161 (68)	194 (86)	**<0.001**	161 (68)	117 (86)	**<0.001**
Follow-up intervention	22 (9)	61 (27)	**<0.001**	22 (9)	21 (15)	**<0.001**

Table S6 Continued.

	Confirmed DPD			Only functional confirmed DPD		
	No, (N = 653)	Yes, (N = 243)	*P*	No, (N = 653)	Yes, (N = 140)	*P*
Ascites drainage	26 (4)[n]	51 (21)[b]	**<0.001**	26 (4)	38 (28)	**<0.001**
Readmission						
Readmission	403 (62)	198 (81)	**<0.001**	403 (62)	103 (74)	0.015
For re-intervention	38 (9)	80 (40)	**<0.001**	39 (9)	38 (37)	**<0.001**
Long-term complications						
Recurrent pancreatitis	124 (21)	72 (30)	**<0.001**	124 (21)	24 (22)	1.000
Chronic pancreatitis	42 (7)	42 (17)	**<0.001**	42 (7)	10 (9)	0.554
Endocrine pancreatic insufficiency	130 (23)	111 (46)	**<0.001**	130 (23%)	55 (48)	**<0.001**
Exocrine pancreatic insufficiency	120 (21)	99 (41)	**<0.001**	120 (21)	52 (46)	**<0.001**

Data are presented as n (%) or median (P25-P75).
*Binomial regression (binary data): patients (n=8) who died in the first week after admission were excluded for analysis. Patients excluded within one year after admission and therefore excluded in case potential outcome was not reached yet. [$]After the Bonferroni correction was applied, the p-value considered statistically significant was <0.0025. The statistically significant p-values are stated in bold.
N indicates *number;* DPD, *disrupted or disconnected pancreatic duct;* RR, *Relative Risk;* CI, *Confidence Interval;* ICU, *intensive care unit;* PCD, *percutaneous catheter drainage*

Table S7 Univariate comparison of clinical outcome, interventions and long-term complications occurring more than 7 days after admission in patients with and without functional DPD and clinical

		Functional DPD		
	Overall, N = 243	**No, N = 103**	**Yes, N = 140**	***P*[$]**
Death pancreatitis related				
Death after 7 days	36 (15)	6 (6)	30 (21)	**0.001**
ICU-admission				
Ongoing	99 (56)[a]	31 (40)[o]	68 (68)[v]	**<0.001**
New onset	101 (42)[b]	9 (29)[p]	21 (31)[w]	0.065
Organ failure				
Ongoing	78 (49)[c]	19 (18)	59 (42)[x]	**<0.001**
Ongoing multi-organ failure	58 (79)[d]	16 (89)[q]	42 (76)[y]	0.009
New onset	95 (61)[e]	33 (32)[q]	62 (45)[z]	0.061
New onset multi-organ failure	68 (74)[f]	24 (73)[q]	44 (75)[aa]	0.148
Infected necrosis	197 (81)[g]	72 (70)	125 (90)	**<0.001**
Gastrointestinal complications^	72 (30)[h]	23 (22)	49 (36)[bb]	0.033
Interventions				
Pancreatic intervention	221 (91)	89 (86)	132 (94)	0.042
Percutaneous catheter drainage	178 (73)	62 (60)	116 (83)	**<0.001**
Need for additional intervention	194 (86)[i]	77 (87)[r]	117 (86)[cc]	1.000
Follow-up intervention	61 (72)	40 (45)	21 (15)	**<0.001**
Ascites drainage	51 (21)[j]	13 (13)	38 (28)[dd]	0.006
Readmission				
Readmission	198 (81)	95 (92)	103 (74)	**<0.001**
For re-intervention	80 (40)	42 (44)	38 (37)	0.028
Long-term complications				
Recurrent pancreatitis	72 (34)[k]	48 (48)[s]	24 (22)[ee]	**<0.001**
Chronic pancreatitis	42 (20)[l]	32 (32)[s]	10 (9)[ff]	**<0.001**
Endocrine pancreatic insufficiency	111 (51)[m]	56 (55)[t]	55 (48)[gg]	0.342
Exocrine pancreatic insufficiency	74 (34)[n]	36 (36)[u]	38 (36)[hh]	1.000

Data are presented as n (%) or median (interquartile range).[$]After the Bonferroni correction was applied, the p-value considered statistically significant was <0.0025.
Missing patients: a=66, b=4, c=1, d=5, e=3, f=6, g=1, h=2, i=17, j=2, k=32, l=33, m=26, n=28, o=26, p=1, q=1, r=14, s=3, t=1, u=2, v=40, w=3, x=1, y=4, z=2, aa=5, bb=2, cc=3, dd=2, ee=29, ff=30, gg=25, hh=26
N indicates *number;* DPD, *disrupted or disconnected pancreatic duct;* ICU, *intensive care unit*

PART II

CHAPTER VIII

Perforation and fistula of the gastrointestinal tract in patients with necrotizing pancreatitis: *a nationwide prospective cohort*

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ABSTRACT

Objective

The aim of this study was to explore the incidence, risk factors, clinical course and treatment of perforation and fistula of the gastrointestinal (GI) tract in a large, unselected cohort of patients with necrotizing pancreatitis.

Background

Perforation and fistula of the GI tract may occur in necrotizing pancreatitis. Data from large, unselected patient populations on the incidence, risk factors, clinical outcomes, and treatment are lacking.

Methods

We performed a post hoc analysis of a nationwide prospective database of 896 patients with necrotizing pancreatitis. GI tract perforation and fistula were defined as spontaneous or iatrogenic discontinuation of the GI wall. Multivariable logistic regression was used to explore risk factors and to adjust for confounders to explore associations of the GI tract perforation and fistula on the clinical course.

Results

A perforation or fistula of the GI tract was identified in 139 (16%) patients, located in the stomach in 23 (14%), duodenum in 56 (35%), jejunum or ileum in 18 (11%), and colon in 64 (40%). Risk factors were high C-reactive protein within 48 hours after admission [odds ratio (OR): 1.19; 95% confidence interval (CI): 1.01–1.39] and early organ failure (OR: 2.76; 95% CI: 1.78–4.29). Prior invasive intervention was a risk factor for developing a perforation or fistula of the lower GI tract (OR: 2.60; 95% CI: 1.04–6.60). While perforation or fistula of the upper GI tract appeared to be protective for persistent intensive care unit admission (OR: 0.11, 95% CI: 0.02–0.44) and persistent organ failure (OR: 0.15; 95% CI: 0.02–0.58), perforation or fistula of the lower GI tract was associated with a higher rate of new onset organ failure (OR: 2.47; 95% CI: 1.23–4.84). When the stomach or duodenum was affected, treatment was mostly conservative (n =54, 68%). Treatment was mostly surgical when the colon was affected (n=38, 59%).

Conclusion

Perforation and fistula of the GI tract occurred in one out of six patients with necrotizing pancreatitis. Risk factors were high C-reactive protein within 48 hours and early organ failure. Prior intervention was identified as a risk factor for perforation or fistula of the lower GI tract. The clinical course was mostly affected by involvement of the lower GI tract.

INTRODUCTION

Acute pancreatitis is one of the most common gastrointestinal (GI) diseases causing hospital admission and has a rising incidence.[1] An important determinant for the severity of the disease is the development of necrosis of (peri-)pancreatic tissue, which occurs in 20% of patients.[2] Subsequently, infection of the necrotic tissue occurs in one-third of patients with necrotizing pancreatitis.[3,4] A less common complication in patients with necrotizing pancreatitis is perforation or fistula of the GI tract. Perforation and fistula, defined as discontinuation of the GI wall either without or with connection with another organ, of the GI tract may involve the stomach, duodenum, jejunum, ileum, and colon.[5,6]

GI fistulas have a wide range in reported incidence, ranging from 3% to 67%.[1,6–11] Most of the GI fistulas are described within the upper GI tract (i.e., stomach, duodenum), which often can be treated conservatively with a wait and see approach.[5,9] Perforation or fistula of the GI tract may severely impact patients' condition and lead to other complications, such as hemorrhage, deterioration of nutritional status, and sepsis,[9,11–13] especially when the colon is involved.[9,10,14–16] Despite potential benefits of nonsurgical approaches to colonic GI fistulas,[5,9,17–19] invasive surgical treatment is still recommended for colonic GI fistulas following acute necrotizing pancreatitis.[14,16,20]

Despite the fact that perforation and fistula of the GI tract are recognized in clinical practice, data on this topic are scarce, and consist mostly of small series of selected patients or case reports.[1,6–11] Subsequently, the magnitude of this entity remains unknown and guidelines on management are lacking. Therefore, these complications can often be missed, possibly leading to avoidable morbidity and mortality. This may be prevented by early detection and treatment by identifying high-risk patients early in the disease course. We therefore performed an observational study in a large unselected cohort of patients with necrotizing pancreatitis with the aim to explore the incidence, risk factors, clinical course and treatment of perforation and fistula of the GI tract.

METHODS

Study design and population

This was a post hoc long-term analysis of patients included in the nationwide prospective database (PWN CORE) of the Dutch Pancreatitis Study Group. A subset of these patients was included in previous randomized trials on invasive management of necrotizing pancreatitis.[3,21] All patients with acute pancreatitis in the nationwide registration cohort between November 2005 and December 31,

2015 were screened for eligibility. This time period was chosen to ensure follow-up of patients. For the current study, we included all adult patients with necrotizing pancreatitis, defined as a computed tomography severity index (CTSI) score of three or more. An expert radiologist (TLB) reviewed all abdominal radiological images to determine the CTSI score, to assess the presence and location of peripancreatic collections and (peri)pancreatic necrosis, and to evaluate signs of perforation and fistula of the GI tract. Patients were excluded if they had signs of chronic pancreatitis according to the M-ANNHEIM criteria,[22] pancreatic carcinoma at admission, or a traumatic etiology of pancreatitis. For the current study, the need for ethical approval was waived by the medical ethics committee. It was conducted in accordance with the principles of the Declaration of Helsinki. This study was reported according to the "Strengthening the Reporting of Observational studies in Epidemiology" (STROBE) guideline.[23] All patients or their legal representatives gave written informed consent for registration. Treatment of acute pancreatitis was according to the international guidelines for management of acute pancreatitis.[18,19]

Patient follow-up and data collection

Using a predefined, standardized case-record form, collection of data from medical records on multiple patient factors was performed. Clinical data were collected prospectively during the initial hospital admission and follow-up data were collected retrospectively. An additional data collection for long-term follow-up of all patients was performed in January 2020 to complete the data capture including data regarding perforation or fistula of the GI tract. If at any time before or during follow-up a patient was transferred to a different hospital, all the required follow-up data were retrieved from those institutions. All data were imported by one author (HCT) in Open Clinica, a Good Clinical Practice-certified data management software, and subsequently verified by a second author (SMvD). Discrepancies were resolved by consensus during research meetings of the Dutch Pancreatitis Study Group.

Study outcomes and definitions

All definitions were established after careful consideration of the current literature in research meetings of the Dutch Pancreatitis Study Group and are provided in the Supplementary Appendix Table S1.

Perforation and fistula of the GI tract (stomach, duodenum, jejunum, ileum, or colon) confirmed with either imaging, endoscopy or surgery, were defined as a) perforation: a spontaneous or iatrogenic discontinuation of the gastrointestinal wall without a connection with another organ, or as b) fistula: spontaneous or iatrogenic discontinuation of the gastrointestinal wall with a

connection with another organ (e.g., pancreas or cutis (enterocutaneous fistula)). An enterocutaneous fistula was defined as a fistula, but could occur after a spontaneous or iatrogenic perforation. A subdivision was made in perforations or fistula of the upper (gastric and duodenum) and lower (jejunum, ileum, and colon) GI tract. When a perforation or fistula of the GI tract was only seen on imaging, images were reviewed by an expert radiologist (TLB). Symptomatic perforation and fistula of the GI tract were defined as productive perforation and fistula by means of findings of GI content in external drain or hematemesis or melena. Asymptomatic perforation and fistula of the GI tract were defined as a radiological finding without GI content in external drain or hematemesis or melena. Intentional iatrogenic fistula as a result of endoscopic drainage were excluded from the definition of perforation or fistula of the GI tract due to the intentional nature. The cause of each perforation and fistula of the GI tract was defined as either spontaneous (ischemia/necrosis or diagnosis of a perforation or fistula with no prior invasive intervention), iatrogenic (confirmed iatrogenic cause by an inadvertent perforation during endoscopic intervention, percutaneous catheter drain or surgery) or unknown (no distinction between spontaneous or iatrogenic could be made, a combination could be possible). No distinction between perforation and fistula was made because it was in clinical practice not always possible to distinguish between the two entities.

Clinical course variables included pancreatitis-related mortality (death which occurred during admission for pancreatitis), total length of hospital stay, readmission and number of readmissions and (long-term) complications. Treatment and healthcare resources included pancreatic interventions, other interventions, intensive care unit (ICU) admission, length of ICU stay, single organ failure, multiple organ failure, and persistent organ failure during the entire follow-up. ICU stay and organ failure were classified as “early” or “delayed” ICU stay. Early was defined as within one week after admission and delayed was defined as new or persistent organ failure after three weeks after admission. This cut-off value was deliberately chosen because it was not always possible to assess with full certainty when the perforation or fistula developed. A previous study has shown an onset of perforation and or fistula after four to eight weeks after onset of disease.[24] To be sure not to miss any previously developed perforation or fistula (based on the development of infected necrosis and subsequently pancreatic intervention) we have chosen a three-week cut-off value. Treatment of perforation or fistula of the GI tract consisted of conservative measurements, including patients with a percutaneous drain in situ at diagnosis, minimal invasive measurements, including percutaneous and endoscopic treatment strategies or invasive measurements, including surgery.

Statistical analysis

Patients' characteristics, incidence and clinical course were reported descriptively. Descriptive numerical data were reported as mean with SD when normally distributed and as median with interquartile ranges (IQR: P25–P75) when not normally distributed. Categorical data were shown as frequencies and percentages. A multivariable logistic regression model to determine risk factors for developing a perforation or fistula of the upper and lower GI tract was fitted when deemed possible, which was predefined as having more than 50 events of the outcome. The clinical course was compared for patients with and without perforation or fistula of the GI tract. Subgroup analyses were performed to compare clinical course of patients with and without symptomatic perforation or fistula of the GI tract. Statistical comparison was performed using the Fisher exact test or χ^2 test for categorical data and the Student t test or the Mann- Whitney U test for continuous data. Univariate analysis will be presented in the Supplementary Appendix S4. Multivariable logistic regression models that adjusted for confounding to ascertain the independent effect of perforation or fistula of the GI tract were fitted for several clinical outcomes. The presence of perforation or fistula of the GI tract was used as a dependent variable. The variables included as covariates to adjust for potential confounding varied by clinical outcome and consisted of a combination of age, C-reactive protein, sex, American Society of Anesthesiologists (ASA) classification, presence of parenchymal necrosis, extent of necrosis, occurrence of infected necrosis or early onset of organ failure or abdominal compartment syndrome (i.e., the last three all before diagnosis of a perforation or fistula of the GI tract). The variables included in the regression model are presented in the Supplementary Appendix Table S5. If applicable, we calculated relative risk or adjusted odds ratios (OR) with their respective 95% confidence intervals (95% CI). Treatment strategies for perforation or fistula of the GI tract were reported descriptively for each location and subsequently for comparing with and without symptomatic perforation or fistula of the GI tract. A P value <0.05 was considered statistically significant. Statistical analysis was performed using R (R version 4.1.2 (2021-11-01); R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between November 2005 and December 2015, 2289 patients with acute pancreatitis were registered in the nationwide prospective registry. A total of 896 patients met the study criteria for necrotizing pancreatitis and were included in the current study (Fig. 1). Median age of the patients at time of admission for

the initial episode of acute pancreatitis was 58 (IQR: 47–69) years. Parenchymal necrosis with or without extrapancreatic necrosis occurred in 542 (60%) patients and 354 (40%) patients had extrapancreatic necrosis only. Infected necrosis occurred in 481 (54%) patients. A total of 468 (52%) patients underwent an invasive intervention for (peri-)pancreatic collections. Pancreatitis-related mortality from the initial admission until last follow-up date was 12%. Median follow-up was 75 (IQR: 41–151) months.

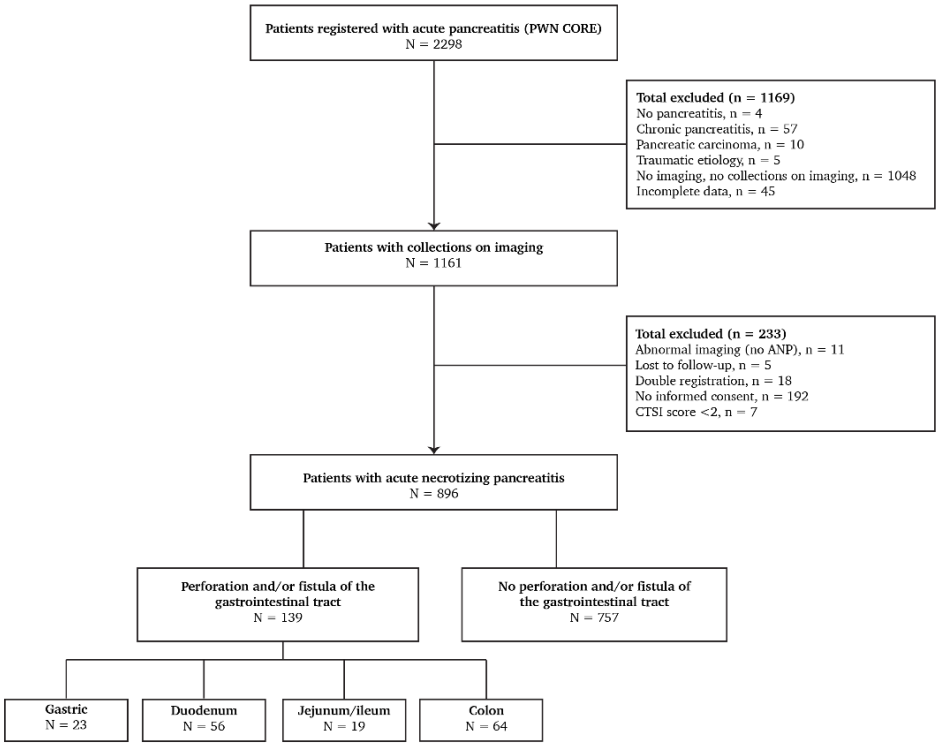

Figure 1 Inclusion flowchart
CTSI indicates *computed tomography severity index*

Perforation and fistula of the GI tract

Patients' characteristics at admission and clinical disease course are provided in Table 1. Interventions and complications are summarized in the Supplementary Appendix Table S2. A perforation or fistula of the GI tract occurred in 139 (16%) patients after a median of 52 (IQR: 28–85) days after admission. In 96 (69%) of these patients, an invasive intervention was performed before diagnosis of the GI perforation or fistula (baseline characteristics of patients with prior and no prior

intervention are presented in the Supplementary Appendix Table S3. There was a median of 31 (IQR: 12–60) days between the first intervention and diagnosis of the GI perforation or fistula and a median of 13 (4–27) days between the last intervention and diagnosis of the perforation or fistula. In the 139 patients who developed a perforation or fistula, a total of 162 perforations or fistulas were identified. The location was stomach in 23 (14%) patients, the duodenum in 56 (35%) patients, the jejunum or ileum in 19 (12%) patients and the colon in 64 (40%) patients.

Symptoms at presentation of perforation or fistula, etiology, and diagnostic modalities used are presented in Table 2. Most often the diagnosis of a perforation or fistula was an incidental finding (n= 91, 65%) and were asymptomatic. Fortyeight (35%) patients had a symptomatic perforation or fistula. Diagnosis of a perforation or fistula of the GI tract was achieved through finding fecal content in external drain fluid in 31 (22%) patients, oral administered methylene blue in external drain fluid in four (4%) patients, fistulography in 35 (25%) patients, gastroduodenoscopy in 30 (22%) patients, computed tomography in 47 (34%) patients, magnetic resonance imaging in two (1%) patients, surgery in 36 (26%) patients, and autopsy in seven (5%) patients (i.e., multiple modalities may be used in patients).

Risk factors

Independent risk factors for developing a perforation or fistula of the GI tract are presented in Table 3. High C-reactive protein within 48 hours after admission and organ failure within seven days after admission were associated with a perforation or fistula of the GI tract (adjusted OR: 1.26; 95% CI: 1.04–1.55 and adjusted OR: 2.24; 95% CI: 1.30–3.86, respectively). Intervention prior to the diagnosis of a GI perforation or fistula was found to be associated with the development of perforation or fistula of the lower GI tract (adjusted OR: 2.60; 95% CI: 1.04–6.60).

Table 1 Patients characteristics at admission and clinical course* of patients with necrotizing pancreatitis

		Perforation or fistula of the gastrointestinal tract		
Variables	**Overall, N = 896**	**No, N = 757**	**Yes, N = 139**	**P**
Age (y)	58 (47 – 69)	58 (46 – 69)	59 (50 – 70)	0.13
Male sex	571 (64)	473 (62)	98 (71)	0.08
Body Mass Index (kg/m^2)	27.1 (25 – 30.7)[a]	26.9 (25 – 30.7)[i]	27.8 (25.1 – 30.4)[j]	0.63
Etiology of pancreatitis				
Biliary	432 (48)	373 (49)	59 (42)	0.14
Alcohol	159 (17)	133 (18)	26 (19)	0.72
ASA				
I	298 (33)	255 (34)	43 (31)	0.56
II	471 (53)	390 (52)	81 (58)	0.17
III	123 (14)	108 (14)	15 (11)	0.35
IV	4 (0.4)	4 (1)	-	1.00
Severity of disease				
Leucocytes (10^9/l)	18.2 (14.4 – 22.2)[b]	18 (14.3 – 22.1)[j]	18.6 (14.9 – 22.9)[m]	0.25
C-reactive protein (mg/l)	297 (216 – 377)[c]	293 (208 – 368)[k]	341 (254 – 412)[n]	<0.01
CT severity index	6 (4 -8)[d]	6 (4 – 8)[l]	6 (5 – 10)	<0.01
Parenchymal necrosis[e]	542 (60)	437 (58)	105 (76)	<0.01
<30%	259 (48)	219 (50)	40 (38)	1.00
30-50%	132 (24)	112 (26)	20 (19)	1.00
>50%	150 (28)	105 (24)	45 (43)	<0.01
Pattern parenchymal necrosis[e]				
Right	15 (3)	11 (3)	4 (4)	0.27
Left	52 (10)	47 (11)	5 (5)	0.32
Central	233 (43)	181 (41)	52 (50)	<0.01
Subtotal	76 (14)	52 (12)	24 (23)	<0.01
Diffuse	161 (30)	141 (32)	20 (19)	0.28
Extrapancreatic necrosis only	354 (40)	320 (42)	34 (25)	<0.01
Early ICU-admission†	309 (35)[f]	221 (29)	88 (63)[f]	<0.01
Early organ failure‡	223 (25)[g]	157 (21)[g]	66 (47)	<0.01
Persistent single organ failure	61 (7)[h]	52 (7)[h]	9 (6)	1.00
Persistent multiple organ failure	137 (15)[h]	85 (11)[h]	52 (37)	<0.01
Death pancreatitis related§	106 (12)	78 (10)	28 (20)	<0.01

Data are presented as n (%) or median (interquartile range: P25-P75).
*Clinical course variables are reported regardless of timing of diagnosis of perforation or fistula of gastrointestinal tract.
†ICU admission within 21 days after admission.
‡Organ failure within 7 days after admission.
§Death pancreatitis related is defined as death during admission or readmission for acute pancreatitis or complications due to acute pancreatitis.
Missing patients: a=494, b=82, c=125, d=8, e= pattern and extent necrosis missing in 1 patient, f=6, g=4, h=5, i=428, j=66, k=105, l=1, m=16, n=20.
ASA indicates *American Society of Anesthesiologists*, assessed based on the patient's history just prior to admission, there were no patients with ASA class 5; CT*, computed tomography*; ICU*, intensive care unit*

Table 2 Clinical presentation and used diagnostic modalities

Variables	Stomach N = 23	Duodenum N = 56	Jejunum/ileum N = 19	Colon N = 64
Clinical symptoms				
Asymptomatic	16 (52)	38 (68)	11 (58)	38 (59)
Symptomatic	7 (30)	18 (32)	8 (42)	26 (41)
Hematemesis/melena	3 (13)	6 (11)	2 (11)	3 (5)
Signs of gastrointestinal content in external drain fluid	4 (17)	12 (21)	6 (32)	23 (36)
Intervention before diagnosis	14 (61)[*]	35 (63)[†]	12 (63)[‡]	46 (72)[§]
Diagnostic modality[d]				
Gastrointestinal content in external drain fluid	4 (17)	8 (14)	6 (33)	22 (34)
Methylene blue in external drain fluid	-	2 (4)	1 (6)	1 (2)
Fistulography	3 (13)	17 (30)	7 (39)	13 (20)
Endoscopy	8 (35)	20 (36)	2 (11)	3 (5)
CT	9 (39)	17 (30)	3 (17)	27 (42)
MRI	2 (4)	-	-	-
Surgical	2 (9)	9 (16)	7 (39)	30 (47)
Autopsy	1 (4)	2 (4)	2 (11)	5 (8)

Data are presented as n (%).
[a]Type of first intervention: percutaneous catheter drain n=8, endoscopic transluminal drain n=3, ascites drain n=1, laparotomy n=2. Type of last intervention: percutaneous catheter drainage n=9, endoscopic transluminal drain n=2, laparotomy n=3.
[†]Type of first intervention: percutaneous catheter drain n=24, endoscopic transluminal drain n=3, ascites drain n=5, laparotomy n=3. Type of last intervention: percutaneous catheter drainage n=22, endoscopic transluminal drain n=1, ascites drain n=2, laparotomy n=3, minimal invasive surgery or VARD n=6, PTC drain n=1.
[‡]Type of first intervention: percutaneous catheter drain n=6, endoscopic transluminal drain n=1, ascites drain n=1, laparotomy n=2, minimal invasive surgery or VARD n=1. Type of last intervention: percutaneous catheter drainage n=5, endoscopic transluminal drain n=1, laparotomy n=2, minimal invasive surgery or VARD n=3.
§Type of first intervention: percutaneous catheter drain n=20, endoscopic transluminal drain n=3, ascites drain n=10, laparotomy n=10, minimal invasive surgery or VARD n=2. Type of last intervention: percutaneous catheter drainage n=28, ascites drain n=1, laparotomy n=8, minimal invasive surgery or VARD n=6, endoscopic transluminal necrosectomy n=1.
CT indicates *computed tomography*; MRI, *magnetic resonance imaging*; VARD, *video assisted retroperitoneal debridement*; PTC, *percutaneous transhepatic cholangiography*

Table 3 Risk factors for developing a perforation or fistula of the gastrointestinal tract

	Perforation or fistula of the gastrointestinal tract					
	Overall, N = 139		**Upper GI tract, N = 78**		**Lower GI tract, N = 74**	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age (y)	1.01 (1.00 – 1.03)	0.07	1.02 (1.00 -1.03)	0.12	1.00 (0.98 – 1.02)	0.82
Male sex	1.33 (0.85 – 2.12)	0.22				
ASA 3+4	0.55 (0.28 – 1.04)	0.08				
CRP (mg/l)	**1.19 (1.01 – 1.39)**	**0.04**	**1.26 (1.04 – 1.55)**	**0.02**	1.06 (0.87 – 1.29)	0.59
Right necrosis	2.76 (0.56 – 10.54)	0.16				
Left necrosis	0.58 (0.13 – 1.84)	0.41				
Central necrosis	1.54 (0.79 – 2.96)	0.20				
Subtotal necrosis	1.16 (0.42 – 3.16)	0.78				
Necrosis 30-50%	0.73 (0.35 – 1.52)	0.41				
Necrosis >50%	1.70 (0.77 – 3.77)	0.19	**2.27 (1.24 – 4.08)**	**0.01**	1.49 (0.79 – 2.74)	0.20
Infected necrosis*	1.81 (0.92 – 3.56)	0.09	**3.44 (1.52 – 7.81)**	**<0.01**	1.02 (0.43 – 2.53)	0.96
Early organ failure	**2.76 (1.78 – 4.29)**	**<0.01**	**2.24 (1.30 – 3.86)**	**<0.01**	**2.13 (1.21 – 3.72)**	**0.01**
Prior intervention†	1.03 (0.52 – 2.07)	0.92	0.49 (0.22 – 1.09)	0.07	**2.60 (1.04 – 6.60)**	**0.04**

*before diagnosis perforation or fistula of the gastrointestinal tract, or overall in case of no occurrence of perforation or fistula of the gastrointestinal tract.
†before diagnosis perforation or fistula of the gastrointestinal tract, or overall in case of no occurrence of perforation or fistula of the gastrointestinal tract.
OR indicates *odds ratio*; CI, *confidence interval*; ASA, *American Society of Anesthesiologists*; CRP, *c-reactive protein*

Clinical course

Multivariate analysis on the clinical course is presented in Table 4. Of the 139 patients with a perforation or fistula of the GI tract, 49 (36%) patients were admitted in the ICU at time of diagnosis of the perforation or fistula of the GI tract. After diagnosis, new admission to the ICU occurred in 28 (21%) patients. Organ failure was present in 46 (34%) patients at time of diagnosis, new organ failure after diagnosis occurred in 22 (17%). Pancreatitis-related mortality did occur more often in patients with a perforation or fistula of the GI tract (P< 0.01), but an independent association was not found (adjusted OR: 1.25; 95% CI: 0.66–2.29). The presence of a perforation or fistula of the upper GI tract was associated with less persistent ICU admission for more than three weeks after admission (adjusted OR: 0.11; 95% CI: 0.02–0.44) and less persistent organ failure after three weeks after admission (adjusted OR: 0.15; 95% CI: 0.02–0.58). Associations were also found between a perforation or fistula of the lower GI tract and new onset organ failure after three weeks after admission (adjusted OR: 2.47; 95% CI: 1.23–4.84). Symptomatic perforation or fistula of the GI tract was not associated with a worse clinical outcome.

Table 4 Clinical course in patients with perforation or fistula of the gastrointestinal tract and the different locations*

	Upper GI tract		Lower GI tract	
	No, N = 818	**Yes, N = 78**	**No, N = 822**	**Yes, N = 74**
Death				
All pancreatitis related	93 (11%)	13 (17%)	86 (10%)	20 (27%)
OR (95% CI); P	0.67 (0.29 – 1.44); 0.32		1.49 (0.71 – 3.06); 0.28	
After 21 days after admission	74 (9%)	11 (15%)	69 (9%)	16 (23%)
OR (95% CI); P	1.02 (0.40 – 2.37); 0.97		0.94 (0.38 – 2.19); 0.90	
ICU-admission				
New after 21 days after admission	174 (19%)[a]	24 (32%)[e]	141 (18%)[b]	30 (43%)[i]
OR (95% CI); P	0.58 (0.27 – 1.15); 0.13		1.41 (0.71 – 2.72); 0.31	
Persistent admission after 21 days after admission	**124 (16%)[b]**	**26 (34%)[e]**	116 (15%)[h]	34 (49%)[f]
OR (95% CI); P	**0.11 (0.02 – 0.44); 0.01**		2.71 (0.87 – 7.89); 0.07	
Organ failure				
New after 21 days after admission	126 (16%)[c]	23 (31%)[f]	**123 (15%)[b]**	**26 (38%)[g]**
OR (95% CI); P	0.48 (0.20 – 1.03); 0.07		**2.47 (1.23 – 4.84); 0.01**	
Persistent organ failure 21 days after admission	**101 (13%)[d]**	**16 (22%)[g]**	87 (11%)[d]	30 (44%)[g]
OR (95% CI); P	**0.15 (0.02 – 0.58); 0.02**		1.51 (0.43 – 4.88); 0.50	

*Binomial regression (binary data). Data are presented as n (%).
Patients who died (n=21) within 21 days after admission were excluded for this analysis, this included 5 patients with a diagnosis of perforation or fistula of the gastrointestinal tract within 21 days after admission. Data was not imputed.
Missing patients: a=27, b=24, c=26, d=35, e=2, f=4, g=6, h=22
OR, indicates *odds ratio*; CI, *confidence interval*; ICU, *intensive care unit*

Treatment of perforation or fistula

Details on treatment of patients with a perforation or fistula of the GI tract are provided in Table 5. No differences in treatment strategy or number of deaths were found for patients with or without symptoms (Supplementary Appendix Table S6).

Gastric perforation or fistula (n= 23) was treated conservatively without any invasive intervention in 15 (65%) patients, of whom six (40%) patients already had a percutaneous catheter drain in situ. Drainage of the perforation or fistula was performed in five (22%) patients, with percutaneous drainage in one (20%) and endoscopic drainage through dilatation of the perforation or fistula in four (36%) patients. In three (13%) patients, an attempt was made to close the perforation or fistula, all by means of suturing the defect: one (33%) patient required a relaparotomy with drainage of the abscess and one (33%) patient died.

Table 5 Treatment strategies for the different locations of perforation or fistula of the gastrointestinal tract with and without symptoms

	Gastric, N=23	Duodenum, N=56	Jejunum/ileum, N=19	Colon, N=64
Death without specific treatment	**2 (9)**	**8 (14)**	**3 (16)**	**7 (11)**
Conservative*	15 (65)	39 (70)	10 (56)	22 (34)
Percutaneous catheter drainage in situ	6 (40)	27 (69)	7 (70)	11 (50)
Drainage of perforation or fistula	**5 (22)**	**14 (25)**	**3 (17)**	**4 (6)**
Percutaneous (new drain)	1 (20)	6 (43)[b]	1 (33)[d]	4 (100)[f]
Endoscopic	4 (80)†	8 (57)	2 (67)	-
Dilatation of the fistula or perforation	4 (100)	8 (14)	1 (50)	-
Closure of perforation or fistula	**3 (13)**	**3 (5)**	**6 (33)**	**38 (59)**
Endoscopic	-	-	1 (17)	-
Endoscopic clips	-	-	1 (50)	-
Surgical	3 (100)[a]	3 (100)[c]	5 (83)[e]	38 (100)[g]
Sutures	3 (100)	1 (33)	2 (40)	4 (11)
Stoma	-	-	3 (60)[h]	30 (79)[i]
Both sutures and ileostomy	-	-	-	4 (11)[i]
Other	-	2 (67)‡	-	-

Data are presented as n (%).
*Conservative treatment includes no action to let the perforation or fistula heal spontaneousloy, medical therapy or leaving the perforation or fistula heal with a percutaneous catheter drain already in situ.
†In 1 (8%) patient this was in addition to the percutaneous drain already in place. # =
‡In 1 patient decompression laparotomy with percutaneous catheter drainage and in 1 patient a new percutaneous catheter drain and a percutaneous trans hepatic cholangiography drain and reconstruction of the duodenum by a gastro- and jejunostomy with a side-to-side Roux-en-Y
[a]1 patient died after surgical closure of perforation or fistula: [b]2 patients died after a new percutaneous drain, [c]1 patient died after surgical treatment, [d]1 patient died after placement of a new percutaneous catheter drain, [e]1 patient died after surgical treatment, [f]1 patient died after an additional percutaneous catheter drain, g = 9 patients died after surgical treatment. [h]1 (33%) patient had a stoma reversal, in two (67%) patients the stoma was permanent, [i]21 (62%) patients had a stoma reversal, in 13 (38%) patients the stoma was permanent.

Perforation or fistula of the duodenum (n=56) was treated conservatively without any invasive intervention in 39 (70%) patients, of whom 27 (69%) patients already had a percutaneous catheter drain in situ. In 14 (25%) drainage of the perforation or fistula was performed: percutaneous drainage in six (43%) patients and endoscopic drainage through dilatation of the perforation or fistula in eight (57%) patients. In three (5%) patients, an attempt was made to close the perforation or fistula surgically, one patient (33%) required multiple surgical procedures and eventually underwent duodenal reconstruction. One (33%) patient died after the surgical attempt to close the perforation or fistula.

Jejunum or ileum perforation or fistula (n= 19) was treated conservatively without any invasive intervention in 10 (65%) patients, of whom seven (70%)

patients had a percutaneous catheter drain in situ. Drainage was performed in three (17%) patients, by means of percutaneous catheter drainage in one (33%) patient and endoscopic drainage or dilatation of the fistula or perforation in two (67%) patients. In six (33%) patients, an attempt was made to close the perforation or fistula, endoscopically in one (17%) patient and surgically in five (83%) patients. One (17%) patient died after surgical treatment and one (17%) patient required relaparotomy with drainage after and eventually an ileostomy after the initial attempt to close the perforation surgically.

Colon perforation or fistula (n= 64) was treated conservatively without any invasive intervention in 22 (34%) patients, of whom 11 (50%) patients had a percutaneous catheter drain in situ. Drainage of the perforation or fistula was performed in four (6%) patients, all with percutaneous drainage. In 38 (59%) patients, an attempt was made to close the perforation or fistula surgically (suturing the defect n= 4, ileostomy n=30, both sutures and ileostomy n= 4). Nine (24%) patients died after the surgical procedure, 10 (26%) patients required additional intervention (total parenteral nutrition due to persistent fistula n=1, relaparotomy with drainage of abscess n=5 and relaparotomy with ileostomy n= 3).

