Severe acute pancreatitis

Improving outcome

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SANDRA VAN BRUNSCHOT

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Severe Acute Pancreatitis

IMPROVING OUTCOME

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CHAPTER 1

General introduction and thesis outline

Background

The last decades, knowledge of acute pancreatitis has rapidly evolved. The founding of the nationwide Dutch Pancreatitis Study Group (DPSG) in 2002, has contributed significantly to improving diagnosis and treatment. However, much still remains to be investigated, especially in patients with severe acute pancreatitis. The general aim of this thesis is to further improve the understanding as well as to further improve clinical outcome of patients suffering from severe acute pancreatitis. The research in this thesis follows earlier research performed in the framework of the DPSG. Therefore, the aims are relatively broad. This thesis starts with a general overview of the treatment of necrotizing pancreatitis in **chapter 2**. This introduction on necrotizing pancreatitis is followed by two different parts of scientific work. The first part aims on diagnosis and clinical decision making and the second part on further development of minimally invasive approaches to infected pancreatic necrosis in patients suffering from severe acute pancreatitis.

Aims

The first part of this thesis aims to answer the following questions:

- Has the revised version of the Atlanta classification improved the interobserver agreement and, if so, has this improved generalizability of results in the literature on diagnosis and outcome of patients with acute pancreatitis?
- Is the Dutch nationwide expert panel on acute pancreatitis helpful for the treating physician in a local hospital during the treatment of acute pancreatitis? In other words, are classification of disease and treatment advice feasible and helpful on an E-consultation basis?
- What is the natural course of encapsulation and gas formation within necrotic collections in time?
- Can early complications of acute pancreatitis be reduced by early enteral feeding?

In the second part of this thesis the following aims are addressed:

- What do we know about the incidence, clinical course, treatment, and outcome of abdominal compartment syndrome (ACS), as a rare and often fatal complication of acute pancreatitis?
- Can the results of a minimally invasive step-up approach through the retroperitoneum be further improved by an endoscopic transluminal approach for patients with infected necrosis?

Outline

It has turned out to be notoriously difficult to compare outcomes of studies presented from different centers in the past decades. This is caused by lack of uniformity in global terminology and definitions used, and non-standardized reporting of results in the literature. These issues have been addressed by an international panel of experts and led to revision of the 1992 Atlanta classification. The revised Atlanta classification is both a clinical as well as a morphologic classification system. In **chapter 3**, the interobserver agreement and generalizability of the revised Atlanta classification are studied.

Clinical decision making regarding the indication, timing and method for invasive intervention in necrotizing pancreatitis is challenging. This is the result of the overall low incidence of infected necrotizing pancreatitis and its heterogeneous and complex clinical course. As a consequence, individual centers may not develop sufficient experience to adequately diagnose and treat these patients. In 2006, the DPSG launched a 24/7/365, online, nationwide, multidisciplinary expert panel. This panel aims to support Dutch clinicians with treatment advice in difficult clinical decisions concerning patients with acute necrotizing pancreatitis. In **chapter 4**, the rationale, design, value, and results of this expert panel are described.

Decision-making on invasive intervention in necrotizing pancreatitis is based on clinical, biochemical, and imaging features. Two imaging features stand out in the decision-making process: encapsulation and the presence of gas configurations within (extra-) pancreatic collections. Gas configurations are regarded pathognomonic for infected necrosis and intervention is generally, and dogmatically, postponed until full encapsulation (i.e. walled-off necrosis). Although it is often stated that both features develop mostly after 4 weeks, reliable data is lacking. In **chapter 5** the natural history of encapsulation of collections and gas configurations, during the disease course of necrotizing pancreatitis is evaluated

Major infections (i.e. infected pancreatic necrosis, pneumonia and bacteremia) have a large impact on outcome in acute pancreatitis. These infections are thought to be mediated by bacterial translocation from the gut provoked by disturbed intestinal motility, bacterial overgrow, and increased mucosal permeability. Research has led to insights that enteral tube feeding is believed to stimulate intestinal motility (thus reducing bacterial overgrowth) and may increase splanchnic blood flow which helps to preserve the integrity of the gut mucosa. Therefore enteral tube feeding potentially plays a role in the prevention of infections. In **chapter 6** this topic is studied in a randomized controlled multicenter trial comparing the effect of early enteral tube feeding with an oral

diet after 72 hours on patients with predicted severe acute pancreatitis.

In the second part of this thesis, the research focusses on improving treatment and outcome in severe acute pancreatitis. One of the most lethal complications in the course of severe acute pancreatitis is abdominal compartment syndrome (ACS). ACS can lead to reduced perfusion and subsequent ischemia of intraabdominal organs followed by further progression of organ failure leading to a potentially fatal downward spiral. Nevertheless, much remains unknown about the incidence, diagnosis, clinical course, optimal treatment, and outcome of ACS in acute pancreatitis. Therefore, a systematic review of the published literature on ACS in acute pancreatitis is performed in **chapter 7**.

The traditional approach to treat infected necrotizing pancreatitis used to be open necrosectomy. Many approaches aiming at less invasive necrosectomy (i.e. laparoscopic necrosectomy, minimally invasive retroperitoneal necrosectomy, sinus tract endoscopy) have been gaining popularity. These less invasive approaches may reduce complications by minimizing surgical trauma in already critically ill patients. The results of the PANTER trial have led to a shift from primary open necrosectomy to a minimally invasive step-up approach, with catheter drainage as first step. The step-up approach reduced mortality and major complications. Furthermore, it reduced endocrine and exocrine pancreatic insufficiency, incisional hernias and costs. Parallel to the PANTER trial, endoscopic necrosectomy has been introduced around the world showing promising results. Endoscopic necrosectomy was compared to minimally invasive surgical necrosectomy in the PENGUIN trial. In this specific subgroup of patients, not improving after drainage as first step of treatment, endoscopy reduced the pro-inflammatory response as well as mortality and major complications. Since this was a small study, we performed several additional studies in order to gain more clarity about endoscopic necrosectomy as novel treatment strategy. In **chapter 8** the current literature on endoscopic necrosectomy is evaluated by performing a systematic review. Nowadays, a step-up approach with drainage as first step of treatment is the general treatment standard. However, if an additional necrosectomy is necessary, it is unclear which method is superior (i.e. open necrosectomy or minimally invasive surgical or endoscopic). Therefore, we also performed a head-to-head comparison of a traditional open necrosectomy with a minimally invasive (i.e. surgical or endoscopic) necrosectomy. The results of this individual patient data meta-analysis (IPDMA), that comprised the largest worldwide cohort of necrosectomy patients, are presented in **chapter 9**.

Another goal was to prospectively compare endoscopic treatment with minimally invasive surgical treatment. Therefore, we performed the randomized

controlled multicenter TENSION trial comparing an endoscopic with a surgical step-up approach in patients with infected necrotizing pancreatitis. In **chapter 10** the results of this study are reported.

Finally, in **chapter 11 and 12** the main findings of this thesis are summarized and discussed, and directions for further research are suggested.

CHAPTER 2

Treatment of necrotizing pancreatitis

Clinical gastroenterology and hepatology 2012

Sandra van Brunschot, Olaf J. Bakker, Marc G. Besselink, Thomas L. Bollen, Paul Fockens, Hein G. Gooszen, and Hjalmar C. van Santvoort for *the Dutch Pancreatitis Study Group*

Abstract

Acute pancreatitis is a common and potentially lethal disease. It is associated with significant morbidity and consumes enormous health care resources. Over the last 2 decades, the treatment of acute pancreatitis has undergone fundamental changes based on new conceptual insights and evidence from clinical studies. The majority of patients with necrotizing pancreatitis have sterile necrosis, which can be successfully treated conservatively. Emphasis of conservative treatment is on supportive measures and prevention of infection of necrosis and other complications. Patients with infected necrosis generally need to undergo an intervention, which has shifted from primary open necrosectomy in an early disease stage to a step-up approach, starting with catheter drainage if needed, followed by minimally invasive surgical or endoscopic necrosectomy once peripancreatic collections have sufficiently demarcated. This review provides an overview of current standards for conservative and invasive treatment of necrotizing pancreatitis.

Epidemiology and Diagnosis

Acute pancreatitis is an acute inflammation of the pancreas that in Western countries is mainly caused by gallstones (40%-50%) and alcohol abuse (10%-40%). Other causes (20%-30%) include medication, endoscopic retrograde cholangiopancreatography (ERCP), hypertriglyceridemia, hypercalcemia, and surgery. In around 10% the etiology remains unknown.[1,2]

The pathophysiology of acute pancreatitis is generally considered as a premature or inappropriate activation of digestive enzymes within pancreatic acinar cells, causing autodigestion of the pancreas and surrounding tissues with subsequent local and systemic inflammation.[3,4]

The incidence of acute pancreatitis is increasing. In the United States, acute pancreatitis accounts for more than 200,000 hospital admissions each year.[4-6] In Europe, the incidence ranges from approximately 4-45 per 100,000 patients a year.[2] Acute pancreatitis is associated with significant morbidity and enormous health care resources.[5,7] Overall mortality in acute pancreatitis is approximately 5%.[3]

Diagnosis of acute pancreatitis requires at least 2 of the following 3 features: (1) abdominal pain, typically epigastric; (2) serum amylase or lipase ≥3 times the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT). In most cases, the clinical history and laboratory results accurately provide the diagnosis, and no diagnostic imaging is required. A CECT in the initial 3-4 days of acute pancreatitis might underestimate or miss the amount of necrosis.[8-10] In general, a CECT is advised if a patient does not improve after the first week of treatment to evaluate the extent of local complications.[8] In clinical practice, however, it is not uncommon for patients to undergo CT earlier than 1 week, especially in case of early complications.

Clinical Course

Acute pancreatitis has a mild clinical course in about 80% of patients, in whom the disease resolves spontaneously within about a week.[11] However, about 20% of patients develop severe acute pancreatitis, which is associated with mortality rates of 8% up to 39%.[3] The 1992 Atlanta classification defined severe acute pancreatitis as the presence of organ failure or local complications such as pancreatic necrosis. Pancreatic necrosis occurs in around 15%-20% of patients and is typically diagnosed as focal areas of non-enhancing pancreatic parenchyma on CECT (Figure 1).[3] The Atlanta classification is currently under revision.[12] In the revised classification the definition of necrotizing pancreatitis will not only include patients with pancreatic

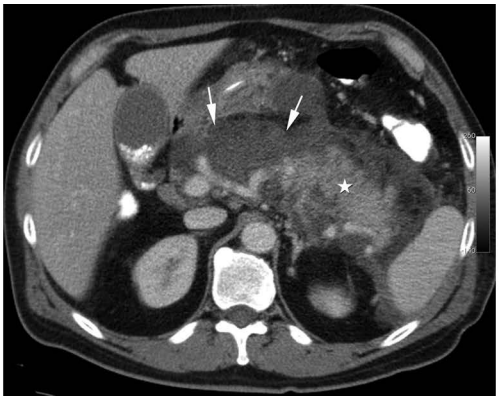

Figure 1. *Acute necrotizing pancreatitis: a 47-year-old man with necrotizing pancreatitis of biliary origin. Perfusion defect is observed at the neck of the pancreas (arrows), with remaining viable pancreatic tissue at the body and tail (asterisk). Note the presence of gallstones.*

necrosis but also patients with extrapancreatic fat necrosis alone (i.e., with normal enhancing pancreatic parenchyma on CECT). Some studies have suggested that patients with extrapancreatic necrosis alone may have a better outcome than patients with pancreatic necrosis. However, extrapancreatic necrosis alone is clinically a more severe entity than acute edematous pancreatitis.[13,14]

Several prognostic scoring systems are used to predict the severity of acute pancreatitis in the first days of admission; among them are Acute Physiology and Chronic Health Evaluation, (modified) Glasgow (Imrie) score, Ranson score, procalcitonin, C-reactive protein, and blood urea nitrogen.[15] These prognostic scoring systems are mainly used for severity stratification in clinical studies, and one can argue about their importance in daily clinical practice.

Theoretically, severe acute pancreatitis is divided in a biphasic clinical course. The first phase (i.e., up to 1-2 weeks after onset of symptoms) is characterized by a proinflammatory immune response. A systemic inflammatory response syndrome often occurs, which is frequently accompanied by failure of 1 or more organ systems.[16-18] Organ failure develops in around 40% of patients with severe acute pancreatitis and is associated with a mortality rate of approximately 30%.[14,19] More than half of the cases of organ failure occur in the first week of admission.[14] Patients with persistent organ failure or multiorgan failure have a worse prognosis than patients with transient organ failure or single organ failure.[3,16,20] It has been suggested that approximately half of the deaths from necrotizing pancreatitis are caused by multiorgan failure in the early phase.[14,20,21]

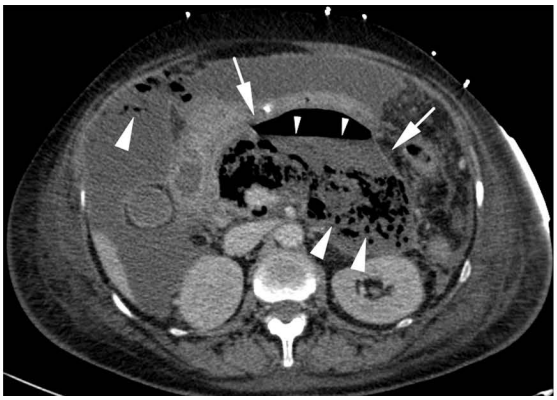

Figure 2. *Infected necrosis: a 55-year-old woman with infected necrotizing pancreatitis. There is a large heterogeneous collection in the pancreatic and peripancreatic area (arrows point at the borders of the collection) with impacted gas bubbles (big arrowheads) and a gas-fluid level (small arrowheads), often a pathognomonic sign of infected necrosis.*

In the second phase of the disease (i.e., after 1-2 weeks from onset of symptoms) the proinflammatory immune response usually subsides. In this phase, the patient's immune system is probably suppressed, which renders patients more susceptible to infectious complications caused by bacterial translocation.[22-24]

The most severe infectious complication in necrotizing pancreatitis is infection of pancreatic or peripancreatic necrosis. The incidence of infected necrosis in patients with necrotizing pancreatitis has remained stable during the last decades (around 30%).[14,25] The peak incidence of infected necrosis is between 2 and 4 weeks after onset of disease.[26]

Infected necrosis is typically suspected when there is persistent sepsis, new-onset sepsis, or progressive clinical deterioration (i.e., signs of sepsis) despite maximal support in the second phase of the disease, without another source of infection. A pathognomonic sign of infected necrosis is impacted peripancreatic or intrapancreatic gas bubbles in a collection on CECT (Figure 2), although this is present in only a minority of patients. In some patients, gas bubbles can also be explained by a fistulous communication between the collection and bowel, which, however, also means the collection is contaminated. A fine-needle aspiration (FNA) for microbiological culture can be performed to diagnose infected necrosis. However, FNA might not always be necessary in patients with necrotizing pancreatitis and suspected infected necrosis. In addition, FNA is associated with a risk of false-negative results.[27] Because suspected infected necrosis no longer represents an immediate indication for invasive treatment, an FNA culture result will not per se guide clinical decisionmaking.

Intervention is generally postponed to 3-4 weeks after onset of disease, and the need for intervention is primarily dictated by clinical deterioration and encapsulation of the infected collection rather than a positive microbiological culture obtained by FNA. A recent Dutch multicenter randomized controlled trial (RCT) demonstrated that a strategy of intervention in patients with clinical suspicion of infected necrosis, without the routine use of FNA, yielded definitive proof of infected necrosis (i.e., positive microbiological cultures from radiological drainage and operation) in more than 90% of patients.[28]

Even though much has changed in the management of necrotizing pancreatitis during the last 20 years, mortality of infected necrosis remains as high as 12%-39%.[14,28-32]

Treatment in the Early Phase

Initial treatment of acute pancreatitis is mainly conservative and focuses primarily on frequent monitoring of the clinical course, pain management, fluid resuscitation, and supportive measures for organ failure.

Supportive Measures

Patients admitted with acute pancreatitis should be closely monitored with adequate amounts of intravenous fluids and pain management. In case of hemodynamic, respiratory, or renal insufficiency with a diuresis of <0.5 mL/kg/h despite adequate fluid resuscitation, or metabolic disorders, patients need to be managed in an intensive care unit.

Aggressive fluid resuscitation is undertaken, especially in the setting of hemoconcentration, which reflects intravascular volume depletion. Prevention or reversal of hemoconcentration is the goal of volume resuscitation. Fluid balance should be maintained and closely monitored.[4] The need for large amounts of fluid administration during the initial 24 hours is associated with poor outcome, and therefore this group of patients should be watched carefully.[33-36] Two retrospective cohort studies suggested that aggressive early fluid resuscitation (at least one-third of the total 72-hour cumulative intravenous fluid volume given during the first 24 hours) is associated with decreased risk of systemic inflammatory response syndrome and organ failure, a lower rate of admission to the intensive care unit, a reduced length of hospital stay, and reduced mortality.[37,38] Most guidelines encourage targeting fluid resuscitation toward correcting hypotension, correcting hemoconcentration, and maintaining adequate urine output.[3,8,37] However, a recent RCT from China demonstrated that aggressive, uncontrolled administration of intravenous fluids in the first days of acute pancreatitis can also be detrimental because it

was related to a 2-fold increase in mortality.[39]

The type of fluid administered has been investigated in 2 studies. A cohort study of 434 patients showed no difference in outcome on the basis of the type of fluid administered,[38] although a recent RCT suggests that lactated Ringer's solution reduces the systemic inflammation compared with fluid resuscitation with normal saline.[40]

Analgesia plays an important role in the treatment of acute pancreatitis. Parenteral analgesics are generally needed. There is no evidence to suggest an advantage of any particular type of medication. When abdominal pain is particularly severe, patient-controlled analgesia is usually preferred. It is important to obtain measurements of bedside oxygen saturation frequently whenever narcotic agents are administered to relieve pain.[3,8]

When organ dysfunction or organ failure is present, supportive treatment should be provided in an appropriate critical care facility.[41]

Several medical treatment options (e.g., platelet-activating factor antagonist [lexipafant], activated protein C) to prevent organ failure in the early phase have been investigated, but none of them have been convincingly shown to be effective.[42,43]

Prevention of Infection of Necrosis

A recent prospective observational study of 731 patients with acute pancreatitis (28% with severe acute pancreatitis) showed that 25% of all patients developed 1 or more infections (i.e., pneumonia, bacteremia, or infected necrosis). Mortality in patients with infection was 30%, whereas 80% of all deceased patients had an infection.[26] In severe acute pancreatitis, disturbed gastrointestinal motility may lead to bacterial overgrowth and failure of the structural mucosal barrier, which may lead to increased gut permeability.[44-47] These events may result in bacteria that cross the gastrointestinal mucosal barrier and invade the systemic compartment, so-called bacterial translocation.[44,48] Bacterial translocation is thought to be the mechanism causing most infections in acute pancreatitis. Strategies aimed at preventing bacterial translocation and subsequent infections have therefore been widely studied in recent years: antibiotics, probiotics, and enteral nutrition.

Antibiotics

Several meta-analyses, including 15 randomized trials, have been published on systemic antibiotics aimed at preventing infectious complications in acute pancreatitis.[49-51] Only 3 RCTs were double-blind placebo-controlled.[52-54] The design, methodological quality, and, most importantly, outcome of the included

studies vary widely.[49] Most meta-analyses did not demonstrate a significant beneficial effect of antibiotic prophylaxis on infection of pancreatic necrosis and mortality.[49-51]

Although the discussion on antibiotic prophylaxis in acute pancreatitis continues, at the moment there is no convincing evidence in favor of routine antibiotic prophylaxis. If a beneficial effect actually exists, it will be difficult to perform a randomized study with sufficient statistical power to demonstrate this effect. Most international guidelines currently do not recommend routine antibiotic prophylaxis.[3,55]

Probiotics

Probiotics are nonpathogenic bacteria that, on delivery to the host's intestinal tract, are believed to prevent bacterial overgrowth, reinforce the mucosal barrier function, and regulate the systemic immune system that may reduce bacterial translocation and subsequent infections. Probiotics have been shown to prevent infections in elective major abdominal surgery.[48] Several studies on probiotics have also been performed in patients with acute pancreatitis. The first 2 double-blind, placebo-controlled, randomized trials from the same study group included 45 and 62 patients, respectively, with predicted severe acute pancreatitis. The first trial showed a significant reduction of infected pancreatic necrosis in patients receiving probiotics. The second trial showed a lower but not significant incidence of multiorgan failure, septic complications, and mortality in the probiotics group.[56,57] The third and largest double-blind, placebo-controlled trial included 298 patients with predicted severe acute pancreatitis. This study did not show an effect of an enterally administered multispecies probiotic mixture on the incidence of infections. However, patients receiving probiotics had an increased mortality as compared with patients receiving placebo (16% vs. 6%; p-value 0.01).[29] This negative effect was associated with an increase in nonocclusive mesenteric ischemia, which was predominantly seen in the patients with multiorgan failure, and has not yet been explained.[58] There is currently strong advice against the use of probiotics in patients with predicted severe acute pancreatitis.

Enteral nutrition

Nutritional support has a fundamental role in the management of severe acute pancreatitis. Besides maintaining adequate caloric intake, nutritional support is important in prevention of infectious complications.

Nutritional support can be achieved through parenteral and enteral feeding. Both strategies have been compared in several randomized trials and meta-

analyses. Results show that enteral feeding significantly reduces mortality, multiorgan failure, systemic infections, and the need for operative intervention compared with parenteral feeding.[59]

Enteral nutrition can be administered through a nasogastric or nasojejunal tube. Two RCTs compared these 2 routes and did not show significant differences between recurrence or worsening of pain, hospital stay, complications, or mortality.[60,61] These studies, therefore, suggested that the simpler, cheaper, and more easily used nasogastric feeding appears to be well tolerated and is as safe as nasojejunal feeding in patients with severe acute pancreatitis. A larger study to further test the safety of nasogastric feeding is currently underway in the United States (SNAP trial, http://Clinicaltrials.gov, NCT00580749).

Experimental and clinical research has shown that the phenomenon of bacterial translocation already takes place within a few hours after onset of symptoms.[22,62] This implies that there is only a very narrow therapeutic window for preventing bacterial translocation and subsequent infections.[26] Theoretically, enteral feeding should therefore be started as early as possible for a beneficial clinical effect. There is evidence in favor of this hypothesis in critically ill patients other than acute pancreatitis. In a meta-analysis of 15 randomized trials comparing early (within 36 hours) versus delayed (after 36 hours) start of enteral feeding on outcome of critically ill intensive care unit patients, early enteral nutrition significantly reduced the incidence of infections and length of hospital stay.[63] In acute pancreatitis, there is only indirect evidence for an early start of enteral feeding. A meta-analysis comparing the effect of enteral versus parenteral nutrition with subgroups based on the timing of start of nutrition showed that an early start of enteral feeding significantly reduced multiorgan failure, pancreatic infections, and mortality.[64] The first randomized trial specifically designed to compare early and selective delayed enteral feeding in predicted severe acute pancreatitis (PYTHON trial) is currently underway in the Netherlands (ISRCTN 18170985).[65]

Endoscopic Retrograde Cholangiopancreatography for Biliary Pancreatitis

Gallstones are the most common cause of acute pancreatitis in the Western world.[2,8] In patients with biliary pancreatitis, decompression of the common bile duct and removal of gallstones or sludge by early ERCP with subsequent sphincterotomy may mitigate the pancreatic inflammation and reduce complications. Several RCTs have investigated the clinical effect of early ERCP in acute biliary pancreatitis.[66-69] From the available evidence, 2 conclusions on the role of ERCP are generally drawn: (1) patients with biliary pancreatitis and concurrent

cholangitis should undergo early ERCP and (2) in predicted nonsevere biliary pancreatitis, ERCP is not beneficial.[3,8] However, the role of early ERCP in patients with predicted severe biliary pancreatitis remains controversial. Although the 2005 United Kingdom guidelines on acute pancreatitis recommend emergency ERCP in these patients,[41] two more recent US guidelines state that the value of early ERCP in predicted severe biliary pancreatitis without cholangitis is yet undetermined.[3,8] This is due to the fact that the published RCTs included only a small number of patients with predicted severe acute pancreatitis and, hence, were statistically underpowered to detect clinical effects in the group of most severely ill patients.[66-69] A recent updated meta-analysis showed no effect of ERCP on complications or mortality in all patients with predicted severe biliary pancreatitis. However, the pooled sample size was still small (N=126), and sphincterotomy was only performed in 53% of patients.[70]

A recent prospective observational study, including 153 patients with predicted severe biliary pancreatitis without cholangitis, showed no significant reduction of complications after ERCP in patients without radiological or biochemical signs of cholestasis. In the subgroup of patients with cholestasis, however, ERCP was significantly associated with fewer complications, including pancreatic necrosis.[71]

A future large and well-designed randomized trial should study the effect of ERCP in patients with predicted severe biliary pancreatitis without cholangitis, with a predefined subgroup analysis in patients with and without signs of cholestasis.

Early Complications Requiring Intervention

A rare but dramatic complication early in the course of severe acute pancreatitis is abdominal compartment syndrome (ACS).[17] ACS is preceded by intra-abdominal hypertension (IAH), which is defined as an intra-abdominal pressure at or above 12 mm Hg. ACS is diagnosed when the intra-abdominal pressure exceeds 20 mm Hg and there are signs of new organ failure (e.g., respiratory, circulatory, renal).[72] IAH generally occurs early, and in some studies the incidence has been reported to be as high as 59%-78% in patients with severe acute pancreatitis.[73,74] The pathophysiology of IAH is directly related to the pancreatic inflammation, which may cause retroperitoneal edema, fluid collections, ascites, and a paralytic ileus. IAH may also be partly iatrogenic, resulting from aggressive fluid resuscitation. IAH can also manifest in the later phase of acute pancreatitis, associated with local pancreatic complications.[75] The incidence of ACS in severe acute pancreatitis has been reported up to 30% in some studies and is associated with extremely high mortality rates of 46%-75%.[73,74,76,77] ACS

requires immediate measures such as sedation, analgesics, nasogastric decompression, fluid restriction, and diuretics to lower the abdominal pressure. If these measures do not result in a rapid clinical improvement, invasive intervention is required. Percutaneous catheter decompression seems to be effective in resolving ACS in patients with intraperitoneal fluid, abscess, or blood, thereby avoiding the need for surgical decompression.[78] This strategy may improve outcome and is currently evaluated in acute pancreatitis by a randomized trial (http://Clinicaltrials.gov NCT00793715). If percutaneous decompression does not immediately lower the intra-abdominal pressure, surgical decompression laparotomy should be performed.[73,77,78]

In rare cases where decompressive laparotomy is necessary in the early phase of necrotizing pancreatitis, it is advised not to open the retroperitoneum or to perform necrosectomy. At this stage, the necrosis is probably sterile, which means a formal necrosectomy is not indicated and, conversely, may cause severe complications such as bleeding, perforation, infection of necrosis, and death.[79]

Another uncommon but devastating complication requiring early intervention is bowel ischemia. The occurrence of nonocclusive mesenteric ischemia is well known in critically ill patients,[80] and several cases of nonocclusive mesenteric ischemia have been reported in acute pancreatitis.[81] Although data on the incidence and outcome of bowel ischemia in acute pancreatitis are limited, the incidence seems to be low (approximately 4%). However, if present, mortality rates are approaching 100%.[81]

Treatment in the Late Phase

Conservative Treatment

In about two-thirds of patients with necrotizing pancreatitis, the pancreatic or peripancreatic necrosis remains sterile. These patients can develop walled-off pancreatic necrosis late in the disease. Walled-off pancreatic necrosis is characterized by a thickened wall between the necrosis and the adjacent viable tissue (Figure 3). In accordance with international guidelines, patients with sterile necrosis can be successfully managed conservatively (i.e., without any form of radiological, endoscopic, or surgical intervention).[3,17,55] An intervention for sterile peripancreatic collections with fluid and necrosis accommodates the risk of introducing infection of necrosis (55%- 59%).[82,83] Iatrogenic infection of sterile necrosis requires additional interventions and considerably increases morbidity and mortality.[82,84,85] Probably the only exception are patients with persistent mechanical obstruction due to peripancreatic collections, in the absence of clinical signs of infection, causing ongoing nausea, vomiting, pain,

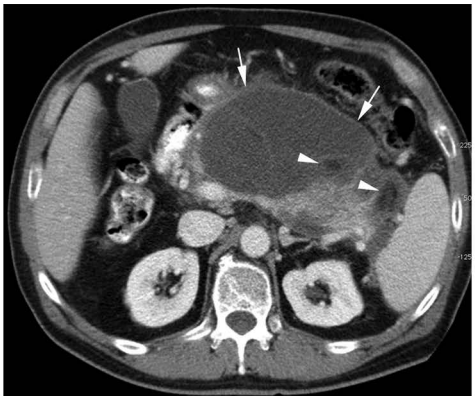

Figure 3. *Walled-off necrosis: a 40-year-old man with necrotizing pancreatitis and walled-off necrosis. A completely encapsulated collection is observed in the pancreatic and peripancreatic area (arrows), with predominant fluid density interspersed with areas of fat density (arrowheads).*

anorexia, and inability to resume oral intake. In this case, the decision for intervention will be solely based on clinical symptoms, supported by CT findings, and should be delayed up to at least 4-6 weeks after onset of symptoms. This is due to the fact that most collections will resolve spontaneously.

In a recent prospective observational study of 639 patients with necrotizing pancreatitis, 62% of patients were treated conservatively. Mortality in these patients was 7%.[14]

Invasive Treatment

Although historically many patients with sterile necrosis also underwent necrosectomy, it is now accepted that the main indication for intervention is infected necrosis.[8,17,41,86]

The timing of intervention has also changed. Necrosectomy was once performed at a very early stage,[79] whereas it is now believed that intervention should be delayed to approximately 3-4 weeks after onset of disease.[27,87,88] To postpone intervention, patients with signs of infected necrosis are initially treated with broad-spectrum antibiotics and maximal support. This allows for encapsulation and demarcation of peripancreatic collections, which may improve conditions for intervention and thereby theoretically decrease the risk of complications such as bleeding and perforation. However, in some patients this is not feasible, and dramatic clinical deterioration will require earlier intervention.

A recent study of 242 patients undergoing intervention for necrotizing pancreatitis showed in a multivariable analysis adjusting for confounding

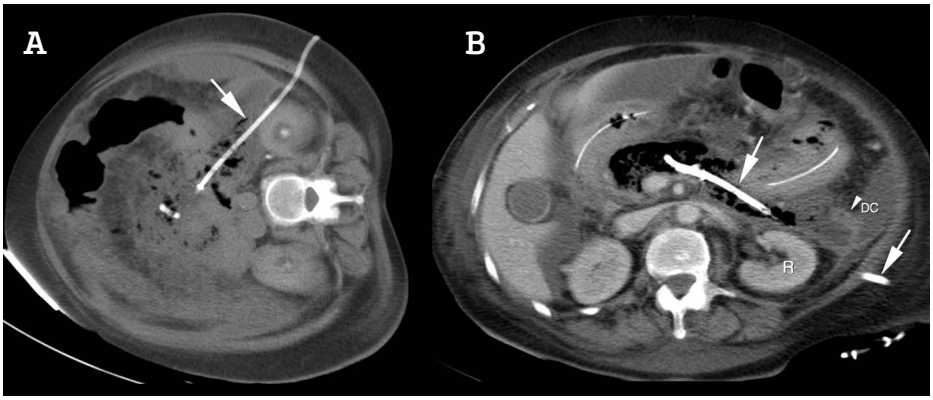

Figure 4. *PCD: a 55-year-old woman with infected necrotizing pancreatitis (same patient as in Figure 2). Axial CT (A) performed in right decubitus position for optimal retroperitoneal positioning of a 12F percutaneous drain (arrow) via the left flank. Successive follow-up CT (B) reveals reduction in size of infected pancreatic collection, with PCD centrally positioned via the left retroperitoneal route (between the descending colon [DC] and the right kidney [R]).*

factors that patients with longer time between admission and intervention had lower mortality: 0-14 days, 56%; 14-29 days, 26%; and >29 days, 15% ($p<0.001$).[14]

It should be noted that there are several reports of patients with infected necrosis who were in such good clinical condition that they allowed treatment with intravenous antibiotics without invasive intervention.[14] However, the vast majority of patients with infected necrosis need to undergo radiological, endoscopic, or surgical intervention at some point.

Primary Open Necrosectomy

The traditional approach to infected necrosis used to be primary open necrosectomy to completely remove the infected necrosis.[25,89] This is an invasive approach associated with a high risk of complications (34%-95%) and mortality (11%-39%) and long-term pancreatic insufficiency.[31,32,86,90-95] As an alternative to primary open necrosectomy, minimally invasive radiological, surgical, and endoscopic techniques for intervention have gained wide popularity.

Minimally Invasive Approaches

Minimally invasive interventions include percutaneous catheter drainage (PCD),[96] endoscopic transluminal drainage (ETD),[97-102] endoscopic (transluminal) necrosectomy (ETN),[98,99,103-112] and minimally invasive retroperitoneal surgical necrosectomy.[28,31,92,113-117] Minimally invasive techniques are thought to induce less physiological stress as compared with open surgical necrosectomy.

Reduced surgical stress might decrease the risk of complications in these often already severely ill patients.

Percutaneous catheter drainage

Image-guided PCD (Figure 4) as primary treatment of infected necrosis was first described in 1998.[96] The rationale of PCD is to treat infected necrosis as an abscess and drain the infected fluid (i.e., pus) under pressure, without removal of necrotic material. Successful drainage of the infected fluid will temporize sepsis and improve patient's clinical condition. This may lead to a situation where the patient is capable of resorbing the necrotic material without the need for formal necrosectomy. PCD is feasible in >95% of patients with infected necrotizing pancreatitis, often via a left-sided retroperitoneal approach.[28,118]

In a recent systematic review of 11 studies with a total of 384 patients receiving PCD for necrotizing pancreatitis, more than half of the patients were successfully treated with PCD alone and thus did not undergo additional necrosectomy.[119] This was confirmed by a recent prospective observational study. In 208 patients undergoing intervention for (suspected) infected necrosis, PCD was performed as the first intervention in 63% of patients, without the need for additional necrosectomy in 35% of patients.[14]

If necrosectomy is still needed after PCD, PCD may have allowed for further encapsulation of the necrotic collections and improvement of the patient's clinical condition. PCD thereby acts as a bridge to surgery. The preferred route for PCD is through the left retroperitoneum, so that the drain can be used as guidance for retroperitoneal surgical necrosectomy.

Minimally invasive retroperitoneal necrosectomy

Several less invasive surgical techniques to perform necrosectomy have been described in recent years. The most commonly used techniques are sinus tract endoscopy,[31,114,120] laparoscopic transabdominal necrosectomy,[121,122] and video-assisted retroperitoneal debridement (VARD).[115-117]

Sinus tract endoscopy involves serial dilatation of a percutaneous catheter drain tract by using fluoroscopic guidance in the operating room, with subsequent necrosectomy by jet irrigation and suction by using a nephroscope or flexible endoscope. Residual solid necrotic tissue is evacuated by using a variety of endoscopic instruments. Several retrospective studies reported a mean morbidity of 25%-88% and mortality of 0%-25%. A median of 3-4 sessions per patient (range, 1-9) were necessary to remove all infected necrosis.[92,114,120]

VARD (Figure 5) can be considered a hybrid between sinus tract endoscopy and an open lumbar approach.[123-125] By using a 5-cm subcostal incision, the

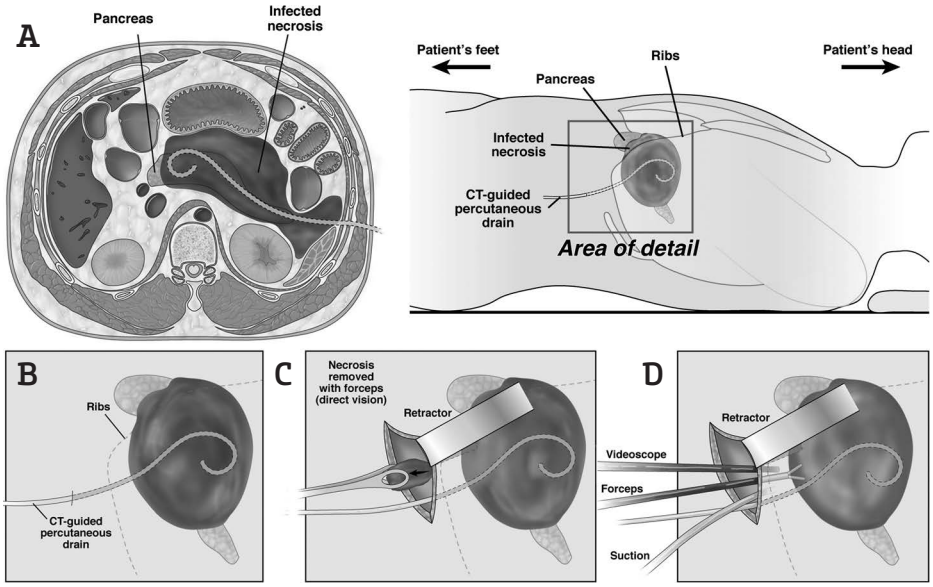

Figure 5. *PCD and VARD. (A) Cross-sectional image and torso depicting a peripancreatic collection with fluid and necrosis. The preferred access route is through the left retroperitoneal space between the left kidney, dorsal spleen, and descending colon. A percutaneous drain is inserted in the collection to mitigate sepsis and postpone or even obviate necrosectomy. The area of detail is shown in (panel B). (C) A 5-cm subcostal incision is made, and the previously placed percutaneous drain is followed into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision with a long grasping forceps. This is followed by further debridement under videoscopic assistance (D).*

previously placed percutaneous catheter drain is followed into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision, followed by further debridement under videoscopic assistance.[116,117] VARD is associated with a morbidity and mortality of 24%-54% and 0%-8%, respectively.[115,116,126] VARD has several advantages; it uses regular surgical equipment, it is a straightforward, semiopen procedure, and it mostly requires only 1 session per patient.

Endoscopic transluminal drainage and necrosectomy.

As an alternative to radiological and surgical techniques, ETD and ETN are gaining popularity. Endoscopic interventions are typically performed under conscious sedation without the need for general anesthesia. This potentially reduces the inflammatory response and may further reduce complications such as new-onset multiorgan failure. First, the collection with infected necrosis is

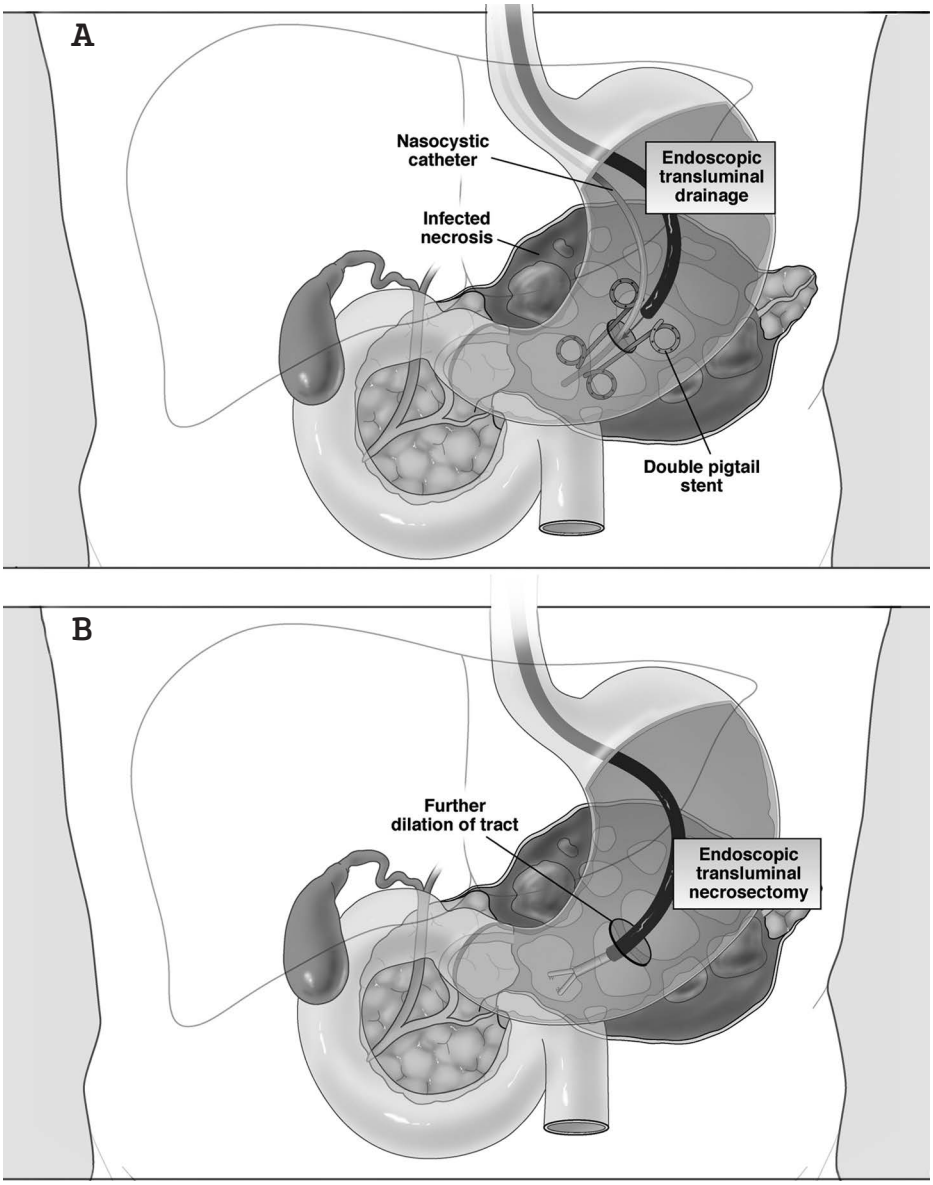

Figure 6. *ETD and ETN. A large peripancreatic collection containing fluid and necrosis is shown. The preferred access route for endoscopic transluminal treatment is through the posterior wall of the stomach. The necrotic collection often bulges into the stomach, facilitating endoscopic transluminal treatment. (A) The collection is punctured through the gastric wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a nasocystic catheter are placed for continuous postoperative irrigation. (B) The cystostomy tract is further dilated, the collection is entered by a forward viewing endoscope, and necrosectomy is performed.*

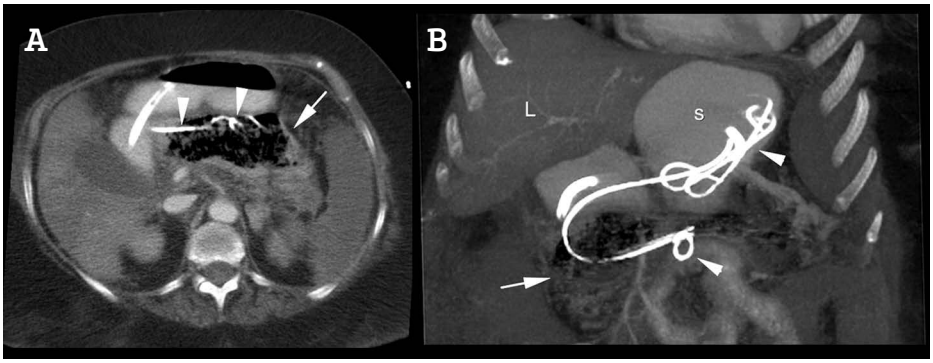

Figure 7. *ETD: a 63-year-old woman with infected necrotizing pancreatitis. Axial CT (A) and coronal reconstructed mean intensity projection (B) show an infected pancreatic collection (arrow) with an endoscopic pigtail drain (arrowheads) positioned inside the collection (L, liver; S, stomach).*

visualized by endoscopic ultrasound to determine the extent of necrosis and the optimal site of drainage. Next, the collection is punctured through the gastric or duodenal wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a nasocystic catheter are placed for continuous postoperative irrigation (Figures 6A and 7). Several retrospective cohort studies show promising results of ETD, with complication rates of 2%-21% and mortality rates of 0%- 6%.[97-102]

In case of no improvement or deterioration after ETD, ETN can be performed to remove infected necrosis. The cystostomy tract is further dilated, the collection is entered by a forward viewing endoscope, and necrosectomy is performed (Figure 6B). At the end of the procedure, 2 double-pigtail stents and a nasocystic catheter are placed. If necessary, ETN can be repeated until the majority of necrotic material is removed.[98,99,103-112] By avoiding any abdominal wall incision, typical complications related to surgical necrosectomy such as incisional hernias, pancreatic fistula, and wound infection will probably be reduced with ETN.

In a recent systematic review of 10 series on ETN in necrotizing pancreatitis, overall mortality after ETN was 5%, and the mean procedure-related morbidity was 27%. In 76% of patients, complete resolution of the necrotic collection was achieved by endoscopic interventions alone. On average, there were 4 endoscopic sessions (range, 1-35) needed to achieve complete resolution.[107] Although these results are promising, there is a risk of selection bias within these studies because the number of critically ill patients with infected necrosis included was relatively low.

