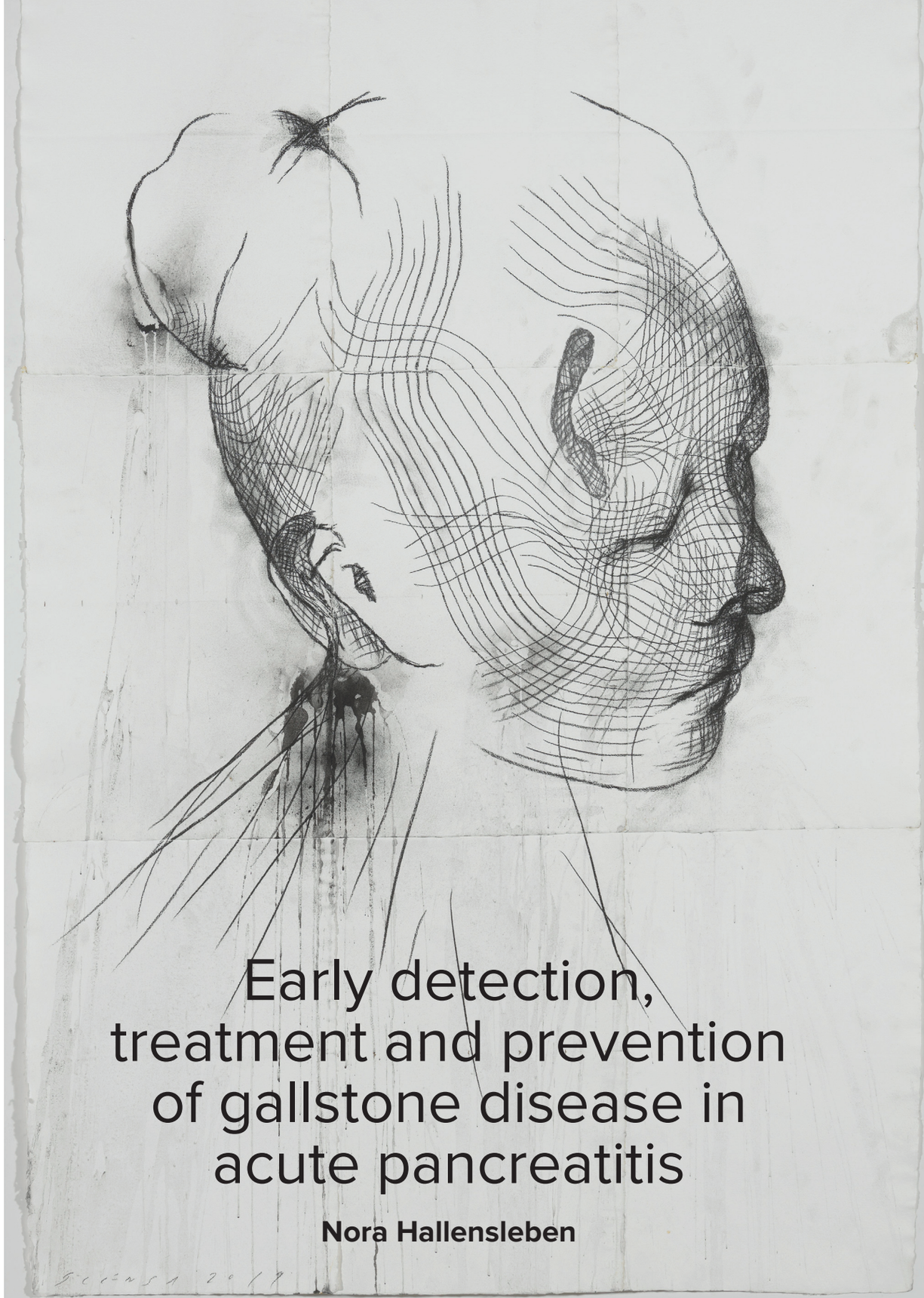

Early detection, treatment and prevention of gallstone disease in acute pancreatitis

Nora Hallensleben

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EARLY DETECTION, TREATMENT AND PREVENTION OF GALLSTONE DISEASE IN ACUTE PANCREATITIS
Thesis, Rotterdam, The Netherlands

ISBN: 978-94-6483-515-1

Paranimfen: Bart Cortjens & Alexander de Porto
Cover: Invisibles IX, Jaume Plensa, courtesy of Galerie Lelong & Co. Paris
Printed by: Ridderprint

Part of the researched described in this thesis was financially supported by the Netherland Organization for Health Research and Development (ZonMw).

Early Detection, Treatment and Prevention of Gallstone Disease in Acute Pancreatitis

Vroege detectie, behandeling en preventie van galsteenziekte bij acute pancreatitis

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. dr. A.L. Bredenoord
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden
op dinsdag 19 december 2023 om 10.30 uur

door

Nora Daphne Louise Hallensleben

geboren te ‘s-Gravenhage

Erasmus University Rotterdam

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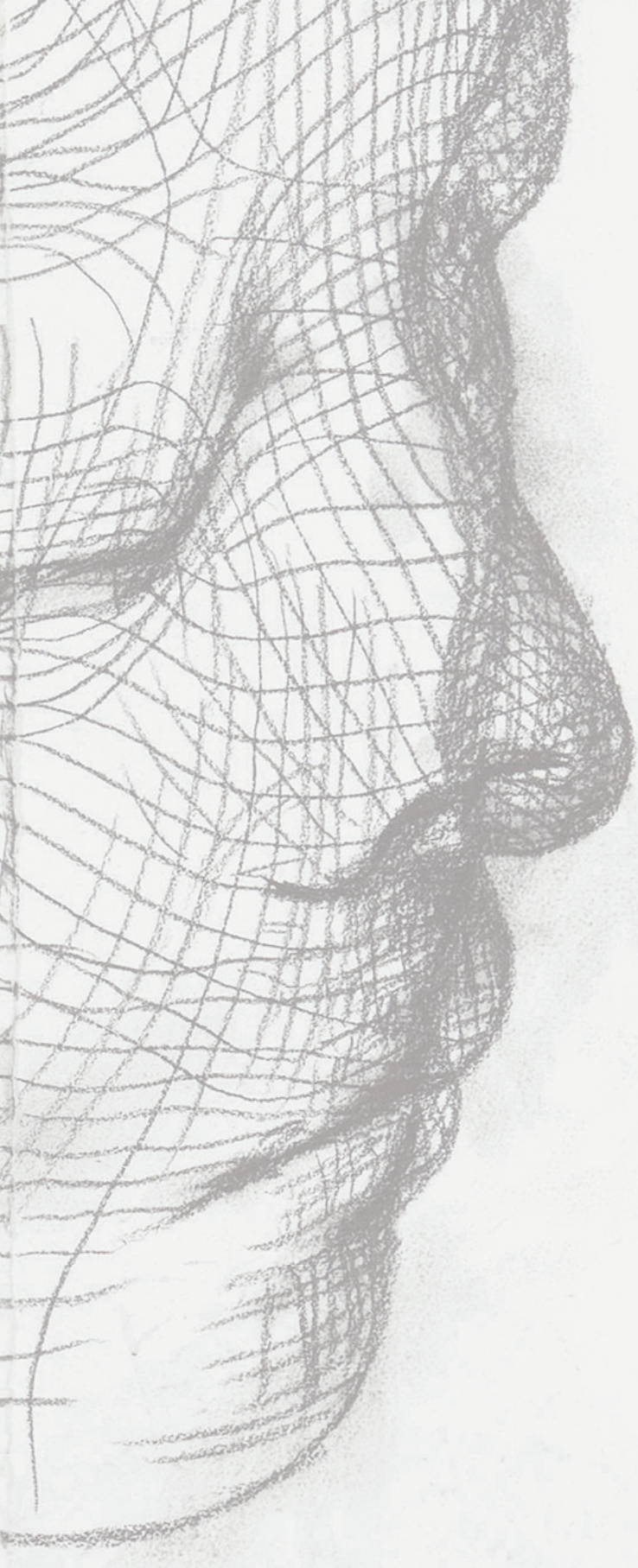

Introduction
and outline of the thesis

Acute pancreatitis

Acute pancreatitis (AP) is an inflammatory process of the pancreas. It is one of the most common gastro-intestinal causes for acute hospital admission, and over the years its incidence has been steadily rising. The overall annual number of AP admissions in the Netherlands, rose from 27.8 in 2013 to 41.2 per 100 000 person-years in 2019.[1] In other Western countries the same trend has been observed.[2] The overall mortality rate of acute pancreatitis is between 1-2% for patients with a mild disease course, but increases to around 30% in patients that develop infected necrosis.[3-5]

Based on the revised Atlanta criteria, acute pancreatitis is diagnosed when two of the following three criteria are fulfilled: 1) typical abdominal pain, 2) more than three times elevated serum amylase/lipase and 3) signs of acute pancreatitis on imaging.[6]

Severity of AP can be predicted during admission, which can be useful for the therapy, monitoring and counselling of patients. Even though the available scoring systems (e.g. Systemic Inflammatory Response criteria, APACHE-II score, modified Glasgow score or serum CRP levels) lack accuracy and are in some cases not user-friendly, guidelines do advise to use one or more of these prediction systems to predict the disease severity, in order to determine the required level of care for the AP patient.[7,8]

To date, there is no curative therapy available for AP. The care for AP patients is supportive and in the acute phase it consists of three main pillars: fluid resuscitation, pain management and nutritional support. In 2013 the International Association of Pancreatology and the American Pancreatic Association developed an evidence based guideline on all aspects of AP diagnosis and treatment.[7] Since 2013 many new trials regarding the management of acute pancreatitis have been performed. In Chapter 1, we aimed to formulate an answer to the following research question: *What new evidence on the management of acute pancreatitis has become available through randomized controlled trials since 2012?*
To answer this question we have reviewed all randomized controlled trials that were performed between 2012 and 2017 on the subject of AP and added these to the existing knowledge base that supported the IAP/APA practice guidelines, thus, making an updated guideline.

In the three parts of this thesis new research on three major topics in acute pancreatitis will be combined.

Part I - Diagnostic work-up in acute pancreatitis

In the Western world, acute pancreatitis is most frequently caused by gallstones (40-50% of cases). Alcohol use is the second most frequent cause that accounts for 20% of cases.[9,10] During the acute phase of the disease an attempt should be made to determine the etiology, as this potentially guides clinical decision-making in the acute phase and during follow-up care. Guidelines state that the minimal diagnostic work-up consists of 1) a detailed medical history including medication use, and family history, 2) laboratory testing (liver panel, triglycerides and calcium levels) and 3) a transabdominal ultrasound. If, the etiology remains unclear after this routine work-up, this is referred to as 'idiopathic acute pancreatitis' (IAP). Many causes of AP cannot be reliably identified when using the standard work-up. This potentially leads to the omission of certain treatments which are indicated based on the actual underlying etiology diagnosis. This in turn can lead to recurrent pancreatitis.

Two research questions were posed in this part of the thesis:

What is the diagnostic use and yield of additional diagnostic work-up in presumed idiopathic acute pancreatitis? (Chapter 2)

Our hypothesis was that etiological diagnoses are missed due to lack of additional diagnostic work-up such as endoscopic ultrasound or MRCP, and that the etiology of AP is therefore not adequately diagnosed in all cases. To explore this, we performed a nationwide cohort study on the diagnostic work-up of acute pancreatitis in the Netherlands and assessed the use and yield of different diagnostics in relation to the recurrence rate of IAP.

Does a pragmatic cholecystectomy reduce recurrent acute pancreatitis in IAP patients? (Chapter 3)

Our hypothesis was that, because many patients with IAP have occult biliary disease (undiagnosed), performing cholecystectomy after an episode of IAP might reduce recurrence rates. We have conducted a systematic review and meta-analysis to summarize the available evidence to explore if additional research in this area would be indicated.

Part II - Urgent ERCP in acute biliary pancreatitis

Acute biliary pancreatitis is caused by (transient) ampullary obstruction, gallstones or sludge obstructing the flow of pancreatic juice causing an inflammatory reaction of the pancreas. The duration of obstruction seems to be related to disease severity.[11] Therefore, early biliary decompression using endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) has been suggested as a treatment for acute biliary pancreatitis.

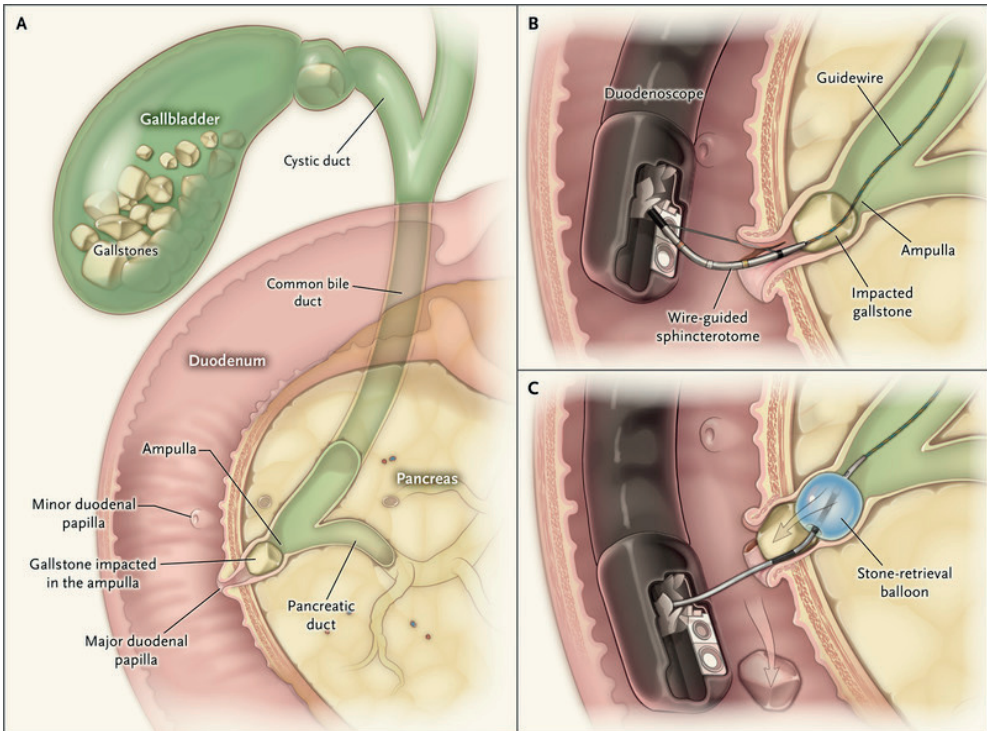

Figure 1 - ERCP is a procedure developed to diagnose and treat diseases of the pancreatobiliary system. During the procedure, a flexible endoscope is passed through the mouth, esophagus and stomach into the duodenum to reach Vaters papilla. In the papilla the pancreatic duct and common bile duct pass into the duodenum. Using contrast injection and X-ray the pancreatobiliary system is visualized. A range of instruments is available to perform treatment such as endoscopic sphincterotomy or bile duct clearance during ERCP.[12]

Multiple studies and meta-analyses that compare urgent ERCP to conservative treatment in acute biliary pancreatitis have been published.[13-16] However, data on the beneficial effect of urgent ERCP on the disease course is inconsistent. The studies are of moderate methodological quality and have several limitations. Endpoints vary between studies, the timing of ERCP is inconsistent, endoscopic sphincterotomy (ES) is not performed in all cases, both predicted mild and predicted severe patients are included and in many cases also patients with concomitant cholangitis are included.

To settle this debate and investigate the entire spectrum of urgent ERCP in acute biliary pancreatitis, three research questions were formulated for this second part of the thesis:

Does urgent ERCP with ES improve outcomes in patients with a predicted mild acute biliary pancreatitis? (Chapter 4)
We hypothesized that in patients with a low risk of complications of AP, in other words a 'predicted mild disease course of AP', urgent bile duct clearance using ERCP with ES does not improve outcomes. We conducted a post-hoc analysis of the prospective, multicenter Dutch Pancreatitis Study Group PWN-CORE cohort to analyze the effect of urgent ERCP with ES on disease severity in patients with predicted mild acute biliary pancreatitis without cholangitis.

Does urgent ERCP with ES improve the outcome in patients with a predicted severe acute biliary pancreatitis without cholangitis? (Chapter 5)
The hypothesis for this chapter was, that in patients with a predicted severe acute biliary pancreatitis the potential benefit of urgent biliary decompression outweighs the potential complication risks of ERCP with ES, and that urgent ERCP with ES will improve outcomes for these patients as compared to a conservative treatment strategy. We performed a multicenter randomized controlled trial, the APEC trial, to compare urgent ERCP with ES to a conservative treatment strategy in patients with a predicted severe acute biliary pancreatitis without cholangitis. The primary outcome was severe complications or mortality.

Does a targeted approach using EUS- guided ERCP with ES improve outcomes in patients with a predicted severe acute biliary pancreatitis? (Chapter 6)
For this final chapter we added a prospective cohort to the APEC trial as a third treatment arm, the APEC-2 study. In this cohort patients with predicted severe acute biliary pancreatitis without cholangitis were treated with an urgent endoscopic ultrasound (EUS) guided ERCP with ES. The same inclusion and exclusion criteria and the primary outcome measure of the APEC trial were used in this cohort. Patients in this cohort were compared to the patients in the conservative arm of the APEC trial. We hypothesized that a targeted approach with ERCP with ES, only in case of proven common bile duct stones or sludge, improves outcomes in predicted severe biliary pancreatitis.

Part III – Follow-up care

Follow-up of patients after AP is needed to initiate treatment of underlying etiological diagnosis to prevent recurrent pancreatitis, and to explore if complications of acute pancreatitis have occurred. After biliary pancreatitis, a cholecystectomy is advised to prevent recurrent biliary events, including recurring AP. In patients with a mild disease course, cholecystectomy needs to be performed during index admission.[17] However, in patients with a necrotising biliary pancreatitis the optimal timing of cholecystectomy is unclear. We therefore posed the following research question:

What is the optimal timing of cholecystectomy in necrotizing biliary pancreatitis? (Chapter 7)

A post-hoc analysis of a prospective cohort of patients with necrotizing acute pancreatitis was performed. We assessed the current timing of cholecystectomy and established the optimal time point for cholecystectomy taking into account both the risk of recurrent biliary events and the periprocedural risks of the cholecystectomy.

A possible complication of acute pancreatitis is loss of the exocrine function of the pancreas. Which can be transient or permanent. Only small studies are available that report on the incidence of pancreatic exocrine insufficiency (PEI) after acute pancreatitis. In the last chapter of this thesis we focused on PEI:

What is the incidence of (transient) PEI after acute pancreatitis? Are there differences in incidence between subgroups of etiologies and disease severity? (Chapter 8)

Our hypothesis is that PEI is a common complication after acute pancreatitis, especially after severe pancreatitis. We conducted a systematic review and meta-analysis focusing on incidence of PEI and we compared the data on incidence of PEI between different subgroups.

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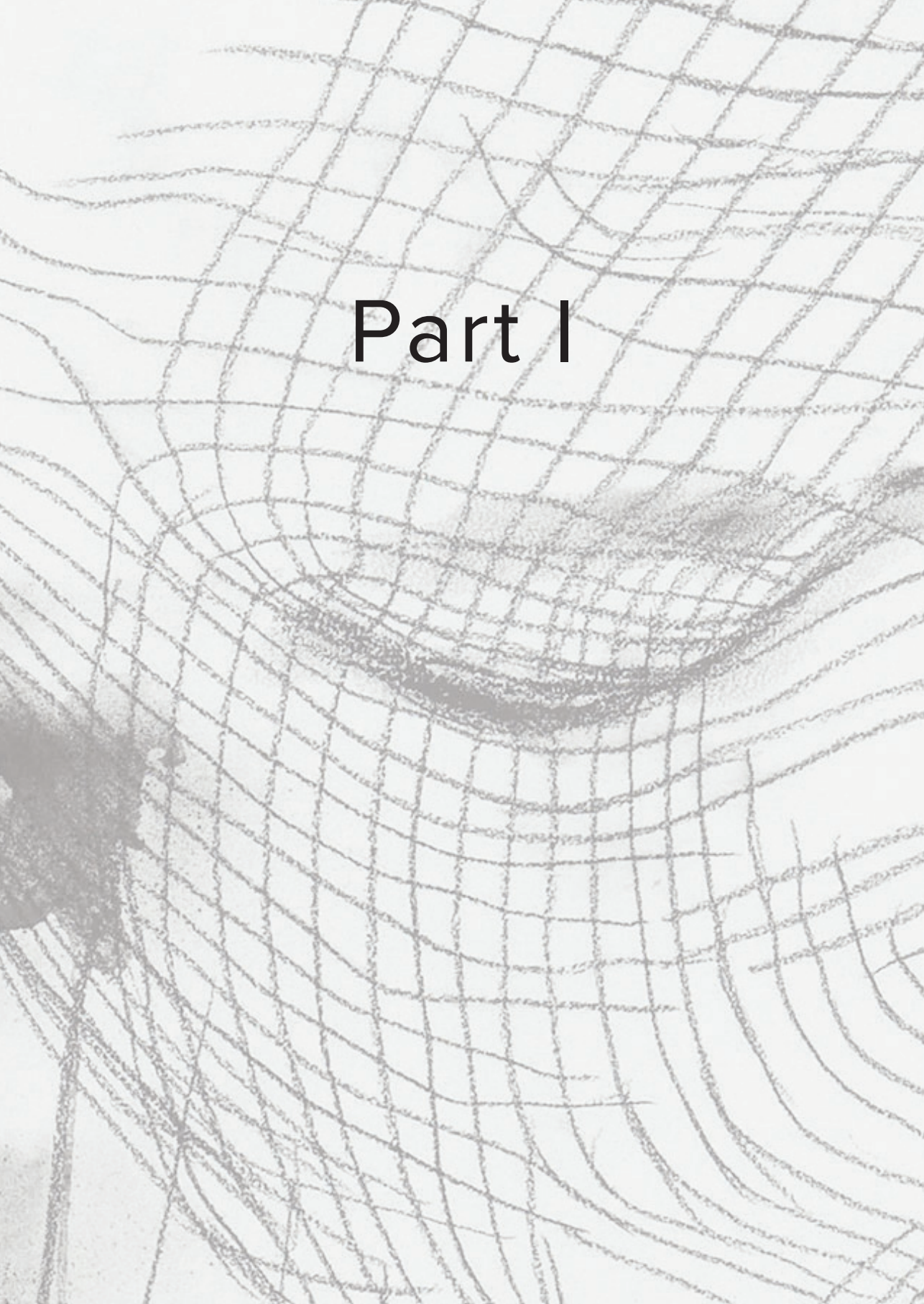


Part I

DIAGNOSTIC WORK-UP IN ACUTE PANCREATITIS

Chapter 1
Acute pancreatitis: recent advances through randomised trials
Gut, 2017

Chapter 2
The diagnostic work-up and outcomes of “presumed” idiopathic acute pancreatitis: a post-hoc analysis of a multicentre observational cohort
United European Gastroenterology Journal, 2020

Chapter 3
Recurrence of idiopathic acute pancreatitis after cholecystectomy: systematic review and meta-analysis
British Journal of Surgery, 2020

Chapter 1

Acute pancreatitis: recent advances through randomised trials

Nora D.L. Hallensleben*, Sven M. van Dijk*, Hjalmar C. van Santvoort, Paul Fockens, Harry van Goor, Marco J. Bruno, Marc G. Besselink for the Dutch Pancreatitis Study Group

* Contributed equally

Gut, 2017

Abstract

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

Significance of this study

Early phase

- Primary management of acute pancreatitis consists of (early goal-directed) fluid resuscitation with Ringer's lactate and adequate pain control
- Endoscopic retrograde cholangiography/ endoscopic sphincterotomy should be performed urgently in case of concomitant cholangitis, should not be performed in predicted mild biliary pancreatitis and is controversial in predicted severe biliary pancreatitis.
- Prophylactic use of antibiotic or probiotics is not indicated
- In patients with acute pancreatitis, regardless of severity, a normal oral diet can be started once the acute pain is resolving
- Nasoenteric tube feeding is indicated only when sufficient oral intake is not reached after 3-5 days

Beyond the early phase

- Cholecystectomy should be performed during the index admission for mild biliary pancreatitis
- Intervention for infected necrotising pancreatitis should preferably be delayed until the phase of walled-off necrosis
- The step-up approach, either endoscopic or surgical, is the preferred treatment of infected necrotising pancreatitis

Aftercare

- In (presumed) idiopathic pancreatitis, a repeat abdominal ultrasound and ultimately EUS may detect microlithiasis/sludge in up to half of patients, warranting cholecystectomy
- Alcohol abstinence support programmes can prevent recurrent alcoholic pancreatitis
- Attention should be paid to potential endocrine and exocrine insufficiency after necrotising pancreatitis

Background

With over 26 000 hospital admissions in the UK each year, acute pancreatitis is among the most common GI conditions requiring acute hospitalisation.[1] The worldwide incidence of acute pancreatitis is rising, thus further increasing its burden on healthcare services.[2] Acute pancreatitis is an inflammatory process which causes a local and systemic inflammatory response syndrome (SIRS). Although the majority of patients have a mild disease course, around 20% will develop moderate or severe pancreatitis, with necrosis of the (peri)pancreatic tissue and/or (multiple-)organ failure (figure 1).[3] Over the last decades, the treatment of acute pancreatitis has gradually developed towards a tailored, multidisciplinary approach, with a distinctive role for endoscopic, radiological and surgical treatment strategies. Much of the new evidence on the treatment of acute pancreatitis arises from randomised controlled trials (RCTs), which are universally considered as the reference standard for comparing treatment strategies in medicine. Random allocation of patients, if possible blinded, keeps all known and unknown variables constant except for the allocated treatment, thereby measuring the 'true' effect of the investigated treatment. In the past decade, numerous RCTs have had a great impact on the treatment of acute pancreatitis. This review provides an overview of current clinical practice concerning the diagnosis, classification and treatment of acute pancreatitis, while focusing on the outcomes of these RCTs.

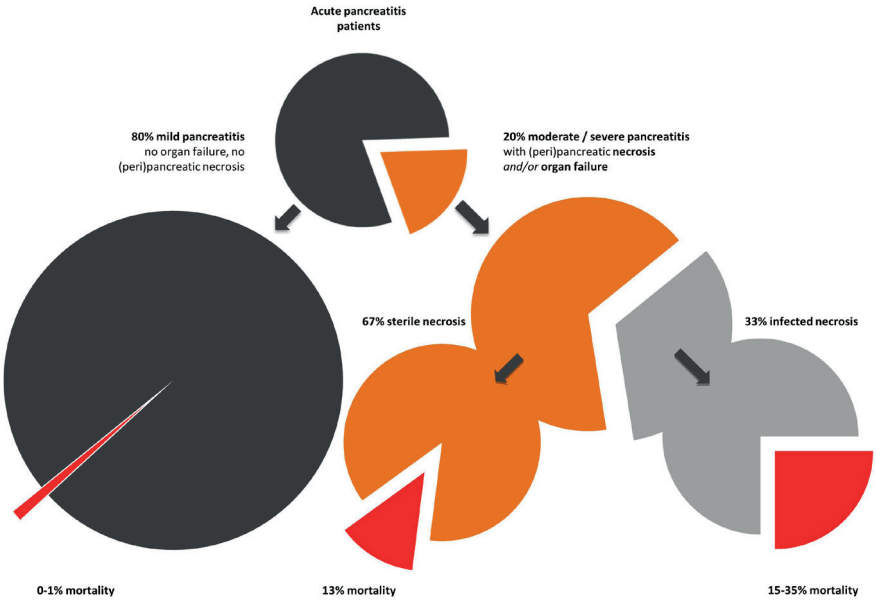


Figure 1 - Mortality rates of acute pancreatitis

Methods

For this review the most recent international evidenced-based guidelines on acute pancreatitis, the 2012 International Association of Pancreatology / American Pancreatic Association (IAP/APA) guidelines,[4] were used as the starting point. PubMed was searched for studies, specifically RCTs, published after the IAP/APA guideline using the following terms:

Pancreatitis (MeSH Terms) OR (acute pancreatitis (Title))

All articles regarding chronic pancreatitis and malignant disease were excluded. Two authors (SvD and NH) assessed all English articles concerning RCTs on adults published between June 2012 and February 2017. In total 490 articles were found of which all potential 'practice changing' RCTs were incorporated within this review. Additionally, relevant articles from the reference list of the included articles were reviewed as well as new, evidence-based guidelines on acute pancreatitis published after the IAP/APA guideline.

Early phase of acute pancreatitis

Diagnosis

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

Aetiology

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

hypertriglyceridemia, surgery and trauma. Determining the aetiology of acute pancreatitis is of importance, as it partly drives early management as well as the follow-up strategy. Standard work-up of acute pancreatitis includes medical history, physical examination, laboratory tests (liver enzymes, triglycerides, calcium) and transabdominal ultrasound. In 10-25% of cases the aetiology of the pancreatitis remains unclear. Idiopathic pancreatitis requires additional diagnostic work-up in the form of a repeat transabdominal ultrasound and ultimately an endoscopic ultrasound (EUS).[4] Meta-analyses show that in around 61% of cases an aetiology can be established by EUS. This includes the detection of microlithiasis or biliary sludge (41%),

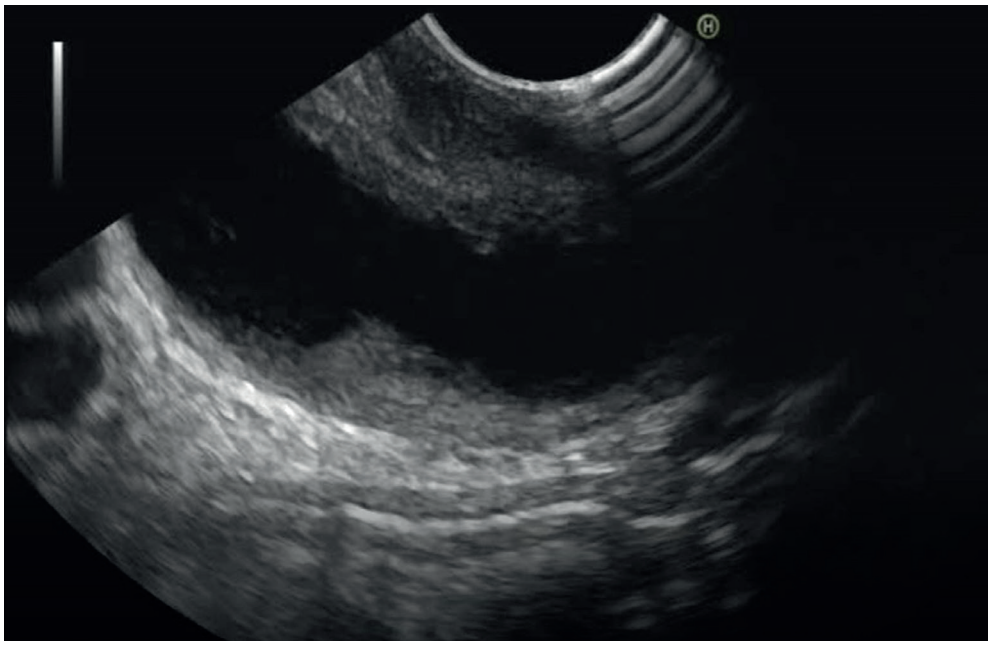


Figure 2 – Linear EUS image of sludge in gallbladder

for which cholecystectomy is required to prevent recurrences (Figure 2), but also other causes such as chronic pancreatitis or pancreatic tumours.[9]

Prediction of severity

Prediction of severity of acute pancreatitis is used to identify patients at low or high risk of developing complications. This is useful both for triaging patients for the proper level of monitoring and for stratification of patients for inclusion in RCTs. Multiple scoring systems are available that combine clinical and laboratory findings to determine the likelihood of a severe disease course: the acute physiology and chronic health evaluation II (APACHE-II), Ranson score, modified Glasgow/Imrie score, SIRS criteria, bedside index for the severity

in acute pancreatitis and harmless acute pancreatitis score, while single laboratory parameters such as C-reactive protein (CRP) can also be used.
Approximately 50% of all patients have predicted severe pancreatitis. Although only half of these will ultimately develop (moderately) severe pancreatitis, virtually none of the patients with predicted mild pancreatitis will do so. Mortality of predicted severe pancreatitis is approximately 10%, as compared to <1% in patients with predicted mild pancreatitis. The scoring systems are therefore primarily used to exclude the possibility of developing severe pancreatitis. Since the accuracy of the various predictive scoring systems is comparable,[10] the IAP/APA guideline advises to use persistent (>48 hours) SIRS because of its relative simplicity.[4]

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

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

Five RCTs using different fluid resuscitation protocols have been conducted.[12,17–20] Two of these RCTs in 76 and 115 patients with severe acute pancreatitis show that rapid, uncontrolled fluid resuscitation (10-15/ml per kg per hour or a until a haematocrit <35% within 48h) significantly worsened the rates of infections, abdominal compartment syndrome, the need for mechanical ventilation and even mortality.[17,18] One RCT in 60 patients with predicted

mild pancreatitis demonstrated that aggressive fluid hydration with Ringer's lactate (20ml/kg bolus followed by 3ml/kg/h) compared to standard hydration with Ringer's lactate (10 mL/kg bolus followed by 1,5 ml/kg/h) improved a composite endpoint (i.e. 'clinical improvement within 36h').[19] So, both too little as well as too much fluid administration in the acute phase of pancreatitis can be harmful, possibly dependent on the severity of the pancreatitis. As advised by the IAP/APA guideline, early goal directed therapy with adequate monitoring might therefore remain the preferred solution.[4]

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

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

Pain management

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

Antibiotics and probiotics as prophylaxis

One of the most lethal complications of acute pancreatitis is secondary infection of pancreatic or peripancreatic necrosis.[31] This is thought to occur as a result of bacterial translocation from the gut.[32] Several double-blind RCTs failed to show a reduction of infection of (peri)pancreatic necrosis through the prophylactic use of antibiotics,[33–35] as confirmed by meta-analyses.[36,37] Antibiotics are therefore only indicated when infection is either proven or clinically suspected. In order to prevent bacterial translocation, attempts were made to influence the intestinal microbiome using probiotic bacteria. Two RCTs compared probiotic bacteria with placebo in 62 and 45 patients with severe acute pancreatitis and reported promising results.[38,39] A subsequent multicentre RCT in 296 patients with predicted severe pancreatitis, however, showed increased rates of mortality and non-occlusive mesenteric ischemia in patients receiving probiotics.[40] Therefore, administration of probiotics is currently considered contraindicated in the treatment of (predicted) severe pancreatitis.

Nutrition

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

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

oral caloric intake after 3-5 days. It was previously believed that nasogastric feeding in acute pancreatitis would increase the risk of aspiration, and increase inflammation and pain as a result of stimulation of the pancreatic excretion. However, as 3 RCTs found nasogastric feeding non-inferior to nasojejunal feeding.[54–56] Consequently, both routes of enteral feeding are now considered feasible and safe.[57] In patients with (predicted) mild pancreatitis, 3 RCTs have shown that a normal oral diet can be resumed once the pain is decreasing.[58–60]

ERC in biliary pancreatitis

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

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

The use of routine (early) ERC with ES in predicted severe biliary disease course is controversial. Several RCTs,[61–63,65,67,68] subsequent meta-analyses and guidelines provide conflicting advice on this issue.[69] A possible explanation for these discrepancies are the differences in the definitions used for biliary

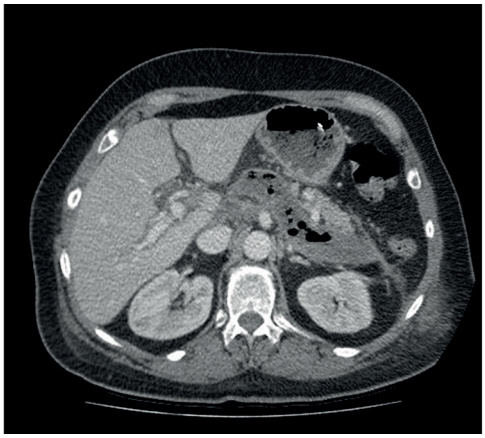
pancreatitis and cholangitis, as well as differences in patient populations and in timing and quality of the ERC. For example, in some studies ERC was performed in non-biliary pancreatitis, in other studies patients with cholangitis were randomised while these patients should always undergo ERC and sphincterotomy was not performed routinely. Recently, a multicentre RCT* comparing routine early ERC plus ES with conservative treatment in 232 patients with predicted severe acute biliary pancreatitis but without cholangitis, was completed and results are awaited (the APEC-trial, ISRCTN97372133).[70]

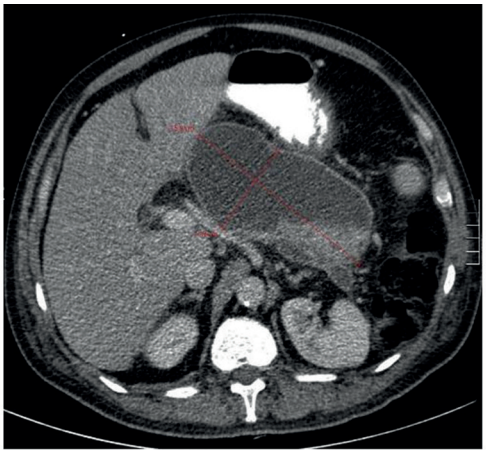
The use of EUS for the detection of CBD stones is emerging in biliary pancreatitis. The sensitivity and specificity of EUS for CBD stone detection are superior to both transabdominal ultrasound and serum markers. As ERC with ES is presumably most effective in patients with persisting CBD stones, an EUS-first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

Beyond the early phase

Imaging

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





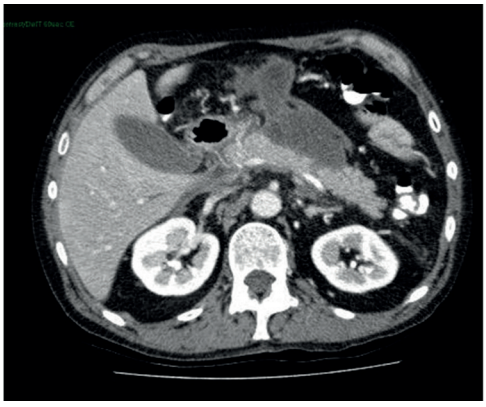


Figure 3 - Peripancreatic necrosis, a form of necrotising pancreatitis
Figure 4 - Walled-off necrosis
Figure 5 - Infected necrotic collection, with gas configurations, on day 20 after onset of disease, Not fully encapsulated

and (peri)pancreatic collections.[4,64]
The terminology of (peri)pancreatic collections has changed in the revised Atlanta classification.[5] In case of interstitial pancreatitis these collections are referred to as 'acute pancreatic fluid collections' (APFC), and in case of necrotising pancreatitis as 'acute necrotic collections' (ANC). Over time, acute collections either resolve spontaneously or mature with encapsulation of fluid and/or necrotic tissue. In ANC this leads to walled-off necrosis (WON) (Figure 4).[5,78] The process of encapsulation mostly takes around 4-6 weeks. If the necrotic collections remain sterile, patients can be treated conservatively. Intervention is only indicated in case of infection. In sterile collections interventions should only be considered in case of mechanical obstruction and/or failure to thrive which persists for 6-8 weeks.

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

If infection of a necrotic collection is proven or clinically highly suspected, antibiotic treatment is indicated. The preferred antibiotics are broad-spectrum, with the capability of penetrating the necrotic pancreatic tissue, according to local antibiotics protocol. A positive culture may be used to switch to targeted antibiotics. Although there are some series with high success rates of solely antibiotic treatment, most patients will eventually need an intervention (ie catheter drainage, necrosectomy) to treat infected necrosis (Figure 6).[82–84] Antibiotics are therefore mostly used to support patients until collections become encapsulated (WON). This is presumed to facilitate safer interventions with a lower risk of bleeding and less re-interventions. Some experts, however, question this delay in treatment and suggest immediate catheter drainage.[85] A multicentre RCT* is currently comparing immediate vs postponed drainage in 104 patients with infected necrotising pancreatitis (POINTER trial; ISCRTN33682933).

Intervention

Historically, patients with necrotising pancreatitis underwent early laparotomy to debride the necrotic tissue. This was associated with high mortality rates, probably because these often severely ill patients could not endure the extra 'hit' of the surgical trauma.[86,87] Current guidelines therefore advocate to delay interventions until the stage of WON[4,64]. In a multicentre RCT*, 88 patients with infected necrotising pancreatitis were randomised between necrosectomy via laparotomy or a step-up approach. This approach consisted of percutaneous catheter drainage followed, in case of lack of clinical improvement, by video-assisted retroperitoneal debridement (VARD).[82] The step-up approach reduced the composite endpoint (i.e. death or major complications) from 69% to 40% (risk ratio 0.57; 95% CI 0.38–0.87; p=0.006). Another finding was that 35% of patients in the step-up arm could be treated with catheter drainage only, and did not require a necrosectomy.[82]

The step-up approach is now considered the standard practice of care for patients with infected pancreatic necrosis and has been implemented in all major guidelines.[4,64] Catheter drainage is only followed by necrosectomy when clinically indicated. Several methods of surgical necrosectomy are available; either open or minimally invasive techniques. As RCTs comparing these methods 'head-to-head' are lacking, the optimal method of necrosectomy remains unclear. Retrospective studies suggest a decreased risk of complications using minimally invasive techniques.[88,89]

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

Aftercare

Prevention of recurrence

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

In patients with biliary pancreatitis, cholecystectomy will reduce the risk of recurrence but its optimal timing has been debated. In severe biliary pancreatitis it is common practice to delay cholecystectomy until the patient has recovered and local signs of inflammation have resolved or until at least 6 weeks after discharge.[102] In mild biliary pancreatitis, current guidelines recommend cholecystectomy during the same hospital admission. Several clinical audits have shown that guideline adherence is poor, cholecystectomy is often delayed.[99,103–107] Concerns about the perceived increased difficulty of surgical dissection after pancreatitis, resulting in higher surgical complication rates,[108,109] and logistical challenges with busy emergency theatre lists[104,110] have probably contributed to these delays. A recent multicentre RCT* in 266 patients with mild biliary pancreatitis demonstrated that same-admission cholecystectomy reduced the recurrence rate of gallstone-related complications from 17% to 5% as compared to interval cholecystectomy after 4 weeks (RR 0.28, 95% CI 0.12–0.66; p=0.002).[111] This included a reduction of recurrent biliary pancreatitis from 9% to 2% (RR 0.27; CI 0.08–0.92, p=0.03). Same-admission cholecystectomy was not associated with increased technical difficulty or complications and decreased overall costs.[111,112]

The value of cholecystectomy has also been investigated in acute idiopathic pancreatitis. A multicentre RCT in 85 patients showed that routine elective laparoscopic cholecystectomy reduced the rate of recurrent pancreatitis from 30% to 10% (p=0.016) as compared to conservative management. However, since routine EUS was not included in the work-up of (presumed) idiopathic pancreatitis, the treatment effect of cholecystectomy may have been

overestimated in this trial. Many patients with presumed idiopathic pancreatitis patients may in fact have had acute biliary pancreatitis. This was also reflected in the large percentage (59%) of gallbladders in which biliary stones or sludge were found at pathological examination in this RCT.[113]

Exocrine and endocrine insufficiency

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

Future

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

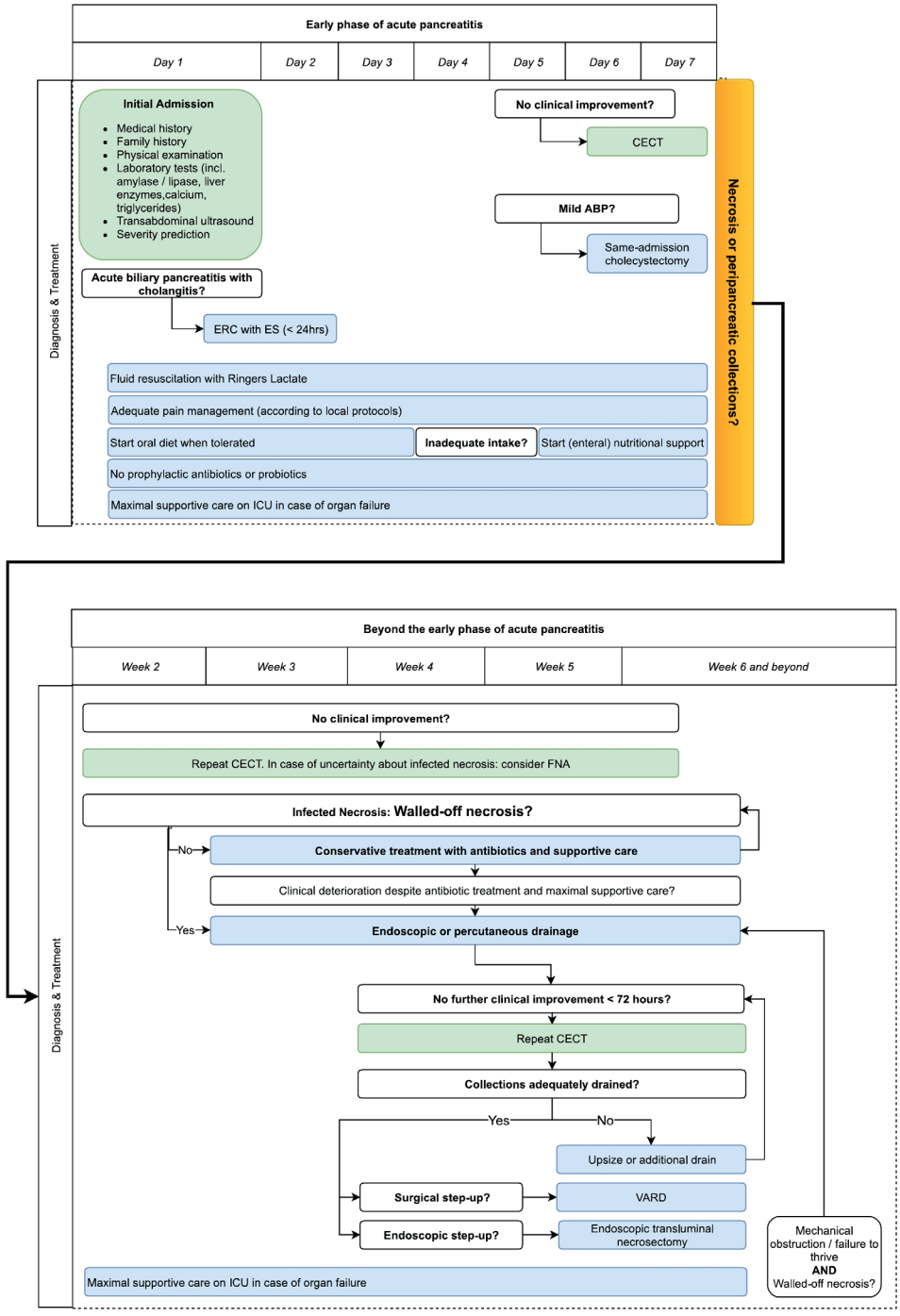


Figure 6 - Flowchart acute pancreatitis. CECT, contrast-enhanced CT; ERC, endoscopic retrograde cholangiography; ES, endoscopic sphincterotomy; VARD, video-assisted retroperitoneal debridement.

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Chapter 2

The diagnostic work-up and outcomes of “presumed” idiopathic acute pancreatitis: a post-hoc analysis of a multicentre observational cohort

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United European Gastroenterology Journal, 2020

Abstract

Introduction

After standard diagnostic work-up, the aetiology of acute pancreatitis remains unknown in 16 to 27% of cases, a condition referred to as idiopathic acute pancreatitis (IAP). Determining the aetiology of pancreatitis is essential, as it may direct treatment in the acute phase and guides interventions to prevent recurrent pancreatitis.

Methods

Between 2008 and 2015, patients with acute pancreatitis were registered prospectively in nineteen Dutch hospitals. Patients who had a negative initial diagnostic work-up with regard to the underlying aetiology of their pancreatitis were labelled "presumed" IAP. The aim of this study was to assess the use of diagnostic modalities and their yield to establish an aetiology in "presumed" IAP, and to assess recurrence rates both with and without treatment.

Results

Out of the 1,632 registered patients, 191 patients had a first episode of "presumed" IAP, of whom 176 (92%) underwent additional diagnostic testing: CT (n=124, diagnostic yield 8%), EUS (n=62, yield 35%), MRI/MRCP (n=56, yield 33%), repeat ultrasound (n=97, yield 21%), IgG4 (n=54, yield 9%), and ERCP (n=15, yield 47%). In 64 of 176 patients (36%) an aetiological diagnosis was established, mostly biliary (n=39). In 13 out of 176 of patients (7%) a neoplasm was diagnosed. If additional diagnostic workup revealed an aetiology, the recurrence rate was lower in the treated patients than in the patients without a definite aetiology (15% versus 43%, p=0.014).

Conclusion

Additional diagnostic testing revealed an aetiology in one-third of "presumed" IAP patients. The aetiology found was mostly biliary, but occasionally neoplasms were found. Identification of an aetiology with subsequent treatment reduced the rate of recurrence.

Significance of this study

What is established knowledge on this subject?