DISCUSSION

Although perforation and fistula of the GI tract are well recognized as a severe complication of acute pancreatitis, high quality data to guide clinical decision making are largely lacking. This large nationwide cohort study reveals a 16% incidence of a perforation or fistula of the GI tract in patients with necrotizing pancreatitis, and an incidence of 25% in patients with infected necrosis. High C-reactive protein, and early organ failure were identified as independent risk factors. A prior invasive intervention was identified as a risk factor for a perforation or fistula of the lower GI tract. We show that the clinical course of patients with necrotizing pancreatitis is apparently negatively impacted by a perforation or fistula of the lower GI tract, while a perforation or fistula of the upper GI tract appeared to be protective. Perforation or fistula of the upper GI tract closed spontaneously in the majority of the patients, while colon perforation and fistula were predominantly treated surgically.

There is wide variation in the reported incidence (3%–67%) of perforation or fistula of the GI tract.[1,6–11] This could be explained by the different study populations (e.g., cohort consisting of patients with infected necrosis only) and limited number of patients included in previously published studies. The incidence found in the present study is in line with two recent studies,[8,9] but

slightly higher than reported in other studies,[1,7,10] which could be due to the fact that we included only patients with necrotizing pancreatitis. In addition, our study has a high incidence of infected necrosis, which is explained by the fact that we have included patients from the intervention studies PANTER and TENSION.[3,21]

Failure of the intestinal barrier is thought to be associated with severe local inflammatory response, which may, especially when infected necrosis occurs, erode blood vessels directly, enhance thrombosis and reduce capillary perfusion.[25] In addition, inflammation and exposure to pancreatic enzymes can also lead to vascular thrombosis and worsening of the condition of the GI tract leading to the formation of edema, thrombosis, ischemia and necrosis.[6,11,26] Eventually this may cause perforation and the formation of a fistula of the GI tract.[11] In addition, a perforation or fistula can also be iatrogenic through puncture of the GI wall or through erosion of the drain against the - already vulnerable - GI wall. Since there is no standardized diagnostic work-up to evaluate for potential perforations or fistulas of the GI tract before the patient undergoes an intervention, it is difficult to determine whether the perforation of fistula was already present. The run-up to the development of a iatrogenic or spontaneous perforation or fistula is different, the outcome, however, remains the same: either a perforation or fistula of the GI tract. Furthermore, there might be a difference in clinical course between acute perforations and chronic fistula formation.

The colon is more prone to ischemia as a result of low-flow state or the hemodynamic response to sepsis, as compared with the stomach and the jejunum and ileum due to the better blood supply of these organs.[11,12,20] More specifically, the transverse colon and the splenic flexure of the colon are closely related to the pancreas and inflammation of the body and tail may cause extrinsic impression and are therefore the most common sites involved.[26] Inflammation of the body of the pancreas as a factor for developing a complication of the colon could explain the finding that central necrosis is an independent risk factor for developing a colon perforation or fistula. Prior intervention was found to be a significant risk factor for developing a fistula or perforation of the lower GI tract, but was not found to be significant in developing overall or upper GI perforations or fistulas. This might be explained by the lower GI tract, especially the colon, being more exposed and vulnerable due to inflammation and intervention. A previous study reported diagnosis of a GI fistula four to eight weeks after onset of pancreatitis in the majority of the patients.[24] This is in line with our findings (i.e., a median of 52 d). These results confirm the suggestion that the occurrence of a perforation or fistula of the GI tract is associated with a prolonged exposure to the peripancreatic or pancreatic inflammation and necrosis or to prolonged percutaneous catheter drainage, which starts with inflammation and ends with

perforation or obstruction. Therefore, timely drainage of infected necrosis could potentially decrease the risk of perforation or fistula of the GI tract. However, intervention may also play a role in the development of a perforation or fistula and therefore the risks should be considered. The recent published POINTER trial did, however, not show superiority of immediate catheter drainage (<24 h after diagnosis of infected pancreatic necrosis), as compared with a delayed catheter drainage strategy. A postponed catheter drainage required less interventions for infected pancreatic necrosis and eventually over one-third patients did not require any intervention at all.[27] Therefore, identifying the patients at higher risk for developing a perforation or fistula of the GI tract is important. Potential risk factors for developing a perforation or fistula of the GI tract were evaluated. High C-reactive protein and early organ failure were found to be independent risk factors. One other previous study also showed that infected necrosis was found to be a risk factor for developing a perforation or fistula of the GI tract.[8] This previous study also showed early enteral nutrition to be a protective factor. This could have been influenced by bias (i.e., patients not tolerating enteral nutrition may have been more critically ill) or it might be explained by preservation of the gut mucosal integrity, inhibition of bacterial overgrowth and translocation and reduction of the systemic inflammation and risk of infected necrosis.[28–30] With regards to colonic perforation, the presence of at least two collections in different locations seemed to be a significant risk factor.[31,32] Unfortunately, both data regarding early nutrition and the number and location of collection were not available for our study.

Surgical or radiological interventions, especially open necrosectomy, may also be a direct cause of perforation or fistula of the GI tract.[15,20,21,33] The management of infected necrosis has changed over the years from open to minimally invasive techniques used in a step-up approach.[21] In the present study, patients from the period before and after the implementation of the step-up approach were included. Overall, 68% of the patients underwent an invasive intervention before diagnosis of a perforation or fistula of the GI tract. This supports the notion that surgical intervention may increase the risk of GI complications. A previous smaller study from our group, however, suggested that the method of invasive management did not affect the incidence of GI fistula.[21] Furthermore, another smaller trial also observed no difference in occurrence of perforation of a visceral organ or enterocutaneous fistula requiring intervention between patients who underwent endoscopic step-up approach and surgical step-up approach (8% vs. 17%).[3] Unfortunately, minimally invasive therapy cannot be seen as the solution to prevent perforation or fistula of the GI tract in patients with infected necrotizing pancreatitis.

Perforation or fistula of the GI tract is associated with increased morbidity

due to subsequent complications such as hemorrhage and sepsis.[5,7] In our study, the presence of a perforation or fistula of the GI tract was associated with a more severe clinical course with a higher rate of ICU admissions and organ failure. These results are in line with a single-center study.[9] They also found an increased mortality in patients with a fistula of the colon,[9] this could not be confirmed with the results of our study. It is hypothesized that spontaneous passage of the peripancreatic of pancreatic necrosis into the GI tract could improve the clinical status of the patient with resolution of pressure symptoms, by creating a natural drainage route.[5,34] This is similar to the route created when an endoscopic drainage is performed. This could explain the less severe disease course in patients with a gastric or duodenal complication, in whom a spontaneous cause was most often found. In the present study, mortality was not found to be significantly higher in patients with a GI complication compared with those without, which was also reported in previous studies.[5,11]

In the current study, perforation or fistula of the stomach, duodenum, jejunum, and ileum could most often be treated conservatively, either with or without percutaneous drains already in situ. Perforations or fistulas of the colon were most often treated surgically. As reported in previous studies, the location of the perforation or fistula may determine the treatment strategy, with spontaneous resolution in the majority of the complications of the upper GI tract while a perforation or fistula of the colon require surgical intervention in the majority.[5,11,14,16,20,35] There are, however, some reports showing potential benefits from conservative or less invasive measurements, such as percutaneous catheter drainage or endoscopic therapy, for patients with a perforation or fistula of the colon.[17–20] In our study, a total of 29% of the patients with a colon perforation or fistula could be successfully treated without invasive intervention or with less invasive techniques, such as percutaneous catheter drainage or endoscopic therapy. Due to the increase in experience in the field of endoscopy, this number could be even higher in current clinical practice. Due to the complexity and accessibility of the colon perforation or fistula and the potential fecal contamination during the procedure, however, endoscopic or other less invasive interventions may be difficult. Since we had no prospective treatment protocol when a perforation or fistula occurred, it was decided by the treating clinician which treatment was applied, according to local preference and experience. In addition to the current idea that colon perforations or fistulas still need to be treated surgically, this will generally also have been the first choice. Potentially, more of these patients could have been treated without invasive intervention, depending on the patients' clinical condition. In our study, we have shown the magnitude of the problem and the clinical consequences, which have not been reported in this manner before. Since the variation in location of the perforation or fistula

is large, we cannot recommend specific treatment strategies with the current data. A more proactive diagnostic approach is, however, probably worthwhile. As for treatment, a tailored step-up approach, starting with conservative measures followed by minimally invasive measurements and eventually surgical treatment in absence of clinical improvement, could be considered for these patients. Future prospective studies are needed to define these approaches.

In conclusion, perforation or fistula of the GI tract occur in almost one out of six patients with necrotizing pancreatitis. The colon and duodenum are mostly commonly affected. C-reactive protein, early organ failure and abdominal compartment syndrome were identified as independent risk factors. The incidence rose to one in four patients with infected necrosis. Perforation or fistula of the GI tract are independently associated with a worse clinical course, especially for patients in whom the colon was affected. Perforation or fistula of the upper GI tract closed spontaneously in the majority of the patients, while colon perforation or fistula were predominantly treated surgically. Early recognition and optimal treatment of perforation or fistula of the GI tract may improve the clinical outcomes and thereby quality of life of patients with necrotizing pancreatitis.

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SUPPLEMENTARY APPENDIX

Table S1 Definitions

Pancreatic necrosis	Diffuse or focal area(s) of non-enhancing pancreatic parenchyma as detected on contrast enhanced CT (CECT)
Extrapancreatic necrosis	Persistent peripancreatic fluid collections on CECT in the absence of pancreatic parenchymal non-enhancement
Infected necrosis	One of the following: a) gas configurations on contrast-enhanced CT or b) positive culture from either a fine needle aspiration or the first drainage procedure from the (peri)pancreatic collection/walled-off necrosis
Pancreas intervention	All invasive interventions for (peri)pancreatic collections and/or necrosis (e.g. percutaneous catheter drainage, endoscopic transluminal drainage, surgical or endoscopic necrosectomy), without ascites drainage or decompression laparotomies
Perforations and fistulas of the gastrointestinal tract	Perforations and fistulas of the gastrointestinal tract (stomach, duodenum, jejunum, ileum or colon) confirmed with either imaging, endoscopy or surgery, were defined as: 1. Perforation: a spontaneous or iatrogenic discontinuation of the gastro-intestinal wall without a connection with another organ 2. Fistula spontaneous or iatrogenic discontinuation of the gastro-intestinal wall with a connection with another organ (e.g. pancreas or biliary tract) 3. Intestinal necrosis causing perforation confirmed with either imaging, endoscopy, or surgery In this study, no distinction is made between perforations and fistulas in the analysis. When a perforation or fistula of the gastrointestinal tract was only seen on imaging, images were reviewed by an expert radiologist (TLB).
Spontaneous cause	No abdominal intervention before diagnosis of gastrointestinal perforation or fistula
Iatrogenic cause	A non-intended gastrointestinal perforation or fistula caused by a known iatrogenic cause (e.g. drain)
Unknown cause	A gastrointestinal complication in which an iatrogenic cause cannot be excluded and therefore no certain distinction can be made between a spontaneous and iatrogenic cause
Enterocutaneous fistula	Enterocutaneous fistula is defined as secretion of fecal material from a percutaneous drain, drainage canal after removal of drains, or from a surgical wound, either from small or large bowel
Organ failure*	
Cardiovascular	Systolic blood pressure < 90 mmHg despite adequate fluid resuscitation, or need for vasopressor support
Pulmonary	PaO2 < 60 mmHg despite FiO2 30%, or the need for mechanical ventilation
Renal	Serum creatinine > 177 mmol/L after rehydration or need for hemofiltration or hemodialysis
Early organ failure	Occurrence of organ failure within the first seven days after admission
Multiple organ failure	Failure of 2 or more organ systems on the same day
Abdominal compartment syndrome	Intra-abdominal pressure ≥20mmHg
Pancreatic exocrine insufficiency	Exocrine insufficiency is defined as an abnormal fecal elastase test (<200 mg/g) or the need for oral pancreatic-enzyme supplementation to treat clinical symptoms of steatorrhea (not present before onset pancreatitis)
Pancreatic endocrine insufficiency	Endocrine insufficiency is defined as insulin or oral antidiabetic drugs required (not present before onset pancreatitis)
Chronic pancreatitis	Defined according to the M-ANNHEIM criteria[4]

*Definitions are adapted from the Atlanta classification[1] and the same as previously used in the PANTER and TENSION trial[2,3]. No occurrence of organ failure is assumed in the absence of lab and/or information in the discharge letter and/or notes.

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Table S2 Clinical outcomes, interventions and complications regardless of timing diagnosis perforation or fistula of the gastrointestinal tract

		Perforation or fistula of the gastrointestinal tract		
Variables	**Overall, N = 896**	**No, N = 756**	**Yes, N = 139**	***P****
Clinical outcomes				
Death pancreatitis related	106 (12)	78 (10)	28 (20)	<0.01
Death after 21 days after admission	85 (9)	62 (8)	23 (17)	<0.01
Readmission	601 (67)	501 (66)	100 (72)	0.20
Readmission for re-intervention	118 (13)	85 (11)	33 (24)	<0.01
Hospital stay length†	53 (24 – 100)	45 (21 – 88)	104 (67 – 171)	<0.01
ICU-admission overall	452 (50)	341 (45)	111 (80)	<0.01
Length of ICU-stay	1 (0 – 18)[a]	0 (0 – 11)[l]	20 (2 – 50)[l]	<0.01
New ICU admission >21 days after admission	171 (19)[b]	124 (16)[m]	47 (34)[t]	<0.01
Persistent ICU admission >21 days after admission	150 (17)[c]	94 (12)[n]	56 (40)[g]	<0.01
Organ failure	377 (42)	273 (36)	104 (75)	<0.01
Transient SOF	52 (6)	39 (5)	13 (9)	0.07
Persistent SOF	322 (36)	232 (31)	90 (65)	<0.01
Transient MOF	59 (7)	46 (6)	13 (9)	0.19
Persistent MOF	228 (25)	155 (20)	73 (53)	<0.01
New onset organ failure >21 days after admission	149 (17)[d]	106 (14)[n]	43 (31)[u]	<0.01
Persistent organ failure >21 days after admission	117 (13)[e]	75 (10)[o]	42 (30)[v]	<0.01
Early organ failure	223 (25)[f]	157 (21%)[f]	66 (47)	<0.01
Early persistent MOF	137 (15)[g]	85 (11)[g]	52 (37)	<0.01
Interventions				
Pancreatic intervention	468 (52)	347 (46)	121 (87)	<0.01
Percutaneous catheter drainage	320 (36)	225 (30)	95 (68)	<0.01
Length of PCD*	77 (47 – 135)	69 (42 – 115)	96 (67 – 158)	<0.01
Endoscopic transgastric drainage	181 (20)	149 (20)	32 (23)	0.36
Necrosectomy	271 (30)	200 (26)	71 (51)	<0.01
ETN	80 (9)	69 (9)	11 (8)	0.75
Surgical necrosectomy	199 (22)	136 (18)	63 (45)	<0.01
VARD	83 (9)	56 (7)	27 (19)	<0.01
Other SN	124 (14)	84 (11)	40 (29)	<0.01
Need for additional intervention	356 (76)	255 (74)	101 (83)	<0.01
Other interventions				
Ascites drainages	87 (10)	55 (7)	32 (23)	<0.01

Table S2 Continued.

Variables	Overall, N = 896	Perforation or fistula of the gastrointestinal tract		*P**
		No, N = 756	Yes, N = 139	
PTC-drain	41 (5)	24 (3)	17 (12)	<0.01
Thorax drainages	85 (10)	59 (8)	26 (19)	<0.01
Complications				
Abdominal compartment syndrome	32 (4)	16 (2)	16 (12)	<0.01
Bleeding	98 (11)	61 (8)	37 (27)	<0.01
Thrombosis	177 (20)	130 (17)	47 (34)	<0.01
Long-term complications				
Recurrent pancreatitis	196 (25)[h]	173 (25)[p]	23 (21)[w]	0.34
Chronic pancreatitis	84 (11)[i]	71 (10)[q]	13 (12)[x]	0.62
Endocrine pancreatic insufficiency	241 (30)[j]	186 (27)[r]	55 (49)[y]	<0.01
Exocrine pancreatic insufficiency	219 (28)[k]	168 (25)[s]	51 (46)[z]	<0.01

Data are presented as n (%) or median (interquartile range: P25-P75).
*Univariate analysis.
†Overall length of hospital stay including initial admission and readmissions.
Missing patients: a=2, b=29, c=26, d=30, e=41, f=4, g=5, h=105 patients died <1 year, i=109 patients died <1 year, j=102 patients died <1 year, k=103 patients died <1 year, l=1, m=23, n=21, o=31, p=76 patients died <1 year, q=79 patients died <1 year, r=76 patients died <1 year, s=75 patients died <1 year, t=6, u=9, v=10, w=29 patients died <1 year, x=30 patients died <1 year, y=26 patients died <1 year, z=28 patients died <1 year.
OR indicates *adjusted odds ratio*; CI, *confidence interval*; ICU, *intensive care unit*; SOF, *single organ failure*; MOF, *multiple organ failure*; PCD, *percutaneous catheter drainage*; VARD, *video assisted retroperitoneal debridement*; ETN, *endoscopic transluminal necrosectomy*; SN, *surgical necrosectomy*; PTC, *percutaneous transhepatic cholangiodrain*

Table S3 Patients characteristics at admission and clinical course* of patients a perforation or fistula of the gastrointestinal tract with and without an invasive intervention before diagnosis

		Prior invasive intervention		
Variables	**Overall, N = 139**	**No, N = 43**	**Yes, N = 96**	***P***
Age (y)	59 (50 – 70)	66 (57 – 73)	58 (49 – 68)	0.01
Male sex	98 (71)	30 (70)	68 (71)	1.00
Body Mass Index	27.8 (25.1 – 30.4)[a]	27.5 (25.5 – 29)[d]	28.4 (24.9 – 30.8)[g]	0.50
Etiology of pancreatitis				
Biliary	59 (42)	20 (47)	39 (41)	0.58
Alcohol	26 (19)	5 (12)	21 (22)	0.24
ASA				
I	43 (31)	16 (37)	27 (28)	0.32
II	81 (58)	23 (54)	58 (60)	0.46
III	15 (11)	4 (9)	11 (12)	1.00
Severity of disease				
Leucocytes (10^9/l)	18.6 (14.9 – 22.9)[b]	18.7 (15.5 – 23)[e]	18.6 (14.5 – 22.8)[h]	0.39
C-reactive protein (mg/l)	341 (254 – 412)[c]	304 (241 – 408)[f]	347 (257 – 422)[i]	0.20
CT severity index	6 (5 – 10)	6 (4 – 8)	8 (6 – 10)	0.09
Parenchymal necrosis	105 (76)	30 (70)	75 (78)	0.30
<30%	40 (38)	15 (35)	25 (26)	0.32
30-50%	20 (19)	5 (12)	15 (16)	0.61
>50%	45 (43)	10 (23)	35 (37)	0.17
Pattern parenchymal necrosis				
Right	4 (4)	1 (2)	3 (3)	1.00
Left	5 (5)	2 (5)	3 (3)	0.65
Central	52 (50)	15 (35)	37 (39)	0.71
Subtotal	24 (23)	4 (9)	20 (21)	0.14
Diffuse	20 (19)	8 (19)	12 (13)	0.43
Extrapancreatic necrosis only	34 (25)	11 (26)	8 (13)	0.01
Early ICU-admission	88 (63)	20 (47)	68 (71)	<0.01
Early organ failure	66 (47)	21 (49)	45 (47)	0.86
Early persistent single organ failure	9 (6)	3 (7)	6 (6)	1.00
Early persistent multiple organ failure	52 (37)	15 (35)	39 (41)	0.58

Data are presented as n (%) or median (interquartile range: P25 – P75).
*Clinical course variables are reported regardless of timing of diagnosis of perforation or fistula of gastrointestinal tract.
Missing patients: a=66, b=16, c=20, d=24, e=4, f=7, g=42, h=12, i=13.
ASA indicates *American Society of Anesthesiologists*, assessed based on the patient's history just prior to admission, there were no patients with ASA class 5; CT, *computed tomography*; ICU, *Intensive Care Unit*

Table S4 Univariate analysis of clinical outcomes for perforation or fistula of the gastrointestinal tract and the different locations

	All locations			Gastric			Duodenum			Jejunum/ileum			Colon		
Variables	**No N = 757**	**Yes N = 139**	***P***	**No N = 873**	**Yes N = 23**	***P***	**No N = 840**	**Yes N = 56**	***P***	**No N = 878**	**Yes N = 18**	***P***	**No N = 832**	**Yes N = 64**	***P***
Death															
All pancreatitis related	78 (10)	28 (20)	<0.01	104 (12)	2 (9)	1.00	95 (11)	11 (20)	0.08	100 (11)	6 (32)	0.02	89 (11)	17 (27)	<0.01
After 21 days after admission	62 (8)	23 (17)	<0.01	83 (10)	2 (9)	1.00	76 (9)	9 (16)	0.10	82 (9)	3 (16)	0.41	71 (9)	14 (22)	<0.01
ICU-admission															
New after 21 days after admission	125 (17)[a]	48 (35)[d]	<0.01	167 (19)[f]	6 (26)	0.42	155 (19)[f]	18 (32)	0.02	166 (19)[f]	7 (37)	0.07	147 (18)[a]	26 (41)[d]	<0.01
Persistent admission after 21 days after admission	93 (12)[b]	57 (41)	<0.01	144 (17)[b]	6 (26)	0.25	129 (15)[b]	21 (38)	<0.01	142 (18)[b]	8 (42)	0.01	119 (14)[b]	31 (48)	<0.01
Organ failure															
New after 21 days after admission	106 (14)[b]	44 (33)[e]	<0.01	146 (17)[g]	4 (17)	1.00	131 (16)[a]	19 (35)[k]	<0.01	143 (16)[f]	7 (39)[d]	0.02	127 (15)[a]	23 (37)[k]	<0.01
Persistent organ failure after admission	76 (10)[c]	44 (33)[b]	<0.01	117 (14)[h]	3 (15)[i]	0.75	106 (13)[j]	14 (25)[d]	0.01	111 (13)[l]	9 (47)	<0.01	92 (11)[m]	28 (45)[k]	<0.01

Data are presented as n (%).
Missing patients: a=7, b=5, c=15, d=1, e=4, f=8, g=9, h=17, i=3, j=19, k=2, l=20, m=18
ICU indicates *intensive care unit*.

Table S5 Potential confounders in generalized linear model for clinical outcomes (Table 5)

Clinical outcomes - perforation or fistula of the upper gastrointestinal tract	
Death pancreatitis related	
Overall	Perforation or fistula of the upper GI-tract + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis + Occurrence of parenchymal or extrapancreatic necrosis + Parenchymal necrosis of more than 50 percent + Occurrence of organ failure + Occurrence of abdominal compartment syndrome
>21 days after admission	Perforation or fistula of the upper GI-tract + Age + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis + Occurrence of parenchymal or extrapancreatic necrosis + Occurrence of organ failure 21 days after admission + Occurrence of ongoing organ failure after 21 days after admission + Occurrence of abdominal compartment syndrome
ICU-admission	
New ICU-admission after 21 days after admission	Perforation or fistula of the upper GI-tract before new ICU admission + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis before new ICU admission + Occurrence of parenchymal necrosis of more than 50 percent + Presence of central parenchymal necrosis + Presence of subtotal parenchymal necrosis + Occurrence of early organ failure
Persistent ICU-admission after 21 days after admission	Perforation or fistula of the upper GI-tract before persistent ICU admission + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis before persistent ICU admission + Occurrence of parenchymal necrosis of more than 50 percent + Presence of central parenchymal necrosis + Presence of subtotal parenchymal necrosis + Occurrence of early organ failure
Organ failure	
New after 21 days after admission	Perforation or fistula of the upper GI-tract before new onset OF 21 days after admission + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis before new onset OF 21 days after admission + Occurrence of parenchymal necrosis of more than 50 percent + Presence of central parenchymal necrosis + Presence of subtotal parenchymal necrosis + Occurrence of early organ failure
Persistent organ failure 21 days after admission	Perforation or fistula of the upper GI-tract before ongoing OF 21 days after admission + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis before new onset OF 21 days after admission + Occurrence of parenchymal necrosis of more than 50 percent + Presence of central parenchymal necrosis + Presence of subtotal parenchymal necrosis + Occurrence of early organ failure
Clinical outcomes - perforation or fistula of the lower gastrointestinal tract	
Death pancreatitis related	
Overall	Perforation or fistula of the lower GI-tract + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis + Occurrence of parenchymal or extrapancreatic necrosis + Parenchymal necrosis of more than 50 percent + Occurrence of organ failure + Occurrence of abdominal compartment syndrome
>21 days after admission	Perforation or fistula of the lower GI-tract + Age + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis + Occurrence of parenchymal or extrapancreatic necrosis + Occurrence of organ failure 21 days after admission + Occurrence of ongoing organ failure after 21 days after admission + Occurrence of abdominal compartment syndrome

Table S5 Continued.

Clinical outcomes - perforation or fistula of the upper gastrointestinal tract	
ICU-admission	
New ICU-admission after 21 days after admission	Perforation or fistula of the lower GI-tract before new ICU admission + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis before new ICU admission + Occurrence of parenchymal necrosis of more than 50 percent + Presence of central parenchymal necrosis + Presence of subtotal parenchymal necrosis + Occurrence of early organ failure
Persistent ICU-admission after 21 days after admission	Perforation or fistula of the lower GI-tract before persistent ICU admission + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis before persistent ICU admission + Occurrence of parenchymal necrosis of more than 50 percent + Presence of central parenchymal necrosis + Presence of subtotal parenchymal necrosis + Occurrence of early organ failure
Organ failure	
New after 21 days after admission	Perforation or fistula of the lower GI-tract before new onset OF 21 days after admission + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis before new onset OF 21 days after admission + Occurrence of parenchymal necrosis of more than 50 percent + Presence of central parenchymal necrosis + Presence of subtotal parenchymal necrosis + Occurrence of early organ failure
Persistent organ failure 21 days after admission	Perforation or fistula of the lower GI-tract before ongoing OF 21 days after admission + Age + Male sex + ASA class 3 or 4 + Highest CRP in the first 48 hours after admission + Occurrence of infected necrosis before new onset OF 21 days after admission + Occurrence of parenchymal necrosis of more than 50 percent + Presence of central parenchymal necrosis + Presence of subtotal parenchymal necrosis + Occurrence of early organ failure

GI indicates *gastrointestinal*; ASA *American Society of Anesthesiology*; CRP *C-reactive protein*; ICU *intensive care unit*; OF *organ failure*

Table S6 Treatment strategies for the different locations of perforation or fistula of the gastrointestinal tract with and without symptoms

Variables	Gastric				Duodenum			
		Symptomatic				Symptomatic		
	Overall N = 23	No N = 16	Yes N = 7	*P*	Overall N = 56	No N = 38	Yes N = 18	*P*
Conservative*	***15 (65)***	***13 (81)***	***3 (43)***	***0.14***	***39 (70)***	***26 (68)***	***13 (72)***	***1.00***
Percutaneous catheter drainage in situ	6 (40)	*3 (23)*	*3 (100)*	0.32	27 (69)	*13 (50)*	*10 (77)*	0.57
Drainage of perforation or fistula	***5 (22)***	***2 (13)***	***2 (29)***	***0.56***	***14 (25)***	***10 (26)***	***4 (22)***	***1.00***
Percutaneous (new drain)	*1 (20)*	-	*1 (50)*		*6 (43)*	*3 (30)*	*3 (75)*	
Endoscopic	*4 (80)*†	*2 (100)*	*1 (50)*		*8 (57)*	*7 (70)*	*1 (25)*	
Dilatation of the fistula or perforation	4 (100)	2 (100)	1 (100)		8 (14)	7 (100)	1 (100)	
Closure of perforation or fistula	***3 (13)***	***1 (6)***	***2 (29)***	***0.21***	***3 (5)***	**2 (5)**	**1 (6)**	**1.00**
Endoscopic	-	-	-		-	-	-	
Endoscopic clips	-	-	-		-	-	-	
Surgical	*3 (100)*	*1 (100)*	*2 (100)*		*3 (100)*	-	-	
Sutures	3 (100)	1 (100)	2 (100)*		1 (33)	1 (50)	-	
Stoma	-	-	-		-	-	-	
Both sutures and ileostomy	-	-	-		-	-	-	
Other	-	-	-		2 (67)‡	1 (50)	1 (100)	
Outcome								
Survived	20 (91)	14 (87)	6 (86)		45 (80)	29 (76)	16 (89)	
Death	3 (9)[a]	2 (13)[b]	1 (14)[c]	0.53	11 (20)[d]	9 (24)[e]	2 (11)[f]	0.47

Data are presented as n (%).
*Conservative management includes patients who died before treatment of perforation or fistula could take place.
†In 1 (8%) patient this was in addition to the percutaneous drain already in place
‡In 1 patient decompression laparotomy with percutaneous catheter drainage and in 1 patient a new percutaneous catheter drain and a percutaneous trans hepatic cholangiography drain and reconstruction of the duodenum by a gastro- and jejunostomy with a side-to-side Roux-en-Y
[a]Both died after surgical closure of perforation or fistula, [b]oth died after conservative treatment, [c]patient died after surgical treatment, [d]6 (55%) patients died after conservative measures, 2 (18%) patients after a new percutaneous drain, 1 (9%) patients after surgical treatment and 2 (18%) had a poor prognosis and received no invasive treatment, [e]8 (89%) patients died after conservative treatment, 1 (11%) patient died after a new percutaneous drain, [f]1 (50%) patient died after a new percutaneous drain and 1 (50%) died after surgical treatment, [g]1 (20%) patients died after placement of a new percutaneous catheter drain, 1 (20%) after surgical treatment and 3 (60%) had a poor prognosis and received no invasive treatment, [h]2 (33%) patients died after conservative treatment, 1 (67%) patients died after surgical treatment, [i]2 (67%) patients died after conservative treatment and 1 (33%) died after endoscopic treatment, [j]1 (6%) patients died after an additional percutaneous catheter drain, 9 (53%) patients after surgical treatment and 7 (41%) patients had a poor prognosis and received no invasive treatment, [k]7 (58%) patients died after conservative treatment and 5 (42%) patients died after surgical treatment, [l]1 (20%) patients died after percutaneous catheter drain and 4 (80%) patients died after surgical treatment.

	Jejunum/ileum				Colon			
		Symptomatic				Symptomatic		
	Overall N = 19	**No N = 11**	**Yes N = 8**	***P***	**Overall N = 64**	**No N = 38**	**Yes N = 26**	***P***
	10 (56)	***7 (64)***	***3 (27)***	***0.37***	***22 (34)***	***17 (45)***	***5 (19)***	***0.06***
	7 (70)	*5 (71)*	*2 (67)*	0.63	11 (50)	*6 (35)*	*5 (100)*	*0.75*
	3 (17)	***2 (18)***	***-***	***1.00***	***4 (6)***	***1 (3)***	***3 (12)***	***0.30***
	1 (33)	*1 (50)*	-		*4 (100)*	*1 (100)*	*3 (100)*	
	2 (67)	*1 (50)*	-		-	-	-	
	1 (50)	1 (100)	-		-	-	-	
	6 (33)	**2 (18)**	**5 (45)**	**0.32**	**38 (59)**	**20 (53)**	**18 (69)**	**0.21**
	1 (17)	-	*1 (20)*		-	-	-	
	1 (50)	-	-		-	-	-	
	5 (83)	-	*4 (80)*		*38 (100)*	*20 (100)*	*18 (100)*	
	2 (40)	2 (100)	2 (50)		4 (11)	4 (20)	-	
	3 (60)	-	2 (50)		30 (79)	14 (70)	16 (89)	
	-	-	-		4 (11)	2 (10)	2 (11)	
	-	-	-		-	-	-	
	13 (72)	8 (73)	5 (63)		47 (73)	26 (68)	21 (81)	
	5 (28)[g]	3 (27)[h]	3 (37)[i]	1.00	17 (27)[j]	12 (32)[k]	5 (19)[i]	0.39

PART III

LONG-TERM OUTCOME AND PREVENTION OF RECURRENCE AFTER ACUTE PANCREATITIS

PART III

CHAPTER IX

Diagnosis and therapeutic approach to pancreatic exocrine insufficiency after acute pancreatitis

Chapter 21
Clinical Pancreatology for Practising Gastroenterologists and Surgeons
Second Edition 2021

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INTRODUCTION

Around 20% of patients with acute pancreatitis have a clinically severe disease course and may develop necrosis of the pancreatic parenchyma or peripancreatic tissue.[1-3] In 30% of these patients, percutaneous or endoscopic catheter drainage or even necrosectomy is needed to treat secondary infected necrosis.[4,5] Pancreatic exocrine insufficiency can be a long-term complication in these patients.

Pancreatic exocrine insufficiency can be defined as a reduction in pancreatic enzyme secretion or activity in the intestinal lumen to a level below the threshold required to maintain normal food digestion.[6] Pancreatic juice has an important role in digestion and absorption of nutrients. The juice consists of water and bicarbonate secreted by ductal cells. In addition, the pancreatic juice contains several enzymes (digestive proteins), serum proteins, and nondigestive proteins released by the acinar cells.[7] The function of these enzymes is to digest proteins, carbohydrates, and fat.[8] The main consequence of pancreatic exocrine insufficiency is malnutrition with deficiencies of fat-soluble vitamins, several proteins, and micronutrients due to maldigestion.[9] Symptoms will occur when intraduodenal levels of lipase decrease below 5–10% of baseline.[10] This demonstrates the large reserve capacity of the exocrine function of the pancreas.

One of the presumed rationales for developing pancreatic exocrine insufficiency following acute pancreatitis is reduction in the release of enzymes by the acinar cells due to loss of functional parenchyma due to pancreatic parenchymal necrosis.[7,11] Acinar cell damage depends on the interaction of acinar cells with infiltrating leukocytes, particularly macrophages and dendritic cells, which determines the initial severity of injury as well as its resolution.[12]
There is ongoing debate about the duration of pancreatic exocrine insufficiency after an episode of acute pancreatitis. Some suggest that it is a temporary injury whereby the pancreatic exocrine insufficiency will resolve in time,[13] whereas other reports claim that the pancreatic injury is persistent.[14,15]

The incidence of pancreatic exocrine insufficiency is related to the severity of acute pancreatitis.[16] However, the severity of pancreatic exocrine insufficiency is not directly related to the severity of the acute pancreatitis episode.[17] Based on a recent meta-analysis the pooled prevalence of acute pancreatitis, measured by fecal elastase-1 testing, was 19% after mild pancreatitis and 33% after severe pancreatitis.[16] The pooled prevalence of pancreatic exocrine insufficiency in 1495 patients with acute pancreatitis, tested at a mean of 36 months after index admission, was 27% [95% confidence interval (CI) 20.3–35.1].[16] This suggests that almost one-third of the patients with acute pancreatitis suffer from persistent pancreatic exocrine insufficiency. Also, a higher occurrence of pancreatic exocrine insufficiency is seen in patients with alcoholic pancreatitis, as compared with

patients with biliary pancreatitis (23% vs. 10%).[16,18]

SYMPTOMS

Patients with untreated pancreatic exocrine insufficiency may suffer from symptoms of indigestion, flatulence, diarrhea, abdominal pain, or cramps. When the pancreatic insufficiency is more severe, malnutrition and steatorrhea may develop. Severe pancreatic exocrine insufficiency results in weight loss, deficiency of fat-soluble vitamins (A, D, E, K), and mineral deficiencies that can cause metabolic bone diseases.

DIAGNOSIS

Suspicion of pancreatic exocrine insufficiency is generally based on clinical assessment. It is suggested that after an episode of acute pancreatitis, almost one-third of patients suffer from persistent pancreatic exocrine insufficiency. Therefore, despite lack of evidence, it is recommended that fecal elastase is checked in all patients who have had an episode of moderate to severe acute pancreatitis, between three and six months after discharge. In patients with mild pancreatitis, it is recommended that fecal elastase is checked based on clinical assessment at the first visit to the outpatient clinic.