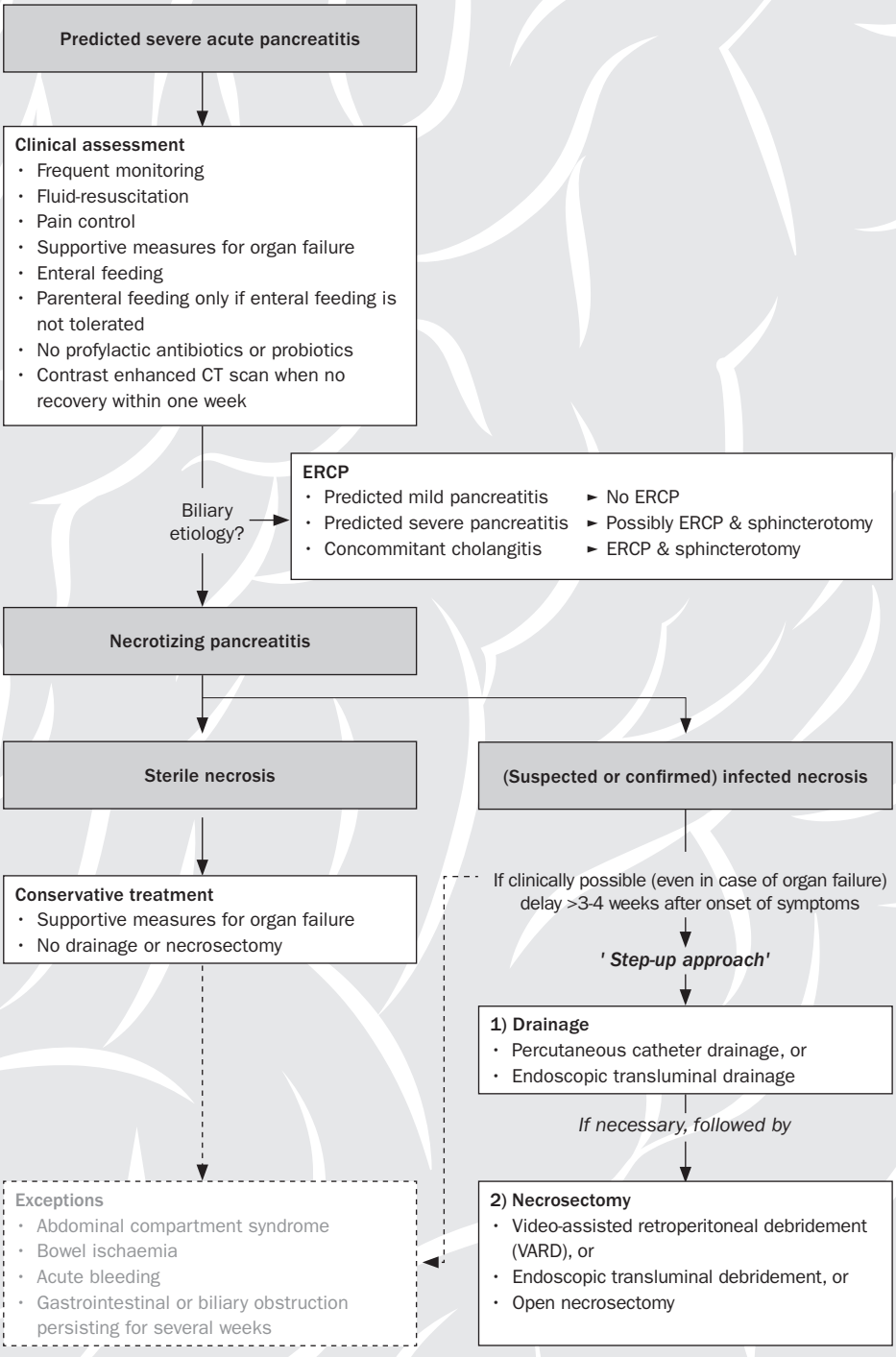

Figure 8. *Treatment algorithm for severe acute pancreatitis.*

A recent pilot RCT showed promising results. ETN significantly reduced the proinflammatory response (measured by serum interleukin-6 levels) as well as the composite clinical end point of major morbidity and mortality compared with surgical necrosectomy.[127]

The step-up approach

The minimally invasive techniques can be applied in a so-called step-up approach.[28,30,128] The first step is catheter drainage (i.e., radiological, percutaneous, or endoscopic transluminal) of the collection with infected fluid and necrosis to mitigate sepsis and postpone or even obviate necrosectomy.[99,119] If drainage does not lead to clinical improvement, the next step is minimally invasive necrosectomy performed either surgically or endoscopically.[92,114,116,117] As compared with open necrosectomy, the step-up approach aims at control of the source of infection rather than complete removal of the infected necrotic tissue. The step-up approach can be performed both surgically and endoscopically.

The PANTER trial compared primary open necrosectomy with a surgical step-up approach in 88 patients with suspected or confirmed infected necrosis.[28] The step-up approach, which used PCD and was followed, if necessary, by VARD, reduced the combined primary end point of death and major complications (i.e., new multiorgan failure, enterocutaneous fistula, perforation, or bleeding) from 69% to 40%. Furthermore, at 6-month follow-up, patients assigned to the step-up approach had a significantly lower rate of incisional hernias and new-onset diabetes. The step-up approach also reduced total costs by 12%. Finally, 35% of patients in the step-up approach group were treated with percutaneous drainage alone and did not need any form of surgery.[28]

These outcomes may further be improved by an endoscopic step-up approach that consists of ETD, followed, if necessary, by ETN. The Dutch Pancreatitis Study Group has recently started a nationwide randomized trial comparing the surgical step-up approach with the endoscopic step-up approach: TENSION (Trial registration: ISRCTN09186711).

Summary

Necrotizing pancreatitis remains a complex and challenging disease, even though several major improvements have occurred in the management of the disease during the last 2 decades. In summary, the initial treatment of necrotizing pancreatitis should primarily focus on fluid resuscitation, pain management, and supportive measures for organ failure. With regard to prevention of infection of necrosis, routine antibiotic or probiotic prophylaxis is not

recommended. Enteral nutrition, compared with parenteral nutrition, appears to be effective in preventing infected necrosis, but the optimal timing of start of enteral feeding requires further study. In patients with biliary pancreatitis and absence of cholangitis, there is no evidence that early ERCP with sphincterotomy is beneficial. However, in the subset of patients with predicted severe biliary pancreatitis and radiological or biochemical signs of cholestasis, early ERCP and sphincterotomy may prevent further complications. Conservative treatment is successful in about two-thirds of patients. Unnecessary intervention for sterile necrosis accommodates the risk of introducing infection and subsequent complications. However, 30% of patients spontaneously develop infection of necrosis and need to undergo invasive intervention. Whenever clinically feasible, intervention is postponed until there is sufficient encapsulation and demarcation of the infected peripancreatic collections, generally 3-4 weeks after onset of symptoms. Primary open necrosectomy has been replaced by a minimally invasive step-up approach that lowers the risk of major morbidity. The initial step is drainage of infected peripancreatic collections, which can be performed image-guided percutaneously or endoscopic ultrasound-guided endoscopic transluminally, depending on anatomic feasibility and local expertise. Catheter drainage is successful as definitive treatment in about 40% of patients. If catheter drainage does not lead to clinical improvement, the next step is minimally invasive drain-guided retroperitoneal necrosectomy or ETN. A treatment algorithm for severe acute pancreatitis is given in Figure 8. Future studies should further elucidate the role of both minimally invasive surgical and endoscopic interventions in patients with necrotizing pancreatitis.

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PART I

Diagnosis, identification and prevention of severe pancreatitis

CHAPTER 3
Describing peripancreatic collections according to the revised Atlanta classification of acute pancreatitis: an international interobserver agreement study
Pancreas 2017

CHAPTER 4
The value of a 24/7 online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis
Gastroenterology 2017

CHAPTER 5
Natural history of gas configurations and encapsulation of necrotic collections on computed tomography in acute pancreatitis
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CHAPTER 6
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CHAPTER 3

Describing peripancreatic collections according to the revised atlanta classification of acute pancreatitis

AN INTERNATIONAL INTEROBSERVER AGREEMENT STUDY

Pancreas 2017

Stefan A. Bouwense, Sandra van Brunschot, Hjalmar C. van Santvoort, Marc G. Besselink, Thomas L. Bollen, Olaf J. Bakker, Peter A. Banks, Marja A. Boermeester, Vincent C. Cappendijk, Ross Carter, Richard Charnley, Casper H. van Eijck, Patrick C. Freeny, John J. Hermans, David M. Hough, Colin D. Johnson, Johan S. Laméris, Markus M. Lerch, Julia Mayerle, Koenraad J. Mortele, Michael G. Sarr, Brian Stedman, Santhi Swaroop Vege, Jens Werner, Marcel G. Dijkgraaf, Hein G. Gooszen, and Karen D. Horvath for *the Acute Pancreatitis Interobserver Study Group*

Abstract

Objectives

Severe acute pancreatitis is associated with peripancreatic morphologic changes as seen on imaging. Uniform communication regarding these morphologic findings is crucial for accurate diagnosis and treatment. For the original 1992 Atlanta classification, interobserver agreement is poor. We hypothesized that for the revised Atlanta classification, interobserver agreement will be better.

Methods

An international, interobserver agreement study was performed among expert and nonexpert radiologists (N=14), surgeons (N=15), and gastroenterologists (N=8). Representative computed tomographies of all stages of acute pancreatitis were selected from 55 patients and were assessed according to the revised Atlanta classification. The interobserver agreement was calculated among all reviewers and subgroups, that is, expert and nonexpert reviewers; interobserver agreement was defined as poor (≤0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80), or very good (0.81-1.00).

Results

Interobserver agreement among all reviewers was good (0.75±0.21) for describing the type of acute pancreatitis and good (0.62±0.19) for the type of peripancreatic collection. Expert radiologists showed the best and nonexpert clinicians the lowest interobserver agreement.

Conclusions

Interobserver agreement was good for the revised Atlanta classification, supporting the importance for widespread adaption of this revised classification for clinical and research communications.

Objectives

Severe acute pancreatitis is often associated with pancreatic and peripancreatic morphologic changes. These changes may consist of peripancreatic edema, peripancreatic necrosis, pancreatic parenchymal necrosis, and different types of peripancreatic collections containing variable amounts of fluid and/or necrosis; these pancreatic and peripancreatic collections may become infected and require intervention. Contrast-enhanced computed tomography (CECT) is used widely to evaluate morphologic changes, which are then correlated with clinical parameters to lead to a disease classification and a treatment plan. Therefore, decisions for treatment are often mainly based on CT findings.[1-3]

The 1992 Atlanta classification was a large step forward in its era.[4] However, with the remarkable advances in imaging technology and patient care, the usefulness of the 1992 Atlanta classification has been challenged.[5] One problem with the 1992 clinically-based approach to the classification was the inability to reproducibly translate morphologic computed tomography (CT) findings into a clear classification resulting in confusion. In fact, when the terms used in the 1992 Atlanta classification were studied for their ability to reliably describe peripancreatic collections on CT, poor interobserver agreement was noted among 5 abdominal radiologists, questioning its clinical usefulness.[6] In the early 2000s, a new set of morphologic terms was developed to describe peripancreatic collections in acute pancreatitis on CT, identified by the acronym 'PANCODE', which stands for pancreatic nonenhancement, collection descripition.[7] It showed good to excellent interobserver agreement among internationally recognized experts, such as gastroenterologists, surgeons, and radiologists.[7] Then, in 2012, the Atlanta classification was revised (see Table A1 for definitions).[8] The revised Atlanta classification incorporated in part the PANCODE morphologic descriptors and combined these and other better-defined terms with clinical parameters to create a new classification that aimed to facilitate communication among treating physicians and between institutions.[8] Whether the revised Atlanta classification offers reliable interobserver agreement is unknown.

We hypothesized that the interobserver agreement among expert and nonexpert radiologists and clinicians has improved with the revised Atlanta classification. Better classification systems should lead to a more objective and accurate communication among physicians, a more uniform clinical decision-making, and a more accurate research communication, which will help improve patient outcomes. The primary aim of this study was to determine the interobserver agreement of the revised Atlanta classification and to investigate the reliability of translating CT morphology into the terms of the revised Atlanta classification for acute pancreatitis.

Methods

Study Population

All abdominal CECTs from patients with predicted severe acute pancreatitis (acute physiology and chronic health evaluation II, >7; Imrie score, >2; C-reactive protein, >150) from 2 Dutch multicenter trials, the PROPATRIA[9] and PANTER[10] trials, were used for this study. All CTs were reviewed by 1 experienced abdominal radiologist (T.L.B.). For every patient, the CT severity index (CTSI; range, 0-10 points) was determined.[3,11,12] Representative CTs of all stages of acute pancreatitis were selected based on the following criteria: use of iodinated contrast material in the pancreatic and/or portal venous phase and availability of a Digital Imaging and Communications in Medicine format (AccuImage Diagnostics Corporation, AccuLite, Version 3.116; San Francisco, Calif) (required for full digital review). Only CTs of patients without an intervention to their peripancreatic collections was used for optimal visualization of their collections.

The design of this study and selection of the CTs was similar to our previous interobserver study.[7]

Reviewers

Two groups of international reviewers were formed, with an equal distribution of experts and nonexperts to represent clinical care in expert centers and community hospitals. Both experts and nonexperts were subdivided into the following subgroups of reviewers: (1) expert radiologists, (2) expert clinicians, (3) nonexpert radiologists, and (4) nonexpert clinicians (Figure 1).

'Expert' was defined as a surgeon, gastroenterologist, or radiologist with at least 10 publications on pancreatic diseases, working in a specialized pancreatic diseases unit.

'Nonexpert' was defined as a surgeon, gastroenterologist, or radiologist, with working experience in the gastrointestinal field but no specific scientific interest in pancreatic diseases as evidenced by no publications on this topic.

Data Collection

Two investigators (S.v.B. and S.A.B.) visited the participating centers and had meetings with the clinicians and radiologists. The study format was fully standardized. First, reviewers were given time to read a sheet with the definitions of pancreatic and extrapancreatic collections, according to the revised Atlanta classification. This was followed by a short PowerPoint presentation explaining the study endpoints, the scoring sheet, and software used. Reviewers were given time to ask additional questions about the reviewing process before they started with the review of the first CT. During the scoring

of CTs, the investigators were not present; they were, however, available solely for technical issues but not for explanation or interpretation of the PANCODE terms or definitions of the revised Atlanta classification. During the review process, the definitions of the revised Atlanta classification remained available.

After the instruction, reviewers assessed the CTs and recorded their data on a scoring sheet:

- First, the reviewers were asked to describe the collection according to the PANCODE criteria.
- Next, the timing of that particular CT was revealed as time in days after onset of symptoms of acute pancreatitis, with emphasis on whether the CT was obtained less than or greater than 4 weeks after onset of symptoms.
- The reviewers then completed the second part of the sheet for the same CT and assigned a classification using the revised Atlanta classification definitions.

This process was repeated for all 55 CTs. In case of multiple collections, the reviewer was asked to describe the clinically most relevant collection.

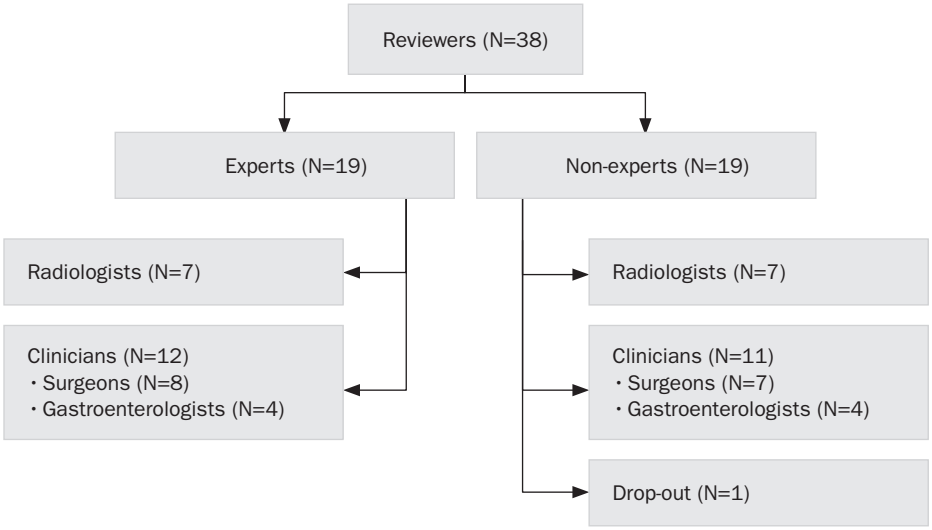

Figure 1. *Distribution of reviewers. The group of experts was an international panel of surgeons, gastroenterologists, and radiologists. All are considered experts in acute pancreatitis as evidenced by at least 10 publications on pancreatic diseases and working in a specialized pancreatic diseases unit. The group of nonexperts was an international panel of surgeons, gastroenterologists, and radiologists. They have working experience in the gastrointestinal field but no special scientific interest in pancreatic diseases as evidenced by no publications on this topic. One nonexpert dropped out because of personal reasons.*

Scoring Sheets

A scoring sheet was used to mimic the following 2-step process involved in disease classification as performed by a treating clinician: step one, to determine the morphologic classification of CT findings; and step two, to combine morphology with clinical parameters to come up with a classification. The first section of each scoring sheet contained descriptive, morphologic terms (PANCODE) (Figure 2).[7] The following are the terms of PANCODE that are used to describe the morphological changes: extent of pancreatic nonenhancement, relation with pancreas, encapsulation, content, mass effect, shape, loculated gas bubbles, and gasfluid level.

The second section of each scoring sheet contained the definitions of the revised Atlanta classification for collections in acute pancreatitis (Figure 3 and online Supplementary Table 1).[8] First, the type of acute pancreatitis needs to be determined (interstitial edematous pancreatitis, necrotizing pancreatitis, or indeterminate), then the type of peripancreatic collection (acute peripancreatic fluid collection, acute necrotic collection, pancreatic pseudocyst, walled-off necrosis, or indeterminate).

During the reviewing process, the reviewers were not allowed to use any other sources of information than the information provided on the study sheets.

Data Analysis

No formal sample size was calculated because of the uncertainty about the expected interobserver agreement between groups. We used a convenient sample of CTs and observers, which was similar to one of our previous studies.[7]

For every item on the scoring sheet, the distribution (e.g., 20% and 80%) of options (e.g., 'yes' and 'no') within the 55 CTs was assessed for each reviewer individually and described by medians with interquartile ranges (IQRs).

To prevent biased or hypothetic estimates of interobserver agreements, we refrained from frequently used approaches such as 'percentage agreement', 'κ', or 'prevalence-adjusted bias- adjusted κ'. Instead, we applied the ratio (ratio κ_{max}) between the observed κ and the maximally achievable κ given the presence of factors constraining observers in their ability to actually agree or disagree beyond chance (κ_{max}).[13] Calculation based on the other approaches is provided in online Supplementary Table 2.

Subgroup analysis was performed in the case of normal distribution of individual measurements by analysis of variance with post-hoc Bonferroni analysis for multiple comparisons; otherwise, a Kruskal-Wallis with post-hoc Mann-Whitney U analysis was performed. p-Values less than 0.05 were considered statistically significant. The following are the subgroups of reviewers that were

Extent of PAncreatic Nonenhancement?

1. Yes

   If 'yes', please choose the extent

   - <30%
   - 30-50%
   - >50%

2. No

Is there a COllection?

1. No
2. Yes

   *If 'yes', please choose one **DE**scription per question:*

   a. Relation with pancreas:
      - Intrapancreatic only
      - Intrapancreatic and adjacent to pancreas
      - Only adjacent to pancreas (no parenchymal perfusion defect)
      - Separate

   b. Encapsulation:
      - Complete
      - Partial
      - None

   c. Content:
      - Homogeneous
      - Heterogeneous (including fat, hermorrhage, loculation/septa, or densities higher than fluid)

   d. Mass effect (=displacement of adjacent structures: vessels, organs etc.):
      - Yes
      - No

   e. Shape:
      - Round or oval
      - Irregular

   f. Loculated gas bubbles:
      - Yes
      - No

   g. Gas-fluid level:
      - Yes
      - No

Figure 2. *Scoring sheet about the descriptive and morphologic terms to evaluate on CT (PANCODE).*

Determine the type of acute pancreatitis (choose one option):

- IEP (intersitial Edematous Pancreatitis)
- Pancreatitis
- Indeterminate

Determine the type of peripancreatic collection (choose one option):

- AFC (Acute Fluid Collection)
- ANC (Acute Necrotic Collection)
- Pancreatic Pseudocyst
- WON (Walled-Off Necrosis)
- Indeterminate

Figure 3. *Scoring sheet about the type of acute pancreatitis and peripancreatic collections as defined by the revised Atlanta classification definitions.*

compared: (1) expert radiologists, (2) expert clinicians, (3) nonexpert radiologists, and (4) nonexpert clinicians.

An interobserver agreement of 0.81 to 1.00 was defined as very good agreement; 0.61 to 0.80, good agreement; 0.41 to 0.60, moderate agreement; 0.21 to 0.40, fair agreement; and less than 0.20, poor agreement.[14]

Results

From a total of 248 patients, 55 CTs were included to cover the complete spectrum of morphologic changes in acute pancreatitis, with emphasis on severe disease (i.e., presence of peripancreatic collections and parenchymal necrosis). Thirty CTs from 30 consecutive patients who did not undergo drainage and/or operative therapy after their CT were selected (5 patients with a CTSI of 1-2, 5 with a CTSI of 3-4, 5 with a CTSI of 5-6, and 15 with a CTSI of 7-10) and 25 consecutive patients with a CT before intervention (percutaneous drainage or operative interventions) or infected necrosis (irrespective of CTSI).

For this selection of patients, the median time between admission and CT was 18 days (IQR, 9-32 days). Of the 55 patients, 60% had infected necrosis proven by bacterial culture (obtained with fine-needle aspiration or during first intervention). Twenty-five of those patients required operative therapy, and 8 patients underwent solely percutaneous catheter drainage. Nine of these 55 patients died (16%).

Thirty-seven reviewers analyzed the CTs (14 radiologists, 15 surgeons, and 8 gastroenterologists) and were subdivided into the following 4 groups: expert radiologists (N=7), expert clinicians (N=12), nonexpert radiologists (N=7), and nonexpert clinicians (N=11).

The distribution of the scored options by all reviewers, including subgroups of reviewers, for the revised Atlanta classification definitions is shown in Table 1. The reviewers scored necrotizing pancreatitis (median, 76%) as the type of pancreatitis in most cases and the peripancreatic collections as acute necrotic collections (median, 45%) or walled-off necrosis (median, 25%). The observer could not score the precise type of peripancreatic collections in a median of 7% of cases. One of the CTs that were reviewed is shown in Figure 4.

In online Supplementary Tables 3, 4, and 5 the scored items for the PANCODE terms are mentioned.

Interobserver Agreement

Among all reviewers, the interobserver agreement for the definitions of the revised Atlanta classification was good for the type of acute pancreatitis and good for the type of peripancreatic collection. Interobserver agreement among the expert radiologists was very good for the type of acute pancreatitis and type of peripancreatic collection. For the nonexpert radiologists, interobserver agreement was good for the type of acute pancreatitis and type of peripancreatic collection. The expert clinicians showed good interobserver agreement for the type of acute pancreatitis and moderate interobserver agreement for type of peripancreatic collection. For the nonexpert clinicians, interobserver agreement was good for the type of acute pancreatitis and moderate for type of peripancreatic collection (Table 2).

Scored Items for All Subgroups

Among the subgroups, interobserver agreement was good among all subgroups with type of acute pancreatitis showing very good to good interobserver agreement and moderate to very good agreement for the type of peripancreatic collection (Table 2, Figures 5, 6).

The greatest interobserver agreement among all scored items was found in the expert radiologists groups, followed by the nonexpert radiologists and expert clinicians. Nonexpert clinicians showed the least interobserver agreement of all subgroups. Comparisons between subgroups are shown in Table 3.

Table 1. The distribution of the scored options for the revised Atlanta classification definitions.

	Expert		Non-expert		Overall
	Radiologists	**Clinicians**	**Radiologists**	**Clinicians**	
Term	N=7	N=12	N=7	N=11	N=37
Type of pancreatitis					
Interstitial edematous pancreatitis	17 (12-23)	22 (20-25)	31 (25 -36)	20 (16-24)	22 (18-26)
Necrotizing pancreatitis	81 (75-88)	78 (75-80)	69 (64-75)	76 (75-80)	76 (71-81)
Indeterminate	2 (0 -2)	0 (0-0)	0 (0-2)	2 (0-7)	0 (0 -2)
Type of peripancreatic collection					
Acute fluid collection	12 (8-16)	15 (13-20)	18 (16-25)	15 (11-18)	13 (10-20)
Acute necrotic collection	53 (46-62)	49 (47-53)	45 (40-47)	47 (38-51)	45 (39-54)
Pancreatic pseudocyst	0 (0-2)	0 (0-0)	0 (0-4)	0 (0-0)	0 (0-2)
Walled-off necrosis	25 (20-32)	27 (25-29)	24 (18-28)	29 (27-31)	25 (18-29)
Indeterminate	6 (4-11)	7 (4 -9)	9 (2-13)	7 (4-16)	11 (5-16)

All values are in percentages and are described by medians (IQR).

Table 2. Interobserver agreement, ratio κ_{max}, among reviewers for the revised Atlanta classification definitions.

	Expert		Non-expert		Overall
	Radiologists	**Clinicians**	**Radiologists**	**Clinicians**	
Term	N=7	N=12	N=7	N=11	N=37
Type of pancreatitis	0.87 (±0.11)	0.79 (±0.21)	0.72 (±0.12)	0.69 (±0.27)	0.75 (±0.21)
Type of peripancreatic collection	0.82 (±0.10)	0.59 (±0.16)	0.77 (±0.09)	0.54 (±0.20)	0.62 (±0.19)

Values are ratio κ_{max}. Values are expressed as mean (SD).

Table 3. Significant differences between subgroups of reviewers for the revised Atlanta classification definitions.

Type of pancreatitis				
	ER	**EC**	**NER**	**NEC**
ER	NA	NS	p=0.025	p=0.025
EC	NS	NA	NS	NS
NER	p=0.025	NS	NA	NS
NEC	p=0.025	NS	NS	NA

Type of peripancreatic collection				
	ER	**EC**	**NER**	**NEC**
ER	NA	p<0.001	NS	p<0.001
EC	p<0.001	NA	p<0.001	NS
NER	NS	p<0.001	NA	p<0.001
NEC	p<0.001	NS	p<0.001	NA

Significant differences between subgroups of reviewers for ratio K_{max}. ER indicates expert radiologist; EC, expert clinicians; NA, not applicable; NEC, nonexpert clinicians; NER, nonexpert radiologists; NS, not significant.

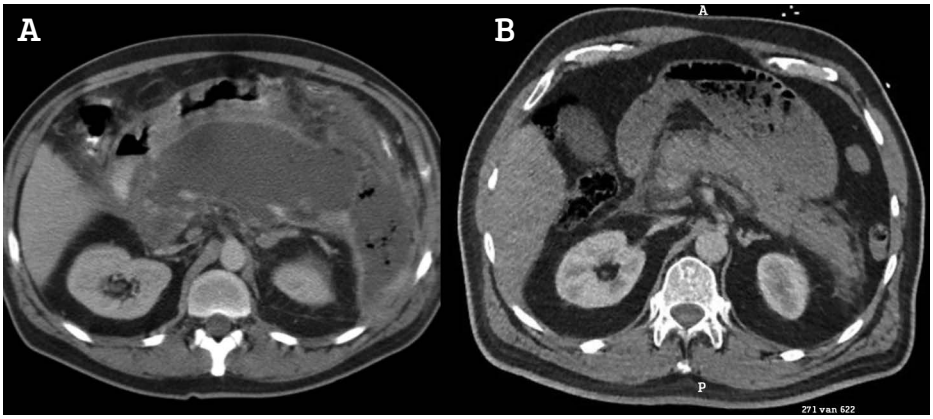

Figure 4. *Two of the 55 CTs reviewed in this interobserver agreement study. (A) Most of the reviewers described this CT as >50% pancreatic nonenhancement with a collection that is intrapancreatic and adjacent to the pancreas, which is partially encapsulated, heterogeneous, with mass effect, irregular shaped, with loculated gas bubbles, and without a gas-fluid level. All reviewers defined the type of pancreatitis as necrotizing pancreatitis. The CT was obtained 21 days after onset of disease. Most of the reviewers defined this as necrotizing pancreatitis* ►

◂ *with a collection defined as an acute necrotic collection. (B) Most of the reviewers described this CT as >50%pancreatic nonenhancement with a collection that is adjacent to the pancreas, which has no encapsulation, heterogenous, no mass effect, irregular shaped, with no loculated gas bubbles, and without a gas-fluid level. The CT was obtained at day 10 after onset of disease. Most of the reviewers defined the type of pancreatitis as necrotizing pancreatitis with an acute necrotic collection.*

Discussion

Our international, multidisciplinary interobserver agreement study showed good interobserver agreement for type of acute pancreatitis and good interobserver agreement for defining the type of peripancreatic collection, according to the definitions of the revised Atlanta classification. This represents a significant and notable step forward in interobserver agreement over the poor interobserver agreement among clinicians noted for the original 1992 Atlanta classification. The ability to classify patients and to agree on that classification is much better with the revised Atlanta classification and lends strong support for its widespread adaption in both the clinical and research communications.

The clinical course of acute pancreatitis can be mild with little morbidity and very low mortality rates, whereas severe acute pancreatitis is marked by high morbidity and mortality.[8,15] Both disease courses are associated with a variety of morphologic changes in the pancreatic and peripancreatic region, all necessitating their own treatment.[8] One of the pitfalls of the 1992 Atlanta classification was that it was a predominantly clinically based system. With advancements in diagnostic imaging over the past 20 years, many management decisions were made based solely on the evaluations of the CTs. This approach meant that radiologists and clinicians were left with trying to translate the ill-defined CT morphology of the patient with pancreatitis into a clinical classification. The result was poor interobserver agreement, leading to confused classifications in both the clinical and research communications. The value of the revised Atlanta classification is that it combines both morphologic and clinical criteria to create a more useful classification system of pancreatitis. Because correct interpretation of CT morphology combined with the clinical status of the patient determines treatment,[16] it is to be expected that with use of the revised Atlanta classification, patient treatment will be improved.

Our study also touched on generalizability issues. Two other similar interobserver studies were performed before this study, using similar methodology. In the first interobserver study, the CTs of patients with necrotizing pancreatitis were scored with the original 1992 Atlanta classification terms[4] by 5 expert radiologists. Interobserver agreement was poor; the generalizability of the

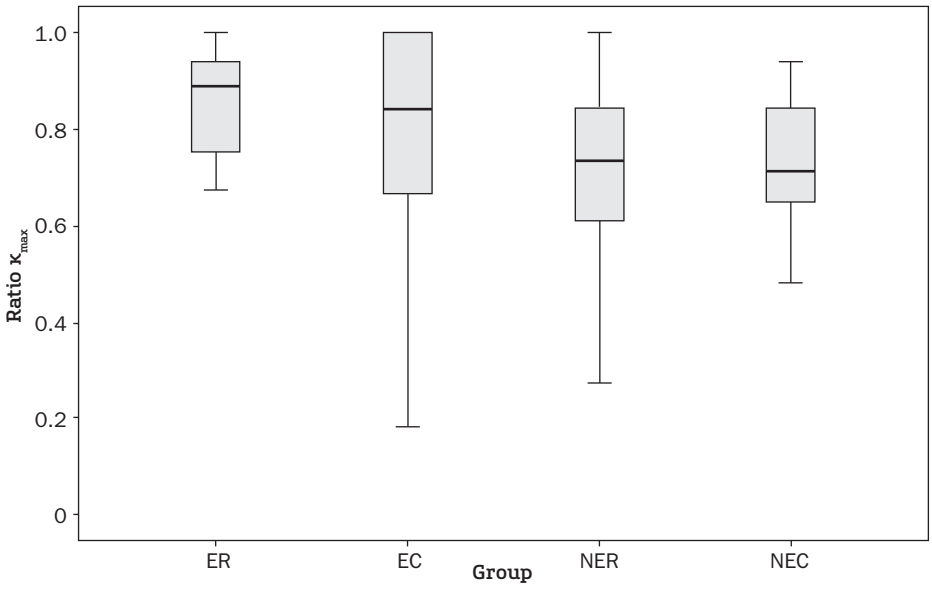

Figure 5. *Boxplot of subgroups of reviewers for the revised Atlanta classification definitions for type of acute pancreatitis. Values are ratio κ_{max}. ER indicates expert radiologist; EC, expert clinicians; NEC, nonexpert clinicians; NER, nonexpert radiologists.*

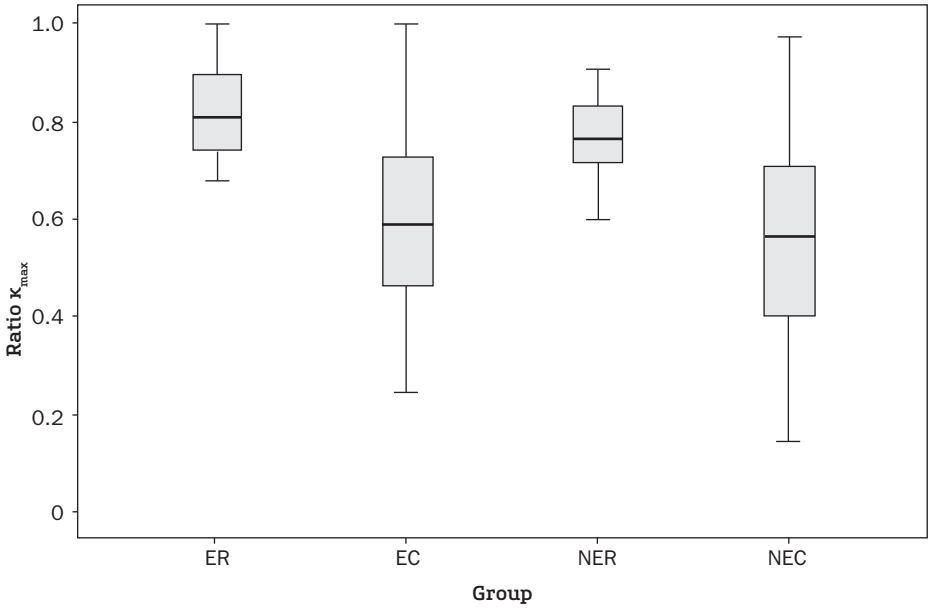

Figure 6. *Boxplot of subgroups of reviewers for the revised Atlanta classification definitions for type of peripancreatic collection. Values are ratio κ_{max}. ER indicates expert radiologist; EC, expert clinicians; NEC, nonexpert clinicians; NER, nonexpert radiologists.*

terms was unknown.[6] The second interobserver study showed good to excellent agreement for the PANCODE terms among expert radiologists and clinicians (6); however, because of the absence of nonexpert reviewers, the generalizability was unknown. In the present study, we included international groups of both expert and nonexpert radiologists and clinicians making these results more relevant to daily practice. Interobserver agreement was best among expert radiologists experienced in pancreatic disorders, followed by the nonexpert radiologists and expert clinicians. Even nonexpert clinicians, however, showed good to moderate agreement. This degree of interobserver agreement represents a substantial advance in international understanding of the classification of severe acute pancreatitis. Using the revised Atlanta classification, all physicians can now look at the same information and arrive generally at the same conclusion regarding disease classification for each patient. Beyond facilitating clinical communication, use of the revised classification should also greatly advance research studies.

Much of the decision-making for the revised Atlanta classification hinges on the proper description of CT morphology, which, according to our results showed, is most uniform among radiologists; this is not surprising. The interobserver agreement was significantly better among radiologists than among clinicians (i.e., surgeons and gastroenterologists). These data support the need for a multidisciplinary approach to severe acute pancreatitis where radiologists and clinicians work together. Based on our data, the radiologist is essential for the proper description of the CT morphology, and the clinician is needed to translate the type of peripancreatic collection into a patient-specific plan of treatment. Moreover, the expert reviewers as a group did better than the nonexpert reviewers, which suggest that interobserver agreement is better in expert centers. How this result is related to the clinical outcome of patients with acute pancreatitis is uncertain; however, one could argue that the availability of multidisciplinary teams along with better interobserver agreement in assigning a disease classification might improve clinical outcomes. Severe acute pancreatitis occurs with relatively low prevalence, and the patients present with many manifestations in symptoms and CT findings. Within this small group, each patient is unique and when distributed over many clinicians within a hospital system that does not treat many severely ill patients annually, it can be difficult for a practitioner to gain the experience and perspective needed. We recommend treating patients with severe acute pancreatitis in multidisciplinary teams of expert radiologists and clinicians.[16,17] This is in line with a growing body of literature that has linked increased procedure and/or case volume with improved outcomes for patients across a variety of

diseases and procedures. Recent evidence suggests that treatment of patients with acute pancreatitis in high volume centers (>120 patients treated a year) results in a decrease in length of intensive care unit stay, length of hospital stay, and mortality.[18]

The revised Atlanta classification is definitely a step forward in the description and management of acute pancreatitis. But this new classification also generates some questions. For instance, does the good interobserver agreement also lead to a better selection of patients for invasive treatment and thereby improved outcomes? Are all terms used in the revised Atlanta classification equally important for clinical decision-making or is treatment dictated by a few descriptive terms, such as content, (extent of) encapsulation, and (presence of) gas bubbles? A known issue with CECT is that it is difficult to distinguish the content (solid versus fluid based) of a peripancreatic collection and has its limitations in determining the extent of encapsulation.[8] In fact, we found only moderate interobserver agreement for the terms content and encapsulation (online Supplementary Table 4). Both terms can be essential in clinical decision-making and for the success of interventions like catheter drainage and necrosectomy. Because magnetic resonance imaging (MRI) and endoscopic ultrasonography can help in better defining the content and encapsulation of a collection,[8] future research should focus on determining the additional value of MRI and endoscopic ultrasonography for describing peripancreatic collections in severe acute pancreatitis. The effect of these diagnostic modalities as adjuncts to interobserver agreement and on the outcome of patients with necrotizing pancreatitis also needs to be evaluated in the light of the revised Atlanta classification.[19,20]

Some limitations have to be taken into account. There are several ways of calculating interobserver agreement. In studies on interobserver agreement for imaging (e.g., ultrasonography, CT, or MRI) in benign and malignant pancreatic disorders, multiple approaches have been described, all with advantages and disadvantages.[21-27] Agreement between 2 reviewers can be calculated by Cohen κ and in case of multiple reviewers with Fleiss κ; however, because of a substantial imbalance in distribution for most of the terms, the Cohen and Fleiss κ could not be used, because the κ statistic is influenced strongly by the prevalence of the attribute.[28,29] An alternative analysis is the intraclass correlation coefficient; however, this analysis looks at the data as groups instead of paired observations, which we wanted to examine in our study. We used the ratio κ_{max}, because it corrects for bias and prevalence, which suits our data best. Another limitation is that the reviewer findings were not compared with a reference standard, for several reasons. First, the aim of this study was not

to define whether the reviewers found the 'correct' diagnosis; however, if the reviewers described morphologic changes similarly, do we all speak the same language? Second, what is the criterion standard for comparison? One could argue that the diagnosis of the official radiology report of a single radiologist is not, per se, better than the agreement of a group of expert radiologists or expert clinicians. Our decision to use descriptions of the images without reference to any subsequent clinical data reflects the 'real world' clinical situation.

In conclusion, present findings highlight a major improvement in interobserver agreement with the 2012 revised Atlanta classification compared with the poor interobserver agreement seen among experts with the 1992 Atlanta classification and lends strong support for complete adoption of the revised Atlanta classification.

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APPENDIX CHAPTER 3

Table A1. The revised Atlanta classification definitions of morphological features of acute pancreatitis.

IEP (interstitial edematous pancreatitis)	**Necrotizing pancreatitis**
Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable necrosis of pancreatic parenchyma or peripancreatic tissues.	Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis.
APFC (acute peripancreatic fluid collection)	**ANC (acute necrotic Collection)**
Peripancreatic fluid associated with IEP with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of IEP. **CT criteria:** • Occurs in the setting of acute interstitial edematous pancreatitis • Adjacent to pancreas (no intrapancreatic extension) • Confined by normal peripancreatic fascial planes • No complete definable wall • Homogeneous collection with fluid density	A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues. **CT criteria:** • Occurs only in the setting of acute necrotizing pancreatitis • Location: intrapancreatic and/or extrapancreatic • No complete definable wall • Heterogeneous and non-liquid density with varying degrees of loculation (some appear homogeneous early in their course)
Pancreatic pseudocyst	**WON (walled-off necrosis)**
An encapsulated collection of fluid outside the pancreas with minimal or no necrosis usually requires more than 4 weeks after onset of IEP to mature and has a well-defined inflammatory wall **CT criteria:** • Well-defined wall; i.e. completely encapsulated • Homogeneous fluid density • No non-liquid component • Well circumscribed, usually round or oval • Maturation usually requires >4 weeks after onset of acute pancreatitis; occurs after interstitial edematous pancreatitis	A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that persists for >4 weeks after onset of necrotizing pancreatitis and has a well-defined inflammatory wall. **CT criteria:** • Location: intrapancreatic and/or extrapancreatic • Well-defined wall, i.e. completely encapsulated • Heterogeneous with liquid and non-liquid density with varying degrees of loculations, (some may appear homogenous) • Maturation usually requires 4 weeks after onset of acute necrotizing pancreatitis

CHAPTER 4

The value of a 24/7 online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis

Gastroenterology 2017

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Brief Report

Acute pancreatitis is the most common gastrointestinal reason for acute hospitalization.[1] Approximately 20% of patients with acute pancreatitis develop necrotizing pancreatitis.[2,3] In approximately 30% of these patients, secondary infection of the necrosis occurs, which almost always requires an invasive intervention.[4,5] Diagnosing infected necrosis on clinical grounds can be difficult. Furthermore, even if infected necrosis is proven, international guidelines advise to postpone invasive intervention to around 4 weeks after disease onset.[6,7] This allows for necrotic collections to encapsulate (i.e., walled-off necrosis), thereby technically facilitating intervention and reducing the risk of complications such as perforation and bleeding.[6,7] However, the clinical condition of some patients does not permit a delay in intervention. Clinical decision making regarding the indications for and timing of invasive intervention and preferred approach (percutaneous, surgical, or endoscopic) can, therefore, be challenging.[8] Moreover, the incidence of infected necrotizing pancreatitis is low and even tertiary referral centers may only treat 10-15 patients per year.[9]

Several international, multidisciplinary, and multicenter approaches have been initiated to improve the care for patients with pancreatitis and facilitate clinical research. In recent years, multiple national study groups have been formed worldwide, for example, in the Netherlands, the United States, Germany, Switzerland, and Hungary.[10-14] Also evidence- and consensus-based guidelines were composed by international experts in the field.[6,7,15,16] International scientific collaborations were initiated, for example, Pancreas2000 (www.pancreas2000.org) and PANCREA (Pancreatitis Across Nations Clinical Research and Education Alliance).[17,18] National and international multidisciplinary surveys were published in an attempt to identify differences and similarities in pancreatitis management strategies.[8,19-21] Finally, several studies have been published that suggested clinical benefit of centralization of pancreatitis care in high-volume centers.[22-26]

In 2006, the Dutch Pancreatitis Study Group (DPSG) introduced another approach to improve the outcome of patients with pancreatitis: We launched a 24/7, online, nationwide, multidisciplinary expert panel for clinicians treating patients with acute necrotizing pancreatitis.[27] This panel aimed to aid all Dutch clinicians in difficult clinical decisions concerning these patients, with treatment advice and assessment of eligibility for ongoing nationwide randomized trials. This report describes the rationale and design of this expert panel and the results of a prospective evaluation among the consulting clinicians and consulted experts.

The expert panel currently consists of 7 surgeons, 4 gastroenterologists, and 4 radiologists with vast experience in treating patients with necrotizing pancreatitis. Initially, the expert panel was instituted to assess eligibility for enrollment in the randomized PANTER trial.[10] During the subsequent PENGUIN trial, TENSION trial [ISRCTN09186711], and the ongoing POINTER trial [ISRCTN33682933], the expert panel proved to be of great value for assessing patient eligibility.[28,29] Soon after implementation, the expert panel became a well-known and widely used consultation board for physicians in all Dutch hospitals regarding the management of necrotizing pancreatitis patients regardless of whether they participated in a trial. In 2009, the expert panel was runner up for the Health-Safety-Prize of the Dutch Health Care Inspectorate.

The expert panel is consulted by filling out a form available on the DPSG website www.pancreatitis.nl (see online Supplementary Figure 1). The consulting clinician provides anonymous patient information, including medical history, clinical course, vital and inflammatory parameters, results from microbiologic cultures, previous interventions, and selected images from the most recent computed tomography (CT) scan. The expert form is e-mailed to the coordinating research fellow at the DPSG datacenter and then forwarded to the members of the expert panel who are alerted by a text message via mobile phone. The experts independently return their advice to the coordinating research fellow as soon as possible. Within 24 hours, the bundled expert advices are forwarded to the consulting clinician (Figure 1).

Between 2010 and 2014, a total of 397 patients with acute necrotizing pancreatitis were assessed by the expert panel (see online Supplementary Materials and Methods). The number of consultations increased annually, from 30 consultations in 2010 to 111 consultations in 2014 (see Appendix, Figure A1). The majority of requests were received from clinicians in nonacademic centers (327/397, 82%) and gastroenterology departments (217/397 [55%]; Table 1). Consultations were requested outside office hours in 191 cases (48%). In 299 cases (75%), the expert panel's advice was returned to the clinician within 24 hours. A median response rate of 7 of the 15 experts (47%) was seen. In most cases, the majority of experts agreed (i.e., ≥75% consensus) on the indication for invasive intervention and approach feasibility. Differing (50/50) advice concerning the indication for invasive intervention was given in 42 cases (11%). Differing advice concerning the technical feasibility of a surgical, endoscopic, and percutaneous approach was given in 16 (4%), 26 (7%), and 10 (3%) cases, respectively.