- The aetiology of acute pancreatitis remains unknown in 16 to 27% of cases
- Acute pancreatitis can be wrongfully classified as IAP due to an incomplete diagnostic work-up
- The yield of the diagnostic process and its effect on recurrence rates have not been previously described

What are significant findings in this study?

- Additional diagnostic work-up can identify an aetiology one-third of "presumed" idiopathic pancreatitis patients
- Diagnostic work-up is not performed according to current guidelines in most cases
- The aetiology most found in 'presumed' idiopathic pancreatitis is occult biliary stones but pancreatic or ampullary tumours are not rare
- Especially in patients with recurrent AP, treatment of underlying aetiologies prevents further recurrences

Introduction

Acute pancreatitis has a wide range of causes, however, in between 16 to 27% of patients the aetiology remains unexplained.[1,2,3,4] The recommended minimal diagnostic work-up in the acute setting of a first episode of acute pancreatitis has been summarized in the IAP/APA evidence-based guidelines and should comprise at least five elements: 1) a detailed personal history 2) a family history; 3) a physical examination; 4) laboratory tests (i.e. liver enzymes, calcium, triglycerides); and 5) a transabdominal ultrasound (TUS).[5] If the aetiology cannot be determined using this work-up, the acute pancreatitis is classified as "presumed" idiopathic acute pancreatitis (IAP).

Several causes of acute pancreatitis cannot be reliably identified with this work-up. For instance, microlithiasis and biliary sludge are missed in up to 34% of patients on TUS.[6] Furthermore, rare causes with a major impact on patients, such as a small pancreatic carcinoma, are easily missed by TUS. If a second TUS remains inconclusive, an endoscopic ultrasound (EUS) is recommended as the next diagnostic step. A systematic review from 2015 showed that EUS may identify an aetiology in 61% of "presumed" IAP patients, mainly microlithiasis or sludge.[7] Other recent studies also confirm the value of EUS in the determination of a biliary aetiology of IAP.[6,8,9,10] In the case of a negative EUS, further diagnostic modalities, such as MRCP and CT, should be considered.[5]

Some studies have reported on the value of MRCP and EUS in IAP, but studies addressing the efficacy of each step in the diagnostic process are lacking. Therefore, in this study, we evaluated the current diagnostic work-up of "presumed" idiopathic acute pancreatitis and the recurrence rate in a multicentre prospective observational cohort. The primary aim of this study is to explore the use of additional diagnostic modalities and associated diagnostic yield to identify underlying aetiologies in "presumed" IAP. The secondary aims are twofold: first, determine the recurrence rate of acute pancreatitis after a first attack of "presumed" IAP, and second, the recurrence rate after treatment of underlying aetiological factors.

Methods

Study design

In this study 19 hospitals, including 5 university hospitals and 14 large teaching hospitals, of the Dutch Pancreatitis Study Group (DPSG) collaborated. Between January 2008 and December 2015, nearly all acute pancreatitis patients admitted to these 19 hospitals were prospectively registered with the

DPSG. The DPSG acute pancreatitis registration is part of four DPSG randomized controlled trials i.e. PYTHON-trial (approved 4/3/2008), PONCHO-trail (approved 22/7/2010), TENSION-trial (approved 31/1/2011) and APEC-trial (approved 12/12/2012) and consists of all patients that did not participate in these trials.[11,12,13,14] The ethical review board approved the protocol for all four trials including the DPSG acute pancreatitis registry. All patients gave written informed consent prior to inclusion. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Study population
Acute pancreatitis was diagnosed according to the revised Atlanta criteria. [15] The patients included had undergone the minimal diagnostic work-up for a first episode of acute pancreatitis.[5] Any additional diagnostic work-up (i.e. repeat TUS, CT, MRI/MRCP, EUS, IgG4 or ERCP) was performed at the discretion of the treating clinician. This was also the case for the treatment strategy for the underlying aetiologies.

To classify a pancreatitis as "presumed" idiopathic, signs of any known aetiological factor had to be absent in the initial diagnostic work-up. The following groups were excluded:

- Patients with a biliary aetiology, defined as a serum alanine transferase (ALT) >2x upper limit of the normal value, a CBD diameter of ≥8mm for age ≤75 and ≥10mm for age >75 years, or gallstones and/or sludge in the gallbladder and/or CBD on the first TUS.[16-18]
- Patients drinking either more than 3 units of alcohol each day, or more than 5 units in the 48 hours prior to the start of abdominal pain.[19,20] Patients were also excluded when the medical records did not specify an amount of alcohol used, but treating clinician considered an alcoholic aetiology as likely.
- Patients with a recent ERCP, recent abdominal trauma, recent abdominal or vascular surgery, or with cystic fibrosis or known autoimmune pancreatitis.
- Patients with a family history of hereditary pancreatitis, i.e. known relatives with chronic or recurrent acute pancreatitis, or with a genetic mutation associated with hereditary pancreatitis.[21]
- Patients with a serum triglycerides level of >1000 mg/dl or 11.2 mmol/l.[22]
- Patients with a serum calcium level corrected for the serum albumin level of >12 mg/dl or 3 mmol/l.[23]

- Patients with chronic pancreatitis according to the MANNHEIM-criteria.[24]
- Patients with medication as a possible aetiology. Medication as an aetiology was considered when medication with a definite association with acute pancreatitis was used (Supplementary Table 1) combined with a reasonable temporal sequence with either the start of the medication or dosage increase one month before the onset of the pancreatitis.[25] Additionally, when patients were using experimental medication (e.g. chemotherapy), and the treating clinicians considered this a likely aetiology of the pancreatitis.
- Patients with known altered anatomy of the pancreas, pancreatic or bile duct(s), i.e. after hepatopancreatobiliary surgery or a pancreas divisum.

In all the patients included in this study the above-mentioned work-up was performed, and was negative for any aetiological factor.

Criteria for the aetiologies found after additional diagnostic work-up were defined according to the above described criteria. Autoimmune pancreatitis was classified as possible aetiological factor when one cardinal feature of the International Consensus Diagnostic Criteria for Autoimmune Pancreatitis established by the International Association of Pancreatology was present.[26]

Data collection

Patients were prospectively followed during the initial episode of pancreatitis by means of regular phone calls to the treating clinician to assess the patient's clinical status and treatment strategy. During follow-up, on-site data collection was performed including: data on the disease course, the physical examinations and laboratory values, imaging during follow-up, data on readmissions and on out-patient hospital visits. To potentially identify any aetiological factor, data from all imaging and other tests performed, for any given indication, were collected. If patients were transferred or referred to other hospitals, data from these admissions and/or visits were also collected. Outcome measures were assessed at a minimum of two years after the initial admission. Before analyses, all study data were verified by two independent researchers (NH, DU).

Outcomes

The primary outcome was the use and yield of additional diagnostic tests in patients in whom initial diagnostic work-up failed to determine an

aetiology during a first episode of acute pancreatitis. The following tests were included: repeat TUS, CT, MRI/MRCP, EUS, ERCP and IgG4 testing. If multiple aetiological factors were found, the factor for which treatment was initiated was considered the main aetiology. Minimal diagnostic work-up was defined as, a family and personal history, laboratory tests and a TUS. Complete diagnostic work-up according to the IAP/APA guideline was defined as undergoing work-up until an aetiology has been established or until all possible diagnostic tests described in the guideline were performed. The secondary outcome was the recurrence rate of acute pancreatitis after a first attack of "presumed" IAP.

Statistical analysis

All analyses were performed using IBM SPSS statistics for Macintosh version 20 (Armonk, NY: IBM Corp). We performed a subgroup analysis in the patients with a first episode of idiopathic acute pancreatitis after initial diagnostic work-up at admission. For every diagnostic modality, the percentage of utilization and the diagnostic yield was determined individually. Diagnostic yield was calculated for each test individually, by dividing the number of positive tests for aetiology by the total number of times this test was performed. The yield was calculated for all available diagnostic modalities with a two-sided 95% confidence interval. Continuous variables are shown as means with standard deviations and in the case of a skewed distribution, as medians with interquartile ranges. Continuous data was analysed using the Student's t-test and Mann-Whitney test. Fisher's exact test of independence and the chi-square test were used, as appropriate, to compare proportions. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Of the 1632 patients registered between 2008 and 2015, 1,615 patients had undergone not more than the minimal standard diagnostic work-up on admission. Seventeen patients who did not have a TUS on admission were excluded. Of these 1,615 patients, a total of 191 (12%) were diagnosed with a first episode of "presumed" IAP (Figure 1). Baseline characteristics are shown in Table 1. Seventy-nine of the patients were female (41%), the median age was 61 years. In total, 31 patients died during follow-up, 5 of whom during the initial admission. Significantly more patients with severe systemic disease (ASA class >2) died compared to more healthy patients and those with mild systemic disease ($p<0.001$). None of the patients died during a recurrent pancreatitis episode.

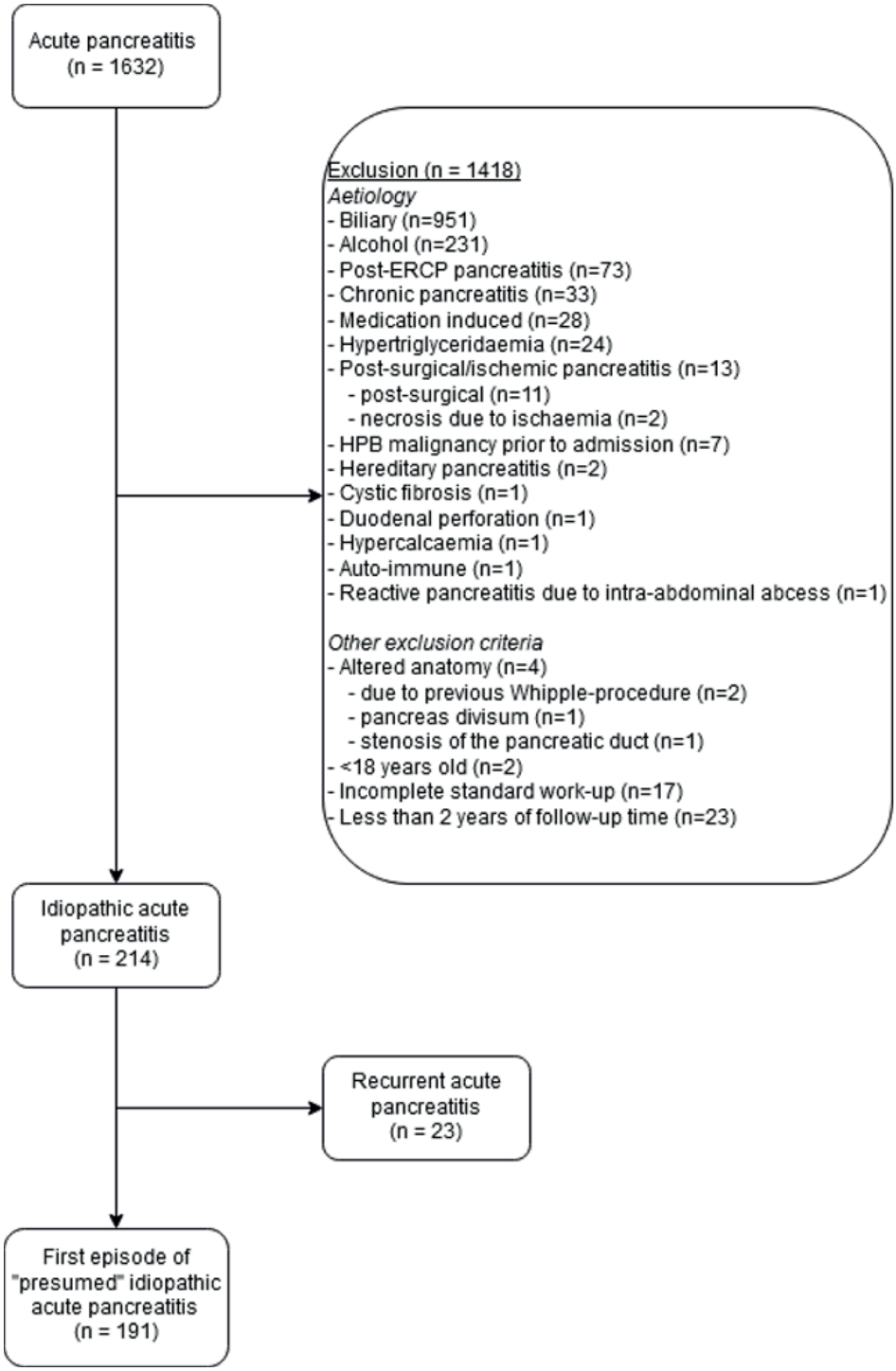

Figure 1 - Flow chart of patient selection

Table 1 - Baseline characteristics of patients with first episode of "presumed" idiopathic pancreatitis

	n=191
Age in years – median (IQR$)	61 (52-72)
Female sex - no. (%)	79 (41%)
ASA score on admissionˆ	
• ASA I - no. (%)	62 (32%)
• ASA II - no. (%)	82 (43%)
• ASA III - no. (%)	46 (24%)
• ASA IV - no. (%)	1 (1%)
BMI+ (n=60, 31%) – median (IQR)	27 (25 – 30)
Medical history	
• Cardiac comorbidity - no. (%)	102 (53%)
• Pulmonary comorbidity - no. (%)	19 (10%)
• Chronic renal failure - no. (%)	8 (4%)
• Diabetes - no. (%)	26 (14%)
• Cholecystectomy prior to IAP- no. (%)	19 (10%)
• Smoking (n=141, 74%) - no. (%)	40 (21%)
Laboratory tests	
• Lipase in U/L (n=112, 59%) – median (IQR)	2,078 (509 – 5480)
• Amylase in U/L (n=168, 88%) – median (IQR)	1,398 (407 – 2516)
• ALT# in U/L– median (IQR)	26 (21 – 37)
• AST& in U/L – median (IQR)	26 (21 – 37)
• Bilirubin in µmol/liter – median (IQR)	10 (7- 17)
• Triglycerides in mmol/L (n=141, 74%) – median (IQR)	1.3 (0.8 – 1.7)
• Calcium (n=179, 94%) in mmol/L – median (IQR)	2.3 (2.2-2.4)
Mortality - no. (%)	31 (16%)
• during index admission - no. (%)	5 (3%)
Follow-up time in years – median (IQR)	4 (3-6)

$ IQR = Interquartile range, ˆASA score: American Society of Anesthesiologists physical status classification system, I= A normal healthy patient, II= mild systemic disease, III= severe systemic disease, IV= severe systemic disease that is a constant threat to life, +BMI= Body Mass Index #ALT= alanine transaminase, &AST= aspartate transaminase.
Note: data was available for all 191 patients unless differently specified behind the characteristic.

Table 2 - Overview of number and yield of diagnostic tests in all patients (n=191)

Test	Patients with diagnostic test – no (%)	Patients with aetiology based on diagnostic test – no (%)	Total of diagnostic tests performed - no	Total times an aetiology was demonstrated - no	Diagnostic yield - percentage (95%CI)
CT	124 (65%)	23 (19%)	456	35	8% (6-11)
Repeat TUS	97 (51%)	28 (29%)	195	40	21% (15-27)
EUS	62 (32%)	27 (44%)	91	32	35% (25-45)
MRCP/MRI	56 (29%)	19 (34%)	84	28	33% (23-43)
ERCP	15 (8%)	7 (47%)	18	8	44% (21-67)
IgG4	54 (28%)	5 (9%)	54	5	9% (1-16)

CT: computed tomography, TUS: trans abdominal ultrasound, EUS: endoscopic ultrasound, MRCP: magnetic resonance cholangiopancreatography, MRI: magnetic resonance imaging, ERCP: endoscopic retrograde cholangiopancreatography, IgG4: immunoglobulin G4

Table 3 - Diagnostic yield of additional diagnostic work-up in the single episode group (n=141)

Test	Patients with diagnostic test – no (%)	Patients with aetiology based on diagnostic test – no (%)	Total of diagnostic tests performed - no	Total times an aetiology was demonstrated - no	Diagnostic yield - percentage (95%CI)
CT	88 (62%)	9 (10%)	294	11	4% (2-6)
Repeat TUS	59 (42%)	12 (20%)	113	14	12% (6-18)
EUS	36 (26%)	13 (36%)	39	14	36% (21-51)
MRCP/MRI	29 (21%)	8 (28%)	43	13	30% (16-44)
ERCP	9 (6%)	5 (56%)	12	6	50% (22-78)
IgG4	30 (21%)	4 (13%)	30	4	13% (1-25)

Table 4 - Diagnostic yield of additional diagnostic work-up in the recurrent pancreatitis group (n=50)

Test	Patients with diagnostic test – no (%)	Patients with aetiology based on diagnostic test – no (%)	Total of diagnostic tests performed - no	Total times an aetiology was demonstrated - no	Diagnostic yield - percentage (95%CI)
CT	36 (72%)	13 (36%)	162	24	15% (10-16)
Repeat TUS	38 (76%)	16 (42%)	80	26	33% (23-43)
EUS	26 (52%)	14 (54%)	52	18	35% (22-48)
MRCP/MRI	23 (46%)	11 (48%)	43	15	35% (21-49)
ERCP	6 (12%)	2 (33%)	6	2	33% (-5-71)
IgG4	24 (48%)	1 (4%)	24	1	4% (-3-12)

Table 5 - Diagnostic work-up in patients with a single episode of idiopathic acute pancreatitis (n=141)

Type of additional test	Total amount of patients that had additional test – no (%)	Biliary aetiology demonstrated - no	Other aetiology demonstrated
CT	88 (62%)	4	3 pancreatic carcinoma 2 chronic pancreatitis 1 neuroendocrine tumour
Repeat TUS	59 (42%)	10	2 pancreatic tumour (1 combined with biliary stones)
EUS	36 (26%)	8	2 ampullary carcinoma 2 chronic pancreatitis 1 neuroendocrine tumour
MRI/MRCP	29 (21%)	4 (1 combined with pancreas divisum)	1 pancreatic carcinoma 1 pancreas divisum 2 chronic pancreatitis
ERCP	9 (6%)	3	1 ampullary carcinoma
IgG4-testing	30 (21%)	-	3 autoimmune
Total for all diagnostic tests$	128 (91%)	22 (1 combined with pancreas divisum)	3 pancreatic carcinoma 3 autoimmune 3 chronic pancreatitis 2 ampullary carcinoma 1 pancreas divisum 1 neuroendocrine tumour

$In case of multiple etiological factors, only the etiological factor that was treated is given in the table

Diagnostic tests

Out of 191 patients with a first episode of "presumed" IAP after minimal diagnostic work-up, 176 (92%) underwent one or more additional diagnostic tests. Fifty-two patients underwent one additional diagnostic test, the remaining 124 underwent more than one test. Forty-one patients (22%) had a complete initial diagnostic work-up according to the IAP/APA guidelines.[5]

The number of additional tests performed and corresponding diagnostic yield are listed in Table 2. In 64 of 176 patients (36%), these additional tests revealed an aetiological factor. EUS and MRI/MRCP were each performed in one third of patients and a second TUS was performed in 97 patients (51%). In 35 (18%) patients, this was done with the specific aim to establish an aetiology. ERCP was performed in 8% of patients, mostly in patients with a clinical suspicion of CBD stones based on laboratory values or imaging i.e. TUS/ERS/MRCP (n=5) or in patients with a suspected tumour of the papilla based on EUS findings (n=4).

Recurrence rate of acute pancreatitis

During a median follow-up of 4 years (IQR 3-6), 50 out of 191 patients (26%) had at least one recurrence, 26 of whom had more than one recurrent episode. In the recurrent pancreatitis group, there were 101 recurrences with a median of 2 per patient (IQR 1-2). Out of 141 patients with a single episode of "presumed" IAP, 128 patients underwent additional diagnostic testing. In 35 cases (27%) an aetiology was found. Of the 50 patients with recurrent episodes of acute pancreatitis, an aetiological factor was identified after additional testing in 29 patients (58%). The diagnostic yield of additional work-up is specified for the single episode group and the recurrent pancreatitis group in Table 3 and Table 4.

Aetiological factors

In Table 5 and Table 6, all aetiological factors found in both the single episode group and the recurrent pancreatitis group are shown. In the total of 191 patients, the most frequent aetiological factor was biliary stones in 39 patients (20%). The percentage of patients in whom an aetiology was detected was twice as high in patients with recurrent pancreatitis than in patients with only one pancreatitis attack (58% versus 27%, p=0.00).

In 13 out of 191 of patients (7%), additional testing revealed an ampullary or pancreatic neoplasm. With 7 out of 141 patients in the single episode group (5%) versus 6 out of 50 in the recurrent AP group (12%), neoplasms were

Table 6 - Diagnostic work-up in patients with recurrent acute pancreatitis (n=50)

Type of additional test	Total amount of patients that had additional test – no (%)	Biliary aetiology demonstrated - no	Other aetiology demonstrated
CT	36 (72%)	6	5 pancreatic carcinoma 1 cystic lesion (pathology showed autoimmune) 1 IPMN
Repeat TUS	38 (76%)	13	2 pancreatic tumour
EUS	26 (52%)	6	3 pancreatic carcinoma (1 combined with biliary stones) 2 IPMN 2 chronic pancreatitis 1 pancreas divisum
MRI/MRCP	27 (54%)	5	2 chronic pancreatitis 1 pancreatic carcinoma 1 autoimmune 1 pancreas divisum
ERCP	6 (12%)	-	1 pancreatic carcinoma 1 pancreas divisum
IgG4-testing	24 (52%)	-	2 autoimmune
Total for all diagnostic tests[$]	48 (96%)	17 (1 combined with pancreas divisum)	6 pancreatic carcinoma (1 combined with biliary stones and chronic pancreatitis) 3 autoimmune (1 based on pathology analysis of resected cystic lesion) 2 chronic pancreatitis 1 IPMN

$In case of multiple etiological factors, only the etiological factor that was treated is given in the table

significantly more common in the recurrent AP group (p=0.043). Five patients were shown to have chronic pancreatitis. Serum IgG4-testing was performed in 54 patients (28%), five of whom had levels of 2 times the upper limit of normal (ULN) or higher. Two patients were treated with prednisone with good clinical response, one of which had characteristic findings of autoimmune pancreatitis on MRI. The other three patients had no signs of autoimmune pancreatitis on imaging and did not receive treatment. One of these patients did have a history of ulcerative colitis and had one recurrent episode, the other patient did not have any recurrences. In one patient autoimmune pancreatitis was diagnosed, after six recurrences, in the pathology sample of a pancreatic mass. No serum IgG4 levels of this patient were available. None of the patients were diagnosed with IgG4-negative autoimmune pancreatitis.

Treatment of aetiological factors

Underlying aetiological factors were treated in 34 out of 64 patients in whom an aetiology was found. The other 30 patients did not receive any treatment for underlying aetiologies.

In the treated group, the treatments performed for underlying aetiological factors were the following: cholecystectomy with/without ERCP with

sphincterotomy (n=22), only ERCP with sphincterotomy (n=3) , prednisone treatment (n=2), pylorus preserving pancreatoduodectomy (n=4), pancreatic tail resection (n=1), distal pancreatectomy and splenectomy (n=1), and a pancreatic duct stent placement (n=1). In 21 of 34 patients (62%), the treatment was started after the initial IAP episode, whereas the other 13 patients (38%) had recurrent AP episodes before the start of treatment. After treatment 29 patients out of 34 patients (85%) were free of recurrences. In the group of patients where additional diagnostic workup revealed an aetiology, the risk of recurrence after treatment was 0.34 (95%CI: 0.137-0.841) compared to the risk of recurrence without treatment. In the subgroup of 50 patients with recurrent AP, the recurrence rate after treatment was 31% versus 97% in patients without treatment ($p<0.001$), the accompanying relative risk of recurrence in the group without treatment 23.4 (95%CI: 3.296- 165.778), compared to the group with treatment.

Discussion

The aetiology of acute pancreatitis remains unknown 16-26% of cases. In our cohort of 1632 AP patients, 12% was idiopathic which is lower compared to other studies such as the Hungarian Pancreatic Study Group cohort that showed a rate of 16.3%.[1-4] Possibly, the strict criteria to define "presumed IAP" in our cohort, especially in regard to absence of a possible biliary aetiology explains this lower rate. For acute pancreatitis, current guidelines advise the diagnostic work-up to comprise at least a thorough personal and family history taking, laboratory tests and a TUS. As a next step, a repeat TUS can be performed to re-assess a potential biliary aetiology. In our cohort half of the patients underwent a repeat TUS with a yield of 21%. Even though current guidelines advise a repeat TUS, few studies have investigated its diagnostic yield in idiopathic acute pancreatitis. Signoretti et al. retrospectively investigated the sensitivity, specificity and accuracy for detecting a biliary origin on repeat TUS in a group of 155 acute pancreatitis patients, of whom 85 underwent a repeat US within 1 week after admission. They found a sensitivity of 82%, a specificity of 75% and an overall accuracy of 78% to detect a biliary aetiology.[27] However, they investigated all AP patients and not specifically IAP patients, including those with a first positive TUS giving ample explanation of why their performance was higher compared to our study. Overall, the diagnostic yield of 21% found in this study, combined with the low costs, safety, and widespread availability of TUS, underscore the diagnostic worth of performing a repeat TUS.

In our study the yield of EUS was 36%, which is low compared to other

studies. Wan et al. found a diagnostic yield for the aetiology of IAP of 64% for EUS in a meta-analysis of 2,338 patients with IAP, with the most common finding being choledocholithiasis and/or cholecystolithiasis (33%).[6] In a recent systematic review a similar diagnostic yield of 62% with 37% biliary aetiology was found.[10] This difference is likely explained by the fact that most studies in this meta-analysis included patients with high serum ALT levels and/or CBD dilatation prior to EUS resulting in a higher a-priori chance of finding biliary stones, thereby increasing the diagnostic yield of EUS. In our study, a biliary aetiology was established using additional work-up in 20% of patients with "presumed" IAP. However, in order to exclude patients with a high likelihood of having a biliary aetiology, the criteria we used to define "presumed" IAP were stricter. Both patients with CBD dilatation and patients with serum ALT levels>2xULN were excluded. Multiple studies have shown that the likelihood of a biliary aetiology is very high in these patients.[16-18] Despite these strict inclusion and exclusion criteria in the current study, we found a sizable portion of "presumed" IAP patients that turned out to have occult biliary disease, underlining the importance and need for an additional and detailed work-up in these patients.

The yield of MRI/MRCP (33%) was similar to other studies. The meta-analyses by Wan et al. showed a yield of 34% for MRI.[6] Previous studies have shown that the yield of finding microlithiasis and sludge is higher in EUS than in MRI/MRCP.[6,28] Especially in the IAP population, where microlithiasis is considered an important aetiological factor, many clinicians consider EUS the preferred second diagnostic step after TUS.

In current practice, ERCP is not routinely performed for diagnostic purposes due to its associated procedural risks compared to other diagnostic modalities.[29] In the current study, 8% of patients did undergo an ERCP, which was mostly performed for reasons of a high clinical suspicion of biliary stones (i.e. jaundice, progressive cholestasis during admission) or because of a suspected anomaly of the papilla on EUS. In these cases with a high clinical suspicion for pathology, the diagnostic yield of ERCP was high (44%). Nevertheless, this was mostly after presumptive diagnosis was already made with another investigational modality which in fact constituted the indication to perform ERCP. On that note, one might argue that ERCP was negative in the majority of patients (56%) in whom this invasive procedure might have been prevented if, for example, a diagnostic EUS was performed prior to ERCP.

Even though current guidelines do not advise IgG4-testing as part of the diagnostic work-up of "presumed" IAP after a first episode, surprisingly, in almost one-third of patients (28%) in this study serum IgG4-levels were measured. In 9% of those patients the serum IgG4-levels were elevated (i.e. 2x ULN or higher), and two of these patients were treated with prednisone with good response. The International Association of Pancreatology published a consensus guideline on diagnostic criteria for autoimmune pancreatitis stating that elevation in serological markers alone is not deemed sufficient for the diagnosis.[26] The work-up for autoimmune pancreatitis in patients included in this study was not uniformly performed according to guidelines.

In this study genetic counselling or genetic testing was not performed. This might be due to patient selection prior to inclusion, as patients with a family history of hereditary pancreatitis, know genetic mutations or younger patients with non-alcoholic calcifying pancreatitis in whom testing already revealed a genetic cause were excluded from this cohort. Omitting genetic counselling might lead to misclassification of patients with hereditary pancreatitis as idiopathic. Therefore, in accordance with the IAP/APA guideline clinicians should consider genetic counselling in recurrent idiopathic acute pancreatitis.[5]

Additional work-up revealed a neoplasm in 13 (7%) "presumed" IAP patients. Acute pancreatitis patients are known to have an increased risk of harbouring pancreatic malignancy.[30] A Danish population-based study, perform found that the pancreatic cancer risk was high in patients with idiopathic acute pancreatitis, with an adjusted Hazard ratio of 2.52 (95% CI 1.83-3.47) at 5-years of follow-up.[31] A previous DPSG study confirmed this finding. In that study, a pancreatic cancer rate of 0.7% was found in 731 patients with a first episode of acute pancreatitis, and the risk was 2% in the subgroup of patients with an unknown aetiology.[32] In both aforementioned studies however, the definition of IAP or "unknown aetiology" was not specified.

Most patients in our study had a single attack of "presumed" IAP with a mild disease course. One-fourth of patients had one or more recurrences, which is comparable to previous studies. [33] In a similar Dutch cohort of 669 patients with acute pancreatitis, researchers found a recurrence rate of 17% overall and of 25% in the 108 included IAP patients.[34] However, in that study the definition of IAP was not as clearly described as in the current study, making it difficult to compare results. As expected, we found that treatment of an underlying aetiology reduced recurrence rates.

Strengths and limitations

The current study comprises a large cohort of patients with a first episode of "presumed" IAP, all of whom were prospectively followed for more than 2 years, thus making sure that late complications, aetiological diagnoses and recurrences could be identified. The criteria we used to define patients with "presumed" IAP after an initial work-up was in accordance with the latest literature consensus. Furthermore, the criteria used to exclude patients with a high likelihood of having biliary pancreatitis, alcohol-related pancreatitis or chronic pancreatitis were more strict compared to most other studies investigating the diagnostic work-up of IAP.

There are also limitations to our study. First, serum triglycerides and calcium levels were not available in all patients. Although hypertriglyceridemia and hypercalcemia are considered rare causes of pancreatitis, in this subgroup of patients with unexplained aetiology the proportion might be higher than in the total AP population. Therefore, omitting these tests might have led to an under-diagnosis of these aetiologies. Second, some caution is advised when interpreting the diagnostic yield of additional imaging. We evaluated all diagnostic tests that were performed, not only tests solely performed with the purpose of establishing an aetiology for the (recurrent) pancreatitis. Furthermore, the finding of an aetiological factor using a test is not definite proof that this factor is the definite cause of the acute pancreatitis.

Conclusion

Our study shows that additional diagnostic work-up can identify an aetiology in one-third of patients with "presumed" IAP. The aetiology most commonly found was biliary. However, in a substantial portion of patients an underlying malignancy was detected. Furthermore, we show that the diagnostic work-up after a first attack of "presumed" idiopathic acute pancreatitis is performed according to current guidelines in less than one-fourth of patients. This is worrisome, as identification of an aetiology with subsequent treatment reduces the risk of recurrences. In light of this observation, better guideline adherence is advised, i.e. a repeat TUS, if necessary followed by either EUS or MRCP in all patients after a first unexplained acute pancreatitis attack.

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Supplementary material can be found at https://supplementary.info

Chapter 3

Recurrence of idiopathic acute pancreatitis after cholecystectomy: systematic review and meta-analysis

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British Journal of Surgery, 2020

Abstract

Background

Occult biliary disease has been suggested as a frequent underlying cause of idiopathic acute pancreatitis (IAP). Cholecystectomy has been proposed as a strategy to prevent recurrent IAP. The aim of this systematic review was to determine the efficacy of cholecystectomy in reducing the risk of recurrent IAP.

Methods

PubMed, Embase and Cochrane Library databases were searched systematically for studies including patients with IAP treated by cholecystectomy, with data on recurrence of pancreatitis. Studies published before 1980 or including chronic pancreatitis and case reports were excluded. The primary outcome was recurrence rate. Quality was assessed using the Newcastle–Ottawa Scale. Meta-analyses were undertaken to calculate risk ratios using a random-effects model with the inverse-variance method.

Results

Overall, ten studies were included, of which nine were used in pooled analyses. The study population consisted of 524 patients with 126 cholecystectomies. Of these 524 patients, 154 (29.4 (95 per cent c.i. 25.5 to 33.3) per cent) had recurrent disease. The recurrence rate was significantly lower after cholecystectomy than after conservative management (14 of 126 (11.1 per cent) versus 140 of 398 (35.2 per cent); risk ratio 0.44, 95 per cent c.i. 0.27 to 0.71). Even in patients in whom IAP was diagnosed after more extensive diagnostic testing, including endoscopic ultrasonography or magnetic resonance cholangiopancreatography, the recurrence rate appeared to be lower after cholecystectomy (4 of 36 (11 per cent) versus 42 of 108 (38.9 per cent); risk ratio 0.41, 0.16 to 1.07).

Conclusion

Cholecystectomy after an episode of IAP reduces the risk of recurrent pancreatitis. This implies that current diagnostics are insufficient to exclude a biliary cause.

Introduction

Acute pancreatitis is an increasing healthcare problem[1] with a wide range of causes. A biliary cause is found in approximately half of patients, followed by alcohol consumption in approximately 20 per cent and less common causes such as medication, hypertriglyceridemia and autoimmune diseases. In as many as one-third of patients, the aetiology of acute pancreatitis remains unknown (initially), and the disease is referred to as idiopathic acute pancreatitis (IAP).[2,3]

Numerous studies have suggested that microlithiasis and sludge might cause a large subset of IAP.[4,5] Small stones (less than 4 mm), usually referred to as microlithiasis[6], and sludge are often difficult to detect by transabdominal ultrasound imaging, especially if located in the common bile duct (CBD). Therefore, in daily practice, many patients who are initially thought to have IAP may, in fact, have biliary pancreatitis. Gallstones, microlithiasis and sludge are all considered as potential biliary causes of pancreatitis. To reduce the risk of recurrent acute pancreatitis, same-admission cholecystectomy is advised for mild biliary pancreatitis.[7]

Some studies[8,9] have advised cholecystectomy after acute pancreatitis if no other aetiology can be found implying the diagnosis of IAP during evaluation. However, the work-up for a potential biliary cause in these studies was incomplete. Endoscopic ultrasound imaging (EUS), which has been shown to detect a biliary aetiology in one-third of patients with IAP, and, to a lesser extent, magnetic resonance cholangiopancreatography (MRCP), were often not done[10].

The primary aim of this systematic review was to determine the efficacy of cholecystectomy in reducing the recurrence rate of pancreatitis in patients with IAP. Patients with presumed IAP and those in whom IAP remained the most likely diagnosis after extensive evaluation were analysed separately.

Methods

This review was written in accordance with PRISMA[11] and MOOSE guidelines[12], and was registered in the PROSPERO database (CRD42017055275).

Definitions

Data were analysed based on the definitions of IAP as outlined in the original articles, and according to current guidelines[13], which define IAP as acute pancreatitis in which no aetiology can be determined by standard diagnostic

evaluation, consisting of a detailed history, laboratory serum tests (liver enzymes, calcium and triglycerides) and imaging (transabdominal ultrasonography on admission and repeated after discharge).

Three types of IAP were defined for the purposes of this study. First, 'original' IAP was defined in accordance with definitions used in the original articles. Second, 'presumed' IAP was defined by diagnosis of IAP after the standard evaluation. Third, 'true' IAP was defined as an acute pancreatitis episode that remained unexplained after both standard diagnostic work-up and additional diagnostic tests such as EUS and MRCP (Fig. 1).

Outcome measures

The primary outcome was recurrence rate of acute pancreatitis, calculated as the proportion of patients experiencing one or multiple episodes of recurrent acute pancreatitis after an index episode of 'original', 'presumed' or 'true' IAP.

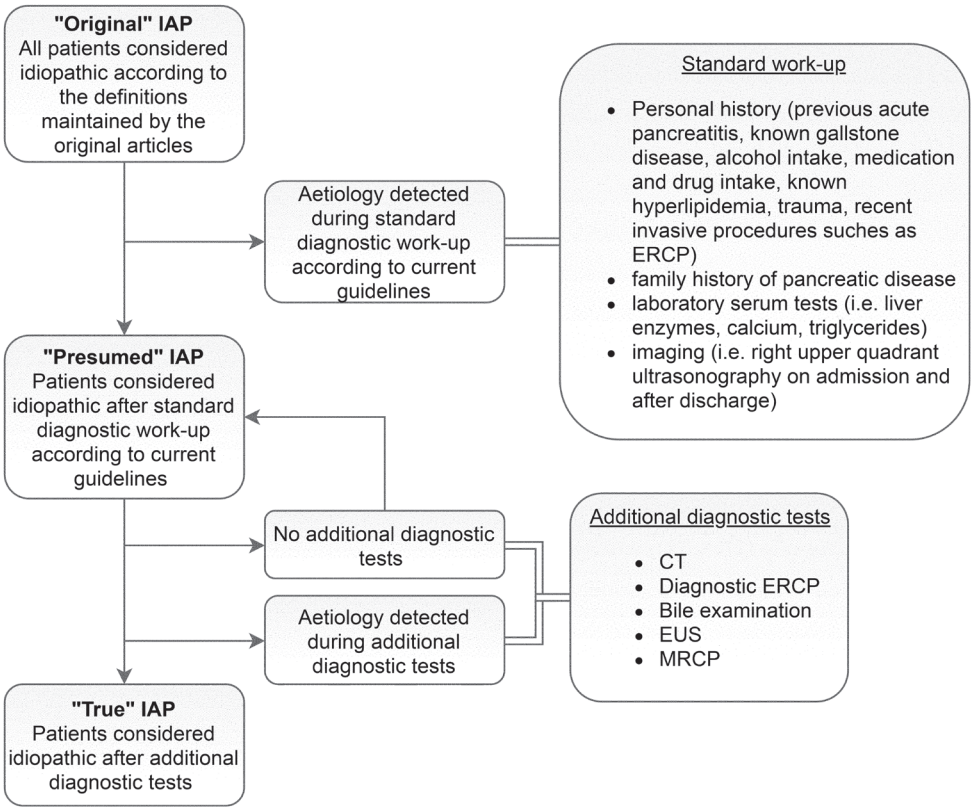

Figure 1 - Diagnostic process and definitions

Secondary outcomes were complications of cholecystectomy, severity of recurrences as defined by the revised Atlanta classification[14], and occurrence of biliary events before cholecystectomy.

Search strategy

Guided by an experienced librarian, the PubMed, Embase and Cochrane Library databases were searched systematically for relevant articles published between inception and 1 September 2018 (Appendix S1, supplementary information). Search terms included 'pancreatitis', 'idiopathic' and 'cholecystectomy'. Studies of adult humans in English were considered. Duplicates were removed and the search results were recorded using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Victoria, Australia).

Study selection

Two reviewers screened potentially relevant articles independently by examining the titles and abstracts. Studies were included if they fulfilled the following criteria: the study cohort comprised patients with IAP; the intervention was cholecystectomy and the comparator conservative treatment; and the outcome was rates of recurrent acute pancreatitis. Exclusion criteria were: letters, comments, case reports, reviews, conference abstracts, book chapters, studies not written in English, and studies published before 1980, owing to discrepancies in diagnostic evaluation before 1980 compared with current state-of-the-art work-up.

The two reviewers read the full text of potentially eligible studies individually. The reference lists of included articles were screened for relevant publications not identified by the initial search. Disagreements regarding eligibility were resolved after joint re-evaluation by the two reviewers.

Data extraction

After selecting studies that met the inclusion criteria, all relevant data from these studies were extracted by two reviewers using a standard form. Relevant data included: study characteristics (authors, years of inclusion, publication year, country, study design, number of patients, duration of follow-up), patient characteristics (sex, age, recurrent or first episode of pancreatitis, number of previous attacks, severity of pancreatitis, previous cholecystectomy), diagnostic evaluation (history, laboratory tests, imaging), interventions (cholecystectomy) and outcome measures. No attempt was made to communicate with the corresponding authors concerning missing

data. Missing information was registered as ‘not reported’ and studies with missing data were excluded from subsequent pooled analyses.

Quality assessment

Two reviewers appraised the quality of the included studies independently using the Newcastle–Ottawa Scale for cohort studies.[15] In tailoring the scale for the purpose of this review, presence of sludge as an exclusion criterion for the intervention and comparator groups was considered to be the most important factor indicating comparability between these groups. Other relevant factors were CBD width, raised serum alanine aminotransferase (ALT) levels, and cholecystectomy before index admission. Follow-up of at least 2 years was considered to be adequate for recurrence to have occurred. Loss to follow-up exceeding 10 per cent was considered likely to introduce bias. Disagreement was resolved after discussion between the two reviewers.

Statistical analysis

Study characteristics, patient characteristics, use of diagnostic tests, treatment with cholecystectomy and secondary outcome measures were reported descriptively.

Pooled recurrence rates from the included studies were reported as proportions and percentages, with two-sided 95 per cent confidence intervals. Recurrence rates were pooled in meta-analysis using a random-effects model with the inverse-variance method to calculate risk ratios with 95 per cent confidence intervals. Subgroup analyses of patients with ‘presumed’ IAP and ‘true’ IAP were undertaken. Statistical between-study heterogeneity was assessed using the I2 statistic. I2 values of less than 25 per cent, 25–49 per cent, 50–75 per cent and more than 75 per cent were considered to indicate low, moderate, high and very high levels of heterogeneity respectively.[16] To evaluate publication bias, a funnel plot was created using Egger’s linear regression method.[17,18]

Results

Study selection

From PubMed (268 records), Embase (711) and Cochrane Library (28) searches, with additional records identified through screening of reference lists (288), ten articles were selected for inclusion in the qualitative analysis. One case–control study[19] included a highly selected group of 23 patients who eventually underwent cholecystectomy. Considering potential selection bias, this study was excluded from the quantitative analyses, leaving nine studies in the meta-analyses (Fig. 2).

Study characteristics

Among the ten included studies, there was one RCT[8], one cross-sectional study[20], six prospective cohort studies[4,5,21-24] and two[9,19] retrospective cohort studies (Table 1). The only RCT[8] compared cholecystectomy with conservative treatment in 85 patients with IAP, with an allocation ratio of 1 : 1. The person enrolling patients in the trial was blinded to the treatment allocation, before block randomization. Patients, physicians and researchers were not blinded. EUS was not used in this RCT, which enrolled patients between January 2009 and January 2013.

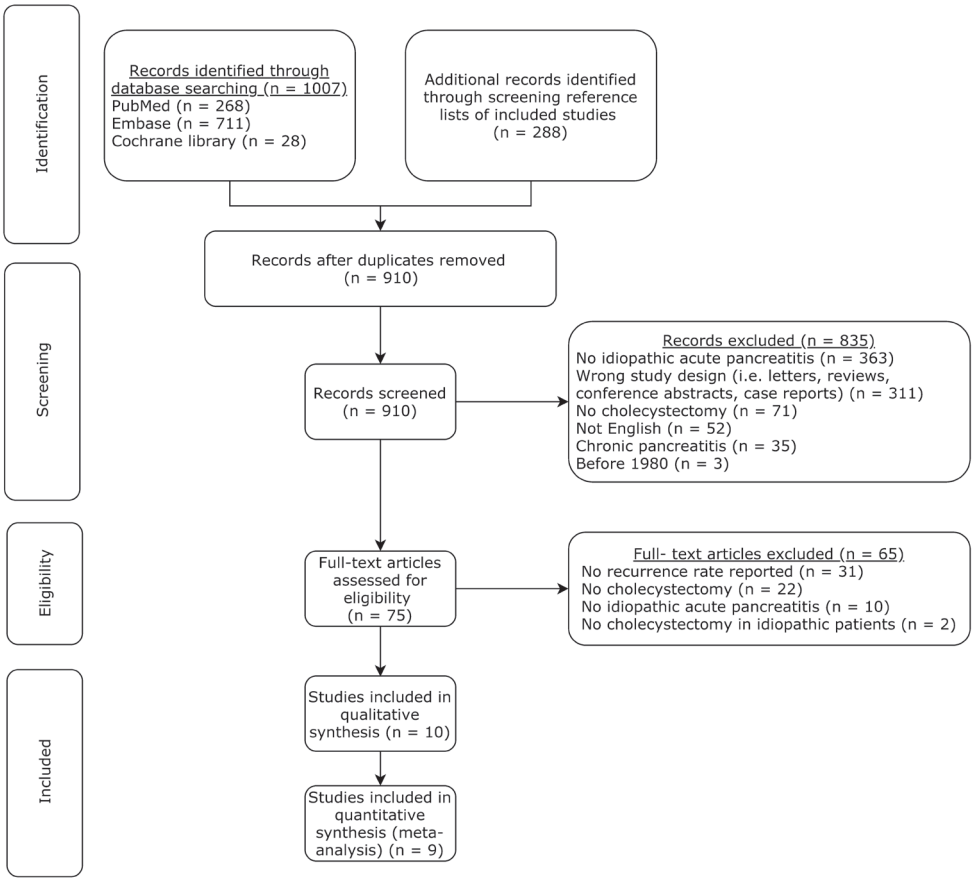

Figure 2 - PRISMA flow chart showing selection of articles for review

TABLE 1 - CHARACTERISTICS OF INCLUDED STUDIES

Reference	Inclusion period	Country	Study design	No. of patients	Follow-up time (months)*
Lee et al. [3]	1980-1988	New Zealand, USA	Prospective cohort study	86	48 (6-84)
Pérez-Martin et al. [17]	1994-1996	Spain	Observational transverse cohort study	18	n.r.
Liu et al. [19]	1996-1997	China	Prospective cohort study	89	22 †
Tandon and Topazian [21]	n.r.	USA	Post hoc analysis of prospective database	41	16 (4-44)
Saraswat et al. [18]	n.r.	India	Prospective cohort study	24	30 (4-48)
Garg et al. [4]	1995-2003	India	Prospective cohort study	75	17.63 (1-156)
Ortega et al. [20]	2005-2009	Spain	Prospective cohort study	49	16 (9) ‡
Trna et al. [16]	1990-2005	USA	Retrospective case-control study	239	99 (8-220) †
Räty et al. [7]	2009-2013	Finland	RCT	85	36 (5-58) †
Stevens et al. [8]	2005-2015	Australia	Retrospective cohort study	195	50 (6) §

Data are presented as no. (%) or median (IQR).

Patient characteristics

In total, 901 patients with acute pancreatitis were included. Among these patients, the cause was biliary in 325, alcoholic in 16, known but unspecified in ten[24], hyperlipidaemia in two and a duodenal duplication cyst in one patient. A total of 547 patients were considered to have 'original' IAP. Of these, 23 patients were included in one case–control study[19] and were excluded from further analyses, leaving 524 patients with 'original' IAP in the meta-analysis. Six cohorts[5,19-23] included patients with recurrent IAP, whereas three studies[4,9,22] did not report this. Only one study[8] excluded patients with a recurrent episode of 'presumed' IAP (Table 2).

Critical appraisal

Most of the studies scored 3[20, 24], 4[5,21-23] or 5[4,19] of a maximum of 9 points on the Newcastle–Ottawa Scale. One study[9] scored 6 points and the RCT[8] scored 8 points. Nearly all studies had trouble ensuring comparability between cohorts. Only one study[19] controlled for the presence of sludge, raised liver enzyme levels and cholecystectomy before index admission (Fig. S1 and Table S1, supplementary information). A funnel plot of the included studies showed a symmetrical plot, making publication bias highly unlikely (Figs S2 and S3, supplementary information).

Table 2 - Characteristics of included patients with idiopathic acute pancreatitis

Reference	No. of patients with IAP	Male	Age (years)*	Recurrent pancreatitis	No. of previous attacks*	Severe pancreatitis	Previous cholecystectomy
Lee et al. (3)	29§	16 (55)	53 (31-79)	n.r.	n.r.	n.r.	0 (0)
Pérez-Martin et al. (17)	18	8 (44)	54	5 (28)	1 (4 patients) and 3 (1 patient)	4 (22) ¶	0 (0)
Liu et al. (19)	18	9 (50)	68 (24-86) †	n.r.	n.r.	n.r.	0 (0)
Tandon and Topazian (21)	31	12 (39)	48.8 (19-87)	17 (55)	44 in 17 patients	n.r.	3 (10)
Saraswat et al. (18)	24	4 (17)	36 (18-56)	24 (100)	4 or more	n.r.	0 (0)
Garg et al. (4)	75	60 (80)	31.9 (14-67)	75 (100)	4.82 (2-10)	n.r.	n.r.
Ortega et al. (20)	49	24 (49)	58 (17) ‡	16 (33)	n.r.	5 (10) #	9 (18)
Trna et al. (16)	23	10 (43)	n.r.	8 (35)	2 (6 patients) and 3 (2 patients)	n.r.**	0 (0)
Räty et al. (7)	85	52 (61)	Intervention group 56†				
Control group 57†	0 (0)	-	4 (5) ††	0 (0)			
Stevens et al. (8)	195	100 (51)	54 (15-93) †	n.r.	n.r.	n.r.	0 (0)
Total	**547**	**295 (54)**	**-**	**145**	**-**	**13**	**12**

values in parentheses are percentages unless indicated otherwise; *values are mean (range), except †median (range) and ‡mean (s.d.). §two of 31 patients initially considered to have idiopathic acute pancreatitis (iap) were later found to have a dilated common bile duct on ct and endoscopic retrograde cholangiopancreatography, and subsequently excluded from analysis. ¶ based on ranson criteria. # based on atlanta classification. ** trna et al. reported 40 patients with severe pancreatitis in the entire cohort but did not specify severity in iap subgroup. ††based on revised atlanta classification. n.r., not reported.