Symptoms of pancreatic exocrine insufficiency vary from patient to patient and are often contributed to other diseases seen in daily clinical practice.[6,19] Mild pancreatic exocrine insufficiency may not cause symptoms and may, therefore, be difficult to detect. This may lead to misdiagnosis or patients who are subsequently left untreated. When pancreatic exocrine insufficiency progresses, symptoms will eventually occur, with fat maldigestion and malabsorption resulting in steatorrhea as the main clinical consequence.[19,20] Early diagnosis of pancreatic exocrine insufficiency leads to early and adequate treatment, which prevents complications associated with malabsorption and malnutrition.[19]

Over the years, various tests for pancreatic exocrine insufficiency have been developed, and these can be divided into direct and indirect function tests (Table 1).[20-23] However, many of these tests have poor sensitivity or specificity, have limited availability, and are invasive and time-consuming.[20-23]

Direct tests of pancreatic function, such as the secretin–cholecystokinin stimulation test and the endoscopic pancreatic function test, involve the direct measurement of pancreatic enzymes and bicarbonate output in duodenal juice obtained after stimulation of the pancreatic gland.[6,21] Direct tests have the highest

accuracy for evaluating pancreatic secretion, but are also invasive, unpleasant for the patient, expensive, and not fully standardized.[6,19,24,25] Examples of indirect tests are fecal tests, such as the 72-hour fecal fat and fecal elastase-1 tests, and 13C-breath tests. Exocrine pancreatic function is evaluated in indirect tests by assessing either the digestive ability of the pancreas or levels of pancreatic enzymes in feces.[19,20] Compared with direct tests, the sensitivity and specificity of indirect tests are variable and lower, but are less invasive, less expensive, and easier to use in clinical routine.[19,26]

Several 13C-breath tests, including the 13C-mixed triglyceride (MTG) breath test, have been developed. It is a simple, noninvasive, and accurate diagnostic tool for pancreatic exocrine insufficiency, with a sensitivity of up to 90%.[21,27-30] The disadvantage of the 13C-MTG breath test is that it produces unreliable results where there is intestinal malabsorption, severe liver disease, or respiratory insufficiency. Also, the 13C-MTG breath test takes longer to complete (up to 8 hours) than the fecal elastase-1 test.[19-21]

A specific enzyme-linked immunosorbent assay is used to determine fecal elastase-1 levels; a value in excess of 200 mg/g is considered normal. The probability of pancreatic exocrine insufficiency increases if levels are lower,[20,31,32] and concentrations below 50 mg/g are associated with pancreatic exocrine insufficiency. In general, pancreatic function tests require interruption of pancreatic enzyme replacement therapy; however, fecal elastase-1 levels are not affected by pancreatic enzyme replacement therapy and, therefore, there is no indication to stop therapy, an important advantage.[19,33]

In mild to moderate pancreatic exocrine insufficiency, fecal elastase quantification is not sufficiently sensitive (54%). In severe pancreatic exocrine insufficiency, sensitivity is high, reaching values close to 100%.[20,33-37] Specificity is also high, 79% for diagnosing mild to moderate pancreatic exocrine insufficiency,[34] but is limited in cases of diarrhea (due to dilution), diabetes, and isolated enzyme deficiencies.[31,34,38]

In summary, the fecal elastase-1 test is recommended as the first-line test of pancreatic exocrine function due to its reliability, ease of use, availability, and cost-effectiveness.[19]

MANAGEMENT

If not recognized in daily clinical practice and thus left untreated, pancreatic exocrine insufficiency may lead to serious complications,[39] such as weight loss, malnutrition, nutritional deficiencies (osteoporosis, osteopenia), increased mortality,[40] and a reduced quality of life.[26,40-45] Therefore, the aim of pancreatic

enzyme replacement therapy is not only to relieve maldigestion-related symptoms, but mainly to achieve a normal nutritional status. In the literature, there is no consensus regarding the threshold for pancreatic exocrine insufficiency in patients after an episode of acute pancreatitis. Several randomized trials have demonstrated improvement in fecal fat excretion after pancreatic enzyme replacement therapy.[46-48] Patients who lose weight, with a daily fecal fat excretion of more than 15g from a diet containing 100g fat daily, and those with relevant maldigestion-related symptoms require pancreatic enzyme replacement therapy.[40] Indication for therapy in patients with a daily fecal fat excretion of less than 15g and asymptomatic steatorrhea is unclear. However, recent literature shows benefit of enzyme substitution in patients with low circulating levels of nutritional parameters.[49] For the diagnosis of pancreatic exocrine insufficiency in chronic pancreatitis, the HaPanEu guideline recommends a threshold for the fecal elastase-1 test of less than 200 μg/g.[50] Therefore, we have decided to retain the cutoff value of less than 200 μg/g in the fecal elastase-1 test as establishing definite pancreatic exocrine insufficiency, and in these patients pancreatic enzyme replacement therapy is recommended. In patients with fecal elastase-1 values between 200 and 500 μg/g with symptoms of pancreatic exocrine insufficiency or signs of malnutrition in blood, the diagnosis of pancreatic exocrine insufficiency can also be established and pancreatic enzyme replacement therapy is recommended. Fecal elastase-1 values above 500 μg/g exclude pancreatic exocrine insufficiency, and therefore pancreatic enzyme replacement therapy is not recommended. Therapy of pancreatic exocrine insufficiency is based on the oral administration of exogenous pancreatic enzymes together with dietary modifications.[20,22,23.26] Pancreatic enzymes secreted from the pancreatic gland increases rapidly in response to oral intake of food, and reach maximal values within 20–60 minutes. Before returning to interdigestive levels, pancreatic enzyme output decreases to a threefold to fourfold sustained increase, which is maintained for three to four hours. In healthy subjects, a maximum lipase output of 3000–6000 IU/min and a mean lipase output of 2000–4000 IU/min occurs after ingestion of a normal mixed meal (300–600 kcal).[7] Pancreatic enzyme replacement therapy should mimic the action of endogenous pancreatic enzymes, and therefore the pancreatic enzymes should be administered either with meals or just after meals.[22,23,51] With oral administration of pancreatic enzymes, encapsulated microgranules deliver a combination of lipase, amylase, and protease into the duodenal lumen, providing sufficient enzymatic activity so that nutrient digestion is restored and malabsorption prevented.[49] Enteric-coated microgranules are designed to be acid-resistant, the pH-sensitive coating dissolving in the duodenum due to its alkaline environment.[7] All pancreatic enzyme preparations are obtained from porcine pancreas and are available in

different forms (enteric-coated, size, etc.). All these preparations are unable to deliver the more than 360 000 IU of active lipase secreted into the duodenal lumen by the pancreas in healthy subjects. However, with pancreatic enzyme replacement therapy, together with the effect of gastric lipase and residual pancreatic exocrine secretion, fat digestion and absorption improves significantly. Enzyme preparations should be able to deliver at least 30 000 IU of active lipase to the duodenum to prevent maldigestion-related symptoms such as steatorrhea.[10,52] A minimum of 40 000–50 0000 Eur.Ph.U lipase per meal is recommended.[40,49] Doses of 72 000 Eur.Ph.U lipase per meal were associated with complication rates of 8–13%, including abdominal pain, abdominal distension, and diarrhea.[47] As previously mentioned, dietary improvements play a crucial role in management of pancreatic exocrine insufficiency. Formerly, a low-fat diet was recommended in patients with pancreatic exocrine insufficiency, but an experimental study of pancreatic exocrine insufficiency in dogs demonstrated that fat digestion and absorption is higher when enzyme supplements are taken together with a high-fat diet compared to a low-fat diet. Therefore, a low fat diet is no longer recommended.[22,53] The recommended diet should be tailored to individual needs and micronutrient intake should be adequate, to improve energy and protein intake. Small frequent meals, avoidance of foods that are difficult to digest, and cessation of alcohol is recommended. To provide extra calories in patients with weight loss and in order to reduce steatorrhea, medium chain triglycerides, which are directly absorbed by the intestinal mucosa, may be useful. Also, patients may require supplements of fat-soluble vitamins.[20,23] In almost half of the patients with pancreatic exocrine insufficiency, normalization of fat digestion does not occur despite the use of enteric-coated enzyme replacement.[54] Low dose of enzymes, acidic intestinal pH, intestinal bacterial overgrowth, and inadequate patient compliance are among the factors causing lack of improvement in maldigestion-related symptoms.[51] Confirmation of proper enzyme administration (timing, dose, etc.) is the first step in guaranteeing optimal efficacy of oral pancreatic enzymes (Figure 1). Secondly, in the case of insufficient effect, inhibition of gastric acid secretion with a proton pump inhibitor should be considered. Thirdly, if symptoms continue, bacterial overgrowth should be detected and treated. Eventually, if there is still no response to adequate pancreatic enzyme replacement therapy, concurrent gastrointestinal comorbidities should be considered.[20,22.23] In the long term, it is important to monitor and follow up patients with pancreatic exocrine insufficiency to ensure sufficient response to enzyme replacement therapy and dietary advice in order to prevent further complications.[26] Follow-up of patients with pancreatic exocrine insufficiency is important for monitoring the potential recovery of exocrine pancreatic function and to reconsider pancreatic enzyme replacement therapy. No standardized guideline regarding follow-up is available,

but we recommend follow-up for at least one year after diagnosis of exocrine pancreatic insufficiency. Evaluation of therapeutic efficacy, normalization of fat digestion, and a normal nutritional status should be demonstrated by means of objective methods such as normalization of the coefficient of fat absorption, 13C-MTG breath test, or specific nutritional parameters. Evaluation based only on clinical factors has been shown to be inappropriate.[9,28,49]

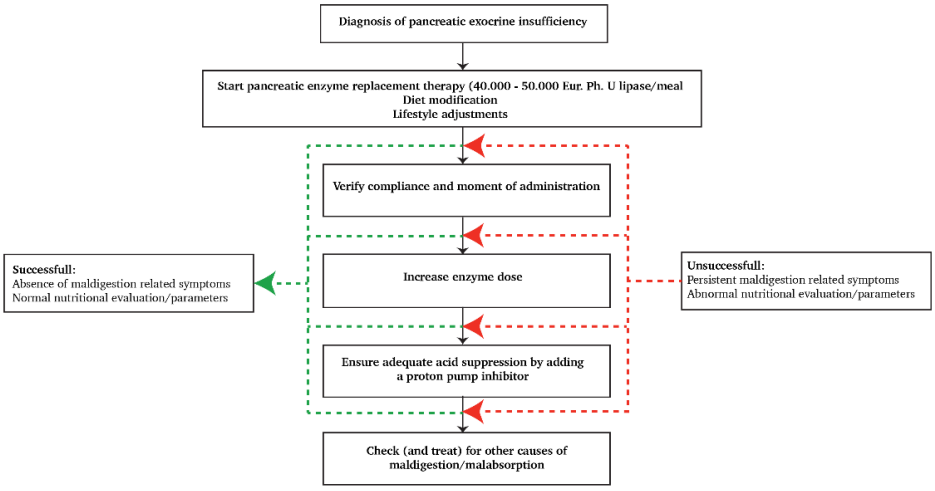

Figure 1 Management of pancreatic enzyme replacement therapy and current recommendations. Sources: adapted from Gheorghe et al. [20] and Domínguez-Muñoz [23].

SUMMARY

Pancreatic exocrine insufficiency is an often underdiagnosed and undertreated condition that occurs in around one-third of patients after an episode of acute (necrotizing) pancreatitis. Fecal elastase-1 is recommended as the first-line test of pancreatic exocrine function due to its reliability, availability, and ease of use. Early diagnosis of pancreatic exocrine insufficiency leads to early and adequate treatment that may prevent complications associated with malabsorption and malnutrition. The aim of pancreatic enzyme replacement therapy is not only to relieve maldigestion-related symptoms, but mainly to achieve a normal nutritional status.

Table 1 Overview of direct and indirect pancreatic function tests

	Advantages	Disadvantages
Direct tests		
Secretin–cholecystokinin Secretin–cerulein Endoscopic pancreatic function test	Gold standard for the quantification of pancreatic secretion Provide information on pancreatic enzyme and bicarbonate production	Invasive Require specialized centers Limited availability No standardization Unpleasant for patients Costly
Indirect tests		
Fecal analysis		
Fecal elastase-1	High sensitivity in moderate to severe pancreatic exocrine insufficiency Not affected by pancreatic enzyme replacement therapy No diet modification required Allows screening of many patients Easy to use Widely available Cost-effective	Limited sensitivity in mild pancreatic exocrine insufficiency Can be affected by diarrhea
Chymotrypsin	No diet modification required Cost-effective	Low sensitivity Not suitable for mild to moderate pancreatic exocrine insufficiency Affected by pancreatic enzyme replacement therapy Chymotrypsin is inactivated during intestinal transit Can be affected by diarrhea
72-hour fecal fat quantification	Gold standard for the quantification of steatorrhea	Not suitable for mild to moderate pancreatic exocrine insufficiency Affected by pancreatic enzyme replacement therapy Not specific to pancreas-related diseases Requires strong patient compliance Time-consuming Unpleasant for patients Limited availability
Breath test		
^{13}C-mixed triglyceride	High sensitivity in moderate to severe pancreatic exocrine insufficiency	Limited sensitivity in mild pancreatic exocrine insufficiency Requires further validation Time-consuming

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PART III

CHAPTER X

A 13,5 years follow-up study of necrotizing pancreatitis: interventions, complications, and quality of life

Submitted

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ABSTRACT

Objective
To describe long term clinical and patient related outcomes in necrotizing pancreatitis.

Design
Long-term follow-up of a prospective multicenter cohort of 373 necrotizing pancreatitis patients (2005-2008) was performed. Patients were prospectively evaluated and received questionnaires. Readmissions (i.e., for recurrent or chronic pancreatitis), interventions, pancreatic insufficiency, and quality of life were compared between initial treatment groups: conservative, endoscopic/percutaneous drainage alone, and necrosectomy. Associations of patient and disease characteristics during index admission with outcomes during follow-up were assessed.

Results
During a median follow-up of 13.5 years (±12 months), 97/373 patients (26%) were readmitted for recurrent pancreatitis. Endoscopic or percutaneous drainage was performed in 47/373 patients (13%), of whom 21/47 patients (45%) were initially treated conservatively. Pancreatic necrosectomy or pancreatic surgery was performed in 31/373 patients (8%), without differences between treatment groups. Endocrine insufficiency (126/373 patients; 34%) and exocrine insufficiency (90/373 patients; 38%), developed less often following conservative treatment ($p<0.001$ and $p=0.016$, respectively). Quality of life scores did not differ between groups. Pancreatic gland necrosis >50% during initial admission was associated with percutaneous/endoscopic drainage (OR4.3 [95%CI 1.5-12.2]), pancreatic surgery (OR3.2 [95%CI 1.1-9.5], and development of endocrine insufficiency (OR13.1 [95%CI 5.3-32.0] and exocrine insufficiency (OR6.1 [95%CI 2.4-15.5] during follow-up.

Conclusion
Acute necrotizing pancreatitis carries a substantial disease burden during long-term follow-up in terms of recurrent disease, the necessity for interventions and development of pancreatic insufficiency, also if treated conservatively during the index admission. Extensive (>50%) pancreatic parenchymal necrosis seems to be an important predictor of interventions and complications during follow-up.

INTRODUCTION

In the treatment of acute necrotizing pancreatitis, conservative treatment for sterile necrosis and a minimally invasive approach towards infected necrosis have shown good short- and long-term clinical results.[1–8] International guidelines are unanimous in their advice on if and when to proceed with interventional treatment during the initial episode of necrotizing pancreatitis.[9–14] The guidelines, however, withhold on recommendations for the long term follow-up of patients after necrotizing pancreatitis, especially when patients were initially treated conservatively. Previously published studies on long-term outcomes still have a relatively short follow-up with medians ranging from 13 to 90 months. Moreover, these studies report mostly on results of selected patients undergoing one specific type of treatment modality for (infected) necrosis[7,8,15,16] or different invasive treatment modalities (e.g., endoscopy, minimally invasive, and invasive surgery) are analysed as one group.[17,18] It is therefore difficult to obtain an overview of the entire clinical spectrum of necrotizing pancreatitis and what the consequences are of each type of treatment during long term follow-up. Long-term outcomes of the group of initially conservatively treated patients are especially unknown. Lastly, contrasting results have been reported on the occurrence of newly diagnosed endocrine and exocrine insufficiency after a primary episode of necrotizing pancreatitis.[19,20].

Given the above, more data are needed on the risk of recurrent disease, the need for (re)interventions, occurrence of endocrine and exocrine pancreatic insufficiency, and the quality of life following both conservative and invasive treatment of necrotizing pancreatitis many years after the initial episode of necrotizing pancreatitis. Awareness of these late interventions and complications as a consequence of initial conservative treatment may guide structured follow-up and inform patients on their prognosis.

We therefore performed a long-term follow-up analysis of an unselected prospective cohort of patients with necrotizing pancreatitis, focusing on recurrent admissions, late onset complications, interventions and quality of life for more than ten years after the first disease episode.

METHODS

Study design

A long-term analysis of a previously established prospective cohort of patients with necrotizing pancreatitis was performed. These patients were originally included in a prospective observational study in one of the eight university

medical centres or in one of the 13 large teaching hospitals of the Dutch Pancreatitis Study Group between June, 2005 and October, 2008 during patient enrolment in the randomized PANTER trial.[3] This cohort comprised of 447 patients with necrotizing pancreatitis. Short term outcome of these patients were previously reported.[2,3] In November 2013, the medical ethical committee of the University Medical Centre Utrecht provided approval for the follow-up study of all patients. The long-term outcome of the 88 patients in the PANTER trial have already been published.[8] The current study included the surviving patients of the entire unselected cohort of 447 patients with necrotizing pancreatitis. The study was conducted in accordance with the Declaration of Helsinki. We adhered to the STROBE guidelines for observational studies.[21] The Dutch Association for patients with pancreatic disease, the 'Alvleeskliervereniging' was actively involved in the design of the study. Their board members are also present during research meetings of the Dutch Pancreatitis Study Group.

Data collection and follow-up

For study purposes, patient visits were planned between June, 2014 and March, 2015. Patients were invited by letter to participate in the follow-up study. Subsequent communication was by letters, telephone calls or outpatient visits. After written informed consent was obtained, patients were invited for an outpatient visit. Quality of life questionnaires (EQ-5D22 and SF-3623) were sent to patients between June, 2014 and March, 2015. Visits were scheduled in hospitals where patients were initially treated, or in case of a rehousing of the patient, in another participating centre. Using a predefined, standardised case-record form, the coordinating investigator (RAH) performed the outpatient visits on multiple patient factors with special attention to readmissions, (pancreatic) radiological, endoscopic and surgical interventions, pain, gastrointestinal complaints (bloating, cramps, steatorrhea, and diarrhoea) and use of antidiabetic medication or pancreatic enzymes during years following the index admission. The quality of life questionnaires were evaluated and completed as necessary. Stool samples were collected at the first round of follow-up for measurement of pancreatic exocrine insufficiency. Faecal elastase-1 was measured in a single stool sample using Schebo Biotech KIT (Elisa). If available, faecal elastase-1 measurements were also collected by electronic chart reviews. When appropriate, physical examination was performed with special attention to abdominal pain and incisional hernias. Additional data collection and verification of data at (referring) hospitals, general practitioners and pharmacies were performed in 2015 and – to obtain long-term follow-up extending beyond 10 years – in 2020. All data were collected by one author (RAH or HCT), and subsequently verified by a second author (RAH or HCT).

Outcome measures

Clinical outcomes included recurrent pancreatitis (as defined by the revised Atlanta classification24) and chronic pancreatitis (as defined by the M-ANNHEIM[25] diagnostic criteria for definite chronic pancreatitis). Pancreatitis related emergency admissions pancreatitis related complications were also evaluated. Invasive interventions associated with necrotizing pancreatitis included: endoscopic retrograde cholangiopancreatography (ERCP), endoscopic transluminal drainage procedures, percutaneous catheter drainage procedures and surgical procedures. 'Pancreatic surgery' included marsupialization, pancreatojejunostomy and pancreatic resection. 'Surgery for complications' included surgical procedures performed as a consequence of necrotizing pancreatitis or prior (invasive) treatment for necrotizing pancreatitis, e.g., reversal of a colostomy following bowel ischemia or hepaticojejunostomy as a result of ductal stenosis. Cholecystectomies and incisional hernia corrections are reported separately and are not included in 'Surgery for complications'. Mortality was also reported.

New onset endocrine pancreatic insufficiency following index admission was defined as the need to start oral antidiabetic medication or insulin. Exocrine pancreatic insufficiency was defined as a faecal elastase-1 level of $<200\ \mu g/g$ feces.[26,27] Medication used for pancreatic endocrine or exocrine insufficiency was verified through contact with general practitioners and pharmacies.

Quality of life at long term follow-up was evaluated using two validated questionnaires (both translated end validated for the Dutch population); the EuroQol health status profile (EQ-5D) and the short form 36-item health survey (SF-36)(Medical Outcomes Trust, Boston, MA).[22,23,28,29] We incorporated the Izbicki pain score in all follow-up interviews, which is frequently used in patients with chronic pancreatitis to assess frequency and intensity of pain attacks, use of pain medication and restriction from daily activities.[30]

Statistical analysis

Data are presented as occurrence of outcomes in the total cohort and subsequently in three main subgroups categorised according to treatment during index admission: 1) patients undergoing conservative treatment only, i.e., without invasive intervention: the 'conservative group'; 2) patients treated with catheter drainage (endoscopic transluminal or radiological percutaneous) only, without the need for endoscopic or surgical necrosectomy: the 'drainage only group' and 3) patients treated with necrosectomy (endoscopic, minimally invasive surgical or open): the 'necrosectomy group'. Continuous outcome measures are presented as mean ± standard deviations (SD) or median and interquartile ranges (IQR) as appropriate. For categorical data the Chi-square test was used and in case of small numbers, the Fisher's exact test. For continuous data, the independent

sample t-test / one-way ANOVA or Mann-Whitney U test / Kruskal Wallis test were used, as appropriate.

Exploratory analyses were performed regarding the difference in outcome in both the SF-36 as the EQ-5D questionnaires following the different treatment strategies (i.e., conservative, drainage only, and necrosectomy) or when major invasive intervention during follow-up was required. The difference in outcome in both the SF-36 as the EQ-5D questionnaires was also explored for patients with or without exocrine and endocrine pancreatic insufficiency.

Secondary, associations between the baseline characteristics 1) aetiology; 2) parenchymal necrosis or only extrapancreatic necrosis; 3) percentage of pancreatic necrosis (i.e. <30%, 30-50% or >50%); 4) location of pancreatic necrosis (i.e. left, right, central, subtotal or diffuse) and 5) invasive treatment during index admission and the outcome measures 1) recurrent pancreatitis 2) catheter drainage; 3) major surgery (i.e., necrosectomy, other pancreatic surgery or surgery for complications); 4) endocrine insufficiency; 5) exocrine insufficiency; and 6) development of chronic pancreatitis, were assessed using logistic regression. All associations were adjusted for age and American Society of Anesthesiologists (ASA) class during index admission, and sex. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Analyses were performed using SPSS 26.0 (IBM Corp. Armonk, NY). P-values <0.05 were considered statistically significant.

RESULTS

Of the 447 patients included in the original prospective cohort, 58 patients (13%) died during index admission. Sixteen patients (4%) were lost to follow-up. The remaining 373 patients were included in the analysis. A patient inclusion flow-chart is shown in Figure 1. Baseline characteristics and treatment during index admission of the 373 included patients are presented in Table 1. The mean follow-up time for the patients who were known to be alive at the time of analyses was 13.5 years (±12 months) after index admission.

Clinical outcomes

All events during long-term follow-up are reported in Table 2. A total of 97 out of 373 patients (26%) were readmitted for recurrent pancreatitis, with no differences between the conservative (n=155/232), drainage (n=24/43) and necrosectomy groups (n=69/96; p=0.18). When readmitted, conservatively treated patients had a shorter length of hospital stay, as compared with patients from the drainage only group, whom subsequently had a shorter length of hospital stay compared with patients from the necrosectomy group.

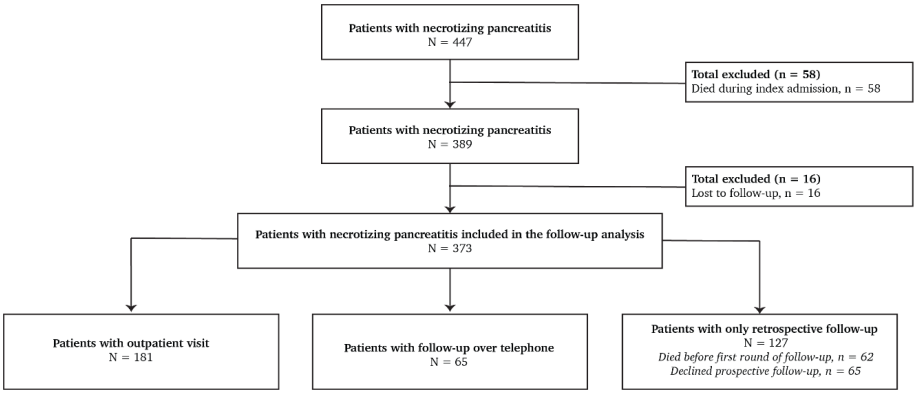

Figure 1 Flowchart patient inclusion

In 84/373 patients (23%), no events related to necrotizing pancreatitis occurred, meaning that these patients were neither readmitted in the hospital for events associated with the index admission nor did they develop chronic pancreatitis or used antidiabetic medication or supplemental pancreatic enzymes. Such an uneventful follow-up occurred more frequently in patients from the conservative and drainage only group (27% and 28% respectively) compared with the necrosectomy group (9%; p=0.002). Progression to chronic pancreatitis occurred in 50/373 patients (13%) and was highest in the patients undergoing invasive intervention. The majority of patients (67%) were readmitted to the hospital during follow-up for additional treatment related to the index admission (e.g., pancreatic interventions, recurrent pancreatitis, cholecystectomies).

During follow-up, 47/373 patients (13%) needed one or more endoscopic or percutaneous catheter drainage procedures as treatment for symptomatic pancreatic fluid collections. In 26 patients (55%), this was in addition to invasive treatment during index admission. Percutaneous and endoscopic catheter drainage modalities during follow-up were used in a similar number of patients. In the remaining 21 patients (45%), who were treated conservatively initially, drainage was performed during follow-up at a median of 7.6 months (IQR 5.6 - 18.7) after start of the initial admission. Indication for drainage was new-onset infected necrosis in 4/21 patients (19%) and for symptomatic collections in 17/21 patients (81%). Drainage in these patients was performed exclusively endoscopically in 17 patients (81%) and in combination with percutaneous catheter drainage in four patients (19%). In addition to catheter drainage during follow-up, six patients (13%) needed endoscopic transluminal necrosectomy, one patient underwent surgical marsupialization and one patient underwent surgical gastrojejunostomy because of a persisting gastric outlet obstruction following

multiple endoscopic catheter drainages and development of chronic pancreatitis.

Surgical and endoscopic procedures performed during follow-up years as a consequence of the index disease or treatment are described in detail in Table 2. Overall pancreatic intervention (pancreatic necrosectomy or other pancreatic surgery) was performed in 31/373 patients (8%) at a median of 13 months (IQR 6 - 36) following the initial episode of necrotizing pancreatitis. Pancreatic necrosectomy (endoscopic or surgical) was performed at a median of 157 months (IQR 88 – 233) after the initial episode. These pancreatic procedures were evenly distributed between treatment groups. Surgery for complications in the 'conservative' and 'drainage only' groups was mainly performed for complications following invasive interventions during follow-up (e.g. incisional hernia following cholecystectomy), whereas most surgery for complications in the 'necrosectomy' group consisted of correcting incisional hernias and colostomy reversal following necrosectomy during index admission.

Progression to chronic pancreatitis occurred in 50/373 patients (13%): in 27/232 patients (12%) following conservative treatment, in 10/43 patients (23%) following drainage only and 13/96 patients (14%) following necrosectomy.

Overall, 126/373 patients (34%) developed endocrine insufficiency following necrotizing pancreatitis (Table 2). In patients from the conservative group this occurred less often (23%; $p < 0.001$), as compared with the patients who underwent an intervention (drainage only; 33% or necrosectomy; 62%). Of the 126 patients who developed endocrine insufficiency, 36 patients (29%) were discharged from index admission with antidiabetic medication and 89 patients (71%) started using antidiabetic medication at a median of 40 months (IQR 20 - 73) after discharge from index admission. Development of endocrine insufficiency did not differ between patients who underwent different methods of necrosectomy (i.e. endoscopic, minimally invasive surgical or open: Supplementary Table 1).

Faecal elastase levels were measured in 239/373 patients (64%). Exocrine insufficiency (i.e. faecal elastase-1 levels <200 μg/g faeces) was diagnosed in 90/239 patients (38%). In 33% of patients of the conservative group, 24% of patients of the drainage group and 50% of patients of the necrosectomy group, exocrine insufficiency developed ($p=0.016$). Of the 90 patients with faecal elastase-1 levels <200 μg/g faeces, 46 patients (51%) used pancreatic enzymes. Of the remaining 44 patients (49%) who did not use pancreatic enzymes, only 11 patients (25%) reported abdominal complaints ($n=8$) and pain ($n=8$) and 33 patients (75%) were free of symptoms. In total, 72 patients (19%) used pancreatic enzymes during follow-up, of whom 46 patients (64%) had faecal elastase-1 levels <200 μg/g faeces, 15 patients (21%) had normal faecal elastase-1 levels and 11 patients (15%) were not tested. Development of exocrine insufficiency did not differ between patients who underwent different methods of necrosectomy

during index admission (Supplementary Table 1).

A total of 96 out of 373 patients (26%) died during follow-up. Seven deaths (7%) were directly related to pancreatic disease; three following multiple organ failure from recurrent acute pancreatitis, one following infectious complications after endoscopic transluminal drainage, one following massive bleeding following endoscopic catheter drainage, one following post-operative complications after hepaticojejunostomy for common bile duct stenosis and one following pancreatic carcinoma.

Table 1 Characteristics at time of index admission of 373 patients with necrotizing pancreatitis included in long term follow-up

		Treatment during index admission			
	All patients N = 373	**Conservative N = 232**	**Drainage only N = 43**	**Necrosectomy N = 96**	***P***
Age (y)	57 (44 - 69)	56 (43 - 70)	58 (44 - 73)	58 (46 - 67)	0.893
Male sex	238 (64)	139 (60)	23 (54)	74 (77)	0.005
Aetiology					0.855
Biliary	182 (49)	113 (49)	19 (44)	50 (52)	
Alcohol	84 (22)	51 (22)	9 (21)	22 (23)	
Other	32 (9)	22 (9)	5 (12)	5 (5)	
Unknown	75 (20)	46 (20)	10 (23)	19 (20)	
ASA class on admission					0.248
I	111 (30)	74 (32)	11 (26)	25 (26)	
II	217 (58)	131 (56)	23 (53)	62 (65)	
III	45 (12)	27 (12)	9 (21)	9 (9)	
Parenchymal necrosis	192 (51)	84 (36)	32 (74)	77 (80)	<0.001
Extrapancreatic necrosis only	181 (49)	148 (64)	11 (26)	19 (20)	<0.001
CT severity index	5 (4 - 8)	4 (4 - 6)	6 (4 - 8)	8 (6 - 10)	<0.001
Extent of pancreatic necrosis					0.002
<30%	77 (40)	45 (54)	15 (47)	18 (23)	
30-50%	58 (30)	18 (21)	11 (34)	29 (38)	
>50%	57 (30)	21 (25)	6 (19)	30 (39)	
Primary infection of necrosis	128 (34)	8 (3)	38 (88)	82 (85)	
Invasive intervention					
None	232 (62)	232 (100)	-	-	
Emergency laparotomy[#]	5 (1)	-	-	3 (3)	
Catheter drainage only	43 (11)	-	43 (100)	-	
Catheter drainage followed by necrosectomy	45 (12)	-	-	45 (47)	
Primary necrosectomy	51 (14)	-	-	51 (53)	

Data are presented as n (%), mean (±, standard deviation), or median (interquartile range: P25-P75)
#2 patient underwent emergency laparotomy without further pancreatic intervention.
Abbreviations: ASA the American Society of Anaesthesiologists CT computed tomography

Table 2 Clinical outcomes, readmissions and invasive interventions during long-term follow-up in 373 patients with necrotizing pancreatitis

		Treatment during index admission			
	All patients N = 373	**Conservative N = 232**	**Drainage only N = 43**	**Necrosectomy N = 96**	***P***
Recurrent pancreatitis	97 (26)	61 (26)	11 (26)	25 (26)	1.00
Number of admissions	1 (1 - 3)	1 (1 - 3)	1 (1 - 4)	1 (1 - 2)	0.97
Chronic pancreatitis[¶]	50 (13)	27 (12)	10 (23)	13 (14)	0.12
Recurrent hospital admission related to pancreatitis	249 (67)	155 (67)	24 (56)	69 (72)	0.18
Number of admissions	2 (1 - 3)	1 (1 - 3)	2 (1 - 5)	3 (2 - 5)	0.01
Days of admission	11 (5 - 25)	8 (3 - 21)	13 (5 - 48)	17 (9 - 43)	0.01
Catheter drainage of pancreatic fluid collection	47 (13)	21 (9)	7 (16)	19 (20)	0.02
Percutaneous	19 (5)	4 (2)	5 (12)	10 (10)	
Endoscopic	33 (9)	21 (9)	2 (5)	10 (10)	
Surgery[§]	198 (53)	114 (49)	19 (44)	64 (67)	0.007
Pancreatic necrosectomy	1 (0)	0	0	1 (1)	-
Other pancreatic surgery	23 (6)	11 (5)[†]	4 (9)[††]	8 (8) [†††]	0.31
For complications after necrotizing pancreatitis	31 (8)	6 (3)[‡]	2 (5)[‡‡]	23 (24)[‡‡‡]	<0.001
Incisional hernia repair	42 (11)	6 (3)	2 (5)	33 (34)	<0.001
Cholecystectomy	158 (42)	107 (46)	12 (30)	38 (40)	0.12
Endoscopy					
Pancreatic necrosectomy	8 (2)	6 (3)	1 (2)	1 (1)	-
ERCP	56 (15)	30 (13)	7 (16)	19 (20)	0.28
Balloon dilatation duodenum	1 (0)	0	0	1 (1)	-
Endocrine insufficiency[||]	126 (34)	53 (23)	14 (33)	59 (62)	<0.001
Oral antidiabetic medication	93 (74)	40 (75)	11 (79)	42 (71)	0.80
Insulin dependent	71 (56)	29 (55)	6 (43)	36 (61)	0.47
Exocrine insufficiency	239 (64)	132 (57)	29 (67)	76 (79)	
Faecal elastase-1 level[#,##]	269 ± 176	293 ± 184	301 ± 148	217 ± 159	0.01
< 200 μg/g	90 (38)	44 (33)	7 (24)	38 (50)	0.02
200+	149 (62)	88 (67)	22 (76)	38 (50)	
Pancreatic enzyme replacement therapy[#]	72 (19)	31 (13)	7 (16)	34 (36)	<0.001
Uneventful follow-up[Ω]	83 (22%)	61 (26)	12 (28)	10 (11)	0.01
Death	96 (26)	62 (27)	13 (30)	21 (22)	0.57
Related to pancreatitis	7 (7)	3 (5)	2 (15)	2 (10)	
Unrelated to pancreatitis	82 (86)	53 (85)	10 (77)	19 (90)	
Unknown	7 (7)	6 (10)	1 (8)	0	

Data are presented as n (%), mean (±, standard deviation), or median (interquartile range: P25-P75)
2 patients that underwent emergency laparotomy but no subsequent pancreatic intervention are not included in the subgroups.
¶ Based on M-ANNHEIM diagnostic criteria.
§ Any kind of surgery performed as a consequence of or related to the index episode or following episodes of necrotizing pancreatitis.
† Five marsupialisation's, two pancreatojejunostomies, one distal pancreatectomy, two Whipple's procedures and one

total pancreatectomy.
†† Two marsupialisation's, one pancreatojejunostomy and one distal pancreatectomy.
††† Four marsupialisation's, two pancreatojejunostomies and two distal pancreatectomies.
‡ Two hemi-colectomies, two gastrojejunostomies, three surgically drained wound abscesses and one laparotomy for bleeding post-marsupialisation.
‡‡ One enterocutaneous fistula correction and short bowel resection due to obstruction/stenosis.
‡‡‡ Eleven enterocutaneous fistula/ileostomy/colostomy corrections, five surgically drained wound abscesses, three gastrojejunostomies, four hepaticojejunostomies, two laparotomies for bleeding and one hemi-colectomy.

Pain and abdominal complaints

In total, 244 out of 373 patients (65%) provided information on abdominal pain and other abdominal complaints (bloating, diarrhea, and anamnestic steatorrhea) which started after the index admission. Twenty percent of the patients from the conservative group reported pain, as did 39% of patients from the drainage group and 42% of patients from the necrosectomy group (p=0.001). In patients who reported pain, a median Izbicki score of 35 (IQR 25 - 53) was reported and scores in the different treatment groups were similar.

In total, 78 patients (32%) reported one or more abdominal complaints. Patients from the conservative group reported abdominal complaints less often than patients from the drainage and necrosectomy groups (23% vs. 35% vs. 47% respectively: p=0.001). All information on pain and abdominal complaints is provided in the Supplementary Table 4.

Quality of life

The SF-36 and EQ-5D questionnaires were completed by 243 of 373 patients (65%). Scores were similar between groups on all domains. The scores in physical component of the SF-36 in all groups were slightly lower than the 50±10 score in the general population, whereas the scores the mental component were not (Table 3).