Clinicians completed a survey in 157 of the 397 consultations (40%; see Appendix Table A1). The expert panel was easily accessible according to 148

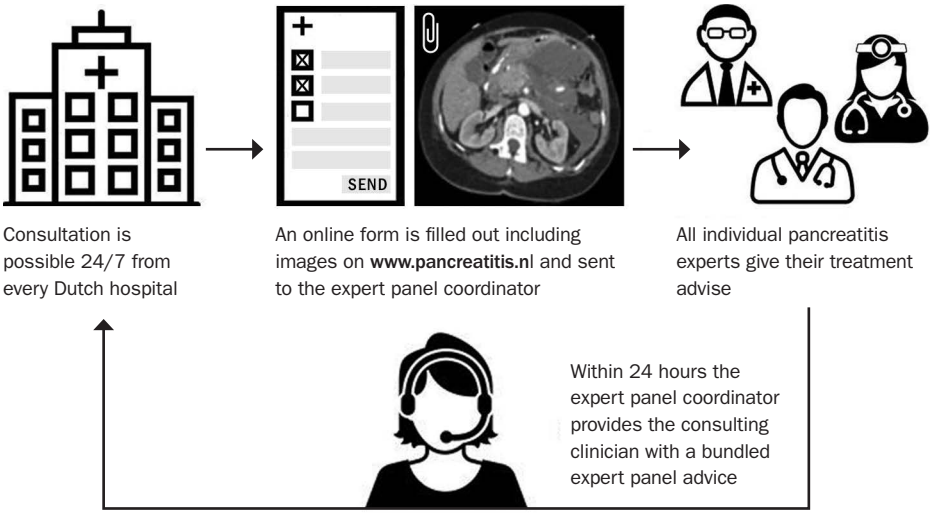

Figure 1. *Work flow expert panel consultation.*

of 157 clinicians (94%) and 138 clinicians (88%) considered it a valuable tool. In total, 132 of 157 clinicians (84%) reported to have followed the expert advice. Among clinicians who answered the question, the expert advice was similar to their own opinion in 132 (84%) cases. In total, 132 clinicians (84%) valued the advice as support for their medical decision.

All 15 experts completed a survey, with a mean experience of 17 years (SD 8) of treating necrotizing pancreatitis patients (see online Supplementary Table 2). They reported a mean workload of 9 minutes (SD 3) per expert advice. According to 14 of the 15 experts (93%), the provided clinical information was usually sufficient to give a treatment advice. Moreover, 12 of the 15 experts (80%) suggested that the availability of a full CT study would be of additional value compared with receiving selected CT images.

To our knowledge, this is the first description of a 24/7, online, nationwide, multidisciplinary expert panel for any disease and undoubtedly for patients with necrotizing pancreatitis. The evaluation shows that our expert panel is feasible within the Dutch health care setting, and considered to be an accessible and valuable tool for treating clinicians. Despite the clinical heterogeneity of necrotizing pancreatitis and the inability of experts to evaluate these patients in person, there was an indifferent expert advice in only 3%-11% of cases. For most consultations, a clear expert advice was provided.

Our evaluation has some limitations. First, no routine reminders were sent to experts asked for an opinion. This may explain the relatively low response rate of 40% (157 of 397 cases). Second, no clinical outcome data were available for

patients evaluated by the expert panel. Therefore, no assessment of the additional clinical value of this expert panel on patients' outcome was performed. An important point of improvement that emerged from our evaluation was to increase the extent and quality of the imaging data (i.e., full CT study rather than selected images). Currently, we are piloting software to exchange complete CTs between participating hospitals.

In conclusion, the described expert panel is a successful example of an approach to coordinate care and research in the field of acute necrotizing pancreatitis. Based on our experience, the DPSG has also started an expert panel for chronic pancreatitis patients. Our example has also been followed by other nationwide study groups having set up similar expert panels, for example, the Dutch Pancreatic Cancer Group and the Dutch Initiative on Crohn and Colitis diseases. A comparable system of an expert panel can be easily and inexpensively implemented in other national and international health care settings and for other diseases. In particular, a multidisciplinary and multicenter approach may lead to improved clinical outcomes and better quality control in clinical studies.

Table 1. Characteristics of expert panel consultations for necrotizing pancreatitis (2010-2014, N=397 cases).

Requests	N (%)
Non-academic centers	327 (82)
Request from	
Gastroenterologist	217 (54)
Surgeon	56 (14)
Intensive Care physician	56 (14)
Other	2 (1)
Unknown	66 (17)
Request during office hours*	206 (52)
Initial admission to expert panel consultation, days (IQR)	26 (16-46)
Patients	
Male patients	280 (71)
Age patient (SD)	57 (±14)
Disease etiology	
Biliary	160 (40)
Alcoholic	80 (20)
Unknown	104 (26)
Other	53 (14)
Patient admitted to	
ICU/MC	133 (33)
Ward	249 (62)
Pediatrics	2 (1)
Outpatient clinic	7 (2)
Unknown	6 (2)
Organ failure	
Single organ	51 (13)
Multiple organs	55 (14)
Temperature ≥38.5	115 (29)
C-reactive protein (IQR)	200 (123-286)
Leucocytes (IQR)	15 (10-21)
Positive cultures	
None	218 (55)
Blood	107 (27)
Sputum	39 (10)
Ascites	27 (7)
Urine	27 (7)
Faeces	23 (6)
Urine	15 (4)
Faeces	12 (3)
Perineum	3 (1)
Wound	2 (1)

Table 1. Continued

Patients	N (%)
Antibiotics started	285 (72)
Diet	
Oral	109 (27)
Enteral tube	205 (52)
Trans parental	27 (7)
Nil per mouth	17 (4)
Combination	36 (9)
Unknown	3 (1)
Disease severity score[#] (IQR)	7 (5-8)
Number of imaging slices (IQR)	9 (5-11)
Imaging to expert panel consultation, days (IQR)	1 (0-3)
Expert panel advice	
Expert advice returned within 24h	299 (75)
Number of expert responses within 24h^ (SD)	6 (±2)
Number of expert responses total^ (SD)	7 (±2)
Advice: indication for invasive intervention	
75-100% no	208 (52)
50-50%	42 (11)
75-100% yes	147 (37)
Advice: surgical step-up possible	
75-100% no	36 (9)
50-50%	16 (4)
75-100% yes	278 (70)
Not reported	67 (17)
Advice: endoscopic step-up possible	
75-100% no	51 (13)
50-50%	26 (7)
75-100% yes	252 (63)
Not reported	68 (17)
Advice: percutaneous catheter drainage possible	
75-100% no	11 (3)
50-50%	10 (3)
75-100% yes	347 (87)
Not reported	29 (7)

IQR, interquartile range; SD, standard deviation.

⋆ Office hours defined as Monday-Friday, 8am-5pm.

[#] *Score 0-10 reported by physician, 10=severe illness.*

^ *Total of 15 experts.*

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APPENDIX CHAPTER 4

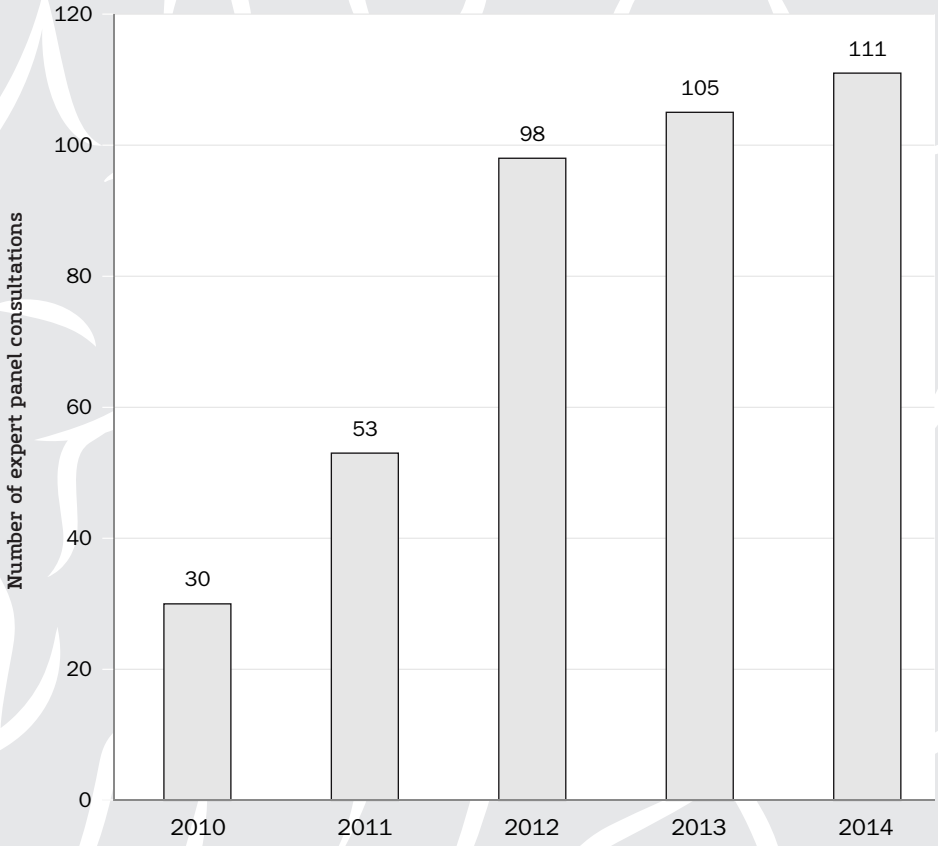

Figure A1. *Number of expert panel consultations 2010-2014.*

Table A1. Survey among clinicians using the online expert panel in the period 2010-2014 (N=157/397 cases).

	N (%)
Expert panel is easily accessible	148 (94)
Too much time to fill out consultation form	
Totally disagree	7 (5)
Disagree	76 (49)
Not agree or disagree	30 (19)
Agree	40 (26)
Fully agree	2 (1)
Advice too late	
Totally disagree	78 (50)
Disagree	62 (40)
Not agree or disagree	9 (6)
Agree	5 (3)
Fully agree	2 (1)
Advice followed	132 (84)
Advice similar to your initial opinion	132 (84)
Used to	
Convince colleagues	82 (52)
Convince surgeons	32 (20)
Convince gastroenterologists	38 (24)
Convince radiologists	17 (11)
Convince ICU physicians	21 (13)
Convince family	2 (1)
Support for medical decision	132 (84)
Valuable initiative	
Totally disagree	13 (9)
Disagree	3 (2)
Not agree or disagree	2 (1)
Agree	41 (26)
Fully agree	97 (62)
Valuable for other diseases	
Totally disagree	5 (3)
Disagree	5 (3)
Not agree or disagree	40 (26)
Agree	71 (46)
Fully agree	33 (22)

CHAPTER 5

Natural history of gas configurations and encapsulation of necrotic collections on computed tomography in acute pancreatitis

Submitted

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Abstract

Background

Decision-making on invasive intervention in patients with clinical signs of infected necrotizing pancreatitis is often related to the presence of gas configurations in and degree of encapsulation of necrotic collections at imaging. Data on the natural history of gas configurations and encapsulation in necrotizing pancreatitis are, however, lacking.

Methods

A post-hoc analysis was performed of a previously described prospective cohort in 15 Dutch hospitals (2004-2008). All computed tomography scans (CTs) performed during hospitalization for necrotizing pancreatitis were categorized per week (1 to 8, and thereafter) and re-assessed by an abdominal radiologist.

Results

A total of 639 patients with necrotizing pancreatitis were included, with median 4 (IQR 2-7) CTs per patient. The incidence of first onset of gas configurations varied per week without a linear correlation: 2-3-13-11-10-19-12-21-12%, respectively. Overall, gas configurations were found in 113/639 (18%) patients and in 113/202 (56%) patients with infected necrosis. The incidence of walled-off necrosis increased per week: 0-3-12-39-62-76-93-97-100% for week 1-8 and thereafter, respectively. Clinically relevant walled-off necrosis (largely or fully encapsulated necrotic collections) was seen in 162/379 (43%) patients within the first 3 weeks.

Conclusions

Gas configurations occur in every phase of the disease and develop in half of the patients with infected necrotizing pancreatitis. Opposed to traditional views, clinically relevant walled-off necrosis occurs frequently within the first 3 weeks.

Introduction

Acute pancreatitis is the most common gastrointestinal disorder requiring hospital admission in the US and its incidence is rising.[1] Necrotizing pancreatitis, defined as necrosis of the pancreatic parenchyma and/or extrapancreatic fat tissue, occurs in around 20% of patients.[2,3] Associated collections in necrotizing pancreatitis (necrotic collections) are either called 'acute necrotic collections' (not fully encapsulated) or 'walled-off necrosis' (fully encapsulated).[4] In case of infected necrosis, an invasive intervention is nearly always needed.[5,6] Current guidelines advice a step-up approach in patients with infected necrosis, starting with catheter drainage. If the patient does not recover with drainage alone, minimally invasive necrosectomy is performed.[5,6] Although overall outcome has improved over the last decade, mortality and morbidity in these patients are still 15% and 40%, respectively.[7]

Decision-making on invasive intervention is influenced by clinical, biochemical, and imaging features. Two imaging features stand out in the decision-making process. First, the presence of gas configurations within necrotic collections is deemed important as this is regarded pathognomonic for infected necrosis. Second, the degree of encapsulation of necrotic collections is relevant because drainage is typically postponed until necrotic collections are largely or fully encapsulated. The timing of invasive intervention in patients with infected necrotizing pancreatitis, however, remains a topic of debate.[8]

It is often assumed that gas configurations occur most often between the second and fourth week and that full encapsulation of necrotic collections occurs at least 4 weeks after symptom onset. Accurate data supporting these statements are, however, lacking.[4] Improved knowledge about the natural course of necrotic collections might support decision-making on timing of invasive intervention. Moreover, it can add to the interpretation and further standardization of clinical research in necrotizing pancreatitis.

The main purpose of this study was thus to evaluate the natural history of gas configurations in and encapsulation of necrotic collections during the disease course of necrotizing pancreatitis. In addition, clinical and radiological factors associated with occurrence of gas and (early) encapsulation in necrotic collections were studied.

Methods

Study design and patients

This study is a post-hoc analysis of a prospective cohort of patients with necrotizing pancreatitis, collected from 2004 to 2008 in 15 Dutch hospitals of the Dutch Pancreatitis Study Group.[9] All contrast-enhanced CTs performed during

the index admission and before any kind of invasive (surgical, endoscopic, or percutaneous) intervention were reassessed by an experienced abdominal radiologist (TLB). Patients with at least one CT confirming the diagnosis of necrotizing pancreatitis were included. Follow-up CTs were performed in case of lack of clinical improvement according to current standard practice. Conservative treatment consisted of intravenous fluid therapy, oral or enteral feeding, and adequate pain management. Invasive interventions were performed in case of (suspected) infected necrosis based on gas configurations on CT, positive culture after fine needle aspiration, or clinical deterioration with no other cause than infected necrosis.[10]

Data-extraction

All CTs were categorized into groups according to duration since onset of disease, i.e. week 1 to 8, and further. If more than 1 CT was performed in a week, the last CT was used for assessment. In all CTs, the presence of first onset of gas configurations was evaluated (see Figure 1 for CT examples). Gas configurations depicted on every follow-up CT in patients undergoing a conservative treatment were not scored in the incidence assessment. The degree of encapsulation was scored as not (0%), moderately (less than 50%), largely (between 50 and 99%), or fully (100%) encapsulated (see CT examples in Figure 2). Walled-off necrosis was defined according to the revised Atlanta classification as fully encapsulated necrotic collections.[4] In clinical practice, however, invasive intervention is contemplated and deemed feasible when infected necrotic collections are largely or fully encapsulated. Hence, besides the original definition of walled-off necrosis we also assessed a more clinically relevant definition of 'walled-off necrosis', defined as necrotic collections that are largely or fully encapsulated. In this line of reasoning, we defined 'early walled-off necrosis' as largely or fully encapsulated collections occurring within 3 weeks after symptom onset, i.e. before the traditional 4 weeks mentioned in the revised Atlanta classification.[4] The following clinical baseline data were available: age, sex, disease etiology, and American Society of Anesthesiologists (ASA) classification.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Outcomes were reported as absolute numbers and percentages for categorical variables. Continuous variables were summarized as either means with corresponding standard deviations (SD) or medians with interquartile ranges (IQR) depending on normality of distribution.

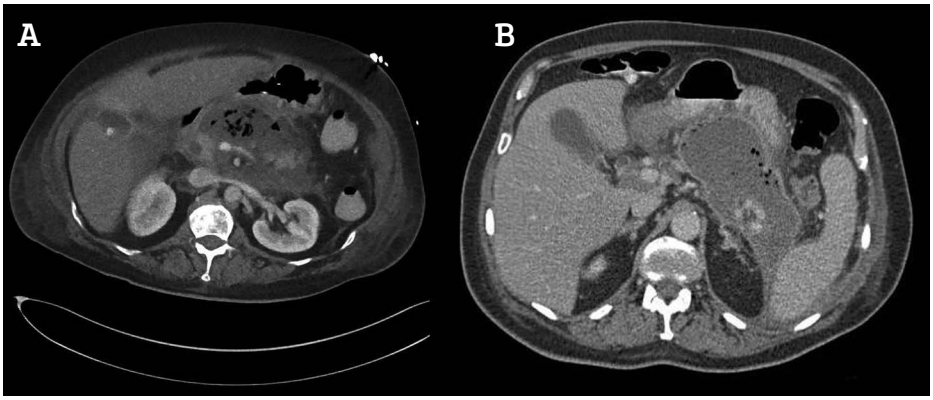


Figure 1. *(A) CT with gas configurations in acute necrotic collection. (B) CT with gas configurations in walled-off necrosis.*

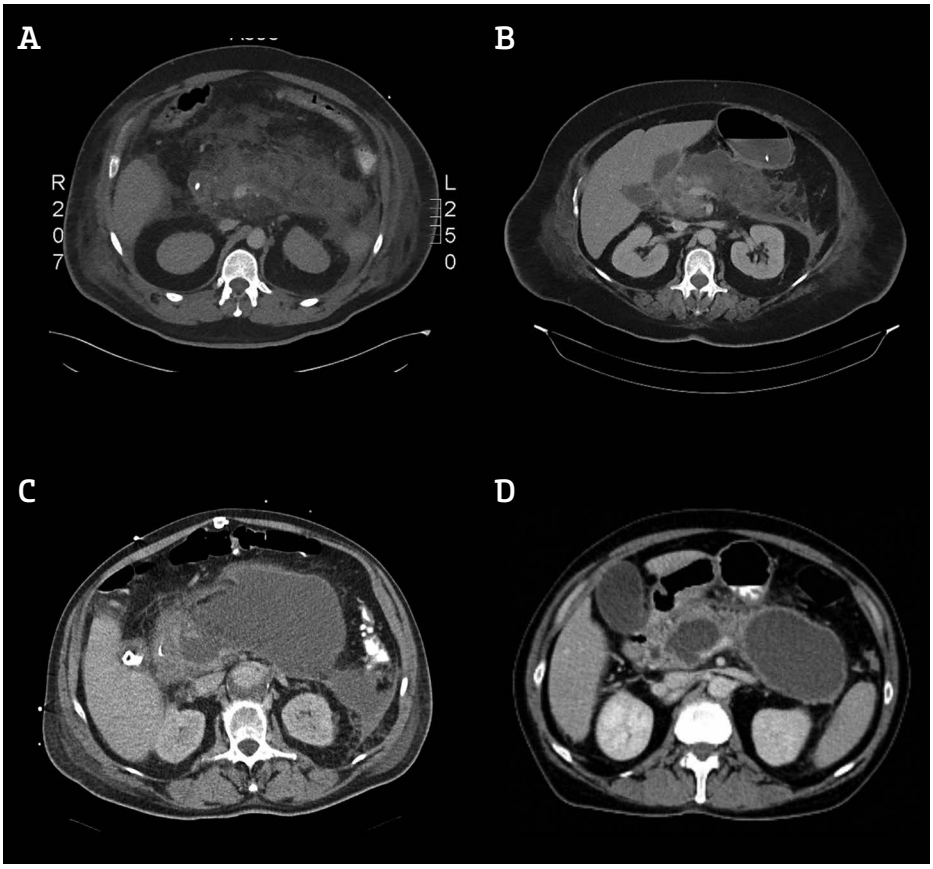


Figure 2. *(A) CT: not encapsulated (0%), (B) CT: moderately encapsulated (<50%). (C) CT: largely encapsulated (50-99%). (D) CT: fully encapsulated /walled-off necrosis (100%).*

Table 1. Clinical and radiological characteristics of 639 patients with necrotizing pancreatitis.

	All patients (N=639)
Age (years)	58 (45-70)
Male sex (%)	398 (62)
Etiology (%)	
Biliary	304 (48)
Alcohol	150 (23)
Other	63 (10)
Unknown	122 (19)
ASA classification on admission (%)	
I (healthy status)	202 (32)
II (mild systemic disease)	347 (54)
III (severe systemic disease)	90 (14)
No. of CTs per patient	
Total	4 (2-7)
Before intervention	3 (2-4)
After intervention	0 (0-3)
CT severity index^	4 (4-8)
Extrapancreatic necrosis alone (%)#	315 (49)
Pancreatic necrosis (%)	324 (51)
Extent of pancreatic necrosis (%)Nn=324	
<30%	132 (40)
30-50%	83 (26)
>50%	109 (34)
No. of necrotic collections	3 (2-5)
Location of necrotic collections, within first 2 weeks (%)	
Left	188 (29)
Right	55 (9)
Central	235 (37)
Bilateral	161 (25)
Gas configurations on CT (%)	
Total	113 (18)
Of 202 patients with infected necrosis	113 (56)

ASA, indicates American Society of Anesthesiologists; CT, computer tomography. Continuous variables are provided as mean (±SD) or median (IQR) depending on normality of distribution. ^ Scores on the CT severity index range from 0 to 10, with higher scores indicating more extensive pancreatic or extrapancreatic necrosis. # No pancreatic necrosis present.

Univariable logistic regression was performed to identify factors associated with the occurrence of gas configurations and for 'early walled-off necrosis'. Factors associated in the univariable analysis ($p<0.1$) were entered into a multivariable logistic regressions analysis (backward stepwise elimination method). A two-sided p-value <0.05 was considered statistically significant for all statistical tests.

Results

The study cohort consisted of 639 patients with necrotizing pancreatitis. Median age was 58 years (IQR 45-70) and 62% (398) of patients were male. A median of 4 (IQR 2-7, range 1-23) CTs were performed per patient (Table 1). The median CT severity index was 4 (IQR 4-8). In 324 (51%) patients, pancreatic parenchymal necrosis was present, in the remainder of 315 (49%) patients there was extrapancreatic necrosis only. A median of 3 (IQR 2-5) necrotic collections were observed per patient, mostly centrally located (i.e. predominantly in the lesser sac and/or transverse mesocolon) or left-sided (i.e. predominantly at the left side of the retroperitoneum), in 235 (37%) and 188 (29%) of patients, respectively.

Gas configurations

In 18% of patients (113 of 639 patients) and in 56% of patients with proven infected necrosis (113 of 202 patients), gas configurations were seen at some point in time. Figure 3 shows the number of patients (in %) in whom first onset of gas configurations were seen on CT per week: w1: 2%; w2: 3%; w3: 13%; w4: 11%; w5: 10%; w6: 19%; w7: 12%; w8: 21%; and >w8: 12%. There was no linear correlation. In a multivariable analysis, age ($p<0.001$), presence of pancreatic necrosis ($p<0.001$), number of necrotic collections ($p=0.018$), and left-sided collections ($p<0.001$) were independently associated with the occurrence of gas configurations (see Table 2A).

Encapsulation

Figure 3 shows the degree of encapsulation related to the number of patients. The incidence of fully encapsulated necrotic collections (walled-off necrosis according to the revised Atlanta classification) increased per week: w1: 0%; w2: 3%; w3: 12%; w4: 39%; w5: 62%; w6: 76%; w7: 93%; w8: 97%; and >w8: 100%. The incidence of largely or fully encapsulated necrotic collections (i.e., clinically relevant walled-off necrosis) increased per week: w1: 1%, w2: 17%, w3: 61%, w4: 88%, w5: 100%, w6: 99%, w7:100%, w8: 100%, >w8: 100%. Early clinical relevant walled-off necrosis (i.e. within the first 3 weeks) was seen in 162 of 379 (43%) patients. Male sex ($p=0.035$), pancreatic necrosis ($p=0.014$), and the

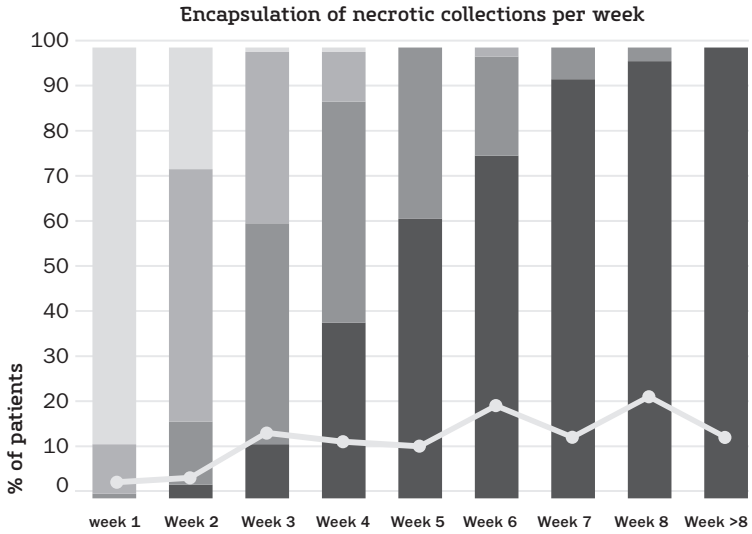
presence of gas configurations (p=0.044) were independently associated with the occurrence of early clinical relevant walled-off necrosis in a multivariable analysis (see Table 2B).

Table 2. (A) Univariable and multivariable logistic regression analysis for factors associated with gas configurations (113 of 639 patients, 18%). (B) Multivariable logistic regression analysis for factors associated with early walled-off necrosis (i.e. within 3 weeks; 162 of 379 patients, 43%).

A	Univariable OR (95% CI)	p	Multivariable OR (95% CI)	p
Age	1.019 (1.005-1.033)	0.006	1.032 (1.016-1.048)	<0.001
Sex (male)	1.301 (0.846-2.001)	0.230		
ASA classification (ASA 3)	1.195 (0.681-2.095)	0.535		
CT severity index	1.309 (1.205-1.422)	<0.001	0.986 (0.852-1.141)	0.852
Presence of pancreatic parenchymal necrosis	4.883 (2.994-7.964)	<0.001	4.046 (2.398-6.826)	<0.001
No. of necrotic collections	1.275 (1.152-1.410)	<0.001	1.160 (1.026-1.312)	0.018
Location of necrotic collection (left vs. non-left)	3.499 (2.225-5.501)	<0.001	2.780 (1.692-4.569)	<0.001

B	Univariable OR (95% CI)	p	Multivariable OR (95% CI)	p
Age	1.004 (0.991-1.018)	0.522		
Sex (male)	0.655 (0.427-1.005)	0.053	0.625 (0.403-0.967)	0.035
ASA classification (ASA 3)	0.957 (0.536-1.707)	0.881		
CT severity index	1.062 (0.974-1.159)	0.173		
Presence of pancreatic parenchymal necrosis	1.852 (1.190-2.881)	0.006	1.761 (1.119-2.772)	0.014
No. of necrotic collections	1.019 (0.917-1.132)	0.730		
Location of necrotic collection (left vs. non-left)	1.233 (0.782-1.944)	0.368		
Gas configurations	1.762 (1.118-2.778)	0.015	1.617 (1.014-2.580)	0.044

ASA, indicates American Society of Anesthesiologists; CT, computer tomography; OR, odds ratio; CI, confidence interval.



	week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week >8
Not encapsulated	88	27	1	1	0	0	0	0	0
Medium encapsulated	11	56	38	11	0	2	0	0	0
Largely encapsulated	1	14	49	49	38	22	7	3	0
Fully encapsulated	0	3	12	39	62	76	93	97	100
Gas Configurations	2	3	13	11	10	19	12	21	12

Figure 3. *Degree of encapsulation and presence of gas configurations in (extra)pancreatic necrotic collection per week. NB. Only patients in whom a CT was performed AND (extra)pancreatic necrotic collections were seen (total N=639 patients); 1st week N=540 (85%); 2nd week N=329 (51%); 3rd week N=195 (31%); 4th week N=142 (22%); 5th week N=87 (14%); 6th week N=59 (9%); 7th week N=43 (7%); 8th week N=34 (5%); beyond 8 weeks N=138 (22%).*

Discussion

This study provides novel information on the natural history of imaging features of first onset of gas configurations and encapsulation in necrotizing pancreatitis. The main findings are that first onset of gas configurations and walled-off necrosis occur in nearly every phase of the disease, well before as after 4 weeks of symptom onset. Although walled-off necrosis becomes more prevalent with time, over 40% of patients already develop clinically relevant walled-off necrosis within the first 3 weeks of disease.

Gas in necrotic collections is thought to be caused by gas-forming bacteria or loss of integrity of the gastrointestinal tract.[5] Both are considered pathognomonic for infected necrosis. Infected necrosis is almost always an indication for invasive intervention since only a small subset (<5%) of patients recover with antibiotic treatment only.[9] Little is known about risk factors for

gas configurations at imaging or timing of its occurrence. According to our study, gas configurations are seen in every phase of the disease, i.e. very early as well as late in the disease course. Gas configurations were more often seen in patients with higher age, parenchymal necrosis, multiple collections, and left-sided collections. The association between these factors and gas configurations may in part be explained by direct contact between necrotic collections and the gastrointestinal tract, facilitating the translocation of bacteria. More research on this topic is, however, required for verification of this association. Also, the relationship between the type(s) of bacteria and occurrence of gas configurations on CT remains contentious and deserves further study.

The 2012 revised Atlanta classification classifies early pancreatic collections into acute peripancreatic fluid collections and acute necrotic collections, that after 4 weeks develop into pancreatic pseudocysts and walled-off necrosis, respectively, when completely encapsulated.[4] Necrotic collections may involve the pancreatic parenchyma and/or extrapancreatic tissues and are considered a different clinical entity with a worse clinical outcome as compared with interstitial edematous pancreatitis.[4,11] Little is known about the natural history of imaging features of necrotic collections. Previous studies have evaluated the natural clinical history of (extra)pancreatic collections, but did not analyze their imaging characteristics or timing of encapsulation. Some have studied the clinical course (i.e. resolution) of pancreatic fluid collections and risk factors associated with the presence of pancreatic collections,[12,13] analyzed clinical and biochemical factors associated with formation of encapsulation (or 'pseudocyst formation'),[12,14] or evaluated resolution of necrotic collections in the later phase of disease by means of endoscopic ultrasound or transabdominal ultrasonography (i.e. not by CT) at different time points (i.e. after 4-6 weeks up to 6 months).[13,15]

The pathophysiology and rate of encapsulation of necrotic collections is as of yet incompletely understood. It is generally assumed that in necrotizing pancreatitis, the premature release of activated pancreatic enzymes and resultant acinar cell injury incites an extensive local and systemic inflammatory response. Locally this might be regarded as a natural defense mechanism in which the body attempts to contain the area of inflammation. Over time, a capsule of granulation tissue is formed at the periphery to separate the inflamed tissue from healthy tissue to mitigate further spread of toxic enzymes and thus to wall off necrotic collections. This natural process of walling off an inflammatory process is likely analogous to an abscess wall formation. It is often stated (but not studied) that the timing of encapsulation takes about 4 weeks and this timescale is incorporated by the revised Atlanta classification. In the current study, however, there was a wide temporal range in which necrotic collections

eventually became walled-off. In 85% of patients, it took well over 4 weeks for necrotic collections to become completely walled off, whereas in 3% and 12% complete encapsulation was already noted during the second and third week, respectively. Moreover, early clinically relevant walled-off necrosis (within the first 3 weeks) occurred in 43% and was more seen in male patients, patients with parenchymal necrosis, and patients with gas configurations (i.e. parameters associated with poorer clinical outcome[16,17]). The reason for the wide temporal range and observed associations with early encapsulation remain speculative. Possibly, the magnitude of inflammatory response incited locally together with immune-mediated and patient factors could result in necrotic collections becoming walled-off early or late. More research on this topic is, however, needed.

Our study has several limitations. First, for this study, CTs were assessed by one abdominal radiologist. Therefore, no interobserver agreement could be calculated. Since other studies show good agreement for type of necrotic collection, presence of intraluminal gas in necrotic collections, and presence of a wall among experienced radiologists,[18] we expect our results to be reproducible. Second, follow-up CTs were not routinely (for example, weekly) performed but rather on the discretion of treating physicians, often based on change in a patient's condition. This is in line with standard practice as routinely performing CT is not justifiable out of costs and radiation burden perspectives. Third, we defined 'clinically (relevant) walled-off necrosis' as necrotic collections that are largely or fully encapsulated. We feel that in clinical practice the distinction between collections that are not or only moderately encapsulated are treated different (conservative therapy) compared with those that are largely or fully encapsulated (invasive therapy possible). More data are needed to determine whether this definition more closely relates to clinical management than the original definition.

Results of this study could have therapeutic implications because the knowledge of gas configurations and early encapsulation might influence the timing to proceed to an earlier invasive intervention in a subset of patients with infected necrosis. Current international guidelines, however, advice to postpone invasive intervention for at least 4 weeks in patients with (suspected) infected necrotizing pancreatitis until walled-off necrosis is present because intervention is believed to be safer in walled-off necrosis (e.g. less bleeding).[5,6] This advice is primarily based on studies in which patients underwent early primary open necrosectomy (within first 2 weeks) which was associated with worse outcome.[19-21] Nowadays, standard treatment of infected necrosis is primary catheter drainage. At least 35%-50% of patients do not need additional

necrosectomy after catheter drainage and this is associated with a lower risk for complications.[7,22] Since catheter drainage is the first step of treatment which does not require fully encapsulated necrotic collections, some suggest that early and proactive drainage could prevent clinical deterioration, improve outcome, and shorten hospital stay.[23,24] This hypothesis is currently being studied in the Dutch multicenter randomized controlled POINTER trial (ISRCTN33682933). This study compares immediate catheter drainage with postponed catheter drainage in patients with proven or suspected infected necrotizing pancreatitis.

In conclusion, opposed to common views, gas configurations and walled-off necrosis are seen in every phase of the disease in patients with necrotizing pancreatitis. This may have therapeutic implications in a subset of patients with infected necrosis and early walled-off necrosis.

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CHAPTER 6

Early versus on-demand nasoenteric tube feeding in acute pancreatitis

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Abstract

Background

Early enteral feeding through a nasoenteric feeding tube is often used in patients with severe acute pancreatitis to prevent gut-derived infections, but evidence to support this strategy is limited. We conducted a multicenter, randomized trial comparing early nasoenteric tube feeding with an oral diet at 72 hours after presentation to the emergency department in patients with acute pancreatitis.

Methods

We enrolled patients with acute pancreatitis who were at high risk for complications on the basis of an Acute Physiology and Chronic Health Evaluation II score of 8 or higher (on a scale of 0 to 71, with higher scores indicating more severe disease), an Imrie or modified Glasgow score of 3 or higher (on a scale of 0 to 8, with higher scores indicating more severe disease), or a serum C-reactive protein level of more than 150 mg per liter. Patients were randomly assigned to nasoenteric tube feeding within 24 hours after randomization (early group) or to an oral diet initiated 72 hours after presentation (on-demand group), with tube feeding provided if the oral diet was not tolerated. The primary end point was a composite of major infection (infected pancreatic necrosis, bacteremia, or pneumonia) or death during 6 months of follow-up.

Results

A total of 208 patients were enrolled at 19 Dutch hospitals. The primary end point occurred in 30 of 101 patients (30%) in the early group and in 28 of 104 (27%) in the on-demand group (risk ratio, 1.07; 95% confidence interval, 0.79 to 1.44; p=0.76). There were no significant differences between the early group and the ondemand group in the rate of major infection (25% and 26%, respectively; p=0.87) or death (11% and 7%, respectively; p=0.33). In the on-demand group, 72 patients (69%) tolerated an oral diet and did not require tube feeding.

Conclusions

This trial did not show the superiority of early nasoenteric tube feeding, as compared with an oral diet after 72 hours, in reducing the rate of infection or death in patients with acute pancreatitis at high risk for complications. (Funded by the Netherlands Organization for Health Research and Development and others; PYTHON Current Controlled Trials number, ISRCTN18170985.)

Background

Acute pancreatitis is the most common gastrointestinal disease leading to hospital admission, and its incidence continues to rise.[1-4] Most patients with acute pancreatitis recover uneventfully and are discharged after a few days.[5,6] In 20% of patients, the disease course is complicated by major infection, such as infected pancreatic necrosis, which is associated with a mortality of 15%.[7-11]

A meta-analysis of eight randomized trials involving 348 patients showed that nasoenteric tube feeding, as compared with total parenteral nutrition, reduced the rate of infections and mortality among patients with severe pancreatitis.[12] These infections are thought to be mediated by bacterial translocation from the gut, provoked by disturbed intestinal motility, bacterial overgrowth, and increased mucosal permeability.[13-18] Nasoenteric tube feeding is believed to stimulate intestinal motility - thus reducing bacterial overgrowth - and may increase splanchnic blood flow, which helps to preserve the integrity of the gut mucosa.[19,20] Total parenteral nutrition lacks the trophic effect of enteric feeding and is associated with central venous catheter-related infections as well as metabolic complications.[21]

A meta-analysis of randomized trials involving acutely ill patients admitted to the hospital for indications other than pancreatitis showed a 22% reduction in the rate of major infection when nasoenteric tube feeding was started very early (≤36 hours after admission or surgery) as compared with a later start.[22] Similarly, nonrandomized studies of acute pancreatitis have shown that nasoenteric tube feeding started within 48 hours after admission, as compared with a start after 48 hours, significantly reduced the rate of major infection and in some studies even reduced mortality.[23-26]

On the basis of these potential benefits, American and European nutritional societies recommend routine early nasoenteric tube feeding in all patients with severe pancreatitis.[27-29] Guidelines from gastroenterologic and pancreatic societies, however, state that, regardless of disease severity, tube feeding is indicated when patients are not able to tolerate an oral diet for up to 7 days.[30,31] Unfortunately, it takes 3 to 4 days after admission to make this assessment,[32] and by that time the window of opportunity for effective prevention of infection with early tube feeding has passed.[7] To address this problem in the management of acute pancreatitis, we compared the effects of early nasoenteric tube feeding with those of an oral diet started at 72 hours, with a switch to nasoenteric tube feeding only in the case of insufficient oral intake.

Methods

Study participants

The protocol of the Pancreatitis, Very Early Compared with Selective Delayed Start of Enteral Feeding (PYTHON) trial has been published previously[33] and is available with the full text of this article at NEJM.org. The study was conducted according to the protocol. Adults with a first episode of acute pancreatitis who were at high risk for complications (i.e., patients predicted to have severe pancreatitis) were eligible to undergo randomization. Patients were considered to be at high risk for complications if, within 24 hours after presentation to the emergency department, the Acute Physiology and Chronic Health Evaluation (APACHE) II[34] score was 8 or higher (on a scale of 0 to 71, with higher scores indicating more severe disease), if the Imrie or modified Glasgow score[35] was 3 or higher (on a scale of 0 to 8, with higher scores indicating more severe disease), or if the serum C-reactive protein level was more than 150 mg per liter.[36] These assessments predict the development of complications during the course of the disease. Pancreatitis was diagnosed if at least two of the three following features were present: typical abdominal pain, a serum lipase or amylase level that was more than 3 times the upper limit of the normal range, or characteristic findings on cross-sectional imaging of the abdomen. The exclusion criteria are given in the online Supplementary Appendix, available at NEJM.org.

Study design and oversight

The PYTHON trial was a multicenter, randomized, controlled superiority trial performed in six university medical centers and 13 large teaching hospitals of the Dutch Pancreatitis Study Group. Patients were randomly assigned in a 1:1 ratio either to nasoenteric tube feeding initiated within 24 hours after randomization (the early group) or to an oral diet starting at 72 hours (the on-demand group). Randomization was performed centrally by the study coordinator with the use of a Web-based system that used permuted-block randomization with a concealed, varying block size. Randomization was stratified according to treatment center and a dichotomized APACHE II score (<13 vs. ≥13); the latter stratification factor was used because patients with an APACHE II score of 13 or higher are at increased risk for major infection.

All the patients or their legal representatives provided written informed consent. The study protocol was approved by the institutional review board of the University Medical Center Utrecht and by all the participating centers. All the authors vouch for the veracity and completeness of the data and data analyses. The sponsors were not involved in the design or conduct of the study or in the preparation of the manuscript or the decision to submit it for publication.

Study procedures

Patients underwent randomization within 24 hours after presentation to the emergency department. Those assigned to early nasoenteric feeding received a nasojejunal feeding tube as soon as possible but not later than 24 hours after randomization. Feeding tubes were placed endoscopically or radiologically, according to local practice. Nasoenteric feeding was administered as Nutrison Protein Plus (Nutricia). After tube placement, feeding was started at 20 ml per hour during the first 24 hours and was gradually increased (see the online Supplementary Appendix). In the two study groups, full nutrition was defined as an energy target of 25 kcal per kilogram of body weight per day for patients in the intensive care unit (ICU) and 30 kcal per kilogram per day for patients in the ward.[28,37,38]

Patients assigned to an oral diet did not receive nutrition by any means other than that provided by standard intravenous fluids during the first 72 hours after presentation to the emergency department. Exceptions were made for patients who requested oral food during this 72-hour period. At 72 hours, all the patients in the on-demand group were given an oral diet. If an oral diet was not tolerated, it was offered again after 24 hours. If an oral diet still was not tolerated after 96 hours from the time of presentation, nasoenteric feeding was started after the placement of a nasojejunal tube, and the same procedure was followed as in the early group.

End points

The primary end point was a composite of major infection or death within 6 months after randomization. Major infection was defined as infected pancreatic necrosis, bacteremia, or pneumonia (for definitions, see Box S1 in the online Supplementary Appendix). Predefined secondary end points included the development of necrotizing pancreatitis as diagnosed on the basis of computed tomography (CT) performed 5 to 7 days after admission (because pancreatic parenchymal necrosis may take up to 72 hours to develop) and the development of organ failure after randomization.

Data collection and end-point assessment

Dieticians registered the caloric intake and calculated energy-intake targets during the first week after admission on the basis of actual body weight. All CT studies were interpreted by an author who is an experienced radiologist and who was unaware of the treatment assignments. An adjudication committee, consisting of four pancreatic surgeons and a gastroenterologist who were unaware of the treatment assignments, individually evaluated each patient

for the occurrence of the primary end point before interim and final analyses. Disagreements with respect to major infection were resolved during a plenary consensus meeting.

Patient safety

An independent data and safety monitoring committee evaluated the progress of the trial and examined safety end points after the completion of follow-up in each consecutive group of 25 patients. Adverse events were listed and presented to the data and safety monitoring committee in an unblinded fashion.

Statistical analysis

The expected incidence of the primary end point in the on-demand group was based on data from individual patients in the placebo group of a previous randomized trial.[39] For the early group, data from randomized trials comparing nasoenteric with parenteral nutrition were used to estimate the incidence.[33,40-42] The sample-size calculation was based on an expected reduction in the primary composite end point associated with early tube feeding from 40 to 22%.[33] We estimated that a sample of 208 patients would provide the study with at least 80% power, at a two-sided alpha level of 5% and assuming a 1% loss to follow-up. Analysis was based on the intention-to-treat method, with the exclusion only of patients for whom the adjudication committee, whose members were unaware of the treatment assignments, decided before any analysis that the diagnosis of acute pancreatitis was incorrect.

Predefined subgroups included patients with an APACHE II score below 13 and those with a score of 13 or higher at randomization. Two post hoc subgroup analyses were performed: one for patients with the systemic inflammatory response syndrome (SIRS, as defined by the Consensus Conference criteria of the American College of Chest Physicians-Society of Critical Care Medicine) at randomization, because such patients are at high risk for complications,[43] and one for a low or high body-mass index (BMI; the weight in kilograms divided by the square of the height in meters), since the BMI differed significantly between the two treatment groups at baseline.

An interim analysis of the primary end point was performed after 50% of the patients had completed 6 months of follow-up. The interim analysis was performed by an independent statistician, who was unaware of the treatment assignments, applying the Peto approach with symmetric stopping boundaries at a p-value of less than 0.001.[33,44]

For the final analyses, a two-sided p-value of less than 0.05 was considered to indicate statistical significance. p-Values were not adjusted for multiple testing.

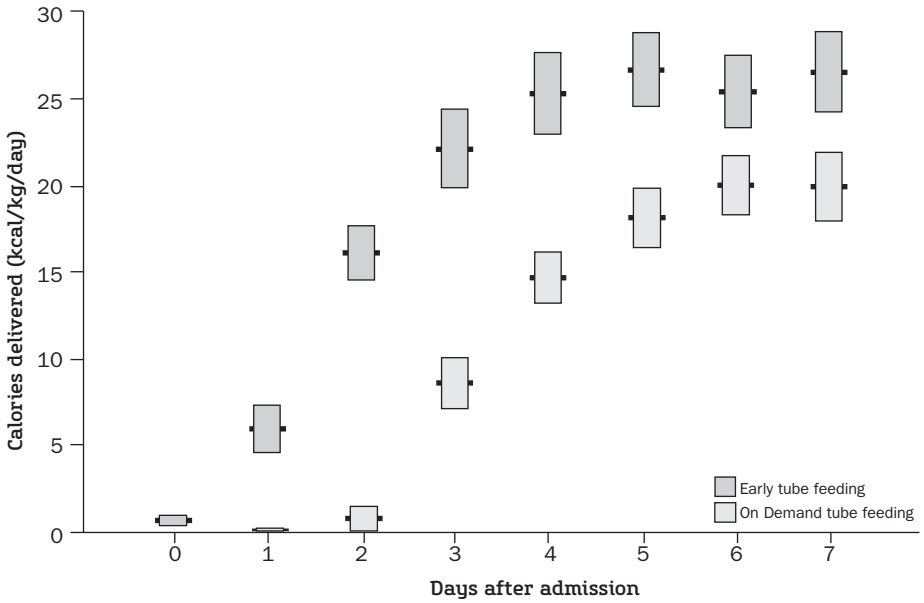

Figure 1. *Calories delivered with the use of early versus on-demand nasoenteric tube feeding. Each rectangle shows the mean value (horizontal line) and 95% confidence interval (top and bottom of the rectangle).*

Caption Table 1 ►

 # Data: no. (%) ⋆ Plus–minus values are means ±SD. There were no significant between-group differences at baseline, except for bodymass index (p=0.01).