Diagnostic evaluation

The definition of IAP varied widely among the included studies. None of the studies reported use of standard diagnostic work-up as described in the International Association of Pancreatology/American Pancreatic Association guideline[13] to determine the most likely aetiology. Most notably, definitions of alcoholic and biliary aetiology varied broadly between studies (Table S2, supplementary information). Two studies[19,21] excluded patients based on raised levels of liver enzymes. Although all studies considered cholelithiasis on imaging to be an exclusion criterion for IAP, four[19,21,23,24] did not require ultrasonography in all patients or did not mention which imaging modality was used. One study[9] included patients with raised ALT levels, and another[8] included patients with raised levels of liver enzymes, but only if MRCP was negative for CBD stones. Only five studies considered CBD dilatation[4,20] or presence of biliary sludge on imaging[5,20,24] to be indicative of biliary aetiology. One study[9] reported explicitly on the presence of biliary sludge on transabdominal ultrasound imaging, but chose to consider this as indicative of IAP. Repeat transabdominal ultrasonography was commonly employed; five studies[4,5,8,20,21] used it in all included patients, and two[22,24] in part of the cohort.

Eighteen of the 524 patients (3.4 per cent) with 'original' IAP appeared to have a demonstrable aetiology after review of the results of standard work-up; the disease was classified as 'presumed' IAP in the remaining 506 patients. Additional diagnostic testing comprised CT[4,5,8,22,24], endoscopic retrograde cholangiopancreatography[4,5,21,22,24], microscopic bile examination[4,5,20,21, 23,24], EUS[5,22-24] and MRCP.[8,9,23,24] Additional diagnostic tests demonstrated biliary disease in 25.8 per cent (111 patients), chronic pancreatitis in 15.2 per cent (47; although only 1 study[23] reported diagnostic criteria for chronic pancreatitis), pancreatic divisum in 3.9 per cent (12), neoplasms in 1.3 per cent (4) and ascariasis, choledochal cyst and choledochocele in 0.3 per cent (1). In total, a previously unknown potential cause of acute pancreatitis was found using additional tests in 165 patients (32.6 per cent) (Table S3, supplementary information).

Cholecystectomy

Of 524 patients with 'original' IAP, 126 (24.0 per cent) underwent cholecystectomy during follow-up. To create a subgroup of patients with 'true' IAP, several groups of patients were excluded: those in whom an aetiology was established during either standard (18) or additional (165) work-up, those for whom it was not sufficiently reported whether biliary disease was present (195)[9] and patients in whom the disease course during follow-up was unclear (2).[23]

In the subgroup of 144 patients with 'true' IAP, 36 cholecystectomies (25.0 per cent) were performed (Fig. S4, supplementary information).
One study[8] also reported pathology results for the gallbladder. Microlithiasis was observed on pathological examination in 23 of 39 gallbladders.

Complications of cholecystectomy
One study[9] reported one bile duct injury in 66 cholecystectomies, and two studies[8,22] reported no complications in 13 and 39 cholecystectomies respectively. In total, there was one complication in 118 cholecystectomies (0.8 (95 per cent c.i. 0 to 2.5) per cent). Cholecystectomy complication rates were not reported in the remaining studies.

Recurrence
Of the 524 patients with 'original' IAP, 154 had at least one recurrence during follow-up (29.4 (95 per cent c.i. 25.5 to 33.3) per cent). Meta-analysis of this group showed that the recurrence rate among patients managed conservatively was significantly higher than that in patients who underwent cholecystectomy (140 of 398 (35.2 per cent) versus 14 of 126 (11.1 per cent); risk ratio 0.44, 95 per cent c.i. 0.27 to 0.71) (Fig. S5, supplementary information). Similarly, in the subgroup of 506 patients with 'presumed' IAP, the recurrence rate was higher among patients who received conservative treatment (139 of 387 (35.9 per cent) versus 14 of 119 (11.8 per cent); risk ratio 0.45, 0.28 to 0.73) (Fig. 3).
Among 144 patients with 'true' IAP, 46 had at least one recurrence during follow-up (31.9 (30.8 to 46.8) per cent). In pooled analysis, the recurrence rate was 11 per cent (4 of 36) in the cholecystectomy group and 38.9 per cent (42 of 108 patients) in the conservative treatment (risk ratio 0.41, 0.16 to 1.07) (Fig. 4).
There was no statistical between-study heterogeneity in any of the pooled analyses (I2 =0 per cent).
None of the included studies reported severity of recurrences.

Biliary events before cholecystectomy
The occurrence of biliary events (cholecystitis, biliary colic, obstructive choledocholithiasis, biliary pancreatitis and cholangitis) was not reported systematically. Three studies briefly mentioned biliary events before cholecystectomy. One study[22] reported no biliary events, and another[20] reported one patient with a recurrent episode of acute (biliary) pancreatitis, after which cholecystectomy was performed. The third study[4] reported 13 patients with recurrent episodes of biliary pancreatitis, five of whom were treated by cholecystectomy and three by endoscopic sphincterotomy.

Study or Subgroup	Cholecystectomy Events	Total	Conservative management Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Lee	0	1	18	28	3.8%	0.39 [0.03, 4.39]	1992
Pérez-Martín	0	3	3	15	2.9%	0.57 [0.04, 8.97]	1998
Liu	0	13	0	5		Not estimable	2000
Tandon	0	5	5	26	2.9%	0.41 [0.03, 6.44]	2001
Saraswat	0	2	4	22	3.1%	0.85 [0.06, 12.21]	2004
Garg	4	14	22	53	28.3%	0.69 [0.28, 1.67]	2007
Ortega	1	11	6	38	5.5%	0.58 [0.08, 4.29]	2011
Räty	4	34	13	41	21.2%	0.37 [0.13, 1.03]	2015
Stevens	5	36	68	159	32.1%	0.32 [0.14, 0.75]	2016
Total (95% CI)		**119**		**387**	**100.0%**	**0.45 [0.28, 0.73]**	
Total events	14		139				

Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 7 (P = 0.96); I² = 0%
Test for overall effect: Z = 3.29 (P = 0.001)

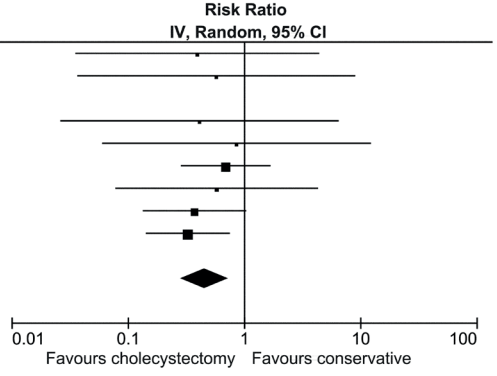

Figure 3 - Pooled analysis of recurrence of pancreatitis in patients with 'presumed' idiopathic acute pancreatitis treated with cholecystectomy versus conservative management. Risk ratios are shown with 95 per cent confidence intervals. A random-effects inverse-variance model was used for meta-analysis.

Study or Subgroup	Cholecystectomy Events	Total	Conservative management Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Lee	0	0	2	8		Not estimable	1992
Pérez-Martín	0	0	0	4		Not estimable	1998
Liu	0	0	0	4		Not estimable	2000
Tandon	0	0	3	10		Not estimable	2001
Saraswat	0	0	3	6		Not estimable	2004
Garg	0	0	18	18		Not estimable	2007
Ortega	0	2	3	17	12.6%	0.86 [0.06, 12.75]	2011
Räty	4	34	13	41	87.4%	0.37 [0.13, 1.03]	2015
Total (95% CI)		**36**		**108**	**100.0%**	**0.41 [0.16, 1.07]**	
Total events	4		42				

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.81 (P = 0.07)

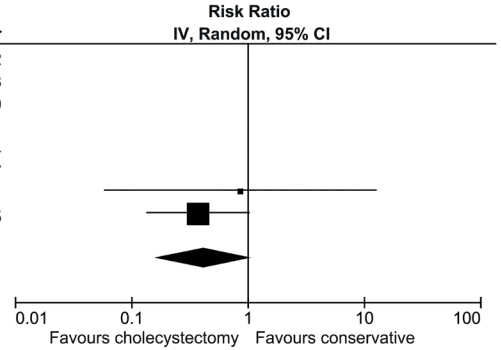

Figure 4 - Pooled analysis of recurrence of pancreatitis in patients with 'true' idiopathic acute pancreatitis treated with cholecystectomy versus conservative management. Risk ratios are shown with 95 per cent confidence intervals. A random-effects inverse-variance model was used for meta-analysis.

Discussion

This systematic review and meta-analysis showed that cholecystectomy might reduce the risk of recurrence of IAP. This effect appeared to be independent of the evaluation before making the diagnosis of IAP.

The efficacy of cholecystectomy in preventing biliary events after biliary pancreatitis is undisputed[7]. The results of this review are therefore in line with the theory that a significant number of patients with 'presumed' and 'true' IAP actually have biliary pancreatitis. This is exemplified by the high rate of microlithiasis on pathological examination of the gallbladder[8]. Previous research[10] has suggested that additional diagnostic work-up with EUS and MRCP may detect a biliary cause in patients with IAP, after negative transabdominal ultrasonography and biochemical tests. In the present study, however, the impact of cholecystectomy in reducing recurrence of acute pancreatitis appeared to be independent of the preoperative evaluation, either including or excluding MRCP and EUS. Possible explanations for this are the suboptimal sensitivity of MRCP for the detection of sludge and lack of a standardized approach to EUS.

Another intriguing finding is the larger number of other pancreatic disorders observed in the included studies, apart from biliary disease. Most notably, chronic pancreatitis was diagnosed in 15.2 per cent and neoplasms in 1.3 per cent. Additionally, pancreas divisum was found in 12 patients (3.9 per cent), although a causative relationship between pancreas divisum and acute pancreatitis is debated.[25]

The present results should be interpreted in light of several shortcomings. First, most of the included studies were small in size, especially the subgroup of the 144 patients with 'true' IAP, in whom only 36 cholecystectomies were performed. This subgroup analysis showed no significant difference in recurrence rate after cholecystectomy, possibly owing to insufficient sample size. Second, there was heterogeneity between studies as some included both patients with a first episode of IAP and those with recurrent IAP, and definitions of IAP differed across studies. Partly owing to evolving insights regarding work-up of IAP and availability of diagnostic tests, many of the included studies did not undertake complete standard and additional diagnostic testing according to current international guidelines.[13] This may have led to the inclusion of patients in whom a biliary aetiology could have been demonstrated if standard and additional diagnostic tests had been carried out properly. Including those in whom biliary disease went undiagnosed

may have led to overestimation of the effect of cholecystectomy in IAP. Third, only one study[8] had a randomized design, but this trial was not sham-controlled and the patients were not blinded. Undergoing surgery may influence the patient's lifestyle, and previous literature[26] has shown that cessation of alcohol and nicotine use are particularly effective in preventing recurrence. Fourth, cholecystectomy was almost always undertaken only in patients with proven biliary disease after additional investigation. Only one study[23] that performed EUS, and one[8] that performed MRCP if indicated in 28 patients, undertook cholecystectomies in patients with 'true' IAP (Fig. 4). This confounding by indication creates a clear overestimation of the effect of cholecystectomy. In the most relevant subgroup studied in this review, patients with 'true' IAP, this overestimation is reduced to an important extent.

Future studies should address discrepancies in defining IAP as opposed to biliary pancreatitis. Reaching international consensus regarding the criteria for diagnosis of aetiologies is desirable, and would facilitate unambiguity in research as well as in clinical practice. A guideline-based proposal of such criteria is provided in Fig. S6 (supplementary information). Future studies in IAP should also focus on patients with either a first episode of IAP or recurrent pancreatitis, as these two groups appear to have distinct disease courses and should be considered as separate entities.[27]

This review has shown that cholecystectomy could potentially reduce the recurrence rate in patients diagnosed with 'true' IAP. However, the results for this subgroup were not statistically significant, probably because of the relatively small sample size. Thus, there appears to be some merit in treating IAP pragmatically by cholecystectomy to prevent recurrence, as suggested in previous studies.[8,9] On the other hand, with further standardization and improvement of diagnostic work-up, it should be possible to identify most patients with biliary aetiology. The wide variety of aetiologies revealed by additional investigation in the included studies underlines the value of additional diagnostic tests, at least in recurrent idiopathic pancreatitis. More research is needed to determine the importance of routine additional diagnostic work-up and to establish whether the yield of extra information could outweigh the efficacy of a pragmatic cholecystectomy in preventing recurrence.

The present review supports the hypothesis that many patients with IAP have occult biliary disease by showing an apparent reduction in recurrence after cholecystectomy in patients in whom no additional preoperative biliary

diagnostics were undertaken. This underlines the need for a more thorough evaluation before the diagnosis of IAP can be made. Additional research is needed in patients with ‘true’ IAP after optimal testing for biliary aetiology to determine the efficacy of cholecystectomy in this specific population.

Acknowledgements
The authors thank F. S. van Etten-Jamaludin for support in creating an adequate search strategy.

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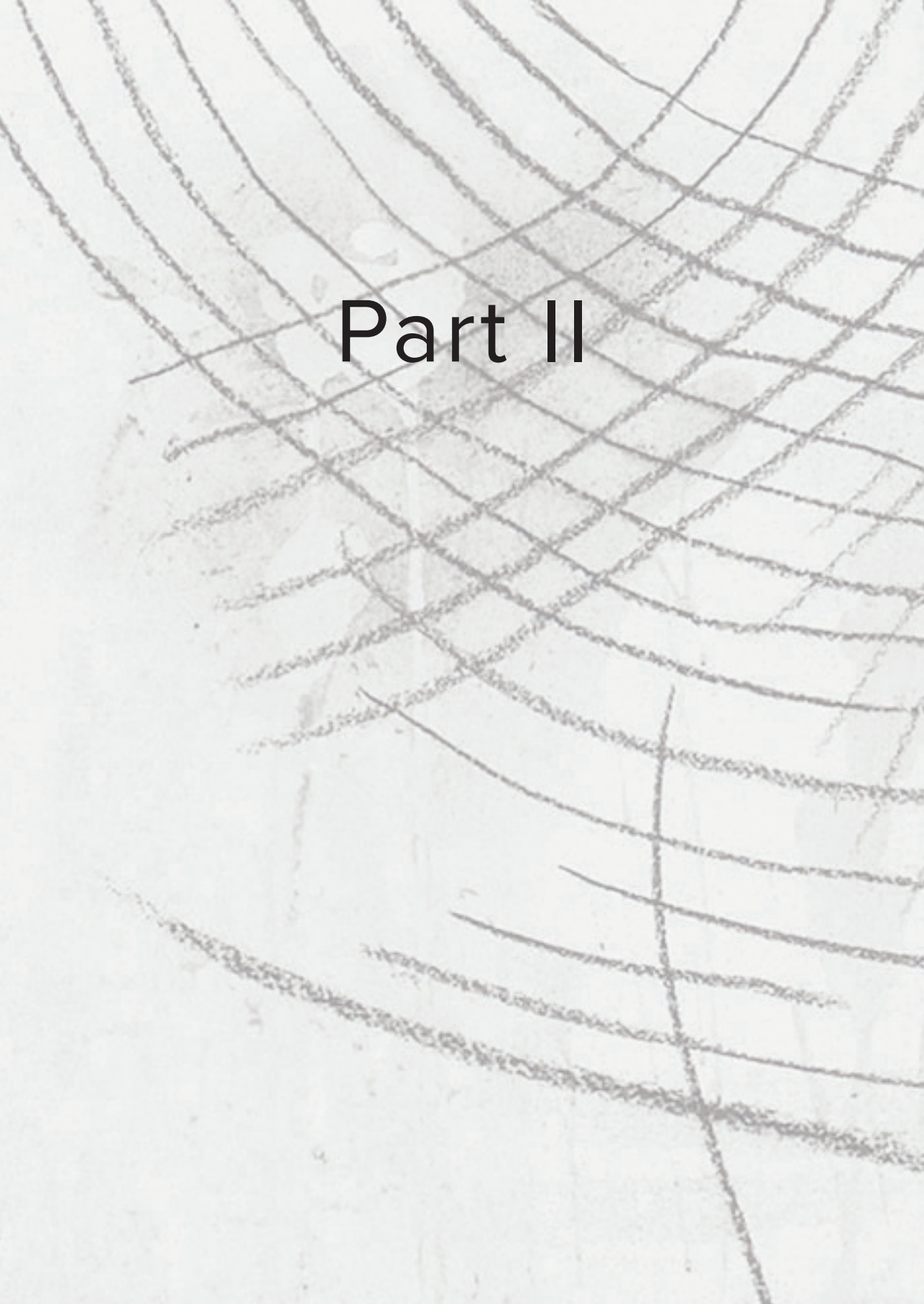
Supplementary material can be found at https://supplementary.info



Part II

URGENT ERCP IN ACUTE BILIARY PANCREATITIS

Chapter 4
No role for urgent endoscopic retrograde cholangiopancreatography in patients with predicted mild acute biliary pancreatitis
Submitted for publication

Chapter 5
Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy verus conservative treatment in predicted severe gallstone pancreatitis (APEC): a multicentre randomised controlled trial
Lancet, 2020

Chapter 6
Patient selection for urgent endoscopic retrograde cholangio-pancreatography by endoscopic ultrasound in predicted severe acute biliary pancreatitis (APEC-2): a multicentre prospective study
Gut, 2023

Chapter 4

No role for urgent endoscopic retrograde cholangiopancreatography in patients with predicted mild acute biliary pancreatitis

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Submitted for publication

Abstract

Introduction

Despite guideline recommendations, urgent ERCP is frequently performed in patients with acute biliary pancreatitis in the belief that it improves the clinical course of the disease.

Methods

We performed a post-hoc analysis on a prospective cohort of patients with predicted mild acute biliary pancreatitis without cholangitis, to assess the clinical value of urgent ERCP within 72 hours after symptom onset. Urgent ERCP was compared with a conservative approach in patients with cholestasis and patients without cholestasis. The primary outcome was severity of acute pancreatitis.

Results

In total 347 patients were included of whom 178 (51%) had cholestasis. Urgent ERCP was performed in 65 patients (19%) at a median of 1 day (IQR 0-1) after symptom onset. In the cholestasis group 47 patients (26%) underwent urgent ERCP versus 18 patients (11%) in the group without cholestasis. Patients who underwent urgent ERCP developed a more severe disease course compared to the conservative group (25% vs 13%, RR 1.83; 95% CI 1.10-3.01; p=0.04), which was also the case in the subgroup of patients with cholestasis (25% vs 10%, RR 2.57; 95% CI 1.27-5.24; p=0.01). This difference remained statistically significant in a regression model that included urgent ERCP, age and cholestasis (adjusted OR: 2.32; 95% CI 1.66-4.60, p=0.02).

Conclusion

In patients with predicted mild acute biliary pancreatitis without cholangitis, urgent ERCP was associated with a more severe disease course. This study provides no support for urgent ERCP in patients with predicted mild acute biliary pancreatitis regardless of the presence of cholestasis.

Introduction

Acute biliary pancreatitis (ABP) is caused by an ampullary obstruction that leads to pancreatic inflammation. The duration of the obstruction seems to be related to disease severity.[1] Based on this assumption, urgent decompression using endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy, may ameliorate the disease course. However, ERCP with sphincterotomy is associated with a risk of complications, including aggravation of pancreatitis.[2] A predicted mild ABP usually runs a benign disease course and complications are rare. It is also well known that in many patients gallstones or sludge pass into the duodenum spontaneously.[3,4] Hence, the potential benefits of urgent ERCP in this patient group are limited while the impact of complications associated with an ERCP in patients suffering from an acute pancreatitis episode may be substantial.

Several studies and meta-analyses have compared routine urgent ERCP to conservative treatment or selective use of ERCP in patients with ABP. Data on the role and optimal timing of ERCP however, are inconsistent. Studies are, in most cases, of moderate quality and have several limitations including heterogeneity of study populations, variety of endpoint definitions and a low percentage of sphincterotomy. In most of these studies a combination of patients with a predicted mild and predicted severe disease course were included.[5,6,7,8]

Guidelines suggest against the routine use of ERCP, but state that ERCP with sphincterotomy is probably indicated in patients with cholestasis and should be performed urgently in patients with cholangitis.[9,10] Recently, results of the randomized APEC trial were published, in which urgent ERCP, within 72 hours after symptom onset and within 24 hours after admission, was compared to a conservative treatment strategy in patients with predicted severe acute biliary pancreatitis without cholangitis. Urgent ERCP did not reduce severe complications and mortality in this subgroup of patients.[11]

Despite these recommendations, ERCP remains to be widely used in clinical practice in patients with ABP. Large database studies show that around 30% of ABP patients are treated with ERCP during index admission.[12,13,14,15] Data on the timing of ERCP in these studies is lacking. Kabaria et al. analyzed a US nationwide independent sample data set from 2005 and 2014 and found that there was a significant increasing trend in the use of urgent ERCP procedures over the 10-year study period from 2005-2014. In 2005, 4,601 urgent ERCP procedures (within 72 hours after admission) were

performed in patients with ABP without cholangitis which increased to up to 5,620 urgent ERCP procedures per year in 2014.[16] In Europe and Australia, studies on use of urgent ERCP in ABP show rates between 8 and 50%.[17,18,19] In studies in which predicted severity is reported, around 85-88% of these patients had a (predicted) mild disease course.

In summary, ERCP remains to be frequently performed in patients with ABP regardless of the presence of cholangitis or disease severity. In the current study we aim to assess the frequency of urgent ERCP in patients with a predicted mild acute biliary pancreatitis and compare the clinical outcomes between those who did and did not undergo urgent ERCP.

Methods

Study design

The Dutch Pancreatitis Study Group (DPSG) consists of a group of researchers and clinicians aiming to improve the care and outcomes of acute pancreatitis patients. Between January 2008 and December 2015, all acute pancreatitis patients admitted to one of the participating DPSG hospitals were asked to participate in a prospective acute pancreatitis registry (PWN-CORE). From this registry, we extracted patients with acute biliary pancreatitis from 11 DPSG hospitals, including 3 university hospitals and 8 large teaching hospitals, to be included in this study. We performed a post-hoc analysis of this prospective PWN-CORE cohort. The ethical review board approved the protocol in the participating hospitals and all patients gave written informed consent for inclusion in the DPSG PWN-CORE. This study was performed in accordance with the Declaration of Helsinki and reported in accordance with the STROBE guidelines.[20]

Study population

In this study, we included adult patients with a predicted mild acute pancreatitis of biliary origin, but without concomitant cholangitis. Acute pancreatitis was diagnosed according to the revised Atlanta criteria, i.e. at least two of the following features: (1) abdominal pain consistent with acute pancreatitis, (2) serum amylase/lipase levels >3 times the upper limit of normal, and (3) characteristic findings of acute pancreatitis on imaging (ultrasound, CT, MRI).[21]

A biliary origin was defined as either a serum alanine transferase (ALT) >2x upper limit of the normal value, a dilated common bile duct (CBD) with a diameter of ≥8mm for age ≤75 and ≥10mm for age >75 years, or gallstones

and/or sludge in the gallbladder and/or CBD on imaging (transabdominal/endoscopic ultrasound, CT, MRI/MRCP). Furthermore, signs of other possible etiologies had to be absent (e.g. post-ERCP, medication, trauma, hypercalcemia, hypertriglyceridemia and ongoing alcohol use (>3 units per day, or in case of binge drinking >5 units within 24 hours of the start of abdominal pain)).[22,23,24] A predicted mild disease course was defined as a CRP<151, a Glasgow score of <3 and an APACHE-II score of <8 on admission.[24]

The main exclusion criterion was cholangitis on admission, defined as fever (temperature of >38.5°C with chills or >39°C) combined with progressive cholestasis. Cholestasis was defined as either a dilated common bile duct (CBD) (≥8mm for age ≤75 and ≥10mm for age >75) and/or serum bilirubin of >40µmol/L and was considered progressive in the case of an increase in serum bilirubin of >5 µmol/L relative to the previous measurement. Patients with chronic pancreatitis based on the MANNHEIM criteria were excluded, as well as patients with a previous sphincterotomy and patients with insufficient data to establish an aetiology and/or predict disease severity.[25]
Patients were divided in two groups: an 'urgent' ERCP group and a

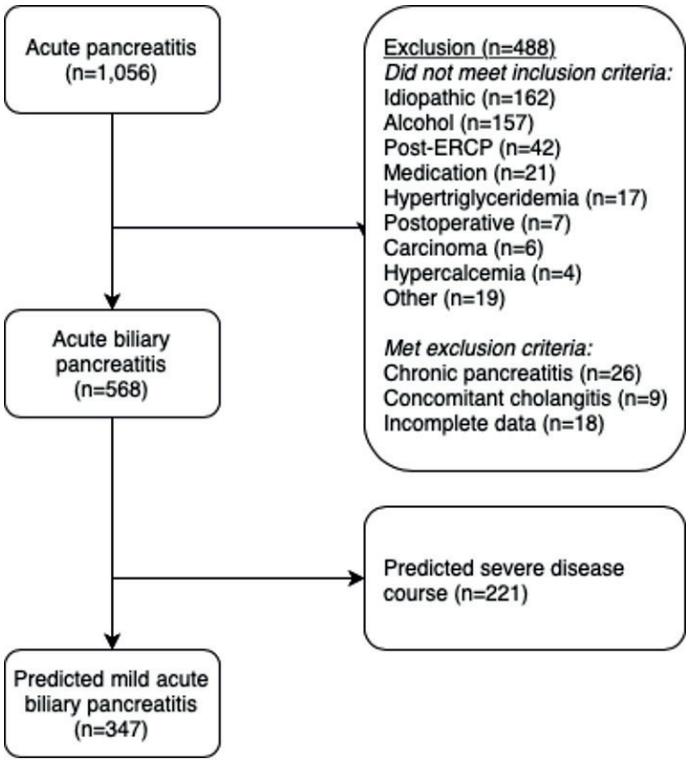

Figure 1 - Flow diagram of patients' inclusion

conservative group. ERCP was considered 'urgent' when performed within 72 hours of symptom onset. Within these two groups, we compared patients with cholestasis and patients without cholestasis. (Figure 1) Patients that underwent a 'delayed' ERCP more than 72 hours after symptom onset were included in the conservative group. ERCP was considered successful when the CBD was cannulated, a sphincterotomy was performed and when stones or sludge (if present) were evacuated completely.

Data collection

Patients were followed-up prospectively during the initial episode of acute pancreatitis by means of regular phone call conversations with their treating clinician.[26] The study team did not interfere with clinical decision making. After a minimum of two years, on-site data collection was carried out. This included data on the disease course, physical examinations and laboratory values, all imaging during follow-up, data on readmissions and data from out-patient hospital visits. Online clinical record forms were used for data collection. If patients were transferred or referred to other hospitals, data from these admissions and/or visits were also collected. All study data was verified by two independent researchers (NDH and DSU) prior to analysis. All authors agreed on the protocol of this study, including the methodology, statistical analyses and endpoints of this study before initiation.

Outcomes

The primary outcome was severity of acute pancreatitis according to the Revised Atlanta criteria. Severity of acute pancreatitis was divided in two categories: 1) mild acute pancreatitis, which is characterised by the absence of organ failure and the absence of local or systemic complications; 2) a combination of moderately severe and severe acute pancreatitis. Moderately severe is characterised by the presence of transient organ failure (<48 hours) or local or systemic complications in the absence of persistent organ failure and the severe acute pancreatitis is characterised by persistent organ failure (single of multiple, >48 hours). Local complications included: acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled of necrosis, but also gastric outlet obstruction, splanchnic and portal vein thrombosis and bowel ischemia/perforation. Because the number of patients with severe pancreatitis in this cohort of predicted mild patients was very small and the difference between moderate severe and severe only lies in duration of organ failure, we chose to combine a moderate severe and a severe disease course in the analysis. Systemic complications included exacerbation of pre-existing comorbidities

(i.e. cardiac or pulmonary disease). Secondary outcomes included the following characteristics: presence of CBD stones/sludge during ERCP, characteristics of ERCP procedures, the success rate of ERCP, ERCP-related complications (supplementary appendix 1), recurrent biliary events after urgent ERCP and conservative treatment, ICU-stay, total hospital stay and mortality. Definitions of biliary events are given in Supplementary appendix Table S2.

Statistical analysis

All analyses were performed using IBM SPSS statistics for Macintosh version 25 (Armonk, NY: IBM Corp). We performed a post-hoc analysis on the subset of patients with ABP with a predicted mild disease course. Continuous variables are shown as medians with interquartile ranges in the case of a skewed distribution, and as means with standard deviations in the case of a normal distribution. The students t-test and Mann-Whitney test were used to analyse continuous data. To compare proportions, the chi-square test was used, and in case one of the groups had a value of zero, the Fisher's exact test of independence was used. A two-sided p-value <0.05 was considered statistically significant. We compared the occurrence of endpoints between the urgent ERCP group and the conservative group. A subgroup analysis was performed on the patients with cholestasis on admission. Logistic regression models were used to investigate a possible association between urgent ERCP, cholestasis, age and disease severity. Univariable and multivariable analysis were performed to adjust for baseline differences between groups. The results of logistic regression analysis are presented as (adjusted) odds ratios (OR) and the 95% confidence interval.

Results

Patients

Between January 2008 and December 2015 a total of 1,056 acute pancreatitis patients were registered with the Dutch Pancreatitis Study Group in 11 hospitals, of whom 577 had biliary pancreatitis. Nine out of 577 patients (1.6%), met the criteria for concomitant cholangitis on admission were excluded. There were 347 patients with ABP and a predicted mild disease course on admission (Figure 2).

Median predictive scores on admission were: CRP 9 (IQR 4-26), Imrie 1 (IQR 0-1) and APACHE-II 4 (IQR 2-6). Patients presented at the emergency department at a median of 1 day (IQR 0-1) after onset of symptoms. A biliary etiology was established based on gallstones on imaging (EUS/US/CT/MRI) in 222 patients (64%), sludge on imaging in 52 patients (15%), a dilated CBD

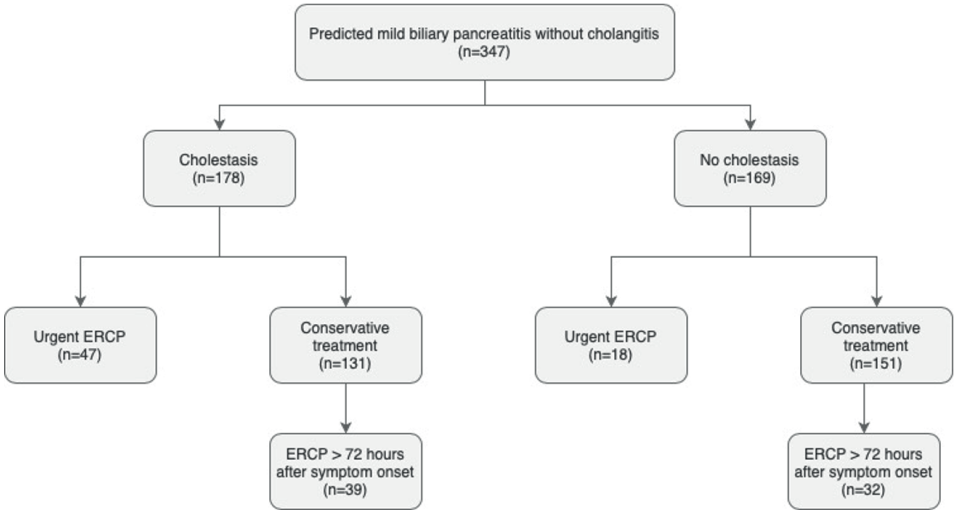

Figure 2 - Flow diagram of patients per subgroup

on imaging in 77 patients (22%) and based on biochemical criteria in 297 patients (86%). Most patients (67%) had multiple criteria for a biliary etiology. Baseline results for both the conservative and ERCP group can be found in Supplementary appendix Table 3. Median follow-up time was 4 years (3-6). Out of 347 patients, 65 (19%) underwent urgent ERCP at a median of 1 day after onset of symptoms. In 34 (53%) patients ERCP was performed at 0-24 hours after symptom onset, in 21 (32%) patients at 24-48 hours, and in 10 (15%) patients at 48-72 hours. Most patients that underwent urgent ERCP had cholestasis (72%). Sixteen patients (25%) underwent more than one ERCP, in most cases shortly after one and other either for persistent stones or stent placement/removal In 3 cases more than 6 months passed after the first ERCP. In the conservative treatment group 211 (75%) out of 282 patients did not undergo an urgent ERCP. A 'delayed' ERCP (>72 hours after symptoms onset) was performed in 71 patients (25%), in 43 (61%) patients this was during index admission (Figure 2). In most cases, the indication for this 'delayed' ERCP was persistent cholestasis, choledocholithiasis, or recurrent acute pancreatitis. Four patients underwent a 'delayed' ERCP for cholangitis (1%). Out of 71 patients, 53 (75%) patients underwent one ERCP, the remaining patients had multiple ERCP procedures. The indication for re-ERCP was choledocholithiasis in most cases.

The median number of patients enrolled per center was 37 (range 2-86). One out of eleven centers did not perform urgent ERCP in any of the patients. In the other centers, the use of urgent ERCP ranged between 6% and 33% of included patients with predicted mild ABP.

Cholestasis

Table 2 - Baseline characteristics of the subgroup of patients with and without cholestasis

Characteristic	Patients with cholestasis n=178			Patients without cholestasis N=169		
	Urgent ERCP (n=47)	Conservative treatment (n=131)	P-value	Urgent ERCP (n=18)	Conservative treatment (n=151)	P-value
Age in years – mean (± SD)	55 (17)	51 (17)	0.14	52 (20)	54 (16)	0.67
Female sex - no. (%)	24 (51%)	73 (56%)	0.58	9 (50%)	85 (56%)	0.61
ASA Class			0.73			0.23
• Healthy status - no. (%)	23 (49%)	58 (45%)		6 (33%)	66 (44%)	
• Mild systemic disease - no. (%)	16 (34%)	53 (41%)		11 (61%)	62 (41%)	
• Severe systemic disease - no. (%)	8 (17%)	17 (13%)		1 (6%)	23 (15%)	
• Severe systemic disease with constant threat to life - no. (%)	0 (0%)	1 (1%)		0 (0%)	0 (0%)	
BMI – median (IQR)	29 (24-32)	28 (25-33)	0.46	28 (25-37)	29 (25-32)	0.84
Severity of disease on admission:						
• APACHE-II score – no. (IQR)	5 (2-6)	4 (2-6)	0.12	4 (2-6)	4 (2-6)	0.74
• Modified Glasgow score no. (IQR)	1 (0-1)	1 (0-1)	0.09	1 (0-1)	1 (0-1)	0.89
• CRP no. (IQR)	10 (5-23)	10 (4-29)	0.87	5 (3-10)	9 (4-27)	0.08
Cholestasis – no. (%)						
• Bilirubin Level (mmol/L)	64 (43-109)	58 (35-88)	0.13	25 (16-34)	16 (11-25)	0.01
• Dilated common bile duct	25 (53%)	68 (52%)	0.41	0 (0%)	0 (0%)	-
Onset of symptoms to admission in days - median (IQR)	1 (0-1)	1 (1-3)	0.01	0 (0-1)	0 (0-1)	0.18

ASA score = American Society of Anaesthesia Physical status Classification System. BMI = Body Mass Index. CRP = C-reactive protein.

Table 2 - Outcomes of the subgroup of patients with and without cholestasis

Characteristic	Patients with cholestasis n=178			Patients without cholestasis N=169		
	Urgent ERCP (n=47)	Conservative treatment (n=131)	P-value	Urgent ERCP (n=18)	Conservative treatment (n=151)	P-value
Severity of pancreatitis			0.01			0.52
• Mild	35 (75%)	118 (90%)		14 (78%)	126 (83%)	
• Moderate severe or severe	12 (25%)	13 (10%)		4 (22%)	25 (17%)	
Individual components of Altanta classification						
• Pancreatic necrosis and/or peripancreatic collections	9 (19%)	10 (8%)	0.05	4 (22%)	22 (15%)	0.49
• Bowel ischemia	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
• Gastric outlet obstruction	1 (2%)	0 (0%)	0.26	0 (0%)	3 (2%)	1.00
• Splanchnic or portal vein thrombosis	1 (2%)	1 (1%)	0.46	1 (6%)	5 (3%)	0.50
• Exacerbation of pulmonary disease	0 (0%)	1 (1%)	1.00	0 (0%)	0 (0%)	-
• Exacerbation of cardiovascular disease	1 (2%)	2 (2%)	1.00	0 (0%)	4 (3%)	1.00
• New onset organ failure						
° New onset transient multi-organ failure	0 (0%)	0 (0%)	-	0 (0%)	1 (1%)	1.00
° New onset persistent multi-organ failure	2 (4%)	1 (1%)	0.17	1 (6%)	2 (1%)	0.29
° New onset transient single organ failure	1 (2%)	1 (1%)	0.46	0 (0%)	1 (1%)	1.00
° New onset persistent single organ failure	1 (2%)	1 (1%)	0.46	0 (0%)	2 (1%)	1.00
Other complications during index admission						
• Cholangitis	2 (4%)	1 (1%)	0.17	0 (0%)	2 (1%)	1.00
• Infected pancreatic necrosis	2 (4%)	4 (3%)	0.66	2 (11%)	5 (3%)	0.16
• Bacteremia	3 (6%)	4 (3%)	0.38	1 (6%)	6 (4%)	0.55
• Pneumonia	5 (11%)	3 (2%)	0.02	0 (0%)	6 (4%)	1.00
• Mortality	2 (4%)	0 (0%)	0.07	1 (6%)	0 (0%)	0.11
All-cause mortality during follow-up	3 (6%)	7 (5%)	0.73	1 (6%)	17 (11%)	0.65
Intensive care admission	4 (9%)	4 (3%)	0.21	1 (6%)	7 (5%)	1.00
Total intensive care stay for patients with ICU admission (days)	0 (0)	0 (0)	0.13	0 (0)	0 (0)	1.00
Total hospital stay (days)	8 (5-12)	6 (4-9)	0.00	8 (4-20)	7 (4-12)	0.59

Data are presented as n(%) unless otherwise specified.

Cholestasis was present in 178 patients (51%), of which 133 (75%) had a serum bilirubin level above 40umol/L. When comparing baseline characteristics between the group with and without cholestasis, comorbidity and predicted severity of disease were similar between groups. More patients in the cholestasis group had gallstones on imaging in the CBD and/or gallbladder (p=0.04), and an elevated serum ALT level (p=0.00) on admission. In the group of patients with cholestasis (n = 178), 47 patients (26%) underwent urgent ERCP and 131 patients (74%) conservative treatment. Baseline characteristics of the urgent ERCP versus conservative treatment groups were similar, except the time of symptom onset to admission, which was longer in the conservative group (p=0.01) (Table 1) Overview of the outcomes for both patients with and without cholestasis are presented in Table 2. Patients in the cholestasis group that underwent urgent ERCP were more likely to develop moderate severe or severe ABP (25% vs 10%, RR 2.57; 95% CI 1.27-5.24; p=0.01). They also had a higher risk of pneumonia (11% vs 2%, RR 4.65; 95% CI 1.16-18.69; p=0.02) and a longer length of hospital stay (median 8 (IQR 5-12) versus 6 (IQR 4-9) days, p=0.00).

ERCP characteristics

Table 3 lists the characteristics of the urgent ERCP procedures. The number of patients in whom sludge or gallstones were found in the common bile duct during urgent ERCP did not differ between the cholestasis and no cholestasis group (p=0.71 for sludge and p=0.26 for stones). Cannulation was successful in 94% of patients and stone extraction was complete in all but one patient. Biliary sphincterotomy was performed in 92% of patients with cholestasis and 94% of patients without cholestasis. Overall, ERCP was successful in 43 patients (92%), and equally successful in the cholestasis and no cholestasis group. The overall complication rate was low (4%).

In the group of 169 patients without cholestasis, 18 patients (11%) underwent urgent ERCP and 151 patients (89%) were treated conservatively. Median serum bilirubin levels were higher in the urgent ERCP group (p = 0.01), all other baseline characteristics were comparable (Table 1).

Primary and secondary outcomes

In Table 2 the primary and secondary outcomes are presented. Severity of disease course and overall complications did not differ between the urgent ERCP group and the conservative group. After adjustment for bilirubin levels in multivariable analysis, urgent ERCP did not have an effect on the severity of disease course in patients without cholestasis (adjusted OR: 1.2; 95% CI;

Table 3 - Characteristics of urgent ERCP

ERCP Characteristics of urgent ERCP	Patients with cholestasis n=47	Patients without cholestasis n=18	P-value
Time from onset symptoms to ERCP in days – median (IQR)	1 (1-2)	1 (1-2)	0.39
EUS performed prior to urgent ERCP – no. (%)	0 (0%)	0 (0%)	-
Duration of ERCP procedure n=18) (minutes) – median (IQR)	30 (18-36)	N/A	-
Stones in common bile duct - no. (%)	19 (43%)	5 (28%)	0.26
Sludge in common bile duct - no. (%)	6 (14%)	3 (17%)	0.71
Common bile duct cannulation - no. (%)	44 (94%)	18 (100%)	0.56
Pancreatic duct cannulation – no. (%)	15 (32%)	3 (17%)	0.35
Stone extraction - no. (%)	21 (45%)	6 (33%)	0.41
Incomplete extractions - no. (%)	0 (0%)	1 (6%)	0.20
Precut performed - no. (%)	8 (17%)	3 (17%)	1.00
Sphincterotomy performed - no. (%)	43 (92%)	17 (94%)	1.00
ERCP successful - no. (%)	43 (92%)	16 (89%)	0.67
ERCP complications			
• Bleeding	1 (2%)	1 (6%)	0.48
• Perforation	0 (0%)	0 (0%)	-
• Cardiopulmonary complications	1 (2%)	0 (0%)	1.00

ERCP= endoscopic retrograde cholangiopancreatography.

0.36 - 4.16; p=0.76).

In Table 4 severity of pancreatitis and complications are presented for the urgent ERCP and conservative group irrespective of the presence of cholestasis. Patients who underwent urgent ERCP developed a more severe disease course compared to patients in the conservative treatment group (RR 1.83; 95% CI 1.09-3.07; p=0.03), in particular pancreatic necrosis and/or peripancreatic collections (20% versus 11%). Furthermore, total hospital stay in days was longer in the urgent ERC group. The mortality rate during index admission was higher in the urgent ERCP group (3 (5%) vs 0 (0%) patients, p=0.01). All-cause mortality during follow-up was similar in both groups.

Out of 54 patients with a moderate severe or severe disease course, 25 patients (46%) had cholestasis. Cholestasis was not an independent risk factor for a severe disease course in univariable analysis (RR 1.13; 95% CI: 0.83 – 1.53; p= 0.42). Time of symptom onset before admission was significantly longer in the conservative group. After adjustment for the time of symptom onset before admission in multivariable analysis, urgent ERCP remained associated with a higher risk of developing a moderate severe/severe disease course (adjusted OR: 2.15; 95% CI: 1.08 – 4.28; p = 0.03).
A multivariable logistic regression was performed to assess the impact of

age, timing of ERCP ('urgent' vs 'delayed'), cholestasis, and the interaction between urgent ERCP and cholestasis on severity of acute pancreatitis. There was no evidence for an independent effect of urgent ERCP, cholestasis or the interaction between the two in this model. In the logistic regression model that included age, urgent ERCP and cholestasis, a significant negative effect was found of ERCP on severity of ABP was found (adjusted OR: 2.32; 95% CI 1.66-4.60, p=0.02) The full models are shown in Table 5 and Table 6.

Discussion

The current multicenter prospective cohort study in patients with predicted mild ABP without cholangitis, urgent ERCP did not show any beneficial effect on the disease course. In fact, urgent ERCP was associated with a more severe course compared to conservative treatment, also in patients with cholestasis at admission. Our data add to the body of evidence

Table 4 - Outcomes of acute biliary pancreatitis for the urgent ERCP and conservative treatment group

Characteristic	Urgent ERCP (n=65)	Conservative treatment (n=282)	P-value
Severity of pancreatitis			0.03
• Mild	49 (76%)	244 (87%)	
• Moderate severe or severe	16 (25%)	38 (13%)	
Individual components of Atlanta classification			
• Pancreatic necrosis and/or peripancreatic collections	13 (20%)	32 (11%)	0.07
• Bowel ischemia	0 (0%)	0 (0%)	-
• Gastric outlet obstruction	1 (2%)	3 (1%)	0.57
• Splanchnic or portal vein thrombosis	2 (3%)	6 (2%)	0.65
• Exacerbation of pulmonary disease	0 (0%)	1 (1%)	1.00
• Exacerbation of cardiovascular disease	1 (2%)	6 (2%)	1.00
• New onset organ failure			
° New onset transient multi-organ failure	0 (0%)	1 (1%)	1.00
° New onset persistent multi-organ failure	3 (5%)	3 (1%)	0.08
° New onset transient single organ failure	1 (2%)	2 (1%)	0.46
° New onset persistent single organ failure	1 (2%)	3 (1%)	0.57
Other complications during index admission			
• Cholangitis	2 (3%)	3 (1%)	0.24
• Infected pancreatic necrosis	4 (6%)	9 (3%)	0.28
• Bacteremia	4 (6%)	10 (4%)	0.31
• Pneumonia	5 (8%)	9 (3%)	0.15
• Mortality	3 (5%)	0 (0%)	0.01
All-cause mortality during follow-up	4 (6%)	15 (5%)	0.76
Intensive care admission	5 (8%)	11 (4%)	0.19
Total intensive care stay (days)	0 (0)	0 (0)	0.26
Total hospital stay (days)	8 (5-13)	6 (4-10)	0.02

Data are presented as n(%) unless otherwise specified.

Table 5 - Logistic regression model on severity of ABP model with interaction between cholestasis and urgent ERCP

Variable	P-value	Adjusted OR	95% CI for adjusted OR
Urgent ERCP	0.54	1.45	0.44 - 4.79
Cholestasis	0.18	0.27	0.04 - 1.86
Interaction between cholestasis and urgent ERCP	0.33	2.10	0.48 - 9.20
Age	0.55	1.01	0.10 - 1.02

Table 6 - Logistic regression model on severity of ABP without interaction between cholestasis and urgent ERCP

Variable	P-value	Adjusted OR	95% CI for adjusted OR
Urgent ERCP	0.02	2.32	1.66 – 4.60
Cholestasis	0.21	0.68	0.37 – 1.24
Age	0.50	1.01	1.00 – 1.02

to no longer perform urgent ERC in patients with acute biliary pancreatitis, unless the patient suffers from cholangitis.[11]

In this study we found that 31% of patients with predicted mild ABP underwent ERCP during index admission, and 19% of patients underwent an ERCP within 72 hours after onset of symptoms. In previous studies the timing of ERCP is often not specified making it difficult to make a comparison. Large database studies on the use of ERCP in ABP in the US show that 19% to 34% of patients are undergoing an ERCP during index admission. Three observational studies found that early ERCP (between 24-72 hours after symptom onset or hospital admission) was performed in up to 50% of cases.[17,18,19]

In the current study, patients who underwent urgent ERCP were more likely to develop a moderate severe or severe disease course, also in the subgroup of patients with cholestasis. Patients with cholestasis that underwent urgent ERCP more often developed pneumonia and their hospital stay was significantly longer compared to patients treated conservatively. In the group without cholestasis, these differences were not found. However, as only 11% of patients in this group underwent urgent ERCP, this subgroup might have been too small to detect such an effect. The incidence of post-ERCP pancreatitis, one of the complications of ERCP cannot be measured reliably in ABP patients for obvious reasons. However, urgent ERCP in ABP may induce additional pancreatic trauma thereby changing a predicted mild disease course into a severe one.