Patients who underwent endoscopic or percutaneous catheter drainage, necrosectomy or major surgery during follow-up had statistically significant lower EQ-5D scores (UK value 0.76 [0.69 - 0.97]) and health state score (UK value 70 [56-80]), as compared with patients who did not (UK value 0.81 [0.73-1.00] and UK value 76 [70-85)], respectively: Supplementary Table 2). Quality of life scores did not differ significantly between patients with and without new-onset endocrine insufficiency except for a slight difference in health state score (UK value 78; IQR 68-85 and UK value 75; IQR 60-80, respectively; p=0.03), nor were there differences in the scores of patients with and without new-onset exocrine insufficiency or in the scores of patients with both endocrine and exocrine insufficiency, as compared with patients with neither endocrine nor exocrine insufficiency (Supplementary Table 3).

Patients characteristics and associations with outcome during follow-up

Pancreatic necrosis, as opposed to extra-pancreatic necrosis only, was associated with all outcomes during follow-up; endoscopic or percutaneous catheter drainage (adjusted OR 6.0 (95% CI 2.6 – 14.0), major surgery (adjusted OR 5.2 (95% CI 2.1 – 13.0), endocrine (adjusted OR 5.0 (95% CI 3.0 – 8.2) and exocrine insufficiency (adjusted OR 3.9 (95% CI 2.1 – 7.2), and chronic pancreatitis (adjusted OR 2.2 (95% CI 1.1 – 4.2).

In patients with pancreatic necrosis, >50% gland necrosis was associated with endocrine (adjusted OR 13.1 (95%CI 5.3 – 32) and exocrine insufficiency (adjusted OR 6.1 (95% CI 2.4 – 15.5). Subtotal necrosis was associated with endocrine insufficiency (adjusted OR 23.7 (95% CI 3.1 – 183.4) and all patients with subtotal necrosis developed pancreatic exocrine insufficiency. Also, predominantly central gland necrosis was associated with catheter drainage (adjusted OR 3.7 (95% CI 1.8 – 7.8)) and other pancreatic interventions (adjusted OR 5.2 (95% CI 2.2 – 12.1)). Predominantly right sided pancreatic necrosis was associated with development of chronic pancreatitis (adjusted OR 8.2 (95% CI 1.6 – 42.1)).

Endoscopic or percutaneous catheter drainage only during index admission was associated with the development of chronic pancreatitis (adjusted OR 2.5 (95% CI 1.1 – 5.8)). Patients who underwent necrosectomy during index admission were at increased risk for both endocrine as exocrine insufficiency (adjusted OR 5.1 (95% CI 3.0 – 8.6) and adjusted OR 1.9 (95% CI 1.1 – 3.5), respectively).

All patient characteristics and associations are provided in the Supplementary Table 5.

Table 3 Quality of life after long term follow-up in 243 patients treated for necrotizing pancreatitis

		Treatment during index admission			
	All patients N = 373	Conservative N = 232	Drainage only N = 43	Necrosectomy N = 96	*p*[$]
Questionnaires completed	243 (65)	136 (59)	30 (70)	75 (78)	0.002
SF-36 US standard					
Physical	45 ± 12	46 ± 12	44 ± 11	43 ± 12	0.13
Mental	51 ± 11	51 ± 11	53 ± 10	51 ± 10	0.70
SF-36 Dutch standard					
Physical	46 ± 12	47 ± 12	45 ± 11	44 ± 12	0.16
Mental	49 ± 11	49 ± 11	51 ± 10	49 ± 10	0.66
EQ-5D					
UK values	0.80 (0.69 - 1.00)	0.81 (0.73 - 1.00)	0.74 (0.69 - 1.00)	0.80 (0.69 - 1.00)	0.46
Dutch values	0.84 (0.78 - 1.00)	0.84 (0.78 - 1.00)	0.81 (0.72 - 1.00)	0.84 (0.77 - 1.00)	0.44
Health state score	75 (65 - 85)	75 (68 - 85)	75 (60 - 80)	75 (65 - 80)	0.44

Data are presented as n (%) or as means ± SD as is custom in reporting results of the SF-36 questionnaire and as median (IQR) in the EQ-5D questionnaire. Two patients that underwent emergency laparotomy but no pancreatic intervention were not included in the subgroup analyses for quality of life.
[$]Groups were compared as appropriate with the One-way ANOVA or Kruskal-Wallis test.

DISCUSSION

This is the largest and longest long-term follow-up study on patients from entire clinical spectrum of necrotizing pancreatitis reported thus far. Our study provides unique insights in the late sequelae of necrotizing pancreatitis following different treatment groups of conservative treatment, catheter drainage only, or necrosectomy. Three quarters of the 373 patients suffered from a necrotizing pancreatitis related event during long-term follow-up. Recurrent pancreatitis occurred in a quarter of all patients and six percent of all patients underwent pancreatic surgery, regardless of their initial treatment. Patients who were originally treated conservatively were less likely to undergo additional drainage procedures or surgery for complications and were less likely to develop new-onset endocrine and exocrine pancreatic insufficiency. Necrosis of more than 50% of the pancreatic parenchyma on computed tomography (CT) during index admission was strongly associated with catheter drainage and endoscopic/surgical pancreatic interventions and the development of pancreatic endocrine and exocrine insufficiency during long-term follow-up.

Previous studies have reported on follow-up of patients with necrotizing pancreatitis. All these studies, however, focused on specifically selected subgroups of necrotizing pancreatitis. One combined retrospective and prospective study evaluated endoscopic and surgical interventions during follow-up (44 months) of 86 patients treated with endoscopic transluminal necrosectomy (N=75) and subsequent surgical necrosectomy (N=11) for infected necrotizing pancreatitis.[16] Interventions during follow-up consisted mainly of endoscopic drainage and pancreatic surgery was infrequent.[16] Comparison with our study is difficult, as inclusion of patients and baseline characteristics differ substantially. A retrospective follow-up study of 197 patients with necrotizing pancreatitis demonstrated a substantially higher rate of pancreatic surgery (36%) as compared with our study (6%) and demonstrated that patients with pancreatic ductal injury during index admission are more likely to require surgery during follow-up. This difference could be explained by the difference in patient selection, since the authors categorised the patients by pancreatic ductal anatomy.[17] Another retrospective analysis from Italy included 631 patients with mild (N=558) and severe (N=73) pancreatitis, showed invasive pancreatic intervention during follow-up (52 months) in only nine patients.[18] Unfortunately, prevalence of (extra)pancreatic necrosis was not reported. A recent follow-up study (7 years) of the TENSION trial, comparing the endoscopic step-up approach with the surgical step-up approach, has shown that the endoscopy group needed fewer interventions than the surgery group. Pancreatic insufficiency and quality of life did not differ between groups.[6]

International guidelines recommend a step-up approach for necrotizing

pancreatitis, ranging from conservative treatment with maximal supportive care to performing invasive intervention stepwise (i.e., endoscopic or percutaneous drainage followed, if needed, by necrosectomy).[12,13] The patients in our cohort were prospectively included in hospitals of the Dutch Pancreatitis Study group between 2005 and 2008. During this time, minimally invasive treatment methods (i.e., retroperitoneal percutaneous and endoscopic transluminal drainage) were upcoming, but not yet the standard approach. Direct open necrosectomy was still considered a reasonable first choice of treatment and a subset of our study population were randomized to either the step-up approach or direct open necrosectomy.[3] It therefore remains unclear how many of the patients would have recovered without (direct open) necrosectomy if a less invasive procedure or conservative therapy was primarily initiated and if the late onset complications subsequently would have been different. We separately analysed the outcomes of patient undergoing different types of treatment of the initial episode of necrotizing pancreatitis to provide guidance during follow-up for each of these subgroups. Our aim was not to designate a 'best treatment for infected necrosis', since not all patients can be treated conservatively and might benefit more from invasive treatment and vice versa.

Endocrine and exocrine pancreatic insufficiency are well known outcome measures of follow-up studies on pancreatitis in general and necrotizing pancreatitis in particular, as development of pancreatic insufficiency following pancreatitis is mainly attributed to loss of vital pancreatic tissue.[31] It was therefore not surprising that we found a high percentage of pancreatic necrosis and subsequently necrosectomy during the initial admission as a risk factor for developing pancreatic insufficiency. This may in part be explained by the fact that patients with pancreatic gland necrosis are those who more often need necrosectomy.[32] A systematic review yielded comparable results as in the current study on incidence of exocrine insufficiency following necrotizing pancreatitis (32% and 38% respectively).[20] Unfortunately, studies included in the systematic review reported insufficient data to perform subgroup analyses on extent of pancreatic necrosis.[20] Similarly, new onset endocrine insufficiency was found in 34% of all patients, which corresponds to the findings in a systematic review including 1102 patients (30%).[19] This study demonstrated that severity of disease, classified according to clinical course during index admission (i.e., mild or severe) by the determinant based classification,[33] had minimal effects in the development of endocrine insufficiency.[19] Acute pancreatitis, however, is a disease with a very broad clinical spectrum and in our opinion categorising patients as mild or severe during index admission is of limited value for follow-up studies, as it does not specify the impairment (i.e., necrosis) of the pancreatic gland.[24,33] Furthermore, the recent publication of a long term follow-up study of the randomized PANTER

trial has shown that patients from the step-up group, who underwent fewer necrosectomies, had less pancreatic exocrine insufficiency at final follow-up and a also trend towards less endocrine insufficiency, while pancreatic necrosis was similar between groups.[8] These data suggest that necrosectomy procedures directly contribute to a decrease in pancreatic functional capacity in subsequent years. These results emphasise the importance of acknowledging extent of pancreatic necrosis during index admission. We therefore believe that classifying patients according to the presence of parenchymal necrosis, the location and extent of pancreatic necrosis - especially for follow-up studies - is more suitable. We recommend the well acknowledged computed tomography severity index (CTSI).[34]

A remarkable finding was that 44 out of 90 patients (49%) with faecal elastase-1 levels below 200 $\mu g/g$ faeces were not on pancreatic enzyme replacement therapy, whereas 15 patients (17%) with faecal elastase-1 levels above 200 $\mu g/g$ faeces were. Eleven patients (25%) with faecal elastase-1 levels below 200 $\mu g/g$ faeces who were not on enzyme replacement therapy reported abdominal complaints. These complaints might be indicative of substantial pancreatic exocrine insufficiency and these patients may potentially benefit from enzyme replacement therapy. If untreated, pancreatic exocrine insufficiency can lead to malnutrition, weight loss, and deficiency of fat-soluble vitamins (A, D, E, K) and mineral deficiencies that can cause metabolic bone disease. Of the 15 patients on pancreatic enzyme replacement therapy with faecal elastase-1 levels above 200 $\mu g/g$ faeces, eight still reported abdominal complaints. Their complaints therefore might not have been attributable to pancreatic exocrine insufficiency and hence their enzyme therapy may be unnecessary. This underlines the importance of early and accurate diagnosis of pancreatic exocrine insufficiency.

Quality of life following acute pancreatitis was recently summarised in a systematic review, highlighting the large number of tools used to asses quality of life, and the large variance in follow-up time after which quality of life was assessed, which precluded definitive conclusions.[35] It appears that perceived quality of life is impaired at least during the first one to two years following the admission for acute pancreatitis and that increasing severity of disease may have a negative impact.[35–37] Our study is novel since we compared quality of life in 1) subgroups of different interventions during index admission and 2) included subgroup analyses for treatment during follow-up. Unexpectedly, we found similar quality of life scores in all subgroups. This may be explained by the long interval between the index admission and time of quality of life measurement. As time passes, patients may get accustomed to their (residual) symptoms and medicine use for endocrine and/or exocrine insufficiency, and perceived quality of life may be similar compared with patients free of these disabilities.

Some limitations of our study need to be acknowledged. Firstly, no laboratory test to assess endocrine insufficiency was performed as part of our study. Although follow-up on endocrine insufficiency after necrotizing pancreatitis is common practice in the Netherlands during the first recovery phase, subclinical disease at our long-term follow-up may have been missed. Secondly, quality of life questionnaires were not collected at regular time intervals following discharge (e.g., annually). This precludes judgment on alterations in quality of life in the years following recovery of necrotizing pancreatitis and on potential differences between treatment groups. Thirdly, the initial hospital admissions were in the period 2005-2008. Since then, the invasive management of infected necrotizing pancreatitis has evolved from an open approach to a minimally invasive approach. Consequently, how patients were treated in our cohort may not fully reflect current practice as more patients are primarily treated conservatively or by minimally invasive methods. Our study, however, does provide clear insights in the long term results of all treatment strategies currently available.

In light of future perspectives on the follow-up of necrotizing pancreatitis two points need to be addressed. First, invasive interventions (i.e., catheter drainage, endoscopic, and surgical procedures) were scarce during the second period of our follow-up (2015 – 2020) and mostly occurred in a small subset of patients. Only few patients who did not already undergo such interventions during the first follow-up period had their first 'pancreatitis related' intervention in the later stage of our follow-up (data not shown). We therefore feel it is not necessary for future studies to extend follow-up periods to longer than 10 years. Second, given the outcomes of this study we feel it is appropriate to include long-term recommendations in future acute pancreatitis guidelines, as they may aid clinicians in their assessment of diagnostics, treatment and in their guidance of recovering patients. Our advice would be to securely follow-up on all patients with necrotizing pancreatitis. After an initial measurement of faecal elastase-1 levels during the initial episode, a standardised outpatient visit around 3-6 months after discharge should be implemented. This outpatient visit includes a follow-up faecal elastase-1 measurement, a detailed history on abdominal complaints suggestive for exocrine insufficiency or residual symptoms indicative of intra-abdominal complications (e.g., fluid collections, pancreatic ductal alterations), and blood glucose measurement. Additional laboratory tests and imaging can subsequently be performed if indicated.

In conclusion, the disease burden during long-term follow up of necrotizing pancreatitis is substantial in terms of disease recurrence, pancreatic insufficiency, pancreatic drainage and surgery, also patients who were initially treated conservatively. Symptoms or signs indicating complications with the need for further diagnostic investigations and potential treatment are not always obvious

for patients. This warrants a systematic follow-up of all patients, especially those with over >50% of pancreatic necrosis, after an initial episode of necrotizing pancreatitis. Incorporating advices on follow-up in future guidelines could facilitate its implementation in clinical practice.

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SUPPLEMENTARY APPENDIX

Table S1 Outcome measures during follow-up in 96 patients that underwent necrosectomy for necrotizing pancreatitis during index admission

Outcome measure	Method of necrosectomy			*P*
	Open necrosectomy N = 58	VARD N = 30	Endoscopic necrosectomy N = 8	
Death	13 (22)	6 (21) [##]	2 (25)	0.98
Recurrent pancreatitis	18 (31)	5 (17)	2 (25)	0.35
Catheter drainage	12 (21)	6 (20)	1 (13)	0.86
Pancreatic necrosectomy	0	0	1 (13)	-
Other pancreatic surgery[†]	5 (8)	3 (10)	0	0.67
Surgery for complications[‡]	14 (24)	8 (27)	1 (13)	0.71
Incisional hernia repair	22 (38)	9 (30)	2 (25)	0.64
Cholecystectomy	21 (36)	14 (47)	3 (38)	0.63
New onset endocrine insufficiency[||]	36 (62) [#]	19 (63)	4 (57) [#]	0.96
Exocrine insufficiency[§]	26 (57)	8 (35)	4 (57) [#]	0.22
Supplemental enzyme use	24 (41)	8 (27)	2 (29) [#]	0.36
Chronic pancreatitis[¶]	10 (17)	2 (7)	1 (13)	0.39
Uneventful follow-up[Ω]	4 (7)	3 (10)	2 (25)	0.26

Data are presented as n (%).
[##] Data missing in two patients. [#] Data missing in one patient.
[†] Includes marsupialisation's, pancreatojejunostomies and surgery including pancreatic resection.
[‡] For pancreatitis related complications, including enterocutaneous fistula/ileostomy/colostomy corrections, surgically drained wound abscesses, hepatiocojejunostomies, gastrojejunostomies, and laparotomy for interventional complication management.
[||] Defined as the need for oral antidiabetic medication or insulin.
[§] Faecal elastase-1 test was performed in 46 patients in the Open necrosectomy group, in 23 patients in the videoscopically assisted retroperitoneal debridement group and in 7 patients in the endoscopic transluminal necrosectomy group.
[¶] Based on the M-ANNHEIM diagnostic criteria.
[Ω] No recurrent admission related to necrotizing pancreatitis, no new-onset chronic pancreatitis and no use of antidiabetic medication or supplemental pancreatic enzymes.

Table S2 Quality of life in patients that underwent pancreatic or major abdominal surgery during follow-up of necrotizing pancreatitis

	Pancreatic intervention or major surgery		
	No, N = 195	**Yes, N = 48**	***P*[#]**
SF-36 US standard			
Physical	46 ± 12	43 ± 12	0.18
Mental	51 ± 10	50 ± 11	0.55
SF-36 Dutch standard			
Physical	47 ± 12	44 ± 12	0.15
Mental	49 ± 10	49 ± 12	0.68
EQ-5D - median			
UK values	0.81 (0.73 - 1.00)	0.76 (0.69 - 0.97)	0.048
Dutch values	0.84 (0.78 - 1.00)	0.81 (0.70 - 0.97)	0.04
Health state score	76 (70 - 85)	70 (56 - 80)	0.003

*Data are reported as means ± SD as is custom in reporting results of the SF-36 questionnaire and as median (IQR) in the EQ-5D questionnaire. Pancreatic intervention during follow-up is defined as catheter drainage (endoscopic or percutaneous) of pancreatic fluid collections, pancreatic necrosectomy (endoscopic or surgical), or other pancreatic surgery in the years following the index admission. Major surgery consists of hepaticoojejunostomy, gastrojejunostomy, bowel resection or colostomy reversal

[#]Groups were compared as appropriate with the Students t-test or Mann-Whitney U test.

Table S3 Quality of life in patients with new onset endocrine and exocrine insufficiency after necrotizing pancreatitis*

	Endocrine insufficiency			Exocrine insufficiency			Endocrine and exocrine insufficiency		
	Yes N = 81	No N = 162	*P*	Yes N = 83	No N = 150	*P*	Yes N = 48	No N = 118	*P*
SF-36 US standard									
Physical	44 ± 12	46 ± 12	0.32	44 ± 12	47 ± 12	0.47	46 ± 11	47 ± 11	0.64
Mental	50 ± 11	52 ± 10	0.45	51 ± 11	51 ± 10	0.68	51 ± 10	52 ± 10	0.58
SF-36 Dutch standard									
Physical	45 ± 12	47 ± 12	0.35	45 ± 12	47 ± 12	0.46	47 ± 11	47 ± 11	0.64
Mental	48 ± 11	50 ± 10	0.43	49 ± 11	49 ± 11	0.46	49 ± 10	50 ± 10	0.62
EQ-5D - median (IQR)									
UK values	0.80 (0.69 - 1.00)	0.80 (0.73 - 1.00)	0.45	0.80 (0.69 - 1.00)	0.80 (0.69 - 1.00)	0.50	0.80 (0.73 - 1.00)	0.80 (0.73 - 1.00)	0.62
Dutch values	0.84 (0.75 - 1.00)	0.84 (0.78 - 1.00)	0.29	0.84 (0.72 - 1.00)	0.84 (0.78 - 1.00)	0.49	0.84 (0.78 - 1.00)	0.84 (0.78 - 1.00)	0.49
Health state score	75 (60 - 80)	78 (68 - 85)	0.03	75 (60 - 85)	75 (70 - 85)	0.33	75 (60 - 80)	78 (70 - 85)	0.14

* Quality of life was scored through validated, patient reported questionnaires. The scores on the SF-36 physical and mental health components range from 0 to 100, with higher scores indicating better quality of life. Linear transformations were performed to standardize the scores to a mean score of 50 ± 10 in a general US and Dutch population. The utilities of the observed health score profiles on the EQ-5D are based on the time trade-off elicitation technique from interviews with adults from the US general population and the Dutch general population, respectively.[ref Lamers2005, Shaw2005] The utilities of the observed health score profiles on the EQ-5D are based on the time trade-off elicitation technique from interviews with adults from the US general population (Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005; 43(3): 203-220), UK general population (Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095–1108) and the Dutch general population (Lamers LM, Stalmeier PF, McDonnell J, et al. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. Ned Tijdschr Geneeskd 2005;149:1574–1578), respectively. Utilities range from either -0.109 (US), -0.594 (UK) or - 0.330 (Dutch), indicating serious health problems, to 1.0, indicating no problems at all. The Health state scores range from 0 to 100, with higher scores indicating better perceived health. Data are reported as means ± SD as is custom in reporting results of the SF-36 questionnaire and as median (IQR) in the EQ-5D questionnaire.

Groups were compared as appropriate with the Students t-test or Mann-Whitney U test.

Table S4 Pain and subjective abdominal complaints following necrotizing pancreatitis in 244 patients*

		Treatment during index admission			
	All patients N = 244	**Conservative N=138**	**Drainage only N=31**	**Necrosectomy N=73**	***P***
Pain	70 (29)	27 (20)	12 (39)	31 (42)	0.001
IZBICKI score#	35 (25-53)	34 (22-50)	38 (31-69)	34 (25-53)	0.37
Complaints	78 (32)	32 (23)	11 (35)	35 (47)	0.001
Cramps	41 (17)	14 (10)	7 (23)	20 (27)	0.004
Bloating	44 (18)	19 (14)	7 (23)	18 (25)	0.11
Diarrhoea	29 (12)	10 (7)	4 (13)	15 (20)	0.02
Steatorrhea	19 (8)	8 (6)	4 (13)	7 (10)	0.33

Date are presented as n (%).
* Two patients that underwent emergency laparotomy but no pancreatic intervention are not included in the subgroup analyses
# The IZBICKI pain score ranges from 0 to 100, incorporating frequency and severity of pain, use of pain medication and inability from daily activities. Higher scores indicate more severe pain. Reported as medians (IQR).

Table S5 Associations of patients characteristics at index admission with outcome measures during follow up*

Characteristics	Outcome measure					
	Recurrent pancreatitis N=97	Catheter drainage# N = 45	Major surgery$ N = 38	Endocrine insufficiency N = 109¶	Exocrine insufficiency¥ N = 86	Chronic pancreatitis N = 37||
Aetiology						
Biliary, N = 182	*reference*	*reference*	*reference*	*reference*	*reference*	*reference*
Alcohol, N = 84	1.5 (0.7 - 2.8)	0.6 (0.3 - 1.4)	0.9 (0.4 - 2.4)	1.6 (0.9 - 2.9)	1.6 (0.8 - 3.3)	1.2 (0.5 - 2.6)
Other, N = 107	1.7 (0.9 - 3.0)	0.5 (0.2 - 1.2)	1.3 (0.6 - 3.0)	1.3 (0.7 - 2.1)	1.3 (0.6 - 2.5)	1.3 (0.6 - 2.6)
Pancreatic necrosis, N = 194	0.9 (0.5 - 1.4)	**6.0 (2.6 - 14.0)**	**5.2 (2.1 - 13.0)**	**5.0 (3.0 - 8.2)**	**3.9 (2.1 - 7.2)**	**2.2 (1.1 - 4.2)**
Pancreatic necrosis %						
<30%, N = 79	*reference*	*reference*	*reference*	*reference*	*reference*	*reference*
30-50%, N = 58	1.0 (0.4 - 2.1)	**6.3 (2.3 - 17.3)**	**4.3 (1.5 - 12.1)**	2.1 (1.0 - 4.3)	**2.4 (1.01 - 5.8)**	0.9 (0.4 - 2.2)
>50%, N = 57	0.7 (0.3 - 1.6)	**4.3 (1.5 - 12.2)**	**3.2 (1.1 - 9.5)**	**13.1 (5.3 - 32.0)**	**6.1 (2.4 - 15.5)**	0.9 (0.3 - 2.2)
Location of necrosis						
Left, N = 24	0.7 (0.2 - 2.0)	**0.1 (0.02 - 0.97)**	0.2 (0.02 - 1.3)	1.1 (0.4 - 2.7)	0.4 (0.1 - 1.2)	0.3 (0.1 - 1.2)
Right, N = 7	2.3 (0.5 - 11.8)	0.6 (0.06 - 4.8)	1.8 (0.3 - 9.8)	2.0 (0.4 - 10.6)	0.9 (0.2 - 4.4)	**8.2 (1.6 - 42.1)**
Central, N = 74	1.5 (0.8 - 2.9)	**3.7 (1.8 - 7.8)**	**5.2 (2.2 - 12.1)**	1.4 (0.8 - 2.5)	1.1 (0.6 - 2.3)	**2.2 (1.01 - 4.7)**
Subtotal, N = 20	0.5 (0.1 - 1.8)	1.4 (0.5 - 4.0)	0.9 (0.2 – 3.4)	**23.7 (3.1 - 183.4)**	∞	0.8 (0.2 - 3.1)
Diffuse, N = 69	0.9 (0.4 - 1.8)	**0.4 (0.2 - 0.9)**	**0.2 (0.07 - 0.6)**	**0.3 (0.1 - 0.5)**	**0.5 (0.2 - 0.9)**	0.5 (0.2 - 1.2)

Table S5 Continued.

Characteristics	Outcome measure					
	Recurrent pancreatitis N=97	**Catheter drainage[#] N = 45**	**Major surgery[$] N = 38**	**Endocrine insufficiency N = 109[¶]**	**Exocrine insufficiency[ᵀ] N = 86**	**Chronic pancreatitis N = 37[||]**
Treatment						
Conservative, N = 232	*reference*	*reference*	*reference*	*reference*	*reference*	*reference*
Drainage only, N = 43	1.0 (0.5 - 2.3)	2.0 (0.8 - 5.2)	1.7 (0.6 – 4.8)	1.8 (0.9 – 3.6)	0.7 (0.3 - 1.8)	**2.5 (1.1 – 5.8)**
Necrosectomy, N = 96	0.9 (0.5 - 1.6)	**2.3 (1.2 – 4.6)**	1.8 (0.8 – 3.8)	**5.1 (3.0 – 8.6)**	**1.9 (1.05 - 3.5)**	1.1 (0.5 – 2.3)

* Patient characteristics during the index admission are associated with outcomes during follow-up using logistic regression analyses. All logistic regression analyses on the outcome measures are corrected for sex, age and ASA class during index admission. Values in bold text indicate a statistically significant association.

[#] Includes both percutaneous and endoscopic transluminal drainage of pancreatic fluid collections.

[$] Includes pancreatic necrosectomy (also endoscopic transluminal necrosectomy), marsupialisations, pancreatojejunostomies, pancreatic resections, hepaticoojejnuostomies, bowel resection and gastrojejunostomies.

[¶] Defined as the need for oral antidiabetic medication or insulin.

[ᵀ] Defined as faecal elastase-1 $< 200\ \mu g/g$ faeces.

[¶] Independent of the result faecal elastase-1 test.

[||] According to the diagnostic M-ANNHEIM criteria.

∞ All patients with subtotal pancreatic necrosis had pancreatic exocrine insufficiency.

PART III

CHAPTER XI

Endoscopic ultrasonography detects aetiology in one-third of patients with idiopathic acute pancreatitis (PICUS): *a prospective multicentre cohort study*

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ABSTRACT

Background
In 25% of patients with acute pancreatitis, no cause can be determined after standard diagnostic work-up: idiopathic acute pancreatitis (IAP). IAP is associated with a high pancreatitis recurrence rate of 25%, possibly related to occult gallstone disease.

Objective
This study aimed to determine the diagnostic yield of endoscopic ultrasonography (EUS) in patients with a first episode of presumed IAP and the pancreatitis recurrence rate in 'EUS-negative IAP'.

Methods
We conducted a prospective multicentre cohort study in 106 patients with a first episode of IAP, who underwent EUS after complete diagnostic work-up according to international guidelines, including imaging after resolution of pancreatitis. The primary outcome measure was detection of aetiology by EUS. Secondary outcome measures included adverse events after EUS, recurrence rate in 'EUS-negative IAP', and quality of life during one-year follow-up.

Results
A total of 105 patients with a first episode of IAP underwent EUS in 24 hospitals. In 34 (32%) patients, EUS detected aetiology: gallstone disease (24%), chronic pancreatitis (7%), and neoplasms (3%). During one-year follow-up, pancreatitis recurrence rate was 17% (12/71) in patients with 'EUS-negative IAP' and 6% (2/34) in patients with a positive EUS. Post-EUS pancreatitis occurred in one patient (1%). Recurrent pancreatitis was associated with lower quality of life ($p=0.022$).

Conclusion
This prospective multicentre study showed that EUS following negative diagnostic workup identified an aetiology in one-third of patients with a first episode of IAP, and thus EUS is advised in this scenario. The high pancreatitis recurrence rate in 'EUS-negative IAP' warrants further study.

INTRODUCTION

In approximately 25% of patients with acute pancreatitis, no aetiology is found after routine work-up.[1,2] According to international guidelines, this work-up includes medical history, laboratory investigations and (repeat) transabdominal ultrasound but does not include endoscopic ultrasonography (EUS). When the routine work-up is negative, these patients are considered to have idiopathic acute pancreatitis (IAP).[3] In a previous post-hoc analysis of a prospective cohort of 191 patients with a first episode of IAP, more than a quarter of patients experienced at least one pancreatitis recurrence.[4]

After negative transabdominal ultrasound in patients with IAP, EUS may be used to detect gallstones or other causes of pancreatitis such as neoplasms and chronic pancreatitis.[3,5-7] Although international guidelines recommend EUS for patients with IAP, this is a weak recommendation based on evidence of low quality. Therefore, EUS is not routinely performed.[3] A recent systematic review reported that EUS in patients with IAP had a diagnostic yield of 59% and was associated with an apparent lower pancreatitis recurrence rate. However, the 22 studies included in this meta-analysis, of which 16 prospective studies, were of poor quality, with none of the studies performing standard diagnostic work-up prior to EUS according to guidelines and using questionable definitions for positive EUS.[8] Thus, in order to reach strong recommendation in future clinical guidelines on the added value of EUS in patients with IAP, a large prospective multicentre cohort study is necessary, with a homogenous group of patients with a first episode of IAP after full diagnostic work-up according to international guidelines and with adequate follow-up on recurrence.

We therefore performed this prospective multicentre study to determine the diagnostic yield of EUS in patients with a first episode of presumed IAP for detection of aetiology, and to determine the acute pancreatitis recurrence rate in patients with 'EUS-negative IAP'.

METHODS

Study design

The PICUS cohort study was a prospective multicentre study, conducted in 24 hospitals of the Dutch Pancreatitis Study Group. This study was performed according to the Declaration of Helsinki and to the Guideline for Good Clinical Practice. The Medical Ethics Review Committee of the Academic Medical Centre assessed the study (May 28th 2018). Local board approval was obtained in all other participating centres. All patients provided written informed consent

for participation in this study. The study protocol was prospectively registered (Netherlands Trial Registry; NL7066) and described previously in greater detail.[9] This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement for cohort studies and the Standards for Reporting of Diagnostic Accuracy statement (Supplementary material 1).[10, 11]

Study population

Adult patients with a first episode of IAP, without a known aetiology after standard diagnostic work-up, as recommended by the 2013 International Association of Pancreatology/American Pancreatic Association evidence-based guidelines on management of acute pancreatitis were eligible for participation.[3] Acute pancreatitis was defined according to the 2012 Revised Atlanta criteria.[12] Main exclusion criteria were: 1) known aetiology, 2) chronic pancreatitis, as defined by the M-ANNHEIM criteria,[13] 3) prior episode of acute pancreatitis, 4) altered anatomy, prohibiting the visualization of the gallbladder, bile ducts, pancreas or pancreatic duct via EUS (e.g., history of Roux-en-Y gastric bypass), and 5) diagnostic EUS aimed to determine aetiology before inclusion.

Standard diagnostic work-up comprised the following: detailed personal and family history (alcohol use, recent endoscopic retrograde cholangiopancreaticography (ERCP), recent start or changes in use of drugs associated with acute pancreatitis, recent major abdominal trauma or abdominal surgery, familial and hereditary pancreatitis, and cystic fibrosis-related pancreatitis), laboratory tests (blood serum alanine transaminase (ALT), triglyceride and calcium level, corrected for blood serum albumin level on admission), and imaging (transabdominal ultrasonography, magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreaticography (MRCP) after clinical recovery).

Study procedure and follow-up

All included patients underwent EUS in an outpatient setting after resolution of acute pancreatitis. EUS was performed according to the technique of Hawes and Fockens,[14] with a linear or a radial scope, at the discretion of the endosonographist. The endosonographist systematically recorded procedural characteristics and outcome of EUS. Follow-up was completed one year after inclusion. Patients filled out Short Form-36 questionnaires at inclusion, after 6 months and after one year to assess quality of life.[15]

Outcome measures

The primary endpoint was the number of patients in whom EUS detected a

potential cause for the pancreatitis episode. An EUS was considered positive when a highly probable or definitive cause for the acute pancreatitis was found. Chronic pancreatitis was defined, according to the M-ANNHEIM criteria, as pancreatic calcifications or five or more of the following: enlarged gland, cysts, echo-poor or echo-rich lesions, accentuation of lobularity, increased duct wall echogenicity, irregularity, dilation or calcification of the main pancreatic duct or visible side branches (e.g., with dilation).[13] Anatomical anomalies (e.g., divisum) are not considered a certain aetiology in first episode IAP and are therefore not considered as positive imaging.[16] An exact definition of positive EUS and other relevant definitions are provided in Supplementary material 2.

Secondary endpoints included adverse events after EUS, recurrence rate of acute pancreatitis, severity of recurrent acute pancreatitis, readmission, additional invasive procedures (cholecystectomy, endoscopic sphincterotomy), length of hospital stay, quality of life, and mortality. A cost analysis will be performed and published separately.

Sample size calculation and statistical analyses

We assumed a diagnostic yield of EUS of 30% based on two previous studies,[17,18] adjusted for our criteria for inclusion and positive imaging. Assuming a drop-out rate of 10%, using a two-sided significance level of 0.05 and a power of 80%, a total of 106 patients are needed to attain a 95% confidence interval (CI) with a range smaller than 10% above and below the assumed yield (95% CI: 20.8-39.2).

All included patients were evaluated for primary and secondary endpoints at one year after inclusion. All analyses were done according to the intention-to-treat principle. Baseline variables are presented in percentages or as mean with standard deviation (SD), or in case of a skewed distribution as median with interquartile range (IQR). Primary and secondary outcome measure are presented as percentages with 95% CI, as mean with SD or median with IQR, as appropriate.

Predefined subgroup analyses were performed to identify potential predictors for positive EUS and for recurrence of acute pancreatitis, using the $\chi 2$ test or the Fisher's exact test, as appropriate, for the following variables: body mass index (BMI) (cut-off at 30 kg/m2), previous cholecystectomy, alcohol use (i.e. no alcohol use vs. <5 units/day), local adverse events from the IAP episode, imaging after clinical recovery, experience of endosonographist, and type of scope and sedation. Additionally, a similar post-hoc subgroup analysis for presence of hepatic steatosis or cirrhosis was performed as this could impede interpretation of EUS. For recurrence rate, predefined subgroup analyses were also performed for patients with a positive and negative EUS, and in patients with a positive EUS, for patients who were and were not treated adequately, using the $\chi 2$ test or

the Fisher's exact test, as appropriate.

The paired t-test was used to compare quality of life during follow-up to baseline. A modern repeated measures analysis was performed, using a mixed effects model, to determine the effect of positive EUS and of recurrence of acute pancreatitis on quality of life.[19]

Missing data was considered no event. A two-tailed p value of <0.05 was considered statistically significant. All analyses were performed in SPSS version 26 for Microsoft Windows.

RESULTS

Between September 6, 2018 and September 27, 2019, 957 consecutive patients with acute pancreatitis were admitted and screened in 24 of the participating hospitals, of whom 106 were included (figure 1).

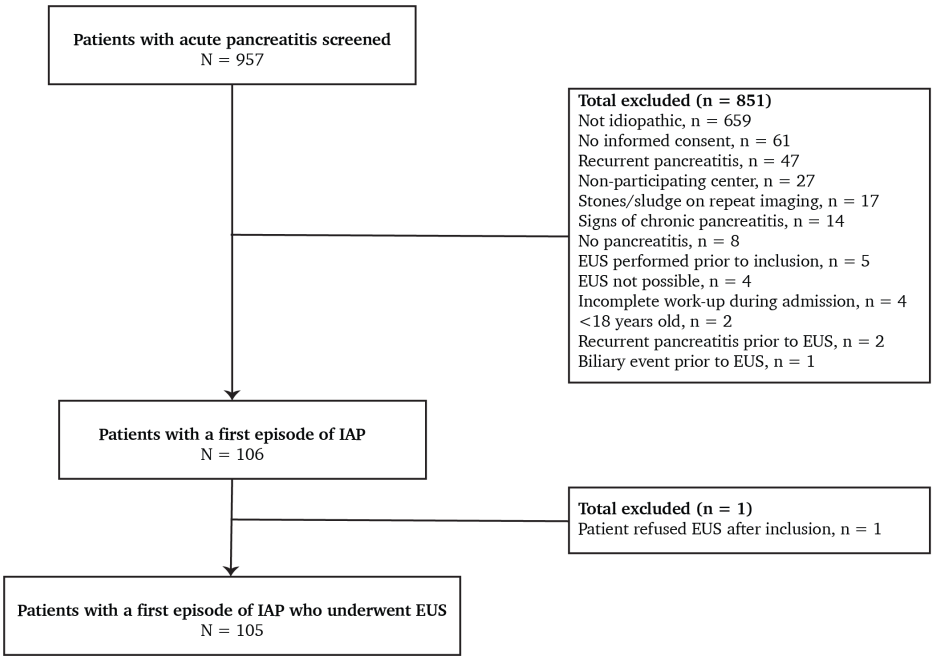

Figure 1 Inclusion flowchart
EUS indicates *endoscopic ultrasound*; IAP, *idiopathic acute pancreatitis*

Patient characteristics

The majority of the included patients were male (n=63, 59.4%). The mean age was 60 years (SD 14.2). In 8 patients (7.5%), cholecystectomy was already performed before admission for IAP. The median time of hospital stay for the initial episode of IAP was 4 days (IQR 2-7). The disease course was (moderately) severe in 19 patients (17.9%), with acute necrotic collections in 12 (11.3%), acute (peri-)pancreatic fluid collections in 8 (7.5%), walled-off necrosis in one (0.9%) and/or splenic vein thrombosis in one patient (0.9%).