† Body-mass index is the weight in kilograms divided by the square of the height in meters. ‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease.[34] § Patients with an APACHE II score of 13 or higher constituted a predefined subgroup. ¶ Imrie or modified Glasgow[35] scores range from 0 to 8, with higher scores indicating more severe disease. ‖ The systemic inflammatory response syndrome (SIRS) was diagnosed with the use of the Consensus Conference criteria of the American College of Chest Physicians–Society of Critical Care Medicine. ⋆⋆ Organ failure was defined as a modified Marshall score of 2 or more (on a scale of 0 to 12, with higher scores indicating more severe disease), as proposed in the revised Atlanta classification of acute pancreatitis.[45] Multiple organ failure was defined as failure of two or more organs on the same day.

Table 1. Characteristics of the patients at baseline.

Characteristic	Early Tube Feeding (N=101)	On-Demand Tube Feeding (N=104)
Female sex#	46 (46)	45 (43)
Age – yr*	65±16	65±15
Cause of pancreatitis#		
Gallstones	59 (58)	56 (54)
Alcohol abuse	14 (14)	23 (22)
Other	28 (28)	25 (24)
Body-mass index – no./total no. (%)†		
<25	20/99 (20)	33/103 (32)
25 to <35	69/99 (70)	67/103 (65)
≥35	10/99 (10)	3/103 (3)
Disease severity		
APACHE II score‡		
Mean*	11±4	11±5
≥13§	32 (32)	29 (28)
Imrie or modified Glasgow score¶		
Median	2	2
Range	0-6	0–5
C-reactive protein – mg/liter		
Median	70	75
Interquartile range	21-179	11-189
SIRS#‖	63 (62)	70 (67)
Respiratory failure#	30 (30)	27 (26)
Multiple-organ failure#**	6 (6)	5 (5)
Duration – hr		
Onset of symptoms to presentation at the emergency department		
Median	12	13
Interquartile range	5-28	4-33
Presentation at the emergency departement to randomization		
Median	13	11
Interquartile range	5-19	4-19

Results

Enrollment and randomization

From August 2008 through June 2012, a total of 867 patients were assessed for eligibility (Figure A1 in the Appendix). A total of 208 patients (24%) were enrolled and randomly assigned to early nasoenteric tube feeding (102 patients) or an oral diet with tube feeding if required (106). The adjudication committee excluded 3 patients who had undergone randomization and had been incorrectly diagnosed with acute pancreatitis (2 patients had gastric carcinoma and 1 had intestinal volvulus). A total of 101 patients in the early group and 104 in the on-demand group were included in the intention-to-treat analysis. Baseline characteristics, presented in Table 1, were equally distributed between the groups except for the mean (±SD) BMI (29±5 in the early group vs. 27±5 in the on-demand group, p=0.01).

Details regarding the number of calories delivered during the first week after admission and the timing of feeding are shown in Figure 1, and in Table S1 in the online Supplementary Appendix. As specified by the protocol, patients in the early group received feeding earlier than those in the on-demand group. Nasoenteric tube feeding in the early group was started a median of 8 hours after randomization and a median of 23 hours after presentation to the emergency department, as compared with initiation of an oral diet 64 hours after randomization and 72 hours after presentation in the on-demand group (p<0.001) (Table S1 in the online Supplementary Appendix). A total of 5 of 104 patients (5%) assigned to ondemand feeding requested and received food within the first 72 hours after presentation.

Outcomes

Primary End Point

The primary composite end point of major infection or death occurred in 30 patients (30%) in the early group, as compared with 28 (27%) in the on-demand group (risk ratio, 1.07; 95% confidence interval [CI], 0.79 to 1.44; absolute risk difference, 3 percentage points; 95% CI, -9 to 15; p=0.76). Major infections occurred in 25% of the patients in the early group and in 26% of those in the on-demand group (p=0.87) (Table 2). Mortality was 11% in the early group, as compared with 7% in the on-demand group (p=0.33), and most of the deaths were related to persistent multiple organ failure (defined as failure of two or more organs on ≥3 consecutive days).

Table 2. Primary and secondary end points, according to the intention-to-treat analysis.

Outcome	Early Tube Feeding (N=101)	On-Demand Tube Feeding N=104)	Risk Ratio (95% CI)	p-value
Primary composite end point:				
Infection or death[#]	30 (30)	28 (27)	1.07 (0.79–1.45)	0.76
Secondary end points:				
Infection[#†]	25 (25)	27 (26)	0.97 (0.70–1.34)	0.87
Infected pancreatic necrosis	9 (9)	15 (14)	0.74 (0.43–1.26)	0.28
Bacteremia	17 (17)	18 (17)	0.98 (0.68–1.43)	1.00
Pneumonia	12 (12)	13 (13)	0.97 (0.63–1.50)	1.00
Death[#]	11 (11)	7 (7)	1.27 (0.85–1.89)	0.33
Necrotizing pancreatitis[#‡]	64 (63)	65 (62)	1.06 (0.77–1.47)	0.76
CT severity index[*§]	4±2	4±3	-	0.29
ICU admission after randomization[#]	18 (18)	20 (19)	0.95 (0.66–1.38)	0.86
Mechanical ventilation[#]	12 (12)	14 (13)	0.93 (0.60-1.44)	0.84
New-onset organ failure – no./total no. at risk (%)[¶]				
Single organ failure	26/67 (39)	31/73 (43)	0.92 (0.65–1.32)	0.73
Persistent single organ failure	10/67 (15)	10/73 (14)	1.05 (0.65–1.70)	1.00
Multiple organ failure	7/67 (10)	6/73 (8)	1.14 (0.67–1.95)	0.77
Persistent multiple organ failure	4/67 (6)	4/73 (5)	1.05 (0.51–2.14)	1.00

*# Data: no. (%) * Plus-minus values are means ±SD. Risk ratios are for early tube feeding as compared with on-demand tube feeding. ICU denotes intensive care unit. † Patients may have had more than one type of infection. ‡ Necrotizing pancreatitis was defined as pancreatic parenchymal necrosis or extrapancreatic necrosis.*[45,46] *In nine patients (9%) in the early group and seven (7%) in the on-demand group, no CT was performed. § Scores on the CT severity index range from 0 to 10, with higher scores indicating more extensive pancreatic or extrapancreatic necrosis. ¶ New-onset organ failure was defined as organ failure that was not present at randomization. Persistent organ failure was defined as organ failure present on 3 or more consecutive days (>48 hours). Multiple organ failure was defined as failure of two or more organs on the same day.*

Table 3. Nutrition tolerance and gastrointestinal events.*

Outcome	Early Tube Feeding (N=101)	On-Demand Tube Feeding (N=104)	Risk Ratio (95% CI)	p-value
Nutrition variable				
Need for nasoenteric feeding tube#	NA	32 (31)	-	-
Dislodging of nasoenteric feeding tube – no./total no. (%)†	38/99 (38)	14/32 (44)	0.95 (0.77-1.16)	0.68
Obstruction of nasoenteric feeding tube – no./total no. (%)†	11/99 (11)	4/32 (12)	0.97 (0.70-1.33)	0.76
Need for insertion of nasogastric tube for decompression#‡	19 (19)	23 (22)	0.90 (0.62-1.30)	0.61
Need for parenteral nutrition#‡	5 (5)	10 (10)	0.66 (0.32-1.37)	0.28
Days from admission to full tolerance of oral diet§			-	0.001
Median	9	6		
Interquartile range	6-12	5-10		
Gastrointestinal event#¶				
Nausea	32 (32)	37 (36)	0.91 (0.68-1.24)	0.66
Vomiting	19 (19)	26 (25)	0.82 (0.57-1.20)	0.31
Aspiration‖	0	4 (4)	-	0.12
Ileus**	10 (10)	11 (11)	0.96 (0.60-1.54)	1.00
Diarrhea	21 (21)	29 (28)	0.81 (0.57-1.17)	0.26

*# Data: no. (%) * NA denotes not applicable. † Dislodging or obstruction of the nasogastric tube was noted in case-record forms by the attending physician or nurse. The denominator is the number of patients who had a feeding tube inserted. Two patients in the early group declined tube feeding. ‡ The need for a nasogastric tube to be inserted for decompression or the need for parenteral nutrition was indicated by the attending physician. § Full tolerance of an oral diet was defined as tolerance of the oral diet without receipt of any other type of nasoenteric or parenteral nutrition. ¶ Gastrointestinal events were assessed during each day of the hospital stay. ‖ Data are for suspected aspiration as noted by a physician or nurse in the case-record forms. ** Ileus was diagnosed by the attending physician and noted in the case-record forms.*

Secondary End Points

Necrotizing pancreatitis developed in 63% of the patients in the early group and in 62% of those in the on-demand group. A total of 18% of the patients in the early group and 19% of those in the on-demand group required ICU admission (Table 2).

In the on-demand group, 32 patients (31%) required nasoenteric tube feeding; 72 patients (69%) tolerated an oral diet and did not require tube feeding (Table 3). In 9 of these 32 patients (28%), tube feeding was prompted by the use of mechanical ventilation. The on-demand tubefeeding strategy reduced the number of days to full tolerance of an oral diet (9 days with the early strategy versus 6 days with the on-demand strategy, p=0.001). Gastrointestinal events occurred frequently, but the frequency did not differ significantly between the groups.

Attenuation of the acute inflammatory response was hypothesized to be part of the beneficial effect of early feeding. However, such an effect did not occur (Figure S3 in the online Supplementary Appendix).

In a predefined subgroup analysis restricted to patients with an APACHE II score of 13 or higher at randomization, the occurrence of the primary end point did not differ significantly between the two treatment groups (Table S3 in the online Supplementary Appendix). Post hoc subgroup analyses also did not show a significant between-group difference in the primary end point for patients with SIRS at randomization or those with a BMI of less than 25 or 35 or more (Table S3 in the online Supplementary Appendix). No significant differences were observed in health care utilization except for the number of tube placements (145 tube placements in the early group versus 57 in the on-demand group, p<0.001) (Table S4 in the online Supplementary Appendix).

Discussion

This multicenter, randomized trial involving patients with acute pancreatitis who were at high risk for complications did not show that an early start of nasoenteric tube feeding was superior to the introduction of an oral diet after 72 hours, with tube feeding only if required, in reducing the composite end point of major infection or death. With the oral diet and on-demand tubefeeding strategy, only approximately one third of patients required a nasojejunal feeding tube.

The absolute between-group difference in the primary end point was 3 percentage points, with the 95% confidence interval ranging from 9 percentage points lower to 15 percentage points higher. These findings do not support clinical guidelines recommending the early start of nasoenteric tube feeding in all

patients with severe acute pancreatitis in order to reduce the risks of infection and death. However, this trial was not powered to exclude a substantial benefit of early feeding.

The results of our trial differ from those of previous trials and observational studies.[12,23-26] Previous trials showed an improved outcome after early nasoenteric tube feeding as compared with total parenteral nutrition. This may be explained in part by complications associated with providing total parenteral nutrition, such as catheter-related infections.[21] The negative outcome of our study, as compared with the outcomes in these previous trials, is not explained by differences in the timing of early tube feeding or the severity of pancreatitis in the study participants. The timing of early nasoenteric tube feeding in our study was similar to the timing in the previous studies. In addition, we used similar criteria for enrolling patients at high risk for complications, and we observed similar rates of major infection and death.

Previous observational studies investigating the initiation of nasoenteric tube feeding within 48 hours after admission, as compared with initiation more than 48 hours after admission, cannot differentiate between cause and effect (i.e., less severely ill patients may have been fed earlier). This is in line with a recently revived debate on the presumed benefit of early enteral feeding in critically ill patients in general. Early enteral feeding is recommended in most current ICU guidelines.[38,47] However, the methodologic quality of the trials that form the basis for these general ICU recommendations has been criticized.[48] Thus, for critically ill patients in general and for those with acute pancreatitis specifically, large, high-quality, randomized, controlled trials that show an improved outcome with early enteral feeding are lacking.[49]

There are several possible explanations for the negative result of our study. First, early enteral feeding may not be as effective as we anticipated. Our hypothesis was that the trophic effect of early enteral feeding would stabilize the integrity of the gut mucosa, reducing inflammation and improving the outcome. Early enteral feeding was not associated with a reduction in any of the variables indicating inflammation (Figure S3 in the online Supplementary Appendix). We did not evaluate gut permeability and bacterial translocation on the basis of the serum intestinal fatty acid-binding protein level or endotoxin exposure.[17,50] Therefore, we cannot determine whether gut permeability was influenced by early feeding in a subset of our patients. Increased gut permeability and bacterial translocation may be restricted to patients with acute pancreatitis who have multiple organ failure,[14] a subgroup that accounted for only a small fraction of the patients in this trial. However, a study of acute pancreatitis in which the rates of multiple organ failure and death were similar

to the rates in our study did show an increase in gut permeability and endotoxin exposure in most patients with severe acute pancreatitis.[51]

Another possibility is that tube feeding in the early group in our trial should have been started even earlier. In a trial involving a small number of patients at one center, it would be possible to start nasogastric tube feeding some hours earlier by using a feeding tube that could be placed at the bedside. In daily practice, however, we believe that an earlier start of tube feeding would not be feasible. Starting an oral diet later in the on-demand group in order to increase the difference in timing between the two study groups would not be ethical because it would put patients at risk for malnutrition.

A third explanation for the negative result may be that the study was too small to detect a difference between the two groups. To our knowledge, this is the largest trial of nutrition in patients with acute pancreatitis that has been performed so far, but the wide confidence interval for the primary end point may indicate that an even larger trial is needed.

Fourth, the widely accepted scoring systems for prediction of severity in acute pancreatitis are only moderately accurate.[52] In early-intervention studies in acute pancreatitis, it is therefore unavoidable that mild or moderate disease will develop in a proportion of patients who were classified at presentation as having severe pancreatitis. Nevertheless, at randomization, approximately one third of our patients had organ failure and two thirds had SIRS. Organ failure is one of the determinants of severe pancreatitis, and SIRS is increasingly recognized as an early indicator of severe pancreatitis.[30,45]

A feeding tube frequently causes discomfort, excessive gagging, or esophagitis and is often dislodged or becomes obstructed, which necessitates the replacement of the feeding tube.[53,54] If tube feeding were restricted to patients who could not tolerate an oral diet, this would result in substantial avoidance of discomfort and costs.

In conclusion, our trial did not show the hypothesized benefit of early nasoenteric tube feeding in patients with acute pancreatitis who were at high risk for complications. The observation that the clinical outcomes of early tube feeding were similar to those of an oral diet initiated at 72 hours, with tube feeding only if required, challenges the concept of the gut mucosa preserving effect of early enteral feeding during acute pancreatitis.

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APPENDIX CHAPTER 6

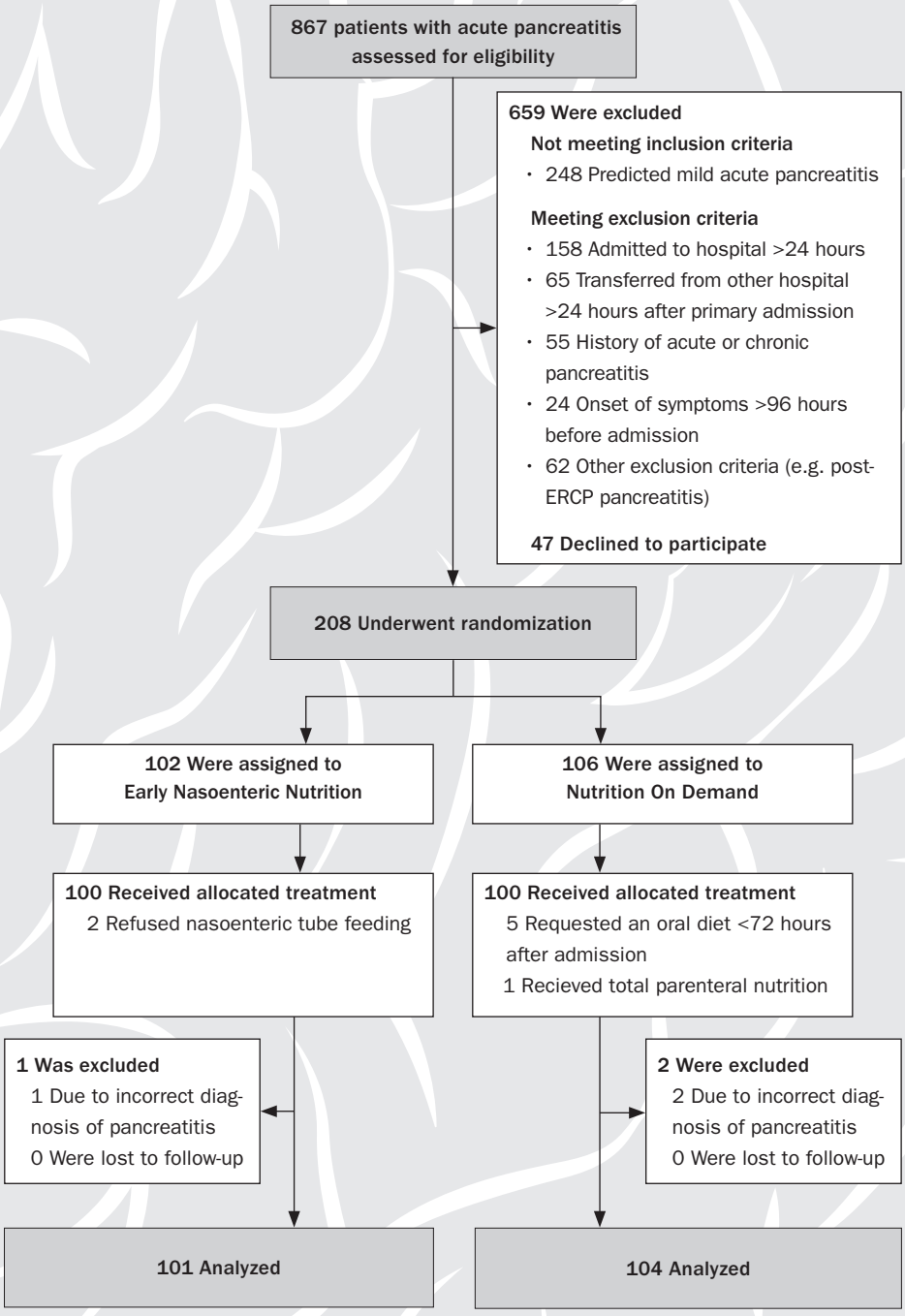

Figure A1. *Trial enrollment, randomization and follow-up.*

PART II

Treatment of severe pancreatitis

CHAPTER 7

Abdominal compartment syndrome in acute pancreatitis

A SYSTEMATIC REVIEW

Pancreas 2014

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Abstract

Abdominal compartment syndrome (ACS) is a lethal complication of acute pancreatitis. We performed a systematic review to assess the treatment and outcome of these patients.

A systematic literature search for cohorts of patients with acute pancreatitis and ACS was performed. The main outcomes were number of patients with ACS, radiologic and surgical interventions, morbidity, mortality, and methodological quality.

After screening 169 articles, 7 studies were included. Three studies were prospective and 4 studies were retrospective. The overall methodological quality of the studies was moderate to low. The pooled data consisted of 271 patients, of whom 103 (38%) developed ACS. Percutaneous drainage of intraabdominal fluid was reported as first intervention in 11 (11%) patients. Additional decompressive laparotomy was performed in 8 patients. Decompressive laparotomy was performed in a total of 76 (74%) patients. The median decrease in intraabdominal pressure was 15 mm Hg (range, 33-18 mm Hg). Mortality in acute pancreatitis patients with ACS was 49% vs. 11% without ACS. Morbidity ranged from 17% to 90%.

Abdominal compartment syndrome during acute pancreatitis is associated with high mortality and morbidity. Studies are relatively small and have methodological shortcomings. The optimal timing and method of invasive interventions, as well as their effect on clinical outcomes, should be further evaluated.

Introduction

Acute pancreatitis runs a severe course in around 20% of patients and is associated with a mortality rate of 8% up to 39%.[1] The most lethal complication in the course of severe acute pancreatitis is abdominal compartment syndrome (ACS). Abdominal compartment syndrome is defined by the World Society of Abdominal Compartment Syndrome (WSACS) as a life-threatening sustained elevation of the intraabdominal pressure (IAP) that is associated with new onset organ failure or acute worsening of existing organ failure.[2] Symptoms of ACS include a tensely dilated abdomen, oliguria, and increased peak airway pressure.[3,4] Intraabdominal pressure is preferably determined using a transurethral probe inserted in the urinary bladder (the transbladder technique).[2,4,5] A summary of the 2013 updated WSACS evidence-based guidelines is shown in Table 1.[2]

The pathophysiology of ACS in acute pancreatitis is thought to be directly related to the inflammation of the pancreas. This inflammation starts a cascade of pancreatic and visceral edema, acute peripancreatic fluid collections, capillary leakage causing ascites, paralytic ileus, and gastric dilatation by upper gastrointestinal tract obstruction leading to an elevated IAP.[6-8] An elevated IAP generally occurs relatively early (often within the first week) after onset of severe acute pancreatitis.[3,9] Abdominal compartment syndrome can also be the result of overly aggressive fluid resuscitation, and sometimes, large peripancreatic collections play a role.[10] Abdominal compartment syndrome can lead to reduced perfusion and subsequent ischemia of intraabdominal organs followed by further progression of the existing organ failure leading to a potentially lethal downward spiral.[5,8] The most affected organs by ACS are the lungs and kidneys.[4]

Because acute pancreatitis is a well-established risk factor for ACS, the 2013 WSACS guidelines recommend routinely measuring of IAP in critically ill patients with acute pancreatitis.[2] The diagnosis of ACS in severe acute pancreatitis is difficult because symptoms may resemble those of other complications, such as systemic inflammatory response syndrome, acute respiratory distress syndrome, infected necrosis, and multiple organ dysfunction syndrome.[4]

In daily practice, many patients with ACS undergo decompressive laparotomy, which obviously has a risk of complications. Therefore, numerous medical, nonmedical, and minimally invasive therapies have been introduced. Several authors, including the 2013 WSACS guidelines, advise percutaneous catheter drainage as the first step of invasive intervention[2,7,9] to potentially obviate the need for decompressive laparotomy.[2]

Various observational cohort studies on ACS in acute pancreatitis have been reported in recent years but much remains unknown about incidence,

diagnosis, clinical course, and optimal treatment. The aim of current study was to evaluate the published cohorts on ACS in acute pancreatitis for methodological limitations, differences in patient populations, treatment strategies, and outcome.

Table 1. Summary of the 2013 ACS guidelines.

	Evidence-based guidelines from the 2013 WSACS2
Definitions	• Intra-abdominal pressure (IAP): the steady-state pressure concealed within the abdominal cavity • Intra-abdominal hypertension (IAH): a sustained or repeated pathological elevation in IAP of ≥12 mmHg • Abdominal compartment syndroom (ACS): a sustained IAP of >20 mmHg (with or without an abdominal perfusion pressure of <60 mmHg) that is associated with new organ dysfunction/failure
Measurement method	**Recommendations:** • Measure IAP when any known risk factor for IAH/ACS is present in a critically ill or injured patient • The standard IAP measurement technique should be the trans-bladder technique. Intraabdominal pressure should be measured at end expiration in the supine position and expressed in millimetres of mercury
Noninvasive treatment	**Suggestions:** • Optimal pain and anxiety relief • Brief trials of neuromuscular blockade as a temporizing measure • Consider the potential contribution of body position to elevated IAP • Liberal use of enteral decompression • Neostigmine, used for the treatment of established colonic ileus • Avoid a positive cumulative fluid balance after the acute resuscitation
Minimal invasive treatment	**Suggestions:** • Use percutaneous catheter drainage to remove (obvious intraperitoneal) fluid (when technically feasible) as first step of treatment
Invasive treatment	**Recommendations:** • Decompressive laparotomy as second step of treatment in cases of overt ACS
Postoperative management	**Recommendations:** • Obtain an early or at least same-hospital-stay abdominal fascial closure in ICU patients with open abdominal wounds • Strategies using negative-pressure wound therapy should be used in patients with open abdominal wounds

Methods

Study Selection

We adhered to the preferred reporting items for systematic reviews and meta-analyses guidelines for reporting on meta-analyses and systematic reviews.[11] A systematic literature search from 1993 (publication of the Atlanta classification for acute pancreatitis[12]) to April 2013 was performed in the PubMed, Embase, and the Cochrane Library according to a protocol designed before data collection. Only articles in English language were included. The search terms are provided in online Supplemental Digital Content Appendix 1.

All titles and abstracts of studies identified by the initial search were screened to select those reporting on ACS in patients with acute pancreatitis. We excluded duplicate references and studies reporting the same data. Subsequently, full-text articles of the selected studies were screened independently by 2 authors to assess eligibility. All cross-references were screened for potentially relevant studies not identified by the initial literature search. The final decision on eligibility was reached by consensus among all authors

The inclusion criteria were as follows:

- a consecutive cohort of at least 30 patients with acute pancreatitis that includes a subgroup of patients with ACS; or
- a consecutive cohort of at least 10 patients with acute pancreatitis and ACS.

The exclusion criteria were as follows:

- no data available on treatment strategy for ACS, morbidity, and mortality;
- no data available on the subgroup of patients with ACS; or
- cohort including chronic pancreatitis (and results for acute pancreatitis not reported separately).

The cutoffs for minimal cohort sizes were arbitrarily chosen. We also performed a systematic search for ongoing randomized controlled trials on ACS in the World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), which includes data from 15 national and international trial registries. We used the search terms abdominal compartment syndrome, intraabdominal hypertension, intraabdominal pressure, and decompressive laparotomy (search date May 16, 2013).

Assessment of Study Quality

All included studies were assessed for quality using 3 previously validated checklists that scored the methodological quality of nonrandomized studies.[13-15] Downs and Black[13] described a checklist with 27 items that can be used for quality assessment for both randomized and nonrandomized studies. The methodological index for non-randomized studies (MINORS) checklist contains

8 items for noncomparative studies and 12 items for comparative studies.[14] MacLehose et al[15] used a modified Downs and Black[13] checklist, which consists of 29 items. In all 3 lists, a low score reflects a high risk of bias, whereas a high score reflects a low risk of bias. To facilitate comparison of these checklists, each score was converted to a score on a 0 to 10 scale as previously reported.[16] No studies were excluded based on their score. The mean of the 0 to 10 scales of all 3 checklists was calculated to determine methodological quality. We defined high methodological quality as a score higher than 8, moderate quality as a score of 6 to 8, moderate-to-low quality as a score of 4 to 6, and low quality with a score lower than 4.

Data Extraction

The following variables were extracted, where available, from the included articles: number of patients with ACS, definition of ACS used, method of IAP measurement, age, sex, etiology, predictive severity scores (e.g., Imrie/modified Glasgow score and Acute Physiology and Chronic Health Evaluation [APACHE] II score), organ failure and intensive care unit (ICU) admission before intervention, computed tomography (CT) severity scores (CT severity index,[17] modified CT severity index,[18] and Balthazar grade[19]), time between hospital admission and occurrence of ACS, IAP, interval between elevated IAP and ACS, interval between elevated IAP and intervention, type of intervention for decompression, total number of interventions, success of intervention on lowering IAP and improving outcome, total length of ICU and hospital stay, complications, and mortality.

The data were extracted for calculation of mortality as primary outcome measure. The numerator for calculation was represented by the number of patients who died. The denominator was represented by the total number of patients with ACS and acute pancreatitis.

Data Analysis

The data were analyzed and reported to describe methodological quality, characteristics of included studies, patient characteristics, and outcome. The baseline characteristics were assessed to determine whether selection bias might have played a role in the outcome of ACS.

Statistical Analysis

Descriptive statistics were used to describe baseline characteristics and outcome variables for all studies separately and for the pooled data. To pool the data of continuous outcomes in systematic reviews, the mean values are

needed. Published studies, however, often only report median, range, and sample size. Hozo et al[20] described a method to calculate the mean using the values of the median, and low and high end of the range. Using this method, we were able to present all data as means and calculated weighted means. Comprehensive Meta-analysis version 2 (Borenstein M, Hedges L, Higgins J et al; Biostat, Englewood, NJ, 2005) was used to generate a forest plot and I^2 to assess the heterogeneity of the results. The I^2 statistic indicates the proportion of total variation among the effect estimates attributed to heterogeneity rather than sampling error and has the advantage of being intrinsically independent of the number of studies. When the test of heterogeneity was not significant ($p>0.05$) and I^2 was less than 30%,[21,22] significant heterogeneity was ruled out.

Results

Literature Search

After removing duplicates, the systematic literature search identified 169 potentially relevant articles. The study selection flow chart is shown in Figure 1. Of the 169 articles, 162 were excluded after reviewing title, abstract, and full-text for the following reasons: non-English articles (N=37), cohorts of patients also including carcinoma, chronic pancreatitis, pancreatic pseudocysts, or pancreatic tuberculosis and results of these subgroups were not reported separately (N=10), cohorts of patients with no information on ACS (N=14), cohorts with fewer than 30 patients with acute pancreatitis or fewer than 10 patients with acute pancreatitis and ACS (N=16), cohorts with solely nonpancreatic disease (N=28), or patients with no pancreatitis (N=13), cohorts who did not report 1 or more essential outcome (i.e., no data on treatment strategy, morbidity, or mortality; N=7), and cohorts excluded because of other reasons (e.g., unable to retrieve IAP, reviews, animal studies or case reports; N=37).

The systematic search for (ongoing) randomized controlled trials identified 1 relevant study (ClinicalTrials.gov, NCT00793715).[23] This DECOMPRESS trial is a multicenter study comparing percutaneous catheter drainage with decompressive laparotomy in patients with ACS during severe acute pancreatitis.

Study Characteristics

In total, 7 studies were included in this systematic review.[3,7,9,24-27] The study characteristics are summarized in Table 2. There were no randomized controlled trials.

Three studies were prospective observational cohort studies[3,24,27] and 4 studies were retrospective observational cohort studies.[7,9,25,26]

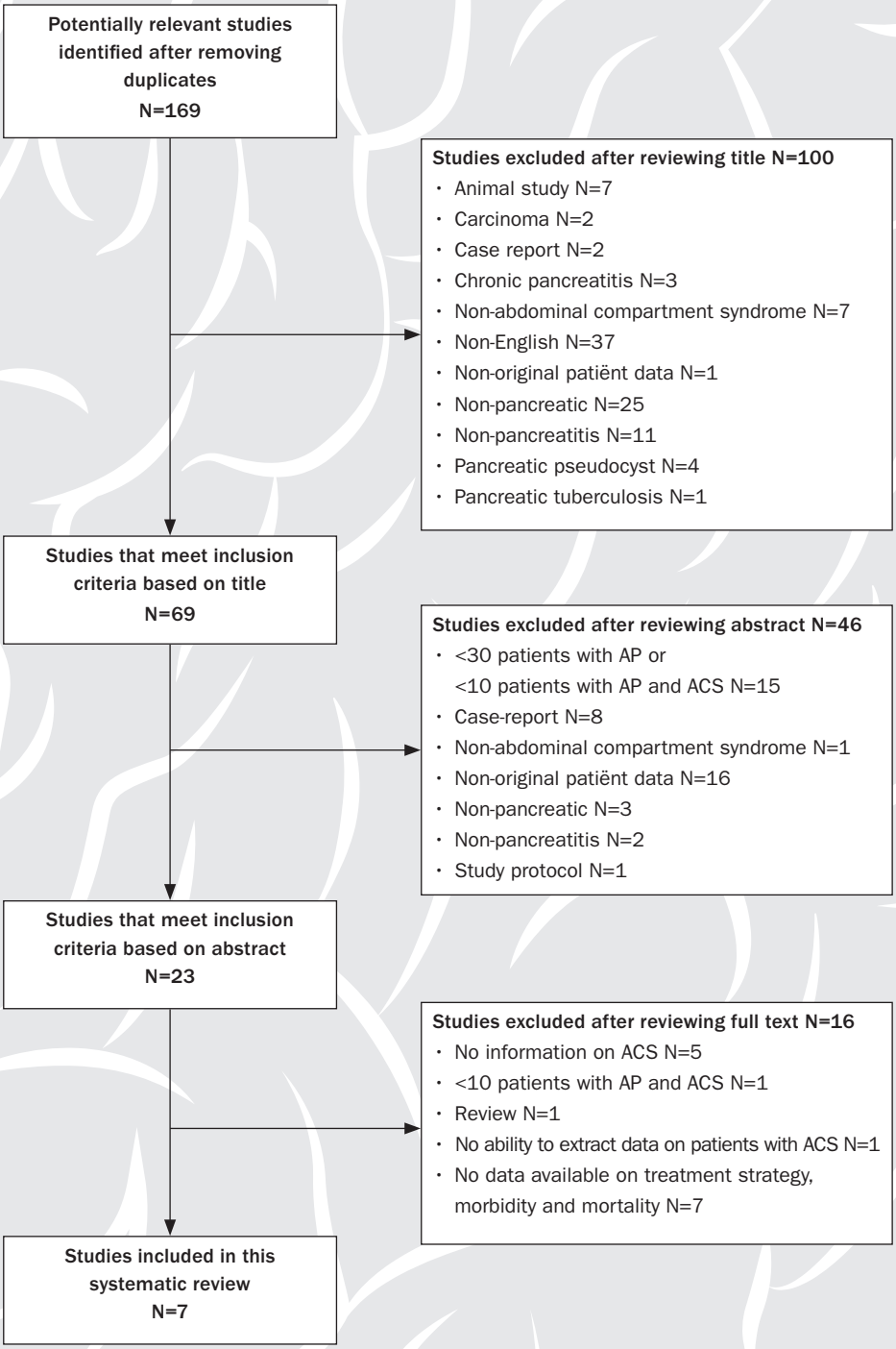

Figure 1. *Study selection flow chart.*

Table 2. Characteristics of the included studies.

Authors	Country	Year	Study design	Inclusion criteria
Bezmarevic et al[24]	Serbia	2012	Prospective observational cohort	Acute pancreatitis (APACHE II score ≥8 and CRP ≥120mg/L) ACS (IAP >20mmHg and new organ dysfunction)
Chen et al[9]	China	2008	Retrospective cohort	Acute pancreatitis (Atlanta criteria) ACS (criteria of the WSACS)
Davis et al[25]	Canada	2013	Retrospective cohort	Acute pancreatitis (Atlanta criteria) ACS (IAP >20 mmHg associated with acute organ failure)
De Waele et al[3]	Belgium	2005	Prospective observational cohort	Severe acute pancreatitis (Atlanta criteria) ACS (no definition reported)
Leppäniemi et al[26]	Finland	2011	Retrospective cohort	Severe acute pancreatitis (Atlanta criteria) ACS (no definition reported)
Mentula et al[7]	Finland	2010	Retrospective cohort	Severe acute pancreatitis (Atlanta criteria) ACS (IAP >20mmHg and new organ dysfunction)
Tao et al[27]	China	2003	Prospective observational cohort	Severe acute pancreatitis (diagnostic criteria Chinese Medical Association (1996)) ACS (Banks and Freeman[1])

Table 3. Methodological quality of the included studies.

Authors	MINORS checklist	0-10	Checklist for nonrandomized trials
Bezmarevic et al[24]	6	3.8	13
Chen et al[9]*	12	5.0	19
Davis et al[25]*	12	5.0	18
De Waele et al[3]*	10	4.6	14
Leppaniemi et al[26]	2	1.3	7
Mentula et al[7]	3	1.9	10
Tao et al[27]	1	0.6	4

Technique used	Total no. patients	No. patients with ACS	Study period (month)
Decompressive laparotomy, percutaneous abdominal decompression and drainage	51	6	2009-2010 (14)
Enterokinesia, percutaneous abdominal decompression and drainage and/or decompressive laparotomy	74	20	2002-2006 (48)
Decompressive laparotomy	45	16	2005-2009 (48)
Decompressive laparotomy	44	4	2000-2004 (52)
Subcutaneous linea alba fasciotomy	10	10	Not reported
Surgical decompression	26	26	2002-2007 (60)
Surgical decompression	21	21	1998-2003 (55)

0-10	MacLehose checklist	0-10	Mean MINORS, Downs, and MacLehose checklist
4.6	24	6.0	4.8
6.8	28	7.0	6.3
6.4	30	7.3	6.2
5.0	25	6.2	5.3
2.5	15	3.7	2.5
3.6	22	5.5	3.7
1.4	13	3.2	1.7

From 4 studies, a selection of the reported cohort was included because this subgroup had ACS, fulfilled the selection criteria, and the outcomes were reported separately.[3,9,24,25] Four studies used the definition of ACS proposed by the 2013 WSACS guidelines, one study used a different definition, and 2 studies did not report definitions used.

Methodological Quality

The quality scores are shown in Table 3. There were no studies that scored high on methodological quality. Two studies scored moderate,[9,25] 2 studies scored moderate to low,[3,24] and 3 studies scored low.[7,26,27]

Patient Characteristics

The included studies comprised a total of 271 patients with acute pancreatitis and 103 patients with acute pancreatitis and ACS. The number of patients per study ranged from 10 to 74. Three studies included only patients with acute pancreatitis and ACS.[7,26,27] The other 4 studies were cohorts of patients with acute pancreatitis with a subgroup of patients who developed ACS. One study included 21 patients with ACS but described 23 ACS episodes because 2 patients had a recurrent episode of ACS.

Patient characteristics of the individual studies are shown in Table 4. The weighted means of baseline characteristics are given in Table 5. Three studies did not report patient characteristics on the subgroup of patients with ACS but for the entire cohort or a selection of patients with intraabdominal hypertension (IAH).[3,9,24] A total of 74% of all patients were male, and the mean age was 53 years. Six studies (146/271 patients) reported on etiology, which was alcoholic in 56 (38%) patients, biliary in 53 (36%) patients, hyperlipidemia in 15 (10%) patients, iatrogenic in 5 (3%) patients, and of other origin in 17 (8%) patients. The mean follow-up was 51 months (Table 2).

Of the 7 studies, 5 (67/103 patients) reported APACHE II scores. The mean APACHE II score was 18. All 7 studies reported organ failure. However, different definitions for organ failure were used. Five studies (76/103 patients) reported ICU admission, and all patients in these studies were admitted to the ICU. Seven studies reported the IAP. The mean IAP 24 hours after admission was 28 mm Hg. The difference in IAP between patients with acute pancreatitis and ACS and patients with acute pancreatitis without ACS was not reported. The prevalence of IAH was reported in all studies; the overall prevalence was 66% (149/226 patients). The overall study prevalence of ACS in the included cohorts was 38% (103/271 patients). Three studies reported only patients with acute pancreatitis and ACS. When these studies were excluded, the study prevalence of IAH and

ACS was 54% (92/169 patients) and 22% (46/214 patients), respectively. There was significant heterogeneity for prevalence (I^2=76%, p=0.006). The average number of days between diagnosis of ACS and first intervention was less than 1, as was reported in 5 studies.

Outcome

The clinical outcome of patients with acute pancreatitis and ACS in the individual studies is shown in Table 6 and the calculated weighted means in Table 5.

Of the 103 patients with ACS, 87 (84%) underwent an invasive intervention; this was reported in all studies. The type of first intervention was reported in 6 studies and was percutaneous catheter drainage of intraabdominal fluid in 11 (13%) patients and surgical decompression in 76 (87%) patients. No operation was performed in 16 (16%) of the 103 patients with ACS. In 8 (73%) patients with percutaneous drainage as first intervention, additional surgical decompression was necessary. Surgical decompression consisted of a full-thickness midline laparotomy (N=66), a subcutaneous linea alba fasciotomy (N=17), or full- thickness transverse bilateral subcostal laparotomy (N=1). Patients underwent a median of 4 operations (range, 1-4), as was reported in 3 studies (42/103 patients).

Four studies (60/109 patients) reported the decrease in IAP after surgical decompression. The median IAP decreased from 33 (range, 30-36 mm Hg) to 18 mm Hg (range, 15-20 mm Hg). In these studies, elevated IAP was associated with concomitant organ failure. Three studies reported the effect of decompression on organ failure.[3,9,26] In 1 study, the authors reported a significant difference in improvement of physiologic parameters (i.e., mean arterial pressure, heart rate, arterial oxygenation, and urine output) within 24 hours after decompression.[9] Both other studies[3,26] used different methods of reporting organ failure (i.e., the percentage of patients with organ failure, Multiple Organ Dysfunction Score [MODS] or Sequential Organ Failure Assessment [SOFA] score) before and after decompression. Therefore, comparison of results was not possible.

The overall mortality rate (including patients without ACS) was 26% (69/271 patients), with a range of 18% to 46% per study. The overall mortality rate in patients with acute pancreatitis and ACS was 49% (50/103 patients), with a range of 25% to 83% per study. Mortality in the ACS subgroup is shown in a forest plot (Figure 2). There was substantial heterogeneity for mortality (I^2=57%, p=0.03). The mortality in patients with acute pancreatitis without ACS was 11% (19/168 patients).

Table 4. Patient characteristics of the included studies.

Study	No. patients wtih ACS	M/F (%)	Mean age	Etiology	Mean APACHE II score	Mean Glasgow-Imrie score on admission	Mean CRP	Ranson score
Bezmarevic et al[24]	6	23/6 (79/21)*	55*	A:6 B:13 Hy: 5 Ia: 1 O: 4*	16*	nr	180*	nr
Chen et al[9]	20	23/21 (52/48)†	63†	A:5 B:26 Hy:7 O:6†	16†	nr	nr	4†
Davis et al[25]	16	16/0 (100/0)	56	A:7 B:7 Ia: 0 O:2	23	10	nr	6
De Waele et al[3]	4	15/6 (71/29)‡	53‡	A:8 B:7 Hy:3 O:3‡	21‡	nr	34‡	7‡
Leppäniemi et al[26]	10	9/1 (90/10)	46	A:9 Ia:1	nr	nr	nr	nr
Mentula et al[7]	26	23/3 (88/12)	42	A:21 Ia: 3 O: 2	nr	nr	nr	nr
Tao et al[27]	21	14/7 (67/34)	41	nr	19	nr	nr	nr

** No data available on patients with ACS only, data reported of whole cohort of patients with acute pancreatitis. † No data available on patients with ACS only, data reported for patients with IAP >12 mm Hg. ‡ No data available on patients with ACS only, data reported for patients with IAP >15 mm Hg. A, indicates alcoholic; B, biliary; Hy, hyperlipidemia; Ia, iatrogeneous; nr, not reported; O, other; SAP, severe acute pancreatitis.*

Pancreatic necrosis, N (%)	Patients admitted in ICU, N (%)	Organ failure, N (%)	Mean IAP (24 h of admission), mmHg	Time of admission after disease onset, d	Mean time SAP to ACS, d	IAH in whole cohort, N (%)	ACS in whole cohort, N (%)	Mean diagnosis ACS to first intervention, d
25 (86)*	nr	Single, 5 (17) Multiple, 24 (83)*	15*	1*	8*	27 (53)	6 (12)*	1*
nr	20 (100)	MODS, 18	37	nr	1	44 (60)	20 (27)	1
nr	16 (100)	SOFA, 9	29	nr	nr	nr	16 (36)	1
20 (95)‡	21 (100)‡	Pulmonary, 20 (95) Cardiovascular, 19 (91); Renal, 18 (86)‡	37	nr	nr	21 (48)‡	4 (9)	nr (6 within 2 d, overall range, 1-17)
nr	10 (100)	SOFA, 12	31	nr	nr	10 (100)	10 (100)	nr
nr	26 (100)	SOFA, 12	31	2	nr	26 (100)	26 (100)	1
nr	nr	Pulmonary, 21 (100); Cardiovascular, 21 (100); Renal, 21 (100)	32	nr	28	21 (100)	21 (100)	1 (9 within 5 h, 6 within 5-10 h, 1 after 14 h, 1 after 19 h, and 1 after 22 h)

Table 5. Weighted means for baseline and outcome.

	No. studies	No. patients	Mean
Follow-up, mo	6	93	39
Methodological quality	7	103	4.4
Sex (M/F), %	7	167	74/26
Age, y	7	167	53
Etiology (B, A, Ia, Hy, O), %	6	146	A, 38; B, 36; Hy, 10; Ia, 3; O, 13
APACHE II	5	131	18
CRP	2	50	119
RANSON	3	81	5
Glasgow-Imrie	1	16	10
ICU admission, %	5	93	100
IAP, mmHg	7	126	28
IAH, %	6	226	66
ACS, %	7	271	38
Time from onset of symptoms to admission, d	2	55	1
Time SAP to ACS, d	3	70	12
Diagnosis of ACS to first intervention, d	5	112	<1
No. patients undergoing interventions, %	7	103	100
Decompressive laparotomy as first intervention, %	7	103	74
Percutaneous intervention as first intervention, %	7	103	11
No operation for ACS, %	7	103	16
Midline laparotomy, %	7	103	67
Bilateral subcostal laparotomy, %	7	103	1
Subcutaneous linea alba fasciotomy, %	7	103	17
Decrease of IAP after surgical decompression, mmHG	4	60	15
Median no. reoperations per patient	3	42	3
Total hospital stay, d	3	47	76
Total ICU stay, d	2	31	23
Mortality in the ACS group, %	7	103	49
Mortality in patients without ACS, %	4	168	11
Mortality in whole cohort, %	7	271	26
Complications (total in all cohorts)	7	103	158
Pancreatic infection, %	2	46	52
Septic shock, %	3	47	47
MODS, %	3	34	68
Enterocutaneous fistula, %	3	52	23
Pancreatic fistula, %	3	52	6
Intraabdominal infection, %	3	57	39
Incisional hernia, %	2	26	46

A, indicates alcoholic; B, biliary; Hy, hyperlipidemia; Ia, iatrogeneous; O, other; SAP, severe acute pancreatitis.