Several acute pancreatitis treatment guidelines provide guidance in which

clinical scenarios ERCP should be performed. An overview of current guidelines can be found in supplementary appendix Table S4. In summary, most guidelines advise against the routine use of urgent ERCP and state that urgent ERCP is only indicated in case of cholangitis. An overview of randomized controlled trials and meta-analyses pertaining to urgent ERCP in ABP can be found in supplementary appendix Table S5 and S6. Most trials on early ERCP included a heterogeneous study population with both predicted severe and predicted mild ABP patients. Three out of ten trial included only (predicted) severe ABP patients, two of which also included cholangitis patients.[11,27,28] Early ERCP within 72 hours after admission had a beneficial effect on either APACHE-2 score in the study of Chens et al, and clinical symptoms, complications and mortality in the study by Zhou et al.[27, 28]

In the third study, the APEC-trial, only patients with a predicted severe disease course but without cholangitis were included. In the APEC study, urgent ERCP within 24 hours after admission and within 72 hours after symptom onset did not reduce a composite endpoint of major complications and mortality.[11] The other seven RCTs included both (predicted) mild and (predicted) severe ABP patients, with a majority of (predicted) mild patients in all trials.[22,23,29,30,31,32,33] In five trials there was a beneficial effect of early ERCP, in two of these studies this was only seen in predicted severe ABP patients and not in the patients with a predicted mild disease course. All these trials also included patients with concomitant cholangitis.[22,29,30,32,33] In two trials, one study including only patients with a biliary obstruction[23], and one study only including patients without a biliary obstruction[31], there was no beneficial effect of early ERCP on complications and mortality. Folsch et al. even found a higher rate of respiratory failure in the early ERCP group.[31] Recently, the results of a study investigating whether urgent ERCP is beneficial in patients with predicted severe ABP and confirmed biliary obstruction by EUS, the APEC-2 study, also showed no benefit of urgent ERCP.[34]

In summary, it seems that only studies in which patients with cholangitis were included show a beneficial effect of early ERCP. This is supported by the APEC trial in patients with predicted severe ABP excluding patients with cholangitis which did not show a beneficial effect of urgent ERCP with ES. In the acute phase of ABP however it is challenging to establish a diagnosis of concomitant cholangitis. In both the APEC trial and the current study stringent criteria for concomitant cholangitis were used.

The recommendations of recent meta-analyses are increasingly restrictive

regarding the indication of ERCP in ABP (Supplementary Table S6). The most recent meta-analysis by Shresta et al. that also includes the APEC-trial concludes that there is no benefit of early ERC in patients with acute biliary pancreatitis without cholangitis.[5] Based on this meta-analysis and the current study, a beneficial effect of urgent ERCP in mild ABP is absent. In fact, the current study suggests that urgent ERCP might even be harmful. Possible explanations for this finding are that the ERCP itself has a harmful influence on the disease course though the same mechanism that causes post-ERCP pancreatitis. The infection risk via bacterial translocation might also be higher. Also, respiratory aspiration during the procedure causing a pneumonia and periods of hypotension due to sedation may have a negative effect.

Randomized controlled trials investigating the benefit of urgent ERCP in patients with predicted mild ABP patients without cholangitis are lacking. We believe however that the cumulative body of evidence including the current study, convincingly shows that urgent ERCP in these patients should not be performed.

Some limitations of our study should be considered. First, even though patients were followed prospectively, analyses were performed post-hoc. Therefore, the decision to perform urgent ERCP was up to the treating clinicians. This reflects clinical practice but led to more patients in the urgent ERCP group with cholestasis compared to the conservative group. It is possible that selection bias played a role, and that patients that underwent urgent ERCP had more pain compared to the patients that were treated conservatively. Nevertheless, in a multivariable model cholestasis was not shown to be an independent risk factor for a severe disease course.

Second, we had no data on the level of experience of the endoscopists that performed the ERCP procedures. However, cannulation was successful in 94% of urgent ERCP procedures, suggesting that experienced endoscopists performed these procedures. Third, we included patients based on their predicted disease severity at admission. Predictive scores get more accurate when measured over a longer time period (i.e. 48 hours). However, the window to perform an ERCP at a time when it is expected to be most effective to ameliorate the disease course through early de-obstruction of the biliary and pancreatic duct, does not allow for a prolonged observation period.

The main strength of this study is that we investigated a large group of patients with mild ABP with and without cholangitis. Inclusion was based on

stringent criteria and detailed data was available regarding the timing and specifics of the ERCP procedures, and on the disease course. Urgent ERCP was successful in 92% of patients, that is canulation of the CBD and removal of stones or sludge when present. The rate of procedural complications was low (4%).

In conclusion, this study did not show a beneficial effect of urgent ERCP in patients with a predicted mild ABP without cholangitis, irrespective of biochemical cholestasis or signs of biliary obstruction on imaging. In fact, urgent ERCP seemed harmful, also in patients with cholestasis. Therefore, based on the current available evidence including this study, urgent ERCP cannot be advised in patients with ABP, unless there is concomitant cholangitis.

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Supplementary material can be found at https://supplementary.info

Chapter 5

Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy verus conservative treatment in predicted severe gallstone pancreatitis (APEC): a multicentre randomised controlled trial

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Lancet, 2020

Summary

Background

It remains unclear whether urgent endoscopic retrograde cholangio-pancreatography (ERCP) with biliary sphincterotomy improves the outcome of patients with predicted severe gallstone pancreatitis without concomitant cholangitis. We did a randomised trial to compare urgent ERCP with sphincterotomy versus conservative treatment in patients with predicted severe acute gallstone pancreatitis.

Methods

In this multicentre, parallel-group, assessor-masked, randomised controlled superiority trial, patients with predicted severe (Acute Physiology and Chronic Health Evaluation II score ≥8, Imrie score ≥3, or C-reactive protein concentration >150 mg/L) gallstone pancreatitis without cholangitis were assessed for eligibility in 26 hospitals in the Netherlands. Patients were randomly assigned (1:1) by a web-based randomisation module with randomly varying block sizes to urgent ERCP with sphincterotomy (within 24h after hospital presentation) or conservative treatment. The primary endpoint was a composite of mortality or major complications (new-onset persistent organ failure, cholangitis, bacteraemia, pneumonia, pancreatic necrosis, or pancreatic insufficiency) within 6 months of randomisation. Analysis was by intention to treat. This trial is registered with the ISRCTN registry, ISRCTN97372133.

Findings

Between Feb 28, 2013, and March 1, 2017, 232 patients were randomly assigned to urgent ERCP with sphincterotomy (n=118) or conservative treatment (n=114). One patient from each group was excluded from the final analysis because of cholangitis (urgent ERCP group) and chronic pancreatitis (conservative treatment group) at admission. The primary endpoint occurred in 45 (38%) of 117 patients in the urgent ERCP group and in 50 (44%) of 113 patients in the conservative treatment group (risk ratio [RR] 0.87, 95% CI 0.64–1.18; p=0.37). No relevant differences in the individual components of the primary endpoint were recorded between groups, apart from the occurrence of cholangitis (two [2%] of 117 in the urgent ERCP group vs 11 [10%] of 113 in the conservative treatment group; RR 0.18, 95% CI 0.04–0.78; p=0.010). Adverse events were reported in 87 (74%) of 118 patients in the urgent ERCP group versus 91 (80%) of 114 patients in the conservative treatment group.

Interpretation

In patients with predicted severe gallstone pancreatitis but without cholangitis, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality, compared with conservative treatment. Our findings support a conservative strategy in patients with predicted severe acute gallstone pancreatitis with an ERCP indicated only in patients with cholangitis or persistent cholestasis.

Funding

The Netherlands Organization for Health Research and Development, Fonds NutsOhra, and the Dutch Patient Organization for Pancreatic Diseases.

Research in context

Evidence before this study

Patients with gallstone pancreatitis frequently undergo endoscopic retrograde cholangiography (ERCP) with biliary sphincterotomy to remove obstructing gallstones with the intention to ameliorate the disease course. Before embarking on the current trial, we performed a systematic review using PubMed, Embase, the Cochrane Library, NHS Economic Evaluation Database of studies published until May 2012 with the search terms “ERCP” and, “gallstone” and “pancreatitis”. Six trials fulfilled the inclusion criteria.

Based on this systematic review, ERCP did not reduce mortality but did reduce complications in patients with gallstone pancreatitis at high risk for developing complication. These trials, however, have significant shortcomings such as heterogeneous patient populations, ERCPs performed relatively late after hospital admission, no routine sphincterotomy, no separate evaluation of patients with cholestasis, and various endpoint definitions. More importantly, the pooled sample size of patients with predicted severe gallstone pancreatitis without cholangitis was too small to detect differences of urgent ERCP in endpoints as major complications or mortality. As widely agreed, it therefore remains unclear whether ERCP truly improves outcome in these patients.

Added value of this study

This trial answers the question whether urgent ERCP with biliary sphincterotomy should be performed in patients with predicted severe acute gallstone pancreatitis, with or without cholestasis, but without cholangitis. We found that urgent ERCP with biliary sphincterotomy did not reduce the composite endpoint of major complications or mortality, as compared with conservative treatment. Although cholangitis occurred more often in patients treated conservatively, this had no negative impact on overall outcome.

Implications of all the available evidence

Urgent ERCP with biliary sphincterotomy should not be done routinely in patients with predicted severe acute gallstone pancreatitis and is indicated only in patients with concomitant cholangitis. With this strategy, around two thirds of patients are spared an invasive procedure from which they gain no benefit but could have procedure-associated complications.

Introduction

Acute pancreatitis is among the most common gastrointestinal diagnoses for acute inpatient hospital admission, and its incidence is increasing worldwide because of increased rates of obesity and gallstones.[1,2] Gallstones are the most common cause of acute pancreatitis.[3,4] The initiating event is impaction of gallstone stones or sludge in the common bile duct and ampulla.[5,6] Patients with gallstone pancreatitis can develop cholangitis, organ failure, and other life-threatening complications.[7–9] During endoscopic retrograde cholangiopancreatography (ERCP), retained gallstones are visualized visualised, biliary sphincterotomy is done, and gallstones are extracted.

Guidelines recommend urgent ERCP in patients with gallstone pancreatitis with concomitant cholangitis and suggest that ERCP might be beneficial in patients with cholestasis but without cholangitis.[8,10–12] In patients with gallstone pancreatitis without cholangitis and without significant cholestasis, it is unclear whether urgent ERCP is beneficial. Nevertheless, observational studies have shown that in as much as half of such patients an ERCP is performed.[13,14] Unfortunately, previous randomised trials on this subject have substantial shortcomings. First, patients with concomitant cholangitis, patients with a predicted mild disease course, and even patients with a non-gallstone aetiology were included.[15–19] Second, in most trials ERCP was done up to 3 days after hospital admission. Presumably, for biliary decompression to be effective in preventing complications, ERCP needs to be done as early as possible after onset of the disease — ie, after onset of symptoms.[15,17,20] Third, in previous trials only a small proportion of patients had a biliary sphincterotomy.[16,17,19,21] Because microlithiasis can easily be missed on cholangiogram during ERCP, and as small gallstones in particular are known to cause pancreatitis, this limitation is particularly relevant.[22,23] Performing sphincterotomy routinely during ERCP is also supported by a previous study showing that sphincterotomy reduced complications irrespective of the presence of gallstones on cholangiogram.[13] Furthermore, biliary sphincterotomy decompresses the biliary tract, which potentially ameliorates the disease course.[5,24–27] In return, ERCP with sphincterotomy is an invasive procedure that is associated with complications in up to 10% of patients.[28,29] Finally, the study populations of the individual trials and of subsequent meta-analyses were too small to detect an effect of ERCP in the group of patients with gallstone pancreatitis with a predicted severe disease course. It therefore remains unclear whether urgent ERCP with biliary sphincterotomy is beneficial in patients with predicted severe acute gallstone pancreatitis, with and without cholestasis, but without cholangitis.

We did a multicentre randomised controlled trial to investigate whether urgent ERCP with sphincterotomy is superior to conservative treatment in patients with predicted severe acute gallstone pancreatitis.

Methods

Study design and participants

The APEC (Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus Conservative treatment) trial was a multicentre, parallel-group, assessor-masked, randomised controlled superiority trial done in 26 hospitals in the Netherlands. The trial was done according to the previously published trial protocol (appendix pp 27–40).[30] All adult patients presenting to the emergency department with acute gallstone pancreatitis were assessed for eligibility by the local physician. Acute pancreatitis was defined as the presence of at least two of the following criteria: upper abdominal pain; serum amylase or lipase concentration more than three times the upper serum limit of normal; or features of acute pancreatitis on imaging.[12] Patients with a predicted severe disease course were eligible for randomisation on the basis of an Acute Physiology and Chronic Health Evaluation (APACHE-II) score of eight or more, Imrie (or modified Glasgow) score of three or more, or serum C-reactive protein concentration higher than 150 mg/L within 24h of admission.[31–35] Gallstone pancreatitis was defined by either biliary sludge or gallstones on imaging, a dilated common bile duct on imaging (>8 mm in patients aged ≤75 years or >10 mm in patients aged >75 years), or an alanine aminotransferase concentration of more than twice the upper limit of normal.[8,12,36–38] Exclusion criteria included cholangitis, pancreatitis due to other causes, a previous sphincterotomy or needle knife precut, or a history of chronic pancreatitis (see appendix p 3 for additional inclusion and exclusion criteria). Cholangitis was defined as fever in combination with either common bile duct stones, a dilated common bile duct, or (progressive) cholestasis (see appendix p 7 for detailed definition). Written informed consent was obtained from each participant. The APEC trial was done in accordance with the Declaration of Helsinki and the Dutch law regarding research involving human participants. The ethical committee of the Erasmus MC University Medical Center in Rotterdam, Netherlands, approved the trial protocol.

Randomisation and masking

Patients were randomly assigned (1:1) by the central study coordinators to urgent ERCP with biliary sphincterotomy or conservative treatment with a web-based randomisation module with randomly varying block sizes.

At randomisation, patients were stratified according to the presence of cholestasis and for the region of the hospital (appendix p 3). Cholestasis was defined as a serum bilirubin of more than 2.3 mg/dL (40 µmol/L) or a dilated common bile duct (>8 mm in patients aged ≤75 years or >10 mm in patients aged >75 years) at randomisation. Because of the invasive nature of the intervention, participants and physicians were not masked to treatment assignment.

Procedures

Urgent ERCP with biliary sphincterotomy needed to be done within 24h after presentation at the emergency department and within 72h after symptom onset. Biliary sphincterotomy was done irrespective of whether common bile duct stones were confirmed. ERCP was performed by, or under the direct supervision of, an experienced endoscopist (defined as >400 ERCPs in his or her lifetime and >50 ERCPs annually on average in the previous 3 years). If the common bile duct could not be cannulated, even after precut sphincterotomy, urgent ERCP was abandoned and the patient was treated conservatively.

In the conservative treatment group, patients were managed according to a supportive treatment regimen (appendix pp 3–4). On-demand ERCP with biliary sphincterotomy was done when a patient developed cholangitis. If the attending clinician doubted whether ERCP should be done, the trial coordinator presented the case to a multidisciplinary expert panel, which provided treatment advice within 24h. An elective ERCP was done in the event of persistent cholestasis or retained bile duct stones when the patient had recovered from the initial pancreatitis episode. A CT scan was done 5–7 days after hospital admission for assessment of pancreatic necrosis.

Data were collected by local physicians using a standardised case record form. In-hospital use of health care was registered as part of the data collection. Out-of- hospital use of health care was documented by self-administered questionnaires. All CT scans were reassessed by one experienced radiologist (TLB) masked to treatment allocation. An independent monitor assessed the study documents and compared these with the source documents.

Outcomes

The primary endpoint was a composite of major complications or mortality occurring within 6 months after randomisation. Major complications were defined as new-onset persistent organ failure, pancreatic parenchymal

necrosis, bacteraemia, cholangitis, pneumonia, or pancreatic endocrine or exocrine insufficiency (for definitions, see appendix p 7). Secondary endpoints included the need and length of intensive care admission, the length of hospital stay, readmissions for gallstone-related events, quality of life, and societal costs (including health care costs and out-of-pocket expenses by patients) in the first 180 days after randomisation (see appendix p 31 for full list of secondary endpoints).

A masked adjudication committee of gastroenterologists and surgeons assessed all potential endpoints individually. Disagreements were resolved in a consensus meeting.

An independent Data Safety Monitoring Committee (DSMC) assessed protocol adherence, patient recruitment, and patient safety. Adverse events were reported by treating clinicians to the coordinating investigator, who subsequently reported the events to the Dutch Central Committee for Research Involving Human Subjects. All events were reported unblinded to the DSMC per consecutive group of 60 patients. A continuous sequential safety analysis on death was also done to ensure patients' safety throughout the trial (Pest software, version 4.4).[39]

Statistical analysis

The sample size calculation was based on an expected reduction of the primary endpoint from 46% in the conservative treatment group to 32% in the urgent ERCP with sphincterotomy group, as reported in a nationwide observational study.[13] A correction factor of 2% for both percentages was used to account for the possibilities that ERCP was not done within 24h after presentation or no sphincterotomy was performed. We calculated that 232 patients were required to detect a reduction of the primary endpoint from 48% to 30%, with a power of 80%, a two-sided significance level of 5%, and a 1% dropout rate.

An interim analysis of the primary endpoint was done after 50% of patients were randomly assigned and discharged from hospital. We used a Haybittle-Peto approach to test for a beneficial effect (symmetric stopping boundaries at $p<0.001$); there was no assessment of futility.[40,41] The adjudication committee, masked to treatment assignment, only excluded patients before statistical analyses were done. Final analyses were based on the intention-to-treat principle, with patients being analysed according to allocated treatment group and irrespective of whether sphincterotomy

was successful. Dichotomous data were compared with the Pearson's χ2 test or Fisher's exact test and continuous data with the Mann-Whitney U test. Results are presented as risk ratios (RRs) with corresponding 95% CI. A two-sided p value of less than 0.05 was considered significant. Missing data for the primary and other secondary endpoints were categorised as no event. For other analyses, data were considered to be missing completely at random. The interim analysis and final analysis were done by an independent statistician. A predefined exploratory subgroup analysis was done in patients with cholestasis at randomisation. Logistic regression models were used as formal tests for interaction to assess the potential size of different treatment effects among these subgroups. A post-hoc analysis was done to compare the incidence of the primary endpoint in patients with common bile duct stone extraction during ERCP versus patients in the conservative treatment group.

Results for costs, quality-adjusted life-years (QALYs), and differences between treatment groups are reported with bias-corrected and accelerated 95% CIs to account for sampling variability, based on bootstrapping of 5000 samples. The bootstrap results are reported with quadrants of the incremental costs versus the numbers of patients with poor outcome prevented or versus the numbers of QALYs gained.

For statistical analysis we used IBM SPSS Statistics version 24, R version 3.6.1 (2019-07-05), and the packages epitools (version 0.5.10), survival (version 2.44.1.1), and nlme (version 3.1.140). This trial is registered with the ISRCTN registry, ISRCTN97372133. Details of the statistical analysis and the economic evaluation are provided in the appendix (pp 4–5).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

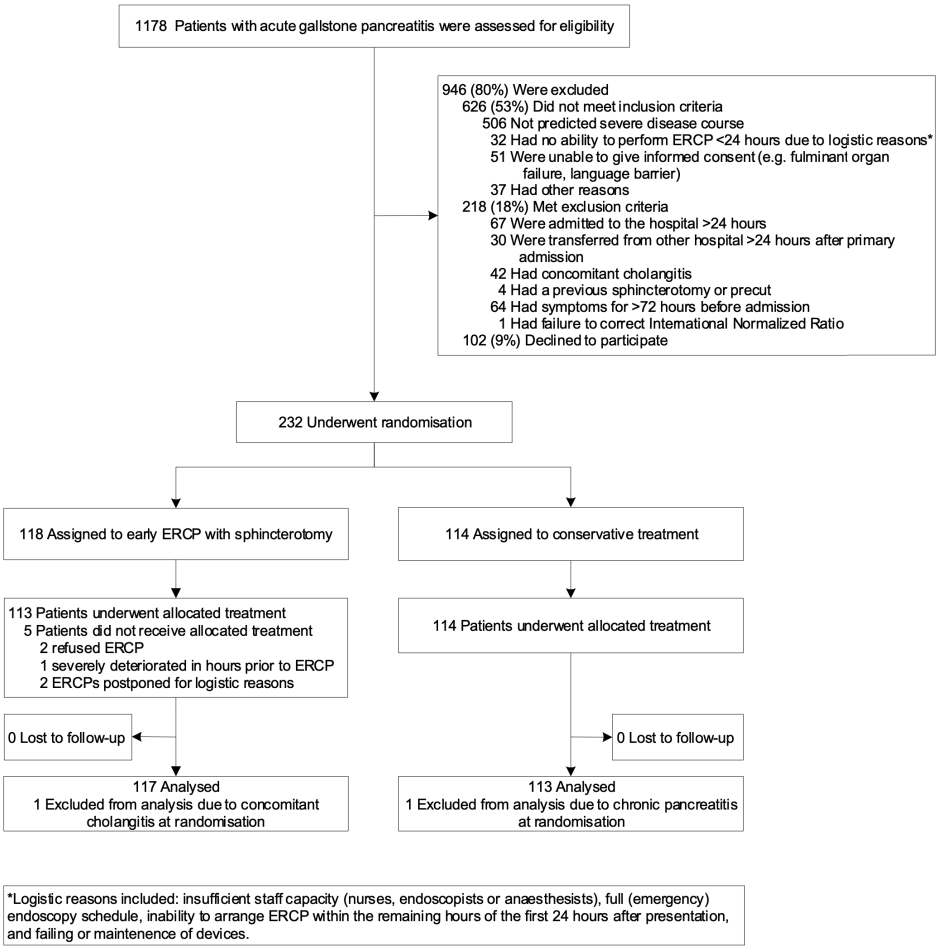

Figure 1 - Enrollment, Randomisation and Follow-up of Patients.

Results

Between Feb 28, 2013, and March 1, 2017, 1178 patients with acute gallstone pancreatitis were assessed for eligibility (figure 1); however, most patients had a predicted mild disease course. 232 patients with a predicted severe disease course were randomly assigned to urgent ERCP with sphincterotomy or conservative treatment. The adjudication committee excluded two patients after randomisation: one patient in the urgent ERCP group with concomitant cholangitis and one patient in the conservative treatment group with chronic pancreatitis.

117 patients in the urgent ERCP group and 113 patients in the conservative treatment group were included in the intention-to-treat analyses. Baseline characteristics of the two groups are shown in table 1. Cholestasis was present in 63 (54%) of 117 patients in the urgent ERCP group and in 67 (59%) of 113 patients in the conservative treatment group.

The primary composite endpoint of major complications or mortality occurred in 45 (38%) of 117 patients in the urgent ERCP group compared with 50 (44%) of 113 patients in the conservative treatment group (RR 0.87, 95% CI 0.64 to 1.18; absolute risk difference 5.79 percentage points, 95% CI –6.93 to 18.50; p=0.37; table 2). In a post-hoc analysis, the primary endpoint occurred in 22 (41%) of 54 patients with common bile duct stone extraction during ERCP compared with 50 (44%) of 113 patients in the conservative treatment group (RR 0.96, 95% CI 0.77 to 1.18; p=0.67). No relevant differences in the individual components of the primary endpoint were found between groups, apart from the occurrence of cholangitis: two (2%) patients in the urgent ERCP group developed cholangitis compared with 11 (10%) patients in the conservative treatment group (RR 0.18, 95% CI 0.04 to 0.78; p=0.010; table 2). Eight (7%) patients in the urgent ERCP group died, compared with ten (9%) patients in the conservative treatment group (RR 0.77, 95% CI 0.32 to 1.89; p=0.57).

In the urgent ERCP group, 24 (21%) of 117 patients were admitted to the intensive care unit, compared with 13 (12%) of 113 patients in the conservative treatment group (RR 1.78, 95% CI 0.96–3.33; p=0.063; appendix p 6). New-onset pulmonary organ failure developed in 20 (17%) patients in the urgent ERCP group, compared with 13 (12%) patients in the conservative treatment group (RR 1.61, 95% CI 0.83–3.14; p=0.16). 14 (12%) patients in the urgent ERCP group were readmitted for gallstone-related events, compared with 24 (21%) patients in the conservative treatment group (RR 0.56, 95%

Table 1 - Baseline characteristics

Characteristic	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)
Female	51 (44%)	53 (47%)
Age, years	69 (13)	71 (12)
Gallstone etiology based on:		
• Gallstones or sludge on imaging	88 (75%)	88 (78%)
• Dilated common bile duct on imaging	24 (21%)	32 (28%)
° Twice the upper limit of normal ALT	103 (88%)	93 (82%)
° Twice the upper limit of normal ALT in the absence of meeting other gallstone criteria	24 (21%)	18 (16%)
Cholestasis	63 (54%)	67 (59%)
• Bilirubin > 2.3 mg/dL (40 µmol/liter)	50 (43%)	51 (45%)
• Dilated common bile duct §	23 (20%)	31 (27%)
ASA class on admission		
• Healthy status	21 (18%)	16 (14%)
• Mild systemic disease	55 (47%)	57 (50%)
• Severe systemic disease	40 (34%)	40 (35%)
• Severe systemic disease with constant threat to life	1 (1%)	0
Body-mass index	28 (6)	29 (6)
Disease severity		
• APACHE II score ¶	11 (9-15)	10 (8-13)
• Imrie score †	2 (1-3)	2 (1-3)
• C-reactive protein in mg/liter	60 (13-166)	38 (11-104)
• SIRS ‡	76 (65%)	61 (54%)
• Organ failure – no. (%) ǀ	29 (25%)	25 (22%)
Onset of symptoms to presentation at emergency department in hours	10 (5-22)	9 (5-18)
Presentation at emergency department to randomisation in hours	15 (7-20)	15 (8-20)

Data are median (range between the first and third quartile), mean (SD) or n (%). ALT denotes alanine aminotransferase, ASA denotes American Society of Anesthesiologists, APACHE II score Acute Physiology and Chronic Health Evaluation and SIRS Systemic Inflammatory Response Syndrome.
§ A dilated common bile duct was defined as more than eight mm in patients ≤75 years or more than 10 mm in patients >75 years on imaging.
* The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ APACHE II score ranges from zero to 71, with higher scores indicating more severe disease.
† Imrie (or modified Glasgow) score ranges from zero to eight, with higher scores indicating more severe disease.
‡ The systemic inflammatory response syndrome (SIRS) was defined according to the consensus-conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine.
ǀ Organ failure was defined as a modified Marshall score of two or more (on a scale of zero to 12, with higher scores indicating more severe disease), as proposed in the revised Atlanta classification.[7]

Table 2 - Primary and Secondary Endpoints

Outcome	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)	Risk ratio (95% CI)	p value
Primary composite endpoint: Mortality or major complication §	45 (38%)	50 (44%)	0.87 (0.64-1.18)	0.37
Secondary endpoints				
Mortality	8 (7%)	10 (9%)	0.77 (0.32-1.89)	0.57
Major complication				
• New-onset organ failure *	22 (19%)	17 (15%)	1.25 (0.70-2.23)	0.45
° Single organ failure	17 (15%)	18 (16%)	0.91 (0.50-1.68)	0.77
° Persistent single organ failure	14 (12%)	9 (8%)	1.50 (0.68-3.33)	0.31
° Multiple organ failure	13 (11%)	13 (12%)	0.97 (0.47-1.99)	0.93
° Persistent multiple organ failure	10 (9%)	8 (7%)	1.21 (0.49-2.95)	0.68
• Cholangitis	2 (2%)	11 (10%)	0.18 (0.04-0.78)	0.01
• Bacteremia	17 (15%)	25 (22%)	0.66 (0.38-1.15)	0.14
• Pneumonia	9 (8%)	10 (9%)	0.87 (0.37-2.06)	0.75
• Pancreatic parenchymal necrosis ¶	17 (15%)	16 (16%)	0.91 (0.50-1.68)	0.77
• Pancreatic endocrine or exocrine insufficiency †	9 (8%)	3 (3%)	2.90 (0.81-10.43)	0.09
Other outcomes				
• CT severity index ¶ ‡	3 (2-5)	3 (2-5)		0.64
• Hospital stay (in days)	13 (9-24)	14 (10-26)		0.67
• Intensive care admission	24 (21%)	13 (12%)	1.78 (0.96-3.33)	0.06
• Intensive care stay (in days)	6 (4-17)	8 (4-35)		0.67
• Readmission for gallstone related complication	14 (12%)	24 (21%)	0.56 (0.31-1.03)	0.058
° Recurrent gallstone pancreatitis	0	10 (9%)	NA	0.001
° Cholangitis	1 (1%)	3 (3%)	0.32 (0.03-3.05)	0.36
° Cholecystitis	10 (9%)	7 (6%)	1.38 (0.54-3.50)	0.50
° Gallstone colic	4 (3%)	7 (6%)	0.55 (0.17-1.83)	0.37
° Choledocholithiasis	1 (1%)	7 (6%)	0.14 (0.02-1.10)	0.033

Risk ratios are for urgent ERCP with sphincterotomy as compared with conservative treatment. Data are median (range between the first and third quartile) or n (%). CT denotes computed tomography. § The same patient may have had multiple events, this was considered as one endpoint.
* New-onset organ failure was defined as organ failure that was not present at randomisation. Persistent organ failure was defined as organ failure that lasted more than 48 hours. Multiple organ failure was defined as failure of two or more organs at the same time.
† Pancreatic insufficiency (endocrine and exocrine) was assessed 6 months after randomisation.
¶ A contrast-enhanced CT was performed five to seven days after hospital admission for assessment of pancreatic necrosis. No CT was performed in 11 (9%) of 117 patients in the urgent ERCP group and in 10 (9) of 113 patients in the conservative group.
‡ CT severity index scores range from zero to ten, with higher scores indicating more extensive pancreatic parenchymal or extrapancreatic necrosis.

CI 0.31–1.03; p=0.058). No patients were readmitted for recurrent gallstone pancreatitis in the urgent ERCP group, compared with ten (9%) patients in the conservative treatment group (p=0.0010). In four of ten patients admitted for recurrent gallstone pancreatitis, cholecystectomy was performed before their first pancreatitis episode. No cholecystectomy was performed during the initial admission in six of ten patients: four had a mild disease course but no same-admission cholecystectomy, one patient had a severe disease course of the pancreatitis, and in one patient cholecystectomy was not performed because of pancytopenia. There was no evidence for a difference in quality of life between study groups (appendix pp 9–12).

In the urgent ERCP group, 112 (96%) of 117 patients underwent ERCP a median of 3h (IQR 1–5) after randomisation, a median of 20h (12–23) after presentation at the emergency department, and a median of 29h (22–44) after onset of symptoms (table 3). Five (4%) patients did not undergo urgent ERCP (details are provided in the appendix p 5). Successful biliary cannulation was achieved in 91 (81%) of 112 patients, all of whom had biliary sphincterotomy. In three of 21 patients, biliary cannulation was not possible because the papilla was situated in a diverticula, and seven of 21 patients had complications of the pancreatitis during urgent ERCP, such as papillary oedema and respiratory insufficiency.

In the conservative treatment group, ERCP was done in 35 (31%) of 113 patients a median of 8 days (IQR 3–34) after randomisation. Biliary sphincterotomy was done in 30 (86%) of 35 patients. The indication for ERCP was cholangitis in 13 patients and persistent cholestasis in 21 patients.

A total of 128 ERCPs were done in the urgent ERCP group compared with 44 in the conservative treatment group (absolute reduction 66%). An ERCP-related compli- cation (see appendix p 8 for definitions) occurred in three (3%) of 112 patients in the urgent ERCP group compared with one (3%) of 35 patients in the conservative treatment group.

In 130 patients with cholestasis at randomisation, the primary composite endpoint occurred in 20 (32%) of 63 patients in the urgent ERCP group, compared with 29 (43%) of 67 patients in the conservative treatment group (RR 0.73, 95% CI 0.47–1.16; p=0.18; table 4). Logistic regression showed no evidence of an interaction between the subgroups with and without cholestasis at baseline and the effect of urgent ERCP on the primary endpoint (odds ratio 0.594, 95% CI 0.20–1.72; p=0.34).

Table 3 - ERCP Characteristics

Characteristic	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)
ERCP performed	112 (96%)	35 (31%)
Total number of ERCPs performed	128	44
ERCPs per patient	1 (1-1)	0 (0-1)
Time from onset symptoms to first ERCP in hours	29 (22-44)	216 (99-832)
Time from presentation to first ERCP in hours	20 (12-23)	211 (75-815)
Time from randomisation to first ERCP in hours	3 (1-5)	187 (67-807)
Duration of first ERCP procedure (minutes) ^	25 (15-40)*	25 (17-50)^
Indication for first ERCP		
• Trial-related	112	0
• Persisting cholestasis	0	21
• Cholangitis according to treating physician	0	5
• Cholangitis according to trial criteria	0	8
• Endoprosthesis placement	0	1
Main bile duct stones or sludge – no./total no. at risk	48 /112 (43%)	23 / 35 (66%)
Common bile duct cannulation – no./total no. at risk	91 / 112 (81%)	32 / 35 (91%)
Pancreatic duct cannulation (unintentional) – no./total no. at risk	40 / 112 (36%)	12 / 35 (34%)
Precut sphincterotomy – no./total no. at risk	24 / 112 (21%)	6 / 35 (17%)
Sphincterotomy – no./total no. at risk	91 / 112 (81)	30 / 35 (86%)
Stone extraction – no./total no. at risk	54 / 112 (48%)	25 / 35 (71%)
• Incomplete – no./total no. at risk	0	1 / 35 (3%)
ERCP-related complications – no./total no. at risk §	3 / 112 (3%)	1 / 35 (3%)

Data are median (range between the first and third quartile) or n (%).
^ Data on the duration of the ERCP procedure was missing in one patient in the urgent ERCP group and in 13 patients in the conservative group.
§ ERCP-related complications included bleeding, perforation, respiratory insufficiency and cardiovascular complications. Definitions are provided in the Supplementary Appendix.

Table 4 - Outcome according to subgroup cholestasis

	Patients with cholestasis (n=130)				Patients without cholestasis (n=100)			
Outcome	Urgent ERCP with sphincterotomy (n=63)	Conservative treatment (n=67)	Risk ratio (95% CI)	p value	Urgent ERCP with sphincterotomy (n=54)	Conservative treatment (n=46)	Risk ratio (95% CI)	p value
Primary endpoint: mortality or major complication	20 (32%)	29 (43%)	0.73 (0.47-1.16)	0.18	25 (46%)	21 (46%)	1.01 (0.66-1.55)	0.95
Mortality	2 (3%)	7 (10%)	0.30 (0.07-1.41)	0.17	6 (11%)	3 (7%)	1.70 (0.45-6.44)	0.50
New-onset organ failure	9 (14%)	9 (13%)	1.06 (0.45-2.51)	0.89	13 (24%)	8 (17%)	1.38 (0.63-3.04)	0.41
Pancreatic parenchymal necrosis	7 (11%)	14 (21%)	0.53 (0.23-1.23)	0.13	10 (19%)	4 (9%)	2.13 (0.72-6.34)	0.16
Bacteremia	8 (13%)	14 (21%)	0.61 (0.27-1.35)	0.21	9 (17%)	11 (24%)	0.70 (0.32-1.53)	0.37
Cholangitis	1 (2%)	6 (9%)	0.18 (0.02-1.43)	0.12	1 (2%)	5 (11%)	0.17 (0.02-1.41)	0.09
Pneumonia	4 (6%)	6 (9%)	0.71 (0.21-2.40)	0.75	5 (9%)	4 (9%)	1.07 (0.30-3.73)	1.00
Pancreatic endocrine or exocrine insufficiency	2 (3%)	1 (2%)	2.13 (0.20-22.88)	0.61	7 (13%)	2 (4%)	2.98 (0.65-13.65)	0.17

Adverse events were reported in 87 (74%) of 118 patients in the urgent ERCP group versus 91 (80%) of 114 patients in the conservative treatment group (see appendix pp 20–26 for full list of adverse events).

Utilisation of health-care resources did not differ between treatment groups, apart from the mean number of ERCPs, which were done more than twice as often in the urgent ERCP group compared with the conservative treatment group (mean difference 0.62; bias-corrected accelerated [BCa] 95% CI 0.36 to 0.81; appendix p 14). The mean societal care costs per patient were €24.627 (USD $27.892) in the urgent ERCP group compared with €24.595 ($27.856) in the conservative treatment group; a mean difference of €32 ($36) in favour of the conservative treatment group (BCa 95% CI –13 030 to 10 845; p=0.994; appendix pp 13–15). Although there was a mean difference of €112 ($127) in favour of the urgent ERCP group from a health-care perspective (€23.746 [$26.894] in the urgent ERCP group vs €23.859 [$27.022] in the conservative treatment group), higher out-of-pocket expenses for the urgent ERCP group did not result in a notable overall cost difference from a societal perspective. Details regarding QALYs and the incremental cost-effectiveness analysis are shown in the appendix (pp 5–6 and pp 16–19, respectively).

Discussion

This multicentre randomised trial in patients with predicted severe acute gallstone pancreatitis found no evidence that urgent ERCP with biliary sphincterotomy reduces the composite endpoint of major complications or mortality, compared with conservative treatment. Although cholangitis occurred more often in patients treated conservatively, this had no measurable negative impact on the overall outcome. We did not observe a notable overall cost difference between treatment groups from a societal perspective. With a conservative strategy and use of ERCP with sphincterotomy only in patients with cholangitis or persistent cholestasis, about two-thirds of patients did not need to undergo ERCP. Our results showed a benefit of urgent ERCP in the number of readmissions for recurrent gallstone pancreatitis or choledocholithiasis. Recurrent gallstone pancreatitis occurred in ten patients treated conservatively, of whom four had a mild pancreatitis initially but no cholecystectomy during the initial admission. Cholecystectomy within the same admission might have prevented recurrent gallstone pancreatitis in these patients.[42]

With 232 enrolled patients, this is the largest trial on ERCP in patients with

predicted severe acute gallstone pancreatitis without cholangitis. Our trial differs from previous trials studying ERCP in gallstone pancreatitis for several reasons.

First, in previous trials only a proportion of patients (19%,[19] 37%,[20] 44%,[17] and 46%[16]) had a predicted severe disease course at admission. In patients at low risk for complications, urgent ERCP with sphincterotomy is not beneficial.[43] In the current trial, we only included patients with a predicted severe disease course, which is reflected by the high prevalence of organ failure (23%) at randomisation. Nonetheless, we did not find a benefit of urgent ERCP with sphincterotomy.

Second, gallstones or biliary sludge are thought to initiate and aggravate pancreatitis, hence the hypothesis that urgent biliary decompression ameliorates the disease course. In previous trials, ERCP was done between 24h and 72h after admission.[15–17,20] In our trial, ERCP was done very early, after a median of 3h after randomisation, 20h after presentation to the emergency department, and 29h after the start of symptoms. Furthermore, when ERCP is done later in the disease course, successful biliary cannulation might be hampered even further by more mucosal and papillary oedema due to the ongoing pancreatic inflammation.

Third, small gallstones and sludge can be easily missed on cholangiography during ERCP and microscopic examination is required to rule out microlithiasis.[23,44,45] This issue is particularly relevant because small gallstones cause acute gallstone pancreatitis.[22] In a post-hoc analysis of our trial, comparing only patients with common bile duct stone extraction during ERCP (n=54) and patients treated conservatively (n=113), we found no difference in the primary endpoint. In previous trials, sphincterotomy was done in only 38–74% of all patients.[16,20] By comparison, in our trial sphincterotomy was done in all patients in the urgent ERCP group in whom biliary cannulation succeeded (81%). Biliary cannulation was unsuccessful in 21 (19%) patients, of whom seven had complications of the pancreatitis during ERCP, such as papillary oedema.

Fourth, a previous trial suggested that ERCP was associated with increased respiratory complications.[19] In severely ill patients these respiratory complications might be triggered by conscious sedation and potential aspiration or by temporarily reduced oxygenation associated with sedation. We observed more intensive care admissions in the urgent ERCP group

than in the conservative treatment group, but no difference in new-onset respiratory failure or duration of intensive care stay.

Fifth, patients with concomitant cholangitis were included in previous studies.[15–17] Because cholangitis is an already established indication for urgent ERCP in acute gallstone pancreatitis, this leads to an overestimation of the beneficial effects of ERCP. In our trial, we excluded patients with acute cholangitis at admission.

Finally, our trial included a predefined subgroup analysis of 130 patients with acute pancreatitis and cholestasis. These patients may theoretically benefit most from urgent ERCP with sphincterotomy.[13,43] Previous studies included only a small number of patients at high risk for complications with concurrent cholestasis. Moreover, various diagnostic criteria for biliary obstruction were used and no separate analyses of patients with biliary obstruction were provided.[15–18,20] We did not observe a significant effect of urgent ERCP in the 130 patients with cholestasis, although a type II error in this subgroup cannot be ruled out.

A possible explanation why urgent ERCP with sphincterotomy within 24h did not show an advantage over conservative treatment could be that the opportunity to positively influence the disease course had already passed at the time of the ERCP despite the fact that it was performed early. Animal models have shown that trypsinogen activation within the pancreas occurs within 10 min after chemically inducing pancreatitis.[46] It is well known that most bile duct stones in patients with gallstone pancreatitis cause only temporary obstruction and pass spontaneously into the duodenum.[47,48] This temporary obstruction already initiates pancreatitis and data from animal models show that this includes intrapancreatic trypsin activation, rupturing of vacuoles releasing active trypsin, and pancreatic autodigestion.[49] In the current trial, urgent ERCP was done after a median 29h after onset of symptoms and common bile duct stones were found in 43% of patients. Even this narrow time window might already be too long to prevent pancreatitis from deteriorating by performing an urgent ERCP with sphincterotomy.

The results of this trial should be interpreted in view of some limitations. First, diagnosis of concomitant cholangitis can be challenging because gallstone pancreatitis by itself can cause fever. We therefore applied more stringent diagnostic criteria for the diagnosis of cholangitis than the international diagnostic criteria for cholangitis.[50] Consequently, we

might have included patients with cholangitis and gallstone pancreatitis. Nevertheless, such bias, if present, would be in favour of the urgent ERCP group because of the clear therapeutic effect of ERCP in patients with cholangitis. Because we did not find any difference between groups, the effect of ERCP is not overestimated by this potential bias. Second, a well known limitation of trials involving patients with acute pancreatitis is the moderate positive predictive value of clinical scoring systems for disease severity.[51] Current scoring systems inevitably lead to the inclusion of patients who at presentation are classified as high risk for developing complications, but who eventually develop a mild pancreatitis. Nonetheless, at the time of randomisation, 60% of patients in our trial had systemic inflammatory response syndrome and 23% of patients had organ failure. Third, we used biochemical and radiological tests for diagnosis of common bile duct stones or sludge rather than endoscopic ultrasound, which has the highest diagnostic accuracy.[52] Endoscopic ultrasound might have identified a subgroup of patients without common bile duct stones or sludge. These patients would potentially not have profited from urgent ERCP with sphincterotomy. Therefore, a promising approach might be to perform urgent ERCP only in those patients in whom gallstones or sludge are confirmed by endoscopic ultrasound. However, endoscopic ultrasound is not uniformly available worldwide (especially not during out-of-office hours) and therefore at the time of initiation of this trial, we chose not to include endoscopic ultrasound.

In conclusion, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality in patients with predicted severe gallstone pancreatitis, compared with conservative treatment. These findings support a conservative strategy with an ERCP indicated only in patients with cholangitis or persistent cholestasis. With this conservative strategy, about two-thirds of patients did not need to undergo ERCP.

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Supplementary material can be found at https://supplementary.info

Chapter 6

Patient selection for urgent endoscopic retrograde cholangio-pancreatography by endoscopic ultrasound in predicted severe acute biliary pancreatitis (APEC-2): a multicentre prospective study

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Gut, 2023

Abstract

Objective

Routine urgent endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy (ES) does not improve outcome in patients with predicted severe acute biliary pancreatitis. Improved patient selection for ERCP by means of endoscopic ultrasonography (EUS) for stone/sludge detection may challenge these findings.

Design

A multicentre, prospective cohort study included patients with predicted severe acute biliary pancreatitis without cholangitis. Patients underwent urgent EUS, followed by ERCP with ES in case of common bile duct stones/sludge, within 24 hours after hospital presentation and within 72 hours after symptom onset. The primary endpoint was a composite of major complications or mortality within 6 months after inclusion. The historical control group was the conservative treatment arm (n=113) of the randomized APEC trial (Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment, patient inclusion 2013-2017) applying the same study design.

Results

Overall, 83 patients underwent urgent EUS at a median of 21 hours (IQR 17-23) after hospital presentation and at a median of 29 hours (IQR 23-41) after start of symptoms. Gallstones/sludge in the bile ducts were detected by EUS in 48/83 patients (58%), all of whom underwent immediate ERCP with ES. The primary endpoint occurred in 34/83 patients (41%) in the urgent EUS-guided ERCP group. This was not different from the 44% rate (50/113 patients) in the historical conservative treatment group (risk ratio [RR] 0.93, 95% CI 0.67–1.29; p=0.65). Sensitivity analysis to correct for baseline differences using a logistic regression model also showed no significant beneficial effect of the intervention on the primary outcome (adjusted odds ratio 1.03, 95% CI 0.56-1.90, p=0.92).

Conclusion

In patients with predicted severe acute biliary pancreatitis without cholangitis, urgent EUS-guided ERCP with ES did not reduce the composite endpoint of major complications or mortality, as compared with conservative treatment in a historical control group.

Significance of this study

What is already known on this topic

- The APEC trial has shown that patients with predicted severe acute biliary pancreatitis do not benefit from routine urgent ERCP with endoscopic sphincterotomy (ES)
- Biliary decompression using ERCP with ES might be beneficial in a sub selection of patients with proven common bile duct stones
- Endoscopic ultrasonography (EUS) is one of the most sensitive diagnostic tools to detect bile duct stones and sludge, it prevents an ERCP in patients in whom stones have already passed into the duodenum spontaneously.
- It is unclear if a targeted approach with EUS-guided ERCP with ES improves outcomes in patients with a predicted severe acute biliary pancreatitis

What this study adds

- In patients with predicted severe acute biliary pancreatitis without cholangitis, urgent EUS-guided ERCP within 24 hours after hospital admission does not reduce severe complications or mortality compared to a conservative treatment strategy.

How this study might affect research, practice or policy

- In patients with predicted acute severe biliary pancreatitis there is no need for early ERCP, not even in case of proven choledocholithiasis.
- In patients with predicted acute severe biliary pancreatitis a conservative strategy should be adopted with ERCP only in case of concomitant cholangitis (urgent indication) and persistent choledocholithiasis (elective indication).

Introduction

With an increasing incidence throughout the years, acute pancreatitis is one of the most common gastrointestinal diseases requiring acute hospital admission.[1,2] Acute biliary pancreatitis (ABP) is caused by gallstones/sludge obstructing the ampulla of Vater, creating a transient obstruction of the pancreatic duct.[3,4] The duration of the pancreatic duct obstruction appears related to the severity of inflammation of the pancreas.[5] Consequently, in an attempt to ameliorate the disease course it seems attractive to decompress the pancreatic duct by removing bile duct stones/sludge with endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) as early as possible. Recent guidelines state that urgent ERCP with ES is warranted in patients with ABP and concomitant cholangitis, and not recommended in patients with a predicted mild disease course, but provide limited guidance on the indication of urgent ERCP with ES in patients with a predicted severe disease course.[6,7,8]

The recently published Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment (APEC) trial, investigated whether urgent biliary decompression using ERCP with ES is beneficial in patients with predicted severe ABP (PSABP) without cholangitis.[9] In this trial, 232 patients were randomized between conservative treatment and urgent ERCP with ES. 'Urgent' was defined as within 24 hours after hospital presentation and within 72 hours after symptom onset. Urgent biliary decompression with ERCP with ES did not reduce the composite endpoint of major complications or mortality as compared to conservative treatment.[9] In the APEC trial however, the probability for a biliary origin and the indication for ERCP was based on common bile duct (CBD) dilation, an increase in serum alanine-aminotransferase (ALT) or sludge or stones on imaging (located in the gallbladder or CBD). Studies have shown that elevated liver enzymes and radiological signs of CBD stones are poorly correlated to the actual presence of CBD stones/sludge during ERCP.[10,11] This was confirmed in the APEC trial, where 55% of the patients in the urgent ERCP group did not show CBD stones/sludge during ERCP. After spontaneous stone passage into the duodenum, biliary decompression is no longer necessary and ERCP with ES may even be harmful (e.g. haemorrhage and aggravation of pancreatitis).[12] The most sensitive modality for diagnosing CBD stones/sludge is endoscopic ultrasonography (EUS).[13,14] When EUS is performed immediately before an intended ERCP with ES, it allows to perform ERCP exclusively in patients with confirmed stones/sludge in the CBD who are most likely to benefit.

The APEC trial showed that urgent ERCP with ES had no benefit over a conservative approach in PSABP without cholangitis when inclusion was based on biochemical tests and transabdominal ultrasound. This is supported by a recent meta-analyses that also included the APEC trial.[15] Yet, it remains unclear whether urgent ERCP with ES is beneficial in patients with confirmed bile duct stones/sludge on EUS. Therefore, in this prospective multicentre study we assessed whether a strategy with urgent EUS followed by urgent ERCP with ES in the case of CBD stones/sludge reduces major complications or mortality in patients with PSABP (APEC-2).