The median time from admission to additional imaging after resolution of acute pancreatitis (i.e., repeat transabdominal ultrasonography or MRI/MRCP) was 22 days (IQR 14-37.5). After standard diagnostic work-up during admission, additional imaging was performed after recovery from the acute pancreatitis and was negative for aetiology in all patients: transabdominal ultrasonography in 98 patients (93%), MRI/MRCP in 15 patients (13%) and/or computed tomography (CT) in 16 patients (15% [table 1]).

Table 1 Patient characteristics

Patient characteristics	Total, N=106
Age at admission (y)	59.7 (14)
Female sex	43 (41)
BMI†	27.7 (6)
Previous cholecystectomy	8 (8)
Nicotine use	
No	52 (49)
Stopped	29 (27)
Yes	25 (24)
No alcohol use	43 (41)
Alcohol use (1-5 U/d)	63 (59)
Presence of local adverse events after first episode of IAP	19 (18)
Acute (peri-)pancreatic fluid collection	8 (8)
Acute necrotic collection	12 (11)
Walled-off necrosis	1 (1)
Splenic vein thrombosis	1 (1)
Length of hospital stay (d)	4 (2 – 7)
Laboratory values	
Amylase (U/L)	532.5 (143.5 – 1626.8)
Lipase (U/L)	896 (351 – 3376)
CRP (mg/L)	14.5 (2.9 – 46.3)
ALT (U/L)	25.5 (18 – 37)
Calcium (mmol/L)	2.34 (2.3 – 2.4)
Albumin (g/L)	39.1 (45)
Triglyceride (mmol/L)	1.3 (0.9 – 1.8)

Table 1 Continued.

Patient characteristics	Total, N=106
Imaging before EUS	105 (100)
CT	16 (15)
MRI/MRCP	14 (13)
Repeat abdominal ultrasonography	98 (93)
Time to additional imaging (d)	22 (14 – 37.5)

Data are presented as n (%), as mean (standard deviation) or median (P25-P75).
*No pseudocysts, gastric outlet obstruction, portal vein thrombosis or colonic necrosis were observed in this study.
†missing in three patients
BMI indicate *body mass index;* IAP, *idiopathic acute pancreatitis;* CRP, *C-reactive protein;* ALT, *alanine transaminase;* EUS, *endoscopic ultrasonography;* CT, *computed tomography;* MRI/MRCP, *magnetic resonance imaging/magnetic resonance cholangiopancreaticography.*

Endoscopic ultrasonography

A total of 105 out of 106 included patients (99%) underwent EUS; one patient refused EUS after inclusion. The other 105 patients underwent EUS at a median of 58 days (IQR 39.5-84) after initial admission. The EUS was performed by a gastroenterologist in the majority of the cases (n=96, 91.4%), while in the rest, a supervised gastroenterology resident was the executing endoscopist. Most endoscopists had extensive experience in performing EUS. Eighty percent of the procedures were performed by an endoscopist with more than 400 EUS procedures lifetime (n=84). Nearly all EUS procedures were performed with a linear endoscope (99%, n=104). In 88 procedures (83.8%), patients received midazolam sedation only, while 17 patients (16.2%) received propofol.

Primary endpoint

In 34 of the 105 patients undergoing EUS, a highly probable or definitive aetiology was found (32.4% [95%CI 23.4-41.3]). The majority of patients had (micro-)lithiasis or biliary sludge (n=25, 23.8% [95%CI 16-33.1]). Other observed abnormalities were chronic pancreatitis in seven (6.7% [95%CI 2.7-13.3]) and neoplasms in three patients (2.9% [95%CI 0.6-8.1]). One patient had signs of chronic pancreatitis and biliary stones. In three patients (2.9%), a pancreas divisum was detected during EUS, which was not considered to be positive for aetiology.

In three patients, a neoplasm was detected (2.9%). One patient had a papillary adenoma with low-grade dysplasia and underwent ampullectomy twice during the one-year follow-up. A second patient was diagnosed with main duct intraductal papillary mucinous neoplasm, which proved to be malignant after the patient underwent pylorus-preserving pancreatoduodenectomy. The third patient had an adenocarcinoma of the pancreatic head, treated by neoadjuvant therapy followed by pylorus-preserving pancreatoduodenectomy. This patient

also underwent CT imaging before EUS, which was negative for aetiology, and transabdominal ultrasonography after resolution of acute pancreatitis was performed in all patients, which were also all negative for aetiology.

In one patient (1%), a mild episode of acute pancreatitis occurred within 12 hours after the EUS procedure, for which the patient was admitted for a week. No fine needle aspiration or biopsy had been performed.

Subgroup analyses were performed to determine whether patients' and EUS procedural characteristics were associated with a positive EUS (table 2).

Table 2 Positive endoscopic ultrasonography in subgroups based on several patient characteristics and endoscopic ultrasonography-related factors

	N	Positive EUS	*P*
BMI < 30	74	25 (34)	1.000
BMI > 30†	28	9 (32)	
Cholecystectomy in history	8	1 (13)	0.432
Gall bladder in situ	97	33 (34)	
Alcohol use	62	22 (36)	0.525
No alcohol use	43	12 (28)	
Local adverse events	19	6 (32)	1.000
No local adverse events	86	28 (33)	
Abdominal ultrasonography as repeat imaging	91	29 (32)	0.767
MRI/MRCP as repeat imaging	14	5 (36)	
< 400 EUS performed	21	4 (19)	0.195
> 400 EUS performed	84	30 (36)	
Linear scope	104	34 (33)	1.000
Radial scope	1	-	
No propofol	88	32 (36)	0.052
Propofol	17	2 (12)	
No steatosis or cirrhosis	65	26 (40)	0.052
Steatosis or cirrhosis	40	8 (20)	

Data are presented in n (%).
† missing in three patients
EUS indicates *endoscopic ultrasonography;* BMI, *body mass index;* MRI/MRCP, *magnetic resonance imaging/magnetic resonance cholangiopancreaticography.*

EUS in patients with a gallbladder in situ had a higher yield (33/97 [34%]) than in patients who did not (1/8 [12.5%], p=0.432). In patients with hepatic steatosis or cirrhosis the yield of EUS was twice as low (8/40 [20%]) as in other patients (26/65 [40%], p=0.052). The yield of EUS was higher when performed by an experienced gastroenterologist (more than 400 previously performed EUS procedures) as opposed to less experienced endoscopists (30/84 [35.7%]

vs. 4/21 [10%], respectively, p=0.195). EUS with propofol sedation had with a lower yield (2/17 [11.8%]) than EUS with midazolam sedation (32/88 [36.4%], p=0.052).

During a one-year follow-up period, a total of 20 acute pancreatitis recurrences occurred in 14 patients (13.2%). A quarter of these were (moderately) severe (4 [20%] and 1 [5%], respectively). After EUS detected an aetiology, cholecystectomy and ERCP were performed in 18 (17%) and 6 (5.7%) patients, respectively. Out of the 10 ERCP procedures performed in these 6 patients, 6 were performed with symptomatic choledocholithiasis as indication. Filling defects were observed on 3/6 cholangiographies (50%), and gallstones, microlithiasis and sludge were evacuated in 2, 1 and 1 out of 4 sphincterotomies (50, 25 and 25% respectively). No patients died during the course of this study (table 3).

Table 3 Secondary outcome measures

Secondary endpoints	**Total, N = 106**
Recurrence rate overall	14 (13)
Total number of recurrences	20
Severity of recurrence	
Mild	15 (75)
Moderately severe	4 (20)
Severe	1 (5)
Length of hospital stay (of recurrence)	3.5 (2 – 6)
Cholecystectomy	18 (17)
ERCP	6 (6)
Adverse events after EUS	1 (1)
Mortality	-

Data are presented as n (%) or median (P25-P75).
ERCP indicates *endoscopic retrograde cholangiopancreaticography*; EUS, *endoscopic ultrasonography*.

Secondary endpoints

Subgroup analyses were performed to determine whether patient or EUS procedural characteristics were associated with recurrence of acute pancreatitis (table 4). The IAP recurrence rate was 16.9% in patients with a negative EUS (12/71) as compared to 5.9% in patients with a positive EUS (2/34, p=0.218). The recurrence rate was higher in patients with a gallbladder in situ at initial admission for IAP (14/97 [14.4%]) than in patients after previous cholecystectomy (0/8, p=0.594). Patients with hepatic steatosis or cirrhosis had a higher recurrence rate (8/40 [20%]) than those who did not (6/65 [9.2%], p=0.143).

Quality of life

The quality of life score improved over the course of the one-year follow-up period. While after six months after inclusion, overall quality of life was similar to the overall quality of life at inclusion (mean difference from inclusion 31.7 [SD 164.2], p=0.098), after one year after inclusion, the overall quality of life was significantly higher (mean difference from inclusion 39 [SD 129.6], p=0.015). While EUS positive for aetiology was not associated with changes in quality of life (p=0.867), readmission for acute pancreatitis was associated with an overall lower quality of life (p=0.022 [Supplementary material 3]).

Table 4 Pancreatitis recurrence rate in subgroups based on several patient characteristics and endoscopic ultrasonography-related factors

	N	Pancreatitis recurrence	*P*
EUS positive	34	2 (6)	0.218
EUS negative	71	12 (17)	
BMI < 30	74	10 (14)	1.000
BMI > 30†	28	4 (14)	
Cholecystectomy in history	8	-	0.594
Gall bladder in situ	97	14 (14)	
Alcohol use	62	8 (13)	1.000
No alcohol use	43	6 (14)	
Local adverse events	19	2 (11)	1.000
No local adverse events	86	12 (14)	
Transabdominal ultrasonography as repeat imaging	91	12 (13)	1.000
MRI/MRCP as repeat imaging	14	2 (14)	
Endoscopist performed < 400 EUS performed	21	1 (5)	0.292
Endoscopist performed > 400 EUS	84	13 (16)	
Linear scope	104	14 (14)	1.000
Radial scope	1	-	
No propofol	88	12 (14)	1.000
Propofol (n = 17)	17	2 (12)	
No steatosis or cirrhosis	65	6 (9)	0.143
Steatosis or cirrhosis	40	8 (20)	

Data are presented as n (%).
†missing in 3 patients
EUS indicates endoscopic ultrasonography; BMI, body mass index; MRI/MRCP, magnetic resonance imaging/magnetic resonance cholangiopancreaticography.

DISCUSSION

In this first prospective multicentre cohort study, routine EUS in 106 patients with a first episode of IAP based on standard diagnostic workup detected an aetiology in one third of these patients. The observed aetiologies were mostly gallstone disease (24%), followed by chronic pancreatitis (7%) and neoplasms (3%). Patients with 'EUS negative IAP' have a disproportionally high recurrence rate of 16.9%.

The diagnostic yield of EUS in this study was lower when compared to other studies.[8] This may be explained by the strict diagnostic work-up before EUS in this study. This is the first study that performed complete standard diagnostic work-up according to guidelines, thereby eliminating the risk of overestimating the clinical value of EUS in IAP. In most screened patients in this study, an aetiology was detected by initial standard work-up during admission (659/957; 69%) or during repeat imaging (17/957; 2% [Figure 1]). These patients were excluded from the study. Repeat imaging before EUS was standardized in this study and all patients underwent transabdominal ultrasonography, MRI/MRCP or both before inclusion. Additionally, this study used a strict definition for positive EUS, only including abnormalities that could constitute a highly probable or definitive cause for acute pancreatitis.

An EUS with abnormalities suspicious for chronic pancreatitis had to meet the M-ANNHEIM criteria.[13] Anatomical abnormalities, e.g., pancreas divisum, was also not considered a definitive cause of acute pancreatitis as this is not a certain etiological factor in first episode acute pancreatitis.[16] Therefore, the results of this study are more reliable in clinical practice than previous studies, which have included patients both single and recurrent episodes of IAP, failed to perform adequate diagnostics before EUS and often did not systematically report on clinically relevant long-term outcomes such as pancreatitis recurrence and quality of life.[8]

Before execution of this study, the DPSG agreed on the minimum clinically relevant added yield of EUS in patients with IAP to justify implementation of routine EUS after a first episode of presumed IAP.[9] Given the assumption that most detected aetiologies are treatable, which could prevent pancreatitis recurrence, and that timely diagnosis could positively impact prognosis, a minimum diagnostic yield of 10% was determined. Based on the observation that the aetiology detection rate in this study was three times higher than this predetermined cut-off value, we advise routine use of EUS in patients with a first episode IAP to be included in future guidelines on diagnostics in IAP.

The pancreatitis recurrence rate was nearly three times as high in patients with a negative EUS as in patients with a positive EUS (16.9% vs. 5.9%). It has

been hypothesized that undetected microlithiasis or biliary sludge may cause recurrent IAP episodes. EUS could be false negative due to spontaneous passage of the microlithiasis or sludge, or limited proficiency of the endoscopist or technical sensitivity of EUS. Thus, these patients may benefit from cholecystectomy.[20] A systematic review indeed found a significantly lower recurrence rate in patients with IAP who underwent cholecystectomy as compared to expectant management (11.1% vs. 35.2%, risk ratio 0.44).[21] However, EUS was not performed routinely in these patients. The true value of cholecystectomy in 'EUS negative IAP' remains uncertain. The data provided by this study can be used for the design of a future randomized controlled trial on cholecystectomy in prevention of recurrence in 'EUS-negative IAP'.

These results should be interpreted in light of some limitations. First, there was no association between patient or EUS procedural characteristics and yield of EUS. No subgroup analysis could be made on treatment of aetiology if EUS was positive for aetiology, as only two pancreatitis recurrences were observed in this group. It has been reported previously, in line with our current observations, that the aetiology detection rate is higher in patients with their gallbladder in situ,[8] although this result did not achieve statistical significance. This could be due to a limited sample size, which was powered on EUS detection rate. Second, EUS was performed after resolution of acute pancreatitis. Therefore, uncertainty remains on the value of EUS in a different time frame. Third, the follow-up was limited to one year. The pancreatitis recurrence rate after this follow-up period is unknown.

In conclusion, EUS can safely determine an aetiology in approximately one-third of patients with a first episode of IAP after standard diagnostic work-up failed to detect an aetiology. These findings, together with a low adverse event rate of EUS (1%), support the routine use of EUS in patients with IAP. EUS-mediated detection of aetiology and subsequent treatment appeared to lower the pancreatitis recurrence rate in IAP. Further research is needed to explore effective diagnostic and treatment options to further lower recurrence rate in EUS-negative IAP.

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SUPPLEMENTARY APPENDIX

Table S1 STROBE statement

	No	Recommendation	Listed in section:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title & abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction (last paragraph)
Methods			
Study design	4	Present key elements of study design early in the paper	Methods – study design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods – study design, study procedure and follow-up Results
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods - study population, study procedure and follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods – outcome measures
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods – sample size calculation and statistical analyses
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods – sample size calculation and statistical analyses
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	

Table S1 Continued.

	No	Recommendation	Listed in section:
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results – figure 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results – patient characteristics
		(b) Indicate number of participants with missing data for each variable of interest	Results – table 1
		(c) Summarise follow-up time (eg, average and total amount)	Methods – study procedure and follow-up
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results – primary endpoint
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Results – table 2 & 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results – primary endpoint, secondary endpoints, quality of life
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgements

Table S2 STARD statement

No	Item	Reported in section
TITLE OR ABSTRACT		
1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Not applicable
2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract
INTRODUCTION		
3	Scientific and clinical background, including the intended use and clinical role of the index test	Introduction
4	Study objectives and hypotheses	Introduction (last paragraph)
METHODS		
Study design		
5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Methods – study design
Participants		
6	Eligibility criteria	Methods – study population & eligibility criteria
7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Methods – study population & eligibility criteria
8	Where and when potentially eligible participants were identified (setting, location and dates)	Methods – study design & Results
9	Whether participants formed a consecutive, random or convenience series	Results
Test methods		
10a	Index test, in sufficient detail to allow replication	Methods – endoscopic ultrasonography
10b	Reference standard, in sufficient detail to allow replication	Not applicable
11	Rationale for choosing the reference standard (if alternatives exist)	Not applicable
12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Methods - primary outcome measure
12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Methods - primary outcome measure
13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Not applicable
13b	Whether clinical information and index test results were available to the assessors of the reference standard	Not applicable
Analysis		
14	Methods for estimating or comparing measures of diagnostic accuracy	Not applicable
15	How indeterminate index test or reference standard results were handled	Methods – statistical analyses
16	How missing data on the index test and reference standard were handled	Methods – statistical analyses
17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Methods – statistical analyses
18	Intended sample size and how it was determined	Methods – sample size calculation

Table S2 Continued.

No	Item	Reported in section
RESULTS		
Participants		
19	Flow of participants, using a diagram	Figure 1
20	Baseline demographic and clinical characteristics of participants	Results – patient characteristics
21a	Distribution of severity of disease in those with the target condition	Results – patient characteristics
21b	Distribution of alternative diagnoses in those without the target condition	Figure 1
22	Time interval and any clinical interventions between index test and reference standard	Results – patient characteristics
Test results		
23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Results – Outcome of EUS
24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Not applicable
25	Any adverse events from performing the index test or the reference standard	Results – Outcome of EUS
DISCUSSION		
26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Discussion
27	Implications for practice, including the intended use and clinical role of the index test	Discussion
OTHER INFORMATION		
28	Registration number and name of registry	Methods – study design
29	Where the full study protocol can be accessed	Methods – study design
30	Sources of funding and other support; role of funders	Acknowledgement

Supplementary material 2: definitions

Acute pancreatitis: an acute inflammation of the pancreatic parenchyma, diagnosed when at least two of the three following characteristics are present:[1]

1. Clinical features of acute pancreatitis, such as upper abdominal pain
2. Elevated serum amylase or lipase levels of at least three times the upper limit of normal (ULN)
3. Signs of acute pancreatitis on imaging

Note: no value of the required serum amylase or lipase level is provided as every participating centre has a local laboratory, which is why each centre may use different normal range values.

Idiopathic acute pancreatitis is considered to be present if no aetiology is found in standard work-up, according to the IAP/APA evidence-based guidelines on management of acute pancreatitis,[2] which comprises at least the following tests:

1. A detailed personal and family history, including questions on:
    a. Alcohol use
    b. Recent endoscopic retrograde cholangiopancreaticography (ERCP)
    c. Recent start of or changes in use of drugs associated with acute pancreatitis
    d. Recent major abdominal trauma
    e. Recent abdominal surgery
    f. Familial pancreatitis
    g. Hereditary pancreatitis
    h. Cystic fibrosis related pancreatitis
2. Laboratory tests, including:
    a. Blood serum triglycerides level on admission
    b. Blood serum calcium level, corrected for the serum albumin level, on admission
    c. Blood serum alanine transaminase (ALT) level on admission
3. Imaging via transabdominal ultrasound, magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreaticography (MRCP) after clinical recovery

Note: side branch or mixed type intraductal papillary mucinous neoplasms (IPMN) without dilatation of the pancreatic duct will not be considered to be a causative factor for the pancreatitis episode.

Note: if the imaging is not able to discriminate between gall bladder polyps or concrements, lesions smaller than 10 mm will not be considered an exclusion criterion. Lesions above 10 mm, irrespective of whether they are a polyp or a concrement, are an immediate indication for cholecystectomy, and will be excluded from this study.

Alcoholic pancreatitis: pancreatitis caused by an excess intake of alcohol, diagnosed when biliary aetiology is not demonstrated by standard work-up and the patient has indicated (either by direct or indirect personal history or by findings during physical examination) to have drank at least five units of alcohol in the 24 hours prior to start of abdominal complaints (or in asymptomatic acute pancreatitis: prior to diagnosis)[3-5]

Biliary pancreatitis: pancreatitis caused by biliary stones, microlithiasis or sludge, diagnosed when one of the following features is present:

1. A transient elevated ALT level of more than two times the ULN at diagnosis of acute pancreatitis, in the absence of ALT elevating comorbidity[6]
2. Signs of presence of gallstones, microlithiasis or sludge on imaging, defined as follows:
    a. Gallstones, microlithiasis and/or biliary sludge, either in the gall bladder, ductus cysticus, intrahepatic bile ducts or in the common bile duct (CBD), and/or
    b. A CBD of more than eight mm in patients 75 years old or younger or more than ten mm in patients older than 75 years at diagnosis of acute pancreatitis[7]

Note: no value of the required serum ALT level is provided as the normal range values depend on the sex of the patient and as every participating centre has a local laboratory, which is why each centre may use different normal range values.

Chronic pancreatitis**:** a chronic inflammation of the pancreatic parenchyma, defined as typical clinical history of chronic pancreatitis (such as recurrent pancreatitis or abdominal pain, except for primary painless pancreatitis) and one or more of the following:[8]

1. Pancreatic calcifications
2. Moderate or marked ductal lesions, defined as two or more of the following abnormal features on transabdominal ultrasound, computed tomography (CT) or MRI/MRCP, according to the Cambridge classification:[9]
    a. Main pancreatic duct abnormalities, either enlargement or increased echogenicity of the duct wall (mandatory)
    b. Pancreatic enlargement
    c. Cavities
    d. Duct irregularities including intraductal fillings defects, calculi or duct obstruction
    e. Focal acute pancreatitis
    f. Parenchymal heterogeneity
    g. Irregularities of pancreatic head or body contour
3. Moderate or marked ductal lesions, defined as five or more of the following abnormal features on endoscopic ultrasonography (EUS):
    a. Enlarged gland size
    b. Cysts
    c. Echo-poor lesions (focal areas of reduced echogenicity)
    d. Echo-rich lesions (more than three mm in diameter)
    e. Accentuation of lobular pattern (e.g., echo-poor normal parenchyma surrounded by hyperechoic strands)
    f. Increased duct wall echogenicity
    g. Irregularity of the main pancreatic duct (e.g., with narrowing of the duct)
    h. Dilation of the main pancreatic duct

   i. Visible side branches (e.g., with dilation)
   j. Calcification (of the pancreatic duct)
4. Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation
5. Typical histology of an adequate histological specimen

Note: during initial diagnostic work-up during admission 'marked and persistent exocrine insufficiency' cannot be evaluated properly. Therefore this part of the definition of chronic pancreatitis will not be applicable during standard work-up. However, if the patient does show marked and persistent exocrine insufficiency during follow-up (either during the outpatient clinic visit after repeat transabdominal ultrasound or after the EUS), this will be considered to be diagnostic for chronic pancreatitis. The same is applicable for histology of an adequate histological specimen: this is not part of standard work-up, however, if a typical histological specimen is obtained during follow-up, this will be considered to be diagnostic for chronic pancreatitis.

Clinical recovery from acute pancreatitis: resolution of pancreatic inflammation, present when one of the following criteria is met:

1. Discharge from the hospital
2. Normal inflammation parameters in laboratory tests
3. No signs of pancreatic inflammation on imaging

Cystic fibrosis: an autosomal recessive disorder caused by a mutation in the CFTR gene, resulting in defective chloride channels in epithelial cells, diagnosed by either a concentration in sweat of chloride greater than 60 mmol/L on repeated analysis, confirmation of a CFTR gene mutation, or both.[10]

Cystic fibrosis related pancreatitis: pancreatitis caused by defective ductular and acinar pancreatic secretion, diagnosed when a patient with a history of cystic fibrosis presents with an acute pancreatitis in the absence of another origin.[10]

Familial pancreatitis: acute pancreatitis from any cause that occurs in a family with an incidence that is greater than would be expected by chance alone, given the size of the family and the standardized incidence of pancreatitis within the Dutch population, defined as acute pancreatitis in patients who have two or more direct blood-related family members (parents, children or siblings) who have had an episode of acute pancreatitis.[11-13]

Fever: a body temperature of 38.5˚C or higher.

Hereditary pancreatitis: otherwise unexplained pancreatitis in an individual from a family in which the pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern, defined as pancreatitis in patients with a known mutation in the PRSS1 gene, the SPINK1 gene, the CFTR gene, the CTRC gene, the CLDN2 gene or the CPA1 gene, or

if the patient has a direct family member (parents, children, siblings) with one or more of the above mentioned mutations and has at least one direct family member who has had an episode of acute pancreatitis or has chronic pancreatitis.[13,14]

Hypercalcaemic pancreatitis: acute pancreatitis caused by hypercalcemia and diagnosed when no signs of a biliary pancreatitis are found in standard work-up and the patient has a blood serum calcium level of at least 12 mg/dl or 3 mmol/l, corrected for the serum albumin level, as first measured during admission.[15]

Hypertriglyceridemic pancreatitis: acute pancreatitis based on hypertriglyceridemia and diagnosed if a biliary aetiology is not demonstrated by standard work-up and the patient has a blood serum triglyceride level of at least 1000 mg/dl (or 11.2 mmol/l) under fasting conditions, as first measured during admission.[16]

Hypothermia: a body temperature of 35.9˚C or lower.

Infected (extra)pancreatic necrosis: presence of microorganisms in (extra-)pancreatic necrosis, confirmed by a positive culture obtained by means of fine needle aspiration or from the first drainage procedure or necrosectomy, the presence of gas in the (extra-)pancreatic collection on CT, or the presence of clinical signs of persistent sepsis or progressive clinical deterioration despite maximal support on the intensive care unit (ICU) without other causes for infection (ruled out should be: pneumonia, urinary tract infection, wound infection, endocarditis, abdominal sepsis or any other infection which could be suspected based on the individual patient's clinical presentation).[17]

Medication associated pancreatitis: acute pancreatitis is considered to be caused by drugs when a biliary cause is not demonstrated by standard work-up, the patient uses one or multiple drug(s) listed in the table below, the drug has been started or increased in dosage within a reasonable temporal sequence, in principle 1 month before the onset of the pancreatitis, and has a positive dechallenge (a drug reaction that is confirmed by stopping the drug).[18,19]

Drugs associated with acute pancreatitis

Acetaminophen	Cisplatin	Hydrochlorothiazide	Methyldopa	Pentavalent antimony compounds
Asparaginase	Cytarabine	Interferon alpha	Metronidazole	
Azathioprine	Didanosine	Itraconazole	Octreotide	Phenformin
Bortezomib	Enalapril	Lamivudine	Olanzapine	Simvastatin
Capecitabine	Erythromycin	Mercaptopurine	Opiates	Steroids
Carbamazepine	Estrogens	Mesalazine	Oxyphenbutazone	Sulfasalazine
Cimetidine	Furosemide	Olsalazine	Pentamidine	co-trimoxazole

Microlithiasis: stones or concrements, smaller than four mm, in the gall bladder or the bile ducts.[20]

Murphy's sign: the phenomenon where compression of the right upper quadrant causes the patient to catch their breath due to pain when taking a deep breath.[21]

Pancreas divisum: a congenital malformation of the main pancreatic duct (Wirsung's duct) with two separate ducts (a separate ventral duct of Wirsung and a dorsal duct of Santorini) as opposed to one main duct (of Wirsung).[22]

Positive imaging: positive imaging is defined as imaging during which a definitive cause for the acute pancreatitis episode can be found; or during which abnormalities are visualized constituting a definitive cause, after obtaining tissue and pathological examination. So, if during EUS ductal abnormalities are found, yet not enough to make a certain diagnosis of chronic pancreatitis according to the M-ANNHEIM classification,[8] this imaging is considered to be negative, even though it did show abnormalities. This approach is chosen because the aim of this study is to determine the rate of which EUS can find a causative factor for a previous acute pancreatitis episode. For the same reason, finding of an anatomical abnormality after a first episode of acute pancreatitis is not scored as positive imaging. An overview of the exact findings scored as positive imaging is provided in the table below.

Definition of positive imaging	
Biliary pancreatitis	• Presence of biliary stones, microlithiasis or sludge • Widened CBD, >8 mm in patients <76 years or >10 mm in patients >75 years, in the absence of other CBD • dilating factors (e.g., opioid use, distal stenosis, obstruction of external compression of CBD or papilla[23])
Chronic pancreatitis	• Pancreatic calcifications • >4 of the following abnormal features of the pancreas: 1. Enlarged gland size 2. Cysts 3. Echo-poor lesions (focal areas of reduced echogenicity) 4. Echo-rich lesions (>3 mm in diameter) 5. Accentuation of lobular pattern 6. Increased duct wall echogenicity 7. Irregularity of the main pancreatic duct 8. Dilation of the main pancreatic duct >3.5 mm[24] 9. Visible side branches 10. Calcifications of the pancreatic duct
Neoplasms	• Definitive diagnosis of pathological tissue after histological or cytological evaluation of specimen of an anomaly observed during EUS, for example, hyperplastic or malignant tissue, or auto-immune inflammatory disease • Main duct IPMN or mixed-type IPMN causing dilatation of the pancreatic duct

For each diagnosis, presence of one of the separately mentioned abnormalities is required to be considered as positive imaging. Specimen is not required to be obtained during EUS.
Anatomical anomalies (e.g., divisum) are not considered a certain aetiology in first episode idiopathic acute pancreatitis and therefore not considered as positive imaging.
CBD indicates *common bile duct;* EUS, *endoscopic ultrasonography;* IPMN, *intraductal papillary mucinous neoplasm.*

Post-ERCP pancreatitis: pancreatitis caused by mechanical injury from instrumentation and hydrostatic injury from contrast injection during ERCP, diagnosed if a patient develops a pancreatitis within 24 hours of an ERCP without indications of another origin.[25]

Postoperative pancreatitis: pancreatitis caused by perioperative hypoperfusion of the pancreas, diagnosed if a patient develops a pancreatitis within 24 hours of abdominal surgery in the absence of indications for another origin.[26]

Posttraumatic pancreatitis: pancreatitis caused by pancreatic injury due to trauma to the abdomen, diagnosed when the patient describes a typical blunt trauma to the upper abdomen and pancreatic trauma is visible on imaging.[27]

Recurrence rate: the risk of a recurrent episode of acute pancreatitis.

Sludge: solid material which results from the slow settling of particles dispersed in bile.[20]

Standard work-up:

1. A detailed personal and family history, including questions on:
    a. Alcohol use
    b. Recent ERCP
    c. Recent start of or changes in use of drugs associated with acute pancreatitis
    d. Recent major abdominal trauma
    e. Recent abdominal surgery
    f. Familial pancreatitis
    g. Hereditary pancreatitis
    h. Cystic fibrosis related pancreatitis
2. Laboratory tests, including:
    a. Blood serum triglycerides level, first measured during admission
    b. Blood serum calcium level, corrected for the serum albumin level, first measured during admission
    c. Blood serum ALT level on admission
3. Imaging via transabdominal ultrasound, MRI or MRCP after clinical recovery

Biliary events: acute cholecystitis; biliary colic's requiring readmission; biliary pancreatitis; cholangitis; or obstructive choledocholithiasis needing ERCP.

Acute cholecystitis: an acute inflammation of the gall bladder, diagnosed when one item in A, B and C is present:

A) Local signs of inflammation
    1. Murphy's' sign, or

2. Right upper abdominal quadrant mass, pain or tenderness

B) Systemic signs of inflammation
   1. Fever or hypothermia, or
   2. Elevated C-reactive protein CRP), or
   3. Elevated white blood cell count

C) Imaging findings characteristic of acute cholecystitis[28,29]

Note: acute cholecystitis and cholangitis (see definition below) are defined according to the Tokyo classification which defines fever as a body temperature of 38˚C or higher; however, fever will be defined in this study as hyperthermia of 38.5˚C or higher and hypothermia will be added as a systemic sign of inflammation, as this more accurately reflects clinical practice in the Netherlands.

Biliary colic**:** upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes, often associated with restlessness.[30]

Cholangitis: an inflammation of the bile duct(s), diagnosed when one item in each of the following categories is present:

1. Systemic inflammation
   a. Fever, hypothermia and/or shaking chills
   b. Laboratory data: evidence of inflammatory response (abnormal white blood cell counts (defined as smaller than 4,000/μl or larger than 10,000/μl), increase of serum CRP levels (defined as 1 mg/dl or higher), and other changes indicating inflammation)
2. Cholestasis
   a. Jaundice (defined as a total bilirubin of 2 mg/dl or higher)
   b. Laboratory data: abnormal liver function tests (increased serum alkaline phosphatase, gamma-glutamyltransferase (gamma-GT), aspartate transaminase (AST) and ALT levels (defined as more than 1.5 times the ULN))
3. Imaging
   a. Biliary dilatation
   b. Evidence of the aetiology on imaging (stricture, stone, stent etc.)[28]

Obstructive choledocholithiasis: presence of gallstones, microlithiasis or biliary sludge in the CBD on imaging, requiring an ERCP, according to the treating physician.

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Table S3 Quality of life measured by the Short Form-36 questionnaire

	At inclusion	Follow-up (6m)	Difference from inclusion		Follow-up (1y)	Difference from inclusion	
				P			*P*
Physical functioning	68 (29)[a]	71 (27)[d]	4 (25)	0.2	72 (26)[e]	3 (20)	0.1
Role limitations due to physical health	50 (0 – 100)[a]	88 (0 – 100)[d]	12 (53)	0.05	75 (0-100)[e]	10 (43)	0.05
Role limitations due to emotional problems	100 (8 – 100)[b]	100 (33 – 100)[d]	0.4 (54)	0.9	100 (67-100)[e]	9 (42)	0.08
Energy/fatigue	49 (22)[a]	55 (21)[d]	5 (18)	0.01	55 (21)[f]	5 (19)	0.04
Emotional well-being	73 (16)[b]	74 (18)[d]	1 (16)	0.5	76 (16)[f]	3 (16)	0.1
Social functioning	65 (28)[a]	72 (25)[d]	7 (30)	0.04	73 (26)[f]	7 (30)	0.06
Pain	66 (30)[a]	74 (27)[d]	8 (31)	0.03	72 (27)[f]	6 (31)	0.1
General health	56 (21)[b]	53 (22)[d]	-3 (16)	0.2	56 (24)[f]	-0.4 (17)	0.8
OVERALL	486 (368 – 666)[c]	527 (171)[d]	32 (164)	0.1	541 (170)[f]	39 (130)	0.02

Reported as mean (standard deviation) or median (P25-P75).
Missing patients: a=17, b=18, c=21, d=26, e=30, f=31

Table S4 Modern repeated measures analyses using a mixed model

Analysis 1 - Effect of endoscopic ultrasonography (EUS) outcome on quality of life

						95% Confidence Interval	
Parameter	**Estimate**	**Standard Error**	**Degrees of freedom**	**t value**	***P***	**Lower Bound**	**Upper Bound**
Intercept	531.49	21.92	94.11	24.25	0.00	487.96	575.01
1 year follow-up	-35.49	15.03	76.45	-2.36	0.02	-65.42	-5.56
6 months follow-up	-7.91	15.53	76.35	-0.51	0.61	-38.85	23.02
EUS outcome	5.75	34.19	87.04	0.17	0.867	-62.21	73.71

Analysis 2 effect of pancreatitis recurrence on quality of life

						95% Confidence Interval	
Parameter	**Estimate**	**Standard Error**	**Degrees of freedom**	**t value**	***P***	**Lower Bound**	**Upper Bound**
Intercept	547.68	19.90	86.10	27.52	0.00	508.11	587.24
1 year follow-up	-35.49	15.05	76.19	-2.36	0.02	-65.46	-5.53
6 months follow-up	-7.24	15.50	76.74	-0.47	0.64	-38.11	23.62
Pancreatitis recurrence	-103.91	44.65	86.07	-2.33	0.022	-192.67	-15.15

EUS indicates *endoscopic ultrasonography*

PART III

CHAPTER XII

Optimal timing of cholecystectomy after necrotizing biliary pancreatitis

Gut 2021

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ABSTRACT

Objective

Following an episode of acute biliary pancreatitis, cholecystectomy is advised to prevent recurrent biliary events. There is limited evidence regarding the optimal timing and safety of cholecystectomy in patients with necrotizing biliary pancreatitis.