All studies (103 patients) reported the number of complications; a total of 158 complications were described. Two studies reported pancreatic infection as complication in 24 (52%) of the 46 patients with ACS. Three studies reported on septic shock, which occurred in 22 (47%) of the 47 patients. Enterocutaneous and pancreatic fistulas were reported in 3 studies and occurred respectively in 12 (23%) and 3 (6%) of the 52 patients with ACS. Two studies reported on incisional hernia, which occurred in 12 (46%) of the 26 patients. The first study applied temporary abdominal closure after decompressive laparotomy in all patients followed by delayed abdominal closure (11/ 16 patients) or split-thickness skin graft (5/16 patients).[25] The other study performed a subcutaneous linea alba fasciotomy in all patients; 4 patients required additional laparostomy.[26]

The mean total hospital stay for patients with ACS was 76 days; this was reported in 3 studies (47/109 patients). The total mean ICU stay was 23 days.

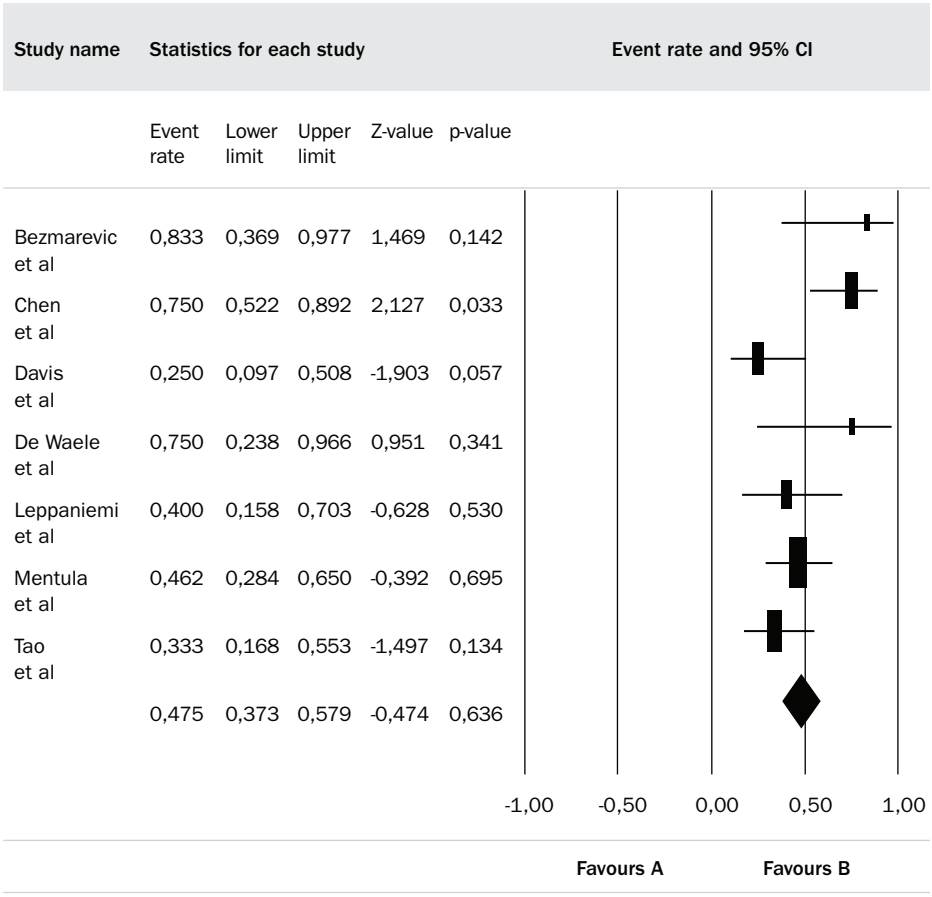

Figure 2. *Forest plot of included studies analyzing mortality of ACS. I^2=57%, p=0.03*

Table 6. Outcome of patients with ACS.

Study	ACS, %	No. patients undergoing intervention	Decompressive laparotomy as first intervention, N (%)	Percutaneus drainage as first intervention, N (%)	No operation for ACS, N (%)	Midline laparotomy, N (%)	Transverse bilateral subcostal laparotomy, N (%)	Subcutaneous linea alba fasciotomy, N (%)	Decrease of IAP after surgical decompression, mmHg	Median No. reoperations per patient	Total hospital stay, d	Total ICU stay, d	Mortality in the ACS group, N (%)
Bezmarevic et al[24]	6 (12)	6 (100)	2 (33)	3 (50)	1 (17)	5 (83)	0	0	nr	1	nr	nr	5 (83)
Chen et al[9]	20 (27)	20 (100)	0	8 (40)	12 (60)	5 (25)	0	0	18	nr	nr	nr	15 (75)
Davis et al[25]	16 (36)	16 (100)	16 (100)	0	0	16 (100)	0	0	nr	nr	146	nr	4 (25)
De Waele et al[3]	4 (9)	4 (100)	4 (100)	0	0	4 (100)	0	0	19	nr	42*	21*	3 (75)
Leppäniemi et al[26]	10 (100)	10 (100)	10 (100)	0	0	0	0	10 (100)	10	1	35	26	4 (40)
Mentula et al[7]	26 (100)	26 (100)	26 (100)	0	0	18 (69)	1 (4)	7 (27)	15	4	nr	nr	12 (46)
Tao et al[27]	21 (100)	21 (100)	18 (86)	0	3 (14)	18 (86)	0	0	nr	nr	nr	nr	7 (33)

All data are reported as mean.

** indicates available on patients with ACS only, data reported for patients with IAP >15 mm Hg.*

nr, indicates not reported.

Mortality in patients with acute pancreatitis without ACS, N (%)	Mortality in whole cohort, N (%)	Complications	Pancreatic Infection	Septic Shock	MODS	Enterocutaneous fistula	Pancreatic fistula	Intraabdominal infection	Incisional hernia	Other
4 (9)	9 (18)	1	nr	1	nr	nr	nr	nr	nr	nr
2 (4)	17 (23)	44	12	14	18	nr	nr	nr	nr	nr
7 (24)	11 (24)	31	nr	nr	nr	7	3	nr	8	· 3 wound dehiscences; · 10 wound infections
6 (15)	9 (33)	3	nr	nr	1	nr	nr	nr	nr	· 2 hemorrhagic shock
-	4 (40)	14	nr	nr	4	2	0	2	4	· 2 postoperative bleeding
-	12 (46)	35	12	nr	nr	3	0	19	nr	· 1 biliary fistula
-	7 (33)	30	nr	7	nr	nr	nr	1	nr	· 11 hemorrhage of upper digestive tract; · 4 pancreatic encephalopathy; · 5 abdominal abscess plus obstruction; · 1 gastric perforation; · 1 colon perforation

Discussion

This systematic review shows that ACS in acute pancreatitis is associated with a mortality rate of 49%. Surgical decompression lowers the IAP considerably. However, it is not possible to relate this decrease in IAP to clinical outcome from the available literature. It therefore remains unknown when and if invasive intervention should be performed and which method (i.e., percutaneous catheter drainage or various surgical decompression techniques) is most effective in clinical outcomes.

The 2013 WSACS guidelines proposed clear definitions for ACS (Table 1).[2] Of the 7 studies in the current review, 5 reported the definitions used for ACS; 4 of them used the WSACS definition, that is, sustained IAP of more than 20 mm Hg associated with new organ failure. Five studies reported on IAP measurements; all used the transvesical method as advised in the same guidelines.[2]

The results of this study should be interpreted, taking into account several shortcomings. The methodological quality of most of the included studies was moderate to low, which reflects a high risk of bias that may have affected the outcome. Patient populations were heterogeneous, and patient characteristics and outcomes were not reported in a uniform manner. Different scoring systems were used to report the severity of the disease (e.g., APACHE II scores, Ranson scores, Glasgow-Imrie scores, or C-reactive protein (CRP)) and organ failure (e.g., SOFA, MODS, single organ failure, multiple organ failure), which made adequate comparison impossible. Furthermore, the number of patients with ACS in the different cohorts was small, with a range of 4 to 26. The incidence of ACS also varied greatly from 9% to 36% between the different cohorts. A mean incidence of ACS in acute pancreatitis of 22% is very high and probably overestimated. This could be a result of the chosen, for this question not specific, inclusion and exclusion criteria. Notably, the reported incidence of ACS in a recent prospective observational cohort study on the outcome of 639 patients with necrotizing pancreatitis who did not meet the eligibility criteria for the current study was as low as 2% (15/639 patients).[28] Conversely, the reported incidences of ACS and associated mortality in patients with severe burn and trauma are comparable with the results in the pooled data of this systematic review.[29-33]

Many patients with overt ACS in whom nonoperative methods have failed undergo surgical decompression. Given the morbidity of open abdominal decompression, noninvasive means of reducing IAP are an appealing alternative. These include sedation, neuromuscular blockade, nasogastric decompression, and correction of a positive cumulative fluid balance. With respect to the latter, aggressive fluid resuscitation is hypothesized to be 1 of the possible causes

of secondary ACS in acute pancreatitis.[10] Mao et al[10] performed a randomized controlled trial comparing rapid fluid expansion (10-15 mL/kg per hour infusion rate) and controlled fluid expansion (5-10 mL/kg per hour infusion rate) in 76 patients with severe acute pancreatitis. There was a significant reduction in the incidence of ACS in the controlled fluid group (33% vs. 72%; $p<0.05$). Mortality rate was also remarkably lower as compared with the rapid fluid group (70% vs. 90%; $p<0.05$).[10] Partly on this basis, the new International Association of Pancreatology (IAP)/American Pancreatic Association (APA) consensus guidelines on acute pancreatitis advise goal-directed fluid therapy with 5 to 10 mL/kg per hour.

In addition to noninvasive treatment strategies, another promising alternative for surgical decompression is percutaneous catheter drainage. The 2013 WSACS guidelines suggest percutaneous catheter drainage as first step of invasive treatment in patients with intraperitoneal fluid because this may alleviate the need for decompressive laparotomy.[2] In current study, only 11% of patients with ACS underwent percutaneous drainage as first intervention. Complications and mortality were unfortunately not reported for this subgroup, and more than half of the patients needed additional decompressive laparotomy after initial percutaneous drainage. Clearly, more data on percutaneous drainage in ACS are needed. A point of concern is the risk of infecting sterile necrotizing pancreatitis by drainage. It would seem preferred to drain intraperitoneal fluid (i.e., ascites) rather than retroperitoneal fluid, but further studies should address this issue. Our systematic search for ongoing randomized controlled trials identified 1 study. The DECOMPRESS trial[23] has now randomized 78 (78%) of the 100 patients with severe acute pancreatitis and ACS to either percutaneous drainage or decompressive laparotomy.

The effects of surgical decompression were poorly reported in the included studies. Only 4 studies described its effect on lowering IAP, and 3 to 6 studies reported its effect on organ function and complications, respectively. Although IAP was consistently lower after decompression, mortality remains considerable. This adds to the question whether invasive intervention for ACS truly improves patient outcomes. Severity of acute pancreatitis may be far more important for the prognosis than solely the presence of ACS. These questions cannot be answered with current available data. In addition, even more detailed information is required, such as whether the degree of increase in IAP per hour affects the need for intervention and which cutoff for IAP should ideally be used if intervention truly is beneficial.

With regard to the technique of surgical decompression, full-thickness midline laparotomy was performed in most patients. In 2 studies, a subcutaneous linea

alba fasciotomy was performed and 1 patient underwent full-thickness transverse bilateral subcostal laparotomy. We were unable to compare the different surgical procedures used because most studies did not differentiated complications and mortality between procedures and some patients underwent multiple interventions. Avoiding full-thickness incision in the midline including skin, subcutaneous tissue, and fascia might be better to prevent fistula formation and incisional hernia. Fascial release through separate lateral skin incisions is an option to achieve decompression, avoiding complications of an open abdomen.

Overall mortality in the ACS group was 49% and almost 5 times as high as the mortality rate in patients with acute pancreatitis without ACS. Seven studies reported the total number of complications. However, the exact nature of these complications was often not reported, as well as the number of patients with 1 or more complications. Furthermore, besides mortality, only 3 studies reported important outcomes as enterocutaneous fistula, pancreatic fistula, and incisional hernia.

This systematic review has identified considerable limitations of the published literature on ACS in acute pancreatitis. Well-designed prospective and preferably randomized studies are required to answer the many remaining questions and establish standards for treatment of this life-threatening complication. These studies should use established definitions of IAH and ACS as well as validated techniques of measuring IAP.

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CHAPTER 8

Endoscopic transluminal necrosectomy in necrotising pancreatitis

A SYSTEMATIC REVIEW

Surgical Endoscopy 2014

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Abstract

Objective

We performed a systematic review to assess the outcome of endoscopic transluminal necrosectomy in necrotising pancreatitis with additional focus on indication, disease severity, and methodological quality of studies.

Design

We searched the literature published between January 2005 and June 2013. Cohorts, including patients with (infected) necrotising pancreatitis, undergoing endoscopic necrosectomy were included. Indication, disease severity, and methodological quality were described. The main outcomes were mortality, major complications, number of endoscopic sessions, and definitive successful treatment with endoscopic necrosectomy alone.

Results

After screening 581 papers, 14 studies, including 455 patients, fulfilled the eligibility criteria. All included studies were retrospective analyses except for one randomized, controlled trial. Overall methodological quality was moderate to low (mean 5, range 2-9). Less than 50% of studies reported on pre-procedural severity of disease: mean APACHE-II score before intervention was 8; organ failure was present in 23% of patients; and infected necrosis in 57% of patients. On average, four (range 1-23) endoscopic interventions were performed per patient. With endoscopic necrosectomy alone, definitive successful treatment was achieved in 81% of patients. Mortality was 6% (28/460 patients) and complications occurred in 36% of patients. Bleeding was the most common complication.

Conclusions

Endoscopic transluminal necrosectomy is an effective treatment for the majority of patients with necrotising pancreatitis with acceptable mortality and complication rates. It should be noted that methodological quality of the available studies is limited and that the combined patient population of endoscopically treated patients is only moderately ill.

Objective

Acute pancreatitis is a common and potentially lethal disease. In approximately 80% of patients, the clinical course is mild and the disease resolves spontaneously within several days. Approximately 20% of patients develop necrotising pancreatitis, which is associated with a mortality rate of 15%.[1] The major cause of death, next to early organ failure, is infection of extrapancreatic or pancreatic necrosis, leading to sepsis and multiple organ failure. Secondary infection of pancreatic necrosis develops in approximately 30% of patients with necrosis and increases mortality to approximately 39%.[1-6] Infected necrosis is virtually always an indication for intervention. In recent years, minimally invasive interventions are gradually replacing traditional open necrosectomy in an attempt to reduce the high rate of mortality (11%-39%) and complications (34%-95%) associated with open necrosectomy.[4,5,7-13]

Currently, a widely used treatment for infected necrosis is a minimally invasive surgical step-up approach, consisting of percutaneous catheter drainage, followed by minimally invasive surgical necrosectomy, when needed.[6] A recent, randomized, controlled trial demonstrated that this approach reduces major complications from 69% to 40% compared with primary open necrosectomy.[6] However, a complication rate of 40% remains high and could potentially be further reduced by expanding the indication for endoscopic necrosectomy. Endoscopic necrosectomy can be performed under sedation without the need for general anaesthesia and has been shown to reduce the inflammatory response and complications, such as new onset organ failure, in these often already critically ill patients.[14] Furthermore, endoscopic necrosectomy avoids a laparotomy or lumbotomy with its related surgical stress and complications, such as wound infection, intestinal or pancreatic fistula, and incisional hernia. Endoscopic necrosectomy was first described by Seifert et al.[15] in 2000. Since then, various observational cohort- studies on endoscopic necrosectomy have been published.

We performed a systematic review of the literature on endoscopic necrosectomy in (infected) necrotising pancreatitis. The objective was threefold: (1) to evaluate success of endoscopic necrosectomy in terms of definitive treatment and relevant clinical outcomes, such as mortality, and complications in individual studies and the pooled data; (2) to explore differences in indication and disease severity among studies to allow comparison of data between series, and comparison of outcome after endoscopic necrosectomy and surgical necrosectomy as reported in the literature; and (3) to perform an in depth-analysis of methodological quality of the available studies to systematically investigate areas of improvement for further research.

Methods

Study selection

The PRISMA guidelines for reporting on meta-analyses and systematic reviews of observational studies were applied.[16] A systematic literature search from January 2005 to June 2013 was performed in PubMed, Embase, and the Cochrane Library according to a prespecified protocol. Only articles written in English were included. The search terms are provided in Appendix 1 of the original article. All titles and abstracts of studies identified by the initial search were screened to select those reporting on patients undergoing endoscopic necrosectomy of (extra-) pancreatic collections associated with acute pancreatitis. Duplicate references were excluded. Full-text papers of the selected studies were screened independently by two authors to assess eligibility. All cross-references were screened for potentially relevant studies not identified by the initial literature search. The final decision on eligibility was reached by consensus between the two screening authors.

Inclusion criteria were: (1) consecutive series of patients with necrotising pancreatitis undergoing endoscopic necrosectomy for (suspected) infected necrosis or symptomatic sterile pancreatic necrosis (i.e., clinical deterioration or significant mechanical obstruction); (2) the following outcomes were reported: percentage of infected peripancreatic collections, number of interventions, endoscopic necrosectomy success rate (i.e., needing no additional percutaneous or surgical intervention), mortality, and complications.

Exclusion criteria were: (1) studies with less than 5 patients; (2) studies also including patients with chronic pancreatitis with results for acute pancreatitis not reported separately; (3) studies on a selected subgroup of patients with acute pancreatitis, classified as 'pseudocysts' or 'pancreatic abscesses' as defined by the 1992 Atlanta classification[17] with results of these subgroups not reported separately; (4) studies including sterile pancreatic necrosis with results of infected pancreatic necrosis not reported separately or, otherwise uncomplicated sterile pancreatic necrosis.

Methodological quality assessment

Studies included in this systematic review were assessed for quality using two validated checklists.[18,19] Downs et al. described a checklist with 27 items (1 point for each item) which can be used for quality assessment for both randomized and nonrandomized studies.[18] The MINORS checklist, proposed by Slim et al., contains 8 items for noncomparative studies and 12 items for comparative studies (maximum of 2 points for each item).[19] In both scoring systems, a low methodological quality score reflects a high risk of bias, whereas a high

score reflects a low risk of bias. To facilitate comparison of both lists, each score was converted to a value on a 0-10 scale. In order to signify the overall methodological quality of each study, a final score was determined by calculating the mean of the Downs and MINORS scores. We defined high methodological quality as a final score ≥8, moderate quality as a score of 6-8, moderate/low quality as a score of 4-6, and low quality as a score ≤3.

Data extraction

The following variables were extracted, where available: number of patients undergoing endoscopic necrosectomy, etiology, predictive severity scores before intervention (e.g., Imrie/Modified Glasgow score and Acute Physiology And Chronic Health Evaluation [APACHE]-II score), organ failure before endoscopic necrosectomy, ICU admission before endoscopic necrosectomy, computed tomography (CT) severity scores (CT severity Index (CTSI)[20], modified CTSI[21], Balthazar grade[22]), indication for intervention, percentage of patients with infected necrosis confirmed by first culture, time between hospital admission and endoscopic necrosectomy, total number of interventions, total length of ICU and hospital stay, definitive successful treatment with endoscopic necrosectomy alone (defined as no need for additional percutaneous or surgical intervention), number of patients requiring an additional percutaneous or surgical intervention, complications, and death.

Primary outcome measures were death and complication rate. The nominator for calculation was represented by the number of patients who died or suffered from reported complications (e.g., bleeding, perforation of a hollow organ, pancreatic fistula). The denominator was the total number of patients with infected necrotising pancreatitis. Patients lost to follow-up were excluded.

Statistical analysis

The data were analysed and reported to describe methodological quality, characteristics of included studies, patient characteristics, and outcome. Descriptive statistics were used to describe baseline characteristics and outcome variables for all studies separately and for the pooled data. In order to pool data of continuous outcomes in systematic reviews average values are needed. However, continuous outcomes are often reported with different summary statistics, such as means, medians, range, and size of the trial, etc. Hozo et al. described a method to calculate or estimate (depending on the sample size) the mean using the values of the median, low and high end of the range, and sample size.[23] We used this method to calculate weighted means for all outcomes.

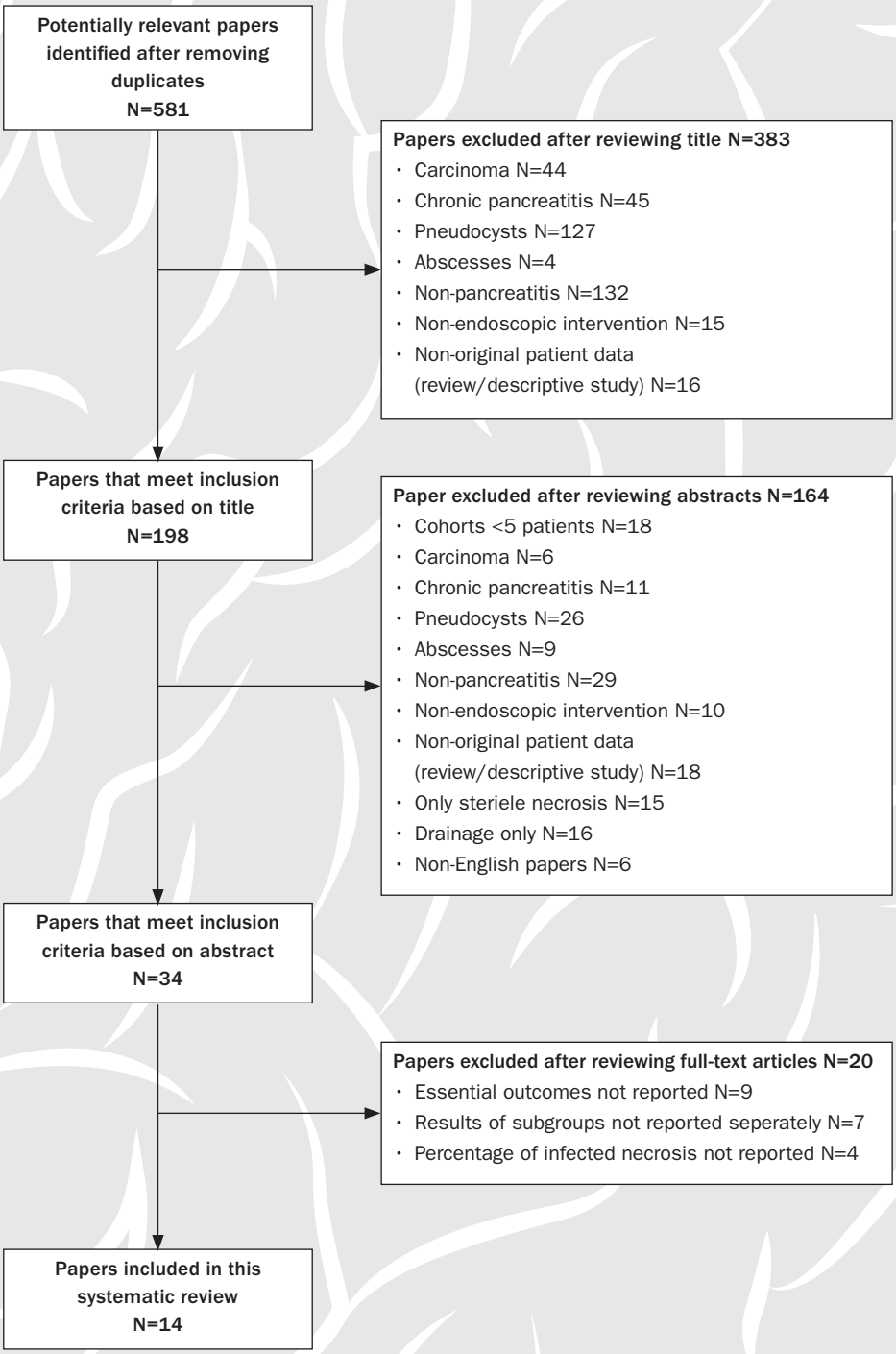

Figure 1. *Study selection flow chart.*

To this end, we received additional data through personal communication with the author of one study.[14]

A forest plots for mortality was generated using Comprehensive Meta-analysis Version 2 (Borenstein M, Hedges L, Higgins J et al., Biostat, Englewood, NJ, 2005). I^2 was calculated to assess heterogeneity. The I^2 statistic indicates the proportion of total variation among the effect estimates attributed to heterogeneity rather than sampling error and has the advantage of being intrinsically independent of the number of studies. Heterogeneity was ruled out when the test of heterogeneity was not significant ($p>0.05$) and I^2 was less than 30%.[24,25]

Results

Literature search

The systematic literature search identified 581 potentially relevant papers after removing duplicates. The study selection flowchart is shown in Figure 1. Of the 581 papers, 567 papers were excluded after reviewing title, abstract, and full-text for the following reasons: cohorts of less than 5 patients (N=18), cohorts of patients with carcinoma (N=50), non-English papers (N=6), cohorts including only sterile necrosis (N=15), cohorts including only endoscopic drainage and no endoscopic necrosectomy (N=16), cohorts also including chronic pancreatitis, 'pseudocysts', 'pancreatic abscesses', and results of these subgroups were not reported separately (N=222), cohorts that did not report one or more predescribed essential outcomes (i.e., number of endoscopic necrosectomy sessions, definitive successful treatment, complications, and death) (N=9) separately, and cohorts excluded because of other reasons (e.g., percentage of infected necrosis was not reported, cohorts of patients receiving nonendoscopic treatment, cohorts of patients receiving treatment for nonpancreatitis diseases, cohorts that did not show original patient data, such as reviews or solely descriptive publications) (N=231).

Study characteristics

A total of 14 studies were included in this systematic review.[14,26-38] Study characteristics are summarized in Table 1.

Seven studies were retrospective, noncontrolled cohort studies; four were retrospective, noncontrolled cohort studies with prospective databases; one was a retrospective, noncontrolled cohort study with a prospective follow-up; one was a retrospective, noncontrolled cohort study in a partially prospective database; and one was a randomized, controlled trial. From four studies, we included a selection of the reported cohort, because only a subgroup fulfilled the selection criteria and data were reported separately.[14,31,34,36]

Methodological quality

Table 2 shows the converted quality scores of the Downs et al. and MINORS checklist on a 0-10 scale and the mean of both checklists. Overall methodological quality was moderate to low (mean 5, range 2-9). The randomized trial scored high, 1 study scored moderate, 11 studies scored moderate to low, and 1 study scored low. Studies scored good on reporting design (e.g., stating a clear purpose, patient characteristics, type of intervention, and outcome), main findings, and adverse events. However, the majority of studies were retrospective and, therefore, scored lower, because they, for example, had no power calculation, no randomized allocation of treatment, no blinding, and did not correct for differences in length of follow-up. Furthermore, no actual probability values with accompanying estimates of the random variability were reported in most studies.

Patient characteristics

The pooled data comprised of 455 patients undergoing endoscopic necrosectomy. The number of patients per study ranged from 5 to 104. Patient characteristics of the individual studies are shown in Table 3. The weighted means of baseline characteristics in the pooled data are given in Table 4. Sixty-three percent of all patients were male, and the mean age was 56 (SD 10) years. Twelve studies (432/455 patients) reported on etiology, which was biliary in 52% of patients, alcoholic in 19%, and of other origin in 29%. On average, follow-up was 23 months (Table 1).

Six of the 14 (43%) studies reported predictive severity scores, CTSI, and/or clinical details before intervention. Mean APACHE-II score was 8 (SD 5), CTSI 7 (SD 2), organ failure before intervention was present in 23% of patients (14/62 patients), and 32% of patients (62/195 patients) were admitted to the ICU before intervention. The average number of days between diagnosis and first intervention was 57 (range 6-510). Fifty-seven percent of patients (261/455 patients) had infected necrosis proven by a positive bacteriological culture of pancreatic or peripancreatic necrosis before or at first necrosectomy. In 11 of the 14 studies, endoscopic transluminal necrosectomy was performed under sedation. One study used moderate sedation or general anaesthesia, one study used conscious sedation with oral intubation, and one study did not report which per procedural sedation was used.

Table 1. Characteristics of the included studies.

Study	Country	Year	Study design	Inclusion criteria
Seewald et al.[36]	Germany	2005	Retrospective cohort	Pancreatic necrosis, endoscopic necrosectomy
Charnley et al.[28]	UK	2006	Retrospective cohort[a]	Infected pancreatic necrosis, endoscopic necrosectomy
Voermans et al.[38]	The Netherlands	2007	Retrospective cohort[b]	Symptomatic organized pancreatic necrosis, endoscopic necrosectomy
Papachristou et al.[33]	USA	2007	Retrospective cohort[b]	Symptomatic or infected WOPN, endoscopic therapy
Escourrou et al.[30]	France	2008	Retrospective cohort[b]	Infected pancreatic necrosis, endoscopic necrosectomy
Schrover et al.[35]	The Netherlands	2008	Retrospective cohort	Infected pancreatic necrosis, endoscopic necrosectomy
Coelho et al.[29]	Brazil	2008	Retrospective cohort	Pancreatic necrosis, endoscopic necrosectomy
Seifert et al.[37]	Germany	2009	Retrospective cohort	Infected pancreatic necrosis, endoscopic necrosectomy
Gardner et al.[31]	USA	2009	Retrospective cohort[c]	Symptomatic WOPN, endoscopic necrosectomy
Gardner et al.[32]	USA	2011	Retrospective cohort	WOPN, endoscopic necrosectomy
Bakker et al.[14]	The Netherlands	2012	Randomized controlled trial	Infected necrotising pancreatitis
Bausch et al.[27]	Germany	2012	Retrospective cohort	WOPN, endoscopic necrosectomy
Abdelhafez et al.[26]	Egypt	2013	Retrospective cohort[b]	WOPN, endoscopic necrosectomy
Risch et al.[34]	Germany	2013	Retrospective cohort	WOPN, endoscopic necrosectomy

WOPN, indicates walled-off pancreatic necrosis.

[a] *Retrospective study in a partially prospective database.*

[b] *Retrospective study in a prospective database.*

[c] *Retrospective study with prospective follow-up.*

[d] *A selection of the cohort reported in the original article.*

[e] *Including 25 patients from Gardner 2009 and 14 patients from Papachristou 2007.*

[f] *Given for the whole cohort.*

Technique used	Number of patients	Study period (month)	Follow-up (month)
EUS, drainage, dilatation, daily necrosectomy + lavage	5[d]	1997 - 2004 (88)	26[f]
EUS, drainage, dilatation, necrosectomy	13	2002 - 2004 (30)	19
EUS, drainage, dilatation, necrosectomy	25	2003 - 2006 (42)	13
EUS/non-EUS, drainage, dilatation, necrosectomy	53	1998 - 2006 (101)	6
EUS, drainage, dilatation, necrosectomy	13	2004 - 2007 (42)	20
EUS, drainage, dilatation, necrosectomy	8	2001 - 2006 (61)	23
Drainage, dilatation, necrosectomy	56	2002 - 2007 (72)	23
EUS, drainage, dilatation, necrosectomy	93	1999 - 2005 (84)	44
EUS/non-EUS, drainage, dilatation, necrosectomy	25[d]	1998 - 2007 (115)	14
EUS/non-EUS, drainage, dilatation, necrosectomy	104[e]	2003 - 2010 (88)	20
EUS, drainage, dilatation, necrosectomy	10[d]	- 2010 (20)	6
EUS, drainage, dilatation, necrosectomy	18	1998-2010 (144)	nr
Drainage, dilatation, necrosectomy	10	2011-2012 (17)	10
EUS, drainage, dilatation, necrosectomy	22[d]	2006-2011 (69)	28

Table 2. Methodological quality of the included studies.

Study	MINORS checklist[a] [19]	Checklist for (non-) randomized trialsa [18]	Mean MINORS and Downs checklist	Methodological quality
Seewald et al.[36]	2,5	1	1,8	Low
Charnley et al.[28]	6,3	3	4,7	Moderate/low
Voermans et al.[38]	6,3	3,3	4,8	Moderate/low
Papachristou et al.[33]	6,3	3,3	4,8	Moderate/low
Escourrou et al.[30]	7,5	3,3	5,4	Moderate/low
Schrover et al.[35]	6,3	3,3	4,8	Moderate/low
Coelho et al.[29]	6,3	3,3	4,8	Moderate/low
Seifert et al.[37]	6,3	3,7	5	Moderate/low
Gardner et al.[31]	5	3,3	4,2	Moderate/low
Gardner et al.[32]	5	3,3	4,2	Moderate/low
Bakker et al.[14]	9,2	9,6	9,4	High
Bausch et al.[27]	6,3	4,1	5,2	Moderate/low
Abdelhafez et al.[26]	7,5	5,6	6,6	Moderate
Risch et al.[34]	6,3	3,7	5	Moderate/low

[a] *All scores are 0-10, with 10 reflecting the highest methodological score.*

Caption Table 3 ►

nr, indicates not reported; A, alcoholic; B, biliary; Ia, iatrogeny; O, other. [a] *A selection of the cohort reported in the original article.* [b] *Including 25 patients from Gardner 2009 and 14 patients from Papachristou 2007.* [c] *Given for the whole cohort.*

Table 3. Patient characteristics of included studies.

Study	Number of patients	M/F (%)	Age (mean)	Etiology	APACHE- II score (mean)	CT severity index (mean)	Organ failure (%)	ICU admission (%)	Infected necrosis (%)	Collection size in cm (mean)	Diagnosis to first intervention in days (mean)	Drainage as first intervention (%)	Drainage to necrosectomy in days (mean)
Seewald et al.[36]	5[a]	5/0 (100/0)	62	B: 3, A: 1, O: 1	nr	nr	nr	5 (100)	5 (100)	14.5	nr	5 (100)	nr
Charnley et al.[28]	13	9/4 (69/31)	50	nr	9	7	4 (31)	5 (38)	11 (85)	nr	nr	0	0
Voermans et al.[38]	25	12/13 (48/52)	56	B: 10, A: 5, O: 10	nr	nr	nr	nr	19 (76)	11	144	25 (100)	4
Papachristou et al.[33]	53	28/25 (53/47)	61	B: 37, A: 1, Ia: 5, O: 10	6	nr	nr	18 (34)	20 (38)	16	49	53 (100)	18
Escourrou et al.[30]	13	12/1 (92/8)	55	B 7, A: 3, O: 3	13	8	4 (31)	13 (100)	13 (100)	14	28	0	0
Schrover et al.[35]	8	2/6 (25/75)	53	nr	7	6	2 (25)	0	8 (100)	nr	36	8 (100)	nr
Coelho et al.[29]	56	30/26 (54/46)	44	B: 35, A: 12, O: 9	nr	nr	nr	nr	25 (45)	18	35	56 (100)	nr
Seifert et al.[37]	93	63/30 (68/32)	57	B: 43, A: 28, Ia: 5, O: 17	nr	nr	nr	19 (20)	50 (54)	11.4	41	54 (58)	nr
Gardner et al.[31]	25[a]	17/8 (68/32)	61	B: 15, A: 1, O: 9	nr	7 (±1.6)	nr	nr	19 (76)	14.8 (±5)	74	0	0
Gardner et al.[32]	104[b]	67/37 (64/36)	58	B: 48, A: 18, O: 38	nr	7	nr	nr	40 (38)	15	46	104 (100)	nr
Bakker et al.[14]	10[a]	6/4 (60/40)	62	B: 6, A: 2, O: 2	10	8	4 (40)	2 (20)	10 (100)	nr	48	9 (90)	nr
Bausch et al.[27]	18	10/8 (56/44)	54	B: 5, A: 4, O: 9	nr	nr	0	nr	13 (72)	nr	78	0	0
Abdel-hafez et al.[26]	10	6/4 (60/40)	44	B: 4, A: 2, Ia: 1, O: 3	9	nr	nr	nr	7 (70)	13	65	10 (100)	8
Risch et al.[34]	22[a]	22/5 (82/18)[c]	63[c]	B: 13, A: 8, O: 6[c]	nr	nr	nr	nr	21 (78)[c]	nr	nr	22 (100)	nr

Outcome

The clinical outcomes after endoscopic necrosectomy in the individual studies are given in Table 5 and the calculated weighted means in Table 4. The overall mortality rate was 6% (28/455 patients) with a range of 0%-15% per study. Two studies reported the in hospital mortality rate, whereas 12 studies described the mortality rate within the follow-up period. Mortality is shown in a forest plot (Figure 2). There was no substantial heterogeneity for mortality (I^2<30%, p=0.93). There was no correlation between mortality and the percentage of patients with infected necrosis. Mortality seems higher in patients with organ failure before intervention. Because only six studies reported APACHE-II scores and CTSI before intervention, we were unable to draw conclusions about their correlation with mortality. Complications occurred in 36% of patients (163/455 patients). The most common complication was bleeding, which occurred in 18% (76/420 patients) of patients. Bleeding was treated endoscopically by endoscopic coagulation, epinephrine injections, or clips in 93% of patients; 7% of patients required angiography with coiling or surgery. Pancreatic fistula occurred in 5% (9/187), spontaneous perforation of a hollow organ (apart from the stomach or duodenum due to the intervention) in 4% (9/249), and air embolism in 1% (2/207) of patients.

On average, 4 (range 1-23) endoscopic sessions were performed per patient; 382 of 455 patients (84%) were treated with endoscopy alone. The remaining subgroup of patients underwent one or more additional percutaneous or surgical interventions. Of this subgroup, additional intervention was percutaneous in 18 patients, surgical in 46 patients, percutaneous and surgical in 7 patients, and other in 2 patients. Main indications for intervention were persistent collections, recurrent collections, extended necrosis, perforation of a hollow organ, and bleeding. Primary endoscopic necrosectomy was successful as definitive treatment in 81% (372/455) of patients.

Table 4. Weighted means for baseline and outcome.

	Number of studies	Number of patients	Mean
Follow-up (mo)	13	437	23
Methodological quality	14	455	5
Sex (M/F) (%)	14	455	63/37
Age (ys)	14	455	56
Etiology (B; A; Ia; O) (%)	12	432	52; 19; 3; 26
APACHE-II score	6	107	8
CTSI	6	173	7
Organ failure (%)	5	62	23
ICU admission (%)	7	195	32
Infected necrosis (%)	14	455	57
Collection size (cm)	9	384	14
Diagnosis to first intervention (days)	10	377	57
Drainage as first intervention (%)	14	455	92
Drainage to necrosectomy (days)	7	157	7
Number of endoscopic sessions	13	437	4
Endoscopy alone (%)	14	455	84
Additional procedures (%)	14	455	16
Definitive resolution (%)	14	455	81
Mortality (%)	14	455	6
Complications (%)	14	455	36
Bleeding (%)	12	420	18
Perforation (%)	6	249	4
Air embolism (%)	3	207	1
Pancreatic fistula (%)	5	187	5

Table 5. Outcome of included studies.

Study	Number of patients	Number of endoscopic sessions (mean)	Endoscopy alone (%)	Additional procedures	Definitive resolution (%)[c]	Mortality (%)	Complications (%)
Seewald et al.[36]	5[a]	15	3 (60)	2: surgery	3 (60)	0	3 (60)
Charnley et al.[28]	13	5	9 (69)	2: surgery, 2: percutaneous	9 (69)	2 (15)	2 (15)
Voermans et al.[38]	25	2	23 (92)	2: surgery	24 (96)	0	12 (48)
Papachristou et al.[33]	53	3	28 (53)	5: surgery, 13: percutaneous, 7: surgery and percutaneous	28 (53)	3 (6)	34 (64)
Escourrou et al.[30]	13	2	11 (85)	2: percutaneous	11 (85)	0	10 (77)
Schrover et al.[35]	8	4	6 (75)	2: surgery	6 (75)	1 (13)	3 (38)
Coelho et al.[29]	56	5	49 (88)	6: surgery	49 (88)	2 (4)	6 (11)
Seifert et al.[37]	93	6	80 (86)	12: surgery, 1: transesphageal fenestration	75 (81)	7 (8)	27 (29)
Gardner et al.[31]	25[a]	4	24 (96)	1: surgery	22 (88)	0	8 (32)
Gardner et al.[32]	104[b]	4	102 (98)	2: surgery	95 (91)	7 (7)	38 (37)
Bakker et al.[14]	10	4	8 (80)	2: surgery	8 (80)	1 (10)	5 (50)
Bausch et al.[27]	18	nr	10 (56)	7: surgery 1: percutaneous	9 (50)	1 (6)	8 (44)
Abdelhafez et al.[26]	10	1	10 (100)	0	9 (90)	1 (10)	4 (40)
Risch et al.[34]	22[a]	4	19 (86)	3: Surgery	19 (86)	3 (14)	3 (13)[d]

nr, indicates not reported. [a] *A selection of the cohort reported in the original article,*

[b] *Including 25 patients from Gardner 2009 and 14 patients from Papachristou 2007*

Bleeding (%)	Perforation of a hollow organ (%)	Air embolism (%)	Pancreatic fistula (%)	Other
2 (40)	nr	nr	nr	1: recurrent pseudocyst
nr	nr	nr	nr	2: DM type 1
9 (36)	nr	nr	nr	1: perforation of cystic wall, 2: recurrent pseudocyst
9 (17)	1 (2)	nr	2 (4)	1: gallbladder puncture, 1: loss of access to collection, 5: DVT, 3: ischaemia/perforation/peritonitis, 3: clostridium difficille colitis, 2: ileus, 1: bowel obstruction, 5: recurrent/persisting pseudocyst, 1: flank abscess
3 (23)	nr	nr	4 (31)	3: sepsis
1 (13)	1 (13)	nr	nr	1: relaps of AP
2 (4)	0	nr	nr	3: secondary infected collection, 1: stent clogging
13 (14)	nr	2 (2)	2 (2)	1: oesophageal variceal haemorrhage, 5: perforation of the necrosis into the abdominal cavity, 1: seizure, 1: intracerebral hemorrhage, 1: pneumoperitoneum, 1: colonic fistula
8 (32)	nr	nr	nr	8: recurrent collection
21 (20)	2 (2)	1 (1)	nr	1: bacteremia, 6: recurrent collection, 1: secondary infected collection, 3: pneumoperitoneum, 3: recurrent pancreatitis, 1: clostridium colitis
0	0	0	1 (10)	2: DM, 2: persisting collections
3 (17)	5 (28)	nr	0	nr
4 (40)	nr	nr	nr	1: aspiration
1 (5)	nr	nr	nr	1: myocardial infarction

[c] *Definitive resolution with only endoscopic necrosectomy.*

[d] *Given for the whole cohort.*

Study name	Statistics for each study					Event rate and 95% CI
	Event rate	Lower limit	Upper limit	Z-value	p-value	Total
Seewald et al	0.083	0.005	0.622	-1.623	0.105	0/5
Charnley et al	0.154	0.039	0.451	-2.218	0.027	2/13
Voermans et al	0.019	0.001	0.244	-2.753	0,006	0/25
Papchristou et al	0,057	0,018	0,161	-4,733	0,000	3/53
Escourrou et al	0,036	0,002	0,384	-2,289	0,022	0/13
Schover et al	0,125	0,017	0,537	-1,820	0,069	1/8
Coelho et al	0,036	0,009	0,132	-4,577	0,000	2/56
Seifert et al	0,075	0,036	0,150	-6,382	0,000	7/93
Gardner et al	0,019	0,001	0,244	-2,753	0,006	0/25
Gardner et al 2011	0,067	0,032	0,135	-6,717	0,000	7/104
Bakker et al	0,100	0,014	0,467	-2,084	0,037	1/10
Bausch et al	0,056	0,008	0,307	-2,753	0,006	1/18
Abdelhafez et al	0,100	0,014	0,467	-2,084	0,037	1/10
Risch et al	0,136	0,045	0,348	-2,971	0,003	3/22
	0,073	0,051	0,102	-13,378	0,000	

Figure 2. *Forest plot of included studies analyzing mortality. I^2=0,000 p=0.922*

Discussion

This systematic review shows that endoscopic transluminal necrosectomy is a safe and effective minimally invasive treatment in infected necrotising pancreatitis. More than 80% of patients were treated successfully with endoscopic necrosectomy alone. This was associated with a mortality rate of 6% and complication rate of 36%.

Of note, the methodological quality of the vast majority of included studies was moderate to low. Furthermore, the vast majority of included studies did not report on the most relevant parameters of disease severity (e.g., APACHE-II score, preoperative organ failure, and infected necrosis) or outcome measures. Only two studies reported clear definitions for organ failure and only one study reported definitions for pancreatic fistula and perforation of a visceral organ. Just little more than half of the patients had proven infected necrosis. This is low, because the main indication for intervention in necrotising pancreatitis is nowadays considered to be infected necrosis.[9,39,40] In accordance with international guidelines, patients with sterile necrosis often can be successfully managed conservatively (i.e., without any form of radiologic, endoscopic, or surgical intervention).[41,42]

The only exception for intervention in patients with sterile necrosis are patients with gastrointestinal or hepatobiliary obstruction persisting for several months and perhaps in very few patients with progressive organ failure despite maximal supportive therapy in the intensive care unit.[39,40,43] Iatrogenic infection of sterile necrosis by percutaneous or transluminal drainage is a well-recognized risk that needs to be avoided.[44,45] Thus, intervention in the case of sterile necrosis is, in our opinion, obsolete and potentially harmful. Of the included studies, intervention could probably been avoided in a considerable number of patients. Patients with infected necrosis are generally thought to be more severely ill compared with patients with sterile necrosis. This study however showed no correlation between the percentage of patients with infected necrosis and mortality. Five studies had a high percentage of patients with infected necrosis and low mortality. This could be a result of the fact that these studies were relatively small, had lower quality scores, and the majority did not report disease severity before intervention. Several studies were excluded for this review, because they did not report data on the percentage of patients with infected necrosis.