Methods

Study design and participants

This multicentre, prospective cohort study was performed in 15 Dutch hospitals. The outcomes of this study were compared to the outcomes of the conservative treatment group of the APEC trial.[9,16] In the APEC-2 study the 15 participating centres were selected based on their high inclusion rates during the APEC trial and their ability to organize EUS and consecutive ERCP with ES within 24 hours after hospital presentation. We adhered to the protocol used in the APEC trial, except for the EUS procedure performed prior to ERCP in all included patients.[16] Inclusion and exclusion criteria for this study were identical to those in the original APEC trial.[9] Inclusion for this study commenced after the recruitment period of the APEC-trial. A detailed description of the study design inclusion and exclusion criteria, the conservative and investigational treatment, data collection, outcome measures and management of missing data can be found in Supplementary appendix part 1 and part 2.

Investigational treatment

In the current study, we assessed a strategy with urgent EUS followed by urgent ERCP with ES in the case of CBD stones/sludge ('urgent EUS-guided ERCP'). EUS needed to be performed within 72 hours after symptom onset and within 24 hours after presentation at the emergency department. If gallstones/sludge in the CBD were detected during EUS, ERCP with ES was performed subsequently. EUS was considered positive when persistent echogenic intraluminal material was seen in the CBD or common hepatic duct, with or without posterior acoustic shadow. If no gallstones/sludge were detected during EUS or when the bile ducts could not be visualized during EUS, the patient was treated conservatively. EUS and ERCP were both carried out by, or under the direct supervision of, an experienced endosonographist and interventional endoscopist.

Outcomes

The primary endpoint was a composite endpoint of major complications or mortality occurring within 6 months after inclusion. Major complications included: bacteraemia, cholangitis, new onset persistent organ failure (>48 hours or <48 hours and leading to death), pancreatic parenchymal necrosis, pneumonia, and pancreatic endocrine or exocrine insufficiency (Supplementary appendix Part 3). Secondary endpoints included: the incidence of the individual components of the primary endpoint, occurrence of new onset organ failure (transient = <48 hours or persistent >48 hours, single or multiorgan), ERCP-related complications (definitions in Supplementary appendix Part 4), length of hospital stay, intensive care unit (ICU) admission, length of ICU stay, number of interventions (i.e. endoscopic, radiological, or surgical), readmission for biliary events (i.e. recurrent biliary pancreatitis, cholecystitis, biliary colic, cholangitis, and choledocholithiasis), and quality of life. Quality of Life was measured using the SF-36 questionnaire. The follow-up of this study was 6 months.

Patient and Public Involvement

The Dutch Pancreatitis Study Group (DPSG) has close ties with the Dutch Patient Association for Pancreatic Diseases. This association was actively involved in the design of the APEC trial and also partially funded the trial. This APEC-2 study was an additional part of the APEC trial and as such the design was discussed during DPSG meetings that included representation of the patient association. Once the trial has been published, participants will be informed of the results through the DPSG website.

Statistical analyses

The sample size calculation of this study was based on data from the interim analysis of the APEC trial since full trial results were not yet available. Cholestasis or bile duct stones on transabdominal ultrasound in the conservative group were used as a proxy for bile duct obstruction. In the APEC trial, the prevalence of the composite endpoint in the patients in the conservative study group with cholestasis or bile duct stones was 45%. In the ERCP with ES group the composed endpoint was seen in 29% of patients that had CBD stones during ERCP that were successfully removed. As a result, in case of bile duct obstruction, a reduction of 16 percentage points in the composite endpoint was achieved after ERCP with ES. To account for the possibility of missed small stones in the conservative group and intention bias (i.e. actors perceive a greater motivation to complete a task when the underlying indication to perform the procedure is supposedly more scientifically based),

an additional 5 percentage points reduction of the primary endpoint was expected in the group that would be treated with urgent EUS-guided ERCP with ES. Using a Chi-square test without continuity correction we established that with an expected reduction of 21 percentage points in the composite endpoint, a 2-sided significance level of 5 and a 1% dropout rate, a total of 78 patients needed to be included to have a power of 80%. Patients in whom the composed primary endpoint could not be assessed due to withdrawal of informed consent were replaced. Furthermore, to provide a total of 78 evaluable patients for the per-protocol analysis, additional patients were added to replace patients that did not undergo EUS or in whom EUS was incomplete, and patients in whom ERCP was not successful. The adjudication committee was only allowed to exclude patients before the statistical analyses were performed, these patients were not replaced but were excluded from the analyses. The composite primary endpoint and the individual components of the primary endpoint were analysed according to the intention-to-treat principle. A per-protocol analysis that only included the patients that underwent urgent EUS, was also performed. All other secondary endpoints were analysed according to the intention-to-treat principle.
Continuous data were compared with the Mann-Whitney U test, dichotomous data with the Pearson's χ^2 test or Fisher's exact test. A two-sided p value of <0.05 was considered statistically significant. Results are presented as risk ratios (RRs) with their corresponding 95% confidence interval (CI).

The analyses of the primary endpoint and the quality of life analyses were performed by an independent statistician (NE). As this study comprised a prospective cohort series and a historic comparison group, logistic regression models were used for sensitivity analyses to investigate the influence of potential confounders on the primary outcome. In this model we included clinically relevant potential confounders including age, sex, ASA classification, organ failure at baseline and the study arm to investigate the effect of these factors on our primary outcome. For statistical analysis IBM SPSS Statistics version 25 and R version 4.1.3 (2022-03-10) were used.

Results

Between 15 August 2017 and 21 August 2019, 522 patients with ABP were assessed for eligibility. Figure 1 shows the inclusion flowchart. Most eligible patients did not meet the inclusion criteria due to a predicted mild disease course. Eighty-seven patients with a predicted severe disease course were included in this study, of whom four were excluded due to either withdrawal of consent (n=2) or cholangitis at inclusion (n=2). Subsequently,

83 patients were included in the analyses. In the urgent EUS-guided ERCP group, 81 patients (98%) underwent EUS. In two patients, EUS and ERCP were cancelled after inclusion by the treating physician, due to rapidly developing organ failure. The patients from this prospective cohort were compared to a cohort of the APEC randomized trial, consisting of 113 patients with PSABP that were treated conservatively.[9] Both a per-protocol analysis and intention-to-treat analysis were performed. Full results and the inclusion flowchart of the per-protocol analysis can be found in the Supplementary appendix Part 5.

TABLE 1 - BASELINE CHARACTERISTICS

Characteristic	Urgent EUS ± ERCP with ES (n=83)	Conservative treatment (n=113)	p-value
Age in years – mean (SD)	70 (11)	71 (12)	0.65
Female sex - no (%)	37 (45)	53 (47)	0.75
ASA score			0.03
• Healthy status - no (%)	16 (19)	16 (14)	
• Mild systemic disease - no (%)	52 (63)	57 (50)	
• Severe systemic disease - no (%)	15 (18)	40 (35)	
BMI (kg/m^2) – mean (SD)	29 (5)	29 (6)	0.58
Severity of disease on admission			
• APACHE-II score – median (IQR)	10 (9-13)	10 (8-13)	0.87
• Modified Glasgow score – median (IQR)	2 (2-3)	2 (1-3)	0.24
• CRP – median (IQR)	78 (28-164)	38 (11-104)	0.003
• SIRS – no (%)	45 (54)	61 (54)	0.97
• Organ failure - no (%)	7 (8)	25 (22)	0.01
Biliary aetiology			
• Gallstones on imaging - no (%)	57 (69)	88 (78)	0.19
• Dilated common bile duct on imaging – no (%)	18 (22)	32 (28)	0.32
• Serum ALT>2 times the upper limit of normal - no (%)	77 (93)	93 (82)	0.03
• Serum ALT>2 times the upper limit of normal in absence of other biliary criteria - no.(%)	23 (28)	18 (16)	0.05
Cholestasis			
• Bilirubin (>40umol/L, >2.3mg/dL) - no (%)	46 (55)	51 (45)	0.16
• Dilated common bile duct on imaging - no (%)	18 (22)	31 (27)	0.36
Time from onset of symptoms to presentation at emergency department in hours – median (IQR)	11 (5-20)	9 (5-18)	0.38

ASA score = American Society of Anesthesia Physical status Classification System. BMI = Body Mass Index. CRP = C-reactive protein. SIRS = Systemic Inflammatory Respons Syndrome Score. ALT =Alanine aminotransferase.

Baseline characteristics

Baseline characteristics are shown in Table 1. In the urgent EUS-guided ERCP group fewer patients were included with severe systemic disease and organ failure (defined as a Modified Marshall Score of 2 or higher which could indicate either single or multi organ failure) at baseline.[17] In this group baseline CRP

levels were higher. Cholestasis was present in 53 out of 83 patients (64%) in the urgent EUS group and in 67 out of 113 patients (59%) in the conservative treatment group.

Primary and secondary endpoints
The primary composite endpoint of major complications or mortality occurred in 34 out of 83 patients (41%) in the urgent EUS group compared to 50 out of 113 patients (44%) in the conservative treatment group (RR 0.93, 95%CI 0.67-1.29, p=0.65). Apart from a difference in the occurrence of pancreatic exocrine insufficiency, no other differences were found in the individual components of the primary endpoint. Pancreatic exocrine insufficiency was observed in 9 patients (11%) in the urgent EUS group and in 2 patients (2%) in the conservative group (RR 6.13, 95% CI 1.36-27.62, p=0.01). Exocrine insufficiency was defined by a low faecal elastase at three months after inclusion and the use of enzyme replacement therapy at six months after inclusion. By using a faecal elastase level of <200 mg/g, irrespective of replacement therapy, the difference remained significant between groups (23 patients (33%) versus 13 patients (18%), respectively (RR 1.82, 95%CI of RR 1.01-3.30, p=0.04)).
Five patients (6%) died in the in the urgent EUS group versus 10 patients (9%) in the conservative group (RR 0.68, 95%CI 0.24-1.91, p=0.46). An overview of the primary and secondary endpoints is presented in Table 2. In Supplementary appendix part 6, the data of the urgent ERCP with ES group of the APEC trial are added to Table 1 (S5), Table 2 (S6) and Table 5 (S7) for a more detailed overview.

Sensitivity analyses were used to investigate the effect of both the baseline differences between groups and other relevant clinical parameters on the primary outcome. (Table 3) Logistic regression analysis showed no significant relation between sex, ASA grade or organ failure at baseline and the effect of urgent EUS-guided ERCP on the primary endpoint (adjusted odds ratio 1.03, 95%CI 0.56-1.90, p=0.92). The ASA score did not have a significant effect (OR 0.70, 95%CI 0.26-1.84 and OR 0.70, 95%CI 0.34-1.41), neither did organ failure (OR 1.79, 95%CI 0.80-4.00), although in the latter case a possible effect could not be ruled out completely. Age did show a significant effect. (Table 3)
Hospital stay was shorter in the urgent EUS group versus the conservative treatment group, with a median of 11 days (IQR 6-22) and 14 days (IQR 10-26) respectively (p=0.03). ICU admission was required in 14 patients (17%) in the urgent EUS group compared to 13 (12%) the conservative group (RR 1.48, 95% CI 0.74-2.99, p=0.27).

The results from the per-protocol analysis, including 75 patients, did not differ meaningfully from the intention-to-treat analysis. (Supplementary appendix Part 5).

TABLE 2 - PRIMARY AND SECONDARY ENDPOINTS – INTENTION-TO-TREAT ANALYSIS

Outcome	Urgent EUS ± ERCP with ES (n=83)	Conservative treatment (n=113)	Risk Ratio (95% CI)	p-value
Primary composite endpoint Major complications or mortality	34 (41)	50 (44)	0.93 (0.67-1.29)	0.65
Secondary endpoints				
Death	5 (6)	10 (9)	0.68 (0.24-1.91)	0.46
New-onset persistent organ failure	14 (17)	17 (15)	1.12 (0.59-2.14)	0.73
• Single organ failure (any duration)	12 (15)	18 (16)	0.91 (0.46-1.78)	0.78
• Persistent single organ failure	8 (10)	9 (8)	1.21 (0.49-3.00)	0.68
• Multiple organ failure (any duration)	7 (8)	13 (12)	0.73 (0.31-1.76)	0.48
• Persistent multiple organ failure	5 (6)	8 (7)	0.85 (0.29-2.51)	0.77
Cholangitis	6 (7)	11 (10)	0.74 (0.29-1.92)	0.54
Bacteraemia	13 (16)	25 (22)	0.71 (0.39-1.30)	0.26
Pneumonia	7 (8)	10 (9)	0.95 (38-2.40)	0.92
Pancreatic parenchymal necrosis	19 (23)	18 (16)	1.47 (0.81-2.56)	0.22
Pancreatic endocrine or exocrine insufficiency	9 (11)	3 (3)	4.08 (1.14-14-63)	0.02
• Endocrine insufficiency	3 (4)	2 (2)	2.04 (0.35-11.95)	0.42
• Exocrine insufficiency*	9 (11)	2 (2)	6.13 (1.36-27.62)	0.01
• Hospital stay in days	11 (6-22)	14 (10-26)	-	0.03
• ICU admission	14 (17)	13 (12)	1.48 (0.74-2.99)	0.27
• ICU stay in days	9 (5-21)	8 (4-35)	-	0.91
• Readmission for biliary complication	6 (7)	24 (21)	0.34 (0.15-0.80)	0.01
• Recurrent biliary pancreatitis	2 (2)	10 (9)	0.27 (0.06-1.21)	0.06
• Cholangitis	1 (1)	3 (3)	0.46 (0.05-4.29)	0.48
• Cholecystitis	3 (4)	7 (6)	0.58 (0.16-2.19)	0.42
• Biliary colic	1 (1)	7 (6)	0.19 (0.02-1.56)	0.08
• Choledocholithiasis	0 (0)	7 (6)	-	0.02

Data are presented as no. (%) or median (IQR). *Data on faecal elastase levels in stool were missing for 43 patients (22%), details on medication use for pancreatic insufficiency was available for all patients.

TABLE 3 - LOGISTIC REGRESSION MODEL OF PREDICTING FACTORS FOR THE PRIMARY ENDPOINT OF SEVERE COMPLICATIONS OR DEATH

Variable	Odds ratio	95% CI for Odds ratio	Wald	p-value
Study arm	1.03	0.56-1.90	0.01	0.92
Age	0.97	0.94-0.99	6.02	0.01
Female sex	0.73	0.41-1.32	1.09	0.27
Organ failure at baseline	1.79	0.80-4.00	1.99	0.16
ASA classification			1.04	0.59
ASA classification (1)	0.70	0.26-1.84	0.53	0.47
ASA classification (2)	0.70	0.34-1.42	1.00	0.32
Constant	10.36		3.82	0.05

Biliary complications and adverse events

Biliary complications occurred less often in the urgent EUS group; 6 patients (7%) in the urgent EUS group versus 24 patients (21%) in the conservative treatment group (RR 0.34, 95% CI 0.15-0.80, p=0.01) including recurrent biliary pancreatitis (2% versus 9%, p=0.06) and choledocholithiasis (0% versus 6%, p=0.02) (Table 2).

In total, 24 (12%) patients had a cholecystectomy before inclusion. Out of the remaining 172 patients, 100 patients (58%) underwent cholecystectomy at a median of 59 days (IQR 25-96) after inclusion. In the conservative treatment arm the median time to cholecystectomy was 75 days (IQR 45-109) and in the urgent EUS group 42 days (IQR 11-87), which was longer in the conservative group (p=0.02).

Out of 138 patients that did not have pancreatic necrosis, 14 underwent same admission cholecystectomy, 10 of whom were part of the EUS-guided ERCP group. More patients in the urgent EUS-guided ERCP group underwent same admission cholecystectomy compared to the conservative group (p=0.01). As previously reported, 10 patients (9%) in the conservative group were readmitted with recurrent biliary pancreatitis. Of these, four patients had a cholecystectomy prior to randomization, four patients had a mild disease course but did not undergo same-admission cholecystectomy, one patient had a severe disease course and did not undergo a cholecystectomy, and one patient had pancytopenia leading to delayed cholecystectomy.[9] In the urgent EUS-guided ERCP group two patients (2%) were readmitted for recurrent biliary pancreatitis, of whom one had a cholecystectomy prior to inclusion and one underwent cholecystectomy between the initial pancreatitis episode and the recurrent episode.

Adverse events occurred in 63 out of 83 patients (76%) in the EUS group versus 90 out of 113 patients (80%) in the conservative treatment group (RR 0.95, 95% CI 0.82-1.11, p=0.53). All adverse events are presented in Supplementary appendix Part 7.

Procedural characteristics of EUS and ERCP

In the urgent EUS group, 81 patients (98%) underwent EUS at a median of 29 hours (IQR 23-42) after symptom onset and 21 hours (IQR 17-23) after presentation at the emergency department (Table 4). In two patients, EUS and ERCP were cancelled after inclusion by the treating physician, due to rapidly developing organ failure. EUS was positive in 48 patients (58%), all of whom underwent immediate ERCP. Median time between EUS and ERCP was 10 minutes (IQR 5-33). In the group with a positive EUS, 14 out of 48 patients (29%) had only sludge/microlithiasis in the bile ducts and 34 (71%) had one or multiple stones.

TABLE 4 - CHARACTERISTICS OF FIRST EUS PROCEDURE

Study group*	Urgent EUS ± ERCP with ES (n=83)
EUS performed	81 (98)
Time from onset symptoms to first EUS (hours)	29 (23-42)
Time from presentation to first EUS (hours)	21 (17-23)
Duration of first EUS procedure (minutes)	14 (8-18)
First EUS performed by trainee under direct supervision	0 (0)
Papilla visualized	71 (86)
• Gallstones or sludge in papilla (n=71)	17 (24)
Common bile duct visualized	80 (96)
• Diameter of common bile duct (n=78)	7 (5-9)
• Gallstones or sludge in common bile duct	47 (59)
Cystic duct visualized	35 (42)
• Gallstones or sludge in cystic duct	5 (14)
Proximal biliary tract visualized	59 (71)
• Gallstones or sludge in proximal biliary tract	1 (1)
Stones visualized on EUS	48 (58)

Data are presented as no. (%) or median (IQR). *No EUS procedures were performed in the conservative group

In the urgent EUS group, 53 patients (64%) underwent ERCP with ES. In 48 patients, performance of ERCP was based on urgent EUS-findings. ALT levels at baseline did not differ between patients with and without stones and/or sludge in the CBD (237 U/L (IQR 122-401) versus 237 U/L (IQR 148-443), p=0.77).

In five patients (6%) the initial EUS investigation during admission was negative, but these patients underwent ERCP at a later stage. Three patients had progressive cholestasis and CBD stones were found and removed during ERCP (9 days, 22 days and 2 months after the initial EUS, respectively). One patient had cholangitis due to a CBD stenosis due to pancreatitis. The fifth patient had intraabdominal biliary leakage secondary to a liver abscess for which a biliary stent was placed. ERCP characteristics of all first ERCP procedures, including these five patients, are shown in Table 5.

In the conservative group, an indication to perform ERCP occurred in 35 of 113 (31%) patients a median of 8 days (IQR 3–34) after inclusion. Sphincterotomy was performed in 30 of 35 patients (86%). The indication for ERCP was persistent cholestasis in 21 patients (19%) and cholangitis in 13 patients (12%), in 25 patients (71%) stones were found and extracted. In each group one patient had a procedural complication, in the urgent EUS group a patient developed post sphincterotomy bleeding 9 days after the initial procedure and in the conservative group one patient had a cardiovascular complication.

TABLE 5 - CHARACTERISTICS OF FIRST ERCP PROCEDURE

Study group	Urgent EUS ± ERCP with ES (n=83)	Conservative treatment (n=113)
ERCP performed	53 (64)	35 (31)
Total number of ERCPs performed	65	44
ERCPs per patient	1 (1-1)	0 (0-1)
Total number of first ERCPs performed based on EUS results	48 (58)	0
Time from onset symptoms to first ERCP (hours)	31 (24-48)	216 (99-832)
Time from presentation to first ERCP (hours)	22 (19-24)	211 (75-815)
Time between EUS and ERCP (minutes)[&]	10 (5-33)	-
Duration of first ERCP procedure (minutes)[^]	24 (16-43)	25 (17-50)
Indication for first ERCP		
• Study-related	48	0
• Progressive cholestasis and/or suspicion of CBD stones	3	21
• Cholangitis according to treating physician	1	5
• Cholangitis according to study criteria	-	8
• Endoprosthesis placement	1	1
Main bile duct stones or sludge on cholangiography*	42 (79)	23 (66)
Common bile duct cannulation*	48 (91)	32 (91)
Pancreatic duct cannulation*	27 (51)	12 (34)
Pre-cut sphincterotomy*	16 (30)	6 (17)
Sphincterotomy*	48 (91)	30 (86)
Stone extraction*	45 (85)	25 (71)
• Incomplete*	1 (2)	1 (3)
ERCP-related complications[‡]	1 (2)	1 (3)

Data are no. (%) or median (IQR), unless otherwise stated. &Data on time between EUS and ERCP was missing in 1 patient ^Data on the duration of the ERCP procedure was missing in 4 patient in the urgent EUS group and in 13 patients in the conservative treatment group. *Denominators are the number of patients who had ERCP (ie, 53 in the urgent EUS group and 35 in the conservative treatment group). ‡ERCP-related complications included bleeding, perforation, respiratory insufficiency, and cardiovascular complications. Definitions are provided in the supp appendix Part 4.

In the current APEC-2 study, 30 different endoscopists performed the ERCP procedures, of whom 16 (53%) also performed ERCP procedures for the APEC-trial. Out of these 30 endoscopists, 20 (67%) also performed the EUS procedures, for the other 10 endoscopists a colleague performed the EUS.
In patients in whom ERCP was performed based on EUS, biliary cannulation was achieved in 43 out of 48 patients (90%) (Table 6). Unintentional pancreatic duct cannulation was seen in 50% of patients. Out of 24 patients that underwent an urgent ERCP based on EUS results and had PD cannulation, 8 developed pancreatic necrosis (33%). In the remaining 23 patients in whom the PD was not cannulated 5 (22%) developed pancreatic necrosis. This difference was not statistically significant (p=0.37). When looking at infected necrosis results are similar: 3 out of 24 (13%) patients in the PD cannulation group developed infected necrosis versus 3 out of 23 (13%) in the no PD cannulation group, p= 0.96.

In five patients, biliary cannulation could not be achieved; in three patients there was an inflammatory stenosis of the duodenum which could either not be passed or prohibited adequate exposure of the papilla, and in two patients biliary cannulation failed. Complete stone extraction was achieved at the initial ERCP in 42 patients (88%). In one patient stone extraction was incomplete and a biliary stent was placed.

TABLE 6 - CHARACTERISTICS OF ERCP PROCEDURES PERFORMED BASED ON EUS RESULTS

Study group	Urgent EUS ± ERCP with ES (n=83)
Total number of ERCPs performed – no. of procedures	56
ERCPs per patient	1 (1-1)
Time from onset symptoms to first ERCP (hours)	31 (24-48)
Time from presentation to first ERCP (hours)	22 (19-24)
Time from EUS to ERCP (minutes)	10 (5-33)
Duration of first ERCP procedure (minutes)	24 (15-45)
First ERCP performed by trainee under direct supervision	0
Common bile duct stones or sludge on cholangiography[$]	40 (83)
Common bile duct cannulation	43 (90)
Pancreatic duct cannulation	24 (50)
Pre-cut sphincterotomy	15 (33)
Sphincterotomy*	43 (90)
Stone extraction[&]	42 (88)
• Incomplete	1 (2)
ERCP-related complications	1 (2)

Data are no. (%) or median (IQR), unless otherwise stated. $ Cholangiography data was not available in 5 patients. *in one patient stones had passed between EUS and ERCP & A pancreatic duct stent was placed

Quality of life analysis and costs

The association between treatment strategy and quality of life over time was investigated using linear mixed models. There was no significant difference in quality of life as measured with the SF-36 questionnaire, between study groups at 1 month, 3 months and 6 months after inclusion (Supplementary appendix part 8). During the study period data on utilization of healthcare was registered. However, we have decided to omit the cost-effectiveness analysis as the health intervention in this study was not beneficial. An interesting finding that bares economical relevance is that patients who underwent EUS spend a median of 3 days less (11 (IQR 6-22) versus (14 (IQR10-26) in hospital compared to patients who did not undergo EUS. This translates to a saving of 1428,- euro based on the average unit cost of an inpatient hospital day at the general ward in the Netherlands.[18]

Discussion

This prospective multicentre APEC-2 cohort study found that urgent EUS in patients with PSABP, followed by urgent ERCP with ES in the case of bile duct stones/sludge, did not reduce the composite endpoint of major complications or mortality as compared to the conservative arm of the APEC randomized trial. In 58% of patients, bile duct stones/sludge were found with urgent EUS within 24 hours after presentation at the emergency department and within 72 hours of start of symptoms. Immediate ERCP with ES was performed successfully in 90% of patients with a low complication rate (2%).

Anderloni et al. performed a prospective study on early EUS-guided ERCP with ES (within 48 hours after admission) in 71 patients with ABP with a predominantly predicted mild disease course.[11] CBD stones were found in 31 patients (44%), all of whom underwent ERCP. Clinical outcomes of the pancreatitis episode and rates of recurrent biliary events were not reported. In addition, De Lisi et al. performed a meta-analysis comparing EUS-guided ERCP with ERCP in ABP including 7 studies with a total of 545 patients of whom 188 had a severe ABP. An EUS-guided strategy prevented 57%-74% of ERCP procedures. However, clinical superiority could not be established.[13] In contrast to our study, most patients included in this meta-analysis had a predicted mild disease course. Moreover, we identified more CBD stones (58% vs 29%), presumably because we included patients very early in their disease course, leaving less time for stones to migrate into the duodenum spontaneously.

With regard to the individual components of the primary endpoint, we only found that PEI occurred more frequently in the intervention group. The occurrence of endocrine insufficiency did not differ between groups and patients in the urgent EUS-guided ERCP group had the same level of pancreatic parenchymal necrosis as the conservatively treated patients. We believe that this is not an actual effect but an incidental finding.

Readmission for recurrent biliary events, especially recurrent biliary pancreatitis, was more frequent in the conservative treatment group compared to the urgent EUS-guided ERCP group. Cholecystectomy is the most effective strategy to prevent recurrent biliary events after ABP, both in the case of a mild and a severe disease course.[19,20] In case of a mild disease course, cholecystectomy should be performed during the same admission. In the conservative treatment group however, four out of ten patients had a mild disease course, but did not undergo a same-admission cholecystectomy.

In those patients, the chance of recurrent biliary pancreatitis might have been reduced if a same-admission cholecystectomy was performed. Therefore, we cannot recommend urgent EUS-guided ERCP in the acute phase of biliary pancreatitis to prevent recurrent biliary events.

There are some limitations of our study that need consideration. First, this study was not a randomized trial, but comprised of a prospective cohort series that was compared with the control group from a recently published randomized controlled trial, the APEC-trial, which means that bias cannot be excluded.[9] To minimize the risk of bias in the current study, we used the same protocol (e.g. eligibility criteria, endpoints etc.) as in the original trial with an preprocedural EUS to the urgent ERCP with ES arm. Consecutive patients were included in the same group of hospitals, they were followed closely and treated by experienced endoscopists with a documented track record in doing both the EUS and ERCP with ES procedures. Most endoscopists were also involved in the original APEC trial. Some differences in baseline characteristics were observed between the groups, such as fewer patients with organ failure at baseline in the urgent EUS-guided ERCP group, despite similar APACHE-II scores, modified Glasgow scores and SIRS scores. Sensitivity analyses confirmed that these differences did not have an impact on the primary outcome of this study.
Based on this evidence we believe that early EUS-guided ERCP is not indicated in patients with PSABP that do not have cholangitis. Only a randomised controlled trial will yield a higher level of evidence. A potentially more practical and feasible approach, would be a stepped-wedge cluster randomized trial in which at random and sequential crossover of hospitals/clusters from control (no ERCP) to intervention (early EUS-guided ERCP) takes place until all clusters are exposed.

In conclusion, the combined results of the current prospective APEC-2 study and the original APEC-trial show that in patients with a PSABP without cholangitis, urgent ERCP with ES, even when guided by EUS, does not reduce major complications or mortality. Therefore, we recommend a conservative treatment strategy in patients with a PSABP, with an ERCP only in case of concomitant cholangitis (urgent indication) and symptomatic and/or persistent choledocholithiasis (elective indication).

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Supplementary Appendix

Detailed description of the methods

Study design and participants

All patients presenting to the emergency department with acute pancreatitis were assessed for eligibility. Inclusion and exclusion criteria for this study were identical to those in the original APEC trial.[1] Acute pancreatitis was defined according to the revised Atlanta criteria, as the presence of at least two out of the following criteria: 1) upper abdominal pain, 2) serum amylase or lipase concentration more than three times the upper limit of normal, or 3) features of acute pancreatitis on imaging.[2] A predicted severe disease course was defined as an Acute Physiology and Chronic Health Evaluation (APACHE II) score of eight or more, an Imrie score of three or more, or if the C-reactive protein serum level was higher than 150 mg/L within 24 hours of presentation at the emergency department.[3,4,5,6,7]

Biliary pancreatitis was defined by either biliary sludge or gallstones on imaging, a dilated CBD on imaging (>8 mm in patients ≤75 years of age, or >10 mm in patients >75 years of age) or a serum alanine aminotransferase (ALT) level of more than twice the upper limit of normal.[8,9,10]

Exclusion criteria included pancreatitis due to other causes than biliary, a previous sphincterotomy or needle knife pre-cut, suspected bacterial cholangitis or a history of chronic pancreatitis. Cholangitis was defined as fever in combination with either proven CBD stones, a dilated CBD or (progressive) cholestasis (detailed definitions and an overview of all inclusion and exclusion criteria can be found in Supplementary Appendix Part 2 - Table S1). Written informed consent was obtained from each participant. This study was performed in accordance with the Dutch law regarding research involving human subjects and the Declaration of Helsinki. The ethical committee of the Erasmus MC University Medical Centre in Rotterdam, the Netherlands, approved both the trial protocol of the APEC trial and the current APEC-2 study protocol. The study protocol was registered with the ISRCTN registry (ISRCTN15545919). This study was reported in accordance with the STROBE guidelines.[11]

Investigational treatment

In the conservative group, ERCP with sphincterotomy was performed only if a patient developed cholangitis after inclusion, or in case of persistent cholestasis or retained bile duct stones after recovery from the initial acute pancreatitis episode.

Details on EUS procedure
EUS was used only to investigate the presence of gallstones or sludge, other information (e.g. appearance of the papilla, incidental findings) were not recorded in the study database.

EUS and ERCP were both carried out by, or under the direct supervision of, an experienced endosonographist and interventional endoscopist. This was defined as a lifetime experience of more than 400 EUS/ERCPs performed for choledocholithiasis as a primary responsible investigator and more than 50 EUS/ ERCPs annually on average in the previous three years. Pending on experience, EUS and ERCP procedures were performed by a single operator or by two distinct specialists. Prophylactic rectal nonsteroidal anti-inflammatory drugs (diclofenac 100mg) were administered in an attempt to prevent aggravation of pancreatitis. Biliary sphincterotomy was mandated in all patients undergoing ERCP. Bile swaps were not obtained in this study. When biliary cannulation was not successful, even after pre-cut sphincterotomy, the procedure was abandoned and the patient was treated conservatively, with re-ERCP in case of persistent cholestasis or cholangitis.

Data collection
Standardized case record forms were used by local clinicians to collect data and patients underwent a CT scan 5 to 7 days after hospital presentation to assess the presence of pancreatic (parenchymal) necrosis. All scans were re-assessed by an experienced radiologist (TLB). Use of both in-hospital and out-of-hospital utilization of healthcare was registered, either as part of data collection or by self-administered questionnaires. An independent monitor compared the study documents with source data to ensure proper data collection.

The follow-up of this study was 6 months and patients were followed up closely. Case record forms were completed by the treating clinicians regarding the components of the primary outcome. Furthermore, a team of researchers visited all participating hospitals to collect all available data on these patients including vitals, laboratory results, microbiology results, radiology results, correspondence and admission records. Treating clinicians received twice-weekly phone calls from researchers to follow-up on patients during admission to ensure no components of the primary endpoint were missed. If patients were referred to other hospitals, data from those hospitals was also collected. Lastly, phone calls to patients were made at 1, 3 and 6 months after inclusion to ask after any symptoms and/or new hospital admissions.

An adjudication committee consisting of two surgeons and three gastroenterologists assessed all potential endpoints individually. Disagreements were resolved during a consensus meeting.

During the original APEC trial, an independent Data Safety Monitoring Committee (DSMC) assessed protocol adherence, patient recruitment, and patient safety. Adverse events were reported by treating clinicians to the coordinating investigators, who reported the events to the Dutch Central Committee for Research involving human subjects. All events were reported to the DSMC per consecutive group of 60 patients.[1]

Statistical analysis – handling of missing data

Missing data for the primary endpoint and the individual components of the primary outcome were classified as no event for both the intention-to-treat analysis and the per-protocol analysis. Follow-up 6 months and for all but one of the individual components of the primary endpoint all data was available. For this component, pancreatic exocrine insufficiency, medication use was available for all patients and secondly, patients were also invited to provide a faecal sample at 3 months after inclusion. Not all patients have provided these samples. In accordance with the APEC trial, we chose to regard missing data in these cases as 'no event', assuming that patients with complaints might be more likely to undergo medical tests. Data on mortality was acquired for all patients for which reason correction for survival versus no survival for the primary endpoint was not needed.

For analyses of other endpoints than the primary endpoint, data were considered to be missing completely at random and a complete case analysis was performed.

TABLE S1 - INCLUSION CRITERIA AND EXCLUSION CRITERIA

INCLUSION CRITERIA
Acute pancreatitis; defined as the presence of at least 2 out of the following 3 criteria: • Pain in the upper abdomen • Serum amylase and/or lipase concentration > 3 times the upper limit of normal • Signs of pancreatitis on CT or MRI/MRCP
Predicted severe course of the acute pancreatitis attack based on either one of the following positive scores within <24 hours after admission: • CRP >150 mg/L • Imrie score ≥ 3 (as per original APEC-trial protocol) • APACHE II score ≥ 8 (as per original APEC-trial protocol)
High probability ABP based on at least one of the following criteria: • Gallstones and/or biliary sludge on imaging (US, CT or MR) • Dilated common bile duct on imaging (US, CT or MR) defined as >8mm in patients ≤ 75 years or > 10mm in patients >75 years • ALAT > two times upper limit of normal (≒ 80 U/L, no absolute numerical value is chosen because of multicentric design with upper limits of normal varying between hospitals and differences in upper limit of normal values between men and women)
Ability to perform both EUS and ERCP within 24 hours after presentation at the ED department and within 72 hours after symptom onset
Age ≥ 18 year
Written informed consent
In case of a previous episode of necrotizing pancreatitis, patient should be fully recovered (confirmed on imaging)
EXCLUSION CRITERIA
Cholangitis*
AP due to other causes such as alcohol abuse (either chronic >4 units/day or binge drinking), metabolic causes (hypertriglyceridemia, hypercalcemia), medication, trauma, etc.
Previous precut sphincterotomy and/ or sphincterotomy
Chronic pancreatitis
Anticoagulation that cannot be corrected with co-fact or fresh frozen plasma below an International Normalized Ratio below 1.5
Pregnancy
***DEFINITION CHOLANGITIS:**
Body temperature • 38.5 degrees or higher with chills, without an obvious other cause or fever (e.g. cystitis, pneumonia, thrombophlebitis, etc), **OR** • 39 degrees or higher regardless of chills, without an obvious other cause for fever. **AND EITHER** • Choledocholithiasis on US, CT, EUS or MRI/MRCP, **OR** • In the absence of gallstones and/or sludge, a dilated common bile duct on imaging (US, CT or MR) defined as >8mm in patients ≤ 75 years or > 10mm in patients >75 years, **OR** • Progressive cholestasis for at least two consecutive days AND a bilirubin 40 µmol/L [> 2.3 mg/dL].

As per the APEC-trial[1]

TABLE S2 – DEFINITIONS OF THE COMPOSED PRIMARY ENDPOINT

Event	Definition
New-onset organ failure	New-onset (i.e. not present at randomisation) and persistent (i.e. >48 hours) failure of organ(s) according to the modified Marshall score[2,12] For patients with organ failure at baseline, it was decided by the adjudication committee, that organ failure could still be achieved as an endpoint when the patient scored a Modified Marshal score more than 2 points higher that baseline scores.
Pancreatic necrosis	Presence of diffuse or focal areas of pancreatic non-enhancement on contrast enhanced CT performed at 5-7 days after admission
Bacteremia	Demonstrated with positive blood cultures. For non-pathogens (e.g. Coagulase negative staphylococci) at least 2 samples have to be positive. In the case of positive blood cultures that were taken pre-randomisation, it patients could no longer achieve 'bacteremia' as an endpoint. They could achieve the other endpoints of the composite endpoint.
Cholangitis	Highest in-hospital body temperature in previous 24 hours: ≥ 38.5°C with chills, without an obvious other cause (e.g., cystitis, pneumonia, thrombophlebitis, etc), or 39°C without chills, without an obvious cause for fever, **and either**: • Choledocholithiasis on abdominal US, CT, EUS or MRI, or in the absence of gallstones and/or sludge • A dilated common bile duct on imaging defined as >8mm in patients ≤75 years or >10mm in patients >75 years **or** • Progressive cholestasis for at least two consecutive days and a bilirubin >2.3 mg/dL (40 µmol/L)
Pneumonia	Coughing, dyspnoea, chest film showing infiltrative abnormalities, lowered arterial blood gas with positive sputum culture. If in intensive care, a positive endotracheal culture is mandatory.
Exocrine pancreatic insufficiency	Fecal elastase <200µg/g and the need for pancreatic enzyme supplementation at 3 months after discharge; this requirement was not present before onset of pancreatitis
Endocrine pancreatic insufficiency	The need for insulin or oral antidiabetic drugs at 3 months after discharge; this requirement was not present before onset of pancreatitis
Recurrent biliary event	Biliary events (recurrent acute gallstone pancreatitis, cholecystitis, biliary colics, or cholangitis)

As per the APEC-trial[1]

TABLE S3 – DEFINITIONS OF ERCP-RELATED COMPLICATIONS

Event	Definition
Clinically relevant bleed	The presence of melena, hematochezia or hematemesis, in combination with a hemoglobin drop of 1.3 mmol/L or the need for blood transfusion (defined according to the American Society for Gastrointestinal Endoscopy ASGE)[13]
Perforation	New development of free gas on imaging with progressive complaints of abdominal discomfort and pain after ERCP, or perforation detected at surgery
Respiratory insufficiency	pO2<60mmHg despite FiO2 of 30% or requiring mechanical ventilation
Cardiovascular complications:	
• Acute myocardial infarction	(1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischemic symptoms; (b) development of pathologic Q-waves on the ECG; (c) ECG changes indicative of ischemia (ST segment elevation or depression); or (d) coronary artery intervention (e.g., coronary angioplasty)[14]
• Cerebrovascular accident	Defined by the clinical event and subsequent findings on cross- sectional imaging investigations
• Shock	Systolic blood pressure below 90 mmHg despite adequate fluid resuscitation or need for inotropic catecholamine support

Per protocol analysis

Figure 1 shows the inclusion flowchart for the per-protocol analysis. In 8 out of 83 patients either EUS or ERCP was not successful. Consequently, 75 patients that underwent urgent EUS and subsequent ERCP with ES in case of bile duct stones or sludge were included in the per-protocol analysis. To ensure sufficient statistical power for the per-protocol analysis, it was required to replace patients in whom either EUS or the subsequent ERCP were not successful, as defined in the study protocol. During the study period nine patients were replaced, two because of consent withdrawal, and seven because of an unsuccessful EUS or ERCP. One out of the eight patients in whom EUS or ERCP was not successful was erroneously not replaced during the study period. This resulted in one missing patient for the per-protocol analysis. In the per-protocol analysis, no significant difference was found in the primary endpoint between the conservative and urgent EUS group (Table S4). Simulation by adding one extra 'dummy patient' to replace the missing patient and compare the groups (n=76) with this patient having either achieved the primary endpoint or not, did not change results (p=0.31 and p=0.23, respectively).

TABLE S4 - PRIMARY ENDPOINTS - PER-PROTOCOL ANALYSIS

Outcome	Urgent EUS ± ERCP with ES (n=75)	Conservative treatment (n=113)	Risk Ratio (95% CI)	p-value
Primary composite endpoint: Major complications or mortality – no (%)	27 (36)	50 (44)	0.81 (0.56-1.17)	0.26
Secondary endpoints				
Death – no (%)	2 (3)	10 (9)	0.30 (0.07-1.34)	0.09
New-onset persistent organ failure – no (%)	9 (12)	17 (15)	0.80 (0.38-1.70)	0.55
• Single organ failure (any duration)	9 (12)	18 (16)	0.75 (0.35-1.59)	0.45
• Persistent organ failure	6 (8)	9 (8)	1.00 (0.37-2.71)	0.99
• Multiple organ failure (any duration)	5 (7)	13 (12)	0.58 (0.22-1.56)	0.27
• Persistent multiple organ failure	3 (4)	8 (7)	0.56 (0.16-2.01)	0.38
Cholangitis – no (%)	4 (5)	11 (10)	0.55 (0.18-1.66)	0.28
Bacteraemia – no. (%)	9 (12)	25 (22)	0.54 (0.27-1.10)	0.77
Pneumonia – no (%)	4 (5)	10 (9)	0.60 (0.20-1.85)	0.37
Pancreatic parenchymal necrosis – no. (%)	15 (20)	18 (16)	1.26 (0.66-2.33)	0.47
Pancreatic endocrine or exocrine insufficiency - no. (%)	8 (11)	3 (3)	4 (1.10-14.66)	0.02
• Endocrine insufficiency	2 (3)	2 (2)	1.51 (0.22-10.47)	0.68
• Exocrine insufficiency	8 (11)	2 (2)	6.02 (1.32-27.60)	0.01

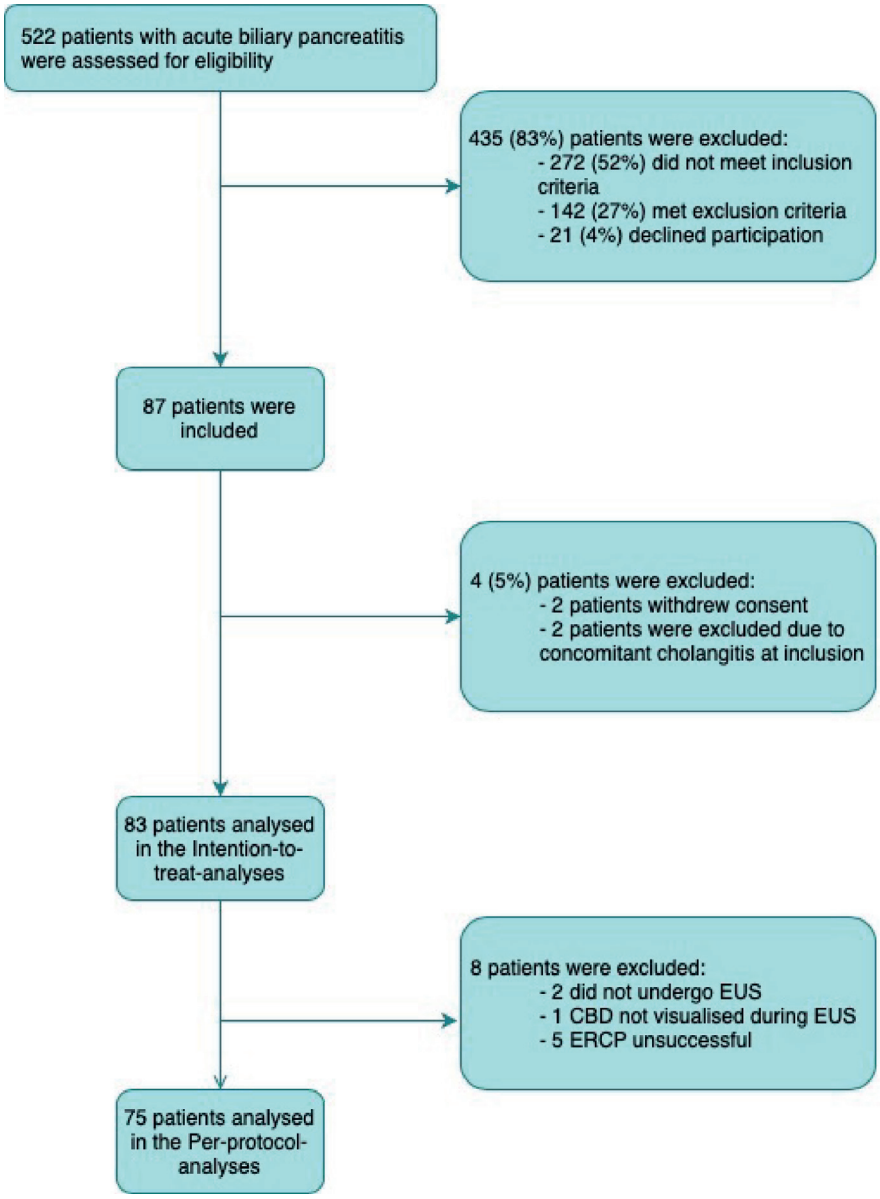

Figure S1 – Inclusion flowchart of patients included in the per-protocol analysis

TABLE S5 - BASELINE CHARACTERISTICS – INCLUDING URGENT ERCP WITH ES ARM OF APEC TRIAL

Characteristic	Urgent EUS ± ERCP with ES (n=83)	Conservative treatment (n=113)	Urgent ERCP with ES (n=117)
Age in years – mean (SD)	70 (11)	71 (12)	69 (13)
Female sex - no (%)	37 (45)	53 (47)	51 (44%)
ASA score			
• Healthy status - no (%)	16 (19)	16 (14)	21 (18)
• Mild systemic disease - no (%)	52 (63)	57 (50)	55 (47)
• Severe systemic disease - no (%)	15 (18)	40 (35)	40 (34)
• Severe systemic disease with constant threat to life			1 (1)
BMI (kg/m^2) – mean (SD)	29 (5)	29 (6)	28 (6)
Severity of disease on admission			
• APACHE-II score – median (IQR)	10 (9-13)	10 (8-13)	11 (9-15)
• Modified Glasgow score – median (IQR)	2 (2-3)	2 (1-3)	2 (1-3)
• CRP – median (IQR)	78 (28-164)	38 (11-104)	60 (13-166)
• SIRS – no (%)	45 (54)	61 (54)	76 (65)
• Organ failure - no (%)	7 (8)	25 (22)	29 (25)
Biliary aetiology			
• Gallstones on imaging - no (%)	57 (69)	88 (78)	88 (75)
• Dilated CBD on imaging – no (%)	18 (22)	32 (28)	24 (21)
• Serum ALT>2 times the upper limit of normal - no (%)	77 (93)	93 (82)	103 (88)
• Serum ALT>2 times the upper limit of normal in absence of other biliary criteria - no.(%)	23 (28)	18 (16)	24 (21)
Cholestasis			
• Bilirubin (>40umol/L, >2.3mg/dL) - no (%)	46 (55)	51 (45)	50 (43)
• Dilated common bile duct on imaging - no (%)	18 (22)	31 (27)	23 (20)
Time from onset of symptoms to presentation at emergency department in hours – median (IQR)	11 (5-20)	9 (5-18)	10 (5-22)

ASA score = American Society of Anesthesia Physical status Classification System. BMI = Body Mass Index. CRP = C-reactive protein. SIRS = Systemic Inflammatory Respons Syndrome Score. ALT =Alanine aminotransferase.

TABLE S6 - PRIMARY AND SECONDARY ENDPOINTS –INCLUDING URGENT ERCP WITH ES ARM OF APEC TRIAL

Outcome	Urgent EUS ± ERCP with ES (n=83)	Conservative treatment (n=113)	Urgent ERCP with ES (n=117)
Primary composite endpoint Major complications or mortality	34 (41)	50 (44)	45 (38)
Secondary endpoints			
Death	5 (6)	10 (9)	8 (7)
New-onset persistent organ failure	14 (17)	17 (15)	22 (19)
• Single organ failure (any duration)	12 (15)	18 (16)	17 (15)
• Persistent single organ failure	8 (10)	9 (8)	14 (12)
• Multiple organ failure (any duration)	7 (8)	13 (12)	13 (11)
• Persistent multiple organ failure	5 (6)	8 (7)	10 (9)
Cholangitis	6 (7)	11 (10)	2 (2)
Bacteraemia	13 (16)	25 (22)	17 (15)
Pneumonia	7 (8)	10 (9)	9 (8)
Pancreatic parenchymal necrosis	19 (23)	18 (16)	17 (15)
Pancreatic endocrine or exocrine insufficiency	9 (11)	3 (3)	9 (8)
Hospital stay in days	11 (6-22)	14 (10-26)	13 (9-24)
ICU admission	14 (17)	13 (12)	24 (21)
ICU stay in days	9 (5-21)	8 (4-35)	6 (4-17)
Readmission for biliary complication	6 (7)	24 (21)	14 (12)
• Recurrent biliary pancreatitis	2 (2)	10 (9)	0
• Cholangitis	1 (1)	3 (3)	1 (1)
• Cholecystitis	3 (4)	7 (6)	10 (9)
• Biliary colic	1 (1)	7 (6)	4 (3)
• Choledocholithiasis	0 (0)	7 (6)	1 (1)

Data are presented as no. (%) or median (IQR).