Design

A post hoc analysis of a multicentre prospective cohort. Patients with biliary pancreatitis and a CT severity score of three or more were included in 27 Dutch hospitals between 2005 and 2014. Primary outcome was the optimal timing of cholecystectomy in patients with necrotizing biliary pancreatitis, defined as: the optimal point in time with the lowest risk of recurrent biliary events and the lowest risk of complications of cholecystectomy. Secondary outcomes were the number of recurrent biliary events, periprocedural complications of cholecystectomy and the protective value of endoscopic sphincterotomy for the recurrence of biliary events.

Results

Overall, 248 patients were included in the analysis. Cholecystectomy was performed in 191 patients (77%) at a median of 103 days (P25–P75: 46–222) after discharge. Infected necrosis after cholecystectomy occurred in four (2%) patients with persistent peripancreatic collections. Before cholecystectomy, 66 patients (27%) developed biliary events. The risk of overall recurrent biliary events prior to cholecystectomy was significantly lower before 10 weeks after discharge (risk ratio 0.49 (95% CI 0.27 to 0.90); p=0.02). The risk of recurrent pancreatitis before cholecystectomy was significantly lower before 8 weeks after discharge (risk ratio 0.14 (95% CI 0.02 to 1.0); p=0.02). The complication rate of cholecystectomy did not decrease over time. Endoscopic sphincterotomy did not reduce the risk of recurrent biliary events (OR 1.40 (95% CI 0.74 to 2.83)).

Conclusion

The optimal timing of cholecystectomy after necrotizing biliary pancreatitis, in the absence of peripancreatic collections, is within 8 weeks after discharge.

INTRODUCTION

Gallstones and biliary sludge are the most common cause of pancreatitis.[1-2] In order to avoid recurrent biliary events after an episode of biliary pancreatitis, such as cholangitis, recurrent acute pancreatitis and acute cholecystitis, international guidelines advise to perform a cholecystectomy.[3-5] A randomized trial in patients with mild biliary pancreatitis has shown that same-admission cholecystectomy is safe and reduces recurrent biliary events, especially recurrent pancreatitis, as compared with interval cholecystectomy.[6] In patients with necrotizing biliary pancreatitis, however, there is no high-level evidence regarding the optimal timing of cholecystectomy.[7] With respect to the appropriate timing of cholecystectomy, a risk assessment between recurrent biliary events and the potentially higher risk of (surgical) complications (especially in case of persistent peripancreatic collections) should be performed.

A recent systematic review of 11 guidelines demonstrated that only four guidelines specify a time frame for performing a cholecystectomy in patients with peripancreatic collections.[8] Namely, to delay surgery until these collections have completely resolved or at least 6 weeks after onset of disease in case of persistent collections.[5,9-11] The remaining seven guidelines merely state that clinicians should postpone cholecystectomy until local and/or systemic signs of inflammation have subsided.

The recommendations from these guidelines are based on six studies that compare early with delayed cholecystectomy in necrotizing biliary pancreatitis. These studies were published between 1978 and 2007.[12-17] These studies have several limitations: sample sizes are relatively small (<50 patients in five out of six studies), use of different definitions for disease and for 'early' and 'delayed' cholecystectomy, and lastly in some studies a more aggressive treatment strategy was used compared with current practice.[8]

When cholecystectomy is not (yet) considered possible, endoscopic sphincterotomy (ES) may reduce the risk of recurrent biliary events but the protective value in patients with necrotizing biliary pancreatitis remains unclear.[18]

Therefore, the aims of this study are to determine the optimal timing of cholecystectomy in patients with necrotizing biliary pancreatitis inferred from the association between the timing and occurrence of recurrent biliary events and procedural-related complications, and to determine the protective value of ES in preventing recurrent biliary events.

METHODS

Study design

This is a post hoc analysis of a prospective observational cohort study to investigate the optimal timing of cholecystectomy in patients after necrotizing biliary pancreatitis. The study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology guidelines.[19]

Study population

Adult patients with moderate severe or severe acute biliary pancreatitis with peripancreatic collections were selected from a cohort of acute pancreatitis patients. Patients were either included in a previous trial of the Dutch Pancreatitis Study Group (PANTER, PYTHON, TENSION) or included in the registration cohort of patients potentially eligible for inclusion in the PANTER-trial in the time period between 2005 and 2014.[20-22]

Patients with severe and moderate severe acute biliary pancreatitis according to the revised Atlanta Classification, with a CT severity index (CTSI) score of three or more were included. Acute pancreatitis was defined according to the revised Atlanta Classification.[23,24] A biliary aetiology was assumed if patients fulfilled any of the following criteria: (1) gallstones and/or sludge diagnosed on imaging (e.g., transabdominal ultrasound or CT), (2) a dilated common bile duct (CBD) (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) or (3) a serum alanine aminotransferase (ALT) level >2 times higher than normal values at admission, in absence of other causes of acute pancreatitis or signs of chronic pancreatitis.[25-28] The CTSI score is the sum of the scores obtained with the Balthazar Score and the evaluation of pancreatic necrosis, the full scoring system can be found in online supplemental table S1.[29] The following patients were excluded: patients who died during index admission before the cholecystectomy, patients who had less than 3 months follow-up after discharge and did not undergo cholecystectomy within those 3 months and patients who had already undergone cholecystectomy before the first episode of biliary pancreatitis.

Patient and public involvement

Due to the post hoc nature of this study, patients have not been directly involved in the design. However, the Dutch Pancreatitis Study Group has close ties with the Dutch Association for patients with pancreatic disease, the 'Alvleeskliervereniging'. This association was actively involved in the design of the above-mentioned trials and registration cohort.

Data collection

Clinical data were collected prospectively during patients' inclusion in the various trials. An expert radiologist (TLB) reviewed all CT images to assess the CTSI, the presence and location of peripancreatic collections, and to determine the presence of gas within peripancreatic collections. Data on readmissions for biliary complications and cholecystectomy were obtained from the medical records at the end of follow-up in 2019. If a patient was transferred to a different hospital at any time during follow-up, all the required follow-up data were retrieved from those institutions.

Acute pancreatitis treatment

Initial treatment of acute pancreatitis was according to the international guidelines for management of acute pancreatitis and included resuscitation and analgesia.[5] Guidelines on timing of cholecystectomy were not provided within the study protocols; cholecystectomy was performed at the discretion of the treating clinician. The decision to proceed with a cholecystectomy was made when a patient was deemed fit for surgery by the treating surgeon and after consultation of an anaesthesiologists, taking into account the physical condition of the patient with normalisation of dietary intake, resolution of infection and the absence of clinical or laboratory signs of active inflammation. Cholecystectomy was performed laparoscopically if deemed feasible. An intraoperative cholangiography was not performed routinely. The indication for ES varied between hospitals and local guidelines and was left at the discretion of the clinician. Patients with infected peripancreatic necrosis and/or collections were treated conservatively with surgical, radiological, or endoscopic interventions if deemed necessary according to the study protocols of randomized trials or according to the treating clinician. Follow-up of the evolution of peripancreatic collections before cholecystectomy was left to the discretion of the treating clinician.

Study outcomes

The primary endpoint of the study was the optimal timing of cholecystectomy inferred from the association between its timing and the occurrence of recurrent biliary events before cholecystectomy, and procedural-related complications. Optimal timing was defined as: the optimal point in time with the lowest risk of recurrent biliary events and the lowest risk of complications of cholecystectomy. The secondary endpoint of the study was the assessment of the effect of ES on the occurrence of biliary events.

Definitions

Biliary events included choledocholithiasis needing endoscopic retrograde

cholangiopancreatography (ERCP), cholangitis, acute cholecystitis and recurrent acute biliary pancreatitis. Choledocholithiasis had to be identified on imaging (endoscopic) ultrasound, CT, magnetic resonance cholangiopancreatography (MRCP) or MRI, and an ERCP had to be performed. Acute cholecystitis was defined according to the 2018 Tokyo classification (Table 1).[30] Cholangitis was defined as: acute abdominal pain, serum bilirubin level greater than 40 μmol/L and/or a dilated CBD and/or choledocholithiasis on ultrasound, CT, endoscopic ultrasound or MRCP/MRI in combination with a body temperature greater than 38·5°C with chills of 39·0°C or higher regardless of chills and without an obvious other cause for fever.[31] The same criteria as for the first episode were used to determine the biliary aetiology of the recurrent pancreatitis. Between the first episode and recurrent episode, the patient should have been pain-free and the new episode should be presented with acute abdominal pain with either an amylase or lipase serum level of ≥3 times the upper limit or proven acute pancreatitis on imaging. Biliary leakage was defined according to the Amsterdam criteria.[32] When either blood transfusion, radiological and/or surgical intervention or conversion was required this was defined as bleeding. Infected necrosis was defined by either: (1) a positive culture of peripancreatic necrotic tissue obtained through fine-needle aspiration or, (2) a positive culture of peripancreatic necrotic tissue obtained from the first drainage procedure or operation, or (3) the presence of gas within collections on CT. Occurrence of infected necrosis after cholecystectomy was defined as an infection that developed within 1 month after the cholecystectomy.

Table 1 TG18 Diagnostic criteria for acute cholecystitis

Definite diagnosis: one item in A + one item in B + C
A. Local signs of inflammation: Murphys' sign or right upper quadrant mass, pain or tenderness
B. Systemic signs of inflammation: 1) fever, 2) elevated C-reactive protein, 3) elevated white blood cell count
C. Imaging findings characteristic of acute cholecystitis

Cited from Yokoe et al. 2018[30]

Statistical analysis

All analyses were performed using SPSS Statistics V.24.0 (IBM Corporation). Continuous data were reported as medians with interquartile ranges (P25–P75) when not normally distributed or as mean with standard deviation (SD (±)) when normally distributed. Categorical data are shown as frequency and percentages. Between-group differences were analysed using the Mann-Whitney U (non-normal distribution) or unpaired t-test (normal distribution) test for continuous data, and Fisher's exact test or χ^2 test for categorical data. Risk ratios

and Odds Ratios were calculated with their respective 95% Confidence Intervals. The optimal timing of cholecystectomy was determined through the calculation of risk ratios of biliary events and adverse events at the various time points that a cholecystectomy was performed. We started calculating the risk ratios from 2 weeks before the 25th percentile to 2 weeks before the median with a 2-week interval. This amounted to 4, 6, 8, 10 and 12 weeks, respectively. A two-sided $p<0.05$ was considered statistically significant. Multivariable logistic regression was performed with ES as main variable and serum bilirubin and serum ALT levels during the first 48 hours of admission as co-variables to ascertain the protective value of ES.

RESULTS

In total, 945 patients with acute pancreatitis were enrolled in the registry and pre-mentioned randomized trials, of whom 328 patients had necrotizing biliary pancreatitis with peripancreatic collections and a CTSI score >3. As shown in figure 1, 80 patients met the exclusion criteria, 37 patients died during index admission due to multiorgan failure, 8 patients underwent cholecystectomy during necrosectomy for infected pancreatic necrosis and were therefore excluded from analysis (figure 1). Baseline characteristics of the included and excluded patients are provided in online supplemental table S2. Baseline characteristics of the 248 candidates eligible for cholecystectomy are provided in table 2. Mean follow-up was 76 (±30) months.

Current practice

Of the 248 patients with necrotizing biliary pancreatitis and peripancreatic collections, 191 (77%) patients underwent cholecystectomy. Cholecystectomy was performed at a median of 103 days (P25–P75: 46–222) after discharge. In 57 (23%) patients, no cholecystectomy was performed during initial admission or follow-up. Patients who had no cholecystectomy were older ($p<0.01$), had a higher American Society of Anesthesiologists grade ($p=0.01$), higher Acute Physiology And Chronic Health Evaluation-II (APACHE-II) scores at admission ($p<0.01$) and more often infected necrosis ($p=0.01$). Overall mortality was 13%, 3 (1%) patients died from the (ongoing) necrotizing pancreatitis. Baseline characteristics of patients with and without cholecystectomy and with reasons for omitting cholecystectomy are presented in online supplemental tables S3, S4.

Follow-up abdominal imaging to assess the development of peripancreatic collections prior to cholecystectomy was not performed in all patients. In 42% of the 191 patients who underwent cholecystectomy, no imaging was performed,

despite the fact that in 69% of these patients collections were present during index admission. In 59 (31%) patients, abdominal imaging was performed within 14 days before cholecystectomy, with persistent peripancreatic collections in 28 (15%) patients. Of these patients, infection of peripancreatic collections occurred in 4 (14%).

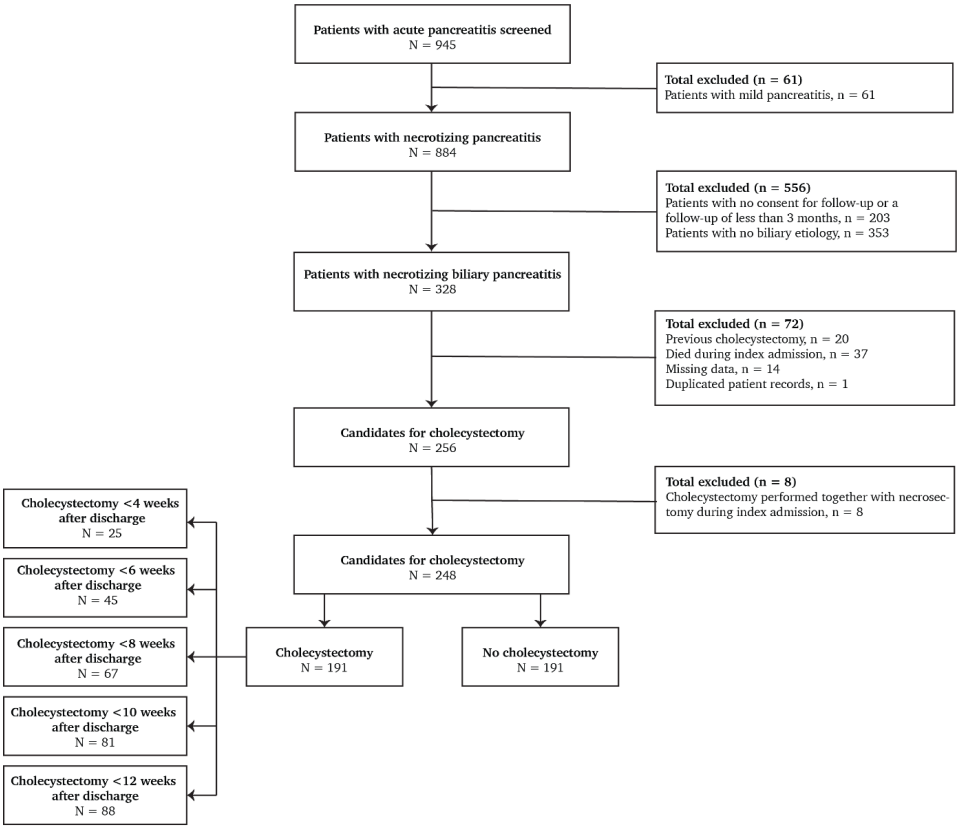

Figure 1 Inclusion flowchart

Association between the timing of cholecystectomy and recurrent biliary events

During admission for acute pancreatitis, 19 (8%) patients were diagnosed with cholecystitis and 9 (4%) patients with cholangitis. A total of 57 of 248 (23%) patients had a biliary event after their initial episode of acute pancreatitis, of whom 56 were readmitted. Recurrent biliary pancreatitis occurred in 21 (9%) patients, cholangitis in 13 (5%), cholecystitis in 18 (7%) patients and 28 (11%) patients underwent an ERCP for choledocholithiasis. There was no significant

difference in the occurrence of recurrent pancreatitis between patients with pancreatic necrosis or peripancreatic necrosis alone (12 (9%) vs 9 (8%); p=0.82), also no significant difference was found between patients with <50% pancreatic necrosis or ≥50% pancreatic necrosis (10 (10%) vs 3 (18%); p=0.40). The median time between discharge and first recurrent biliary event was 85 (P25–P75: 32–256) days.

The risks of a recurrent biliary event before and after cholecystectomy at 4, 6, 8, 10 and 12 weeks, respectively are summarised in Table 3. The risk of a recurrent biliary event after discharge was lower (risk ratio 0.49 (95% CI 0.27 to 0.90); p=0.02) when the cholecystectomy was performed within 10 weeks after discharge. The risk of recurrent pancreatitis before cholecystectomy was lower when cholecystectomy was performed within 8 weeks after discharge (risk ratio 0.14 (95% CI 0.02 to 0.99); p=0.02). One patient had pre-existing heart failure and died of organ failure during readmission for cholecystitis. In the group of patients who did not undergo cholecystectomy, recurrent biliary events occurred in 13 (23%) patients. Obstructive choledocholithiasis was seen in 5 (9%), cholecystitis in 3 (5%), cholangitis in 3 (5%) and recurrent pancreatitis in 6 (11%) patients. Recurrent biliary events after cholecystectomy are listed in online supplemental table S5. Baseline characteristics of patients divided over a 2-week time timing interval are presented in online supplemental table S6.

Table 2 Baseline characteristics of 248 patients with necrotizing biliary pancreatitis

	Overall, N = 248
Age (y)	60 (±15)
Women	116 (47)
BMI[a]	27 (25 – 31)
ASA grade on admission	
I	104 (42)
II	126 (51)
III	18 (7)
First episode of pancreatitis	245 (99)
History of abdominal surgery	51 (21)
Liver enzymes at admission	
Bilirubin (μmol/l)[b]	28 (17 – 50)
AST (units/l)[c]	174 (80 – 314)
ALT (units/l)[d]	199 (84 – 379)
AP (units/l)[e]	122 (91 – 172)
GGT (units/l)[e]	303 (160 – 552)
Predicted severity of pancreatitis on admission	
APACHE-II	8 (±4)
Imrie score	3 (±2)

Table 2 Continued.

	Overall, N = 248
Imaging severity	
CT severity index	6 (4 – 8)
Parenchymal necrosis	130 (52)
<30% necrosis	57 (23)
30 – 50% necrosis	37 (15)
>50% necrosis	38 (15)
Extra pancreatic necrosis only	118 (48)
ICU admission	87 (35)
Organ failure	65 (26)
Infected necrosis before cholecystectomy	109 (44)
Invasive intervention for infected necrosis	108 (44)
Length of initial hospital stay in days	23 (13 – 68)
Follow-up (m)	76 (±30)

Data are presented as n (%), mean (±, standard deviation), or median (interquartile range: P25-P75)
Note: data were available for all 248 patients unless differently specified: a=87, b=27, c=38, d=25, e=29
BMI, *indicates body mass index;* ASA, *American Society of Anesthesiologists;* APACHE, *Acute Physiology And Chronic Health Evaluation;* CT, *computed tomography;* AST, *aspartate aminotransferase;* ALT, *alanine aminotransferase;* AP, *alkaline phosphatase;* GGT, *gamma-glutamyl transferase;* ICU, *intensive care unit*

Timing of cholecystectomy and complications

Difficulty and complications of cholecystectomy before and after cholecystectomy at 4, 6, 8, 10 and 12 weeks, respectively, in 191 patients with necrotizing biliary pancreatitis are shown in Table 4. In total, 22 out of 166 (13%) of the laparoscopic cholecystectomies were converted to an open procedure and 25 (13%) primary open cholecystectomies were performed. A subtotal cholecystectomy was performed in 8(4%) patients. Complications of cholecystectomy (including infected necrosis) occurred in 22 (12%) patients, of whom 6 (3%) had an intraoperative and/or postoperative bleeding and 7 (4%) had a bile duct injury (type A, 5 patients; type B, 2 patients). Infected necrosis within 31 days after laparoscopic cholecystectomy occurred in four (2%) patients, in one patient laparoscopic procedure was converted to an open cholecystectomy. The risk of complications of cholecystectomy (including infected necrosis) did not decrease significantly over time. There was no significant difference in the occurrence of adverse events (with and without infected necrosis) between the patients with pancreatic necrosis and peripancreatic necrosis alone (15 (12%) vs 11 (9%); p=0.68 and 8 (6%) vs 6 (5%); p=0.79, respectively).

Table 3 Recurrent biliary events before cholecystectomy in 248 patients with necrotizing biliary with cholecystectomy at 4, 6, 8, 10, and 12 weeks after discharge, respectively

	<4 weeks N = 25	**>4 weeks N = 223**	**<6 weeks N = 45**	**>6 weeks N = 203**	**<8 weeks N = 67**	**>8 weeks N = 181**	**<10 weeks N = 81**	**>10 weeks N = 167**	**<12 weeks N = 88**	**>12 weeks N = 160**
Overall biliary events	2 (8)	55 (25)	8 (18)	49 (24)	10 (15)	47 (26)	11 (14)	46 (28)	11 (13)	46 (29)
	RR 0.32 (0.08 – 1.25) $p = 0.08$		RR 0.74 (0.38 – 1.45) $p = 0.44$		RR 0.58 (0.31 – 1.07) $p = 0.09$		**RR 0.49 (0.27 – 0.90) $p = 0.02$**		**RR 0.44 (0.24 – 0.80) $p < 0.01$**	
Choledocholithiasis	-	28 (13)	4 (9)	24 (12)	6 (9)	22 (12)	6 (7)	22 (13)	6 (7)	22 (14)
	$p = 0.09$		RR 0.75 (0.27 – 2.06) $p = 0.80$		RR 0.74 (0.31 – 1.74) $p = 0.65$		RR 0.56 (0.24 – 1.33) $p = 0.21$		RR 0.50 (0.21 – 1.18) $p = 0.14$	
Cholecystitis	2 (8)	16 (7)	4 (9)	14 (7)	4 (6)	14 (8)	5 (6)	13 (8)	5 (6)	13 (8)
	RR 1.12 (0.27 – 4.57) $p = 0.700$		RR 1.29 (0.45 – 3.73) $p = 0.75$		RR 0.77 (0.26 – 2.26) $p = 0.79$		RR 0.79 (0.29 – 2.15) $p = 0.78$		RR 0.70 (0.26 – 1.90) $p = 0.61$	
Cholangitis	-	13 (6)	1 (2)	12 (6)	1 (2)	12 (7)	1 (1)	12 (7)	1 (1)	12 (8)
	$p = 0.37$		RR 0.38 (0.05 – 2.82) $p = 0.47$		RR 0.23 (0.03 – 1.70) $p = 0.20$		RR 0.17 (0.02 – 1.30) $p = 0.07$		**RR 0.15 (0.02 – 1.15) $p = 0.04$**	
Recurrent pancreatitis	-	21 (10)	1 (2)	20 (10)	1 (2)	20 (11)	1 (1)	20 (12)	1 (1)	20 (13)
	$p = 0.14$		RR 0.23 (0.03 – 1.64) $p = 0.14$		**RR 0.14 (0.02 – 0.99) $p = 0.02$**		**RR 0.10 (0.01 – 0.76) $p < 0.01$**		**RR 0.09 (0.01 – 0.67) $p < 0.01$**	
Readmission for biliary event	2 (8)	54 (24)	9 (20)	47 (23)	12 (18)	44 (24)	13 (16)	43 (26)	13 (15)	43 (27)
	RR 0.33 (0.09 – 1.27) $p = 0.08$		RR 0.86 (0.46 – 1.63) $p = 0.84$		RR 0.74 (0.42 – 1.31) $p = 0.31$		RR 0.62 (0.36 – 1.09) $p = 0.11$		**RR 0.55 (0.31 – 0.97) $p = 0.04$**	

Data are presented as n (%). Risk ratios (RR) are presented with 95% confidence interval.

Table 4 Difficulty cholecystectomy and adverse events in 191 patients after necrotizing biliary pancreatitis with cholecystectomy at 4, 6, 8, 10, and 12 weeks after discharge, respectively

	<4 weeks N = 25	>4 weeks N = 166	<6 weeks N = 45	>6 weeks N = 146	<8 weeks N = 67	>8 weeks N = 124	<10 weeks N = 81	>10 weeks N = 110	<12 weeks N = 88	>12 weeks N = 103
Overall adverse events	3 (12)	19 (11)	3 (7)	19 (13)	7 (10)	15 (12)	8 (10)	14 (13)	9 (10)	13 (13)
	RR 1.05 (0.33 – 3.29) $p = 1.00$		RR 0.51 (0.16 – 1.65) $p = 0.30$		RR 0.86 (0.37 – 2.01) $p = 0.82$		RR 0.78 (0.34 – 1.76) $p = 0.65$		RR 0.81 (0.36 – 1.81) $p = 0.66$	
Abscess or biloma	1 (4)	15 (9)	1 (2)	15 (10)	4 (6)	12 (10)	5 (6)	11 (10)	6 (7)	10 (10)
	RR 0.44 (0.06 – 3.21) $p = 0.70$		RR 0.22 (0.03 – 1.59) $p = 0.12$		RR 0.62 (0.21 – 1.84) $p = 0.43$		RR 0.62 (0.22 – 1.71) $p = 0.43$		RR 0.70 (0.27 – 1.86) $p = 0.60$	
Infected necrosis*	2 (8)	2 (1)	2 (4)	2 (1)	2 (3)	2 (2)	2 (3)	2 (2)	2 (2)	2 (2)
	RR 6.64 (0.98 – 45.04) $p = 0.08$		RR 3.24 (0.47 – 22.38) $p = 0.24$		RR 1.85 (0.27 – 12.84) $p = 0.61$		RR 1.36 (0.20 – 9.44) $p = 1.00$		RR 1.17 (0.17 – 8.14) $p = 1.00$	
Adverse events during cholecystectomy	1 (4)	13 (8)	1(2)	13 (9)	3 (5)	11 (9)	4 (5)	10 (9)	4 (5)	10 (15)
	RR 0.0.51 (0.07 – 3.74) $p = 0.70$		RR 0.25 (0.03 – 1.86) $p = 0.19$		RR 0.51 (0.15 – 1.75) $p = 0.39$		RR 0.54 (0.18 – 1.67) $p = 0.40$		RR 0.45 (0.15 – 1.44) $p = 0.27$	
Bleeding	1 (4)	5 (3)	1(2)	5 (3)	3 (4)	3 (2)	3 (4)	3 (3)	3 (3)	3 (3)
	RR 1.33 (0.16 – 10.90) $p = 0.57$		RR 0.65 (0.08 – 5.41) $p = 1.00$		RR 1.85 (0.38 – 8.92) $p = 0.43$		RR 1.36 (0.28 – 6.56) $p = 0.70$		RR 1.17 (0.24 – 5.65) $p = 1.00$	
Bile duct injury	1 (4)	6 (4)	1 (2)	6 (4)	1 (2)	6 (5)	1 (1)	6 (6)	1 (1)	6 (6)
	RR 1.11 (0.14 – 8.81) p = 1.00		RR 0.54 (0.07 – 4.37) $p = 1.00$		RR 0.31 (0.04 – 2.51) $p = 0.43$		RR 0.23 (0.03 – 1.84) $p = 0.24$		RR 0.20 (0.02 – 1.59) $p = 0.13$	
Difficulty cholecystectomy										
Adhesions[a]	18 (72)	105 (68)	27 (63)	96 (71)	40 (63)	83 (72)	48 (62)	75 (74)	51 (61)	72 (76)
	RR 1.06 (0.81 – 1.38) $p = 0.82$		RR 0.89 (0.69 – 1.15) $p = 0.35$		RR 0.87 (0.69 – 1.08) $p = 0.24$		RR 0.85 (0.69 – 1.05) $p = 0.14$		**RR 0.80 (0.65 – 0.99) $p = 0.04$**	
Gall spill[a]	12 (48)	83 (54)	27 (63)	68 (50)	35 (55)	60 (52)	43 (56)	52 (51)	48 (57)	47 (50)
	RR 0.89 (0.58 – 1.37) $p = 0.67$		RR 1.26 (0.94 – 1.67) $p = 0.16$		RR 1.05 (0.79 – 1.39) $p = 0.76$		RR 1.10 (0.83 – 1.44) $p = 0.55$		RR 1.16 (0.88 – 1.52) $p = 0.37$	

Table 4 Continued.

	<4 weeks N = 25	>4 weeks N = 166	<6 weeks N = 45	>6 weeks N = 146	<8 weeks N = 67	>8 weeks N = 124	<10 weeks N = 81	>10 weeks N = 110	<12 weeks N = 88	>12 weeks N = 103
Conversion to open[b]	3 (12)	19 (12)	4 (9)	18 (13)	6 (9)	16 (13)	8 (10)	14 (13)	8 (9)	14 (14)
	RR 1.01 (0.32 – 3.17) $p = 1.00$		RR 0.71 (0.25 – 1.99) $p = 0.60$		RR 0.69 (0.29 – 1.68) $p = 0.48$		RR 0.77 (0.34 – 1.74) $p = 0.65$		RR 0.66 (0.29 – 1.49) $p = 0.37$	
Subtotal cholecystectomy[c]	-	8 (5)	1 (2)	7 (5)	1 (2)	7 (6)	1 (1)	7 (7)	2 (2)	6 (6)
	$p = 0.60$		RR 0.46 (0.06 – 3.60) $p = 0.68$		RR 026 (0.03 – 2.06) $p = 0.26$		RR 0.19 (0.02 – 1.52) $p = 0.14$		RR 0.38 (0.08 – 1.84) $p = 0.29$	
Drain placement[d]	4 (16)	29 (19)	5 (12)	28 (20)	6 (9)	27 (23)	9 (12)	24 (23)	11 (13)	22 (22)
	RR 0.87 (0.33 – 2.25) $p = 1.00$		RR 0.58 (0.24 – 1.40) $p = 0.26$		**RR 0.41 (0.18 – 0.94) $p = 0.03$**		RR 0.51 (0.25 – 1.04) $p = 0.08$		RR 0.58 (0.30 – 1.13) $p = 0.12$	

Data are presented as n (%). Risk ratios (RR) are presented with 95% confidence interval.
*Within 31 days after cholecystectomy
Note: data were available for all 191 patients unless differently specified: a=12, b=6, c=11, d=9

Role of ES

ES was performed in 117 (47%) patients of 248 patients with necrotizing biliary pancreatitis after a median of 1 day (P25–P75: 0–21). Indication for ES is listed in online supplemental table S7. The same number of patients underwent ES in the early cholecystectomy group (<10 weeks after discharge) compared with the delayed group (>10 weeks after discharge) (34 (42%) vs 83 (50%); p=0.89). ES was performed during the index admission in 92 (79%) patients, and 70 (60%) patients had an ES within 1 day after admission. In 21 (18%) patients in whom an ES was performed, biliary events had occurred before performing ES. Baseline characteristics of patients who had ES and those who did not were comparable, except for APACHE-II score and serum bilirubin and alkaline phosphatase levels. During ERCP, gallstones were found in the CBD in 57 (48%) and sludge was seen in the CBD in 32 patients (27%). None of the patients underwent an ES as an elective procedure for the prevention of recurrent biliary events. We observed no statistical difference in the percentage of patients with CBD stones at ERCP between those with ≥50% necrosis (47 patients, 51%) and those <50% (10 patients, 59%) (p=0.21). Out of 117 patients that underwent ES, 87 also underwent cholecystectomy. The proportion of cholecystectomies was comparable between patients with and without ES: 87 of 117 (74%) versus 104 of 131 (79%), respectively. The median time to cholecystectomy was 99 days (P25–P75: 52–189) in patients who had ES and 108 days (P25–P75: 37–244) days in patients who did not undergo ES. The occurrence of recurrent biliary events did not differ between patients who had ES and those who did not (risk ratio 1.16 (95% CI 0.73 to 1.85); p=0.54; Table 5). ES had no protective value on the occurrence of biliary events overall (adjusted OR 1.44 (95% CI 0.74 to 2.83)) or on the occurrence of recurrent pancreatitis (adjusted OR 0.36 (95% CI 0.08 to 1.59)). This was independent of the timing of ES before cholecystectomy.

Table 5 Recurrent biliary events before cholecystectomy in 248 patients with necrotizing biliary pancreatitis who did or did not undergo sphincterotomy

	Endoscopic sphincterotomy		
	Yes, N = 117	**No, N = 131**	**Risk ratio (95% CI)**
Recurrent biliary event (after ES*)	28 (24%)	27 (21%)	RR 1.16 (0.73 – 1.85), p = 0.54
Obstructive choledocholithiasis	11 (9%)	11 (8%)	RR 1.12 (0.50 – 2.49), p = 0.83
Cholecystitis	11 (9%)	9 (7%)	RR 1.37 (0.59 – 3.19), p = 0.49
Cholangitis	5 (4%)	5 (4%)	RR 1.12 (0.33 – 3.77), p = 1.00
Recurrent pancreatitis	3 (3%)	8 (6%)	RR 0.42 (0.11 – 1.55), p = 0.22

Data are presented as n (%).
*After endoscopic sphincterotomy in patients who underwent sphincterotomy after admission, overall recurrent biliary events in patient who did not undergo sphincterotomy.
ES *indicates endoscopic sphincterotomy;* CI, *confidence interval*

DISCUSSION

This is the first large nationwide multicentre cohort study based on prospectively collected data on the timing of cholecystectomy in patients with necrotizing biliary pancreatitis. We found that cholecystectomy is delayed in the majority of patients with necrotizing biliary pancreatitis up to a median of a 100 days after discharge. This is in line with current guidelines, which state that cholecystectomy should be delayed at least 6 weeks or until peripancreatic collections are resolved.[8] Our study, however, also shows that in current clinical practice the presence or absence of peripancreatic collections is often not re-evaluated before cholecystectomy.

Our main findings are that the risk of biliary events, particularly recurrent pancreatitis, increases when cholecystectomy is postponed, with a turning point at 8 weeks after discharge for recurrent pancreatitis and 10 weeks for recurrent biliary events overall. The latter risk increases significantly from 19% before 10 weeks to 31% after 10 weeks after discharge. The present results show that the risk of biliary events increases beyond 8 weeks after discharge. The reason for this tipping point at 8 weeks could not be readily extracted from the study data. A possible explanation might be that patients with smaller bile stones are at particular risk for early stone migration. It also may be related to the fact that patients after having been severely ill and fed by means of (par)enteral nutrition, after discharge will resume their own diet with increased caloric density and fat content possibly provoking early gall stone migration.

To our knowledge, no prospective comparative studies have been published on the occurrence of biliary events in patients with necrotizing biliary pancreatitis, making it difficult to compare our results with the literature. In contrast, the risk of recurrent biliary events in patients with mild pancreatitis and a delayed cholecystectomy has been investigated in several prospective studies. Three studies showed that the readmission rate for biliary events before cholecystectomy was significantly higher in the group of patients who underwent delayed cholecystectomy.[18,33,34] These findings were confirmed in the multicenter randomized PONCHO trial, where same-admission cholecystectomy for mild acute biliary pancreatitis was compared with interval cholecystectomy (6 weeks after discharge). Herein, 17% of patients had recurrent biliary events in the interval group versus 5% in the same admission group.[6] Overall, these and our results confirm that delaying cholecystectomy exposes a patient to a higher risk of recurrent biliary events, both in mild and moderate to severe biliary pancreatitis, although the optimal timing differs according to disease severity.

Other major factors to take into consideration with regard to the timing of cholecystectomy are procedural complications and the risk of infection of peripancreatic necrosis.

The results of this study show that cholecystectomy after acute necrotizing pancreatitis is a challenging procedure that is often associated with complications, most importantly bleeding (3%) and bile duct injury (4%). Furthermore, surgeons often chose a primary open procedure (13%) and conversion from a laparoscopic to an open procedure occurred in 13% of cases. However, as shown in table 3, the timing of cholecystectomy did not appear to be associated with a higher risk of these complications or infected necrosis. We believe that according to the results of our study, a cholecystectomy after severe pancreatitis cannot be compared with a routine cholecystectomy. It is conceivable that (past) inflammation and peripancreatic collections lead to more adhesions, poorer visibility and demarcation of anatomical structures during cholecystectomy or even altered anatomy of the biliary duct system. It might be difficult to gain access to the hepatic hilum and a difficult dissection, especially in patients who underwent invasive treatment for infected necrosis (e.g., drainage, necrosectomy). To prepare for the latter eventualities, preoperative imaging (CT or MRI) can be performed to evaluate the biliary anatomy (combined with the evaluation of the collections). A difficult procedure should be assumed when preparing for cholecystectomy after necrotizing pancreatitis. This should be taken into account when preparing and counselling the patient for surgery, choosing the surgical team and the timing of the cholecystectomy. We believe that if a large collection is present in or near the head of the pancreas or when there is intra-abdominal involvement, this can also lead to a more difficult dissection in these patients. Furthermore, if the patient has had interventions for infected necrosis (e.g., drainage or necrosectomy), conversion to an open procedure might be preferable.

According to current guidelines, follow-up imaging in patients with biliary pancreatitis and collections appears the most appropriate in case of relevant clinical findings or when invasive treatment is anticipated, rather than routine follow-up.[35] In clinical practice, however, follow-up of peripancreatic collections is often omitted, even when cholecystectomy is planned.