The historical treatment of infected necrotising pancreatitis has always been surgical necrosectomy. Many cohort studies on surgical necrosectomy have been published over the past decade. These series can be compared to the literature on endoscopic necrosectomy in many ways. First, sample sizes of

endoscopic necrosectomy series are comparable to open and minimally invasive surgical necrosectomy series. However, surgical necrosectomy series more often are prospective cohort studies and therefore score better on methodological quality. Second, patients in endoscopic necrosectomy series seam less ill with a lower rate of infected necrosis compared with surgical series. If we compare the patients from the recent randomized PANTER study who underwent a minimally invasive surgical step-up approach[6] with the patients from the current pooled dataset, there are obvious differences in baseline characteristics: APACHE-II scores (15 vs. 8), organ failure rate (49% vs. 23%), ICU admission rate (54% vs. 32%), and the percentage of patients with proven infected necrosis (91% vs. 57%) were all higher in the surgical group. This is confirmed by the results of a recent systematic review on videoscopic-assisted retroperitoneal debridement (VARD).[46] In the pooled data of 128 patients undergoing VARD mean APACHE-II score was 14, organ failure was present in 40% of patients, 60% of patients were admitted to the ICU before intervention, and 91% of patients had infected necrosis. Third, the number of procedures performed with endoscopic necrosectomy seems higher than for surgical necrosectomy. In this review, there was a wide range regarding the number of procedures needed, ranging from 1 to 23 sessions with a mean of 4 sessions per patient. In minimally invasive surgical series, an average of three (range 1-5) procedures were needed per patient.[46] This may lead to a difference in costs. Unfortunately, the included studies did not report total hospital stay and costs. We therefore cannot draw firm conclusions on this matter. Although more procedures may be needed, endoscopic necrosectomy seems less invasive than surgical necrosectomy and potentially induces less surgical stress, which could reduce complications and improves outcome. Fourth, successful definitive treatment with endoscopy seems higher (i.e., 81% in the current study) compared with minimally invasive surgical necrosectomy (i.e., 61% in a recent review).[46] Mortality in the endoscopic necrosectomy series was lower compared with minimally invasive surgery (6% vs. 13%).[46] This could, however, reflect the difference in baseline characteristics or be due to the fact that both the surgical and endoscopy studies are not powered to show a difference in solely mortality. Overall, the percentage of complications between endoscopic and surgical series seems comparable (36% vs. 35%).[46] The pancreatic fistula rate, however, is apparently much lower after endoscopic necrosectomy than after surgical necrosectomy (5% vs. 17%).[46] This is an obvious difference because endoscopic necrosectomy avoids any abdominal wall incision. However, pancreatic fistula is associated with severe morbidity and therefore is an important outcome measure. The incidence of bleeding, mostly controlled by direct endoscopic coagulation,

epinephrine injection or clips, does not seem different between endoscopic and surgical necrosectomy (18% vs. 13%).[46] The percentage of perforations also is the same (4% vs. 4%).[46]

Theoretically, by avoiding a laparotomy or lumbotomy and general anaesthesia, endoscopic necrosectomy induces less inflammatory stress and can reduce the number of early and late complications as new onset organ failure, intestinal and/or pancreatic fistula, and incisional hernia.[14] Furthermore, general anaesthesia is known to induce or prolong systemic inflammation in critically ill patients.[47] A potential limitation of endoscopic necrosectomy is that acute complications, such as perforations and to a lesser extend bleedings, are more difficult to manage endoscopically. Importantly, endoscopic necrosectomy is an advanced type of intervention that not only requires the expertise from an interventional endoscopist, but also the dedicated involvement of interventional radiologists and pancreatic surgeons to manage potential complications. For this reason, endoscopic necrosectomy procedures should only be performed in expert centers with multidisciplinary expertise.

There are some limitations to this systematic review. First, most included studies were relatively small and retrospective analyses were performed. A formal assessment of the methodological quality of selected studies showed that most studies scored only 'moderate to low'. Furthermore, baseline data on disease severity before intervention and clear definitions for organ failure and complications were poorly reported. When reported, scores were relatively low compared with most surgical series, suggesting a less ill patient category.[6] The lack of uniform patient selection criteria has undoubtedly led to selection bias. Lastly, the primary endpoint in most studies was radiologic findings (e.g., complete resolution of collections op CT), which does not necessarily correlate with current disease stage and outcome in every patient.

What are the implications of this study for clinical practice? In case of infected necrosis, 'drainage first' avoids surgery in approximately 35% of patients.[6] Knowing that, it may be advisable to perform endoscopic treatment in a step-up fashion: i.e., endoscopic transluminal drainage first, if necessary followed by endoscopic transluminal necrosectomy. Endoscopic necrosectomy is being used with increasing frequency worldwide. However, as with the introduction of any new technical procedure, for example laparoscopic cholecystectomy, rapid, widespread, clinical implementation often precedes firm scientific proof and also is associated with increased complication rates.[48-50] Large prospective or preferably randomized trials are required to confirm the favourable results of this systematic review and reliably compare endoscopic necrosectomy to surgical necrosectomy. We strongly recommend that these studies only include patients

with (suspected) infected necrotising pancreatitis and well- describe baseline criteria (e.g., etiology, APACHE-II, CTSI, organ failure, percentage of infected necrosis, days from initial admission to necrosectomy) and clinically relevant outcome measures (e.g., number of endoscopic procedures, mortality, complications such as bleeding, perforation, fistula). Such a study is currently enrolling patients (controlled trials ISRCTN09186711).

Endoscopic transluminal necrosectomy is a good treatment option for patients with infected necrotising pancreatitis. However, the favourable results of this systematic review should be regarded in the light that the pooled data comprises of moderately ill patients and the methodological quality of the included studies is limited.

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CHAPTER 9

Minimally invasive and endoscopic versus open necrosectomy for necrotising pancreatitis

A POOLED ANALYSIS OF INDIVIDUAL DATA FOR 1980 PATIENTS

Gut 2017

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Abstract

Objective

Minimally invasive surgical necrosectomy and endoscopic necrosectomy, compared with open necrosectomy, might improve outcomes in necrotizing pancreatitis, especially in critically ill patients. Evidence from large comparative studies is lacking.

Design

We combined original and newly collected data from 15 published and unpublished patient cohorts (51 hospitals; 8 countries) on pancreatic necrosectomy for necrotising pancreatitis. Death rates were compared in patients undergoing open necrosectomy versus minimally invasive surgical or endoscopic necrosectomy. To adjust for confounding and to study effect modification by clinical severity, we performed two types of analyses: logistic multivariable regression and propensity score matching with stratification according to predicted risk of death at baseline (low: <5%; intermediate: ≥5% to <15%; high: ≥15% to <35%; and very high: ≥35%).

Results

Among 1980 patients with necrotising pancreatitis, 1167 underwent open necrosectomy and 813 underwent minimally invasive surgical (N=467) or endoscopic (N=346) necrosectomy. There was a lower risk of death for minimally invasive surgical necrosectomy (OR, 0.53; 95% CI 0.34 to 0.84; p=0.006) and endoscopic necrosectomy (OR, 0.20; 95% CI 0.06 to 0.63; p=0.006). After propensity score matching with risk stratification, minimally invasive surgical necrosectomy remained associated with a lower risk of death than open necrosectomy in the very high-risk group (42/111 vs. 59/111; risk ratio, 0.70; 95% CI 0.52 to 0.95; p=0.02). Endoscopic necrosectomy was associated with a lower risk of death than open necrosectomy in the high-risk group (3/40 vs. 12/40; risk ratio, 0.27; 95% CI 0.08 to 0.88; p=0.03) and in the very high-risk group (12/57 vs. 28/57; risk ratio, 0.43; 95% CI 0.24 to 0.77; p=0.005).

Conclusion

In high-risk patients with necrotising pancreatitis, minimally invasive surgical and endoscopic necrosectomy are associated with reduced death rates compared with open necrosectomy.

Introduction

Approximately 20% of patients with acute pancreatitis develop necrosis of the pancreas and peripancreatic tissue.[1] These patients have a prolonged disease course with a high risk of complications such as multiple organ failure, secondary infection of the necrosis and death.[1,2] Many patients with necrotising pancreatitis ultimately need to undergo pancreatic necrosectomy.[1-4]

Death rates after pancreatic necrosectomy recently reported by international specialist centres vary from 0% to 25%.[5-12] This variation may be explained by differences in case-mix or by differences in treatment strategies and local expertise. Several changes in the treatment of patients with necrotising pancreatitis have occurred over the last 20 years. First, the timing of intervention has shifted from very early in the disease course to around 3-4 weeks after onset of symptoms.[3,4,13] Second, the indication for necrosectomy has changed from sterile necrosis to predominantly infected necrosis.[3,4,14] Third, percutaneous or endoscopic drainage of the necrotic collection is now often the first step in treatment before necrosectomy.[15] Finally, as an alternative to open necrosectomy, minimally invasive surgical necrosectomy and the even less invasive endoscopic necrosectomy are increasingly being performed.[7-10,12]

Minimally invasive necrosectomy is thought to be beneficial in the acute phase by inducing less surgical stress, thereby lowering the proinflammatory response, especially in already critically ill patients.[16,17] Another advantage is the avoidance of the long-term morbidity of a large abdominal incision. Studies that directly compare minimally invasive necrosectomy with open necrosectomy for primary clinical outcomes are scarce. A few retrospective studies have been performed, but these were mostly small and hampered by selection bias and confounding.[12,18] The only available randomised trial included only 20 patients.[17] Despite the lack of evidence in favour of minimally invasive surgical and endoscopic necrosectomy, these techniques are increasingly popular in the treatment of necrotising pancreatitis. This, combined with the fact that necrotising pancreatitis is a complex and relatively rare disease, makes it unlikely that a trial with a sufficiently large sample size to study mortality will ever be performed. It therefore remains unclear if minimally invasive necrosectomy methods reduce death rates, especially in the context of other recent changes in the treatment of necrotising pancreatitis. As a result, open necrosectomy remains a valid option and is still practised worldwide.[3,11,19,20]

In this international collaborative project, we combined original patient data from published and unpublished cohorts on pancreatic necrosectomy in specialist centres worldwide. We compared death rates of open necrosectomy with minimally invasive surgical and endoscopic necrosectomy in a

large number of patients. This allowed for several approaches to adjust for confounding and to study effect modification by clinical severity. We hypothesised that minimally invasive necrosectomy reduced death rates.

Methods

Study design

We combined original study data from patients undergoing pancreatic necrosectomy in 51 hospitals who were included in 15 cohorts from specialist pancreatic centres in the USA and Canada (N=4), UK (N=4), Germany (N=2), Hungary (N=2), The Netherlands (N=1), India (N=1) and Brazil (N=1). The cohorts were identified by a predefined systematic literature search. A total of 13 cohorts were published previously.[6-10,19,21-27]For four of these cohorts,[7,10,19,24] additional patients were included of whom the data were unpublished and two cohorts consist of entirely unpublished data. Details on the search, eligibility criteria, included cohorts and quality assessment/risk of bias of individual studies are in the Appendix, Figure A1 and in the online Supplementary Appendix. Once the corresponding author of a cohort agreed to participate, case record forms containing original and additional individual patient data regarding baseline characteristics, method of intervention and clinical outcomes were collected. All data were anonymised. The institutional review boards of the participating centres approved study protocols, if appropriate. The study design was predefined and prospectively registered (www.crd.york.ac.uk/PROSPERO: CRD42014008995). We adhered to the STROBE guidelines (The Strengthening the Reporting of Observational Studies in Epidemiology) and the PRISMA-IPD guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data).[28,29]

Data collection

Data were collected in a standardised manner using an electronic case record form. The following baseline variables were collected: sex, age, tertiary referral, cause of pancreatitis, catheter drainage before necrosectomy, time from hospital admission to necrosectomy, Acute Physiology and Chronic Health Evaluation II (APACHE-II) score and organ failure ≤24 hours before necrosectomy, documented infection of necrosis, and year of necrosectomy. Method of necrosectomy (i.e., open necrosectomy, minimally invasive surgical necrosectomy or endoscopic necrosectomy), complications and death were also recorded. Further details on data collection and definitions of variables are provided in the online Supplementary Appendix (p5-6).

Data were checked for consistency and plausibility. Data were missing in 8 of

the 13 baseline variables, with a range of 0.2%-4.7%. Missing data were imputed by multiple imputation using chained equations. More information on missing data and imputation is available in the online Supplementary Appendix (p6-7).

Statistical analysis

Patients undergoing open necrosectomy were compared with patients undergoing minimally invasive surgical necrosectomy and with patients undergoing endoscopic necrosectomy. The primary endpoint was in-hospital death during index admission. Readmissions within 10 days after discharge from index admission were considered as part of the index admission. Patients were analysed according to the intention-to-treat principle. We anticipated that certain prognostic baseline variables that are associated with death, such as measures of disease severity, would not be evenly distributed among treatment groups. This could be due to selection bias in the individual cohorts or because clinical severity played a role in deciding which method of necrosectomy was performed (i.e., confounding by indication or confounding by severity).[30] To adjust for confounding and to explore effect modification by clinical severity, we performed two main analyses.

The first main analysis was a multivariable logistic regression analysis to evaluate the association between different methods of necrosectomy and death. Formation of a directed acyclic graph was used to aid selection of covariates to be included in the model (see online Supplementary Appendix (p7-13)).[31] The following factors were included as covariates: age, documented infected necrosis, study cohort, time since hospital admission, year of necrosectomy and severity of disease parameters within 24 hours of necrosectomy, and APACHE-II score, cardiovascular failure, pulmonary failure and renal failure. To study the effect of disease severity as a modifier on the outcome, we performed a secondary analysis in which an interaction term for severity with method of necrosectomy was added to the final multivariable model. We chose the APACHE-II score at time of necrosectomy (i.e., APACHE <7, ≥7 to <11, ≥11 to <15, and ≥15) as the disease severity indicator in these analyses because it is a composite of clinical and laboratory parameters indicative of disease severity at a specific point in time.[32]

The second main analysis was a propensity score-matched analysis with risk stratification. Recognising severity of disease as a possible effect modifier (i.e., the beneficial effect of minimally invasive necrosectomy is greater in more severely ill patients), all patients were stratified according to their predicted risk of death at baseline. To accomplish this, a prediction model for the risk of death determined at baseline (i.e., within 24 hours before necrosectomy)

was developed using the data from patients undergoing open necrosectomy (i.e., the control group).[33] First, the univariable association was determined between death and all of the following baseline characteristics: study cohort, sex, age, year of necrosectomy, cause of pancreatitis, tertiary referral, catheter drainage before necrosectomy, documented infected necrosis, time since hospital admission and severity of disease parameters within 24 hours of necrosectomy, APACHE-II score, cardiovascular failure, pulmonary failure and renal failure. All factors with $p<0.1$ were included in a multivariable regression analysis, with forced entry of sex and infected necrosis (i.e., a variable hypothesised to have major prognostic value). Variables were excluded using stepwise backward elimination ($p>0.05$). Variables that remained independently associated with death in the multivariable model were study cohort, age, APACHE-II score, cardiovascular failure, pulmonary failure and renal failure. Performance of the model was very good with an area under the curve of 0.85. We chose this method as opposed to classifying severity of pancreatitis in general by the recently revised Atlanta classification[1] or the determinant-based classification of acute pancreatitis severity[34] because we specifically wanted to determine disease severity at the time of necrosectomy.

Using this model, patients in each treatment group were assigned to one of four baseline categories of predicted risk of death: low (<5%); intermediate (≥5% to <15%); high (≥15% to <35%); or very high (≥35%). Further details on the prediction model and risk stratification are available in the online Supplementary Appendix (p7). Within the four risk groups, patients were matched using their propensity score to create cohorts of patients with similar baseline characteristics. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics and allows one to design and analyse an observational study so that it mimics some of the characteristics of a randomised trial.[35] We developed a non-parsimonious multivariable logistic regression model to estimate a propensity score for minimally invasive surgical necrosectomy and endoscopic necrosectomy. This included study cohort as a cofactor to adjust for potential hidden confounders (e.g., better supportive intensive care in more recent years). Details of the individual variables included in the model are provided in the online Supplementary Appendix (p8). Patients undergoing minimally invasive surgical necrosectomy or endoscopic necrosectomy were matched 1:1 with patients undergoing open necrosectomy using their propensity score with the nearest neighbour matching algorithm without replacement (a calliper width equal to 0.2 of the SD of the logit score was used). Standardised differences were estimated for all the baseline covariates to assess imbalance before matching and balance after matching. A standardised

difference of less than 10% indicates appropriate balance.[35]

Results of multivariable regression analysis are given as ORs and 95% CIs. Differences in death rates were tested with the McNemar's test for paired data in the matched cohorts. Comparisons of death rates are presented as risk ratios. All tests were two-tailed and p-values of less than 0.05 were considered statistically significant.

Predefined subgroup analyses were performed for patients with infected necrosis and for patients who underwent previous catheter drainage. Several other sensitivity analyses were performed in the comparison of minimally invasive necrosectomy and open necrosectomy (see online Supplementary Appendix (p8)). We also compared endoscopic necrosectomy with minimally invasive surgical necrosectomy on the primary outcome death using propensity score matching and risk stratification.

Results

Study population

We included 1980 patients who underwent pancreatic necrosectomy; a total of 1167 patients underwent open necrosectomy, 467 patients underwent minimally invasive surgical necrosectomy and 346 patients underwent endoscopic necrosectomy. Baseline characteristics for the entire study population and per study cohort are presented in the online Supplementary Appendix (p21-23). A total of 325 out of 1980 patients (16%) in the study died during index admission.

Logistic regression adjusted analysis

While adjusting for confounders (i.e. cohort, age, documented infected necrosis, study cohort, time since hospital admission, year of necrosectomy and severity of disease parameters within 24 hours of necrosectomy, APACHE-II score, cardiovascular failure, pulmonary failure and renal failure), method of necrosectomy was significantly associated with death (see online Supplementary Appendix (p24). Compared with open necrosectomy, minimally invasive surgical necrosectomy displayed an OR of 0.53 (95% CI 0.34 to 0.84; p=0.006), and endoscopic necrosectomy an OR of 0.20 (95% CI 0.06 to 0.63; p=0.006).

Inclusion of the interaction term 'disease severity (APACHE-II score) by method of necrosectomy' showed that endoscopic necrosectomy was associated with less mortality irrespective of the APACHE-II score (OR 0.13; 95% CI 0.02 to 0.95; p=0.04). The interaction term 'APACHE-II score by minimally invasive surgical necrosectomy' confirmed that clinical severity is an effect modifier, as minimally invasive surgical necrosectomy only remained associated with less mortality in patients with the highest APACHE-II scores (OR 0.27; 95% CI 0.08 to 0.88; p=0.03).

Detailed results of this secondary regression analyses are provided in the online Supplementary Appendix (p25).

Propensity score-matched analysis with risk stratification

Using a multivariable prediction model (see online Supplementary Appendix (p26)), patients were stratified according to their predicted risk of death at baseline. Stratification was considered successful because there were no major differences in predicted risk of death for patients undergoing open necrosectomy, minimally invasive surgical necrosectomy and endoscopic necrosectomy, respectively: low-risk group: median 2% (IQR, 1%-3%) vs. median 3% (IQR, 0%-4%) vs. median 4% (IQR, 2%-4%); intermediate-risk group: median 9% (IQR, 7%-11%) vs. median 9% (IQR, 7%-12%) vs. median 10% (IQR, 8%-12%); high-risk group: median 24% (IQR, 18%-29%) vs. median 22% (IQR, 19%-29%) vs. median 22% (IQR, 19%-27%); and very high-risk group: median 52% (IQR, 43%-64%) vs. median 58% (IQR, 45%-78%) vs. 51% (IQR, 42%-72%).

Subsequently, a total of 376 patients who underwent minimally invasive surgical necrosectomy were matched with 376 patients who underwent open necrosectomy, and a total of 198 patients who underwent endoscopic necrosectomy were matched with 198 patients who underwent open necrosectomy. Baseline characteristics in each risk group for unmatched and matched cohorts are presented in Tables 1 and 2. In the unmatched cohorts, although predicted risk of death was similar within each of the four risk groups, significant imbalance in individual baseline characteristics remained after risk stratification, as indicated by standardised mean differences greater than 10%. The matched cohorts were well balanced for all baseline characteristics because none of the standardised differences exceeded 10%. There was sufficient overlap in propensity scores as is shown in the online Supplementary Appendix Figures 4 and 5.

Actual death rates in the matched cohorts in each risk group are shown in Figure 1. Minimally invasive surgical necrosectomy was associated with a lower risk of death than open necrosectomy in the very high-risk group (risk ratio 0.70; 95% CI 0.52 to 0.95; p=0.02). Endoscopic necrosectomy was associated with a lower risk of death than open necrosectomy in the high- risk group (risk ratio 0.27; 95% CI 0.08 to 0.88; p=0.03) and the very high-risk group (risk ratio 0.43; 95% CI 0.24 to 0.77; p=0.005), with judgement suspended in the intermediate-risk group (risk ratio 0.14; 95% CI 0.02 to 1.10; p=0.06).

Subgroup and sensitivity analyses

The propensity score-matched analysis was also performed in the subgroups of patients with documented infected necrosis (403 patients (86%) in the minimally

invasive surgical group, 197 patients (57%) in the endoscopic group and 885 patients (76%) in the open necrosectomy group) and in patients who underwent previous catheter drainage (436 patients (93%) in the minimally invasive surgical group, 178 patients (51%) in the endoscopic group and 210 patients (18%) in the open necrosectomy group). Baseline characteristics for the unmatched and the matched cohorts and the actual death rates after matching are provided in the online Supplementary Appendix (p27-42). Results were in line with the primary analyses.

Exclusion of patients undergoing necrosectomy before 3 weeks (i.e., <22 days) after admission from the matched cohorts resulted in loss of nearly half of all pairs in each of the two compared groups. Patients undergoing minimally invasive necrosectomy still had lower death rates, although statistical significance was no longer reached (see online Supplementary Appendix p59).

As alternative risk stratification, patients were stratified according to their APACHE-II score within 24 hours before necrosectomy (i.e., <7, ≥7 to <11, ≥11 to <15, and ≥15) and matched with propensity score matching (online Supplementary Appendix (p43-48)). Similar to the primary analyses, minimally invasive surgical necrosectomy and endoscopic necrosectomy were associated with a lower actual death rate in the higher APACHE-II groups (see online Supplementary Appendix (p49-50)).

In addition to death, other study outcomes included postoperative complications (i.e., bleeding and pancreatic fistula), number of necrosectomies and hospital stay after necrosectomy. In the matched cohorts, bleeding occurred in 5%-19% of patients and was more frequent in the higher risk of death groups. There was no statistically significant difference for the complication bleeding between minimally invasive necrosectomy methods and open necrosectomy. Pancreatic fistula occurred in 4%-35% of patients, was more frequent in patients at lower risk of death and occurred more often in patients who underwent open necrosectomy. Overall, patients who underwent minimally invasive surgical necrosectomy had the longest hospital stay after necrosectomy (median over the four risk groups ranging from 32 to 59 days), followed by open necrosectomy (median ranging from 21 to 52 days) and endoscopic necrosectomy (median ranging from 5 to 42 days). The number of necrosectomies was highest in the endoscopic groups (median ranging from 3 to 4), followed by the minimally invasive surgical groups (median ranging from 2 to 3) and open necrosectomy groups (median 1). Detailed results with respect to all other outcomes in each risk group are provided in the online Supplementary Appendix (p51-54).

In our secondary comparison of endoscopic necrosectomy with minimally

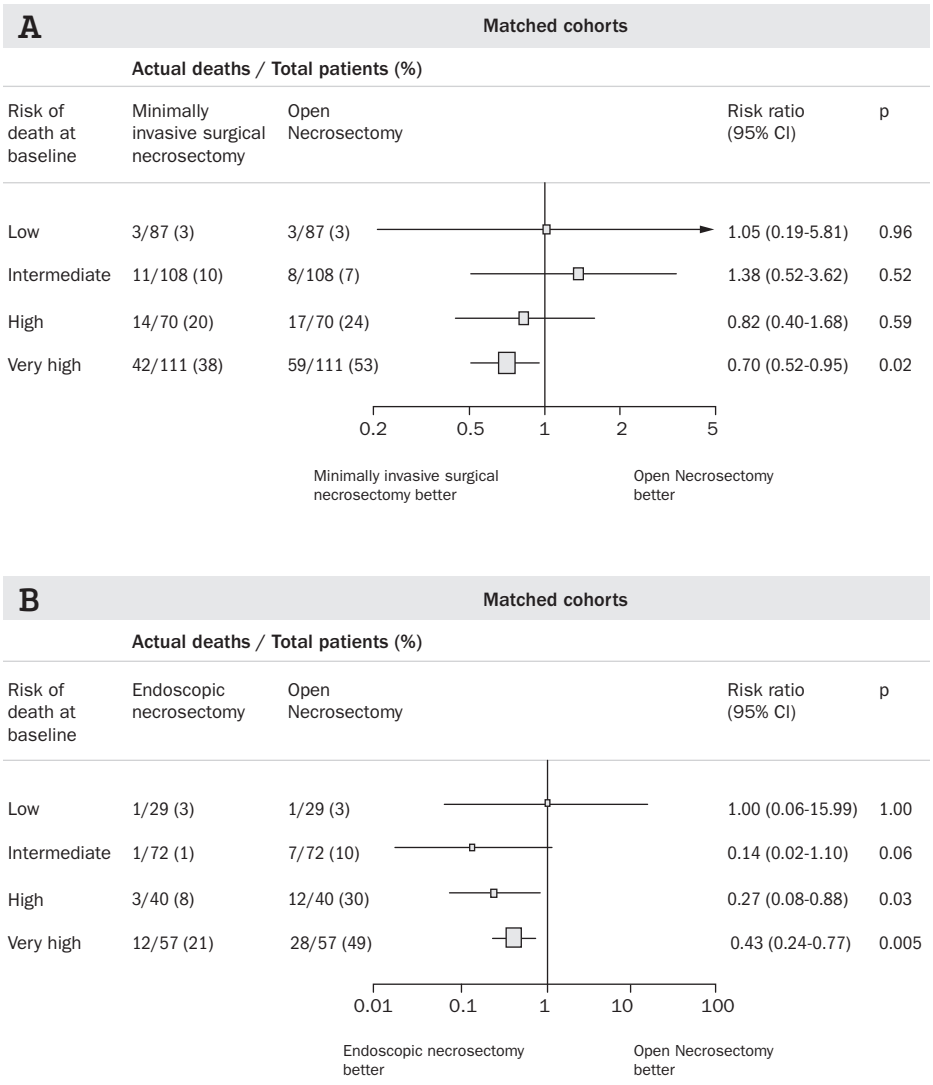

Figure 1. *Death rates in patients undergoing minimally invasive surgical necrosectomy and endoscopic necrosectomy as compared with patients undergoing open necrosectomy. Shown are actual death rates / total patients (%) for patients undergoing minimally invasive surgical necrosectomy (A) and endoscopic necrosectomy (B) as compared with patients undergoing open necrosectomy in the propensity-score matched cohorts. Patients are stratified in four risk groups based on predicted death at baseline (Low: <5%, Intermediate: ≥5% to <15%, High: ≥15% to <35% and Very high: ≥35%) which was determined by a multivariable prediction model incorporating study cohort (ie, to adjust for hidden confounders), age, APACHE-II score, cardiovascular failure, pulmonary failure, and renal failure in the 24 hours before necrosectomy.*

invasive surgical necrosectomy, 215 patient pairs were matched. Baseline characteristics before and after matching in each risk group are presented in the online Supplementary Appendix (p55-57). In the matched cohorts, the differences in death rates between the endoscopic groups and minimally invasive surgical groups were not statistically significant (see online Supplementary Appendix (p28)).

Discussion

In this international collaborative study involving 1980 patients with necrotising pancreatitis from 51 hospitals across 8 countries, minimally invasive surgical necrosectomy or endoscopic necrosectomy compared with open necrosectomy significantly decreased mortality among high-risk patients. In contrast to meta-analyses which pool data directly from published results (i.e., paper analysis), this study provides a combined analysis of original, individual patient data of previously published cohorts (including unpublished data from ongoing registries) and unpublished cohorts.

A large number of, mostly retrospective, cohort studies have reported outcomes of patients undergoing minimally invasive pancreatic necrosectomy. Few studies, however, have directly compared minimally invasive necrosectomy with open necrosectomy. One meta-analysis, based on paper analysis of four studies, compared 215 patients undergoing minimally invasive surgical necrosectomy with 121 patients undergoing open necrosectomy.[18] Mortality was 17% after minimally invasive surgical necrosectomy versus 30% after open necrosectomy (OR 0.43; 95% CI 0.01 to 8.60; p=0.06). This meta-analysis, however, suffered from significant heterogeneity. Another single- centre study compared 274 patients undergoing minimally invasive surgical necrosectomy with 120 patients undergoing open necrosectomy; mortality was 15% vs. 23% (p=0.06).[12] Our study, with individual patient data, differed from these earlier studies because of its much larger sample size, and as a consequence the possibility to analyse different risk groups and to adjust for the effects of confounding and selection bias. Moreover, this study was novel in performing a head-to-head comparison of patients undergoing different methods of necrosectomy, in contrast to a previously published randomised study comparing open necrosectomy with a step-up approach (i.e., catheter drainage followed, if necessary, by minimally invasive necrosectomy)[15] and a recently finished trial comparing an endoscopic step-up approach with a surgical step-up approach (ISRCTN09186711).

How can the lower death rates after minimally invasive necrosectomy be explained? It is well known that, in various diseases, minimally invasive

surgical techniques induce less surgical stress and thereby lead to a lower systemic proinflammatory response compared with open surgery.[36,37] This was also demonstrated in necrotising pancreatitis: in the only randomised trial that compared endoscopic necrosectomy with surgical necrosectomy (a total of 20 patients), endoscopic necrosectomy reduced the levels of the proinflammatory cytokine interleukin (IL)-6 during the 7 days after the procedure.[17] The more pronounced proinflammatory response invoked by open necrosectomy may facilitate organ failure or worsen pre-existing organ failure, especially in patients who are already suffering from a severe inflammatory condition such as necrotising pancreatitis.[15] This seems of particular importance because organ failure is the main determinant for mortality in patients with necrotising pancreatitis, especially in the presence of infected necrosis.[38] The same trial that demonstrated lower levels of IL-6 after endoscopic necrosectomy also showed lower rates of postprocedure multiple organ failure.[17] A reduction in multiple organ failure with less surgical stress was also seen in another randomised trial that compared primary catheter drainage with open necrosectomy in 88 patients with necrotising pancreatitis.[15] In contrast with these previous trials,[15,17] we did not study the rate of organ failure as a surrogate outcome. Our study was designed to evaluate the most relevant clinical endpoint of mortality, with a sufficiently large number of patients, even in the subgroups of the most severely ill patients.

Our results suggest that patients with necrotising pancreatitis who are severely ill should undergo minimally invasive surgical or endoscopic necrosectomy instead of open necrosectomy, given the expertise in these minimally invasive techniques is available. If the expertise is absent and the patient is clinically unfit for transport to a tertiary referral centre, open necrosectomy may still be acceptable. In the propensity score-matched analysis, we did not find significantly lower death rates in the low-risk and intermediate-risk groups. These patients, who are in a relatively stable clinical condition, seem capable of sustaining the larger surgical stress and proinflammatory hit induced by open necrosectomy. Another explanation may be that, due to their lower a priori risk of death, the subgroup of less severely ill patients was too small to detect a difference in death between methods of necrosectomy. This is supported by the wide 95% CIs observed in these groups (Figure 1). One could therefore argue that open necrosectomy is still a reasonable treatment option in these patients. However, other reasons to prefer minimally invasive necrosectomy techniques are lower rates of pancreatic fistula as shown in our study and lower rates of long-term complications such as incisional hernias and endocrine or exocrine pancreatic insufficiency.[15,17]

To fill the existing evidential gap on clinical outcome superiority for the increasing popularity of minimally invasive necrosectomy, the primary aim of our study was to compare minimally invasive necrosectomy with open necrosectomy on the outcome in-hospital death. In our secondary analysis we compared endoscopic necrosectomy with minimally invasive surgical necrosectomy. Although endoscopic treatment is considered the least invasive necrosectomy method, we did not find a statistically significant decrease in mortality. This could be explained by a type II error. Endoscopic techniques are rapidly developing, for example with the recent introduction of lumen apposing metal stents which show promising results with high clinical success rates.[39] It is therefore expected that in the evolution of necrosectomy techniques, a shift will occur from open necrosectomy to minimally invasive necrosectomy to an increase in the use of endoscopic techniques.

Our study does not have the preferred design of a randomised trial. It is therefore possible that measurement errors and hidden or unknown confounding factors, which are not accounted for in our analyses, may have influenced results. Using per-protocol predefined case record forms for data extraction and well-defined patient inclusion criteria, however, reduced the risk of measurement errors to a minimum. The included cohorts did not capture data on preoperative imaging, such as extent and location of peripancreatic necrosis on CT. These factors likely influenced the decisions to perform minimally invasive or open necrosectomy in certain patients. For instance, small and centrally located peripancreatic collections are best accessible by endoscopy, whereas collections extending to the paracolic gutter may prefer a minimally invasive surgical approach. Notably, not all patients with necrotising pancreatitis are candidates for minimally invasive techniques. A small minority of patients with extensive collections may only be suitable for an open surgical approach. Also, the time period in which necrosectomy was performed may have introduced unknown confounders (e.g., supportive treatment on the intensive care unit may have improved over the years). As all three necrosectomy methods were performed in the most recent years (1998 and onward), overlap was judged to be sufficient for adjustment for year of necrosectomy in our first main (multivariable regression) analyses. This does not exclude all risks of lack of overlap in the regression analysis, however, because it may have led to extrapolation of the results from previous years to newer years. The insufficient overlap in the variable 'year of necrosectomy' between minimally invasive necrosectomy methods and open necrosectomy precluded the inclusion of year of necrosectomy as a factor in the propensity score matching. Too many patients from the control group (i.e., open necrosectomy) would have been excluded, which

would have led to a significant loss of matched pairs. We performed our study in the largest known cohort of patients undergoing necrosectomy for necrotising pancreatitis. In our analyses, we adjusted for important factors widely recognised as being associated with death. Unfortunately, the risk of residual confounding, which can only be eliminated by a randomised design, remains apparent. A randomised trial with a sample size large enough to detect a difference in mortality will, however, be very difficult to realise and no such trial is currently planned. Future randomised studies concentrating on patient-oriented outcomes such as health-related quality of life and hospital stay may serve as a valuable alternative. Until these are available, large observational studies, despite their inherent risk of persisting bias, yield the best available evidence to guide clinical decision making in this severe and complex disease. Because patients from 51 hospitals across 8 countries and 3 continents were included in this study, we believe our results are generalisable to patient populations with necrotising pancreatitis.

In conclusion, among severely ill patients with necrotising pancreatitis, minimally invasive surgical necrosectomy and endoscopic necrosectomy are associated with reduced death rates compared with open necrosectomy.

Table 1. Baseline characteristics before and after propensity score matching of patients undergoing minimally invasive surgical necrosectomy or open necrosectomy.

Characteristic	Before matching		
	Minimally invasive surgical necrosectomy (N=97)	Open necrosectomy (N=377)	Standardised difference (%)
Low risk of death (<5%)			
Male sex[#]	65 (68)	276 (73)	12.7
Age	43±12	44±13	9.5
Cause[#]			
Gallstones	50 (51)	111 (29)	46.2
Alcohol	28 (29)	177 (47)	38.0
Other	19 (20)	89 (24)	9.7
APACHE-II score*	6.0±3.4	7.7±4.2	47.0
Cardiovascular failure[#*†]	0 (0)	7 (2)	19.7
Pulmonary failure[#*‡]	3 (3)	30 (8)	21.2
Renal failure[#*§]	2 (2)	10 (3)	4.2
Documented infected necrosis[#¶]	88 (91)	279 (74)	47.0
Tertiary referral[#]	77 (80)	205 (55)	56.3
Time since hospital admission, days	56±53	51±133	5.2
	Minimally invasive surgical necrosectomy (N=119)	**Open necrosectomy (N=343)**	**Standardised difference (%)**
Intermediate risk of death (≥5% to <15%)			
Male sex[#]	82 (69)	229 (67)	5.1
Age	54±15	53±14	5.9
Cause[#]			
Gallstones	65 (55)	139 (40)	29.2
Alcohol	29 (24)	119 (35)	23.0
Other	25 (21)	85 (25)	9.6
APACHE-II score*	7.9±3.0	10.0±4.1	57.9

After matching		
Minimally invasive surgical necrosectomy (N=87)	Open necrosectomy (N=87)	Standardised difference (%)
63 (72)	61 (70)	4.1
44±12	45±14	5.7
40 (46)	38 (44)	5.5
28 (32)	27 (31)	1.5
19 (22)	22 (25)	8.0
6.3±3.4	6.0±3.7	6.3
0 (0)	0 (0)	0
3 (3)	3 (3)	0.5
2 (2)	2 (2)	3.9
79 (90)	79 (90)	0.6
68 (78)	68 (78)	1.2
56±54	66±158	7.6
Minimally invasive surgical necrosectomy (N=108)	**Open necrosectomy (N=108)**	**Standardised difference (%)**
74 (69)	73 (68)	2.0
54±14	55±13	6.2
56 (52)	53 (49)	5.3
28 (26)	30 (28)	3.3
24 (22)	25 (23)	2.6
8.2±2.8	8.1±3.5	4.6

Table 1. Continued

Characteristic	Before matching		
	Minimally invasive surgical necrosectomy (N=119)	Open necrosectomy (N=343)	Standardised difference (%)
Intermediate risk of death (≥5% to <15%, continued)			
Cardiovascular failure#*†	3 (3)	65 (19)	53.2
Pulmonary failure#*‡	8 (7)	113 (33)	68.1
Renal failure#*§	5 (4)	42 (12)	29.7
Documented infected necrosis#¶	95 (80)	270 (79)	3.2
Tertiary referral#	95 (80)	208 (61)	43.3
Time since hospital admission, days	48±41	30±27	50.0
	Minimally invasive surgical necrosectomy (N=120)	**Open necrosectomy (N=225)**	**Standardised difference (%)**
High risk of death (≥15% to <35%)			
Male sex#	65 (54)	140 (62)	17.5
Age	57±13	58±14	7.1
Cause#			
Gallstones	72 (60)	88 (39)	43.0
Alcohol	31 (25)	81 (36)	23.2
Other	17 (15)	56 (25)	26.3
APACHE-II score*	10.1±4.3	12.8±4.2	62.2
Cardiovascular failure#*†	25 (21)	98 (44)	51.2
Pulmonary failure#*‡	25 (21)	145 (65)	97.6
Renal failure#*§	7 (6)	65 (29)	64.7
Documented infected necrosis#¶	97 (81)	182 (81)	0.5
Tertiary referral#	99 (83)	160 (71)	27.4
Time since hospital admission, days	35±22	24±19	56.4

After matching		
Minimally invasive surgical necrosectomy (N=108)	Open necrosectomy (N=108)	Standardised difference (%)
3 (3)	3 (3)	5.8
8 (8)	6 (6)	8.4
5 (5)	4 (4)	6.0
87 (81)	88 (82)	2.0
84 (78)	82 (76)	4.3
43±33	41±36	5.1

Minimally invasive surgical necrosectomy (N=70)	Open necrosectomy (N=70)	Standardised difference (%)
43 (61)	44 (63)	4.1
59±13	59±14	4.2
35 (50)	36 (51)	1.7
21 (30)	21 (30)	0.6
14 (20)	13 (19)	3.0
11.3±3.9	11.2±3.5	0.9
20 (29)	22 (31)	4.3
23 (32)	24 (34)	4.8
7 (10)	7 (10)	2.8
60 (85)	61 (87)	3.3
58 (83)	58 (83)	0.4
29±14	29±22	1.6

Table 1. Continued

Characteristic	Before matching		
	Minimally invasive surgical necrosectomy (N=131)	Open necrosectomy (N=222)	Standardised difference (%)
Very high risk of death (≥35%)			
Male sex#	81 (62)	146 (66)	8.2
Age	63±12	62±14	5.5
Cause#			
Gallstones	74 (56)	99 (44)	23.7
Alcohol	37 (29)	66 (30)	2.3
Other	20 (15)	57 (26)	26.8
APACHE-II score*	16.8±5.7	16.6±5.3	3.3
Cardiovascular failure#*†	91 (69)	179 (81)	25.9
Pulmonary failure#*‡	90 (69)	182 (82)	30.9
Renal failure#*§	59 (45)	123 (55)	21.0
Documented infected necrosis#¶	123 (94)	154 (69)	67.3
Tertiary referral#	115 (88)	168 (76)	31.4
Time since hospital admission, days	30±15	22±18	50.3

 # Data: N (%). ± Values are mean ±SD. A value of less than 10.0% of the standardised difference indicates a negligible difference between groups. Patients are stratified in four risk groups based on predicted death at baseline, which was determined by a multivariable prediction model incorporating study cohort, APACHE-II score, cardiovascular failure, pulmonary failure and renal failure in the 24 hours before necrosectomy (details on prediction model in the online Supplementary Appendix p7).

** Within 24 hours before necrosectomy. † Circulatory systolic blood pressure <90 mm Hg, despite adequate fluid resuscitation or need for inotropic catecholamine support. ‡ PaO_2 <60 mm Hg, despite FIO_2 of 30% or need for mechanical ventilation. § Creatinine level >177 µmol/L after rehydration or need for haemofiltration or haemodialysis. ¶ Positive microbiological culture from fine-needle aspiration before necrosectomy or from first catheter drainage before necrosectomy or from primary necrosectomy.*

	After matching		
	Minimally invasive surgical necrosectomy (N=111)	Open necrosectomy (N=111)	Standardised difference (%)
	68 (62)	70 (63)	2.6
	62±12	63±13	0.9
	62 (56)	66 (60)	7.3
	30 (27)	29 (26)	1.2
	19 (17)	16 (14)	8.5
	17.0±5.7	17.1±5.5	1.2
	81 (74)	84 (76)	5.8
	79 (72)	78 (70)	2.0
	53 (48)	50 (45)	4.4
	103 (93)	105 (95)	7.5
	95 (86)	92 (83)	5.4
	30±15	28±19	8.9

Table 2. Baseline characteristics before and after propensity score matching of patients undergoing endoscopic necrosectomy or open necrosectomy.

Characteristic	Before matching		
	Endoscopic necrosectomy (N=31)	**Open necrosectomy (N=377)**	**Standardised difference (%)**
Low risk of death (<5%)			
Male sex[#]	22 (71)	276 (73)	5.3
Age	39±11	44±13	49.4
Cause[#]			
Gallstones	10 (32)	111 (29)	6.3
Alcohol	8 (26)	177 (47)	45.2
Other	13 (42)	89 (24)	39.8
APACHE-II score*	3.3±2.9	7.7±4.2	124.8
Cardiovascular failure[#*†]	0	7 (2)	19.5
Pulmonary failure[#*‡]	0	30 (8)	42.4
Renal failure[#*§]	0	10 (3)	23.4
Documented infected necrosis[#¶]	12 (39)	279 (74)	76.5
Tertiary referral[#]	25 (81)	205 (55)	57.8
Time since hospital admission, days	88±118	51±133	29.7
	Endoscopic necrosectomy (N=120)	**Open necrosectomy (N=343)**	**Standardised difference (%)**
Intermediate risk of death (≥5% to <15%)			
Male sex[#]	85 (71)	229 (67)	9.2
Age	50±14	53±14	2.1
Cause[#]			
Gallstones	57 (48)	139 (40)	14.3
Alcohol	29 (24)	119 (35)	23.4
Other	34 (28)	85 (25)	8.0
APACHE-II score*	6.5±3.1	10.0±4.1	96.7

After matching		
Endoscopic necrosectomy (N=29)	**Open necrosectomy (N=29)**	**Standardised difference (%)**
21 (72)	21 (72)	1.4
39±11	40±10	1.1
8 (28)	8 (28)	0.3
8 (28)	8 (28)	0.3
13 (44)	13 (44)	0.1
3.7±2.9	3.1±2.8	10.0
0	0	0
0	0	0
0	0	0
11 (38)	12 (41)	8.4
23 (79)	23 (79)	3.2
89±121	86±203	7.6
Endoscopic necrosectomy (N=72)	**Open necrosectomy (N=72)**	**Standardised difference (%)**
49 (68)	48 (67)	2.4
53±14	54±13	3.6
33 (46)	34 (47)	1.2
20 (28)	21 (29)	3.1
19 (26)	17 (24)	4.7
7.4±2.8	7.4±3.6	0.5

Table 2. Continued

Characteristic	Before matching		
	Endoscopic necrosectomy (N=120)	Open necrosectomy (N=343)	Standardised difference (%)
Intermediate risk of death (≥5% to <15%, continued)			
Cardiovascular failure#*†	0	65 (19)	68.1
Pulmonary failure#*‡	1 (1)	113 (33)	94.5
Renal failure#*§	0	42 (12)	52.9
Documented infected necrosis#¶	59 (49)	270 (79)	64.3
Tertiary referral#	80 (67)	208 (61)	12.8
Time since hospital admission, days	48±51	30±27	42.9
	Endoscopic necrosectomy (N=133)	**Open necrosectomy (N=225)**	**Standardised difference (%)**
High risk of death (≥15% to <35%)			
Male sex#	68 (51)	140 (62)	22.9
Age	59±12	58±14	6.0
Cause#			
Gallstones	66 (50)	88 (39)	21.5
Alcohol	27 (20)	81 (36)	35.8
Other	40 (30)	56 (25)	11.7
APACHE-II score*	8.9±2.9	12.8±4.2	105.2
Cardiovascular failure#*†	11 (8)	98 (44)	88.2
Pulmonary failure#*‡	7 (5)	145 (65)	158.9
Renal failure#*§	2 (2)	65 (29)	82.6
Documented infected necrosis#¶	76 (57)	182 (81)	53.3
Tertiary referral#	96 (72)	160 (71)	2.1
Time since hospital admission, days	59±84	24±19	57.7

	After matching		
	Endoscopic necrosectomy (N=72)	Open necrosectomy (N=72)	Standardised difference (%)
	0	0	0
	1 (1)	1 (1)	6.7
	0	0	0
	46 (64)	47 (65)	3.1
	46 (64)	45 (63)	1.0
	36±30	37±29	2.9
	Endoscopic necrosectomy (N=40)	Open necrosectomy (N=40)	Standardised difference (%)
	23 (58)	25 (63)	9.2
	60±13	60±14	1.5
	16 (40)	18 (45)	5.1
	13 (32)	12 (30)	3.5
	11 (28)	10 (25)	2.8
	10.6±2.8	10.5±2.7	5.4
	9 (23)	10 (25)	4.5
	7 (18)	7 (18)	1.5
	2 (5)	3 (8)	6.2
	32 (80)	32 (80)	2.7
	29 (73)	31 (78)	9.3
	27±15	27±20	3.5

Table 2. Continued

Characteristic	Before matching		
	Endoscopic necrosectomy (N=62)	Open necrosectomy (N=222)	Standardised difference (%)
Very high risk of death (≥35%)			
Male sex[#]	40 (65)	146 (66)	2.3
Age	64±14	62±14	10.9
Cause[#]			
Gallstones	37 (60)	99 (44)	30.6
Alcohol	14 (22)	66 (30)	16.1
Other	11 (18)	57 (26)	19.7
APACHE-II score*	16.0±6.2	16.6±5.3	11.9
Cardiovascular failure[#*†]	33 (53)	179 (81)	60.5
Pulmonary failure[#*‡]	35 (56)	182 (82)	57.6
Renal failure[#*§]	18 (29)	123 (55)	55.3
Documented infected necrosis[#¶]	50 (81)	154 (69)	26.8
Tertiary referral[#]	48 (77)	168 (76)	3.8
Time since hospital admission, days	36±24	22±18	65.0

 # Data: N (%). ± Values are mean ±SD. A value of less than 10.0% of the standardised difference indicates a negligible difference between groups. Patients are stratified in four risk groups based on predicted death at baseline, which was determined by a multivariable prediction model incorporating study cohort, APACHE-II score, cardiovascular failure, pulmonary failure and renal failure in the 24 hours before necrosectomy (details on prediction model in the online Supplementary Appendix p7).