TABLE S7 - CHARACTERISTICS OF FIRST ERCP PROCEDURE - INCLUDING URGENT ERCP WITH ES ARM OF APEC TRIAL

Study group	Urgent EUS ± ERCP with ES (n=83)	Conservative treatment (n=113)	Urgent ERCP with ES (n=117)
ERCP performed	53 (64)	35 (31)	112 (96)
Total number of ERCPs performed	65	44	128
ERCPs per patient	1 (1-1)	0 (0-1)	1 (1-1)
Total number of first ERCPs performed based on EUS results	48 (58)	0	0
Time from onset symptoms to first ERCP (h)	31 (24-48)	216 (99-832)	29 (22-44)
Time from presentation to first ERCP (h)	22 (19-24)	211 (75-815)	20 (12-23)
Time between EUS and ERCP (min)&	10 (5-33)	-	-
Duration of first ERCP procedure (min)^	24 (16-43)	25 (17-50)	25 (15-40)
Indication for first ERCP			
• Study-related	48	0	112
• Progressive cholestasis and/or suspicion of CBD stones	3	21	0
• Cholangitis according to treating physician	1	5	0
• Cholangitis according to study criteria	-	8	0
• Endoprosthesis placement	1	1	0
Main bile duct stones or sludge on cholangiography*	42 (79)	23 (66)	48 (43)
Common bile duct cannulation*	48 (91)	32 (91)	91 (81)
Pancreatic duct cannulation*	27 (51)	12 (34)	40 (36)
Pre-cut sphincterotomy*	16 (30)	6 (17)	24 (21)
Sphincterotomy*	48 (91)	30 (86)	91 (81)
Stone extraction*	45 (85)	25 (71)	54 (48)
• Incomplete*	1 (2)	1 (3)	0
ERCP-related complications	1 (2)	1 (3)	3 (3)

Data are no. (%) or median (IQR), unless otherwise stated. &Data on time between EUS and ERCP was missing in 1 patient ^Data on the duration of the ERCP procedure was missing in 4 patient in the urgent EUS group and in 13 patients in the conservative treatment group. *Denominators are the number of patients who had ERCP (ie, 53 in the urgent EUS group, 35 in the conservative treatment group and 112 in the urgent ERCP with ES group). ‡ERCP-related complications included bleeding, perforation, respiratory insufficiency, and cardiovascular complications. Definitions are provided in the supp appendix Table 3.

TABLE S8 – OVERVIEW OF ALL ADVERSE EVENTS IN THE URGENT EUS-GUIDED ERCP GROUP

Patients in prospective cohort		232-262	263-319	N	%
(S)AE's					
Safety Parameters	Death	AP234, AP245, AP249	AP282, AP309	4	6%
	ICU admission	AP234, AP240, AP245, AP253	AP271, AP273, AP280, AP291, AP293, AP300, AP318	11	16%
Complications ERCP	Bleeding	AP240	AP267	2	3%
	Perforation			0	0%
	Respiratory insufficiency during EUS and/or ERCP	AP248		1	1%
Other complications	Intraabdominal abcess	AP253	AP286	2	3%
	(Re-)ERC	AP252	AP273	2	3%
	Acute myocardial infarction	AP238		1	1%
	Cardiac arrhythmia	AP234, AP240, AP247, AP259	AP263, AP276, AP280	7	10%
	Anemia treated with transfusion and/or medication	AP240, AP248, AP252, AP257, AP259,	AP263, AP267, AP309, AP318	9	13%
	Bacteremia	AP234, AP240, AP243, AP246, AP252	AP269, AP270, AP273, AP274, AP280, AP293, AP299, AP318	13	19%
	Cardiomyopathy, dilated apex of left ventricle		AP309	1	1%
	Cholangitis	AP234, AP240,	AP266, AP270, AP273, AP278, \AP280, AP292	8	12%
	Cholecysitis treated operatively		AP267, AP287	2	3%
	Cholecystitis treated with percutaneous drainage	AP257	AP302	2	3%
	Cholecystoduodenal fistula		AP267	1	1%
	Clostridium infection	AP259	AP309	2	3%
	ICU aquiered weakness	AP240		1	1%
	Cerebrovascular accident	AP234		1	1%
	Bowel ischemia	AP245		1	1%
	Decompensatio cordis	AP242, AP259	AP286, AP302, AP303	4	6%
	Delerium	AP238, AP240, AP248, AP249, AP253	AP288, AP318	7	10%
	Biloma treated with percutaneous drainage	AP253		1	1%

Patients in prospective cohort		232-262	263-319	N	%
Other complications	Fistula (enteral/cutaneous or other)		AP310	1	1%
	Fracture	AP243	AP277, AP285	3	4%
	Cholangiocarcinoma of the gallbladder	AP257		1	1%
	Peritonitis		AP273	1	1%
	Bile duct injury	AP252	AP286, AP306	3	4%
	Gastroenteritis		AP267	1	1%
	Infected (peri)pancreatic fluid collection	AP234, AP246, AP248, AP249	AP263, AP273, AP289, AP318	8	12%
	Hypertension	AP242, AP246	AP269	3	4%
	Electrolyte disorder (other)	AP234, AP240, AP248	AP283, AP318, AP319	6	9%
	Hypokalemia or hyperkalemia	AP233, AP236, AP239, AP241, AP244, AP246, AP248, AP251, AP258, AP259,	AP264, AP266, AP267, AP278, AP283, AP303, AP313, AP318	18	26%
	Ileus/ gastroparesis	AP234, AP248	AP270, AP273, AP283, AP293	6	9%
	Gout		AP263, AP277	1	1%
	Liver abces treated with percuteneous drainage	AP252		1	1%
	Melaena		AP267	1	1%
	Morbus Kahler		AP282	1	1%
	Multiorgan failure	AP234, AP240, AP245, AP253		4	6%
	Necrotising pancreatitis treated with intervention		AP294	1	1%
	Renal insufficiency/renal failure		AP267, AP279, AP280, AP282, AP286, AP300	6	9%
	Oral candidiasis	AP242	AP286	2	3%
	Pencreatic insufficiency	AP241, AP246	AP281, AP311, AP317, AP318	6	9%
	Pancreatic parenchymal necrosis	AP241, AP249, AP261	AP262, AP266, AP267, AP273, AP280, AP282, AP293, AP317, AP318	12	17%
	peripancreatic fluid collection	AP233, AP238, AP247, AP261	AP267, AP283, AP309	7	10%
	Pleural effusion	AP253	AP280	2	3%
	Pneumonia	AP234, AP240, AP241, AP246, AP249	AP266, AP270, AP273, AP282, AP283, AP289	11	16%

Patients in prospective cohort		232-262	263-319	N	%
Other complications	Urinary tract infection	AP233, AP236, AP238, AP244, AP246, AP249, AP252	AP271, AP278, AP304, AP306, AP318	12	17%
	Pylorusstenosis		AP296	1	1%
	Recurent pancreatitis	AP252, AP258	AP273, AP290	4	6%
	Respiratoiry insufficiency	AP243, AP249	AP271, AP280, AP291, AP293, AP300	7	10%
	Retained CBD stone	AP254	AP290	1	1%
	Septic shock	AP253		1	1%
	Biliary colics		AP287	1	1%
	Jugular vein thrombosis			0	0%
	Splanchic thrombosis	AP233, AP240, AP249	AP294	4	6%
Total number of (S)AEs				**221**	
Number of patients with one or more (S) AEs in EUS-guided ERCP arm		AP233, AP234, AP236, AP238, AP239, AP240, AP241, AP242, AP243, AP244, AP245, AP246, AP247, AP248, AP249, AP251, AP252, AP253, AP254, AP257, AP258, AP259, AP261, AP262	AP263, AP264, AP266, AP267, AP270, AP271, AP273, AP274, AP276, AP277, AP278, AP279, AP280, AP281, AP282, AP283,AP285, AP288, AP289, AP290, AP291, AP292, AP293, AP294, AP296, AP299, AP300, AP302, AP303, AP304, AP306, AP309, AP310, AP311, AP313, AP317, AP318, AP319		62/82 (76%)

Quality of life analysis

The quality of life was measured using the 36-Item Short Form Survey at 1 month (0-59 days), 3 months (60-120 days) and 6 months (120-220 days) after inclusion. Data was missing for some patients at some time points. Table S7.1 shows the number and proportion of missing values for each individual domain per period.

TABLE S9 - NUMBER AND PROPORTION OF MISSING VALUES

Variable	Month 1	Month 3	Month 6
General health	56 (29%)	51 (26%)	73 (37%)
Social functioning	52 (27%)	49 (25%)	72 (37%)
Health change	52 (27%)	49 (25%)	69 (35%)
Physical functioning	53 (27%)	50 (26%)	72 (37%)
Role physical health	58 (30%)	55 (28%)	77 (39%)
Role emotional health	60 (31%)	55 (28%)	75 (38%)
Bodily pain	54 (28%)	50 (26%)	71 (36%)
Vitality	52 (27%)	49 (25%)	73 (37%)
Mental health	53 (27%)	49 (25%)	73 (37%)

Following the SF36 manual the summary scores PCS and MCS were only calculated for patients who had at least 50% of the relevant items observed.

In the analysis missing values were handled in three different ways to explore the potential impact of the missing values:

1. when a patient had at least 50% of the items in a scale observed, the scores were calculated on the observed part of the items, otherwise the score was left missing and the observation was excluded from the analysis (i.e., following the instructions of the SF36 manual).
2. Best case scenario: missing values were replaced with the best possible value.
3. Worst case scenario: missing values were replaced with the worst possible value.

In all three scenarios, the score was set to 0 for patients that had died.

An overview of the distribution of the data for each of the components in both arms under scenario 1 is shown in Figure S7.2. In Figure 7.3 the distribution of the data across all time-points (1, 3 and 6 months) is shown.

Figure S2 - Health related quality of life measured by the 36-item Short Form Health Survey: distribution of the values at 1, 3 and 6 months after inclusion.

Note. GH = general health, SF = social functioning, HT=Health Change, PF = physical functioning, RP = role physical, RE = role emotional, BP = bodily pain, VT = vitality, MH = mental health, PCS = physical component summary, MCS = mental component summary.

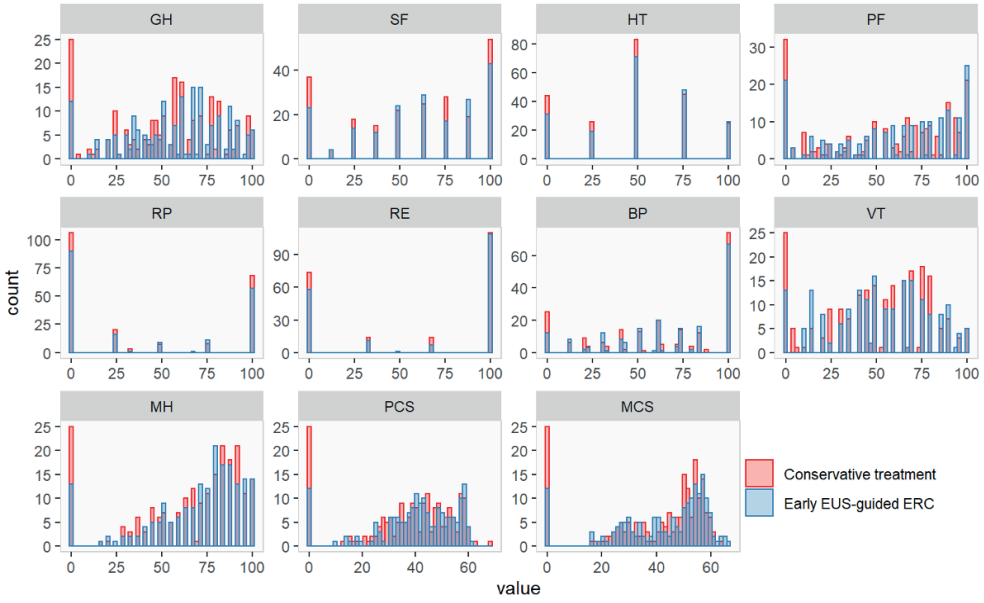

Figure S3 - Health related quality of life measured by the 36-item Short Form Health Survey: distribution of the values across all time-points (1, 3 and 6 months) after inclusion.

Note. GH = general health, SF = social functioning, HT=Health Change, PF = physical functioning, RP = role physical, RE = role emotional, BP = bodily pain, VT = vitality, MH = mental health, PCS = physical component summary, MCS = mental component summary.

To evaluate the association between treatment and MCS and PCS, respectively as well as differences in treatment effects over time, we fitted linear mixed models that included treatment arm, time, and their interaction. To take into account correlation between repeated measurements of the same patient, a random intercept and a random effect for the time of measurement (with an unstructured variance-covariance matrix) were used.

The results are visualised in Figure 7.4 and shown in Table 7.5. Shown are the expected response over time for each treatment arm under the three scenarios with corresponding 95% confidence intervals.

There was no evidence for a difference in quality of life between the two treatment strategies. Only in the extremely unlikely scenario where all patients with missing responses would have had the worst possible score, the expected quality of life would differ at six months and the score in the urgent EUS-guided ERCP group would be better than in the conservative group.

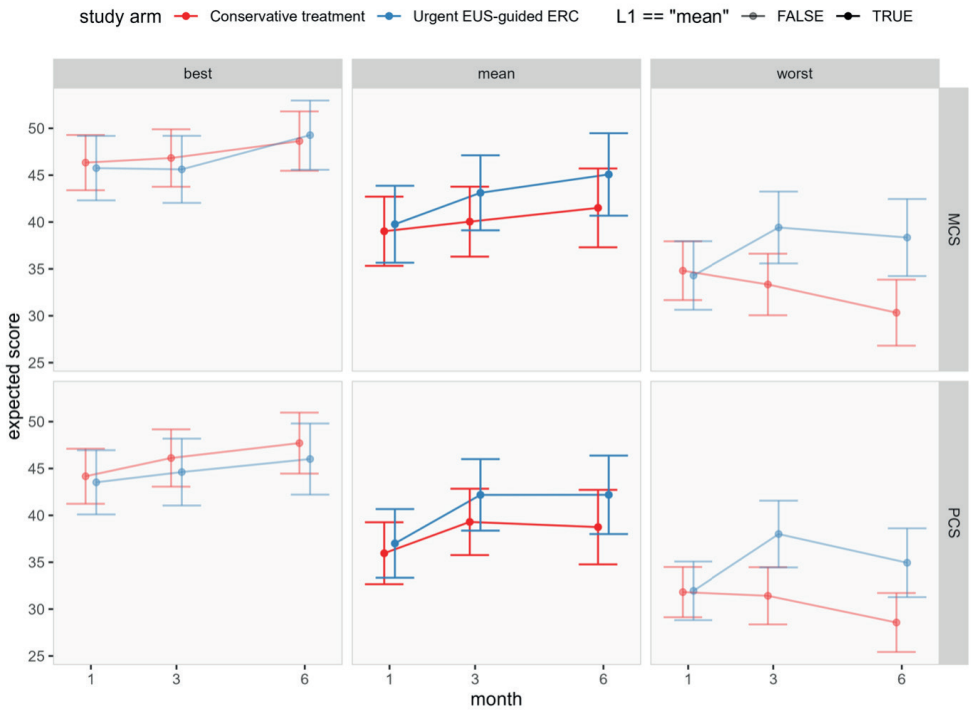

Figure S4 - Regression coefficients and 95% confidence intervals (lower, upper) from the linear mixed models using different scenarios for the missing values.

Note. GH = general health, SF = social functioning, HT=Health Change, PF = physical functioning, RP = role physical, RE = role emotional, BP = bodily pain, VT = vitality, MH = mental health, PCS = physical component summary, MCS = mental component summary.

TABLE S10 - REGRESSION COEFFICIENTS AND 95% CONFIDENCE INTERVALS (LOWER, UPPER) FROM THE LINEAR MIXED MODELS USING DIFFERENT SCENARIOS FOR THE MISSING VALUES.

	MCS				PCS			
variable	**coefficient**	**lower**	**upper**	**p value**	**coefficient**	**lower**	**upper**	**p value**
Mean value imputation								
• (Intercept)	39.021	35.337	42.705	0.000	35.959	32.661	39.257	0.000
• Arm: Urgent EUS-guided ERC	0.747	-4.773	6.266	0.790	1.049	-3.885	5.983	0.675
• Time: Month 3	1.021	-1.549	3.592	0.434	3.341	1.283	5.398	0.002
• Time: Month 6	2.489	-0.904	5.883	0.150	2.788	-0.103	5.680	0.059
• Arm: Urgent EUS-guided ERC : month 3	2.331	-1.385	6.047	0.218	1.836	-1.128	4.799	0.223
• Arm: Urgent EUS-guided ERC : month 6	2.821	-2.035	7.678	0.253	2.396	-1.726	6.519	0.253
Worst case imputation								
• (Intercept)	34.810	31.685	37.935	0.000	31.813	29.141	34.485	0.000
• Arm: Urgent EUS-guided ERC	-0.512	-5.329	4.305	0.834	0.137	-3.982	4.256	0.948
• Time: Month 3	-1.469	-4.081	1.144	0.270	-0.394	-2.556	1.769	0.721
• Time: Month 6	-4.479	-7.688	-1.270	0.006	-3.243	-6.029	-0.457	0.023
• Arm: Urgent EUS-guided ERC : month 3	6.591	2.577	10.606	0.001	6.450	3.128	9.773	0.000
• Arm: Urgent EUS-guided ERC : month 6	8.528	3.597	13.459	0.001	6.238	1.956	10.519	0.004
Best case imputation								
• (Intercept)	46.342	43.403	49.281	0.000	44.170	41.243	47.098	0.000
• Arm: Urgent EUS-guided ERC	-0.589	-5.119	3.942	0.798	-0.643	-5.156	3.870	0.779
• Time: Month 3	0.490	-2.232	3.212	0.724	1.947	-0.779	4.673	0.161
• Time: Month 6	2.295	-0.823	5.412	0.149	3.538	0.400	6.676	0.027
• Arm: Urgent EUS-guided ERC : month 3	-0.622	-4.805	3.561	0.770	-0.854	-5.043	3.335	0.689
• Arm: Urgent EUS-guided ERC : month 6	1.225	-3.566	6.015	0.616	-1.055	-5.878	3.767	0.667

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Part III

FOLLOW-UP CARE

Chapter 7
Optimal timing of cholecystectomy after necrotising biliary pancreatitis
Gut, 2021

Chapter 8
Pancreatic exocrine insufficiency following acute pancreatitis: systematic review and study level meta-analysis
Pancreatology, 2018

Chapter 7

Optimal timing of cholecystectomy after necrotising biliary pancreatitis

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Gut, 2021

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 necrotising biliary pancreatitis.

Design

A post-hoc analysis of a multicentre prospective cohort. Patients with biliary pancreatitis and a computed tomography 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 necrotising 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 – 0.90]; p = 0.02). The risk of recurrent pancreatitis before cholecystectomy was significantly lower before 8 weeks after discharge (risk ratio 0.14 [0.02 – 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 (odds ratio 1.40 [95% CI, 0.74–2.83]).

Conclusion

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

Significance of this study

What is already known about this subject?

- After an episode of mild biliary pancreatitis, same-admission cholecystectomy is advised to prevent recurrent biliary events.
- Cholecystectomy after acute necrotising pancreatitis is potentially associated with an increased risk of complications
- In patients with necrotising biliary pancreatitis there is no high-level evidence for the optimal timing of cholecystectomy

What are the new findings?

- In current clinical practice the presence or absence of peripancreatic collections are often not evaluated before cholecystectomy.
- The risk of recurrent biliary events, particularly recurrent pancreatitis is high and increases when cholecystectomy is postponed, with a turning point at 8 weeks after discharge.
- Delaying cholecystectomy did not reduce the risk of periprocedural complications including infected necrosis.

How might it impact on clinical practice in the foreseeable future?

- Before cholecystectomy, assessment of the presence or absence of peripancreatic collections should be performed
- Cholecystectomy, in the absence of peripancreatic collections, is preferably performed before 8 weeks after discharge due to the increased risk of recurrent biliary events.
- Endoscopic sphincterotomy does not reduce the risk of recurrent biliary events in patients with necrotising biliary pancreatitis.

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 randomised 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 necrotising 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 eleven 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 six 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 necrotising 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 5 out of 6 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 to 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 necrotising biliary pancreatitis remains unclear.[18]

Therefore, the aims of this study are to determine the optimal timing of cholecystectomy in patients with necrotising 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 necrotising biliary pancreatitis. The study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) 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 computed tomography 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 computed tomography [CT]), (2) a dilated common bile duct (>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 Supplementary Table S1[29]. The following patients were excluded: patients who died during index admission before the cholecystectomy, patients who had less than three months follow-up after discharge and did not undergo cholecystectomy within those three months, and patients who had already undergone cholecystectomy before the first episode of biliary pancreatitis.

All patients gave written informed consent and the ethical review board approved all three trials and the registration cohort. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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 was 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 normalization 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 randomised 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 ERCP, cholangitis, acute cholecystitis, and recurrent acute biliary pancreatitis. Choledocholithiasis had to be identified on imaging (endoscopic) ultrasound, CT, magnetic resonance cholangiopancreatography (MRCP) or magnetic resonance imaging (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 common bile duct 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: A. a positive culture of peripancreatic necrotic tissue obtained through fine-needle aspiration or, B. a positive culture of peripancreatic necrotic tissue obtained from the first drainage procedure or operation, or C. the presence of gas within collections on CT. Occurrence of infected necrosis after cholecystectomy was defined as an infection that developed within one month after the cholecystectomy.

TABLE 1 - TG18 DIAGNOSTIC CRITERIA FOR ACUTE CHOLECYSTITIS

Diagnostic criteria for acute cholecystitis
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
Definite diagnosis: one item in A + one item in B + C
Cited from Yokoe et al. 2018[30]

Statistical analysis

All analyses were performed using SPSS Statistics version 24.0 (IBM Corporation, USA). Continuous data were reported as medians with interquartile ranges (P25 – P75) when not normally distributed or as mean with standard deviation (±) 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 ORs were calculated with their respective 95% CIs. 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 two weeks before the 25th percentile to two weeks before the median with a two 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 48h 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 randomised trials, of whom 328 patients had necrotising biliary pancreatitis with peripancreatic collections and a CTSI score >3. As shown in Figure 1, eighty patients met the exclusion criteria, 37 patients died during index admission due to multiorgan failure, eight 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 the Supp. Appendix (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 necrotising 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 ASA grade (p=0.01), higher Acute Physiology and Chronic Health Evaluation – II (APACHE-II)scores at admission (p<0.01),

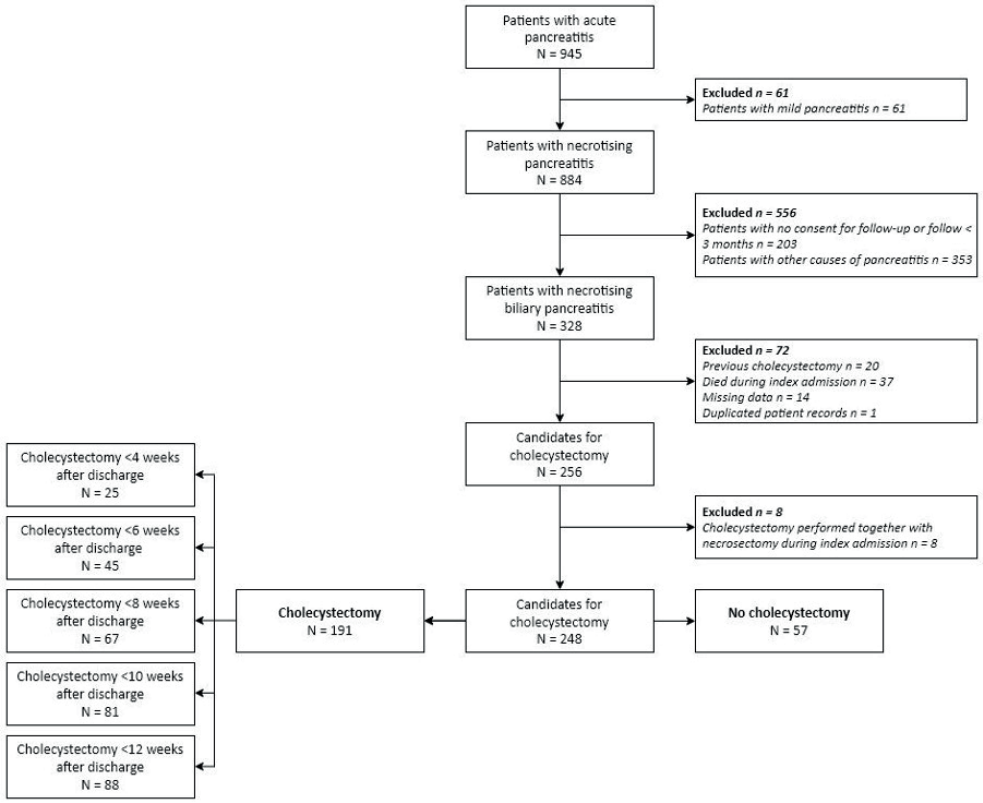

Figure 1 - Inclusion flowchart

and more often infected necrosis (p = 0.01). Overall mortality was 13%, 3 (1%) patients died from the (ongoing) necrotising pancreatitis. Baseline characteristics of patients with and without cholecystectomy and with reasons for omitting cholecystectomy are presented in the Supp. appendix (Table 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%). Of these patients, infection of peripancreatic collections occurred in 4 (14%).

TABLE 2 - BASELINE CHARACTERISTICS OF 248 PATIENTS WITH NECROTISING BILIARY PANCREATITIS

Characteristic	Overall N = 248
Age (years)	60 (±15)
Women	116 (47%)
BMI (n = 161, (16%))	27 (25 – 31)
ASA grade on admission	
• 1	104 (42%)
• 2	126 (51%)
• 3	18 (7%)
First episode of pancreatitis	245 (99%)
History of abdominal surgery	51 (21%)
Liver enzymes at admission	
• Bilirubin (µmol/l) (n = 221, 89%)	28 (17 – 50)
• AST (units/l) (n = 210, 85%)	174 (80 – 314)
• ALT (units/l) (n = 223, 90%)	199 (84 – 379)
• AP (units/l) (n = 219, 88%)	122 (91 – 172)
• GGT (units/l) (n = 219, 88%)	303 (160 – 552)
Predicted severity of pancreatitis on admission	
• APACHE-II	8 (±4)
• Imrie score	3 (±2)
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 (months)	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.
BMI 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

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, 0.27–0.90]; 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 [0.02 – 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 underwent 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 Supp. appendix (Table S5). Baseline characteristics of patients divided over a two-week time timing interval are presented in Supp. appendix (Table S6).

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 necrotising 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).

Role of endoscopic sphincterotomy

ES was performed in 117 (47%) patients of 248 patients with necrotising biliary pancreatitis after a median of one day (P25 – P75: 0 – 21). Indication for ES are listed in Supp. appendix (Table S7). The same number of patients underwent ES in the early cholecystectomy group (<10 weeks after discharge) compared to 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 one 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 common bile duct in 57 (48%) and sludge was seen in the common bile duct 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 were 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, 0.73–1.85]; p=0.54; Table 5). ES had no protective value on the occurrence of biliary events overall (odds ratio 1.44 [95% CI, 0.74–2.83]) or on the occurrence of recurrent pancreatitis (odds ratio 0.36 [95% CI, 0.08-1.59]). This was independent of the timing of ES before cholecystectomy.

TABLE 3 - RECURRENT BILIARY EVENTS BEFORE CHOLECYSTECTOMY IN 248 PATIENTS WITH NECROTISING BILIARY PANCREATITIS 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	0 (0%)	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	0 (0%)	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	0 (0%)	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	

TABLE 4 - DIFFICULTY CHOLECYSTECTOMY AND ADVERSE EVENTS IN 191 PATIENTS AFTER NECROTISING 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	

	<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
Difficulty cholecystectomy										
Adhesions (n = 179, %)	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 (n = 179, %)	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	
Conversion to open (n = 185, %)	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 (n = 180, %)	0 (0%)	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 (n = 182, %)	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 (%).
*Within 31 days after cholecystectomy

TABLE 5 - RECURRENT BILIARY EVENTS BEFORE CHOLECYSTECTOMY IN 248 PATIENTS WITH NECROTISING BILIARY PANCREATITIS WHO DID OR DID NOT UNDERGO SPHINCTEROTOMY

	Overall N = 248
Age (years)	60 (±15)
Women	116 (47%)
BMI (n = 161, (16%))	27 (25 – 31)
ASA grade on admission	
Follow-up (months)	76 (±30)

Data are presented as n (%)
ES endoscopic sphincterotomy, NA not applicable, *after endoscopic sphincterotomy in patients who underwent sphincterotomy after admission, overall recurrent biliary events in patient who did not undergo 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 necrotising biliary pancreatitis. We found that cholecystectomy is delayed in the majority of patients with necrotising 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 six 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 necrotising 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 multicentre randomised 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, albeit 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 necrotising 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 4, 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 to 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, pre-operative 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 necrotising 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 intraabdominal 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 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 necrotising pancreatitis'.[7] Early cholecystectomy in acute necrotising pancreatitis has its risks, as seen both in literature and in clinical practice. Previous studies have shown that 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 necrotising pancreatitis. In our study the evaluation of the pancreatic and peripancreatic collection over time after necrotising 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 4 patients, in 3 patients prophylactic antibiotics were administered during cholecystectomy. In 1 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 (four 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 two to four 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 summarised in the flowchart in Figure 2.

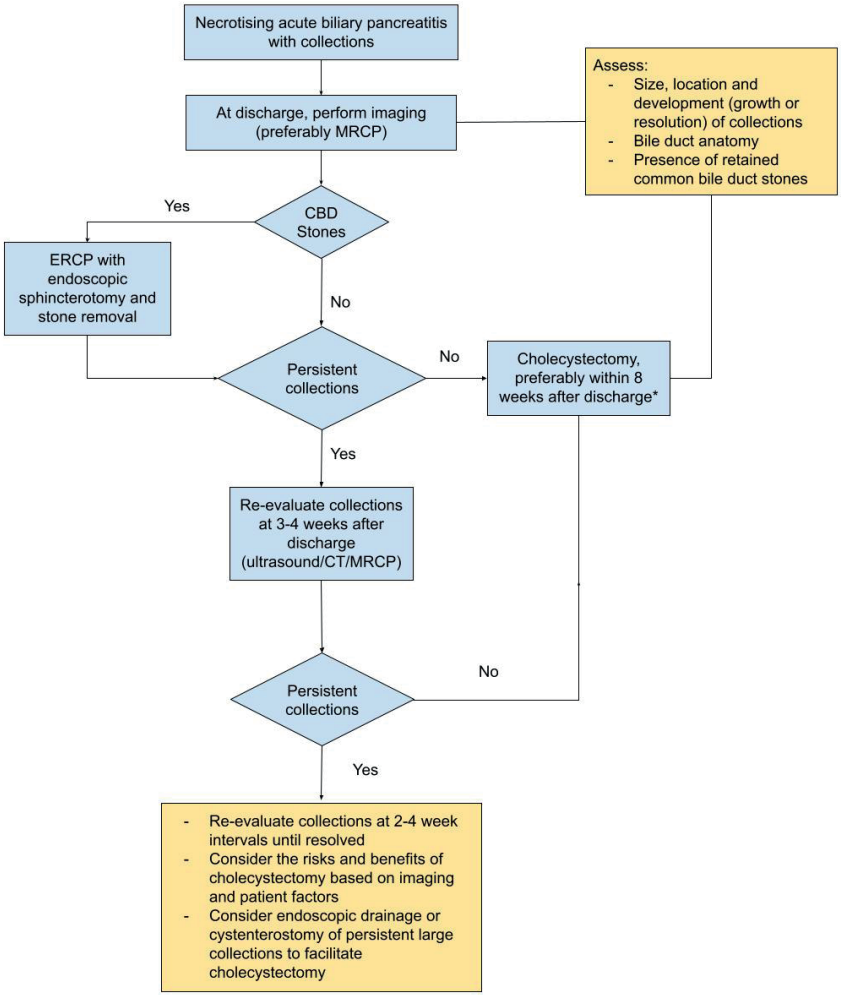

Figure 2 - Flowchart on follow-up after nectrotising billiary pancreatitis and timing of cholecystectomy

Nealon and colleagues prospectively followed 151 patients with acute necrotising 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%] versus 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, endoscopic sphincterotomy 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 to 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 albeit 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 necrotising 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 in also in severely ill patients with necrotising 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 (e.g. 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 necrotising 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 necrotising biliary pancreatitis.

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Chapter 8

Pancreatic exocrine insufficiency following acute pancreatitis: systematic review and study level meta-analysis

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Pancreatology, 2018

Abstract

Objectives

This study systematically explores the prevalence of pancreatic exocrine insufficiency (PEI) after acute pancreatitis in different subgroups of etiology (biliary/alcoholic/other), disease severity and follow-up time (<12, 12-36 and >36 months after index admission).

Methods

PubMed and EMBASE databases were searched, 32 studies were included in this study level meta-analysis.

Results

In a total of 1495 patients with acute pancreatitis, tested at a mean of 36 months after index admission, the pooled prevalence of PEI was 27.1% (95%-confidence interval [CI]: 20.3%-35.1%). Patients from seven studies (n=194) underwent direct tests with pooled prevalence of 41.7% [18.5%-69.2%]. Patients from 26 studies (n=1305) underwent indirect tests with pooled prevalence of 24.4% [18.3%-31.8%]. In subgroup analyses on patients that underwent fecal elastase-1 tests, PEI occurred more often in alcoholic pancreatitis (22.7% [16.6%-30.1%]) than in biliary pancreatitis (10.2% [6.2%-16.4%]) or other etiology (13.4% [7.7%-22.4%]; P=0.02). Pooled prevalence of PEI after mild and severe pancreatitis was 19.4% [8.6%-38.2%] and 33.4% [22.6%-46.3%] respectively in studies using fecal elaste-1 tests (P=0.049). Similar results were seen in patients without (18.9% [9.3%-34.6%]) and with necrotizing pancreatitis (32.0% [18.2%-49.8%]; P=0.053). Over time, the prevalence of PEI decreased in patients who underwent the fecal elastase-1 test and increased in patients who underwent the fecal fat analysis.

Conclusions

After acute pancreatitis, a quarter of all patients develop PEI during follow-up. Alcoholic etiology and severe and necrotizing pancreatitis are associated with higher risk of PEI. The prevalence of PEI may change as time of follow-up increases.

Introduction

Acute pancreatitis may be complicated by loss of exocrine pancreatic function. This is typically depicted by a loss of pancreatic cell mass and functional capacity because of pancreatic necrosis, which occurs in around 20% of patients.[1,2] Around 30% of patients with necrotizing pancreatitis need catheter drainage and / or pancreatic necrosectomy as treatment of infected necrosis.[3,4] During removal of infected necrosis, adjacent vital pancreatic tissue may also be damaged which reduces the functional reserve capacity of the remnant pancreas even further. Other explanations for functional loss after acute pancreatitis include secondary impairment of hormonal mediators or neural stimuli, damaged receptors that control enzyme releasing acinar cells or obstructions in the exocrine ductal system through altered anatomy caused by the inflammation.[5]

The pancreatic gland has two main functions; synthesis and endocrine secretion of insulin for glycemic control, and synthesis and exocrine secretion of enzymes for digestion of fat, protein and carbohydrate in the gut. Impaired function of the endocrine pancreas causes diabetes mellitus, which is a well-known complication and reported to be newly diagnosed in around a quarter of all patients after acute pancreatitis.[6] Pancreatic exocrine insufficiency causes insufficient digestion and uptake of foods, which may lead to indigestion, flatulence, diarrhea and, in severe form, steatorrhea and malnutrition. Consequences are weight loss, vitamin and mineral deficiencies and metabolic bone disease.[7] Therapy of pancreatic exocrine insufficiency consists of supplemental pancreatic enzymes to be taken with every meal or snack to substitute the deficient endogenous pancreatic enzyme production.[8]

Pancreatic exocrine insufficiency is a common complication of pancreatic cancer and chronic pancreatitis.[9,10] Several, mainly small clinical studies, report on pancreatic exocrine insufficiency in the follow-up of acute pancreatitis.[11] Between these studies, etiology of pancreatitis, severity of disease, diagnostic tests for pancreatic exocrine insufficiency and follow-up time differs substantially, which severely impedes comparability of results. Published reviews on exocrine insufficiency after acute pancreatitis are narrative or focus on specific subgroups of patients.[11-13] We conducted a systematic review of studies reporting on exocrine insufficiency in the follow-up of acute pancreatitis and performed a study level meta-analyses to explore the prevalence of pancreatic exocrine insufficiency in different subgroups of etiology, severity of disease and follow-up time.

Methods

This systematic review and study level meta analyses was performed according to the MOOSE guidelines for reporting meta-analysis of observational studies.[14] The protocol for this study was registered in the PROSPERO international prospective register of systematic reviews (CRD42015029733).

Search strategy

We searched for studies reporting on pancreatic exocrine insufficiency following acute pancreatitis in PubMed and EMBASE databases. No restrictions on publication date were set. The search was performed on November 16, 2017 with the following items in both Mesh terms and plain text:

1; (exocrine pancreas) OR (exocrine) OR (pancreatic funct*) OR (pancreas funct*) OR (pancreatic dysfunct*) OR (pancreas dysfunct*) OR (pancreatic insufficien*) OR (pancreas insufficien*) AND 2; (Pancreatitis) AND (acute OR necro*).

Detailed searches for both databases are available online at the PROSPERO website (CRD42015029733) and in the supplementary appendix (p 2).

Study selection

Included were studies 1) including patients with acute pancreatitis; 2) that reported on diagnostic laboratory testing for pancreatic exocrine insufficiency; 3) during follow-up, i.e. at least 3 months after discharge of index admission. Excluded were 1) studies that reported on patients with chronic pancreatitis only or studies that reported on patients with chronic and acute pancreatitis, but data of these two groups were not reported separately; 2) studies including fewer than 10 patients; 3) animal studies; 4) studies reporting in other than English language and 5) unpublished studies and conference abstracts. Two investigators (RAH, DJM) screened titles and abstracts for eligibility and included studies by consensus in collaboration with a third investigator (NDH). Reference lists of included publications were screened for relevant studies that were not identified by the initial search, primarily by title and if eligible, by abstract and full text.

Data extraction

Using a predefined data extraction file, three investigators (RAH, NDH and DJM) extracted the following variables from the included studies: first author and country, study period and year of publication, study design and inclusion criteria, number of patients included, sex, age, etiology of acute pancreatitis,

severity of disease, number of patients with pancreatic necrosis, number of patients that underwent pancreatic necrosectomy, test method to diagnose pancreatic exocrine insufficiency, timing and reference values of pancreatic exocrine insufficiency tests, number of patients with pancreatic exocrine insufficiency according to performed test, etiology of pancreatitis of patients with exocrine insufficiency and number of patients that used supplemental pancreatic enzymes. Extracted data were checked for consistency and plausibility. Any discrepancies were resolved by consensus. If studies reported on pancreatic exocrine insufficiency for subgroups of severity of disease (e.g. non-necrotizing and necrotizing pancreatitis) separately, then data were extracted as such for pooling and meta-analysis. For quality assessment of included studies the Newcastle-Ottawa Scale for non-randomized studies in meta-analyses was used, in which the maximum score is nine points for high quality studies.[15] No attempt was made to complete missing data through communication with corresponding authors. Missing data is reported as 'not reported' and left unhandled in further analyses.

Severity of disease

To compare the prevalence of pancreatic exocrine insufficiency in different subgroups of disease severity, the Atlanta Classification from 1992 was used.[16] Most included studies classified severity of disease by the Atlanta 1992 classification as this was the general standard before the classification was updated in 2012. The classification defines mild acute pancreatitis by an uneventful recovery without organ failure or necrosis and severe acute pancreatitis by organ failure and/or local complications such as necrosis.[16] The Atlanta 2012 classification of acute pancreatitis includes a third category of moderate severe acute pancreatitis in addition to mild and severe acute pancreatitis.[17] Studies not reporting severity according to Atlanta 1992 were reclassified, if possible, to the Atlanta 1992 classification of mild or severe acute pancreatitis. For example, studies including only patients with necrosis were classified as 'severe'. Studies reporting only that a subgroup of patients did not have necrosis were not re-classified as 'mild' because no data of possible organ failure was presented and thus, uncertainty remains for the classification 'mild' or 'severe'. It was not deemed possible to re-classify severity of disease from the Atlanta 1992 to the Atlanta 2012 classification based on the available data.

Data processing and statistical analysis

Weighted means were estimated for the variables age and follow-up time to pancreatic exocrine insufficiency test through methods described by Hozo et al.[18]

TABLE 1 - STUDY CHARACTERISTICS*

Author and year of publication	Country	Study design	Index admission interval	Inclusion criteria	Exclusion criteria	Timing PEI test†	Method of PEI test†††	Abnormal test level
Andersson 2010[21]	Sweden	Follow-up study of prospective cohort	2001 - 2005	Mild and severe acute pancreatitis	Dementia, malignancy, history of severe pancreatitis, chronic pancreatitis	42 (36 - 53)‡	fecal elastase-1	<200 µg/g
Angelini 1984[32]	Italy	Prospective follow-up	1980 - 1984	Acute pancreatitis	NR	12 - 48††	Secretin	-
Bavare 2004[45]	India	Follow-up of consecutive series	2001 - 2003	Necrotizing pancreatitis	NR	19 (8 - 28)‡‡	fecal fat	>7g/24h
Boreham 2003[34]	United Kingdom	Prospective follow-up	2000 - 2001	First attack of acute pancreatitis	chronic pancreatitis, previous pancreatic surgery	3	fecal elastase-1	<200 µg/g
Bozkurt 1995[31]	Germany	Prospective follow-up	NR	First attack of acute necrotizing pancreatitis	NR	15	Lund test	-
Braganza 1973[33]	United Kingdom	Follow-up of consecutive series	1967 - 1971	Suspected pancreatic disease	Incomplete follow-up, gastrojejunostomy, patient intolerance, no liver scan	12	Secretin	-
Brunschot 2017[40]	The Netherlands	Randomized controlled trial	2011 - 2015	(infected) necrotizing pancreatitis	Recurrent or chronic pancreatitis, pancreatic invasive intervention	6	fecal elastase-1	<200 µg/g
Chandrasekaran 2015[44]	India	Follow-up study of prospective cohort	2008 - 2009	Severe acute pancreatitis	Pseudocysts, chronic pancreatitis, continued alcohol abuse	26	fecal fat	>7g/24h
Ganesh Kamath 2016[25]	India	Prospective follow-up	2009 - 2013	Recurrent acute pancreatitis	Pancreatic neoplasia / cancer	37	Acid steatocrit	>7g/24h
Ganesh Pai 2017[26]	India	Prospective follow-up	2013 - 2015	Recurrent acute pancreatitis after corrected treatable cause	Pancreatic / periampullary carcinoma	12	fecal elastase-1	<200 µg/g
Garip 2013[35]	Turkey	Follow-up of consecutive series	2003 - 2007	Acute pancreatitis	< 6 months follow-up	32 (6 - 48)	fecal elastase-1	<200 µg/g
Gupta 2009[43]	India	Prospective follow-up	2005 - 2006	Severe acute pancreatitis	Chronic alcoholic pancreatitis, incomplete evaluation.	31 ± 5	fecal fat	>7g/24h

Author and year of publication	Country	Study design	Index admission interval	Inclusion criteria	Exclusion criteria	Timing PEI test†	Method of PEI test†††	Abnormal test level
Ibars 2002[22]	Spain	Follow-up study of prospective cohort	1994 - 1995	Acute biliary pancreatitis	Previous acute pancreatitis, necrosectomy, no CT-scan, no cholecystectomy	12	fecal fat	>7g/24h
John 1997[51]	South Africa	Follow-up of consecutive series	1994	Acute pancreatitis	NR	9 (2 - 16)	fecal chymotrypsin	<3U/g
Koziel 2017[36]	Poland	Prospective follow-up	2011 - 2012	Acute pancreatitis	Moderate acute pancreatitis, chronic pancreatitis	14 ± 4	fecal elastase-1	<200 µg/g
Małecka-Panas 1996[30]	Poland	Prospective follow-up	NR	Acute alcoholic pancreatitis	NR	60	Secretin	-
Migliori 2004[27]	Italy	Prospective follow-up	NR	Acute pancreatitis	NR	4 - 18††	secretin or AACT	AACT <14%
Mitchell 1983[52]	United Kingdom	Prospective follow-up	NR	Acute pancreatitis	NR	2-72††	BTP-test	<57% PABA recovery
Nikkola 2017[37]	Finland	Prospective follow-up	2001 - 2005	Alcoholic pancreatitis	Previous pancreatitis, symptoms of chronic pancreatitis, upper abdominal surgery	126 (36-156)‡‡	fecal elastase-1	<200 µg/g
Rana 2014[23]	India	Retrospective analyses	2009 - 2012	Endoscopic drainage of pancreatic necrosis	Recurrent or chronic pancreatitis, pancreatic surgery	7 - 118††	fecal fat	>7g/24h
Reddy 2007[48]	India	Follow-up of consecutive series	1996 - 1998	Pancreatic necrosectomy	NR	22 (15 - 36)‡‡	fecal fat	>7g/24h
Reszetow 2007[38]	Poland	Follow-up of consecutive series	1993 - 1999	Biliary or alcoholic pancreatitis, Pancreatic necrosectomy for infected necrosis,	Other etiology	61 ± 23	fecal elastase-1	<200 µg/g
Sabater 2004[46]	Spain	Prospective follow-up	1994 - 1998	Severe acute pancreatitis	Patients without local necrosis	12	secretine, fecal chymotrypsin and fecal fat	- / >6U/g / >7g/24h
Seidensticker 1995[29]	Germany	Retrospective analyses	NR	Acute pancreatitis	NR	34 ± 36	secretin	-

Author and year of publication	Country	Study design	Index admission interval	Inclusion criteria	Exclusion criteria	Timing PEI test†	Method of PEI test†††	Abnormal test level
Seligson 1982[28]	Sweden	Prospective follow-up	1972 - 1973	Acute pancreatitis	NR	57	cholecystokinin	-
Symersky 2006[47]	The Netherlands	Prospective follow-up	1990 - 1996	Biliary or post-ERCP pancreatitis	Alcoholic etiology	54 (12 - 90)	fecal fat	>7g/24h
Tsiotos 1998[49]	United States of America	Follow-up study of prospective cohort	1983 - 1995	Pancreatic necrosectomy	NR	60 (3 - 132)	fecal fat	>7g/24h
Tu 2017[39]	China	Follow-up of consecutive series	2016	Acute pancreatitis	Recurrent or chronic pancreatitis, diabetes, chronic diarrhea, intestinal tuberculosis, Crohn's disease, incomplete records	30‡	fecal elastase-1	<200 µg/g
Uomo 2009[41]	Italy	Follow-up of consecutive series	1990 - 1993	Necrotizing pancreatitis	NR	179 ± 13	fecal elastase-1	<200 µg/g
Vujasinovic 2014[42]	Slovenia	Prospective follow-up	NR	Acute pancreatitis	NR	32 ± 52	fecal elastase-1	<200 µg/g
Winter Gasparoto 2015[50]	Brazil	Follow-up of consecutive series	2002 - 2012	Necrotizing pancreatitis, age between 18 and 70	Severe comorbidity, malignancy, illiteracy	35	fecal fat; Sudan Stain	-
Xu 2012[24]	China	Follow-up of consecutive series	2003 - 2008	Acute pancreatitis	Cystic fibrosis, pancreatic cancer, chronic or recurrent pancreatitis, pancreatic or gastrointestinal surgery, gastrinoma, Crohns disease, chronic renal failure, pneumonia	29	fecal elastase-1	<200 µg/g

* NR = not reported. DM = details missing; article describes subgroups separately or not all patients in cohort were tested for pancreatic exocrine insufficiency. BTP = N-benzoyl-l-tyrosyl-p-aminobenzoic acid. PABA = p-aminobenzoic acid.
† PEI = pancreatic exocrine insufficiency. Values in months by mean ± SD (or range) if provided; ‡ median (interquartile range if provided); ‡‡ median (range); or †† range
††† for description of all available tests on pancreatic exocrine insufficiency see http://www.uptodate.com/contents/pancreatic-exocrine-function-tests

Using a random effects model, pooled prevalence and associated 95% confidence intervals (CI) were calculated for pancreatic exocrine insufficiency for direct and indirect test method separately because of fundamental differences between both test types. During direct tests (e.g. secretine testing), pancreatic secretory content is collected and analyzed by duodenal intubation which is a highly specialized procedure demanding considerable patient tolerance. Indirect tests (e.g fecal elastase-1 and fecal fat analysis) measure the consequence of pancreatic exocrine function in stool, breath or serum and are more convenient and widely available, but generally less sensitive for mild pancreatic exocrine insufficiency.[19]

Subsequently, we performed meta-analytic subgroup analyses to 1) explore the role of the etiology of acute pancreatitis in the prevalence of pancreatic exocrine insufficiency, 2) explore pancreatic exocrine insufficiency in different subgroups of disease severity and 3) explore possible fluctuation of pancreatic exocrine insufficiency over time by comparing studies of different follow-up periods (≤ 12 months, 13 - 36 months and > 36 months). These subgroup analyses were performed only on studies that used 1) the fecal elastase-1 test and 2) the fecal fat analysis test. A maximum of two studies reported on other indirect test methods than fecal fat or fecal elastase-1, which precluded further subgroup analyses (Table 1). Studies including direct test methods reported insufficient data for subgroup analyses (Table 1 and 2). Chi-square and Fishers' exact tests were performed for comparisons between and within subgroups as appropriate. To test between-study heterogeneity in different subgroups we used I2-statistics. I2 values of <25%, ≥25% - <50%, ≥50% - <75% and ≥75% were classified as low, moderate, high and very high heterogeneity respectively.20 Data processing and statistical analyses were performed in Microsoft Office Excel 2013 and R version 3.2.1.