Studies investigating the relation between early cholecystectomy and infected necrosis are mostly retrospective in design and sample sizes are small.[12-17] This is reflected in a 2013 Cochrane review stating that there is 'no evidence to support or refute early cholecystectomy for patients with necrotizing pancreatitis'.[7] Early cholecystectomy in acute necrotizing pancreatitis has its risks, as seen both in literature and in clinical practice. Previous studies have shown that persisting inflammation/peripancreatic collections can lead to a more difficult surgical dissection, increasing the risk of bile duct injuries and other complications. Furthermore, to prevent complications, patients need to be 'fit for surgery', which might not be the case very early after an episode of necrotizing pancreatitis. In our study, the evaluation of the pancreatic and peripancreatic collection over

time after necrotizing pancreatitis was not performed in a consistent manner, making it difficult to draw definitive conclusions. The safety of a very early cholecystectomy in light of the presence of collections and subsequent the risk of developing infected necrosis is still up for debate.

Furthermore, infected necrosis occurred in four patients, in three patients prophylactic antibiotics were administered during cholecystectomy. In one patient, information regarding antibiotic administration was not available. Given the low number of events, the added value of periprocedural antibiotics could not be evaluated. If there are no collections present, infected necrotizing pancreatitis cannot develop. Therefore, we would recommend standard follow-up imaging (4 weeks after discharge) to evaluate the presence or absence of (peri)pancreatic collections after acute biliary pancreatitis. Subsequently, cholecystectomy should be performed as early as possible when no collections are present. If there are still collections present, imaging should be repeated after 2–4 weeks until collections are resolved. For patient with persistent collections, however, the risk of waiting and the risk of performing a cholecystectomy should be weighted, taking into consideration the size and location of collections. These recommendations are summarized in the flowchart in figure 2.

Nealon and colleagues prospectively followed 151 patients with acute necrotizing biliary pancreatitis and associated collections, comparing early cholecystectomy (before resolution or established persistence of pseudocyst) with a delayed cholecystectomy (>6 weeks after admission or after resolution of pseudocysts). They found that an early cholecystectomy was associated with a higher risk of infected necrosis (16 out of 78 patients (21%) vs 3 out of 109 (3%)) and concluded that a cholecystectomy should be delayed until the collections either resolve or persist beyond 6 weeks.[16] There are substantial differences between the patients investigated in our study compared with those in the study by Nealon et al. In the latter study, patients who underwent early cholecystectomy were referred from other hospitals. This most likely caused inclusion bias, since patients in whom a successful early cholecystectomy was performed in the referring hospitals were not included in this study. Moreover, all patients were admitted to the intensive care unit indicating a group of more severely ill patients.

Another difference is that patients in the delayed group had persistent peripancreatic collections (n=53/89) and underwent open cholecystectomy combined with cystenterostomy. These low numbers of infected necrosis in their delayed group might be related to the simultaneous treatment of collections.

Contrary to previous studies, ES did not prevent recurrent biliary events. Patients in this study underwent ES only for clear indications such as retained CBD stones, there were no ERCP procedures performed solely to prevent recurrent

biliary events. Therefore, bias due to confounding by indication might have played a role in the limited effect of ES found in our study. Nevertheless, a proportion of the patients who did undergo ES, developed biliary events afterwards, which shows that ES does not abolish the risk of biliary events.

Multiple studies, including a systematic review, conclude that the incidence of recurrent pancreatitis after ES was decreased compared with the overall incidence of recurrent pancreatitis without ES. It was concluded that ES might be as effective in reducing the incidence of recurrent acute biliary pancreatitis compared with cholecystectomy, but is inferior in reducing mortality and overall morbidity. The combination of ES and cholecystectomy was deemed superior to either of the treatments alone.[36-38]

Our study has several limitations. First, it comprises a post hoc analysis although of prospectively collected data. Consecutive patients from a set time period admitted to one of the participating hospitals were included in this study, a subset of patients was included in the PANTER-trial and TENSION-trial, which included patients for invasive interventions in infected necrotizing pancreatitis.[22,39] Therefore, the prevalence of infected necrosis before cholecystectomy was relatively high in this cohort. This may have led to a larger group of more seriously ill patients. However, our results show that also in severely ill patients with necrotizing pancreatitis recurrent biliary events often occur and that performing a late cholecystectomy does not reduce the risk of adverse events. Second, timing of cholecystectomy was determined by the treating clinicians and might have been influenced by logistic constraints (eg, waiting time for the cholecystectomy) to perform early surgery leading to an underrepresentation of patients with early cholecystectomy. Third, due to low overall post-cholecystectomy infected necrosis rates, we could not compare the effect of early versus late cholecystectomy on infection rates. This would require a much larger study cohort.

CONCLUSION

There is a substantial risk of recurrent biliary events in the waiting period for cholecystectomy in patients with necrotizing biliary pancreatitis. Our results indicate that the optimal timing of cholecystectomy, in the absence of peripancreatic collections, is within 8 weeks after discharge. We did not observe a role for ES to reduce the risk of recurrent biliary events in patients with necrotizing biliary pancreatitis.

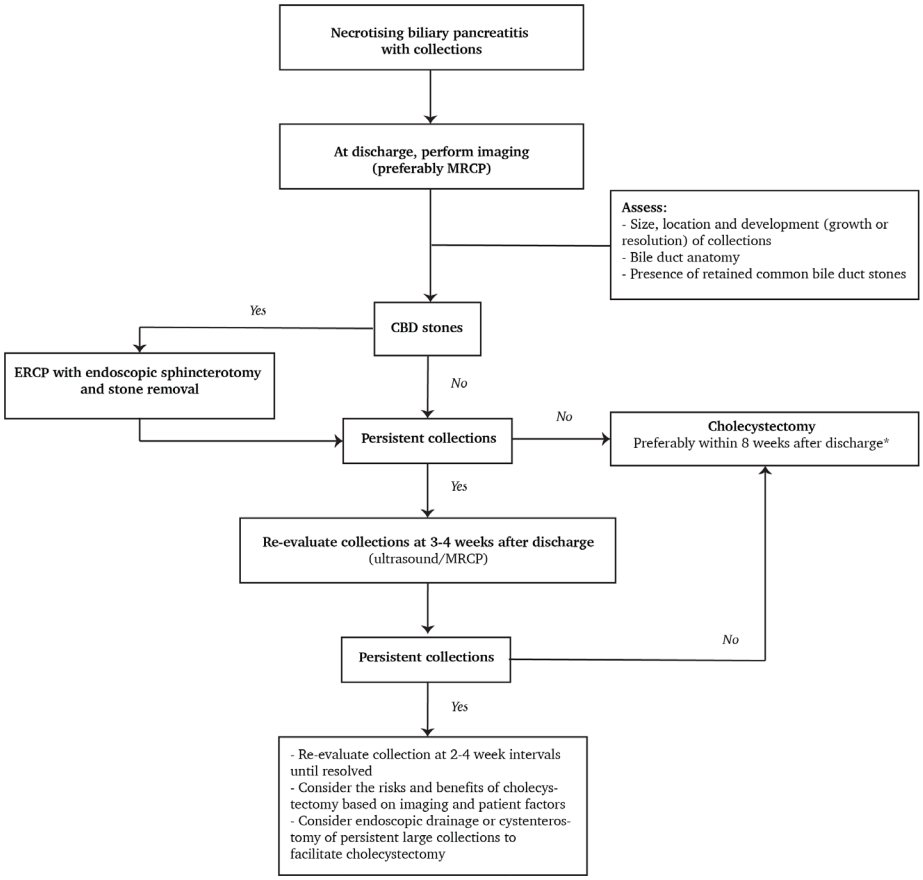

Figure 2 Flowchart on follow-up after necrotizing biliary pancreatitis and timing of cholecystectomy. CBD indicates *common bile duct*; ERCP, *endoscopicretrograde cholangiopancreatography*; MRCP, *magnetic resonance cholangiopancreatography*.

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SUPPLEMENTARY APPENDIX

Table S1 Baseline characteristics of patients who were included and excluded*

	Included, N = 248	Excluded, N = 71	*P*
Age (y)	60 (±15)	66 (±13)	<0.01
Women	116 (47)	32 (45)	0.89
BMI	27.1 (25 – 31)	27.5 (26 – 30)	0.92
ASA grade			
I	104 (42)	26 (37)	0.58
II	126 (51)	32 (45)	0.59
III	18 (7)	11 (16)	0.03
History of abdominal surgery	51 (21)	34 (48)	<0.01
Predicted severity of pancreatitis			
APACHE-II	8 (±4)	10 (7 – 15)	<0.01
Imrie score	3 (±2)	4 (±2)	<0.01
Imaging severity			
CT severity index	6 (4 – 8)	6 (4 – 10)	0.01
Parenchymal necrosis	130 (52)	40 (56)	0.14
<30% necrosis	57 (23)	5 (7)	<0.01
30 – 50% necrosis	37 (15)	15 (21)	0.07
>50% necrosis	38 (15)	20 (28)	<0.01
ICU admission	87 (35)	53 (75)	<0.01
Organ failure	65 (26)	50 (70)	<0.01
Liver enzymes at admission			
Bilirubin (μmol/l)	28 (17 – 50)	31 (19 – 55)	0.83
AST (units/l)	174 (80 – 314)	256 (±206)	0.40
ALT (units/l)	199 (84 – 379)	211 (59 – 386)	0.90
AP (units/l)	122 (91 – 172)	122 (90 – 202)	0.74
GGT (units/l)	303 (160 – 552)	288 (129 – 518)	0.62
Occurrence infected necrosis	109 (44)	42 (59)	0.01
Invasive intervention for infected necrosis	104 (42)	42 (59)	<0.01
Length of initial hospital stay in days	23 (13 – 68)	36 (16 – 85)	0.18
Follow-up (m)	76 (±30)	49 (±66)	<0.01

Data are presented as n (%), median (interquartile range: P25-P75) or mean (± standard deviation).
*Patients excluded after identifying necrotizing biliary pancreatitis (n=328); previous cholecystectomy (n=20), died during index admission (n=37), missing data (n=37).
BMI *indicates body mass index;* ASA, *American Society of Anesthesiologists;* APACHE, *Acute Physiology And Chronic Health Evaluation;* CT, *computed tomography;* AST, *aspartate aminotransferase;* ALT, *alanine aminotransferase;* AP, *alkaline phosphatase;* GGT, *gamma-glutamyl transferase;* ICU, *intensive care unit*

Table S2 Reasons for not having a cholecystectomy in 57 patients

Death shortly after index admission	22 (39)
Risk of complications deemed too high	19 (33)
Cholecystectomy was not indicated (according to the treating clinician)	11 (19)
Shrivelled gallbladder	22 (39)
Unknown	22 (39)

Data are presented as n (%).

Table S3 Baseline characteristics of 248 patients who did and did not undergo cholecystectomy

	Cholecystectomy		
	Yes, N = 191	**No, N = 57**	***P***
Age (y)	58 (48 – 67)	72 (62 – 79)	<0.01
Women	88 (46)	28 (49)	0.76
BMI[a]	26.8 (25 – 31)	27.7 (25 – 31)	0.44
ASA grade			
I	87 (46)	17 (30)	0.05
II	95 (50)	31 (54)	0.55
III	9 (5)	9 (16)	0.01
History of abdominal surgery	37 (19)	14 (25)	0.46
Predicted severity of pancreatitis			
APACHE-II	7 (4 – 10)	9 (7 – 12)	<0.01
Imrie score	2 (1 – 4)	3 (2 – 3))	0.13
Imaging severity			
CT severity index	4 (4 – 8)	6 (4 – 8)	0.09
Parenchymal necrosis	96 (50)	34 (60)	0.23
<30% necrosis	45 (24)	12 (21)	0.86
30 – 50% necrosis	27 (14)	10 (18)	0.53
>50% necrosis	25 (13)	13 (23)	0.09
ICU admission	62 (33)	25 (44)	0.12
Organfailure	50 (26)	15 (26)	1.00
Liver enzymes at admission			
Bilirubin (μmol/l)[b]	28.5 (17 – 50)	27 (17 – 50)	0.83
AST (units/l)[c]	182 (84 – 312)	163 (60 – 326)	0.80
ALT (units/l)[d]	222 (89 – 395)	175 (44 – 349)	0.17
AP (units/l)[e]	121 (87 – 172)	125 (96 – 185)	0.35
GGT (units/l)[e]	334 (176 – 568)	237 (111 – 499)	0.08
Occurrence infected necrosis	75 (39)	34 (60)	0.01
Invasive intervention for infected necrosis	73 (38)	31 (54)	0.03
Length of initial hospital stay in days	21 (13 – 58)	41 (16 – 92)	0.04
Follow-up (m)	85 (70 – 98)	77 (42 – 95)	0.02

Data are presented as n (%), median (interquartile range: P25-P75).
Note: data was available for all 248 patients unless differently specified: a=84, b=27, c=38, d=25, e=29
BMI indicates body mass index; ASA, American Society of Anesthesiologists; APACHE, Acute Physiology And Chronic Health Evaluation; CT, computed tomography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ICU, *intensive care unit*

Table S4 Recurrent biliary events* after cholecystectomy in 191 patients

Overall number of patients with recurrent biliary events	20 (11)
Choledocholithiasis	9 (5)
Cholangitis	2 (1)
Recurrent pancreatitis	22 (12)

Data are presented as n (%).
*More than one type of biliary event may occur in 1 patient.

Table S5 Baseline characteristics of 248 patients with necrotizing biliary pancreatitis over a two-week interval timing of cholecystectomy

	<4 weeks N = 25	>4 weeks N = 223	<6 weeks N = 45	>6 weeks N = 146	<8 weeks N = 67	>8 weeks N = 124	<10 weeks N = 81	>10 weeks N = 110	<12 weeks N = 88	>12 weeks N = 103
Age (y)	53 (±14)	61 (±15)	53 (±14)	61 (±14)	55 (±15)	62 (±14)	56 (±15)	62 (±14)	56 (±15)	62 (±14)
Women	10 (40)	106 (48)	24 (53)	92 (45)	37 (55)	79 (44)	45 (56)	71 (43)	48 (55)	68 (43)
BMI[a]	27 (24-29)	27 (25-31)	27 (25-32)	27 (2-31)	27 (25-31)	27 (25-31)	27 (25-31)	28 (25 – 31)	27 (25-32)	28 (25-31)
ASA grade										
I	9 (36)	95 (43)	20 (44)	84 (41)	30 (45)	74 (41)	38 (47)	66 (40)	42 (48)	62 (39)
II	15 (60)	111 (50)	23 (51)	103 (51)	34 (51)	92 (51)	40 (49)	86 (52)	43 (49)	83 (52)
III	1 (4)	17 (8)	2 (4)	16 (8)	3 (5)	15 (8)	3 (4)	15 (9)	3 (3)	15 (9)
First episode of pancreatitis	25 (100)	220 (99)	45 (100)	200 (99)	67 (100)	178 (98)	81 (100)	164 (98)	88 (100)	157 (98)
History of abdominal surgery	6 (24)	45 (20)	13 (29)	38 (19)	16 (24)	35 (19)	18 (22)	33 (20)	19 (22)	32 (20)
Liver enzymes at admission										
Bilirubin (μmol/l)[b]	26 (18-57)	28 (17 – 50)	29 (18-46)	28 (17-50)	32 (19-53)	26 (17-50)	30 (18-51)	26 (17-50)	30 (18-50)	26 (17-50)
AST (units/l)[c]	137 (49-245)	184 (82-319)	193 (63-320)	170 (82-311)	204 (84-317)	162 (76-313)	195 (95-315)	163 (74-310)	185 (84-297)	168 (75-320)
ALT (units/l)[d]	193 (106-350)	204 (81-384)	217 (95-437)	194 (74-375)	237 (132-441)	178 (70-362)	223 (95-438)	188 (63-357)	217 (95-433)	189 (71-363)
AP (units/l)[e]	132 (103-181)	121 (90-172)	132 (103-192)	119 (88-172)	132 (103-202)	115 (84-169)	129 (100-202)	119 (89-547)	127 (89-195)	119 (91-168)
GGT (units/l)[e]	352 (210-590)	295 (153-549)	307 (202-578)	303 (153-549)	362 (203-605)	286 (153-535)	336 (183-576)	292 (153-547)	319 (175-568)	297 (153-550)
Predicted severity of pancreatitis										
APACHE-II	7 (±4.5)	8 (±4)	7 (±4)	8 (±4)	7 (±4)	8 (±4)	7 (±4)	8 (±4)	7 (±4)	8 (±4)
Imrie score	2 (1-3)	3 (2-4)	2 (±1)	3 (±2)	4 (4-5)	6 (4-8)	2 (±1)	3 (±2)	2 (1-3)	6 (4-8)
Imaging severity										

Table S5 Continued.

	<4 weeks N = 25	>4 weeks N = 223	<6 weeks N = 45	>6 weeks N = 146	<8 weeks N = 67	>8 weeks N = 124	<10 weeks N = 81	>10 weeks N = 110	<12 weeks N = 88	>12 weeks N = 103
CT severity index	4 (4-6)	6 (4-8)	4 (4-6)	6 (4-8)	4 (4-5)	6 (4-8)	4 (4-4)	6 (4-8)	4 (4-5)	6 (4-8)
Parenchymal necrosis	9 (36)	121 (54)	13 (29)	117 (58)	17 (25)	113 (62)	19 (24)	111 (67)	22 (25)	108 (68)
<30% necrosis	5 (20)	52 (23)	7 (16)	50 (25)	10 (15)	47 (26)	11 (14)	46 (28)	11 (13)	46 (29)
30 – 50% necrosis	2 (8)	35 (16)	3 (7)	24 (17)	4 (6)	33 (18)	5 (6)	32 (19)	6 (7)	31 (19)
>50% necrosis	2 (8)	36 (16)	3 (7)	35 (17)	4 (6)	34 (19)	4 (5)	34 (20)	6 (7)	32 (20)
ICU admission			2 (4)	85 (42)	5 (8)	82 (45)	11 (14)	76 (46)	13 (15)	74 (46)
Organ failure	1 (4)	64 (29)	2 (4)	63 (31)	4 (6)	61 (34)	6 (7)	59 (35)	8 (9)	57 (36)
Infected necrosis before cholecystectomy	3 (12)	64 (29)	5 (11)	104 (51)	8 (12)	101 (56)	9 (11)	100 (60)	11 (13)	98 (61)
Invasive intervention for infected necrosis	2 (8)	102 (46)	4 (9)	100 (49)	7 (10%)	97 (54)	8 (10)	96 (58)	10 (11)	94 (59)
Length of initial hospital stay (d)	17 (12-23)	25 (14-75)	15 (9-22)	31 (16-80)	16 (10-23)	39 (17-88)	16 (10-23)	45 (18-93)	16 (10-23)	47 (18-93)
Follow-up (m)	92 (81-101)	82 (59-96)	90 (77-99)	82 (59-96)	90 (79-99)	80 (56-96)	90 (77-98)	80 (53-96)	91 (78-99)	80 (51-95)

Data are presented as n (%), mean (±SD), or median (interquartile range).
Note: data was available for all 248 patients unless differently specified: a=84, b=27, c=38, d=25, e=29
BMI *indicates body mass index;* ASA, *American Society of Anesthesiologists;* APACHE, *Acute Physiology And Chronic Health Evaluation;* CT, *computed tomography;* AST, *aspartate aminotransferase;* ALT, *alanine aminotransferase;* AP, *alkaline phosphatase;* GGT, *gamma-glutamyl transferase;* ICU, *intensive care unit*

Table S6 Indication for ERCP in 117 patients

Prevention progression biliary pancreatitis*	6 (5)
Prevention progression biliary pancreatitis with abnormal liver function tests	30 (26)
Prevention progression biliary pancreatitis with abnormal liver function tests and cholestasis	26 (22)
Abnormal liver function tests	3 (3)
Abnormal liver functions tests and cholestasis	4 (3)
Obstructive icterus	5 (4)
Cholangitis with abnormal liver function tests	3 (3)
Cholangitis with abnormal liver function tests and cholestasis	5 (4)
Status after pancreatitis with choledocholithiasis (no known liver function tests)	4 (3)
Status after pancreatitis, abdominal pain (colic), abnormal liver function tests	4 (3)
Prevention of recurrent biliary events	5 (4)
Unknown indication with abnormal liver function test	3 (3)
Unknown indication with abnormal liver function tests and cholestasis	5 (4)
Unknown indication with no known liver function tests	11 (9)
Other†	3 (3)

Data are presented as n (%).
*No known liver function test or no abnormal liver function test
†Evaluation of the pancreatic duct in 1 patient, rendezvous procedure in 1 patient, status after pancreatitis according to the current guidelines in 1 patient.
ERCP indicates *endoscopic retrograde cholangiopancreatography*

PART IV

SUMMARY AND FUTURE PERSPECTIVES

PART IV

CHAPTER XII

General discussion

This thesis aims to answer several important questions on diagnosis and treatment of necrotizing pancreatitis and its complications (Table 1). The following sections provide an overview of the implications of our findings, conclusions, and future perspectives for the three main topics in this thesis.

Table 1 The 11 main study questions and answers of this thesis

Chapter	Study question and answer
PART I – TREATMENT OF NECROTIZING PANCREATITIS	
II	**What is the step-up approach in the management of infected necrosis?** *Book chapter* When the patient does not improve under antibiotic therapy, pancreatic intervention should be performed according to a step-up approach: gradually 'stepping-up' from minimally invasive interventions (either percutaneous or endoscopic drainage) to invasive interventions (surgical or endoscopic necrosectomy).
III	**How is the current use of antibiotics in necrotizing pancreatitis and what is the clinical consequence?** *Multicenter observational cohort study* There is an overuse of antibiotics in necrotizing pancreatitis. Prolonged duration of antibiotics was associated with more *Enterococcus* spp as a cultured pathogen, while the presence of *Enterococcus* spp in pancreatic tissue was associated with increased organ failure and mortality.
PART II – LOCAL COMPLICATIONS OF NECROTIZING PANCREATITIS	
IV	**What is the current international clinical practice in diagnosis and treatment of disruption or disconnection of the pancreatic duct in patients with necrotizing pancreatitis?** *International expert survey and case vignette study* Consensus among expert pancreatologists regarding the optimal diagnostic and treatment approach is lacking. Agreement was reached in two important areas: 1) MRI/MRCP was the preferred diagnostic modality; and 2) endoscopic transluminal drainage was the preferred intervention for patients with infected (peri)pancreatic necrosis and pancreatic duct disruption or disconnection.
V	**What is the best diagnostic modality to diagnose disruption or disconnection of the pancreatic duct in patients with necrotizing pancreatitis?** *Systematic review* EUS, ERCP, MRCP and secretin-MRCP all appear to be accurate in diagnosing a disruption or disconnection of the pancreatic duct. 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.
VI	**What is the best treatment for disruption or disconnection of the pancreatic duct in patients with necrotizing pancreatitis?** *Systematic review and meta-analysis* The current literature lacks in quantity and quality with only one prospective cohort study available and no randomized controlled studies. The literature is therefore inconclusive about the best treatment of choice.
VII	**What is the current incidence, diagnostic and therapeutic approach and short- and long-term clinical outcome of disruption or disconnection of the pancreatic duct in patients with necrotizing pancreatitis?** *Multicenter observational cohort study* At least one of every four patients with necrotizing pancreatitis suffer from disruption or disconnection of the pancreatic duct which is associated with detrimental, short and long-term interventions and complications. Central and subtotal pancreatic necrosis and high levels of serum CRP in the first 48 hours are independent predictors for disruption or disconnection of the pancreatic duct.

Table 1 Continued.

Chapter	Study question and answer
VIII	**What is the current incidence, clinical outcome, and management of patients with perforation and fistula of the gastrointestinal tract in patients with necrotizing pancreatitis?** *Multicenter observational cohort study* Perforation or fistula of the gastrointestinal tract occurs in almost one out of six patients; it was associated with a worse clinical outcome, especially when the colon was involved. Risk factors for developing a perforation or fistula were high c-reactive protein at admission, organ failure within one week after admission and abdominal compartment syndrome. Perforation or fistula of the gastrointestinal tract were mostly treated conservatively, while those of the lower gastrointestinal tract were treated surgically.
PART III – LONG-TERM OUTCOME AND PREVENTION OF RECCURENCE AFTER ACUTE PANCREATITIS	
IX	**What is the diagnostic and therapeutic approach of pancreatic exocrine insufficiency after acute pancreatitis?** *Book chapter* Fecal elastase-1 is recommended as the first line test of pancreatic exocrine function due to its reliability, availability, and ease of use. Early diagnosis of pancreatic exocrine insufficiency leads to early and adequate treatment that may prevent complications associated with malabsorption and malnutrition. Pancreatic enzyme replacement therapy should be started and is not only to relieve maldigestion related symptoms, but mainly to achieve a normal nutritional status.
X	**What are the interventions and complications during long-term follow-up of patients with necrotizing pancreatitis?** *Multicenter observational cohort study* Acute necrotizing pancreatitis carries a substantial disease burden during long-term follow-up in terms of recurrent disease, the necessity for interventions and development of pancreatic insufficiency, also if treated conservatively during the index admission. Extensive (>50%) pancreatic parenchymal necrosis seems to be an important predictor of interventions and complications during follow-up.
XI	**Can endoscopic ultrasonography detect the true etiology in patients with idiopathic acute pancreatitis?** *Multicenter observational cohort study* This prospective multicenter study showed that EUS following a negative initial diagnostic workup identified an etiology in one-third of patients with a first episode of IAP, and thus EUS is advised in this scenario.
XII	**What is the optimal timing of cholecystectomy after necrotizing biliary pancreatitis?** *Multicenter observational cohort study* There is a substantial risk of recurrent biliary events in the waiting period for cholecystectomy in patients with necrotizing biliary pancreatitis. Our results indicate that the optimal timing of cholecystectomy, in the absence of peripancreatic collections, is within 8 weeks after discharge. We did not observe a role for endoscopic sphincterotomy to reduce the risk of recurrent biliary events in patients with necrotizing biliary pancreatitis.

PART I - TREATMENT OF NECROTIZING PANCREATITIS

Antibiotics are indicated when infected necrosis is clinically or radiologically suspected or proven in patients with necrotizing pancreatitis. When there is no improvement under antibiotic therapy, pancreatic intervention is the next appropriate step. Currently, interventions are performed according to the step-up approach, as summarized in *CHAPTER II*. The area of infected necrosis and its possible interventions remains a developing field. With both the initiation of

the endorotor[6] and developments in the surgical field (i.e., surgical transgastric necrosectomy),[7] the possibilities continue to evolve.

Nevertheless, antibiotics remain the first step in the treatment of infected necrotizing pancreatitis. It continues, however, to be difficult to distinguish between infected necrosis and systemic inflammatory response syndrome in the early stages of the disease. It was therefore unknown whether antibiotics were appropriately used in these patients and what the clinical consequence of antibiotic use was. In *CHAPTER III* we found that antibiotics were started in the majority of patients with necrotizing pancreatitis and often without proven infection. This finding was in line with previous studies,[1–4] however, those studies were small, retrospective and/or based on questionnaires rather than clinical data. Other findings were the insusceptibility to the empirically started antibiotics of the microorganisms found in patients with infected necrosis, the more frequent finding of *Enterococcus* spp when patients had a prolonged duration of antibiotics, and the association of the presence of *Enterococcus* spp in pancreatic tissue with increased organ failure and mortality. Also, in repeat pancreatic cultures, an increase in the presence of multidrug-resistant bacteria and yeast was found. These results clearly show that much work remains to be done on antibiotic management in this patient population. A clear guideline is required on the use of antibiotics and diagnostic testing (i.e., fine needle aspiration), with a potential role for empirical coverage of *Enterococcus* and yeast infections. Strict antibiotic stewardship should be implemented to reduce the over- and misuse of antibiotics. Despite being the first large multicenter cohort study on the whole spectrum of microbiology, antimicrobial therapy and its clinical impact, our results should be interpreted considering some limitations. A part of the antibiotic data was retrospectively – but carefully – collected from electronic medical records. Also, the Netherlands is a country with low antibiotic resistance, therefore data might not be completely generalizable to countries with a high antibiotic resistance.[5] However, especially for countries with high resistance, it also indicates the importance of appropriate and improved antibiotic guidelines for these patients.

FUTURE PERSPECTIVES

The findings of this part of this thesis clearly indicate directions for future research to improve the treatment of patients with necrotizing pancreatitis. First of all, if possible, we should strive to prevent the problem. However, we cannot prevent acute pancreatitis yet, but we may be able to prevent the risk of a severe disease course. Patients at risk for developing infected necrosis need to be identified. Previous research has shown that increased intestinal permeability, measured by three different urine markers, was associated with bacteremia, infected pancreatic necrosis, organ failure and mortality.[11] The composition of

the microbiome has recently been linked to inflammatory cytokine production in healthy subjects.[12] Furthermore, increasing evidence supports that the gut microbiome is the motor of sepsis, whether gut-derived or not.[13] Therefore, the gut microbiome is a promising novel target to improve diagnosis, prevention and treatment of infectious and systematic complications of acute pancreatitis. This crucial role of the gastrointestinal microbiome is currently being investigated by the Dutch Pancreatitis Study Group in the POEMA study. To reduce the risk of developing infectious complications, we should improve this gut dysbiosis. Short-chain fatty acids produced by the gut microbiota, such as butyrate, are known immunomodulators of the host response and exert local beneficial effects on the gut barrier and microbiota.[14] We hypothesize that orally administered tributyrin, a pro-drug of butyrate, might beneficially influence disease progression in acute pancreatitis and may be useful as prophylaxis.

Additionally, current guidelines regarding antibiotics should be brought to attention to decrease the overuse of antibiotics in these patients. Additional research is required to improve the guidelines regarding indication, timing, and type of antibiotic therapy in necrotizing pancreatitis. An antibiotic stewardship can contribute to this, which has demonstrated to decrease the length of hospital stay[15,16] and antimicrobial resistance.[16,17] Since microorganisms were found in half of the patients that were either partial or not susceptible to the empirically started antibiotics, the importance of early culturing of the peripancreatic collections became clear. A minimally invasive way, with little risk but a chance of false-negative results, is to perform a fine needle aspiration.[18] Furthermore, the recent published POINTER trial has shown that 39% of the patients with infected necrosis who were randomized in the postponed drainage group could be treated with antibiotics alone.[19] This demonstrates that an increased focus on optimal antibiotic therapy is needed. Therefore, based on the results in the second chapter, the PIANO trial (Precision use of Antibiotics in Infected NecrOtizing Pancreatitis) was initiated in the Netherlands. In this trial, we will evaluate the effect of implementation of a structured antibiotic stewardship on clinical outcome. Secondly, not all patients will escape a pancreatic intervention despite optimal antibiotic therapy. Although (randomized) studies on interventions in infected necrotizing pancreatitis have improved the outcome of these patients, there is still much to improve. Fortunately, the first results of an EndoRotor case-series are promising,[6] however, we will have to wait for the results of the full study to draw conclusions from this. Despite the potential benefits shown in recent studies[20,21] combined with the decrease in the duration of the procedure, the lumen apposing metal stent might not be suitable for every patient (e.g., in the presence of disruption or disconnection of the pancreatic duct). Future research and developments in the endoscopic field and instruments are needed

to facilitate the gastroenterologists and improve the outcome of endoscopic treatment in these patients. Another important development in the field of pancreatic intervention is the introduction of surgical transgastric necrosectomy. A low readmission and/or repeat intervention rate was found following transgastric necrosectomy. At 6 weeks, 91% of the patients had complete clinical resolution.[7] Future studies should be conducted to provide opportunities for a new trial, randomizing patients to either the surgical/endoscopic step-up approach or to the direct surgical transgastric necrosectomy.

PART II – LOCAL COMPLICATIONS OF NECROTIZING PANCREATITIS

Although disruption or disconnection of the pancreatic duct in necrotizing pancreatitis is increasingly being reported, the exact clinical impact of this complication remains unclear. Particularly, studies on the long-term outcomes in patients with disruption or disconnection of the pancreatic duct are lacking. Since standardized diagnostic and treatment protocols are non-existent, the current consensus among pancreatologists remains unknown. In *CHAPTER IV* we identified a lack of expert consensus regarding the optimal diagnostic and treatment approach for disruption or disconnection of the pancreatic duct. The experts reached agreement in two important areas: 1) MRI/MRCP as the preferred diagnostic modality to evaluate pancreatic duct integrity; and 2) endoscopic transluminal drainage as the preferred intervention for patients with infected (peri)pancreatic necrosis and pancreatic duct disruption or disconnection. These findings implicate that current clinical practice is based on the judgement of the treating clinician rather than evidence-based guidelines. It demonstrates a need for a standardized diagnostic and treatment protocol when a disruption or disconnection is suspected. Although this is the first survey covering this topic, it should be noted that our response rate was limited (51%) compared to previous similar expert surveys.[22,23] Also, with the current design of our study, we couldn't distinguish whether endoscopic transluminal drainage would have been the preferred choice regardless of the pancreatic duct integrity. Furthermore, it was impossible to address all different clinical scenarios in which disruption or disconnection of the pancreatic duct could present itself. That is why we only addressed the, in our opinion, most relevant clinical situations. Since surgery is considered to be the most definitive solution for disruption or disconnection of the pancreatic duct, we acknowledge that the lack of evaluation of the role of surgery – especially in persistent and treatment refractory cases – is a limitation of the study.

As illustrated by the aforementioned chapter, a standardized diagnostic approach is lacking. Therefore, we conducted a systematic review (*CHAPTER V*) on the diagnostic approach for a disruption or disconnection. Except for the varying sensitivity results for abdominal contrast-enhanced CT,[24,25] all diagnostic modalities were found to be accurate in diagnosing disruption or disconnection of the pancreatic duct (sensitivity ranging from 83-100%).[25–31] Therefore, standardized amylase measurements in drain fluid after percutaneous catheter drainage should be implemented in clinical practice. 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. This is the first study comparing the different diagnostic modalities using validated systematic review methods with only few restrictions to the inclusion criteria (i.e., language, type). These results, however, should be taken with caution due to the limited availability of studies on the accuracy of MRCP or EUS and the poor methodological quality and small sample sizes of the existing studies. Also, most studies were not adequately designed to answer our research question (e.g., no clearly defined reference standard), they were performed in selected patient cohorts and no standardized definitions for disruption or disconnection of the pancreatic duct were used, which introduced a high risk of bias. Lastly, it was impossible to compute the specificity in four of the included studies.[24,25,27,32]

As mentioned earlier, no standardized treatment for disruption or disconnection of the pancreatic duct is described in the current guidelines.[33,34] Our systematic review in *CHAPTER VI* demonstrated that the pooled success rates of the different treatment strategies were all relatively high (>80%). Since data on conservative and/or medical treatment of disruption or disconnection of the pancreatic duct are lacking, no (pooled) success rates could be calculated. Therefore, it could not be determined whether all patients needed an intervention. Surgery (i.e., distal pancreatectomy) remains the most definite solution for disruption or disconnection of the pancreatic duct. However, it is accompanied with the high risk of long-term endocrine and exocrine insufficiency.[35,36] It is doubtful whether there will still be a prominent role for surgery with the current pace of innovation in advanced endoscopy. In the absence of definite evidence-based answers, it is fair to consider a 'step-up' therapeutic approach. When the patient fails to improve under conservative therapy, a step-by-step transition can be made to more invasive treatment options. This has been proven successful in other pancreatic conditions.[37–41] This chapter presents the first systematic review including a meta-analysis on the success rates of the different treatments. Although we used a random effects model and performed sensitivity analyses, results should be interpreted with caution due to the high heterogeneity. The

included studies were of low quality: only one study described a prospective cohort, and no randomized controlled studies were found. Furthermore, only results of a single treatment were presented, and it wasn't clear if patients had undergone preceding treatments. Due to the lack of a comparator in the majority of the studies, the uncertainties about the indication and timing of the reported treatments and degree of the disruption or disconnection (i.e., partial or complete), we were unable to make a scientifically sound and valid comparison between different treatments.

In *CHAPTER VII* we showed that disruption or disconnection of the pancreatic duct occurs in at least one in every four patients with necrotizing pancreatitis, which was associated with worse short- and long-term clinical outcomes. Central and subtotal pancreatic necrosis on imaging and high serum CRP in the first 48 hours after admission were found to be independent predictors for developing disruption or disconnection of the pancreatic duct. These findings have several implications for clinical practice: a standardized diagnostic work-up early in the disease course, especially in patients with subtotal and central parenchymal necrosis, should be considered. Subsequently, adequate and timely intervention (i.e., endoscopic rather than percutaneous) can be considered for patients with disruption or disconnection of the pancreatic duct. In addition, a realistic perspective can be offered for both patients with and without disruption or disconnection of the pancreatic duct. This chapter presented the first large long-term follow-up multicenter cohort study partially based on prospective data, reflecting the current clinical practice. Relevant data, however, on the degree of the disruption or disconnection and the drain output volume were lacking. As known by now, a standardized diagnostic approach is missing, therefore we cannot rule out that the other patients did not have disruption or disconnection of the pancreatic duct, which may have resulted in an underrepresentation of the incidence. Since treatment for infected necrosis and specific treatment for disruption or disconnection of the pancreatic duct were indistinguishable from each other, we considered the first intervention for infected necrosis as also the first step of treatment for disruption or disconnection of the pancreatic duct to prevent bias.