** Within 24 hours before necrosectomy. † Circulatory systolic blood pressure <90 mm Hg, despite adequate fluid resuscitation or need for inotropic catecholamine support. ‡ PaO_2 <60 mm Hg, despite FIO_2 of 30% or need for mechanical ventilation. § Creatinine level >177 µmol/L after rehydration or need for haemofiltration or haemodialysis. ¶ Positive microbiological culture from fine-needle aspiration before necrosectomy or from first catheter drainage before necrosectomy or from primary necrosectomy.*

	After matching		
	Endoscopic necrosectomy (N=57)	Open necrosectomy (N=57)	Standardised difference (%)
	37 (65)	35 (61)	5.0
	63±14	63±14	0.4
	34 (59)	33 (58)	0.6
	14 (25)	13 (23)	4.6
	9 (16)	11 (19)	5.3
	16.2±6.4	16.4±5.3	2.8
	33 (58)	34 (60)	4.3
	35 (61)	34 (60)	1.3
	18 (32)	16 (28)	6.2
	46 (81)	46 (81)	0.2
	45 (79)	43 (76)	6.7
	33±17	33±22	2.9

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APPENDIX CHAPTER 9

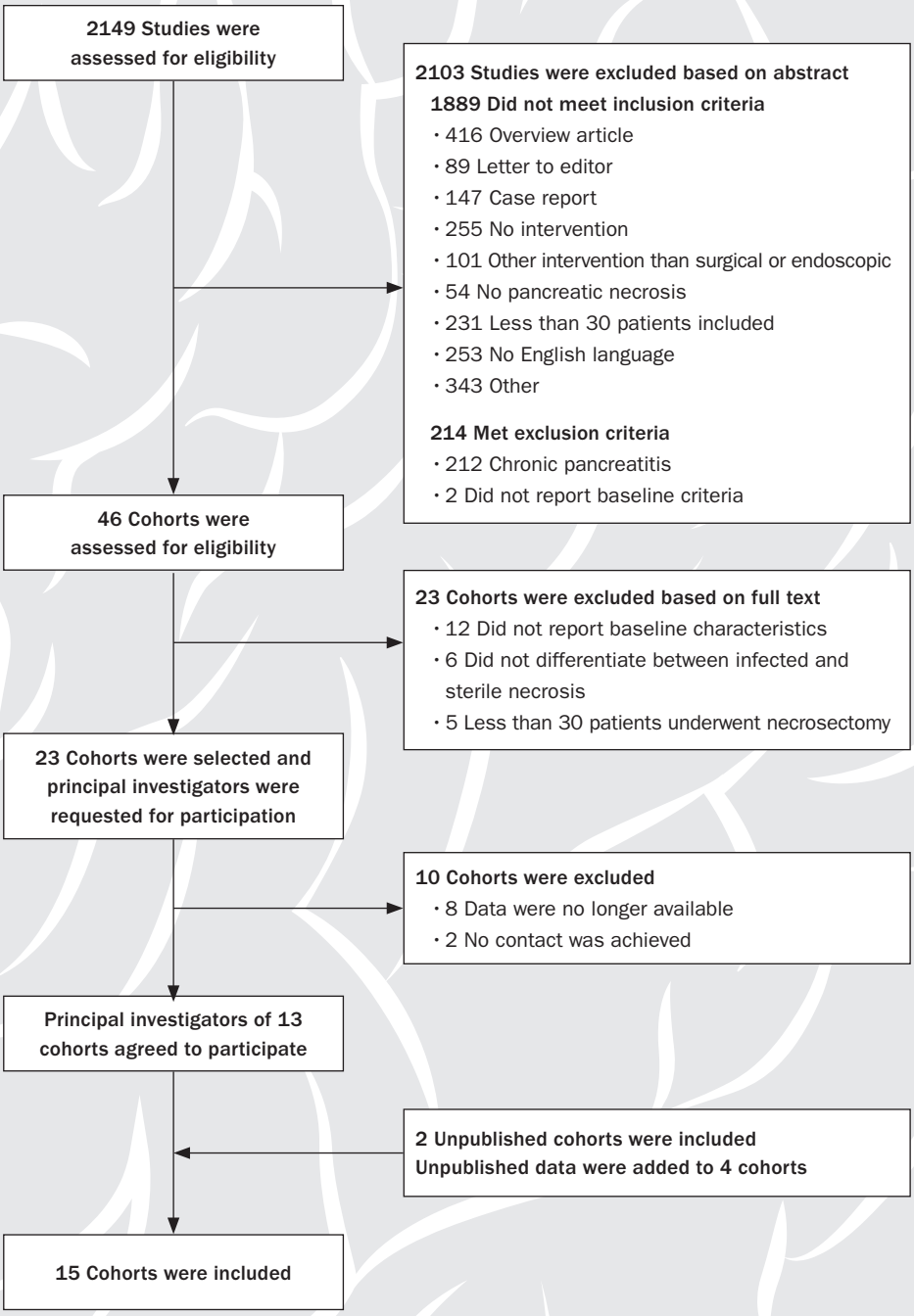

Figure A1. *Study inclusion flow chart.*

CHAPTER 10

Endoscopic or surgical step-up approach for infected necrotising pancreatitis

A MULTICENTRE RANDOMISED TRIAL

The Lancet 2017

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Abstract

Background

Infected necrotising pancreatitis is a potentially lethal disease and an indication for invasive intervention. The surgical step-up approach is the standard treatment. A promising alternative is the endoscopic step-up approach. We compared both approaches to see whether the endoscopic step-up approach was superior to the surgical step-up approach in terms of clinical and economic outcomes.

Methods

In this multicentre, randomised, superiority trial, we recruited adult patients with infected necrotising pancreatitis and an indication for invasive intervention from 19 hospitals in the Netherlands. Patients were randomly assigned to either the endoscopic or the surgical step-up approach. The endoscopic approach consisted of endoscopic ultrasound-guided transluminal drainage followed, if necessary, by endoscopic necrosectomy. The surgical approach consisted of percutaneous catheter drainage followed, if necessary, by video-assisted retroperitoneal debridement. The primary endpoint was a composite of major complications or death during 6-month follow-up. Analyses were by intention to treat. This trial is registered with the ISRCTN registry, number ISRCTN09186711.

Findings

Between Sept 20, 2011, and Jan 29, 2015, we screened 418 patients with pancreatic or extrapancreatic necrosis, of which 98 patients were enrolled and randomly assigned to the endoscopic step-up approach (N=51) or the surgical step-up approach (N=47). The primary endpoint occurred in 22 (43%) of 51 patients in the endoscopy group and in 21 (45%) of 47 patients in the surgery group (risk ratio [RR] 0.97, 95% CI 0.62 to 1.51; p=0.88). Mortality did not differ between groups (9 [18%] patients in the endoscopy group versus 6 [13%] patients in the surgery group; RR 1.38, 95% CI 0.53 to 3.59, p=0.50), nor did any of the major complications included in the primary endpoint.

Interpretation

In patients with infected necrotising pancreatitis, the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group. The outcome of this trial will probably result in a shift to the endoscopic step-up approach as treatment preference.

Introduction

Acute pancreatitis is a potentially lethal disease with increasing incidence. Approximately 10%-20% of patients develop necrosis of pancreatic parenchyma or extrapancreatic tissues.[1,2] Moreover, about one third of these patients develop infection of the necrotic tissue, which generally requires an invasive intervention.[3]

In the past 10 years, the surgical stepup approach, consisting of percutaneous catheter drainage followed, if necessary, by minimally invasive necrosectomy, has replaced open surgery as the standard treatment.[4,5] A randomised trial of the surgical stepup approach versus primary open necrosectomy showed that catheter drainage as a first step obviates the need for necrosectomy in 35%-50% of patients.[4,6]

An endoscopic stepup approach is a potentially less invasive alternative. Endoscopic necrosectomy has shown promising results in reducing complications in several observational studies and one small pilot randomised trial.[7,8] These favourable results were explained by the absence of general anaesthesia and surgical exploration with a reduction of surgical stress and surgery associated complications such as pancreatic fistulas. The endoscopic approach can also be performed in a stepup fashion, starting with endoscopic transluminal drainage, only to be followed by endoscopic necrosectomy if drainage does not result in clinical improvement.

We did a multicentre randomised trial to investigate whether the endoscopic stepup approach is superior to the surgical step-up approach in patients with infected necrotising pancreatitis.

Methods

Study design and participants

In this multicentre, randomised, superiority trial, we recruited adult (≥18 years of age) patients from seven university medical centres and 12 teaching hospitals of the Dutch Pancreatitis Study Group with a high suspicion or evidence of infection of pancreatic or extrapancreatic necrotic tissues (i.e., infected necrosis) with an indication for invasive intervention, for whom both the endoscopic and surgical step-up approach were deemed feasible by a multidisciplinary expert panel. We defined infected necrosis as a positive culture obtained by fine-needle aspiration or the presence of gas within necrotic collections on contrast-enhanced CT. Infected necrosis was suspected in necrotising pancreatitis patients with clinical signs of persistent sepsis or progressive clinical deterioration despite maximal support on the intensive care unit (ICU) without other causes for infection. Key exclusion criteria were previous

invasive interventions for necrotising pancreatitis, chronic pancreatitis, and recurrent acute pancreatitis. Further exclusion criteria are given in the Appendix.

All patients or their legal representatives provided written informed consent before randomisation. The study protocol[9] was approved by the institutional review board of the Academic Medical Centre Amsterdam and all other participating centres, and the study was conducted according to this protocol. All authors vouched for the accuracy and completeness of the data and analyses.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to either the endoscopic step-up approach or the surgical step-up approach. Block randomisation with a concealed, fixed block size and stratified by treatment centres was performed centrally by the study coordinator (SvB and JvG) using a web-based randomisation program. Owing to the unfeasibility of masking, all participants and physicians were aware of treatment allocation.

Procedures

An expert panel consisting of 17 experts (nine gastrointestinal surgeons, four gastrointestinal endoscopists, and four radiologists [including MAB, TLB, MJB, VCC, CHD, CHvE, HvG, J-WH, SHH, JSL, KPvL, VBN, J-WP, RT, HGG, and PF]) assessed the indication, timing, and feasibility of both the endoscopic and surgical step-up approaches for all patients.[4] Whenever possible, randomisation and intervention were postponed until 4 weeks after onset of pancreatitis in line with international guidelines.[5]

Treatment strategies were standardised across sites. Patients assigned to the endoscopy group underwent endoscopic ultrasound-guided transluminal (i.e., transgastric or transduodenal) drainage with placement of two 7 Fr (2.3 mm diameter) double pigtail stents and one 8.5 Fr (2.8 mm) nasocystic catheter as the first step. If drainage alone did not lead to considerable clinical 1 improvement, endoscopic transluminal necrosectomy was performed.[9]

Patients assigned to the surgery group underwent radiological CTguided or ultrasoundguided percutaneous catheter drainage as first step. The preferred route was through the left retroperitoneum with the catheter as guidance for videoassisted retroperitoneal debridement (VARD), if needed. For most collections, this route is the shortest and thereby often the safest. Furthermore, the drain remains retroperitoneal and does not infect the intraabdominal space.[4,10] If drainage was clinically unsuccessful a VARD procedure was performed.[11]

In both treatment groups, additional endoscopic as well as percutaneous

drainage and endoscopic or surgical necrosectomies were allowed. All interventions were done by experienced endoscopists, surgeons, and interventional radiologists. Details on both treatment groups, interventions, postoperative management, and criteria for clinical improvement are given in the Appendix.

Routine laboratory tests were done at randomisation and for the 7 consecutive days after, as per daily clinical practice. Followup visits were 3 and 6 months after randomisation. Patients were asked to complete a questionnaire, a CT was performed, and exocrine and endocrine pancreatic function were measured (Appendix).

Data were collected by local physicians using a standardised case record form (CRF). An independent monitor, unaware of the treatment assignments, checked all endpoints and CRFs with onsite source data. Discrepancies were resolved through consensus among two investigators who were unaware of treatment allocation and not involved in patient care. All CTs were reviewed by an experienced abdominal radiologist (TLB) unaware of the treatment group and outcomes.

Outcomes

The primary endpoint was a composite of major complications or death within 6 months after randomisation. Major complications were defined as new-onset organ failure (i.e., cardiovascular, pulmonary, or renal), bleeding requiring intervention, perforation of a visceral organ requiring intervention (except for the intentionally made perforation during endoscopic treatment), enterocutaneous fistula requiring intervention, and incisional hernia (including burst abdomen). Predefined secondary endpoints included the individual components of the primary endpoint, pancreatic fistula, exocrine and endocrine pancreatic insufficiency, biliary strictures, wound infections, need for necrosectomy, total number of interventions, length of hospital and ICU stay, costs (e.g., costs per patient with poor outcome, costs per quality-adjusted life-year [QALY], and total direct and indirect medical costs), quality of life, and the total number of crossovers between groups (for definitions of these primary and secondary endpoints see the Appendix).

An adjudication committee composed of five surgeons, three endoscopists, and one radiologist performed a blinded outcome assessment. They individually evaluated each patient for the occurrence of the primary endpoint. Disagreements were resolved during a plenary consensus meeting before data analysis started.

After enrolment of each consecutive group of 25 patients, an independent data safety and monitoring committee evaluated the progress of inclusion and safety endpoints for each patient with unblinded data. Patient reports and a list

of potential adverse events were presented to the data safety and monitoring committee (see Appendix).

Statistical analysis

Based on an expected absolute reduction in the primary composite endpoint of 26% (from 43% to 17%) with a two-sided α of 5%, power of 80%, and 2% loss to follow-up, we calculated a total sample size of 98 patients. The expected reduction in the primary endpoint in favour of the endoscopic step-up approach was based on the results of various cohort studies, systematic reviews, and a small randomised controlled pilot trial.[7,12-23]

We present results as relative risks with corresponding 95% CIs. We compared dichotomous data with Fisher's exact test, continuous data with the Mann-Whitney U test, and categorical data with the linear-by-linear association test.

All primary analyses were by intention to treat. We also did per-protocol analyses. We did a formal test of interaction using logistic regression to assess whether treatment effects differed significantly between predefined subgroups (i.e., patients with singular or multiple organ failure at randomisation, academic or non-academic institutions, and time between onset of symptoms and randomisation [<28 vs. ≥28 days]).

We did no interim analyses. We considered a two-sided p-value of less than 0.05 to be statistically significant, and did not adjust p-values for multiple testing. Additional details on the statistical analyses are in the Appendix.

We calculated costs as the product sum of the number of resources used and their respective unit costs. Quality-adjusted life-years (QALYs) were calculated as the product sum of EQ-5D-3L-based health utilities at successive measurements during follow-up (3 and 6 months after randomisation) and the lengths of times in between measurements and baseline. We calculated confidence intervals for between-group differences using bias-corrected and accelerated (BCa) bootstrapping, stratified by treatment group and drawing 1000 samples of the same size as the original sample separately for each group and with replacement. Lastly, we did several non-specified post-hoc analyses of the primary endpoints, which are presented in the Appendix.

This trial is registered with the ISRCTN registry, number ISRCTN09186711.

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.

Results

Between Sept 20, 2011, and Jan 29, 2015, 418 patients with pancreatic or extrapancreatic necrosis in 19 Dutch hospitals were screened, of which 98 were eligible (Figure 1). 51 patients were randomly assigned to the endoscopic step-up approach and 47 to the surgical step-up approach. In each treatment group, one patient did not undergo any intervention because of spontaneous clinical improvement shortly after randomisation. In two other patients in the endoscopy group, owing to the technical difficulty of the drainage procedure, the endoscopist was not able to successfully puncture the collection. These two patients underwent treatment within the surgical step-up approach and were analysed according to the intention-to-treat principle in the endoscopy group. Baseline characteristics were equally distributed between groups (Table 1).

The primary composite endpoint occurred in 22 (43%) patients in the endoscopy group and in 21 (45%) in the surgery group (relative risk 0.97, 95% CI 0.62 to 1.51; p=0.88; Table 2). We observed no significant difference in new-onset single organ failure between groups (Table 2); however, new-onset cardiovascular organ failure and persistent cardiovascular organ failure occurred more frequently in the surgery group (Table 2). We observed no differences in major complications including bleeding, perforation of a visceral organ, enterocutaneous fistula, and incisional hernia. Mortality was similar in both groups (Table 2). The causes of death between both groups did not differ, with most patients dying because of progressive sepsis (2 [22%] of 9 patients in the endoscopy group, 2 [33%] of 6 in the surgery group) and multiple organ failure (4 [44%] in the endoscopy group, 2 [33%] in the surgery group).

The incidence of pancreatic fistulas was lower in the endoscopy group than in the surgery group (Table 2). All patients with pancreatic fistulas required persistent drainage during follow-up and nine (60%) of these patients (one patient in the endoscopy group and eight in the surgery group) underwent an additional endoscopic retrograde cholangiopancreatography with pancreatic sphincterotomy or stent placement. At 6-month follow-up, we observed no differences regarding exocrine and endocrine insufficiency, biliary strictures, and wound infections (Table 2).

Mean length of hospital stay was 16 days shorter in the endoscopy group compared with the surgery group (Table 2). 22 (43%) patients in the endoscopy group and 24 (51%) patients in the surgery group were treated with catheter drainage only (Table 2). The remaining patients underwent necrosectomy, occurring sooner in the endoscopy group compared with the surgery group (Table 2). More necrosectomy procedures were done in the endoscopy group compared with the surgery group.

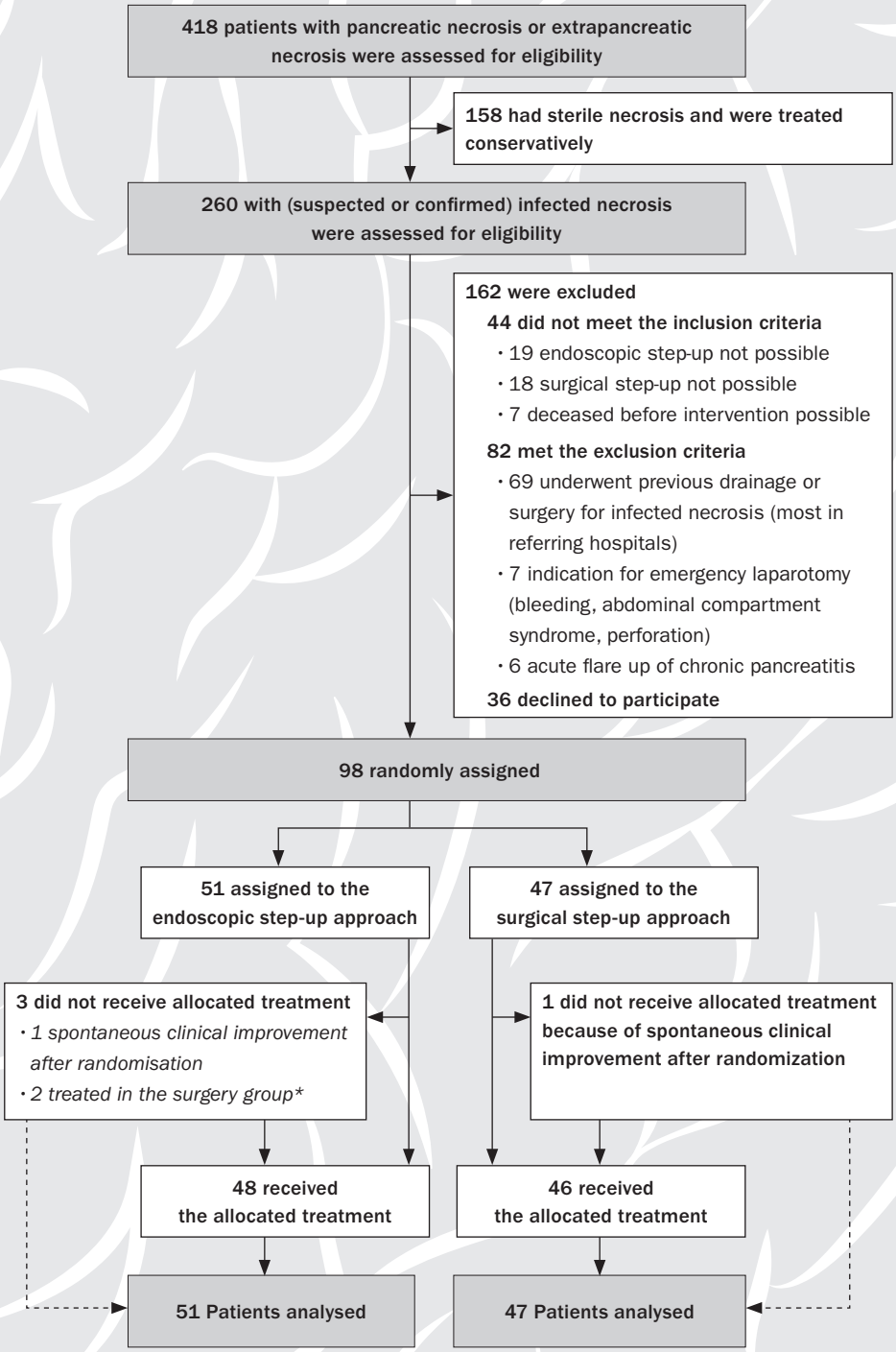

Figure 1. *Trial profile. * endoscopy unsuccesful*

Table 1. Baseline characteristics.

Characteristics	Endoscopic step-up approach (N=51)	Surgical step-up approach (N=47)
Age, years	63 (14)	60 (11)
Female	17 (33%)	18 (38%)
Male	34 (67%)	29 (62%)
Cause of pancreatitis		
Gallstones	26 (51%)	30 (64%)
Alcohol abuse	7 (14%)	7 (15%)
Other*	18 (35%)	10 (21%)
Body-mass index†	29 (25-32)	28 (25-30)
Coexisting condition		
Cardiovascular disease	26 (51%)	18 (38%)
Pulmonary disease	8 (16%)	6 (13%)
Chronic renal insufficiency	4 (8%)	0 (0)
Diabetes	11 (22%)	7 (15%)
ASA class on admission		
I: healthy status	17 (33%)	18 (38%)
II: mild systemic disease	29 (57%)	27 (58%)
III: severe systemic disease	5 (10%)	2 (4%)
CT severity index‡	6 (6-8)	8 (6-10)
Extent of pancreatic necrosis		
<30%	26 (51%)	22 (47%)
30-50%	15 (29%)	10 (21%)
>50%	10 (20%)	15 (32%)
Necrosis extending >5cm down the retrocolic gutters	20 (39%)	22 (47%)

Data are mean (SD), median (IQR), or N (%). ASA, indicates American Society of Anesthesiologists; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; MODS, multiple organ dysfunction syndrome; SOFA, Sequential Organ Failure Assessment. ∗ Includes, among others, medication, anatomic abnormalities, and unknown aetiology. † Data missing in 34 patients. ‡ Data were derived from the CT performed just before randomisation. Scores range from 0 to 10, with higher scores indicating more extensive pancreatic necrosis and extrapancreatic collections. § Data were based on maximum values during the 24 h before randomisation unless stated otherwise. ¶ SIRS was ►

Table 1. Continued

Characteristics	Endoscopic step-up approach (N=51)	Surgical step-up approach (N=47)
Encapsulation of the necrotic collection		
Partial	15 (29%)	14 (30%)
Complete	36 (71%)	33 (70%)
Gas configurations within the necrotic collection	23 (45%)	27 (57%)
Disease severity[§]		
Admitted to the ICU at randomisation	21 (41%)	25 (53%)
SIRS[¶]	33 (65%)	38 (81%)
APACHE II score‖	9 (5-13)	10 (6-13)
APACHE II score ≥20‖	3 (6%)	4 (9%)
Modified Glasgow score**	2 (1-3)	2 (1-3)
Modified MODS[††]	0 (0-1)	0 (0-2)
SOFA score[††]	0 (0-4)	1 (0-3)
C-reactive protein mg/L[‡‡]	168 (105-258)	189 (136-301)
White cell count $x10^{-9}$ per L[§§]	14.4 (9.4-18.0)	13.1 (10.5-17.4)
Single organ failure	13 (25%)	14 (30%)
Respiratory	11 (22%)	13 (28%)
Cardiovascular	11 (22%)	7 (15%)
Renal	3 (6%)	1 (2%)
Multiple organ failure	9 (18%)	7 (15%)
Time since onset of symptoms, days	39 (28-54)	41 (28-52)
Antibiotic treatment at randomisation	10 (20%)	9 (19%)
Tertiary referral	35 (69%)	35 (74%)
Confirmed infected necrosis[¶¶]	46 (90%)	46 (98%)

◂ *defined according to the consensus-conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine.* ‖ *Scores range from 0 to 71, with higher scores indicating more severe disease.* ** *Scores range from 0 to 8, with higher scores indicating more severe disease.* †† *Scores range from 0 to 24, with higher scores reflecting more severe organ dysfunction.* ‡‡ *Data missing in 10 patients.* §§ *Data missing in two patients.* ¶¶ *Confirmed infected necrosis was defined as a positive culture of pancreatic or extrapancreatic necrotic tissue obtained by fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the collection on contrast-enhanced CT.*

Table 2. Primary and secondary endpoints according to the intention-to-treat analysis

	Endoscopic step-up approach (N=51)	Surgical step-up approach (N=47)	Relative Risk (95% CI)	p-value
Primary end point:				
Major complications or death*	22 (43%)	21 (45%)	0.97 (0.62-1.51)	0.88
Secondary end points:				
New-onset organ failure†	-	-		
Pulmonary	4 (8%)	7 (15%)	0.53 (0.16-1.68)	0.27
Persistent pulmonary	4 (8%)	5 (11%)	0.74 (0.21-2.58)	0.63
Cardiovascular	3 (6%)	9 (19%)	0.31 (0.09-1.07)	0.045
Persistent cardiovascular	2 (4%)	8 (17%)	0.23 (0.05-1.03)	0.032
Renal	2 (4%)	6 (13%)	0.31 (0.07-1.45)	0.11
Persistent renal	2 (4%)	6 (13%)	0.31 (0.07-1.45)	0.11
Single organ failure	7 (14%)	13 (28%)	0.50 (0.22-1.14)	0.087
Persistent single organ failure	6 (12%)	11 (23%)	0.50 (0.20-1.25)	0.13
Multiple organ failure	2 (4%)	6 (13%)	0.31 (0.07-1.45)	0.11
Persistent multiple organ failure	2 (4%)	5 (11%)	0.37 (0.08-1.81)	0.20
Bleeding (requiring intervention)	11 (22%)	10 (21%)	1.01 (0.47-2.17)	0.97
Perforation of a visceral organ or enterocutaneous fistula (requiring intervention)	4 (8%)	8 (17%)	0.46 (0.15-1.43)	0.17
Incisional hernia	0	1 (2%)	-	0.30
Death	9 (18%)	6 (13%)	1.38 (0.53-3.59)	0.50
Other end points‡:				
Pancreatic fistula	2/42 (5%)	13/41 (32%)	0.15 (0.04-0.62)	0.0011
Exocrine insufficiency				
Use of enzymes	16/42 (38%)	13/41 (32%)	1.20 (0.66-2.17)	0.54
Fecal elastase <200 mg/g	22/42 (52%)	19/41 (46%)	1.13 (0.73-1.75)	0.58
Steatorrhoea	6/42 (14%)	7/41 (17%)	0.84 (0.31-2.28)	0.73
Endocrine insufficiency	10/42 (24%)	9/41 (22%)	1.08 (0.49-2.39)	0.84
Biliary strictures	3 (6%)	3 (6%)	0.92 (0.20-4.34)	0.92
Wound infections	2 (4%)	3 (6%)	0.61 (0.11-3.52)	0.58

Table 2. Continued

	Endoscopic step-up approach (N=51)	Surgical step-up approach (N=47)	Relative Risk (95% CI)	p-value
Health care use				
Median number of interventions§	3 (2-6)	4 (2-6)	-	0.35
Drainage procedures¶	1 (1-3)	3 (1-5)	-	0.0041
Necrosectomies‖	2 (1-4)	1 (1-1)	-	0.0004
Number of necrosectomies				0.0062
0	22 (43%)	24 (51%)	0.84 (0.55-1.29)	-
1	9 (18%)	18 (38%)	0.46 (0.23-0.92)	-
2	8 (16%)	3 (6%)	2.46 (0.69-8.72)	-
≥3	12 (24%)	2 (4%)	5.53 (1.31-23.42)	-
Additional percutaneous drainage in the endoscopy group	14 (27%)	-	-	-
Additional VARD procedure in the endoscopy group	2 (4%)	-	-	-
Additional endoscopic drainage in the surgical group	-	2 (4%)	-	-
Additional endoscopic necrosectomy in the surgical group	-	0	-	-
Days between first drainage and first necrosectomy				
Median (range)	10 (5-16)	23 (9-62)	-	0.013
Mean (SD)	14 (14)	33 (30)	-	-
Days in ICU within 6 months of randomisation**				
Median (range)	0 (0-3)	2 (0-11)	-	-
Mean (SD)	13 (31)	13 (21)	-	0.31
Days in hospital within 6 months of randomisation				
Median (range)	35 (19-85)	65 (40-90)	-	-
Mean (SD)	53 (47)	69 (38)	-	0.014

Data are N (%), mean (SD), or median (IQR) unless otherwise stated. Relative risk is reported for dichotomous variables for the endoscopic step-up approach as compared with the surgical step-up approach. ICU, indicates intensive care unit; VARD, video-assisted retroperitoneal ►

◂ debridement. ⋆ Multiple events in the same patient were considered as one endpoint. † Organ failure occurring after randomisation and not present 24 h before randomisation. ‡ Patients were assessed 6 months after randomisation; patient deaths were excluded. § This category included all drainage procedures (endoscopic or percutaneous) and necrosectomies (endoscopic or VARD) as part of the endoscopic or surgical step-up approach. ¶ This category included primary drainage procedures (endoscopic or percutaneous) as part of the endoscopic or surgical step-up approach and additional drainage procedures before and after necrosectomy in both treatment groups. ‖ This category included all necrosectomies (endoscopic or VARD procedure) as part of the endoscopic or surgical step-up approach. ⋆⋆ For patients not present in ICU 24 h before randomisation.

We observed no difference in the median number of interventions (drainage or necrosectomy) between groups (Table 2).

The most common adverse events were pneumonia (16 [31%] patients in the endoscopy group vs. 9 [19%] in the surgery group), bacteremia (11 [22%] vs. 6 [13%]), ascites (7 [14%] vs. 8 [17%]), urinary tract infection (6 [12%] vs. 4 [9%]), cholecystitis or cholangitis (4 [8%] vs. 3 [6%]), and atrial fibrillation (3 [6%] vs. 2 [4%]). All adverse events are listed in the Appendix.

Correction for trends in baseline characteristics (i.e., chronic renal insufficiency, systemic inflammatory response syndrome, and modified multiple organ dysfunction syndrome) with multivariable regression analyses did not affect the results (Appendix). Predefined subgroup analyses for time of randomisation and institution showed no significant differences in the primary endpoint (Appendix). We found no differences in outcome in the subgroup of patients with organ failure at randomisation or after correction for imbalances in baseline in this subgroup. Additional per-protocol analyses did not affect the results, except that persistent cardiovascular organ failure no longer differed between groups (Appendix).

The mean costs of the index interventions (i.e., all drainage and necrosectomy procedures) were €3785 in the endoscopy group and €2851 in the surgery group, with a mean difference of €934 (BCa 95% CI -€82 to €2097). The mean total costs per patient from randomisation until 6-month follow-up were €60228 for the endoscopic step-up approach and €73883 for the surgical step-up approach. The resulting mean difference of -€13655 (-€35782 to €10836) per patient was not significant.

The number of QALYs gained for the endoscopy group was 0.2788 (BCa 95% CI 0.2458 to 0.3110) compared with 0.2988 (0.2524 to 0.3398) for the surgery group. The mean difference was -0.0199 (-0.0732 to 0.0395). The savings per loss of a single QALY were €684455. The probability of the endoscopic step-up approach

being cost-effective is 0.896 at a societal willingness-to-pay level of €50000 per QALY (see Appendix for details of the cost analysis).

Discussion

This randomised superiority trial showed that the endoscopic step-up approach was not superior to the surgical step-up approach in reduction of major complications or death in patients with infected necrosis. However, our results showed a benefit in secondary endpoints of endoscopic treatment.

Our results are not in line with a previous small randomised controlled trial,[7] a systematic review,[8] and observational studies[24,25] suggesting clinical superiority of endoscopy. Several possible explanations exist for the differing outcome. First, observational studies have a risk of confounding by indication and most of these studies did not have a well-defined study protocol or clearly described treatment algorithms. Furthermore, patients with sterile collections were also included in some of these studies, which could have led to comparisons of less severe cases with patients with infected necrosis. In our trial, inclusion criteria were strict and were confirmed by an expert panel.

Second, in line with a previously proposed hypothesis, the previous small trial[7] showed that endoscopic treatment led to a less severe pro-inflammatory response and, subsequently, fewer occurrences of new organ failure compared with surgery. These results were also not confirmed in our trial. Although we did not measure the pro-inflammatory response, new-onset single organ failure as a clinical manifestation of immune response did not differ between groups. However, both cardiovascular and persistent cardiovascular organ failure were lower in the endoscopy group. This difference could be the result of the differing designs of both studies. The previous trial[7] compared an endoscopic necrosectomy with a surgical necrosectomy instead of two step-up approaches as in our trial. This trial design also explains the inclusion of more severely ill patients (i.e., patients in whom percutaneous drainage failed) in the previous trial.[7] Moreover, 40% of the surgical patients in the previous study[7] received open necrosectomy as opposed to VARD, whereas in our trial no patients underwent an open necrosectomy. This difference is important because open necrosectomy is thought to be associated with more complications than is VARD.

Third, patients in our trial were more severely ill than those included in the previous trial[7] in terms of ICU stay, presence of systemic inflammatory response syndrome, single or multiple organ failure at randomisation, and the high percentage of patients with confirmed infected necrosis compared with the patients included in previous observational studies.

Finally, our sample size could still have been too small. The number of patients

needed was based on the results of small, mostly observational studies. A small sample size might therefore have overestimated the effect of endoscopic treatment.

51% Of surgical patients were successfully treated with catheter drainage only. This result is higher than the 35% successfully treated in a previous randomised trial,[4] but comparable with a published systematic review.[6] We found that more than 40% of patients in the endoscopy group were also successfully treated with endoscopic drainage only without additional necrosectomy. Previous research has identified male sex, multiple organ failure, increasing percentage of pancreatic necrosis, and heterogeneity of the collection as negative predictors for success of percutaneous catheter drainage in infected necrotising pancreatitis.[26] The total number of necrosectomy procedures in both treatment groups are in line with published data.[4,7]

During the inclusion period, 37 (14%) of 260 patients were excluded because either the endoscopic or surgical approach was deemed not possible. As with percutaneous drainage, endoscopic drainage was feasible in almost all patients included (96%). 14 (27%) Of 51 patients in the endoscopy group needed additional percutaneous catheter drainage mostly when necrosis was extending down retroperitoneally into the pelvis. Despite the need for additional percutaneous drainage, the incidence of pancreatic fistulas was significantly lower in the endoscopy group. All recorded pancreatic fistulas were external (i.e., Pancreatis fistulas). These fistulas might account for serious morbidity (i.e., pain, loss of pancreatic juices), additional interventions, extended hospital stay, and intensified follow-up. So-called internal pancreatic fistulas probably also occurred in the endoscopy group. These internal fistulas, however, are deemed less clinically relevant than external pancreatic fistulas.

The interval between the first drainage and first necrosectomy was notably shorter in the endoscopy group than in the surgery group. This result could be due to a potentially higher threshold in the surgery group to proceed to VARD after catheter drainage compared with the threshold in the endoscopy group to proceed to endoscopic necrosectomy. Additional necrosectomy after endoscopic drainage is a relatively small step, done by the same specialist via the same route. The step from catheter drainage to VARD in the surgery group was larger, with the surgeon performing the minimally invasive surgical necrosectomy after previous drainage done by the radiologist. Furthermore, compared with the endoscopy group, drains in the surgery group were more often repositioned and upsized, and multiple drains were placed more often.[27] This argument is supported by the difference in patients treated with solely catheter drainage in the surgery group between a previous trial[4] (35%) and our current study (50%), indicating more extensive and better drainage in our study.

Moreover, percutaneous drains have a larger diameter and potentially clog less frequently than do endoscopic catheters. These aspects of the surgical step-up approach might have resulted in a prolonged effect of percutaneous drainage, delay of necrosectomy, and, subsequently, prolonged hospital stay.

During the course of the trial, short lumen-apposing fully-covered metal stents were introduced into the medical armatorium, which are gaining popularity in endoscopic treatment. The larger diameter compared with the plastic pigtail stents that were used in this trial potentially leads to better drainage and, hypothetically, fewer necrosectomies. Disadvantages might be migration of the stent, bleeding, perforation, and stent overgrowth.[28-31] In view of insufficient evidence of significant benefit of metal stents over plastic pigtail stents, we decided to use the well studied pigtail stents during the entire study.

Our study has some limitations. First, as mentioned, our sample size was still relatively small. However, because no trends for differences in mortality were seen, a larger trial is unlikely to find a significant difference in mortality. Second, almost one third of patients in the endoscopy group underwent additional percutaneous drainage. Because this was a pragmatic trial, percutaneous drainage was allowed, as would be done in clinical practice in these patients. Third, follow-up was 6 months after randomisation. This length could be too short to detect further benefits or complications of the endoscopic step-up approach on the long term.

Treatment of infected necrosis is complex and mortality remains high despite treatment techniques becoming progressively less invasive and more tailored. In clinical practice, the endoscopic step-up approach is gaining popularity alongside the surgical step-up approach. Our study has shown that both approaches are valid treatment options, although an important clinical advantage of the endoscopic approach is the reduction in external pancreatic fistulas and hospital stay. In our view, patients with infected necrosis should be treated in tertiary referral centres by multidisciplinary teams where both the endoscopic and surgical step-up approach are available, because a combined approach might be required in some patients. Based on current findings, the first step of step-up treatment will most likely be endoscopic, if several options are available. In the future, a tailored approach based on patient characteristics, location of collections, and degree of encapsulation will probably become the new standard.

In conclusion, this multicentre randomised trial did not show the hypothesised superiority of the endoscopic step-up approach in reducing major complications or death in patients with infected necrosis, although the number of pancreatic fistulas and total hospital stay were lower in the endoscopy group.

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APPENDIX CHAPTER 10

Endoscopic or surgical step-up approach for infected necrotising pancreatitis

A MULTICENTRE RANDOMISED TRIAL

Additional information

- Study participants
- Exclusion criteria
- Treatment groups
- General supportive treatment
- Data collection and end point assessment
- Patient safety
- Sample size and statistical analysis
- Definitions of the primary and secondary end points; Box A1
- Post hoc endpoints - additional information; Table A1
- Results of subgroup analyses; Table A2
- Results of per-protocol analyses; Table A3
- Healthcare utilization and cost; Table A4 and A5 and Figure A1 and A2
- Adverse events; Table A6
- Funding and acknowledgements
- Results of sensitivity analysis; Table A7
- References

Study participants

Acute pancreatitis was defined as having at least 2 of the 3 following features: 1) upper abdominal pain, 2) serum lipase or amylase levels above 3 times the upper level of normal and 3) characteristic findings of acute pancreatitis on cross-sectional abdominal imaging.

Exclusion criteria

Exclusion criteria were previous invasive interventions for necrotising pancreatitis, an acute flare up of chronic pancreatitis, recurrent acute pancreatitis, and an indication for emergency laparotomy (i.e. abdominal compartment syndrome, perforation of a visceral organ, bleeding and bowel ischaemia).

Treatment groups

The first step of treatment (step 1) was catheter drainage. This was performed ultrasound guided transluminal in the endoscopic step-up approach and percutaneously in the surgical step-up approach. Criteria similar to the PANTER trial were used to define clinical improvement, failure of drainage and to decide to go to the next step, endoscopic transluminal necrosectomy or surgical necrosectomy (step 2).[1,2] Criteria were similar in both groups. Each step was only considered successful in case of clinical improvement. 'Clinical improvement' was defined as: improved function of at least two organ systems (i.e. circulatory, pulmonary, renal) or at least 10% improvement of two out of three parameters of infection (i.e. C-reactive protein, leucocyte count or temperature) within 72 hours. Deterioration of these parameters by other infectious causes (e.g. an urinary tract infection) were be excluded. Clinical failure was defined as the absence of clinical improvement or clinical deterioration.

If there was no clinical improvement 72 hours after drain placement, a CT scan was made to check the position of the drain. If the position of the drain was adequate and no additional drainable collections were seen, the patient proceeded to the next step (step 2). If the position of the drain was inadequate or an additional drainable collection was seen, a second drain was placed. 72 hours after a second drainage-procedure the patient was again evaluated. In case of improvement, treatment was conservative; otherwise the patient was taken to the next step (step 2). If after drainage, at any moment in time, a deterioration of at least two organ systems (i.e. circulatory, pulmonary, renal), or at least 10% deterioration of two out of three parameters (i.e. C-reactive protein, leucocyte count or temperature), the next step (step 2) was taken. Deterioration of these parameters by other infectious causes (i.e. an urinary tract infection or pneumonia) was excluded.

Group A: Endoscopic transluminal step-up approach

Both approaches were performed, according to a strict protocol, in selected centres with documented expertise (i.e. more than ten EUS-guided transluminal (i.e. transgastric or transduodenal) drainage procedures and five endoscopic necrosectomy procedures performed for infected necrosis in the endoscopy group and at least ten VARD procedures performed in the surgery group) and, if necessary, under supervision of a more experienced endoscopist. All EUS procedures were performed with large channel linear echoendoscopes.

Step 1: endoscopic transluminal drainage

Under sedation, endoscopic ultrasound guided transluminal (i.e. transgastric or transduodenal) drainage of the necrotic collection was performed as the first step of treatment. Two 7 Fr double pigtail stents were inserted into the collection. A naso-cystic catheter was positioned in the fluid collection alongside the inserted stents which was continuously flushed with 1 liter saline/24 hours. This with the intent to keep the drain and tract open and not for removing necrosis. In case of clinical improvement, no necrosectomy was performed and the results were awaited. If necessary, renewed or additional drainage (e.g. endoscopically or percutaneous) was performed after 72 hours. If re-drainage was clinically unsuccessful (according to the criteria for 'clinical improvement') or impossible, endoscopic transluminal necrosectomy was performed (step 2).

Step 2: endoscopic transluminal necrosectomy

The cystogastrotomy was dilated up to 18 mm and the cavity was entered with a therapeutic gastroscope to perform a necrosectomy under direct endoscopic vision. The procedure was completed when most necrotic tissue was removed. Again two 7 Fr plastic double pigtail stents and a naso-cystic catheter were inserted into the collection.

Group B: Surgical step-up approach

This approach was similar to the step-up approach used in the PANTER trial.[2]

Step 1: percutaneous catheter drainage (PCD)

A percutaneous 14 French drain was placed in the (extra-)pancreatic collection under guidance of CT or ultrasound (step 1). Multiple drains were allowed. The preferred route was through the left retroperitoneum, thereby facilitating VARD at a later stage if needed. Furthermore, for most collections this is also the shortest and often safest route, and like this you stay retroperitoneal and do not infect the intraabdominal space. If through the left retroperitoneum was not possible, transperitoneal drainage was performed. Drains were kept open by flushing with 50 ml saline once every 8-hours, with the intent to keep the drains open and not for removing necrosis. In case of clinical improvement, results were awaited. If a collection was inadequately drained after 72 hours, additional drainage (i.e. percutaneous or endoscopically) was performed. If drainage was clinically unsuccessful (i.e. according to the criteria for 'clinical improvement'), or in case of clinical deterioration, the patient underwent a surgical necrosectomy (step 2).