Results

Study selection

The search revealed a total of 2028 articles. Removal of duplicates left 1494 articles for screening on title and abstract after which 55 full text manuscripts were assessed for eligibility. Data from 32 studies were finally included in the analyses (Figure 1).

Study and patient characteristics

Studies originated from 15 countries across 5 continents and were published between 1973 and 2017. Mean follow-up time (i.e. time to test for pancreatic exocrine insufficiency) was 36 months after discharge from index admission.

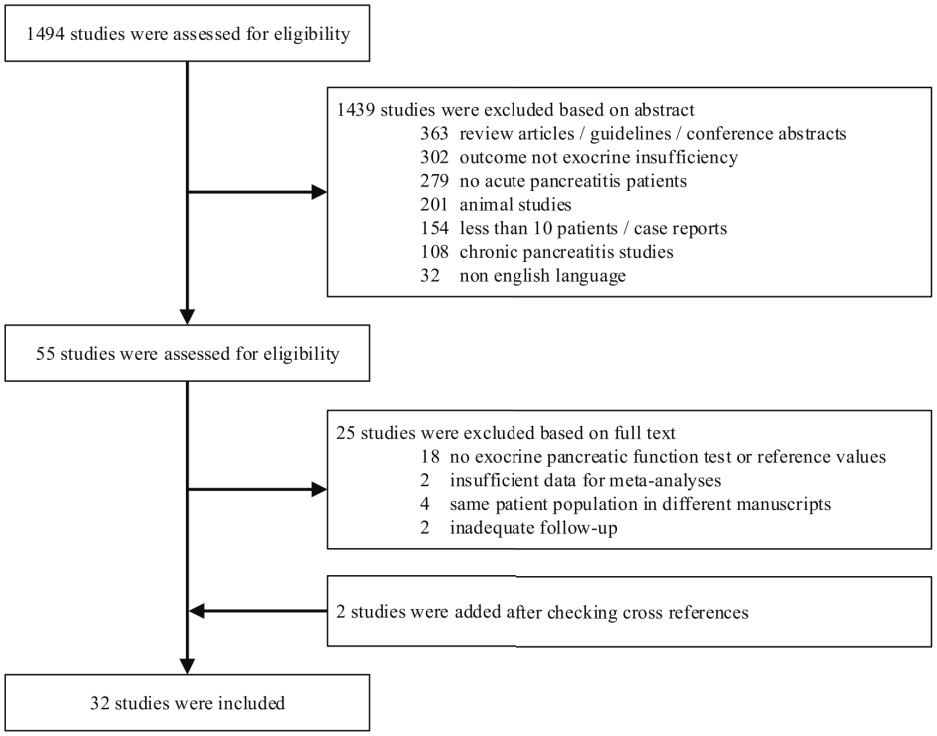

Figure 1 - Study inclusion flow chart

Patients with recurrent episodes of acute pancreatitis were excluded in four studies[21-24] and included in two studies[25,26]. In the other studies no information regarding in- or excluding patients with recurrent pancreatitis was provided. Pancreatic exocrine insufficiency was measured by direct tests in six studies.[27-33] In 24 studies indirect tests were used, of which 12 studies used the fecal elastase-1 test[21-24,26,34-50], nine studies used fecal fat tests[22,23,43-45,47-50], one study used fecal chymotrypsin test[51], one study used the N-benzoyl-l-tyrosyl-p-aminobenzoic (BTP) test[52] and one study the acid steatocrit test[25]. In two studies, both direct and indirect (fecal chymotrypsin, fecal fat, amino acid consumption) tests were used (Table 1).[27,46]

A total of 1495 patients were tested for pancreatic exocrine insufficiency. The number of patients per study ranged from 10 to 150. Data were not reported, or details on subgroups were missing for the variable age in three studies[23,32,33]; sex in eight studies[23,25,31-33,37,40,52]; etiology in eight studies[23,25,26,31-33,40,52]; severity of disease in seven studies[25,26,29,30,33,51,52]; presence of necrosis in 11 studies[21,25,26,29,30,33,36,37,47,51,52] and status of necrosectomy in 14 studies[21,23,25-27,29-33,40,47,51,52] Enzyme replacement therapy was reported in 13 studies[21,23,24,28,30,40,41,43-45,47,49,50] (Table 2).

TABLE 2 - PATIENT CHARACTERISTICS AND OUTCOME PER STUDY*

Author and year of publication	N#	Male N (%)	Age[ı]	Etiology[¥]	Severity[¶]	Necrosis N (%)	Necrosectomy N (%)	PEI by test N (%)	Enzyme treatment[Ω] N (%)
Andersson 2010[21]	40	16 (40)	61 (48 - 68)II	20/10/10	mild + severe	NR	NR	1 (3)	3 (8)
Angelini 1984[32]	21	DM	NR	DM	Severe	21 (100)	DM	2 (10)	NR
Bavare 2004[45]	18	18 (100)	36 (25 - 47)III	4/10/4	Severe	18 (100)	18 (100)	2 (11)	2 (11)
Boreham 2003[34]	23	13 (57)	55 (21 - 77)III	15/5/3	mild + severe	7 (30)	0	7 (30)	NR
Bozkurt 1995[31]	53	DM	21 - 83IV	DM	severe	53 (100)	DM	45 (85)	NR
Braganza 1973[33]	12	NR	NR	NR	NR	NR	NR	1	NR
Brunschot 2017[40]	83	DM	62 ± 13	DM	severe	83 (100)	DM	41 (49)	29 (35)
Chandrasekaran 2015[44]	35	30 (86)	37 ± 10	11/19/5	severe	35 (100)	21 (60)	14 (40)	21 (60)
Ganesh Kamath 2016[25]	37	DM	22 (18 - 33)III	DM	NR	NR	NR	0	NR
Ganesh Pai 2017[26]	38	32 (84)	26 (9 - 55)III	DM	NR	NR	NR	0	NR
Garip 2013[35]	109	58 (49)	57 ± 16	72/9/28	mild + severe	30 (28)	22 (20)	15 (14)	NR
Gupta 2009[43]	30	24 (80)	38 ± 2	15/10/5	severe	21 (70)	25 (83)	12 (40)	4 (13)
Ibars 2002[22]	57	15 (27)	62 ± 14	57/0/0	mild + severe	26 (46)	0	0	NR
John 1997[51]	50	38 (76)	39	5/42/3	NR	NR	NR	11 (22)	NR
Koziel 2017[36]	150	94 (63)	54 ± 17	64/46/40	mild + severe	NR	3 (2)	21 (14)	NR
Małecka-Panas 1996[30]	47	33 (70)	44 ± 10	0/47/0	NR	NR	NR	30 (64)	6 (13)
Migliori 2004[27]	71	57 (80)	46 (18 - 80)	39/36/0	mild + severe	33 (44)	NR	41 (58)	NR
Mitchell 1983[52]	23	DM	22 - 89 IV	DM	NR	NR	NR	7 (30)	NR
Nikkola 2017[37]	45	DM	25 - 71IV	0/45/0	mild + severe	NR	0	11 (24)	NR
Rana 2014[23]	33	DM	DM	DM	severe	33 (100)	DM	11 (33)	3 (9)
Reddy 2007[48]	10	8 (80)	35 ± 8	4/6/0	severe	10 (100)	10 (100)	8 (80)	NR
Reszetow 2007[38]	28	20 (71)	48 ±10	10/18/0	severe	28 (100)	28 (100)	4 (14)	NR

Author and year of publication	N#	Male N (%)	Age[|]	Etiology[¥]	Severity[¶]	Necrosis N (%)	Necrosectomy N (%)	PEI by test N (%)	Enzyme treatment[Ω] N (%)
Sabater 2004[46]	27	12 (44)	62 ± 13	27/0/0	severe	27	12	9 (33)	NR
Seidensticker 1995[29]	33	25 (76)	41 ± 14	8/13/12	NR	NR	NR	0	NR
Seligson 1982[28]	10	8 (80)	54 ± 12	2/7/1	severe	10 (10)	10 (10)	7 (70)	2 (20)
Symersky 2006[47]	34	16 (47)	53 ± 3	26/0/8	mild + severe	NR	NR	14 (41)	10 (29)
Tsiotos 1998[49]	44	33 (75)	58 (20 - 93)	17/5/22	severe	44 (100)	44 (100)	11 (25)	11 (25)
Tu 2017[39]	113	75 (66)	47 ± 1	65/3/45	mild + severe	89 (79)	32 (28)	40 (35)	NR
Uomo 2009[41]	40	17 (43)	48 ± 18	28/0/12	severe	40 (100)	0	0 (0)	0 (0)
Vujasinovic 2014[42]	100	65 (65)	57 ± 14	36/42/22	mild + severe	0	0	21 (21)	NR
Winter Gasparoto 2015[50]	16	9 (56)	48 ± 13	10/4/2	severe	16 (100)	2 (13)	1 (6)	1 (6)
Xu 2012[24]	65	33 (51)	59 (27 - 82)	50/7/8	mild + severe	10 (15)	5 (8)	38 (58)	33 (51)

* NR = not reported. DM = details missing; article describes subgroups separately or not all patients in cohort were tested for pancreatic exocrine insufficiency.
# Number of patients tested on pancreatic exocrine insufficiency
| in years by mean ± SD (or range) if provided; || by median (interquartile range if provided) or ||| by median (range) or by IV range
¥ presented as number of patients in cohort in which etiology of pancreatitis was biliary / alcoholic / other
¶ Severity of pancreatitis was reported in the original manuscript by the Atlanta criteria of 1992 or, if possible, converted to the Atlanta 1992 criteria (e.g. necrotizing pancreatitis was classified as severe pancreatitis). If this was not possible, NR is stated
Ω reported number of patients that used enzymes at time of study.

Quality assessment scores according to the Newcastle-Ottawa Scale are presented in Supplementary Table 1 (appendix p.3); seven studies scored four points[28,30,33,41,47,50,52], 11 studies scored five points[22,29,31,36,38,39,42,45,48,49,51], nine studies scored six points[25-27,32,35,37,43,44,46], three studies scored seven points[23,24,34], one study scored eight points[21] and one study scored nine points[40]. The scores indicate fair to good quality studies.

Meta-analysis

A total of 425 patients had test values indicating pancreatic exocrine insufficiency. Pooled prevalence was 27.1% (95%-CI: 20.3% - 35.1%) and I2 test value was 85.6%, indicating very high heterogeneity between studies. In the seven studies reporting on direct pancreatic function tests[27,27-33], 194 patients were tested on pancreatic exocrine insufficiency. The pooled prevalence was 41.7% (95%-CI: 18.5% - 69.2%) with an I2 test value of 86.0%. In the 26 studies using indirect tests[21-27,34-52] in 1305 patients, pooled prevalence of pancreatic exocrine insufficiency was 24.4% (95%-CI: 18.3% - 31.8%) with an I2 value of 82.3% indicating a very high heterogeneity between studies.

Etiology of pancreatitis

Nine studies (using fecal elastase-1 or fecal fat analysis) including 472 patients reported on both etiology of acute pancreatitis in all tested patients and on disease etiology of patients with pancreatic exocrine insufficiency.[21,22,34,36-38,41,42,48]. In studies reporting on fecal fat analysis, pancreatic exocrine insufficiency was present in 6 out of 88 patients with biliary pancreatitis (pooled prevalence 13.9%, 95%-CI: 1.0% - 71.2%)[22,46,48]; in 5 out 6 patients with alcoholic pancreatitis (83.3%)[48]; and no studies reported on other etiologies.

In studies reporting on fecal elastase-1, pancreatic exocrine insufficiency was present in 13 out of 164 patients with biliary pancreatitis (pooled prevalence 10.2%, 95%-CI: 6.2% - 16.4%)[21,34,36,38,41,42]; in 34 out 160 patients with alcoholic pancreatitis (pooled prevalence 22.7%, 95%-CI: 16.6% - 30.1%)[21,34,36-38,42]; and in 11 out 103 patients with other etiologies (pooled prevalence 13.4%, 95%-CI: 7.7% - 22.4%: P = 0.02)[21,34,36,41,42]. The higher occurrence of pancreatic exocrine insufficiency in alcoholic pancreatitis was consistent in subgroups of disease severity (Table 3a and 3b). I2 values indicated low heterogeneity between studies reporting on fecal elastase-1 (data not shown).

Severity of disease

Of the 22 included studies using fecal elastase-1 or fecal fat analysis, 9 studies reported severity according to the Atlanta 1992 Classification.[21-23,34,43,44,46,47,49] Thirteen studies used other severity classifications of which 11 studies could be (partly) re-classified to the Atlanta 1992 Classification.[24,35,37-42,45,48,50] The remaining two studies reported insufficient data for reclassification.[26,36]

Mild and severe acute pancreatitis

In studies reporting on fecal fat analysis, only one study reported mild acute pancreatitis separately from severe acute pancreatitis, with a prevalence of 22.7%.[47] Ten studies including 251 patients reported results on severe acute pancreatitis, with a pooled prevalence of 30.0% (95%-CI: 18.1% - 45.3%).[22,23,43-50] Among studies reporting on fecal elastase-1, six studies including 178 patients reported results on mild acute pancreatitis[21,24,34,37,39,42] and ten studies including 389 patients reported results on severe acute pancreatitis.[21,24,34,35,37-42] Pooled prevalence of pancreatic exocrine insufficiency was 19.4% (95%-CI: 8.6% - 38.2%) and 33.4% (95%-CI: 22.6% - 46.3%) respectively (P = 0.049). Heterogeneity between studies was very high with I2 = 76.2% for studies reporting on mild acute pancreatitis and I2 = 75.3% for studies reporting on severe acute pancreatitis.

Non-necrotizing and necrotizing pancreatitis

In studies using fecal fat analysis, three studies including 62 patients reported on non-necrotizing pancreatitis.[22,43,47] The pooled prevalence of pancreatic exocrine insufficiency was 22.5% (95%-CI: 3.5% - 69.8%). In nine studies including a total of 230 patients with necrotizing pancreatitis, the pooled prevalence of pancreatic exocrine insufficiency was 24.8% (95%-CI: 14.8% - 38.5%; P = 0.23).[22,23,43-46,48-50] Heterogeneity between studies was very high to high with I2 = 81.2% and I2 = 67.9% respectively. Among studies reporting on fecal elastase-1, seven studies including 271 patients reported results on non-necrotizing pancreatitis[21,24,34,35,37,39,42] and six studies including 277 patients reported results on necrotizing pancreatitis.[34,35,38-41] Pooled prevalence of pancreatic exocrine insufficiency was 18.9% (95%-CI: 9.3% - 34.6%) and 32.0% (95%-CI: 18.2% - 49.8%) respectively (P = 0.053). Heterogeneity between studies was very high with I2 = 80.3% and I2 = 79.2% respectively.

Necrotizing pancreatitis without and with necrosectomy

In the nine studies using fecal fat analysis that reported on necrotizing pancreatitis, four studies included 63 patients that recovered without

TABLE 3A - PANCREATIC EXOCRINE INSUFFICIENCY MEASURED BY FECAL FAT ANALYSIS - SUBGROUPS OF ETIOLOGY OF PANCREATITIS*

	N	Biliary	N	Alcoholic	N	Other	P#
Only mild	0	-	0	-	0	-	
Only severe	3	6 / 57 (15.9%; 2.4 - 58.8%)	1	5 / 6 (83%)	0	-	0.01
Only non-necrotizing	1	0 / 31 (0%)	0	-	0	-	
Only necrotizing	3	6 / 57 (15.9%; 2.4 - 58.8%)	1	5 / 6 (83%)	0	-	0.01
Only necrosis without necrosectomy	2	0 / 41 (0%)	0	-	0	-	
Only necrosectomy	2	6 / 16 (45.0%; 9.0 – 87.2%)	1	5 / 6 (83%)	0	-	0.07

TABLE 3B - PANCREATIC EXOCRINE INSUFFICIENCY MEASURED BY FECAL ELASTASE-1 - SUBGROUPS OF ETIOLOGY OF PANCREATITIS*

	N	Biliary	N	Alcoholic	N	Other	P#
Only mild	2	1 / 26 (6.6%; 1.3 - 27.2)	3	7 / 41 (19.5; 10.0 - 34.5)	3	2 / 29 (9.9; 3.2 - 26.6)	0.07
Only severe	2	0 / 38 (0%)	2	8 / 31 (26.0; 13.6 - 44.1)	2	1 / 34 (4.3; 0.1 - 18.7)	0.01
Only non-necrotizing	2	1 / 26 (6.6%; 1.3 - 27.2)	3	7 / 41 (19.5; 10.0 - 34.5)	3	2 / 29 (9.9; 3.2 - 26.6)	0.07
Only necrotizing	2	0 / 38 (0%)	1	4 / 18 (22.2%)	1	0 / 12 (0%)	-
Only necrosis without necrosectomy	1	0 / 28 (0%)	0	-	1	0 / 12 (0%)	-
Only necrosectomy	1	0 / 10 (0%)	1	4 / 18 (22.2%)	0	-	-

* Shown are number of patients with pancreatic exocrine insufficiency / total number of patients tested for pancreatic insufficiency (pooled prevalence and 95% confidence interval if appropriate).
N indicates number of studies reporting on the specific subgroup. Studies not classifying patients' severity of disease are not reported in the table.
Statistical testing for prevalence difference between biliary and alcoholic etiology.

necrosectomy.[22,23,44,46] The pooled prevalence of pancreatic exocrine insufficiency was 10.7% (95%-CI: 3.5% - 28.1%). In six studies including 126 patients who underwent necrosectomy, the pooled prevalence of pancreatic exocrine insufficiency was 35.2% (95%-CI: 19.6% - 54.8%; P = 0.01).[43-46,48,49] Heterogeneity between studies was moderate to high with I2 = 28.5% and I2 = 70.9% respectively.

Of the six studies reporting on fecal elastase-1 and necrotizing pancreatitis, only two studies specified that 6 out of 47 patients who recovered without necrosectomy had pancreatic exocrine insufficiency (pooled prevalence 22.6%)[34,41] and one study specified that 4 out of 28 (14.3%) patients who underwent necrosectomy had pancreatic exocrine insufficiency.[38]

TABLE 4A - PANCREATIC EXOCRINE INSUFFICIENCY MEASURED BY FECAL FAT ANALYSES AT DIFFERENT TIME INTERVALS.*

	N	≤ 12 months	N	13 - 36 months	N	> 36 months	P
Only mild	0	-	0	-	1	5 / 22 (22.7%)	-
Only severe	3	14 / 86 (18.9%; 7.7 - 39.5%)	5	37 / 109 (33.2%; 15.9 - 56.7%)	2	20 / 56 (48.6%; 9.8 - 88.8%)	0.01
Only non-necrotizing	1	0 / 31 (0%)	1	6 / 9 (66.7%)	1	5 / 22 (22.7%)	<0.01
Only necrotizing	3	14 / 86 (18.9%; 7.7 - 39.5%)	5	31 / 100 (29.5%; 12.3 - 55.5%)	1	11 / 44 (25%)	0.07
Only necrosis without necrosectomy	3	2 / 49 (7.4%; 1.1 - 35.7%)	1	2 / 14 (14.3%)	0	-	
Only necrosectomy	1	3 / 12 (25%)	4	28 / 70 (41.7%; 17.3 - 71.0%)	1	11 / 44 (25%)	0.21

TABLE 4B - PANCREATIC EXOCRINE INSUFFICIENCY MEASURED BY FECAL ELASTASE-1 AT DIFFERENT TIME INTERVALS.*

	N	≤ 12 months	N	13 - 36 months	N	> 36 months	P
Only mild	1	1 / 16 (6.3%)	3	28 / 104 (29.0%; 9.5 - 61.3%)	2	7 / 58 (9.3%; 0.8 - 56.9%)	0.03
Only severe	2	47 / 90 (64.0%; 25.0 - 90.5%)	4	79 / 204 (38.6%; 26.1 - 52.8%)	4	9 / 95 (12.4%; 4.3 - 31.1%)	<0.001
Only non-necrotizing	1	1 / 16 (6.3%)	4	41 / 197 (24.7%; 10.0 - 49.2%)	2	7 / 58 (9.3%; 0.8 - 56.9%)	0.14
Only necrotizing	2	47 / 90 (64.0%; 25.0 - 90.5%)	2	40 / 119 (33.8%; 25.8 - 42.8%)	2	4 / 68 (6.0%; 0.5 - 42.7%)	<0.001
Only necrosis without necrosectomy	1	6 / 7 (85.7%)	0	-	1	0 / 40 (0%)	-
Only necrosectomy	0	-	0	-	1	4 / 28 (14.3%)	-

* Prevalence of pancreatic exocrine insufficiency is presented as exact numbers of patients with pancreatic exocrine insufficiency / total patients in subgroup (pooled prevalence; associated 95% confidence interval).
N indicates number of studies reporting on specific subgroup.

Time of follow-up

Studies were categorized into three groups according to time from discharge to moment of pancreatic exocrine insufficiency test (group1: follow-up ≤ 12 months; group 2: follow-up 13 - 36 months; and group 3: follow-up > 36 months).

In studies using fecal fat analysis, three studies including 117 patients had follow-up time up to 12 months[22,23,46], in five studies including 109 patients follow-up time was between 12 and 36 months[43-45,48,50], and in two studies including 78 patients it was 36 months or longer.[47,49] Pooled prevalence of pancreatic exocrine insufficiency was 11.3% (95%-CI: 2.2% - 42.2%), 33.2% (95%-CI: 15.9% - 56.7%) and 32.6% (95%-CI: 18.9% - 50.0%), respectively (P = 0.046). Heterogeneity was (very) high with I2 values of 80.3%, 73.0% and 81.7% respectively.

In studies using fecal elastase-1, three studies including 144 patients had follow-up time up to 12 months[26,34,40], in five studies including 537 patients follow-up time was between 12 and 36 months[24,35,36,39,42], and in four studies including 153 patients it was 36 months or longer.[21,37,38,41] Pooled prevalence of pancreatic exocrine insufficiency was 26.5% (95%-CI: 8.4% - 58.4%), 26.1% (95%-CI: 13.9% - 43.3%) and 9.4% (95%-CI: 2.9% - 26.3%), respectively (P = 0.04). Heterogeneity was (very) high with I2 values of 81.7%, 92.8% and 69.9% respectively. We also performed the time interval adjusted analyses in different subgroups of disease severity (Table 4a and 4b). In studies using fecal fat analysis, a predominantly increasing trend of pancreatic exocrine insufficiency was seen as follow-up time increased, while in studies using fecal elastase-1 a decreasing trend was seen. Within the subgroups of disease severity, heterogeneity between studies was high or very high (data not shown).

Pancreatic enzyme use

Twelve of the 32 studies including 465 patients reported on supplemental pancreatic enzyme use (Table 2).[21,23,24,28,30,40,41,44,45,47,49,50] Overall, 170 patients tested positive for pancreatic exocrine insufficiency according to the test used and 121 patients used pancreatic enzymes. Pooled prevalence was not calculated as some studies did not did not report which of the patients (with or without pancreatic exocrine insufficiency according to the test) used pancreatic enzymes. For eleven studies, data could be extracted for different subgroups of disease severity. Results for mild and non-necrotizing pancreatitis are identical; from three studies, out of 20 patients with pancreatic exocrine insufficiency, 11 patients used pancreatic enzymes.[21,24,47] Eight studies including 279 patients with necrotizing pancreatitis reported a total of 87 patients with pancreatic exocrine insufficiency and 69 patients using pancreatic enzymes.[23,28,40,41,44,45,49,50] Severe pancreatitis was reported in 343 patients, of whom 120 had pancreatic exocrine insufficiency and 104 used pancreatic enzymes.[21,23,24,28,40,41,44,45,47,49,50]

Discussion

This meta-analysis found a 27.1% pooled prevalence of pancreatic exocrine insufficiency in 1495 patients during the follow-up of acute pancreatitis. Pooled prevalence in patients tested with direct tests was higher (41.7%) than in patients tested by indirect tests (24.4%). In our subgroup analyses, alcoholic etiology of pancreatitis was associated with an increased prevalence of exocrine insufficiency. Pancreatic exocrine insufficiency was diagnosed less often in patients with mild versus severe pancreatitis. A

similar trend was seen for non-necrotizing versus necrotizing pancreatitis. The observed prevalence of pancreatic exocrine insufficiency was lower in studies with longer follow-up that used fecal elastase-1 test, but higher in studies that used fecal fat analysis. In general, the quality of studies was moderate and heterogeneity among studies was (very) high, also following the various subgroup analyses.

This study is the largest meta-analysis on pancreatic exocrine insufficiency following acute pancreatitis and the only study comparing different subgroups of etiology of pancreatitis, disease severity and follow-up time. Das et al. performed a meta-analysis on 8 studies reporting on both endocrine and exocrine pancreatic insufficiency after acute pancreatitis.[12] It included 234 patients and found a pooled prevalence of exocrine insufficiency of 29%, with a decreasing trend over time. A systematic review as part of the development of guidelines for the management of pancreatic exocrine insufficiency after pancreatic surgery, by Sabater et al, indicated that about a quarter of patients have pancreatic exocrine insufficiency after pancreatic necrosectomy.[13] This study also highlighted the trend of a lower prevalence of exocrine insufficiency over time.

A predictable finding of this meta-analysis is that the occurrence of pancreatic exocrine insufficiency is more frequent when pancreatitis was more severe. Dependent on how much vital pancreatic tissue is damaged, more functional reserve capacity of the gland is lost with consequently a higher risk for the development of pancreatic insufficiency. The results of the comparison between patients without and with necrosectomy should be interpreted with caution as the extent of pancreatic necrosis may have been higher (and thereby an increased risk of exocrine insufficiency) in patients who underwent necrosectomy compared with patient who did not. A large study on necrotizing pancreatitis showed that patients with higher percentage of necrosis were more likely to have an indication for necrosectomy.[53] Remarkable is however, that mild pancreatitis, defined as a disease free of local and systemic complications during admission[17], is also complicated by exocrine insufficiency in about 20% of patients during follow-up. This percentage resulted from our subgroup analyses in studies using fecal fat analysis and fecal elastase-1. Actual pancreatic exocrine insufficiency may therefore be even more frequent as direct tests are more sensitive, and are considered ‘the reference standard’ for mild pancreatic exocrine insufficiency.[54,55] Several explanations such as direct toxic damage (alcohol), secondary impairment of neural stimuli or damaged receptors that control enzyme

releasing acinar cells may explain functional loss in absence of morphological alteration.[5] In patients with chronic pancreatitis, sensitivity of the fecal elastase-1 test for mild, moderate and severe pancreatic exocrine insufficiency is 63%, 100% and 100% respectively. The specificity of the fecal elastase-1 test is 93%. A fecal elastase-1 value of <200 µg/g is considered to be abnormal.[54,55] The specificity of fecal chymotrypsin test for pancreatic exocrine insufficiency in patients with chronic pancreatitis and cystic fibrosis is similar to that of the fecal elastase-1 test. Sensitivity is considerably lower with 49% for mild to moderate insufficiency and 85% for severe insufficiency.[56,57]

In the minority of studies, in which both etiology of pancreatitis of the cohort and etiology of pancreatitis of patients with exocrine insufficiency was reported, a higher prevalence of exocrine insufficiency in alcoholic acute pancreatitis was evident. Since studies that included patients with chronic pancreatitis were excluded from the current analysis, this may suggest that some degree of pre-existing chronic damage already was present due to the direct toxic effect of alcohol on the pancreatic gland and/or damage due to continued alcohol consumption after recovery from the index event of acute pancreatitis. This is supported by the study of Mattar et al, in which 15% (5 out of 33) of recovered alcoholics without signs of chronic pancreatitis had exocrine insufficiency measured by the fecal elastase-1 test.[58] This finding could also partly explain the relatively high prevalence of exocrine insufficiency in the group of mild acute pancreatitis. Unfortunately, little information on recurrent episodes of acute pancreatitis was reported in the included studies. All studies excluded chronic pancreatitis, but only four studies made specific notion of excluding patients with recurrent pancreatitis.[21-24] Two studies included patients with recurrent pancreatitis but did not specify severity of disease.[25,26]

In studies using fecal elastase-1, a lower prevalence of pancreatic exocrine insufficiency is observed as time of follow-up increases. This may suggest that the human exocrine pancreatic gland has some degree of regenerative capacity after acute pancreatitis. This is supported by experimental animal models.[59] When analyzing subgroups of disease severity it appears that the positive effect of time on exocrine function is most prominent in subgroups of severe and necrotizing pancreatitis, which is described before.[12,13] Patients with severe pancreatitis may suffer from a large decrease of pancreatic function shortly after the disease which may gradually recover over time. Patients with mild attacks may have less decrease in exocrine function

following the acute phase of the disease, which only partly recovers during follow-up because of pre-existing or continuing damage to the pancreatic gland. On the contrary, studies using the fecal fat analysis showed an increasing trend in the prevalence of pancreatic exocrine insufficiency as time of follow-up increases. This could be attributable to continuing damage from e.g. alcohol and smoking to the pancreatic gland or accelerated decay following an episode of acute disease. The discrepancy in decreasing and increasing trend in the prevalence of pancreatic exocrine insufficiency over time between the two test methods is notable. Considering the diversity of disease presentation of patients in the included studies in our meta-analysis, patient selection is most likely the primary reason for this discrepancy. The possibility of pancreatic function altering over time following acute pancreatitis warrants regular follow-up, with special attention to the adjustment of the supplemental pancreatic enzyme therapy. Furthermore, the exocrine pancreas may become insufficient during the acute phase of pancreatitis, which is shown in animal studies.[11] Physicians should therefore be aware that nutrients might not be digested properly when normal intake is resumed during the recovery phase of the index admission.

A limitation of this study was that we did not contact authors for missing data or unreported variables. As a consequence, subgroup analyses on disease etiology of patients with pancreatic exocrine insufficiency were of limited size. Second, the study design ideally would be that of an individual patient data meta-analysis including pre-defined baseline and outcome variables, but this was deemed not feasible because of the long inclusion period. Third, the time adjusted analyses should be interpreted with caution. Our data are derived from multiple studies with different follow-up time and not from longitudinal studies with repeated measurements at different time points. A prospective study following a large patient cohort for several years would suitable for this purpose. Finally, the (very) high heterogeneity between studies, also in subgroup analyses, limits between study comparability and indicate that meta-analytic results should be interpreted with caution.
We would like to address some general points of attention for future studies reporting on exocrine insufficiency in the follow-up of acute pancreatitis. For adequate interpretation and valuable between-study comparisons, it is important that severity of disease is well described, preferably in terms of accepted disease classifications (e.g. revised Atlanta Classification[17]) and morphologic characteristics. Furthermore, the etiology of acute pancreatitis of both the cohort and the patients with exocrine insufficiency should be acknowledged. Finally, and maybe most importantly, future studies should

include if and which patients use supplemental pancreatic enzymes. This consequence of pancreatic exocrine insufficiency can be a major burden on patients' lives and physicians should be aware which of their patients are at risk.

In conclusion, a quarter of all patients with acute pancreatitis develop exocrine insufficiency during follow-up. Alcoholic acute pancreatitis is associated with an increased risk of exocrine insufficiency. Pancreatic exocrine insufficiency may develop after mild acute pancreatitis, but is more frequent in severe acute pancreatitis. The degree of exocrine pancreatic insufficiency may change as time of follow-up increases, which warrants attention of the physician during the long term follow-up of acute pancreatitis.

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Part IV

DISCUSSION & SUMMARIES

Chapter 9

Summary

The aim of the studies included in this thesis is to optimize diagnosis and treatment of acute pancreatitis. Three different aspects of the care for acute pancreatitis patients are outlined in this thesis, the diagnostic work-up in Part I, the use of urgent endoscopic retrograde cholangiopancreatography (ERCP) for acute biliary pancreatitis in Part II, and the follow-up care in Part III.

Part I - Diagnostic work-up in acute pancreatitis

In Chapter 1 we summarize how to diagnose, classify and manage patients with acute pancreatitis. We outline all new evidence obtained through randomized controlled trials since the publication of the international evidenced-based guidelines on acute pancreatitis, the 2012 International Association of Pancreatology/American Pancreatic Association (IAP/APA) guidelines.

In Chapter 2 we focus on patients with acute pancreatitis in whom an aetiology has not been established after the standard diagnostic work-up, patients with 'presumed' idiopathic acute pancreatitis (IAP). The use of additional diagnostic modalities and their yield to establish an aetiology in patients with 'presumed' IAP were assessed. Furthermore, we compared recurrence rates of IAP in patients with and without treatment for underlying aetiologies. We collected and analysed a nationwide prospective cohort of 1632 patients of whom 191 had a 'presumed' IAP. In total, 176 (92%) of patients underwent additional diagnostic testing and in 64 of 176 patients (36%) an etiological diagnosis was established, mostly biliary (20%). In 7% of patients a neoplasm was diagnosed. If additional diagnostic workup revealed an aetiology, the recurrence rate was lower in the treated patients than in the patients without a definite aetiology (15% versus 43%, p=0.01). In conclusion, additional diagnostic testing revealed an aetiology in one-third of "presumed" IAP patients and identification of an aetiology with subsequent treatment reduced the rate of recurrence.

Given that occult biliary disease has been suggested as an underlying cause of IAP, cholecystectomy has been proposed as a strategy to prevent recurrent IAP. In Chapter 3, we conducted a systematic review and meta-analysis of studies on cholecystectomy to prevent recurrent IAP. Ten studies were included of which nine could be used for the pooled analyses with a total of 524 patients. Recurrent disease was observed in 154 patients (29%). The recurrence rate was significantly lower after cholecystectomy than after conservative management even in patients in whom IAP was diagnosed after more extensive diagnostics. However, in the small subgroup of patients with 'true' IAP in whom biliary disease was

sufficiently excluded, this difference was no longer significant. In conclusion, cholecystectomy may reduce the risk of recurrent pancreatitis in IAP patients. However, this effect might be attributed to occult biliary disease that has not been accurately diagnosed prior to cholecystectomy. Additional research is to assess whether in patients with "true" IAP after optimal testing for biliary aetiology, that is after endoscopic ultrasonography of MRI/MRCP, a cholecystectomy is still efficacious.

Part II - Urgent ERCP in acute biliary pancreatitis

In this part of the thesis the focus lies on urgent ERCP with endoscopic sphincterotomy (ES) as a treatment strategy for acute biliary pancreatitis. Biliary pancreatitis is initiated by a (transient) ampullary obstruction leading to an impeded flow of pancreatic juice that in turn, causes pancreatic inflammation. Longer duration of the obstruction seems to lead to a more severe disease course. Therefore, urgent biliary decompression by ERCP with ES has been proposed as a strategy to ameliorate the disease course. Three studies were conducted to explore the potential benefit of this treatment strategy.

In Chapter 4, the value of urgent ERCP in patients with a predicted mild disease course was investigated. We performed a post-hoc analysis of a prospective cohort consisting of 347 patients with an acute biliary pancreatitis and a predicted mild disease course on admission. Urgent ERCP was compared to a conservative treatment strategy in both patients with and without cholestasis. Half of the included patients had cholestasis. Urgent ERCP within 72 hours after symptom onset was performed in 65 (19%) of patients. Patients that underwent urgent ERCP developed a more severe disease course compared to the conservative group (risk ratio 1.83; 95% CI 1.10-3.01; p=0.04), which was also the case in the subgroup of patients with cholestasis (risk ratio 2.57; 95% CI 1.23-5.24; p=0.01). This effect remained significant in a multivariate regression model that included urgent ERCP, age and cholestasis (adjusted OR: 2.32; 95% CI 1.66-4.60, p=0.02). In conclusion, in patients with a predicted mild disease course, urgent ERCP was associated with a more severe disease course compared to a conservative strategy.

In Chapter 5, we analysed the potential benefit of urgent ERCP in a subgroup of biliary pancreatitis patients with a higher a priori risk of pancreatitis complications, that is, patients with a predicted severe disease course. We performed the APEC trial, a multicentre, randomized controlled superior-

ity trial that compared urgent ERCP with endoscopic sphincterotomy (ES) within 24 hours after hospital presentation to conservative treatment in patients with a predicted severe biliary pancreatitis without cholangitis. In the conservative treatment group, patients were managed according to a supportive treatment regimen. An on-demand ERCP with ES was done if a patient developed cholangitis after randomisation. The primary endpoint was a composite of mortality or major complications. In total 230 patients were analysed, The primary endpoint occurred in 45 (38%) of 117 patients in the ERCP group and in 50 (44%) of 113 patients in the conservative group (risk ratio 0.87; 95% CI 0.64 to 1.18; p=0.37). There were no relevant differences in the rate of mortality or major complications, except for cholangitis which was more often seen in the conservative treatment group. In conclusion, urgent ERCP with ES did not reduce a composite endpoint of mortality and severe complications as compared to a conservative strategy, in patients with predicted severe biliary pancreatitis without cholangitis. The APEC trial has shown that routine urgent ERCP with ES does not improve outcomes in patients with a predicted severe biliary pancreatitis without cholangitis.

In Chapter 6, a third treatment group was added to the APEC trial to investigate if improved selection of patients by endoscopic ultrasound (EUS) may challenge these findings. A multicentre, prospective cohort study (APEC-2) was performed that included patients with a predicted severe biliary pancreatitis without cholangitis. Outcomes of this group were compared with the outcomes in the conservative treatment group (n=113) of the APEC trial. Patients underwent urgent EUS, followed by ERCP with ES in case of common bile duct stones or sludge, within 24 hours after hospital presentation. Inclusion and exclusion criteria, and the composite endpoint were similar to the APEC trial. Overall, 83 patients underwent urgent EUS at a median of 21 hours (IQR 17-23) after hospital presentation. Gallstones or sludge in the bile ducts were detected by EUS in 48 of 83 patients (58%), all of whom underwent immediate ERCP with ES. The primary endpoint occurred in 34 of 83 patients (41%) in the urgent EUS-guided ERCP group as compared to 50 of 113 patients (44%) in the conservative treatment group (risk ratio [RR] 0.93, 95% CI 0.67–1.29; p=0.65). In conclusion, urgent EUS-guided ERCP with ES did not reduce the composite endpoint of mortality and major complications as compared with a conservative treatment strategy.

Part III – Follow-up care

In Chapter 7, we evaluate the optimal timing of cholecystectomy in patients

with a necrotizing biliary pancreatitis, taking into account both the risk of recurrent biliary events and the complication risk of cholecystectomy. Current timing of cholecystectomy and the value of endoscopic sphincterotomy to prevent recurrent biliary events were also investigated. We analysed a prospective cohort of 248 patients with a necrotizing biliary pancreatitis from 27 Dutch hospitals. Cholecystectomy was performed in 191 patients (77%) at a median of 103 days (IQR 46 - 222) after discharge. An interesting finding was that in current clinical practice the presence or absence of peripancreatic collections was often not evaluated before cholecystectomy. The risk of overall recurrent biliary events prior to cholecystectomy was significantly lower within 10 weeks after discharge (risk ratio 0.49 [95% CI 0.27 – 0.90]; p = 0.02) and the risk of recurrent pancreatitis was significantly lower within 8 weeks after discharge (risk ratio 0.14 [95% CI 0.02 – 1.0]; p = 0.02). The complication rate of cholecystectomy did not decrease over time, and endoscopic sphincterotomy did not reduce the risk of recurrent biliary events. In conclusion, before cholecystectomy, assessment of the presence or absence of peripancreatic collections should be performed. Cholecystectomy, in the absence of peripancreatic collections, is preferably performed before 8 weeks after discharge due to the increased risk of recurrent biliary events. A follow-up algorithm was presented in this Chapter to support clinical decision-making.

In Chapter 8, the final chapter of this thesis we investigate the occurrence of a complication of acute pancreatitis, namely (transient) pancreatic exocrine insufficiency (PEI). A systematic review and study-level meta-analysis of 32 studies was conducted to explore the prevalence of PEI after acute pancreatitis in subgroups of aetiology, disease severity and follow-up time. In a total of 1495 patients with acute pancreatitis, tested at a mean of 36 months after index admission, the pooled prevalence of PEI was 27.1% (95% CI 20.3%-35.1%). PEI occurred more often in alcoholic pancreatitis than in biliary pancreatitis or other aetiologies. Pooled prevalence of PEI after mild and severe pancreatitis was 19% and 33% respectively (p=0.049). Over time, the prevalence of PEI decreased in patients who were tested with the faecal elastase-1 test. In summary, a quarter of acute pancreatitis patients develop PEI during follow-up. Alcoholic aetiology and necrotizing pancreatitis are associated with higher risk of PEI. Accurate follow-up of patients after acute pancreatitis including detailed patient history regarding signs and symptoms of PEI is recommendable, as treatment is available for these patients by means of prescribing pancreatic enzyme replacement therapy.

Chapter 10

General discussion

Acute pancreatitis is one of the most common gastrointestinal disorders that requires acute hospitalization. Its incidence has been rising steadily over the years, also in the Netherlands.[1] In this thesis I have combined research on three major topics in acute pancreatitis.

Part I - Diagnostic work-up in acute pancreatitis

There are several known causes of acute pancreatitis of which a biliary aetiology and alcohol use are the most frequent causes.[2,3] Establishing an aetiology in the acute phase of the disease is important as it directs treatment in the acute phase and potentially guides interventions to prevent recurrent pancreatitis.

The standard diagnostic work-up for acute pancreatitis consists of 1) taking the medical history including medication use, and the family history, 2) laboratory testing including a liver panel, calcium and triglycerides, and 3) transabdominal ultrasound.[4] With this strategy however the aetiology remains unknown in 16-27% of acute pancreatitis patients, which is referred to as idiopathic acute pancreatitis (IAP).[5-8] Interestingly IAP has a recurrence rate of around 25% suggesting that in some patients a known cause may have been missed during the first attack.[9] Moreover, as several causes of acute pancreatitis cannot be reliably identified using the standard work-up, we hypothesized that in a substantial proportion of presumed IAP patients underlying causes are missed, most notably a biliary cause.

In a prospective cohort of patients with 'presumed' IAP in whom standard diagnostic work-up did not yield an etiological diagnosis, we assessed whether an expanded work-up would be helpful in establishing an etiological diagnosis. This study showed that additional work-up in the form of repeat transabdominal ultrasound, CT, MRI/MRCP or endoscopic ultrasound (EUS) identifies an aetiology in one-third of patients with 'presumed' IAP. In most of these patients the underlying aetiology was biliary (20%). However, also a non-negligible number of patients appeared to have an underlying malignancy (7%). (Chapter 2)

The clinical implications of this study are substantial. Current guidelines pertaining the diagnostic work-up of acute pancreatitis unanimously recommend the use of transabdominal ultrasound in the acute phase to identify gallstones or biliary sludge. Guidance on how to proceed when the standard work-up is inconsistent or negative is not uniform.[10,11] The widely used international IAP/APA guideline (2013) states that additional imaging

investigations and tests should be performed until the aetiology of acute pancreatitis is established including EUS, followed by MRCP, CT and genetic testing when needed.[4] We show that in daily clinical practice the IAP/APA guideline advice is not accurately followed. Only in 22% of patients a full diagnostic work-up was completed. This is worrisome because in most patients eventually a biliary cause was established. In these patients a timely cholecystectomy could have avoided recurrent pancreatitis attacks. Also, underlying malignancies of the ampulla or pancreas are not identified in a timely manner causing a delay in diagnosis which in turn is associated with a worse prognosis.

As occult biliary disease frequently is an underlying cause of IAP, it has been suggested that cholecystectomy can prevent recurrent IAP.[12,13] We performed a systematic review and meta-analysis of 10 studies on this topic. This analysis showed that the recurrence rate of IAP was significantly lower after cholecystectomy compared to conservative management. When scrutinizing the included studies, it became evident that in some studies a cholecystectomy was not performed in true IAP, but when a biliary cause was established after additional work-up. Therefore, we performed a subgroup analysis only in the subgroup of patients with 'true' IAP in whom additional tests such as EUS or MRI were negative. In this subgroup only 36 out of 144 patients underwent cholecystectomy. Recurrence rates were lower (11% vs 39%) but did not differ significantly, possibly due to this small sample size. Nevertheless, the hypothesis that a large proportion of patients with IAP have in fact occult biliary disease, that is not diagnosed by regular transabdominal ultrasound, is supported by this review (Chapter 3). Cholecystectomy is a surgical intervention with its own periprocedural risks. In case of proven cholecystolithiasis in a patient with acute biliary pancreatitis, the benefit outweighs these risks. However, whether a cholecystectomy is indicated and beneficial in patients with 'true' IAP, that is a negative EUS/MRCP at time of diagnosis and no diagnostic liver panel, remains to be investigated. The DPSG will soon start inclusion of patients in the PICUS-2 trial, investigating this research question.

Part II - Urgent ERCP in acute biliary pancreatitis

Gallstones are the most prevalent cause of acute pancreatitis in Western countries. A biliary cause of acute pancreatitis is found in around 40-50% of patients.[2,3]

The role of endoscopic retrograde cholangiopancreatography (ERCP) in

acute biliary pancreatitis is much debated in the literature. In my thesis, I focused predominantly on the question: can urgent bile duct clearance using ERCP with endoscopic sphincterotomy (ES) ameliorate the disease course in patients with acute biliary pancreatitis?

Current guidelines state that in patients with a predicted mild acute biliary pancreatitis an urgent ERCP is only indicated in case of cholangitis. In clinical practice however, urgent ERCP is frequently performed in an attempt to improve the outcome of patients with acute biliary pancreatitis in both patients with a predicted mild, and predicted severe disease course without cholangitis. In these cases it is hypothesized that early decompression with restoration of pancreatic juice outflow ameliorates the disease course.

For Chapter 4, a cohort of patients with an acute biliary pancreatitis and a predicted mild disease course was extracted from the PWN-CORE prospective database. The benefit of urgent ERCP in both patients with cholestasis and without cholestasis was examined. One fifth of patients in this cohort underwent urgent ERCP with ES. A remarkable and important finding was that patients who underwent an intervention were more likely to have a moderate severe or a severe disease course compared to the patients that were treated conservatively. This was most evident in the subgroup of patients with cholestasis, who also had a higher rate of pneumonia and a longer hospital stay. We conclude that urgent ERCP in acute biliary pancreatitis patients with a predicted mild disease course is not beneficial and in fact might be harmful.

ERCP with ES can be performed to remove retained common bile duct (CBD) stones or sludge to restore papillary outflow of the bile and pancreatic duct in an attempt to improve the disease course. ERCP however is an invasive procedure and associated with a complication rate up to 10%, including aggravation of acute pancreatitis.[14] In patients with a predicted mild disease course it has been firmly established that an (urgent) ERCP is not indicated, as these patients have a very low a priori risk of developing pancreatitis related complications. In patients with a predicted severe disease course however, the benefit of urgent ERCP may well outweigh the risks of ERCP as these patients have a high a priori risk to develop pancreatitis related complications.

Multiple trials have been performed over the years to assess the use of routine urgent ERCP with ES in predicted severe acute biliary pancreatitis. Results are conflicting and all studies have methodological shortcomings

including the inclusion of patients with concomitant cholangitis, inclusion of patients with non-gallstone aetiology, differences in timing of ERCP, and omission of ES.[15-21] To settle the debate, we performed a multicentre randomized controlled trial, the APEC trial, to investigate whether urgent ERCP with ES is superior to conservative treatment in patients with a predicted severe disease course but without cholangitis. In this trial, patient selection was strict. Patients with concomitant cholangitis were excluded based on stringent diagnostic criteria, and only patients with a high risk of complications were included. All ERCP procedures were performed urgently within 24 hours after hospital admission and within 72 hours after symptom onset by experienced endoscopists. The APEC trial showed that urgent ERCP was not superior to conservative treatment in this patient group and the clinical recommendation was issued that routine urgent ERCP with ES in patients with predicted severe acute biliary pancreatitis is not indicated (Chapter 5).