CHAPTER VIII demonstrated that perforation or fistula of the gastrointestinal tract occur in almost one out of six patients with necrotizing pancreatitis and one in four in patients with infected necrotizing pancreatitis. The colon and duodenum were most frequently affected. Risk factors for developing a perforation or fistula were high c-reactive protein at admission, organ failure within one week after admission and abdominal compartment syndrome. Having a perforation or fistula of the gastrointestinal tract was associated with a worse clinical outcome, especially when the colon was involved. The latter location was

also more often treated surgically compared to the spontaneous closure that was seen in patients with a perforation or fistula of the upper gastrointestinal tract. This was the first large-scale observational cohort study on the entire clinical spectrum of perforation or fistula of the gastrointestinal tract. Since we are not proactively looking for this complication in current clinical practice, it is likely that we underestimated the number perforations or fistulas. This may have given an overestimate of the clinical effect. However, some of our endpoints were investigated before and similar results were found.[8–10] Furthermore, due to the wide variation in location and the lack of a standard treatment protocol, we were unable to compare different treatments. Therefore, we cannot provide evidence-based advice, however, a tailored step-up approach (gradually moving from conservative measures to minimally invasive and eventually surgical treatment) could be considered.

FUTURE PERSPECTIVES

This part clearly described the lack of a standardized diagnostic protocol. Although the presence of disruption or disconnection of the pancreatic duct was found to have a detrimental effect on the disease course of patients in retrospective studies, it has not yet been investigated in a prospective study. Therefore, an observational prospective cohort study (POLAR) was designed by the Dutch Pancreatitis Study Group to initiate a standardized diagnostic protocol to identify the accurate incidence and clinical consequences. The current literature is inconclusive about the best treatment for disruption or disconnection of the pancreatic duct. Therefore, more research on the optimal management of these patients is needed. Particularly of those with persistent drain production or with persistent sterile necrosis. Furthermore, indication, timing and long-term success of the different treatment strategies should be addressed to develop a treatment protocol.

Also, once perforation or fistula of the gastrointestinal tract are recognized early, we will be able to conduct research on the treatment of this condition. Based on our results, a step-up approach, starting with conservative measures followed by minimally invasive measurements and eventually surgical treatment in absence of clinical improvement, can be considered. To tailor and define this approach for each type of perforation or fistula of the gastrointestinal tract prospective studies are needed.

PART III – LONG-TERM OUTCOME AND PREVENTION OF RECCURENCE AFTER ACUTE PANCREATITIS

Exocrine pancreatic insufficiency occurred following acute pancreatitis, in one out of three patients.[47] As emphasized earlier, accurate follow-up on the development of exocrine insufficiency should take place. We summarized the current diagnostic and therapeutic approach to pancreatic exocrine insufficiency after acute pancreatic in *CHAPTER IX*. After review of the current literature, the fecal elastase-1 test is recommended as the first-line test. When exocrine insufficiency is diagnosed in an early stage, timely and adequate treatment may prevent complications of malabsorption and malnutrition. Dietary modifications together with pancreatic enzyme replacement therapy play a crucial role in the treatment of exocrine insufficiency by decreasing maldigestion-related symptoms and improving the nutritional status.

In *CHAPTER X* we presented the results of the largest and longest follow-up study on patients with necrotizing pancreatitis and the influence of the treatment during initial admission reported so far. We concluded that the disease burden on long-term of necrotizing pancreatitis was substantial in terms of readmissions, pancreatic insufficiency, pancreatic drainage, and surgery. Three out of four of the included patients had an event related to necrotizing pancreatitis during follow-up and a quarter of all patients had an episode of recurrent pancreatitis. Half of the patients who required endoscopic or percutaneous drainage during follow-up were treated conservatively during the initial admission. Regardless of their treatment during the initial admission, 6% of all patients required pancreatic surgery during follow-up. Parenchymal necrosis of over 50% as seen on CT during the initial admission was strongly associated with pancreatic intervention (both minimally invasive and invasive) during follow-up and development of pancreatic endocrine and exocrine insufficiency. Like any study, our study has some limitations. Subclinical endocrine insufficiency during follow-up may have been missed due to the lack of use of a laboratory test. Because the quality-of-life questionnaires were not collected at regular time intervals, judgment on alterations in quality of life and the differences between treatment groups in the years following recovery of necrotizing pancreatitis should be precluded.

In *CHAPTER XI* we described the results of the first prospective multicenter cohort study on the value of endoscopic ultrasound in patients with idiopathic pancreatitis, which was diagnosed after a strict diagnostic work-up. In one out of three patients an etiology was found on endoscopic ultrasound. When no etiology was found, the pancreatitis recurrence rate was nearly three times higher compared with patients in whom an etiology was found. Our data was limited

by the timing of the endoscopic ultrasound. The endoscopic ultrasound was performed after resolution of acute pancreatitis. Therefore, uncertainty remains on the value of endoscopic ultrasound in a different time frame, particularly when the acute pancreatitis is not resolved yet. Furthermore, the follow-up was one year, the recurrence rate of pancreatitis beyond this point remains unknown. However, since there was a low complication rate, routine use of endoscopic ultrasound in patients with idiopathic pancreatitis is recommended.

While cholecystectomy in mild biliary pancreatitis is performed in the same admission nowadays,[42] in *CHAPTER XII* we found a median time of 100 days after discharge until the cholecystectomy was performed. In this waiting period patients had a substantial risk of recurrent biliary events. This risk was higher if the cholecystectomy was performed after 10 weeks for overall biliary events and after 8 weeks for recurrent pancreatitis. Albeit being a post-hoc analysis, our study was the first prospective study on this topic. Comparing our results with literature was hard since no comparative studies have been published. We did not find an increased risk of infected necrosis in patients who underwent an early cholecystectomy. The number of patients with infected necrosis was too low to statistically compare. Despite current recommendations,[34,43] re-evaluation of the peripancreatic collections was often omitted. Therefore, we cannot say with certainty that peripancreatic collections were present in all patients at the time of the cholecystectomy. This makes it impossible to say anything about the safety of cholecystectomy in the presence of peripancreatic collections. Another important finding was, contrary to previous studies[44–46], that endoscopic sphincterotomy did not prevent recurrent biliary events. Confounding by indication might have played a role in the limited effect of endoscopic sphincterotomy. Nevertheless, biliary events following endoscopic sphincterotomy were seen in a proportion of the patients, which shows that endoscopic sphincterotomy does not abolish the risk of biliary events. Early cholecystectomy was underrepresented in our study, this might be explained by the lack of a prospective or randomized protocol regarding the timing of cholecystectomy. The timing of cholecystectomy could have been influenced by the hospitals' logistics.

FUTURE PERSPECTIVES

No etiology was found in two third of the patients with idiopathic pancreatitis. These patients are at higher risk to develop recurrent pancreatitis. Further research is needed to acquire diagnostic possibilities and subsequently lower the recurrence rate for the patients with (endoscopic ultrasound-negative) idiopathic pancreatitis. Recently, a randomized trial (PICUS-2) was initiated in the Netherlands to assess the effectiveness of laparoscopic cholecystectomy compared to conservative treatment in patients with endoscopic ultrasound-negative

idiopathic pancreatitis. In addition to patients with idiopathic pancreatitis, we also found that patients with necrotizing biliary pancreatitis have a substantial risk of developing recurrent pancreatitis and other biliary events. Based on our data, cholecystectomy should be performed within 8 weeks after discharge. Our data was, however, limited by the lack of follow-up imaging and a lower overall rate of post-cholecystectomy infected necrosis. Future prospective research should focus on the safety of cholecystectomy in the presence of peripancreatic collections. Evaluation of the peripancreatic collections during follow-up should be standardized in future research and clinical practice. A future randomized trial will have to show whether early cholecystectomy in patients with necrotizing biliary pancreatitis is safe and beneficial.

CONCLUSIVE REMARKS

This thesis presented clinical research on the less common and less known complications of acute pancreatitis. Current treatment strategies were reviewed, important discoveries were made, and most importantly new studies were proposed and initiated. These future studies are needed to keep evolving the possibilities for patients with acute pancreatitis, to reduce health-care costs, and to further improve the quality of life of patients following an episode of necrotizing pancreatitis.

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PART IV

CHAPTER XIV

Summary

Acute pancreatitis is an – initially sterile – inflammatory disorder of the pancreas, which is one of the most common gastro-intestinal diseases requiring acute hospitalization.[1,2] Approximately 20% of patients with acute pancreatitis develop necrosis of the parenchyma or extrapancreatic fat tissue.[3–7] The most feared complication in this patient group is secondary infection of the (peri)pancreatic necrosis.[8] The many studies conducted in the past 10-20 years has evolved the treatment approach of infected necrosis from an open surgical approach to a minimally invasive endoscopic and/or surgical approach.[9–14] In addition to general developments in healthcare, this has led to substantial improvements in the treatment and outcome of patients with necrotizing pancreatitis.[9–14] Although our knowledge has exponentially increased, many questions about less common complications remain.

The aim of the studies described in this thesis is to identify the extent of the remaining problems for patients with necrotizing pancreatitis that are '*off the beaten path*' and subsequently optimize the diagnostic and therapeutic approach for these patients.

PART I – TREATMENT OF NECROTIZING PANCREATITIS

Until complications occur, the initial treatment of necrotizing pancreatitis consists of supportive care. Empirical broad-spectrum antibiotics are advised when infected necrosis is suspected.[28-32] If patients fail to improve or show clinical deterioration under antibiotic therapy, intervention of the (peri) pancreatic collection is advised. After publication of the PANTER trial in 2010, the surgical step-up approach- percutaneous catheter drainage followed by minimally invasive necrosectomy - has been considered the standard approach for infected necrosis when patients do not improve under antibiotics.[4,9] Over the past years, endoscopic techniques have evolved introducing the endoscopic step-up approach (endoscopic transgastric drainage followed by endoscopic transgastric necrosectomy). When anatomically suitable, the endoscopic step-up approach has shown a shorter hospital stay and fewer pancreaticocutaneous fistulas compared to the surgical step-up approach.[11] A summary of the current surgical and endoscopic step-up approach in the management of infected necrosis was presented in *CHAPTER II*.

Although antibiotics are recommended when infected necrosis is suspected, it remains difficult to differentiate between clinical deterioration caused by systemic inflammatory response syndrome (SIRS) and clinical deterioration caused by sepsis due to infected necrosis.[15] Additionally, fine needle aspiration

of the peripancreatic collection is currently not recommended resulting in a lack of microbiological cultures at the time of antibiotic initiation making targeted antibiotic therapy difficult. Therefore, optimal antibiotic use remains challenging potentially leading to an overuse and/or misuse of antibiotics.[16–19] In *CHAPTER III* we conducted an observational, multicenter, cohort study to evaluate the current use of antibiotics and the clinical consequences of antibiotic treatment in patients with necrotizing pancreatitis. The results demonstrate an overuse of antibiotics in necrotizing pancreatitis: in 69% of the patients no infection was proven at time of antibiotic initiation. When infected necrosis was confirmed, half of the identified microorganisms were not or partially not susceptible to the empirically started antibiotics. Furthermore, a prolonged duration of antibiotics was found to be associated with more frequent findings of *Enterococcus spp* as the cultured pathogen. The presence of *Enterococcus spp* in pancreatic tissue was associated with increased organ failure and mortality. In repeat pancreatic cultures, an increase in the presence of yeast and multidrug-resistant bacteria was found.

PART II – LOCAL COMPLICATIONS OF NECROTIZING PANCREATITIS

Necrosis of the pancreatic parenchyma may lead to loss of integrity of the pancreatic duct, also known as pancreatic duct disruption or disconnection, resulting in pancreatic fluid leakage to the surrounding tissues.[22,23,24] Standardized guidelines on the diagnostic work-up and treatment are lacking. We assessed the current consensus regarding the diagnostic and therapeutic approach for disruption or disconnection of the pancreatic duct among expert pancreatologists in *CHAPTER IV*. We found that consensus among expert pancreatologists is lacking. Agreement was reached in two important areas: 1) MRI/MRCP was the preferred diagnostic modality; and 2) endoscopic transluminal drainage was the preferred intervention for patients with infected (peri)pancreatic necrosis and pancreatic duct disruption or disconnection.

While ERCP is still considered as the reference standard to diagnose a disruption or disconnection of the pancreatic duct, it is an invasive procedure which also carries a relatively high risk of complications.[25,26] A systematic review on the accuracy of the various diagnostic modalities to assess a pancreatic duct disruption and disconnection in patients with necrotizing pancreatitis was described in *CHAPTER V.* A sensitivity of 100% was demonstrated for amylase measurements in drain fluid and ERCP. The sensitivity for MRCP and for secretin-MRCP was 83%, both with a specificity of 100%. For a combined cohort of MRCP and secretin-MRCP a sensitivity of 92% was found. Abdominal contrast-enhanced

CT had the lowest sensitivity, ranging from 0 to 80%. Based on our results, 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.

The not yet standardized treatment approach of disruption or disconnection of the pancreatic duct includes conservative, medical, endoscopic, or surgical treatment. We have evaluated the different treatment options and the outcomes in a systematic review and meta-analysis presented in *CHAPTER VI*. Although the pooled success rates of these treatment strategies were all high, over >80% (except for conservative treatment, which remains unknown), the literature was lacking in quality with only one prospective cohort study available and no randomized controlled studies. Therefore, we remain inconclusive about the best treatment of choice.

Although the exact clinical impact of disruption or disconnection of the pancreatic duct remains unclear, a complicated course is likely to follow.[22-24,27-35] Both short-term and long-term consequences following a disruption or disconnection of the pancreatic duct in an unselected cohort of patients with necrotizing pancreatitis are lacking. The results of an observational cohort study on current clinical practice and on short- and long-term clinical outcomes in patients with disruption or disconnection of the pancreatic duct are summarized in *CHAPTER VII*. The results demonstrate that disruption or disconnection of the pancreatic duct occurs in at least one in every four patients with necrotizing pancreatitis (27%). Central and subtotal pancreatic necrosis on imaging and high levels of serum C-reactive protein in the first 48 hours after admission were independent predictors for disruption or disconnection of the pancreatic duct. We found disruption or disconnection of the pancreatic duct to be associated with worse short-term and long-term outcomes, such as an increased rate of new-onset intensive care unit admission, new-onset organ failure, infected necrosis, and (repeat) pancreatic interventions. During long-term follow-up, disruption or disconnection of the pancreatic duct increased the risk of (repeat) pancreatic intervention, recurrent pancreatitis, chronic pancreatitis, and endocrine pancreatic insufficiency.

Spontaneous or iatrogenic perforation or fistula of the gastrointestinal is defined as discontinuation of the gastrointestinal wall either with or without connection to another organ, which may involve the stomach, duodenum, jejunum, ileum, and colon.[20,21] A perforation or fistula of the gastrointestinal tract may have a detrimental effect on clinical outcome, data on this topic are however scarce. In *CHAPTER VIII*, the incidence, risk factors, clinical course and treatment

of perforation and fistula of the gastrointestinal tract was assessed. We found that one out of six patients with necrotizing pancreatitis will develop a perforation or fistula of the gastrointestinal tract, the duodenum and colon were most frequently affected (35% and 40%, respectively). Risk factors for developing a perforation or fistula were high c-reactive protein at admission and organ failure within one week after admission. While perforation or fistula of the upper gastrointestinal tract was found to be associated with a lower rate of persistent intensive care unit admissions and a lower rate of persistent organ failure, perforation or fistula of the lower gastrointestinal tract was associated with a higher rate of new onset organ failure. Upper gastrointestinal tract perforations or fistula were mostly treated conservatively, while perforations or fistula of the lower gastrointestinal tract were most frequently treated surgically.

PART III – LONG-TERM OUTCOME AND PREVENTION OF RECCURENCE AFTER ACUTE PANCREATITIS

In *CHAPTER IX* we focused on an often underdiagnosed and undertreated long-term complication of acute pancreatitis named pancreatic exocrine insufficiency. A summary was presented on the diagnostic and therapeutic approach to pancreatic exocrine insufficiency after acute pancreatitis.

Adequate follow-up based on the individual needs following an initial episode of necrotizing pancreatitis cannot be performed due to the lack of high quality data in an unselected cohort of patients.[41–46] In *CHAPTER X* we presented the results of a prospective long-term follow-up study describing interventions, complications, and quality of life over a follow-up period of more than ten years after discharge from the index admission. We concluded that the disease burden on long-term of necrotizing pancreatitis was substantial in terms of readmissions, pancreatic insufficiency, pancreatic drainage, and surgery. Three out of four of the included patients had an event related to necrotizing pancreatitis during follow-up and a quarter of all patients had an episode of recurrent pancreatitis. Half of the patients who required endoscopic or percutaneous drainage during follow-up were treated conservatively during the initial admission. Parenchymal necrosis of over 50% as seen on CT during the initial admission was strongly associated with pancreatic intervention (both minimally invasive and invasive) during follow-up and development of pancreatic endocrine and exocrine insufficiency.

In approximately 25% of patients no etiology is found after routine work-up, which is known as idiopathic acute pancreatitis.[36] Although endoscopic ultrasound is advised in patients with idiopathic acute pancreatitis, the evidence

is of low quality.[4] In *CHAPTER XI* we present the results of the Pancreatitis of Idiopathic origin: Clinical added value of endoscopic UltraSound (PICUS), a prospective observational, multicenter cohort study. In this study all patients with idiopathic pancreatitis underwent an endoscopic ultrasound routinely, finding an etiology in one third of the patients. The observed etiologies were mostly gallstone disease (24%), followed by chronic pancreatic (7%) and neoplasms (3%). Therefore, the routine performance of an endoscopic ultrasound in patients with idiopathic pancreatitis is advised. When no etiology was found, patients had a disproportionally high recurrence rate of 16.9%.

To prevent recurrent biliary events, such as cholangitis, recurrent acute pancreatitis, and acute cholecystitis, a cholecystectomy is recommended following biliary pancreatitis.[4,37,38] Same-admission cholecystectomy in mild biliary pancreatitis reduced recurrent biliary events and could be performed safely.[39] The optimal timing of cholecystectomy in necrotizing pancreatitis remains unknown due to the potential higher risk of complications.[40] The observational study of a prospective cohort, presented in *CHAPTER XII*, aimed to determine the optimal timing of cholecystectomy following necrotizing biliary pancreatitis. A cholecystectomy was performed in 77% of the patients at a median of 103 days after discharge. Infected necrosis following cholecystectomy occurred in four patients (2%) with persistent peripancreatic collections. Before cholecystectomy, 66 patients (27%) developed biliary events. The results demonstrate that the risk of overall recurrent biliary events prior to cholecystectomy was significantly lower if the cholecystectomy was performed before 10 weeks after discharge. The risk of recurrent pancreatitis before cholecystectomy was significantly lower if the cholecystectomy was performed before 8 weeks after discharge. The complication rate of cholecystectomy did not decrease over time. Additionally, we did not observe a role for endoscopic sphincterotomy to reduce the risk of recurrent biliary events in patients with necrotizing biliary pancreatitis.

In conclusion, this thesis focused on the less common, less known and less described complications which can occur in patients with acute pancreatitis. The extent of these complications was evaluated, risk factors were identified and the clinical impact was assessed. The insights in this thesis have resulted in the proposal and initiation of new studies. These future studies are needed to keep improving the treatment and quality of life of patients with acute pancreatitis and to help reduce the ever-increasing healthcare costs.

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PART IV

CHAPTER XV

Summary in Dutch | *Samenvatting in het Nederlands*

Acute pancreatitis is een – initieel steriele – ontsteking van het pancreas. Het is een van de meest voorkomende gastro-intestinale aandoening dat leidt tot een acute ziekenhuisopname.[1,2] Ongeveer 20% van de patiënten met acute pancreatitis ontwikkelt necrose van het pancreasparenchym of het extrapancreatische vetweefsel.[3–7] De meest gevreesde complicatie in patiënten met necrotiserende pancreatitis is secundaire infectie van de (peri)pancreatische necrose.[8] Door de vele studies die in de afgelopen 10-20 jaar zijn verricht is de behandeling van geïnfecteerde necrose geëvolueerd van een open chirurgische aanpak naar een minimaal invasieve endoscopische en/of chirurgische aanpak.[9–14] Dit heft, naast de algemene ontwikkelingen in de gezondheidszorg, geleid tot substantiële verbeteringen in de behandeling en uitkomsten van patiënten met necrotiserende pancreatitis.[9–14] Ondanks de exponentiele groei van onze kennis, vele vragen rondom minder voorkomende complicaties blijven bestaan.

Het doel van de studies beschreven in deze dissertatie is het identificeren van de omvang van de nog aanwezige problemen voor patiënten met necrotiserende pancreatitis en het vervolgens optimaliseren van de diagnostiek en behandeling van deze patiënten.

DEEL I – BEHANDELING VAN NECROTISERENDE PANCREATITIS

Totdat complicaties ontstaan bestaat de behandeling van necrotiserende pancreatitis uit maximale conservatieve ondersteuning. Empirische breedspectrum antibiotica worden geadviseerd wanneer er sprake is van een verdenking op geïnfecteerde necrose.[28-32] Indien patiënt geen verbetering laat zien of zelfs achteruitgaat ondanks antibiotische behandeling, dient te worden overgegaan tot interventie. Na de publicatie van de PANTER trial in 2010 is de chirurgische 'step-up' (stapsgewijze) behandeling – percutane drainage gevolgd, indien nodig, door minimaal invasieve necrosectomie – uitgegroeid tot de standaard behandeling van geïnfecteerde necrose indien patiënten niet verbeteren onder antibiotica.[4,9] Over de afgelopen jaren heeft er veel ontwikkeling plaats gevonden op het gebied van endoscopische technieken wat heeft geleid tot introductie van de endoscopische 'step-up' behandeling (endoscopische transgastrische drainage gevolgd door, indien nodig, endoscopische transgastrische necrosectomie). Indien anatomisch mogelijk, toont de endoscopische 'step-up' behandeling een kortere ziekenhuisopname en minder pancreas-cutane fistels vergelen met de chirurgische 'step-up' behandeling.[11] Een overzicht van de huidige chirurgisch en endoscopische 'step-up' behandeling van geïnfecteerde necrose werd gepresenteerd in *HOOFDSTUK II*.

Antibiotica dient gestart te worden bij een sterke verdenking op geïnfecteerde necrose. Het blijft echter moeilijk om te differentiëren tussen klinische achteruitgang veroorzaakt door een systemische ontstekingsreactie van het lichaam ('systemic inflammatory response syndrome') en klinische achteruitgang door sepsis ten gevolge van geïnfecteerde necrose.[15] Daarnaast wordt het verrichten van een punctie van de (peri)pancreatische collectie momenteel afgeraden, dit resulteert in een gebrek aan microbiologische informatie op het moment dat antibiotica gestart wordt wat het starten van gerichte antibiotische therapie bemoeilijkt. Hierdoor blijft optimaal inzetten van antibiotica een uitdaging wat mogelijk leidt tot overmatig en verkeerd gebruik van antibiotica.[16–19] In *HOOFDSTUK III* verrichtten we een observationele, multicenter, cohort studie om het huidige gebruik en de klinische consequenties van antibiotische behandeling te evalueren in patiënten met necrotiserende pancreatitis. De resultaten tonen een overmatig gebruik van antibiotica in patiënten met necrotiserende pancreatitis: in 69% van de patiënten was er geen infectie aangetoond op het moment dat antibiotica werden gestart. Wanneer geïnfecteerde necrose was bewezen, vonden we dat de helft van de geïdentificeerde micro-organismen deels of niet gevoelig waren voor de empirisch gestarte antibiotica. Daarnaast werd er gevonden dat langdurige antibiotica geassocieerd was met meer *Enterococcus spp* als de gekweekte pathogeen. De aanwezigheid van *Enterococcus spp* in het pancreasweefsel was geassocieerd met orgaan falen en mortaliteit. Wanneer de kweken herhaald werden werd een toename in de aanwezigheid van schimmels en multiresistente bacteriën gevonden.

DEEL II – LOKALE COMPLICATIES TEN GEVOLGE VAN NECROTISERENDE PANCREATTIS

Necrose van het pancreas parenchym leidt mogelijk tot het verlies van integriteit van de ductus pancreatitis, ook wel bekend als disruptie of disconnectie van de ductus pancreaticus. Dit resulteert in lekkage van pancreas vocht naar het omliggende weefsel.[22,23,24] Gestandaardiseerde richtlijnen met betrekking tot de diagnostiek en behandeling ontbreken. We hebben de huidige consensus onder expert pancreatologen met betrekking tot de diagnostiek en behandeling van disruptie of disconnectie van de ductus pancreaticus in kaart gebracht in *HOOFDSTUK IV*. Dit toonde aan dat er een gebrek was aan consensus onder expert pancreatologen. Er werd overeenstemming bereikt op twee belangrijke gebieden: 1) MRI/MRCP was de diagnostische modaliteit die de voorkeur had; en 2) endoscopische transluminale drainage was de geprefereerde interventie

voor patiënten met geïnfecteerde (peri)pancreatische necrose waarbij sprake was van een disruptie of disconnectie van de ductus pancreaticus.

Hoewel ERCP nog steeds wordt beschouwd als de referentiestandaard om een disruptie of disconnectie van de ductus pancreaticus te diagnosticeren, betreft het een invasieve procedure die ook een relatief hoog risico op complicaties met zich meebrengt.[25,26] In *HOOFDSTUK V* is een systematische review beschreven naar de nauwkeurigheid van de verschillende diagnostische modaliteiten om een disruptie of disconnectie van de ductus pancreaticus te diagnosticeren bij patiënten met necrotiserende pancreatitis. Een sensitiviteit van 100% werd aangetoond voor amylasemetingen in drainvocht en ERCP. De sensitiviteit voor MRCP en voor secretine-MRCP was 83%, beiden met een specificiteit van 100%. Voor een gecombineerd cohort van MRCP en secretine-MRCP werd een sensitiviteit van 92% gevonden. De laatste gevoeligheid werd gevonden voor CECT, variërend van 0 tot 80%. Op basis van onze resultaten adviseren wij amylasemetingen in drainvloeistof te standaardiseren na percutane drainage of plaatsing van een chirurgische drain. Gezien de slechte algehele visualisatie van de ductus pancreaticus middels endoscopische echografie en CT bij een aanzienlijk aantal patiënten met necrotiserende pancreatitis en de invasieve aard van ERCP, wordt MRCP of secretine-MRCP aanbevolen als eerste diagnostische modaliteit.

De nog niet gestandaardiseerde behandelingsstrategie voor disruptie of disconnectie van de ductus pancreaticus omvat conservatieve, medicamenteuze, endoscopische of chirurgische behandeling. We hebben de verschillende behandelingsopties en de resultaten geëvalueerd in een systematische review en meta-analyse, waarvan de resultaten zijn gepresenteerd in *HOOFDSTUK VI*. Hoewel de gepoolde succespercentages van deze behandelingsstrategieën allemaal hoog waren, meer dan 80% (behalve voor conservatieve behandeling, die niet te bepalen was), waren de beschikbare studies van lage kwaliteit met slechts één prospectieve cohortstudie en geen gerandomiseerde gecontroleerde studies. Daarom blijven de beste behandeling van keuze onduidelijk.

Hoewel de exacte klinische impact van disruptie of disconnectie van de ductus pancreaticus onduidelijk blijft, wordt er aangenomen dat het leidt tot een gecompliceerd beloop.[22-24,27-35] Zowel de gevolgen op korte als lange termijn na disruptie of disconnectie van de ductus pancreaticus in een niet-geselecteerd cohort patiënten met necrotiserende pancreatitis ontbreekt. De resultaten van een observationele cohortstudie over de incidentie en over de klinische uitkomsten op korte en lange termijn bij patiënten met disruptie of disconnectie van de ductus pancreaticus zijn samengevat in *HOOFDSTUK VII*. De resultaten tonen aan dat disruptie of disconnectie van de ductus pancreaticus optreedt bij ten minste één op de vier patiënten met necrotiserende pancreatitis (27%). Centrale en subtotale pancreasnecrose op beeldvorming en hoge niveaus van

serum C-reactief proteïne in de eerste 48 uur na opname waren onafhankelijke voorspellers voor disruptie of disconnectie van de ductus pancreaticus. Daarnaast vonden we dat disruptie of disconnectie van de ductus pancreaticus geassocieerd is met slechtere korte- en lange termijn uitkomsten, zoals een verhoogd aantal nieuwe opnames op de intensive care, nieuw ontstaan orgaan falen, geïnfecteerde necrose en (herhaalde) pancreas interventies. Tijdens langdurige follow-up verhoogde een disruptie of disconnectie van de ductus pancreaticus het risico op pancreasinterventies, recidiverende pancreatitis, chronische pancreatitis en endocriene pancreasinsufficiëntie.

Spontane of iatrogene perforatie of fisteling van het maagdarm kanaal (maag, duodenum, jejunum of colon) worden gedefinieerd als onderbreking van de gastro-intestinale wand met of zonder verbinding met een ander orgaan.[20,21] Een perforatie of fistel van het maagdarm kanaal heeft mogelijk een negatief effect op de klinische uitkomsten, literatuur over dit onderwerp is echter schaars. In *HOOFDSTUK VIII* hebben we gekeken naar de incidentie, risico factoren, klinisch beloop en behandeling van een perforatie of fistel van het maagdarm kanaal. We vonden dat een op de zes patiënten met necrotiserende pancreatitis een perforatie of fistel van het maagdarm kaneel ontwikkelt, het duodenum en colon waren het meest aangedaan (35% en 40%, respectievelijk). Risicofactoren voor het ontwikkelen van een peroratie of fistel van het maagdarm kanaal waren een hoog c-reactief proteïne in de eerste 48 uur na opname en orgaan falen in de eerste week na opname. Terwijl perforatie of fisteling van het bovenste gedeelte van het maagdarm kanaal geassocieerd was met een lager aantal opnames op de intensive care en minder persisterend orgaan falen, perforatie of fisteling van het onderste gedeelte van het maagdarm kanaal was geassocieerd met meer nieuw ontstaan orgaan falen. Perforatie en fisteling van het bovenste gedeelte van het maagdarm kanaal werden voornamelijk conservatief behandeld, terwijl perforatie en fisteling van het onderste gedeelte van het maagdarm kanaal voornamelijk chirurgisch werd behandeld.

DEEL III – LANGE TERMIJN UITKOMSTEN EN PREVENTIE VAN RECIDIEVEN NA ACUTE PANCREATITIS

In *HOOFDSTUK IX* hebben we ons gericht op een vaak onder gediagnosticeerde en onder behandelde lange termijn complicatie van acute pancreatitis: exocriene pancreasinsufficiëntie. Er werd een samenvatting gepresenteerd van de diagnostische en therapeutische benadering van exocriene pancreasinsufficiëntie na acute pancreatitis.

Adequate follow-up op basis van de individuele behoeften na een eerste episode van necrotiserende pancreatitis kan niet worden uitgevoerd vanwege het ontbreken van studies van hoge kwaliteit in een niet-geselecteerd cohort van patiënten.[41–46] In *HOOFDSTUK X* presenteerden we de resultaten van een prospectieve lange termijn follow-up studie waarin interventies, complicaties en kwaliteit van leven werden beschreven gedurende een follow-up periode van meer dan tien jaar na ontslag van de initiële opname. We concludeerden dat de ziektelast van necrotiserende pancreatitis op de lange termijn aanzienlijk was in termen van heropnames, pancreasinsufficiëntie, pancreasdrainage en chirurgie. Drie van de vier patiënten hadden een voorval gerelateerd aan necrotiserende pancreatitis tijdens de follow-up en een kwart van alle patiënten had een episode van recidiverende pancreatitis. De helft van de patiënten die tijdens de follow-up endoscopische of percutane drainage nodig hadden werd bij de eerste opname conservatief behandeld. Parenchym necrose van meer dan 50% tijdens de initiële opname was sterk geassocieerd met pancreasinterventies (zowel minimaal invasief als invasief) tijdens follow-up en ontwikkeling van endocriene en exocriene pancreasinsufficiëntie.

Bij ongeveer 25% van de patiënten wordt geen etiologie gevonden na routinematig diagnostisch onderzoek, we spreken dan van idiopathische acute pancreatitis.[36] Hoewel endoscopische echografie wordt geadviseerd bij patiënten met idiopathische acute pancreatitis, is de huidige literatuur waarop dit advies gebaseerd is van lage kwaliteit.[4] In *HOOFDSTUK XI* presenteerden we de resultaten van de prospectieve, observationele, multicenter cohortstudie: 'pancreatitis van idiopathische oorsprong: klinische meerwaarde van endoscopische echografie (PICUS)'. In deze studie ondergingen alle patiënten met idiopathische pancreatitis routinematig een endoscopische echografie. Hiermee werd in een derde van de patiënten alsnog een etiologie gevonden: met name biliaire (24%), chronische pancreatitis (7%) en neoplasma (3%). Gebaseerd op deze resultaten adviseren wij om routinematig een endoscopische echografie uit te voeren bij patiënten met idiopathische pancreatitis. Wanneer geen etiologie werd gevonden, hadden patiënten een onevenredig hoog recidiefpercentage van 17%.

Om recidiverende biliaire events, zoals cholangitis, recidiverende acute pancreatitis en acute cholecystitis, te voorkomen, wordt een cholecystectomie aanbevolen na biliaire pancreatitis.[4,37,38] Cholecystectomie gedurende de initiële opname verminderde recidiverende biliaire events en kon veilig worden uitgevoerd bij milde biliaire pancreatitis.[39] Vanwege het mogelijk verhoogde risico op complicaties is de optimale timing van cholecystectomie bij necrotiserende pancreatitis nog onbekend.[40] De observationele studie van een prospectief cohort, gepresenteerd in *HOOFDSTUK XII*, was gericht op het bepalen van de optimale timing van cholecystectomie na necrotiserende biliaire pancreatitis.

Bij 77% van de patiënten werd uiteindelijk een cholecystectomie uitgevoerd, dit gebeurde na een mediaan van 103 dagen na ontslag. Geïnfecteerde necrose na cholecystectomie trad op bij vier patiënten (2%) met persisterende peripancreatische collecties. Voorafgaand aan de cholecystectomie ontwikkelden 66 patiënten (27%) biliaire events. Het risico op recidiverende biliaire events voorafgaand aan cholecystectomie waren significant lager als de cholecystectomie vóór 10 weken na ontslag werd uitgevoerd. Daarnaast was het risico op recidiverende pancreatitis voorafgaand aan de cholecystectomie significant lager als de cholecystectomie vóór 8 weken na ontslag werd uitgevoerd. Het aantal perioperatieve complicaties van cholecystectomie was niet significant lager indien de cholecystectomie later werd verricht. Daarnaast vonden we geen meerwaarde voor endoscopische sfincterotomie bij patiënten met biliaire pancreatitis om het risico op recidiverende biliaire events te verminderen.

Concluderend, deze dissertatie concentreerde zich op de minder vaak voorkomende, minder bekende en minder beschreven complicaties die kunnen optreden bij patiënten met acute pancreatitis. De omvang van deze complicaties werd geëvalueerd, risicofactoren werden geïdentificeerd en de klinische impact werd beoordeeld. De inzichten in dit proefschrift hebben geresulteerd in het voorstellen en het starten van nieuwe onderzoeken. Deze toekomstige studies zijn nodig om de behandeling en kwaliteit van leven van patiënten met acute pancreatitis te blijven verbeteren en om de almaar stijgende zorgkosten te doen helpen verminderen.

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PART I

APPENDICES

List of publications
Acknowledgements | *Dankwoord*
Curriculum vitae

LIST OF PUBLICATIONS

SUBMITTED

Timmerhuis HC, Ngongoni RF, Li AY, McGuire SP, Lewellen KA, Dua MM, Chughtai K, Zyromski NJ, Visser BC. **The Potential Clinical Benefits of Direct Surgical Transgastric Pancreatic Necrosectomy for Patients with Infected Necrotizing Pancreatitis.** *Submitted.*

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CURRICULUM VITAE

Hester Christine Timmerhuis was born on May 20th, 1993 in Groningen, the Netherlands. She was raised together with one sister in Deventer and graduated from the Etty Hillesum Lyceum in Deventer in 2011.

In 2011 she started medical school at the University of Utrecht. During her medical training she joined the Dutch Pancreatitis Study Group as a research student in 2017. The Dutch Pancreatitis Study Group is a multidisciplinary research group that conducts and publishes both national and international leading research on acute and chronic pancreatitis. In addition, the Dutch Pancreatitis Study Group functions as an advisory board for complex cases of acute pancreatitis.

After obtaining her medical degree in 2018, Hester continued her research for the Dutch Pancreatitis Study Group as a PhD candidate at the Sint Antonius Hospital and the University Medical Center Utrecht under the supervision of prof. dr. H.C. van Santvoort and prof. dr. I.Q. Molenaar. Her PhD focused on the severe disease course of acute pancreatitis; necrotizing pancreatitis. During her PhD trajectory she coordinated the POEMA-study, the POLAR-study, and the National Registry for Acute Pancreatitis (PWN CORE). In addition, she has devised and carried out various studies using the PWN CORE database.

In October 2021 she continued her research endeavors at the Department of Surgery at Stanford University, Palo Alto, California as a post-doctoral research fellow.

In September 2023 she started as a resident general practitioner at Amsterdam University Medical Center.