During the time that the APEC-trial was develop and executed, a new imaging technique, endoscopic ultrasonography (EUS), gained popularity. EUS is a highly sensitive tool for detection of bile duct stones and sludge.[22,23] In the APEC trial the probability of a biliary origin, and therewith the indication for urgent ERCP with ES, was based on CBD dilation, an increase in serum alanine-aminotransferase, or sludge or stones on imaging (located in the gallbladder or CBD). Definitive proof of bile duct stones by imaging was not a prerequisite. Of interest, in 55% of patients who underwent urgent ERCP in the APEC trial no CBD stones were found, despite the fact that the ERCP was performed within 24 hours of hospital admission, suggesting that stones had already passed spontaneously into the duodenum. As the APEC trail did not show superiority of urgent ERCP, understandably, the question arose if urgent ERCP might still be beneficial in patients with proven CBD stones. Hence, we performed a new study, adding a third prospective treatment arm to the APEC trial, in which patients with a predicted severe acute biliary pancreatitis without cholangitis were treated with urgent EUS-guided ERCP. All included patients underwent urgent EUS within 24 hours after admission and within 72 hours after symptom onset. ERCP with ES was performed only if gallstones and/or sludge were seen in the bile ducts. This prospective cohort was compared to the conservative arm of the APEC trial. This ‘APEC-2’ study showed that urgent EUS-guided ERCP was not superior to conservative treatment. (Chapter 6)

Together these studies demonstrate that urgent ERCP, even if it is targeted only to patients with proven CBD stones or biliary sludge, does not im-

prove outcomes in patients with acute biliary pancreatitis without cholangitis. A conservative treatment strategy is recommended with ERCP only in case of concomitant cholangitis (urgent indication) and in case of persistent choledocholithiasis (elective indication).

Part III – Follow-up care

In the last part of this thesis the focus is on the follow-up care after the initial acute pancreatitis attack including the performance of a cholecystectomy to prevent recurrent pancreatitis and diagnosis of treatment of (transient) pancreatic exocrine insufficiency.

After acute biliary pancreatitis, it is advised to perform cholecystectomy to prevent recurrent biliary events. These events include not only recurrent biliary pancreatitis, but also other gallstone related complications such as acute cholecystitis, biliary colics and cholangitis. In patients that have a mild disease course, it is well established that same-admission cholecystectomy is a safe and indeed reduces recurrent biliary events.[24] In patients with necrotizing biliary pancreatitis it is more complex to establish when a cholecystectomy should be performed. There are studies that show that early cholecystectomy might lead to infected peripancreatic fluid collections.[25] Studies on the optimal timing of cholecystectomy considering the balance between the risk of recurrent biliary events versus the risk of surgical complications including asymptomatic sterile peripancreatic fluid collections becoming infected, are scarce and of questionable methodological quality.[25-29]

For this reason, we analysed a large national cohort of 328 patients with necrotizing biliary pancreatitis with peripancreatic fluid collections, to establish the optimal timing of cholecystectomy.

We found that the majority of patients underwent cholecystectomy at 3 months after hospital discharge and that in most patients the presence or absence of peripancreatic fluid collections was not evaluated prior to surgery. This was a remarkable finding, as most guidelines advise that cholecystectomy should be performed after peripancreatic collections have dissolved, which can only be established through imaging. The risk of biliary complications in the waiting time for cholecystectomy was significantly increased when cholecystectomy was delayed with a turning point eight weeks after discharge. Delaying cholecystectomy beyond eight weeks did not reduce the risk of periprocedural complications, including infection of

peripancreatic fluid collections.

Based on our results we developed an algorithm to aid clinical decision-making. This flowchart guides the follow-up of patients with necrotizing biliary pancreatitis after discharge. Main components include imaging at discharge and re-evaluation of the collections at 2-4 week intervals. This ensures a tailored approach for each individual patient with necrotizing pancreatitis. Based on the flowchart, regular follow-up imaging and individual patient factors, the risk and benefits of cholecystectomy should be weighed at each re-evaluation moment until the procedure has been performed, preferably within 8 weeks after discharge (Chapter 7).

The last subject in this thesis is the (transient) occurrence of pancreatic exocrine insufficiency (PEI) after acute pancreatitis. Loss of exocrine pancreatic function is a well-known complication in pancreatic cancer and chronic pancreatitis. Several small studies are available that report on (transient) PEI also as a complication of acute pancreatitis. We performed a study-level meta-analysis of these small studies to make synthesis of the available data and explore the prevalence of PEI in subgroups with distinct disease severity and aetiology. The results show that a quarter of acute pancreatitis patients develop PEI. PEI may develop after mild acute pancreatitis but is more frequently seen after severe pancreatitis. Alcoholic acute pancreatitis is a major risk factor.
Multiple studies, including our review, find a decreasing prevalence of PEI over time, indicating that PEI can be a transient complication that resolves over time when recovering from an acute pancreatitis attack.[30,31] This is most likely the case in patients that develop PEI after a mild pancreatitis episode. In patients with pancreatic necrosis, that has led to extensive loss of pancreatic tissue, PEI can have a more permanent character. A recent meta-analysis that included both mild and severe AP patients showed a pooled prevalence of PEI during admission of 62% decreasing significantly during follow-up, but remained as high as 35% at 5 years.[32] In these cases a clinical presentation not unlike chronic pancreatitis can be found, with permanent PEI, sometimes in combination with endocrine pancreatic insufficiency.

Accurate follow-up of patients after acute pancreatitis, including detailed patient history regarding signs and symptoms of PEI, is recommendable, particularly in patients that developed necrotizing pancreatitis in whom PEI can have a permanent character (Chapter 8).

Future research – Immunomodulation, implementation and what else: anaesthesiology!

Part I - Diagnostic work-up in acute pancreatitis

In the future, more awareness must be raised that 'idiopathic' acute pancreatitis is often a misnomer and should be the starting point of further more detailed investigations. In clinical practice the term IAP is often used to characterize patients in whom the aetiology has not yet been established after regular clinical diagnostic work-up. True IAP however, can only be diagnosed when the most sensitive diagnostic investigation modalities have been exhausted. Even though the IAP/APA guidelines on the treatment of acute pancreatitis are almost 10 years old, the recommendations on diagnostic work-up stand firm. Better implementation of this guideline regarding the diagnostic work-up should be a priority to prevent avoidable recurrences of acute pancreatitis. Furthermore, more research on the value of EUS in the diagnostic work-up of IAP is needed. EUS is a highly sensitive tool for the detection of not only gallstones but also signs of chronic pancreatitis and malignancies of the pancreas as well as the papilla in IAP patients.[33] The Dutch Pancreatitis Study Group started a prospective cohort study on this topic in 2018 (the PICUS study) and results are eagerly awaited.

Part II - Urgent ERCP in acute biliary pancreatitis

After years of research on acute pancreatitis treatment, much progress has been made towards a better outcome for our patients, especially in the treatment of infected necrotising pancreatitis. The holy grail in pancreatitis research however represents a treatment preventing or substantially reducing the occurrence of early organ failure that leads to the first peak of mortality. With the APEC-trial and APEC-2 study, we attempted to circumvent the occurrence or reduce the severity of the initial inflammatory reaction in patients with acute biliary pancreatitis patients by urgent biliary decompression through ERCP and ES. Unfortunately, these efforts did not reduce severe complications and mortality, even when selection of patients was optimized using EUS to offer treatment (ERC and ES) only to patients with proven choledocholithiasis.

A promising opportunity for early intervention is to suppress the systemic inflammatory response reaction (SIRS) in acute pancreatitis using immunomodulatory therapy. The Dutch Pancreatitis Study Group will soon start the multicentre randomized study (PLANCTON trial, ISRCTN13860158) to investigate whether early infusion of omega-3-fatty acid infusion inhibits

the SIRS response and reduces new onset organ failure and mortality in acute pancreatitis patients with a high risk of developing severe complications.

As an anaesthesiologist and pain management specialist in training, I cannot help but also point towards another promising strategy to mount the attack on the development of new onset organ failure and pancreatic necrosis, which is the use of thoracic epidural analgesia (TEA). Studies with animal models show that the sympathetic block caused by TEA induces splanchnic vasodilatation that leads to improved perfusion of both pancreatic tissue and gut mucosa. It also the inhibits the pro-inflammatory cytokine release provoked by acute pancreatitis.[34] Preliminary studies on this subject show that TEA might reduce mortality in acute pancreatitis in ICU.[35] A multicentre randomized controlled trial with a clinically relevant endpoint, such as new onset organ failure and mortality, would be an important next step.

Part III - Follow-up care
For the follow-up care of acute pancreatitis patients, evaluation of the clinical application and use of the follow-up flowchart for patients with necrotizing biliary pancreatitis as proposed in this thesis is key. Its feasibility and efficacy should be evaluated In future studies of sufficient sample size. Most likely further refinement of the follow-up algorithm, including all know complications of acute pancreatitis, would offer an even more structured approach and a better outcome for patients.

Last remarks
Over the years, many studies have been performed within the Dutch Pancreatitis Study Group that have revolutionized the diagnosis and treatment of acute pancreatitis. Outcomes and recommendations of these studies are now an integral part of international guidelines. Nevertheless, as also shown in this thesis, implementation of these guidelines in clinical practice needs attention and must be improved, not only by means of future studies, but also by organizing awareness campaigns and initiating educational events.

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Chapter 11

Nederlandse samenvatting

Dit proefschrift heeft als doel om de diagnostiek en behandeling van acute pancreatitis verder te optimaliseren. Er worden drie verschillende aspecten van de zorg voor patiënten met acute pancreatitis uiteengezet, het diagnostisch proces in Deel I, het gebruik van vroege endoscopische retrograde cholangiopancreatografie (ERCP) voor acute biliaire pancreatitis in Deel II en de nazorg in Deel III.

Deel I - Diagnostisch onderzoek bij acute pancreatitis

Hoofdstuk 1 is een update van de internationale evidence-based richtlijn voor acute pancreatitis, welke in 2012 werd opgesteld door de International Association of Pancreatology/American Pancreatic Association (IAP/APA). We zetten de nieuw verschenen acute pancreatitis literatuur op een rij gezet met een specifieke focus op gerandomiseerde studies, die zijn verschenen sinds de publicatie van de IAP/APA richtlijn in 2012. Er wordt samengevat hoe we patiënten met acute pancreatitis conform het meest recent beschikbare bewijs kunnen diagnosticeren, classificeren en behandelen.

In hoofdstuk 2 richten we ons op patiënten bij wie we de etiologie van de acute pancreatitis niet hebben kunnen vaststellen middels de standaard diagnostische work-up die bij opname wordt verricht. Deze patiënten noemen we patiënten met ‘vermoedelijke’ idiopathische acute pancreatitis (IAP). Het gebruik van verschillende vormen van aanvullende diagnostiek en hun mogelijkheden om een etiologie vast te stellen bij patiënten met ‘vermoedelijke’ IAP werden beoordeeld. Tevens vergeleken we de kans op recidief pancreatitis bij patiënten met en patiënten zonder behandeling voor de onderliggende etiologie. We verzamelen en analyseren een landelijk prospectief cohort van 1632 patiënten van wie er 191 een ‘vermoedelijke’ IAP hadden. In totaal ondergingen 176 (92%) van de patiënten een vorm van aanvullend diagnostisch onderzoek en bij 64 van de 176 patiënten (36%) werd een etiologische diagnose gesteld. De meest voorkomende etiologie was biliair (20%). Bij 7% van de patiënten werd een onderliggende maligniteit gediagnosticeerd. Indien aanvullend diagnostisch onderzoek een etiologie aan het licht bracht, was het recidiefpercentage van acute pancreatitis lager bij de behandelde patiënten dan bij de patiënten zonder een duidelijke etiologie (15% versus 43%, p=0,01). Concluderend kan met aanvullende diagnostiek toch een etiologie gevonden bij één derde van de “vermoedelijke” IAP-patiënten. De identificatie van een etiologie met daaropvolgende behandeling verminderde het aantal recidieven.

Occult galsteenlijden is mogelijk een onderliggende oorzaak van IAP. Om

die reden is cholecystectomie voorgesteld als een preventieve strategie om recidief IAP te kunnen voorkomen.

In hoofdstuk 3 hebben we een systematische review en meta-analyse uitgevoerd van studies over de cholecystectomie als secundaire preventie van IAP. Er werden tien studies geïncludeerd waarvan er negen konden worden gebruikt voor de gepoolde analyses, in totaal werden de data van 524 patiënten geanalyseerd. Recidief pancreatitis werd gevonden bij 154 patiënten (29%). Het recidiefpercentage was lager na cholecystectomie dan na conservatieve behandeling, zelfs bij patiënten bij wie IAP werd gediagnosticeerd na aanvullende diagnostiek in de vorm van endoecho (EUS) of MRI. In de kleine subgroep van patiënten met 'werkelijke' IAP bij wie galsteenlijden voldoende was uitgesloten, werd geen significante reductie in de recidiefkans gezien na cholecystectomie. Concluderend zou cholecystectomie het risico op recidief pancreatitis bij IAP-patiënten kunnen verminderen. Het effect kan echter mogelijk worden toegeschreven aan occult galsteenlijden dat onvoldoende onderzocht is voorafgaand aan de cholecystectomie. Toekomstig onderzoek zal moeten aantonen of cholecystectomie een effectieve preventiestrategie voor recidief pancreatitis is bij patiënten met een "werkelijke" IAP bij wie galsteenlijden voldoende is uitgesloten middels endoecho en/of MRI/MRCP.

Deel II - Vroege ERCP bij acute biliaire pancreatitis

In het tweede deel van dit proefschrift ligt de focus op de vroege ERCP met endoscopische sfincterotomie (ES) als behandelstrategie voor acute biliaire pancreatitis. Biliaire pancreatitis wordt geïnitieerd door een (voorbijgaande) obstructie van de papil van Vater, die leidt tot een belemmering van de flow van pancreassappen, die op zijn beurt inflammatie van het pancreasweefsel veroorzaakt. Langere duur van de obstructie lijdt mogelijk tot een ernstiger beloop van de ziekte. Op basis van dit pathofysiologische mechanisme is vroege biliaire decompressie middels ERCP met ES voorgesteld als een strategie om ernstige pancreatitis te voorkomen. We hebben drie studies uitgevoerd om het potentiële voordeel van deze behandelstrategie te onderzoeken.

In hoofdstuk 4 van dit proefschrift werd de waarde van vroege ERCP bij patiënten met een voorspeld mild ziektebeloop onderzocht. We voerden een post-hoc analyse uit van een prospectief cohort bestaande uit 347 patiënten met een acute biliaire pancreatitis en een voorspeld mild ziektebeloop. Vroege ERCP werd vergeleken met een conservatieve

behandelstrategie, zowel bij patiënten met als patiënten zonder cholestase. De helft van de geïncludeerde patiënten had cholestase. Vroege ERCP, binnen 72 uur na start van klachten, werd uitgevoerd bij 65 (19%) patiënten. Patiënten die een vroege ERCP ondergingen, hadden een ernstiger ziekteverloop in vergelijking met de conservatieve groep (risk ratio 1,83; 95% CI 1,10-3,01; p=0,04), dit was tevens te zien in de subgroep van patiënten met cholestase (risk ratio 2,57; 95% CI 1,23-5,24, p=0,01). Het effect bleef significant in een logistisch regressiemodel waarin vroege ERCP, leeftijd en cholestase werden meegenomen (adjusted OR: 2,32; 95% CI 1,66-4,60, p=0,02). Concluderend, was in deze studie de vroege ERCP juist geassocieerd met een ernstiger ziekteverloop vergeleken met een conservatieve strategie bij patiënten met een voorspeld milde acute biliaire pancreatitis zonder cholangitis.

Voor het 5e hoofdstuk onderzochten we de effectiviteit van vroege ERCP in een subgroep van biliaire pancreatitispatiënten met een hoog a priori risico op complicaties, patiënten met een voorspeld ernstig ziekteverloop. We voerden een multicenter, gerandomiseerde, gecontroleerde superioriteitsstudie uit, de APEC-trial. In deze trial werd vroege ERCP met ES binnen 24 uur na ziekenhuisopname vergeleken met een conservatieve behandeling bij patiënten met een voorspelde ernstige biliaire pancreatitis zonder cholangitis. In de conservatieve groep werden patiënten behandeld met ondersteunende therapie (e.g. intraveneus vocht, pijnstilling). Een ERCP met ES werd gedaan indien de patiënt cholangitis ontwikkelde. Het primaire eindpunt was een samengesteld eindpunt van mortaliteit en ernstige morbiditeit. In totaal werden 230 patiënten geanalyseerd. Het primaire eindpunt trad op bij 45 (38%) van de 117 patiënten in de vroege ERCP groep en bij 50 (44%) van de 113 patiënten in de conservatieve groep (risk ratio 0,87; 95% CI 0,64 tot 1,18; p=0,37). Er was geen verschil in de componenten van het primair eindpunt, behoudens in het voorkomen van cholangitis, wat vaker werd gezien in de conservatieve behandelgroep. Concluderend reduceerde vroege ERCP met ES het samengestelde eindpunt van mortaliteit en ernstige complicaties niet bij patiënten met voorspelde ernstige biliaire pancreatitis zonder cholangitis, vergeleken met een conservatieve behandeling. De APEC-trial heeft aangetoond dat routinematige vroege ERCP met ES de uitkomsten van patiënten met een voorspelde ernstige biliaire pancreatitis zonder cholangitis niet verbetert.

In hoofdstuk 6 werd een derde behandelgroep toegevoegd aan de APEC-trial om te onderzoeken of bij een betere selectie van patiënten,

middels endoscopische echografie (EUS) de vroege ERCP met ES wel van toegevoegde waarde is. Een multicenter, prospectief cohortonderzoek (APEC-2) werd uitgevoerd bij patiënten met een voorspelde ernstige biliaire pancreatitis zonder cholangitis. De uitkomsten van deze groep werden vergeleken met de uitkomsten van de patiënten uit de conservatieve behandelgroep (n=113) van de APEC-trial. De patiënten in het cohort ondergingen een vroege EUS, binnen 24 uur na ziekenhuisopname, gevolgd door ERCP met ES in het geval van galwegstenen of sludge in de galwegen op EUS. De inclusie- en exclusiecriteria en het samengestelde eindpunt waren gelijk aan die van de APEC-trial. In totaal ondergingen 83 patiënten een vroege EUS binnen mediaan 21 uur (IQR 17-23) na ziekenhuisopname. Galstenen of sludge in de galwegen werden gevonden tijdens EUS bij 48 van de 83 patiënten (58%). Zij ondergingen aansluitend een ERCP met ES. In de vroege EUS-geleide ERCP groep ontwikkelden 34 van de 83 patiënten (41%) ernstige complicaties of overlijden, in vergelijking met 50 van de 113 patiënten (44%) in de conservatieve groep (risicoverhouding [RR] 0,93, 95% BI 0,67– 1,29; p=0,65). Concluderend, bij patiënten met een voorspeld ernstige biliaire pancreatitis zonder cholangitis verlaagd een urgente EUS-geleide ERCP met ES een samengestelde eindpunt van mortaliteit en ernstige complicaties niet, in vergelijking met een conservatieve behandelstrategie.

Deel III – Nazorg

In hoofdstuk 7 zijn we op zoek gegaan de optimale timing van cholecystectomie bij patiënten met een necrotiserende biliaire pancreatitis, waarbij zowel het risico op recidiverende biliaire complicaties als het complicatierisico van cholecystectomie werden meegewogen. Er werd tevens gekeken naar de huidige timing van cholecystectomie en de endoscopische sfincterotomie als mogelijke interventie om recidief biliaire complicaties te voorkomen bij patiënten met necrotiserende biliaire pancreatitis. We analyseerden een prospectief cohort van 248 patiënten met een necrotiserende biliaire pancreatitis uit 27 deelnemende Nederlandse ziekenhuizen. Cholecystectomie werd uitgevoerd bij 191 patiënten (77%), mediaan 103 dagen (IQR 46 - 222) na ontslag. Een interessante bevinding was dat in de huidige klinische praktijk de aan- of afwezigheid van peripancreatische vocht collecties vaak niet werd onderzocht voorafgaand aan de cholecystectomie. Het risico op recidiverende biliaire complicaties voorafgaand aan de cholecystectomie was significant lager in de eerste 10 weken na ontslag (Risk ratio 0,49 [95% CI 0,27 – 0,90]; p = 0,02) en het risico specifiek op recidief pancreatitis was significant lager in de eerste

8 weken na ontslag (Riskratio 0,14 [95% CI 0,02 – 1,0]; p = 0,02). Het aantal complicaties van cholecystectomie nam niet af bij langer uitstel van de procedure. Endoscopische sfincterotomie verminderde het risico op recidiverende biliaire complicaties niet. Concluderend is het raadzaam om beeldvorming van het abdomen te verrichten voorafgaand aan de cholecystectomie, om eventuele peripancreatische collecties in kaart te brengen. In afwezigheid van peripancreatische vochtcollecties wordt een cholecystectomie bij voorkeur uitgevoerd binnen 8 weken na ontslag vanwege het verhoogde risico op recidiverende biliaire complicaties. We presenteren in dit hoofdstuk een algoritme om klinische besluitvorming ten aanzien van de timing van cholecystectomie te ondersteunen.

In hoofdstuk 8, het laatste hoofdstuk van dit proefschrift, onderzoeken we het optreden van een specifieke complicatie van acute pancreatitis, exocriene pancreasinsufficiëntie (EPI). Een systematische review en meta-analyse op studieniveau van 32 studies werd uitgevoerd om de prevalentie van EPI na acute pancreatitis te onderzoeken in subgroepen van patiënten met verschillende etiologieën, verschil in ernst van de ziekte en in follow-up tijd. We vonden een gepoolde prevalentie van EPI van 27,1% (95% BI 20,3%-35,1%). In totaal werden 1495 patiënten met acute pancreatitis geanalyseerd, waarbij de testen voor EPI 36 maanden na indexopname werden verricht. EPI kwam vaker voor na alcoholische pancreatitis dan na biliaire pancreatitis of andere etiologieën. De gepoolde prevalentie van EPI na milde en ernstige pancreatitis was respectievelijk 19% en 33% (p=0,049). Er werd een lagere prevalentie van PEI gevonden na verloop van tijd bij patiënten die getest werden met de fecale elastase-1-test. Samengevat ontwikkelde een kwart van de patiënten met acute pancreatitis EPI tijdens de follow-up. Alcoholische etiologie en necrotiserende pancreatitis zijn geassocieerd met een hoger risico op EPI. Nauwkeurige follow-up van patiënten na acute pancreatitis, inclusief gedetailleerde anamnese met betrekking tot symptomen van EPI, is aan te bevelen, met name na alcoholische en necrotiserende pancreatitis. Omdat er voor deze groep behandelmogelijkheden beschikbaar zijn, in de vorm van pancreasenzym vervangende therapie.

Part V

APPENDICES

List of Publications

Portfolio

Dankwoord

Curriculum Vitae

About the artwork

List of Publications

In this Thesis

1. Acute pancreatitis: recent advances through randomised trials.
   SM van Dijk*, NDL Hallensleben*, HC van Santvoort, P Fockens, H van Goor, MJ Bruno, MG Besselink for the Dutch Pancreatitis Study Group.
   Gut 2017;66:2024-32.

2. The diagnostic work-up and outcomes of 'presumed' idiopathic acute pancreatitis: A post-hoc analysis of a multicentre observational cohort.
   ND Hallensleben, DS Umans, SAW Bouwense, RC Verdonk, TEH Romkens, BJ Witteman, MP Schwartz, BWM Spanier, R Laheij, HC van Santvoort, MG Besselink, JE van Hooft, MJ Bruno, for the Dutch Pancreatitis Study Group.
   United European Gastroenterol J 2020;8:340-50.

3. Recurrence of idiopathic acute pancreatitis after cholecystectomy: systematic review and meta-analysis.
   DS Umans, ND Hallensleben, RC Verdonk, SAW Bouwense, P Fockens, HC van Santvoort, RP Voermans, MG Besselink, MJ Bruno, JE van Hooft, for the Dutch Pancreatitis Study Group.
   Br J Surg 2020;107:191-9.

4. No role for urgent endoscopic retrograde cholangiopancreatography in patients with predicted mild acute biliary pancreatitis.
   ND Hallensleben, NJ Schepers, DS Umans, NS Erler, WL Hazen, R Quispel, R de Ridder, T Romkens, MP Schwartz, BWM Spanier, HC Timmerhuis, A Voorburg, RC Verdonk, B Witteman, MG Besselink, HC van Santvoort, SAW Bouwense, MJ Bruno for the Dutch Pancreatitis Study Group.
   Submitted for publication.

5. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial.
   NJ Schepers, NDL Hallensleben, MG Besselink, MGF Anten, TL Bollen, DW da Costa, F van Delft, SM van Dijk, HM van Dullemen, MGW Dijkgraaf, CHJ van Eijck, GW Erkelens, NS Erler, P Fockens, EJM van Geenen, J van Grinsven, RA Hollemans, JE van Hooft, RWM van der Hulst, JM Jansen, FJGM Kubben, SD Kuiken, RJF Laheij, R Quispel, RJJ de Ridder, MCM Rijk, TEH Römkens, CHM Ruigrok, EJ Schoon, MP Schwartz, XJNM Smeets, BWM Spanier, ACITL Tan, WJ Thijs, R Timmer, NG Venneman, RC Verdonk, FP Vleggaar, W van de Vrie, BJ Witteman, HC van Santvoort,

OJ Bakker and MJ Bruno, on behalf of the Dutch Pancreatitis Study Group.
Lancet 2020;396:167-76.

6. Patient selection for urgent endoscopic retrograde cholangio-pancreatography by endoscopic ultrasound in predicted severe acute biliary pancreatitis (APEC-2): a multicentre prospective study.
   NDL Hallensleben, PMC Stassen, NJ Schepers, MG Besselink, MGF Anten, OJ Bakker, TL Bollen, DW da Costa, SM van Dijk, HM van Dullemen, MGW Dijkgraaf, B van Eijck, CHJ van Eijck, GW Erkelens, NS Erler, P Fockens, EJM van Geenen, J van Grinsven, W Hazen, RA Hollemans, JE van Hooft, JM Jansen, FJGM Kubben, SD Kuiken, AC Poen, R Quispel, RJJ de Ridder, TEH Römkens, EJ Schoon, MP Schwartz, T Seerden, XJNM Smeets, BWM Spanier, ACITL Tan, WJ Thijs, R Timmer, DS Umans, NG Venneman, RC Verdonk, FP Vleggaar, W van de Vrie, RLJ van Wanrooij, BJ Witteman, HC van Santvoort, SAW Bouwense and MJ Bruno for the Dutch Pancreatitis Study Group.
   Gut 2023.

7. Optimal timing of cholecystectomy after necrotising biliary pancreatitis.
   ND Hallensleben*, H Timmerhuis*, RA Hollemans, S Pocornie, J van Grinsven, S van Brunschot, OJ Bakker, R van der Sluijs, MP Schwartz, P van Duijvendijk, T Romkens, M Stommel, RC Verdonk, MG Besselink, TL Bollen, SAW Bouwense, HC van Santvoort+, and MJ Bruno+ for the Dutch Pancreatitis Study Group.
   Gut 2022;71:974-82.

8. Pancreatic exocrine insufficiency following acute pancreatitis: Systematic review and study level meta-analysis.
   RA Hollemans, NDL Hallensleben, DJ Mager, JC Kelder, MG Besselink, MJ Bruno, RC Verdonk and HC van Santvoort for the Dutch Pancreatitis Study Group.
   Pancreatology 2018;18:253-62.

Other Publications

9. Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis.
   L Boxhoorn, SM van Dijk, J van Grinsven, RC Verdonk, MA Boermeester, TL Bollen, SAW Bouwense, MJ Bruno, VC Cappendijk, CHC Dejong, P van Duijvendijk, CHJ van Eijck, P Fockens, MFG Francken, H van Goor, M Hadithi, NDL Hallensleben, JW Haveman, MAJM Jacobs, JM Jansen, MPM Kop, KP van Lienden, ER Manusama, JSD Mieog, IQ Molenaar,

VB Nieuwenhuijs, AC Poen, J Poley, M van de Poll, R Quispel, TEH Römkens, MP Schwartz, TC Seerden, MWJ Stommel, JWA Straathof, HC Timmerhuis, NG Venneman, RP Voermans, W van de Vrie, BJ Witteman, MGW Dijkgraaf, HC van Santvoort and MG Besselink; Dutch Pancreatitis Study Group.
N Engl J Med 2021;385:1372-81.

10. Do endosonographers agree on the presence of bile duct sludge and the subsequent need for intervention?
R Quispel, HM Schutz, NDL Hallensleben, A Bhalla, R Timmer, JE van Hooft, NG Venneman, NS Erler, BJ Veldt, LMJW van Driel and MJ Bruno.
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11. Aggressive fluid hydration plus non-steroidal anti-inflammatory drugs versus non-steroidal anti-inflammatory drugs alone for post-endoscopic retrograde cholangiopancreatography pancreatitis (FLUYT): a multi-centre, open-label, randomised, controlled trial.
CJ Sperna Weiland, XJNM Smeets, W Kievit, RC Verdonk, AC Poen, A Bhalla, NG Venneman, BJM Witteman, DW da Costa, BC van Eijck, MP Schwartz, TEH Römkens, JM Vrolijk, M Hadithi, AMCJ Voorburg, LC Baak, WJ Thijs, RL van Wanrooij, ACITL Tan, TCJ Seerden, YCA Keulemans, TR de Wijkerslooth, W van de Vrie, P van der Schaar, SM van Dijk, NDL Hallensleben, RL Sperna Weiland, HC Timmerhuis, DS Umans, JE van Hooft, H van Goor, HC van Santvoort, MG Besselink, MJ Bruno, P Fockens, JPH Drenth, EJM van Geenen; Dutch Pancreatitis Study Group.
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Portfolio

Name PhD student: Nora Hallensleben
Erasmus MC Department: Gastroenterology and Hepatology

PhD period: June 2015 – June 2023
Promotor(s): Prof. dr. M.J. Bruno
Co-promotor: Dr. S. A. W. Bouwense

Total workload: 48.4 ECTS

PhD Portfolio - Summary of PhD training and teaching

1. PhD training	Year	Workload (ECTS*)
General courses		
• Biomedical English Writing and Communication	2018	2 ECTS
• Research Integrity	2017	0.3 ECTS
• Statistics	2018	0.5 ECTS
• BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2015	1.5 ECTS
Specific courses (e.g. Research school, Medical Training)		
• RCT Course, Pembroke College, Oxford, UK 21-9-2015 – 25-09-2015	2015	1.5 ECTS
• Building a database in OpenClinica, Clinical Research Unit, Academic Medical Centre, Amsterdam	2016	0.5 ECTS
• Female leadership, Plata Foundation for NLP training	2017	0.5 ECTS
Seminars and workshops		
• Searching PubMed for a CAT, St. Antonius Hospital Academy	2015	0.3 ECTS
• Presenting in English, St. Antonius Hospital Academy	2015	0.5 ECTS
Presentations		
• Poster presentation UEGW, Vienna	2018	0.3 ECTS
• Oral presentation, Open Clinica International Conference, Amsterdam	2019	0.5 ECTS
• Oral presentation Digestive Disease Week, San Diego	2019	0.5 ECTS
• Oral presentation Digestive Disease Days, online	2021	0.5 ECTS
• Oral presentation UEGW, online	2021	0.5 ECTS
(Inter)national conferences		
• Najaarsvergadering NVGE	2015	0.5 ECTS
• Voorjaarscongres NVGE	2016	0.5 ECTS
• Chirurgendagen	2017	0.5 ECTS
• UEGW, Barcelona	2017	1 ECTS
• UEGW, Vienna,	2018	1 ECTS
• Open Clinica conference, Amsterdam	2019	0.5 ECTS
• Digestive Disease Week, San Diego	2019	1 ECTS
• Digestive Disease Days, online	2021	0.5 ECTS
• UEGW, online	2021	1 ECTS
Other		
• Organisation of a pancreatitis congress 'Pancreasday 2016'	2016	2 ECTS
• Coordination of a scientific study group (Dutch Pancreatitis Study group). Includes organising meetings (6 yearly), treasurer of the pancreatitis research foundation, contact with patients association and coordination of a nationwide acute pancreatitis Expertpanel.	2015-2019	10 ECTS (2 hours a week from 2015-2019)
• Grant application for NVGE	2018	1 ECTS
• Coordination of a nationwide acute pancreatitis registry, hiring and managing a team of medical students, database building and support	2017-2019	8 ECTS
• Management of a research nurse (0.8 FTE)	2016-2018	2 ECTS

* 1 ECTS = 28 hours

PhD Portfolio - Summary of PhD training and teaching

2. Teaching	Year	Workload (ECTS*)
Lecturing		
• Lecture on early management of acute pancreatitis, Department of emergency medicine, St. Elisabeth hospital	2016	0.5 ECTS
• Lecture on acute biliary pancreatitis and the APEC-trial, Boston Scientific congress for endoscopy nurses	2016	0.5 ECTS
Supervising Master's theses		
• Martijn Heugen, Timing of Cholecystectomy in Acute Necrotizing Biliary Pancreatitis	2016	1 ECTS
• Devica Umans, Diagnosis and treatment of Idiopathic acute pancreatitis, a post-hoc analysis	2016-2017	2 ECTS
• Sabrina Pocornie, Timing of Cholecystectomy in Acute Necrotizing Biliary Pancreatitis	2017-2018	2 ECTS
• Soerajja Bhoelan, ERC in mild biliary pancreatitis	2017	1 ECTS
• Roel Gorp, ERC for retained CBD stones in mild biliary pancreatitis	2017	1 ECTS
• Cynthia Verloop, ERC in mild biliary pancreatitis	2017-2018	1 ECTS

* 1 ECTS = 28 hours

Dankwoord
Dit proefschrift was er niet gekomen zonder de hulp, steun en inzet van een hele groep familie, vrienden, begeleiders, collega's en patiënten. Graag zou ik een aantal van hen in het bijzonder willen noemen.

Allereerst wil ik de patiënten bedanken die hebben deelgenomen aan de studies. Het is niet niks om je behandeling te laten bepalen door randomisatie en te worden geconfronteerd met het feit dat dokters ook niet altijd weten wat de goede behandeling is. Deelname aan een studie is een bijzondere daad van onbaatzuchtigheid. Dank voor het vertrouwen dat jullie en jullie families in ons hebben gesteld. Dank ook specifiek aan de patiënten van de Alvleeskliervereniging Nederland die nauw samenwerken met de Pancreatitis Werkgroep Nederland.

Dan mijn promotor, Prof. dr. Bruno. Beste Marco, graag wil ik je bedanken voor het in mij gestelde vertrouwen. Je hebt me aangenomen om de APEC-trial af te maken en daarnaast heb ik de mogelijkheid gekregen om een scala aan nieuwe studies op te starten. Je hebt met veel verantwoordelijkheid en ook veel vrijheid gegeven. Naar Zweden, idiopatische projecten met Devica, APEC-2 als amendement indienen en zelfs een technische presentatie op het OpenClinica congres. Het was prettig om jou aan mijn kant te hebben. Bij lastige situaties rondom het onderzoek kon ik vertrouwen op jouw advies en support. Ook op wetenschappelijk vlak heb ik veel van je geleerd. Je snelle en hele scherpe feedback zorgden ervoor dat we onderzoek van een mooi niveau hebben kunnen opleveren.

Beste Stefan, dank dat je mijn copromotor wilde zijn. Ik kan goed met je sparren over onderzoek en ook over de (veel belangrijker) zaken daarbuiten. Ik hoop dat we dat in de toekomst zullen voortzetten. Ik heb veel bewondering voor hoe jij onderzoek, klinisch werk en je gezin weet te combineren. Met name dat je dat met zo'n nuchtere, accepterende en vrolijke houding doet. Mede door Corona zien we elkaar voor het eerst in 4 jaar niet via een scherm maar in levenden lijve tijdens de verdediging van dit proefschrift! Zin in!

Marc Besselink, dank dat je een jaartje mijn copromotor wilde zijn. Wat ben jij aanstekelijk enthousiast! Van elk gesprek met jou kwam ik terug met een enorme aangewakkerde blijheid over hoe geweldig onderzoek is. En anderzijds het gevoel 'heb ik er nu net 15 projecten bij gekregen? En heb ik daar 'ja tuurlijk!' op gezegd?!' Ik heb veel van je geleerd tijdens mijn

promotietraject. Dank voor je begeleiding de afgelopen jaren.

Onze dagelijkse begeleiders in het Antonius, Robert Verdonk en Hjalmar van Santvoort. Robert, dank voor je vrolijke aanwezigheid en prettige begeleiding. Wat ben ik blij dat ik precies op het goede moment met jou een gesprek had over mijn carrière. Bijzonder dat je echt kijkt naar de persoon die je voor je hebt. Een supersuggestie om voor de anesthesie te gaan! Ik zit helemaal op de juiste plek en daar ben ik je eeuwig dankbaar voor. Hjalmar, dank voor je begeleiding tijdens de DC overleggen. Je weet altijd met een scherpe blik de vinger op de zere plek te leggen in onderzoeksvoorstellen en manuscripten, waarmee je het werk net weer naar een hoger niveau weet te tillen.

Graag wil ik de leden van de promotiecommissie bedanken voor de tijd en moeite die u heeft genomen om dit proefschrift kritisch te beoordelen en voor de bereidheid om deel uit te maken van de oppositie.

Tevens de leden van de 'kerngroep' van de PWN die ik nog niet heb benoemd: Prof. dr. Fockens, Prof. dr. van Goor, Prof. dr. Boermeester, Prof. dr. Van Hooft, dr van Geenen en uiteraard de oud arts-onderzoekers en de hoofdonderzoekers van alle deelnemende centra, dank voor meedenken, meewerken en vooral mogelijk maken van de PWN. Dank aan de arts-assistenten van de deelnemende centra voor het aanmelden en includeren van de patiënten. Dank ook aan de afdelingsverpleegkundigen en de endoscopieverpleegkundigen die hun medewerking hebben verleend.

Nicole Erler, dank voor de hulp bij de analyses en vooral voor al het werk dat je aan de Quality of Life analyses van APEC-2 hebt gedaan!

Dank aan de arts-onderzoekers van de PWN met wie ik 'in mijn tijd' het DC gedraaid heb. Ik had me geen betere werkomgeving kunnen wensen dan die twee gekke kamertjes in een hoekje van het Antonius. We konden een beetje ongezien onze eigen toko draaien en ieder nam vanuit het eigen centrum waardevolle ervaringen mee. Jullie waren precies de goede mensen om op aangewezen te zijn.

- Nicolien, jij hebt mij wegwijs gemaakt binnen de PWN en we hebben samen de APEC-trial afgerond. Wat ben jij goed in het overtuigen van dokters om patiënten te includeren, ik heb veel van je geleerd. We zaten niet altijd op één lijn. Ik denk dat we heel trots op onszelf

mogen zijn dat het gelukt is om desondanks steeds samen tot compromissen te komen, elkaar te helpen en de sfeer goed te houden. We hebben veel en goed werk verricht. Ik hoop dat ik ook gauw bij jouw verdediging mag zijn!

- Lieve Xavier, 'brother from another mother' zoals jij dat zo adequaat verwoordde, veel dank voor de geweldige tijd die we hebben gehad op het DC. Ik had me geen beter hoofd kunnen wensen om pennen naar te gooien. Ik heb veel bewondering voor hoe jij stoïcijns hebt doorgewerkt aan je proefschrift. Met al je mooie gekleurde planningen waar je je ook nog echt aan hield. Ik ben blij dat ik je nu een vriend mag noemen, zonder jou en Gijs waren mijn arme kinderen nog steeds nooit in de Efteling geweest. May the force be with you 
- Sven, het was leuk samen op het DC. Goed begin met een sollicitatiegesprek vanuit China! We hebben hard gewerkt en erg gelachen, en natuurlijk samen de allerlaatste APEC-patiënt geïncludeerd. Je hield de etenstijden op het DC altijd goed in de gaten en ik moet nog lachen als ik denk aan jou verbaasde en vooral jaloerse blik als je mij tijdens mijn zwangerschap weer een berg van 100kg lunch inclusief kaas soufflé zag wegwerken. Hopelijk gaat het ons lukken om elkaars kinderen nog eens te zien voor ze 18 zijn ;)
- Janneke en Bob, dank voor de gezelligheid. We hebben veel geploeterd samen en gelukkig ook erg veel gelachen. Tof om te zien dat jullie beiden topchirurgen aan het worden zijn. Meet you on the other side of the steriele doeken.
- Devica, de leerling is de meester ver voorbij! Heel leuk dat je bij mij kwam voor je wetenschappelijke stage en je uiteindelijk dit jaar een prachtig PWN-proefschrift succesvol verdedigd hebt. Ik heb heel erg fijn met je samengewerkt, dank voor het leven dat je in de brouwerij kwam brengen op het DC. Van Harry Potter, Rihanna en Beyonce wordt nu eenmaal alles beter.
- Prinses Sperna Weiland! Jouw komst heeft het leed van het vertrek van Xavier enorm verzacht. We konden het gelijk goed vinden en ik heb genoten van je droge humor en kijk op de wereld. Succes met je opleiding bij de MDL.
- Hester, gefeliciteerd met je prachtige proefschrift. Tof dat we samen het timing stuk hebben afgemaakt, ik vond het heel fijn om met je samen te werken!
- Pauline, fijn dat jij mij voor de laatste periode van de APEC-2 hebt opgevolgd. De studie is vlot vol is geraakt en je hebt veel werk verzet voor dit project. Leuk dat we het zo mooi weg hebben kunnen zetten!

- Sabrina, dank voor al je werk aan het timing stuk. Ik heb erg met je gelachen op het DC. Ik zie je nog zitten: met één hand werken en met de andere Lucas in z'n kinderwagen wiegen. Zie je op m'n trouwerij!
- Rens, Lotte, Daan dank voor de samenwerking
- Dank aan alle studenten die stage hebben gelopen bij mijn 'biliaire pancreatitis tak' en daarmee hebben bijgedragen aan de PWN-CORE.
- Beste huidige PWN-promovendi, te zien aan wat er aan foto's en nieuws voorbij komt op de app doen jullie het fantastisch. Ik wens jullie net zo veel plezier met jullie PWN-tijd als ik heb gehad!

Beste Alkmaarse chirurgen en assistenten, ik ben bij jullie vers uit de schoolbanken gestart als ANIOS. Onder jullie bezielende leiding ben ik in een jaar tijd van coassistent tot dokter geworden. Dank daarvoor, het was een mooie tijd.

Beste Robert Jan Stolker, wat leuk dat je opponent wil zijn bij deze verdediging. Ik ben je dankbaar voor het vertrouwen dat je altijd in me hebt getoond. 'Je kan dit gewoon Noortje, hup!'. Wat ben ik blij dat je een brede kijk hebt op wetenschap, dat je me wat tijd van de opleiding hebt laten gebruiken om dit (toch MDL!) proefschrift af te ronden. Dat gaf enorm veel lucht.
Marcus Klimek, eerlijk gezegd ben ik opgelucht dat jij niet in mijn oppositie zit. Jouw indrukwekkende kennis en kunde op alle vlakken zou me iets teveel zenuwen bezorgen! Fijn dat je Robert Jan bent opgevolgd als opleider, je bent een warm en prettig mens met een enorm hart voor de assistenten en de afdeling.
Dank aan de staf en assistenten van de anesthesiologie en pijngeneeskunde van het Erasmus Medisch Centrum, ik voel me als een vis in het water bij jullie!

Lieve Alexander en Bart, twee hot boys als paranimfen, lucky me! Dank dat ik jullie mocht bijstaan tijdens jullie verdediging en zo geweldig dat jullie er nu staan voor mij. Het was driewegliefde op het eerste gezicht in het eerste jaar geneeskunde en ik ben heel blij dat we na al die jaren nog vrienden zijn. We zijn inmiddels met een indrukwekkende groep van 12 grote en ook kleinere mensen, het wordt alleen maar leuker.

Lieve Mir, dank voor alle afleiding en etentjes!

Jonas, Jari en Juliet, dank dat ik jullie kantoor mocht delen. Dank voor het verdragen van mijn sjaggerijn over de zoveelste resubmission van

APEC-2. Het is wel gelukt! En sorry nog dat ik nooit de afwas deed vanuit ‘feministische overtuiging’ (aka luiheid). Het is een eer om jullie officiële vertrouwenspersoon te mogen zijn!

Jo, dank voor alle steun in de afgelopen jaren. De flatwhites in Pistace op kosten van de baas hebben me de dagen door geholpen, vooral de maandagochtend ;) Fijn dat je me helpt met het plannen van de feestjes!

Lieve papa en mama, Eric en Loes, dank voor jullie liefde en steun in de afgelopen jaren! Zonder de stevige basis die jullie hebben gecreëerd was dit nooit gelukt. Fijn dat ik bij jullie in Vignols mocht komen knallen en dat jullie zoveel op de kindjes gepast hebben zodat ik aan dit proefschrift kon werken. Pap, dank voor de promotie overleggen in het laatste jaren. Goed dat je me er steeds opnieuw aan herinnerd hebt dat een proefschrift schrijven een boemeltreintje is, en geen intercity. Gewoon rustig doorgaan en uiteindelijk is het af. Het is gelukt! Mama, dank voor alle coaching. We kunnen goed brainstormen en samen strategieën bedenken om leuke en ook vervelende situaties op te lossen. Heel fijn om jou aan mijn kant te hebben, ook gewoon voor de gezelligheid! Dank allebei, ik hou van jullie en wat heerlijk om straks zonder onderzoekstaakjes, samen in Vignols vakantie te kunnen vieren!

Lieve Reem, ik wil je enorm bedanken voor alle steun en hulp van de afgelopen jaren. Je bent mijn favoriete persoon om mee samen te werken. Dank voor het opnemen van de PWN-telefoon als ik even wilde douchen (‘Goedemiddag, met Remie Bolte van de Pancreatitis Werkgroep Nederland’). Dank voor je hulp met de bonnetjes van de stichting, voor je werk aan OpenClinica, het vormgeven van dit boekje en alle andere taakjes die je als ‘stille kracht van de PWN’ voor mij hebt gedaan. Dank dat je niet alleen in woord maar ook in daad een feminist bent. Dank voor je grapjes, je optimisme, je vertrouwen in mij, je liefdevolle zorg voor onze kinderen, voor de lol die we samen hebben, voor de staatsloten die je blijft kopen, voor ontbijt en lunch, voor de skiles, voor de kilometers bakfietsen en voor het rare vegan eten dat je met wisselend succes kookt. Ik hou van je lieverd, laten we er samen een top leven van blijven maken.

Lieve Lucas, lieve Lewis, bedankt voor het structureel en blijmoedig verstoren van al mijn pogingen tot thuis werken. Samen is veel leuker dan alleen, ik hou van jullie!

Curriculum Vitae

Nora Daphne Louise Hallensleben was born on November 13th, 1985 in The Hague, the Netherlands.

After finishing high school at the Haags Montessori Lyceum, and after a year working and studying French in Paris, she moved to Amsterdam to study Medicine at the University of Amsterdam.

In 2007 Nora started a minor in Philosophy of Language at the University of Amsterdam parallel to her medical training. In 2010 she paused her studies to complete a full a Bachelor of Philosophy focusing on the topic of Philosophy of Language and especially logical reasoning. She restarted medical internship in 2011 and during that period an interest in research lead her to assist with to two research projects in the field of dermatology, under supervision of prof. dr. de Vries. After completing her medical internships (including internships in the region of Amsterdam and in Sydney, Australia) she graduated medical school in 2014.

Nora continued her career as a medical doctor (ANIOS) at the surgical department of the Alkmaar Medical Center in Alkmaar under supervision of Dr. Schreurs. After which she started as a PhD student at the Dutch Pancreatitis Study Group to coordinate the multicenter APEC-trial. Under the supervision of prof. Bruno (Erasmus Medical Center) and dr. Bouwense (Maastricht UMC+) she designed and conducted multiple research projects on acute pancreatitis. Furthermore, she coordinated the Acute Pancreatitis Registry (PWN-CORE) and supervised multiple medical students during their research internship.

In 2019 Nora started her training as an anesthesiology resident at the Erasmus Medical Center (prof. dr. Stolker and dr. Klimek) and in 2022 her specialty training for pain management specialist (prof. dr. Huygen). She lives happily with her partner Remie and their two sons, Lucas and Lewis, in The Hague.

About the artwork

On the cover and in the inside of this thesis there are sketches from the series 'invisibles' by the artist Jaume Plensa.

A sculpture from this series is made of silver wire and in a light space such as the Palacio the Cristal (picture 1), the faces are both visible and invisible at the same time. When you discover them, questions arise: what do these faces mean? And what are we supposed to do with them?

This visibility/invisibility contradiction and thinking about the consequences of seeing and knowing something, is also what this thesis is about.

Plensa is one of my favourite artists and working in the Erasmus Medical Centre I am lucky enough to walk past 'Duna' (another one of Plensa's sculptures) on a daily basis. I hope you have enjoyed this Plensa embellished book!

Nora

INVISIBLES
Palacio de Cristal, MNCARS, Madrid, Spain
Museo Nacional Centro de Arte Reina Sofía, Madrid, Spain
https://jaumeplensa.com/exhibitions-and-projects/exhibitions/invisibles-palacio-de-cristal