Step 2: VARD (if not possible laparotomy)

VARD is a drain-guided, minimally invasive retroperitoneal procedure, requiring a small incision. Using the retroperitoneal drain for guidance, only loosely adherent necrosis was removed from the collection with video-assistance after which two large bore surgical drains were inserted. A continuous post-operative lavage system (building up to 10 litres saline per 24 hours) was installed. In case of absence of clinical improvement (or deterioration), a CT scan was performed and VARD was repeated. If initial VARD was not possible, for whatever reason, debridement by laparotomy was performed.

If drainage (step 1) fails (clinically or technically) in one of both groups, the next step for the endoscopy group was cross-over to the surgery group and the next step for the surgery group was step 2 (i.e. VARD, if not possible laparotomy). In case of (per) acute clinical deterioration (e.g. bleeding with shock) the decision on therapy was left to the clinician in charge.

Patients were assigned to the endoscopic or surgical step-up approach as the initial and preferred technique. However, all clinically indicated procedures, whether endoscopic or percutaneous, were allowed throughout the course of their disease.

General supportive treatment

All patients received oral nutrition, if tolerated. If this was not tolerated, a nasojejunal feeding tube was introduced and enteral feeding was started. If gastrointestinal feeding was contra-indicated, the patient received parenteral nutrition. No antibiotic prophylaxis was used. In intensive care units selective decontamination of the digestive tract was allowed as this was the standard of care for all patients. Antibiotics were used in case of suspected infected necrosis in order to postpone intervention. Intervention was postponed until (extra)pancreatic collections were demarcated as shown on CT, which usually occurs around 28 days after onset of symptoms.

Data collection and end point assessment

Patients were scored having a primary end point yes or no. So, if one of the components of the primary end point occurred within 6 months after randomisation this was accounted as having a primary end point. Outpatient follow-up visits took place according to the discretion of the responsible physician, but in any case 3 and 6 months after randomisation. All patients underwent a routine contrast enhanced CT 3 and 6 months after randomisation and received a questionnaire (SF-36[3], EQ-5D[4], Health and Labour[5]) 3 and 6 months after randomisation. Exocrine and endocrine pancreatic function were measured in every patient, 3 and 6 months after randomisation with blood glucose measurements and faecal elastase tests.

Patient safety

To optimize patient safety an independent Data Safety and Monitoring Committee (DSMC) evaluated the progress of the trial and examined safety end points after inclusion of each consecutive group of 20 patients. All involved physicians were repetitively asked to report any potential adverse events. These events were listed and presented to the DSMC in an unblinded fashion. The DSMC discussed the implications of the data presented. In addition, all deceased patients were extensively evaluated by the DSMC for cause of death and possible intervention related serious adverse events. The outcome of the meeting of the DSMC was discussed with the trial steering committee and was reported to the responsible investigational review board. All adverse events were reported to the Dutch Central Committee on Research involving Human Subjects and the investigational review board.

Sample size, statistical analysis and economic evaluation

Sample size

Combined results of recently performed non-randomised studies showed that endoscopic transluminal necrosectomy resulted in a combined mortality and major morbidity rate of 17%. Data from the PANTER trial showed a combined mortality and major morbidity rate of 40%. Furthermore, in the VARD group an incisional hernia rate of 7% was seen. Incisional hernia cause pain and patient discomfort. Furthermore, intensified follow-up and additional surgery is required to perform a correction. Assuming that some patients will develop an incisional hernia in the VARD group without having another primary endpoint, the prevalence of mortality and major morbidity in the VARD group, including incisional hernias was estimated to amount to 43%.

Therefore, sample size calculations were based on the assumption that the endoscopy group could reduce the cumulative primary endpoint by 26% (43% to 17%) in comparison with the surgery group. With a 2-sided significance level of 5% and power of 80%, taking into account a 2% drop-out rate, the inclusion of a total of 98 (2x49) patients was required to demonstrate this effect.

Statistical analysis

Variables are summarized as frequencies and percentages, means with standard deviations and in case of skewed distributions as medians with ranges. Results are presented as relative risks with corresponding 95% confidence intervals. Dichotomous data were compared with the use of Fisher's exact test, continuous data with Mann-Whitney U test, and categorical data with the linear-by-linear association test. A two-tailed $p<0.05$ was considered statistically significant. p-Values were not adjusted for multiple testing. Both, intention-to-treat and per-protocol analyses were performed. Predefined subgroup analysis were performed for patients with and without (multiple) organ failure, institution and time between onset of symptoms and randomisation (<28 or ≥28 days). To this end, formal tests for interaction using logistic regression were performed. In the event of imbalance between groups at baseline, logistic regression analysis were used to correct for the effect of the covariates.

Economic evaluation

Set up from a societal perspective, the economic evaluation was performed as a cost-effectiveness as well as cost-utility analysis with, respectively, the costs per alive patient without major complications and the costs per quality adjusted life year as primary economic outcomes. We included the direct and indirect medical and non-medical costs of care. The medical costs included costs

of ICU-care, admission at the general ward, visits to the emergency department, ambulance transfers and all diagnostic and therapeutic procedures during the index admission and re-admissions within 6 months after randomisation. Furthermore, all outpatient clinic consultations and out-of-hospital costs (rehabilitation centre admissions, general practitioner consultations and home care use) during follow-up were included. Direct non-medical costs reflect the non-reimbursable out-of-pocket expenses by patients related to the disease, for example travel to and from health care providers, private household assistance, etc. Data on the use of health care resources were gathered by case record forms, patient questionnaires and hospital information systems. Unit costing was based on the 2015 Dutch manual for costing in health care research.[6,7] Endoscopic drainage and necrosectomy are relatively new intervention modalities for which no standardized costs were available. Therefore, after consulting the financial department of different (academic) centres, a unit cost was composed for these interventions. A top-down cost calculation was performed for the different types of surgery, including VARD. All unit costs are reported in Table A4. The base year for costs was 2014 and all costs are displayed in Euros.

Health utilities were derived from the EQ-5D-3L health status profiles using existing health valuation algorithms from the literature.[8,9] The algorithms were based on the time trade-off elicitation techniques applied to representative samples of the general population in the Netherlands and the United Kingdom (UK).

Analyses were performed based on intention-to-treat. Differences between groups were assessed using accelerated non-parametric bootstrapping to account for sampling variability. Incremental cost-effectiveness ratios were calculated reflecting the extra costs per additional patient alive without major morbidity and the extra costs per additional QALY. Results are graphically shown by a cost-effectiveness plane of 1,000 bootstraps (Figure A1) and the corresponding cost-effectiveness acceptability curve (Figure A2).

Box A1. Definitions of the primary and secondary end points.

	End point	Definition
Primary End point	New onset organ failure	Organ failure occurring after randomisation and not present 24 hours before randomisation: • Pulmonary: a PaO2 <60 mmHg despite FiO2 30%, or the need for mechanical ventilation • Cardiovascular: a systolic blood pressure <90 mmHg despite adequate fluid resuscitation or need for vasopressor support • Renal: a serum creatinine >177 mmol/L after rehydration or need for hemofiltration or hemodialysis (in case patients already suffered from renal insufficiency before this episode of AP [creatinine >177 umol/L] this does not count as renal failure)
	Multiple organ failure	Failure of 2 or more organ systems (respiratory, cardiovascular or renal) at the same moment
	Persistent organ failure	Failure of one or more organ systems for at least 48 hours
	Bleeding requiring intervention	Requiring surgical, radiologic, or endoscopic intervention
	Perforation of a visceral organ requiring intervention	Requiring surgical, radiologic, or endoscopic intervention
	Enterocutaneous fistula requiring intervention	Secretion of fecal material from a percutaneous drain or drainage canal after removal of drains or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery
	Incisional hernia (including burst abdomen)	Full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction
Secondary End points	Pancreatic fistula	Output, through a percutaneous drain or drainage canal after removal of drains from a surgical wound, or any measurable volume of fluid with an amylase content >3 times the serum amylase level
	Exocrine pancreatic insufficiency	Oral pancreatic-enzyme supplementation required to treat clinical symptoms of steatorrhea 6 months after randomisation; this requirement was not present before onset of pancreatitis
	Endocrine pancreatic insufficiency	Insulin or oral antidiabetic drugs required 6 months after randomisation; this requirement was not present before onset of pancreatitis
	Wound infections	A superficial incisional SSI (surgical site infection) and must meet the following criterion: infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and the patient has at least 1 of the following: • purulent drainage from the superficial/deep incision but not from the organ/space component of the surgical site • organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision • at least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion • an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination • diagnosis of superficial/deep incisional SSI by the surgeon or attending physician

Table A1. Additional analysis - post hoc end points.*

	Endoscopic step-up approach (N=51)	Surgical step-up approach (N=47)	Relative Risk (95% CI)	p-value
Organ failure or death - no. (%)Φ	15 (29)	13 (28)	1.06 (0.57-1.99)	0.85
Primary end point including pancreatic fistula - no. (%)±	23 (45)	28 (60)	0.76 (0.52-1.11)	0.15
New-onset organ failure - no. (%)∑	-	-		
Pulmonary organ failure duration - median (range)	3 (2-89) (N=4)	10 (1-36) (N=7)	-	0.85
Persistent pulmonary organ failure duration - median (range)□	3 (3-89) (N=4)	17 (2-36) (N=5)	-	0.65
Cardiovascular organ failure duration - median (range)	2 (1-2) (N=3)	4 (1-14) (N=9)	-	0.06
Persistent cardiovascularorgan failure duration - median (range)□	2 (2-2) (N=2)	6 (2-14) (N=8)	-	0.06
Renal organ failure duration - median (range)	24 (21-26) (N=2)	7 (2-29) (N=6)	-	0.18
Persistent renal organ failure duration - median (range)□	24 (21-26) (N=2)	7 (2-29) (N=6)	-	0.18
Organ failure duration - median (range)	3 (1-89) (N=7)	10 (1-39) (N=13)	-	0.72
Persistent organ failure duration - median (range)□	11 (2-89) (N=6)	12 (2-39) (N=11)	-	0.61
Multiple organ failure duration - median (range)	44 (2-85) (N=2)	6 (1-17) (N=6)	-	0.62
Persistent multiple organ failure duration - median (range)□	44 (2-85) (N=2)	7 (2-17) (N=5)	-	0.85
Days in hospital after first necrosectomy¤ - median (range)	29 (3-456)	34 (2-150)	-	0.93

⋆ This table includes additional end points which were not predefined within our study protocol. These analysis were performed post hoc. Φ New-onset organ failure or death within 6 months after randomisation. ± The originally defined composite primary end point supplemented with Pancreatis fistula within 6 months after randomisation. ∑ New organ failure occurring after randomisation and not present 24 hours before randomisation, duration was presented in days. □ Persistent organ failure was defined as new onset organ failure that lasted for at least 48 hours. ¤ Total number of days a patient was admitted in the hospital after the first necrosectomy was performed, and within 6 months following randomisation (mean and SD were 62 (±91) and 45 (±35) respectively).

Table A2. Results of subgroup analyses for the primary end point.*

Predefined subgroup - No. (%)	Endoscopic step-up approach	Surgical step-up approach	Relative Risk (95% CI)	p-value
Patients with (Multiple) Organ failure	6/13 (46)	5/14 (36)	3.80 (0.26-55.13)	0.33
Patients admitted at academic centre	12/29 (41)	15/29 (52)	0.80 (0.46-1.40)	0.43
Patients with time between onset of symptoms and randomisation of <28 days (vs. ≥28 days)	14/39 (36)	16/37 (43)	0.83 (0.47-1.45)	0.51

** This was a logistic regression analysis for the primary end point in the subgroup of patients with (multiple) organ failure, institution, and time between onset of symptoms and randomisation (<28 or ≥28 days). Data are number and percentages and, if applicable, data are corrected for imbalances in baseline in the respective subgroup.*

Table A3. Results of the predefined per-protocol analysis.*

Outcome	Endoscopic step-up approach (N=48)	Surgical step-up approach (N=48)	Relative Risk (95% CI)	p-value
Primary composite end point:				
Major complications or death	21 (44)	22 (46)	0.95 (0.61-1.49)	0.84
Secondary end points: Major morbidity				
New-onset organ failure	-	-		
Pulmonary	4 (8)	7 (15)	0.57 (0.18-1.83)	0.34
Persistent pulmonary	4 (8)	7 (15)	0.80 (0.23-2.80)	0.73
Cardiovascular	3 (6)	9 (19)	0.33 (0.10-1.16)	0.06
Persistent cardiovascular	2 (4)	8 (17)	0.25 (0.06-1.12)	0.05
Renal	2 (4)	6 (13)	0.33 (0.07-1.57)	0.14
Persistent renal	2 (4)	6 (13)	0.33 (0.07-1.57)	0.14
Organ failure	7 (15)	13 (27)	0.54 (0.24-1.23)	0.13

Table A3. Continued

Outcome	Endoscopic step-up approach (N=48)	Surgical step-up approach (N=48)	Relative Risk (95% CI)	p-value
Secondary end points: Major morbidity (continued)				
New-onset organ failure	-	-		
Persistent organ failure	6 (13)	11 (23)	0.55 (0.22-1.36)	0.18
Multiple organ failure	2 (4)	6 (13)	0.33 (0.07-1.57)	0.14
Persistent multiple organ failure	2 (4)	5 (10)	0.40 (0.08-1.96)	0.24
Bleeding	10 (21)	11 (23)	0.91 (0.43-1.94)	0.81
Perforation of a visceral organ or Enterocutaneous fistula	3 (6)	9 (19)	0.33 (0.10-1.16)	0.06
Incisional herni	0 (0)	1 (2)	-	0.32
Death	9 (19)	6 (13)	1.50 (0.58-3.89)	0.40
Other end points				
Pancreatic fistula	0 (0) N=39	15 (36) N=42	-	0.00
Exocrine insufficiency	-	-		
Enzyms	15 (39) N=39	14 (33) N=42	1.07 (0.58-1.97)	0.63
Fecale elastase <200 mg/g	22 (56) N=39	19 (45) N=42	1.16 (0.73-1.84)	0.32
Steatorroe	6 (15) N=39	7 (17) N=42	0.86 (0.31-2.36)	0.88
Endocrine insufficiency	10 (26) N=39	9 (21) N=42	1.11 (0.5-2.49)	0.66
Biliary strictures	3 (6)	3 (6)	1.00 (0.21-4.71)	1.00
Wound infections	2 (4)	3 (6)	0.67 (0.12-3.81)	0.65

Data are N (%). ⋆ The two patients who were randomised in the endoscopy group but eventually treated in the surgery group (since endoscopic drainage appeared not possible after randomisation) were analysed in the surgery group and the two patients (one in de endoscopy and one in the surgery group) who did not underwent any intervention were excluded.

Healthcare utilization and costs

Economic analysis - results

Costs

Mean volumes and costs of health care utilization per patient and mean differences in costs are shown in Table A5. Mean total costs were €60,228 for the endoscopic step-up approach and €73,883 for the surgical step-up approach, leading to a cost difference of -€13,655 (BCa 95% CI -€35,782 to €10,836).

The mean length of hospital stay was 53 days in the endoscopy group and 69 days in the surgical group (BCa 95% CI -31 to 0). The mean duration of ICU admission was 13 days in both groups. The length of general ward admission differed with -16 days (BCa 95% CI -29 to -2) leading to a cost difference of -€10,769 (BCa 95% CI -€19,784 to -€1,657). Costs for laboratory tests were higher in the surgical group, due to the longer duration of hospital admission (mean difference -€748 (BCa 95% CI -€1,491 to €1)). The costs for the endoscopically performed drainages and necrosectomies appeared to be higher than the surgically performed interventions (€934, BCa 95% CI -€82 to €2,097). Patients who were surgically treated had higher costs for emergency department visits than patients in the endoscopic transluminal approach group. Also costs for outpatient hospital care (i.e. visits to the outpatient clinic) were higher in the surgically treated group. The difference in total costs of inpatient and outpatient hospital care was -€10,294 (BCa 95% CI -€32,609 to €13,849), hence less expensive for the endoscopy group.

Total non-hospital medical costs differed considerably, mainly due to the higher costs for rehabilitation and nursing home admission in the surgery group. Respectively 9 of 51 (18%) and 15 of 47 (32%) patients were admitted to a rehabilitation centre or nursing home in the endoscopic and surgical group, of whom most of the patients to a rehabilitation centre. The mean difference in costs was -€2,659 per patient (BCa 95% CI -€4,780 to -€964). Furthermore, costs for home care were higher in the surgery group.

Travel expenses were slightly higher in the surgically treated group, but represented a very small part of the total costs.

Effect

Death or major morbidity, corrected for organ failure at baseline, occurred in 22 of 51 (43.1%) patients in the endoscopy group (BCa 95% CI 35.3% to 49%) and in 21 of 47 (44.7%) patients in the surgery group (BCa 95% CI 34.0% to 55.3%). The endoscopic step-up approach is not better (1.5%; BCa 95% CI -14.8% to 16.4%) than the surgical step-up approach in preventing patients having a poor outcome following infected necrotising pancreatitis.

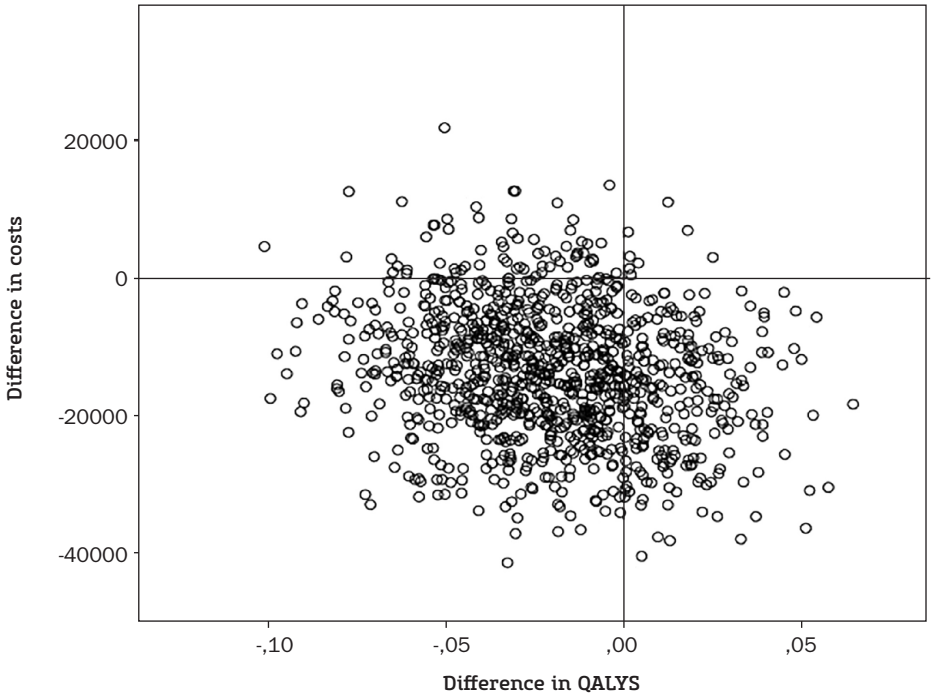

Figure A1. *Cost-effectiveness plane.*

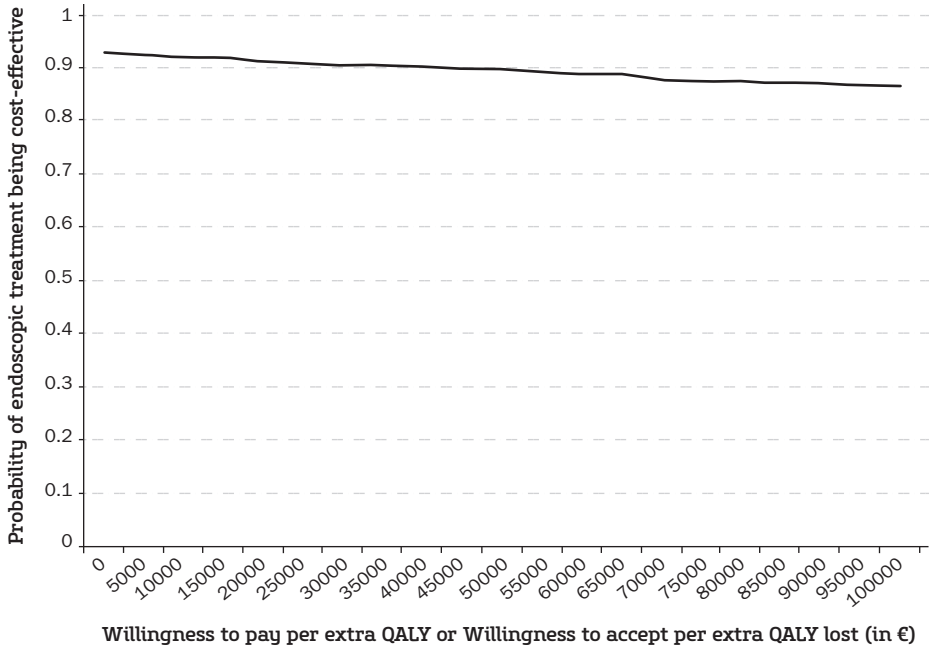

Figure A2. *Cost-effectiveness acceptability curve.*

The number of quality adjusted life-years in endoscopic step-up approach was 0.2788 (BCa 95% CI 0.2458 to 0.3110) against 0.2988 (BCa 95% CI 0.2524 to 0.3398) for the surgical group, based on health valuations from the Dutch general population. The difference. -0.0199 was non-significant (BCa 95% CI -0.0732 to 0.0395). Based on health valuations from the UK general population, similar observations were made with the difference equaling -0.0161 (BCa 95% CI -0.0743 to 0.0464; endoscopy group 0.2495 (BCa 95% CI 0.2116 to 0.2868), surgical group: 0.2656 (BCa 95% CI: 0.2161 to 0.3105)).

Incremental cost-effectiveness ratios

The difference in total costs of -€13,655 (BCa 95% CI -€33,273 to €6,149) divided by the difference of 1.5% in alive patients without major morbidity results in a point-estimated dominating incremental cost-effectiveness ratio of €884,383 saved per death or major morbidity prevented. The savings per loss of a single QALY were €684,455 (Dutch valuation) or €848,129 (UK valuation). The cost-effectiveness plane (Figure A1) for the differences in costs by the differences in QALYs (Dutch valuation) below shows that 0.8% of the 1,000 bootstrap results lie in the upper right, 6.3% in the upper left, 70.4% in the lower left, and 22.5% in the lower right quadrant.

With hardly any results presenting in the upper right and most results presenting in the lower left quadrant the corresponding cost-effectiveness acceptability curve below (Figure A2) may well be interpreted as the probability of endoscopic treatment being cost-effective (Y-axis) for different amounts that should at least be saved to society in order to make the loss of one extra QALY acceptable, the willingness-to-accept. The Figure shows that the endoscopic step-up approach seems good value for money. At a reasonable lower limit of the willingness-to-accept of €50,000 per extra QALY lost, given the functional status of the patient population at hand, the probability of endoscopic step-up being cost-effective is 0.896. Even at a minimum willingness-to-accept of €100,000 per extra QALY lost, the probability of ETN being cost-effective would still be 0.794.

Similar patterns were observed (not shown) for the extra costs per patient whose death or major morbidity would be prevented (probability of 0.883 at €50,000) and for the extra savings per additional QALY lost (UK valuation) (probability of 0.893 at €50,000).

Table A4. Unit costs of resources used per patient with infected necrotising pancreatitis.

Resource	Unit	Units costs*	Source
Hospital stay			
Intensive care unit	Day	1645.00	DMC 2015
General ward - university hospital*	Day	753.37	DMC 2015♦
General ward - community hospital	Day	525.08	DMC 2015♦
Day care	Day	276.00	DMC 2015
Ambulance transfer during admission	Transfer	272.00	DMC 2015
Emergency department visit	Visit	259.00	DMC 2015
Laboratory			
Total costs for all laboratory tests	Per day	47.56	Tariff application
Microbiology[$]			
Culture <2 culture media	Culture	14.27	Tariff application
Culture 2-3 media	Culture	18.59	Tariff application
Culture >3 media	Culture	26.56	Tariff application
Blood Culture	Culture	31.22	Tariff application
Diagnostic radiology			
Abdominal ultrasound	Test	89.61	Tariff application
X-ray - chest	Test	43.94	Tariff application
X-ray - abdomen	Test	45.10	Tariff application
CT-scan - chest	Test	181.44	Tariff application
CT-scan - abdomen	Test	187.84	Tariff application
Endoscopy (except for study interventions)			
Gastroscopy (incl feeding tube placement)	Procedure	317.55	Tariff application
Colonoscopy	Procedure	352.48	Tariff application
Endoscopic ultrasound	Procedure	591.37	Tariff application
ERCP	Procedure	517.81	Tariff application
Study Interventions			
ETD	Procedure	973.00	Top-down cost calculation
ETN	Procedure	1075.00	Top-down cost calculation
PCD	Procedure	408.65	Tariff application[&]
VARD	Procedure	2152.68	Top-down cost calculation

Table A4. Continued

Resource	Unit	Units costs*	Source
Other interventions and surgical procedures			
Ascites or pleural fluid drainage	Procedure	220.81	Tariff application
Gallbladder or PTC drainage	Procedure	338.06	Tariff application
Nephrostomy catheter	Procedure	421.48	Tariff application
Other drainage	Procedure	220.81	Tariff application
Angiography/embolization	Procedure	907.17	Tariff application
Vascular stent	Procedure	962.93	Tariff application
Cholecystectomy	Procedure	1689.85	Tariff application
EL	Procedure	1900.23	Top-down cost calculation
EL + gastro-enterotomy/stoma/cicatrical hernia	Procedure	2349.03	Top-down cost calculation
EL + stoma + splenectomy	Procedure	4228.38	Top-down cost calculation
EL + stoma + necrosectomy	Procedure	2216.75	Top-down cost calculation
Laparoscopy + stoma	Procedure	2447.20	Top-down cost calculation
Stoma construction	Procedure	1423.38	Top-down cost calculation
Re-exploration VARD cavity	Procedure	1647.78	Top-down cost calculation
Thoracotomy	Procedure	3835.68	Top-down cost calculation
Toe amputation	Procedure	988.60	Top-down cost calculation
Necrosectomy of decubitus wound	Procedure	1591.68	Top-down cost calculation
Outpatient clinic visits			
Outpatient clinic visit at academic hospital©	Visit	163.00	DMC 2015
Outpatient clinic visit at community hospital	Visit	80.00	DMC 2015
Non-hospital medical costs			
Rehabilitation Centre	Day	460.00	DMC 2015
General practitioner visit	Visit	33.00	DMC 2015
Home care	Hour	41.50	DMC 2015 %
Productivity loss	Hour	34.75	DMC 2015
Travel expenses	Kilometer	0.19	DMC 2015

◂ *Caption Table A4:*

⋆ Amounts are in Euro's. Costs base year 2014, if necessary costs were converted using Consumer Prices Indices. EL, indicates Exploratory Laparotomy. ♦ Additional costs for medication were calculated using the ratio of medication: costs per day derived from the DMC 2010. & Costs for PCD were calculated as costs for an (ultra-sound guided) drainage + costs for an abdominal CT-scan. $ Culture <2 media: line tip. Cultures 2-3 media: urine, throat, nose, perineum, rectum, MRSA/ BMRO swap, liquor. Cultures >3 media: all materials of abdominal origin, pleural effusion, sputum, wound, pus, bronchial secretion, genital smear. © Costs for telephone appointment were calculated, using 5 minutes as the average duration of a telephone contact. % Different costs for different types of home care exist; the average price of the relevant types of home care was calculated.

Table A5. Mean volumes and costs per patient, comparing an endoscopic and surgical step-up approach in patients with infected necrotising pancreatitis.

Unit	Endoscopic group (N=51)		Surgical group (N=47)		Cost Difference (BCa 95% CI)
	Mean volume	Mean costs (€)	Mean volume	Mean costs (€)	
Hospital stay	53.1	48196	68.9	58685	-10489 (-29816 to 10709)
ICU admission	13.4	22062	13.2	21700	362 (-16148 to 19712)
General ward (total)	39.2	25850	55.4	36619	-10769 (-19784 to -1657)
University hospital	23.1	17387	33.0	24877	-7491 (-17429 to 2622)
General hospital	16.1	8463	22.4	11741	-3024 (-8966 to 2906)
Day care	0.51	141	0.28	76	64 (-48 to 214)
Emergency department visits	0.43	112	0.83	214	-103 (-212 to 0)
Transfer by ambulance	0.12	32	0.28	75	-43 (-103 to 12)
Laboratory	N/A	2528	N/A	3277	-748 (-1491 to 1)
Microbiology	30.9	931	28.3	823	108 (-364 to 646)
Conventional radiology	13.7	1445	15.6	1684	-240 (-688 to 204)
Abdominal CT	4.71	884	5.85	1099	-215 (-457 to 29)
Thoracic CT	0.41	75	0.34	62	13 (-45 to 79)
Abdominal Ultrasound	0.57	51	0.74	67	-16 (-45 to 18)
Thoracic X-ray	5.49	241	6.68	294	-52 (-220 to 110)
Abdominal X-ray	1.73	78	1.09	49	29 (-14 to 74)
Other *	0.78	116	0.85	114	2 (-86 to 87)

Table A5. Continued

Unit	Endoscopic group (N=51)		Surgical group (N=47)		Cost Difference (BCa 95% CI)
	Mean volume	Mean costs (€)	Mean volume	Mean costs (€)	
Endoscopy	2.80	973	2.15	821	153 (-212 to 507)
Gastroscopy (including feeding tube placement)	2.41	766	1.45	459	307 (-17 to 617)
Colonoscopy	0	0	0.04	15	-15 (-37 to -7)
EUS	0.06	35	0.06	38	-3 (-54 to 55)
ERCP	0.33	173	0.60	308	-136 (-322 to 52)
Study interventions	4.31	3785	4.19	2851	934 (-82 to 2097)
PCD	1.10	449	3.51	1436	-987 (-1381 to -565)
VARD	0.04	84	0.64	1374	-1290 (-1744 to -868)
ETD	1.41	1355	0.04	41	1313 (1082 to 1599)
ETN	1.76	1897	0	0	1897 (1180 to 2820)
Other interventions	0.90	387	1.36	519	-132 (-421 to 134)
Ascites drainage	0.29	65	0.47	103	-38 (-127 to 33)
Pleural effusion drainage	0.18	39	0.32	66	-27 (-72 to 20)
PTC-drain	0.14	40	0.17	58	-18 (-95 to 66)
Gall bladder drain	0.02	7	0.06	22	-15 (-44 to 8)
Vascular intervention	0.25	232	0.28	252	-20 (-257 to 185)
Other intervention	0.02	4	0.06	18	-14 (-46 to 9)
Surgical procedures	0.33	722	0.28	493	229 (-262 to 712)
Outpatient clinic contact	2.73	267	3.79	376	-109 (-218 to -1)
Non-hospital medical costs	N/A	945	N/A	4295	-3350 (-5559 to -1643)
Rehabilitation centre/ nursing home (days)	0.75	320	7.49	2979	-2659 (-4780 to -964)
Home care (total hours) (N=75)	13.5	560	29.8	1238	-678 (-1539 to 52)
General Practitioner (N=75)	1.97	65	2.37	78	-13 (-62 to 40)
Travel expenses	N/A	49	N/A	59	-10 (-28 to 8)
Total costs per patient		**60228**		**73883**	**-13655 (-35782 to 10836)**

Table A6. Adverse Events other than primary and secondary end points.*

Adverse Events	Endoscopic step-up approach (N=51)	Surgical step-up approach (N=47)
Gastrointestinal		
Ascites	7	8
Abdominal compartment syndrome	2	0
Cholecystitis or cholangitis	4	3
Gastroparesis	1	1
Reflux oesophagitis	0	1
Rectovaginal fistula	0	1
Jaundice	1	0
Spleen abscess	1	0
Bile duct injury	1	1
Bleeding in the liver	1	0
Ischaemic colitis	1	0
Cardiovascular		
Atrial fibrillation	3	2
Cardiac arrest	0	3
Deep venous thrombosis	4	2
Congestive heart failure	1	1
Myocardial infarction	0	1
Pulmonary		
Pneumonia	16	9
Exacerbation of chronic obstructive pulmonary disease	3	0
Pleural effusion requiring drainage	3	7
Pleura empyema	1	0
Hydro-pneumothorax	1	2
Neurologic		
Delirium	0	2
Hypercapnic coma	0	1
Pulmonary embolus	1	0

Table A6. Continued

Adverse Events	Endoscopic step-up approach (N=51)	Surgical step-up approach (N=47)
Neurologic (continued)		
Epidural abscess	0	1
Hemiparesis	0	1
Trauma capitis	0	1
Urinary tract		
Urinary tract infection	6	4
Pyelonephritis	1	0
Urolithiasis	0	1
Other		
Bacteraemia	11	6
Toxicoderma	1	1

** Adverse events as noted in case record forms by attending physicians and reported to the Data and Safety Monitoring Board. These adverse events were not predefined in the study protocol.*

Economic analysis - conclusive remarks

Endoscopic step-up treatment of infected necrotising pancreatitis is economically superior to the surgical step-up approach as the best alternative available. The TENSION trial could not demonstrate that the endoscopic approach clinically outperformed the surgical approach, but it may lower the cost burden to society.

Table A7. Results of the sensitivity analysis.

	N	p	Exp (B)	95% CI
Primary composite end point:				
major complications or death	98	0.58	0.78	0.31-1.92
Secondary end points - major morbidity				
New-onset organ failure				
Pulmonary	98	0.34	0.53	0.14-1.99
Cardiovascular	98	0.07	0.27	0.06-1.09
Renal	98	0.16	0.30	0.06-1.59
Single	98	0.14	0.45	0.16-1.30
Multiple	98	0.12	0.26	0.05-1.43
Bleeding	98	0.47	0.67	0.23-1.97
Perforation of a visceral organ or Enterocutaneous fistula	98	0.14	0.33	0.07-1.43
Incisional hernia	98	1.00	0.00	-
Death	98	0.64	0.72	0.17-2.94
Other end points				
Pancreatic fistula	83	0.01	0.06	0.01-0.46
Exocrine insufficiency				
Enzyms	83	0.62	1.27	0.49-3.28
Fecal elastase	83	0.41	1.46	0.59-3.59
Steatorroe	83	0.24	0.46	0.12-1.69
Endocrine insufficiency	83	0.64	1.31	0.43-3.97
Biliary strictures	98	0.78	0.78	0.14-4.43
Wound infections	98	0.85	0.84	0.13-5.41

⋆ Baseline characteristics were equally distributed between groups although trends were found for chronic renal insufficiency (4 endoscopic vs. 0 surgical patients; p=0.05), systemic inflammatory response syndrome (SIRS) (33 endoscopic vs. 38 surgical patients; p=0.07), and modified multiple organ dysfunction syndrome (MODS) (median 0, range 0-8 vs. median 0, range 0-6; p=0.06). This table shows the end points corrected for baseline covariates.

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PART III

Summary and future perspectives

CHAPTER 11

Summary

Background

Acute pancreatitis is an acute inflammatory disorder of the pancreas and a common disease. Acute pancreatitis has a mild clinical course in 80% of patients, in whom the disease resolves spontaneously within approximately a week.[1] About 20% of patients develop severe acute pancreatitis. These patients suffer from organ failure or local complications as pancreatic necrosis.[2] This is associated with a high complication and mortality risk. The main cause of death in this group of patients is, besides the development of organ failure, the occurrence of a secondary bacterial infection of the necrotic tissue. The incidence of infected necrosis is approximately 30% in patients with pancreatic necrosis.[3] Infected necrosis is associated with a significant increase in the risk of complications and mortality, increased length of hospital stay and high costs. Infected necrosis is almost always an indication for invasive intervention. Even though much has changed in the management of necrotizing pancreatitis during the last 20 years, mortality of infected necrosis remains as high as 12% to 39%.[3-5] Current treatment of choice is a surgical step-up approach consisting of percutaneous (retroperitoneal) catheter drainage as first step, if necessary, followed by surgical minimally invasive necrosectomy.[5]

The number of patients admitted to the hospital with infected necrotizing pancreatitis is low.[6] As a result, it is difficult for the individual clinician and the individual center to gain and retain sufficient knowledge and expertise in dealing with this complex condition. This awareness has led to the idea to bundle the experience of this complicated form of acute pancreatitis. For this purpose, the Dutch Pancreatitis Study Group (DPSG) was founded in 2002. The DPSG strives to increase insight into the disease acute pancreatitis by conducting research. This leads to the improvement of diagnostics, treatment and also the prevention of complications. This thesis contains results of 8 years of clinical research within the DPSG.

This thesis began in **chapter 2** with an overview of the standard treatment of patients with necrotizing pancreatitis with a focus on both conservative and invasive treatment.

PART I

Diagnosis, identification and prevention of severe pancreatitis

Acute pancreatitis is a complex condition in which it is important to use correct terminology and clear definitions. This is particularly important in establishing the correct diagnosis, for communication between clinicians and for reporting of outcomes in clinical research. In order to promote a more uniform and correct use of terminology, the existing Atlanta classification was revised in 2012.[2] An important adjustment in this revised classification is the subdivision of patients with necrotizing pancreatitis in patients with necrosis of the pancreatic parenchyma with or without necrosis of the extra-pancreatic fat tissue, or patients with only necrosis of the extra-pancreatic fat tissue without necrosis of the pancreatic parenchyma (EXPN). Recent studies indicate that patients with EXPN are at lower risk of complications and mortality.[7] In addition, the revised classification provides clear handles for the morphological description of the type of pancreatitis and extra-pancreatic fluid collections. Thus, the difference between interstitial edema and necrotizing pancreatitis depends on the presence of necrosis. In the early phase (up to 4 weeks and without encapsulation) collections are described as acute fluid collection or acute necrotic collection, respectively, when necrosis is observed on the CT scan. In the late phase (after 4 weeks and with encapsulation) we speak of either a pseudocyst (only fluid, no necrosis) or of walled-off necrosis. The moderate interobserver agreement on this specific topic in the original 1992 Atlanta classification was an additional reason for revising the original classification. In **chapter 3** we examined the interobserver agreement for the revised Atlanta classification. For this purpose, CT scans were evaluated by a large group of experienced and inexperienced radiologists, surgeons and gastroenterologists. In conclusion, the interobserver agreement among all reviewers is good both for describing the type of acute pancreatitis and the type of extra-pancreatic collection. The highest interobserver agreement is between experienced radiologists, whereas inexperienced clinicians have the lowest interobserver agreement. This means considerable progress has been made compared with the 1992 version of the Atlanta classification.

The diagnosis of infected necrosis, the choice for and type of intervention are a persisting challenge. To support this, and to improve the expertise and treatment of this disease, in 2006 a nationwide pancreatitis expert panel was established. This is a online and multidisciplinary advisory body that is available 24/7/365 and provides free treatment counseling within 24 hours. At the time

of study, the expert panel consisted of 15 experts (7 surgeons, 4 gastroenterologists and 4 radiologists) in the field of acute pancreatitis. The methodology of this expert panel and a systematic evaluation of its functioning is described in **chapter 4**. This evaluation shows that the use of the expert panel is feasible in the Netherlands and considered easily accessible and valuable by the consulted physicians. Despite the clinical heterogeneity of necrotizing pancreatitis and the fact that the advisory experts cannot judge the patient themselves, a clear and useful advice was given in the vast majority of consultations (89% to 97%).

The decision for invasive intervention in infected necrotizing pancreatitis is based on a combination of clinical signs of infection and radiological findings. Radiological findings include gas bubbles in the collection and encapsulation on CT. Gas formation in the collections is considered pathognomonic for infection of necrosis and interventions are generally postponed until there is almost complete encapsulation of the collection (called 'walled-off necrosis'). Although it is often mentioned that both entities usually develop around 4 weeks after onset of symptoms, the lack of convincing evidence is undeniable. For this reason, we examined the natural course of extra-pancreatic collections and the timing of encapsulation and gas formation in these collections over time in **chapter 5**. Therefore, all CT scans made during the admission of patients with necrotizing pancreatitis were collected from a previously described prospective cohort.[3] These CT scans were categorized per week (week one to eight since start of symptoms) and evaluated by an experienced pancreatic radiologist. In contrast to previous opinions, most of the collections were already encapsulated 3 weeks after admission and only 50% of the patients actually developed gas in the collection.

Finally, the first part of this thesis deals with the prevention of complications such as infections (i.e. infected necrosis, bacteremia, pneumonia) which are known to negatively affect patient prognosis.[8,9] Clinical and animal experimental studies have indicated that such infections are caused by a combination of bacterial overgrowth secondary to disturbed intestinal motility and increase of mucosal permeability.[9-11] Because enteral nutrition stimulates intestinal motility, bacterial overgrowth is hypothesized to be inhibited. In addition, enteral nutrition stimulates the intestinal blood supply, thus possibly maintaining the integrity of the intestinal wall.[12-14] **Chapter 6** describes a randomized multicenter trial in which the above hypothesis is tested by comparing an early start of nasoenteric tube feeding with a normal diet 72 hours after clinical presentation. For this study, patients with predicted severe pancreatitis were selected. In this PYTHON trial, patients were randomized to nasoenteric tube feeding within 24 hours after randomization (early group) or a normal diet 72

hours after presentation (on-demand group). The second group only received tube feeding when a normal diet was not tolerated. The primary end point was a composite of infections (i.e. infected necrosis, bacteremia or pneumonia) and mortality within 6 months after randomization. A total of 208 patients were randomized. The primary end point did not differ between both groups (30% in the early group and 27% in the on-demand group; p=0.76). There was also no difference between groups in infections (25% vs. 26%; p=0.87) or mortality (11% vs. 7%, p=0.33). In the on-demand group, 69% of the patients tolerated a normal diet and had no indication for tube feeding. In conclusion, the PYTHON trial did not show that early nasoentric tube feeding is superior in reducing the number of infections and mortality compared with a normal diet started 72 hours after presentation in patients with predicted severe acute pancreatitis. The start of a normal diet after 72 hours, instead of routine administration of early nasoenteric tube feeding, leads to similar outcomes and less patient discomfort and costs.

PART II

Treatment of severe pancreatitis

The second part of this thesis focuses on improving treatment of patients with severe acute pancreatitis.

One of the deadliest complications of severe acute pancreatitis is abdominal compartment syndrome (ACS). ACS can lead to a decreased perfusion and ischemia of intra-abdominal organs resulting in an increase in organ failure.[15-17] As acute pancreatitis is a known risk factor for ACS, the 2013 World Society of the Abdominal Compartment Syndrome (WSACS) guideline recommends routine measurement of intra-abdominal pressure in critically ill acute pancreatitis patients.[18] The diagnosis of ACS in patients with severe pancreatitis is difficult as the symptoms overlap with those of other complications such as systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), infected necrosis, and multi organ dysfunction syndrome (MODS).[17] Both in the international literature and the 2013 WSACS guideline, percutaneous catheter drainage is recommended as first step in ACS treatment to potentially prevent surgery.[18-20] In recent years, several observational cohort studies have been published in the field of ACS in acute pancreatitis. However, much remains unknown about the incidence, diagnosis, clinical course and optimal treatment. Evaluating all published cohort studies in the field of ACS in acute pancreatitis was the purpose of the study described in **chapter 7**. This study focused on methodological quality and limitations, differences in

patient population, treatment strategies, and outcome. After a comprehensive literature search, only 7 studies were included. These studies were relatively small and had methodological shortcomings. The majority of patients underwent decompression laparotomy as first step of treatment. Within the studies, ACS was clearly associated with an increase in mortality in patients with acute pancreatitis.

In the randomized multicenter PANTER and PENGUIN trials, performed earlier by the DPSG, two different invasive treatment methods were compared in patients with infected necrosis. The PANTER trial compared a minimally invasive surgical step-up approach with conventional primary open necrosectomy.[5] The step-up approach consisted of percutaneous catheter drainage, if necessary, followed by a minimally invasive surgical necrosectomy (VARD). The results of the PANTER trial showed that the surgical step-up approach significantly reduced the number of major complications and mortality compared to a primary open necrosectomy in patients with infected necrosis. This was mainly attributed to a difference in organ failure in favor of the step-up approach. The PANTER trial also showed that 35% of the drained patients did not need an additional necrosectomy. Although the number of major complications is significantly reduced using the step-up approach, treatment is still associated with a combined risk of mortality and severe complications of around 40%.[5] During inclusion of the PANTER trial, more and more centers worldwide started using a new treatment modality. This so called endoscopic transluminal necrosectomy was developed to further reduce mortality and severe complications since it is even less invasive. General anesthesia is no longer required in this already severely ill group of patients and abdominal wall incisions, with its associated potential complications such as pancreatic fistula, incisional hernia, and wound infections are avoided. The infected necrosis is relatively easily removed endoscopically via stomach or duodenum. To investigate whether such a less invasive approach results in a better outcome, the PENGUIN trial was conducted.[21] In this small pilot trial, the post-procedural pro-inflammatory response (interleukin-6) and the risk of complications following endoscopic necrosectomy were compared with surgical, usually open, necrosectomy. In both study arms 10 patients were included. Endoscopic necrosectomy was associated with a lower pro-inflammatory response and a better clinical outcome than surgical necrosectomy in patients with infected necrosis. As the next step towards yet another RCT, **chapter 8** summarizes the results of published studies on endoscopic necrosectomy. A systematic review of the literature was performed, including all published cohorts between 2005 and 2013 of necrotizing pancreatitis patients who have undergone endoscopic necrosectomy. After screening,

14 studies with a total of 455 patients were included. These studies were small, almost always retrospective and of low methodological quality. The reported mortality and risk of complications were 6% and 36% respectively, with bleeding being the most common complication. In conclusion, endoscopic necrosectomy indeed appears to be a safe and possibly good alternative to surgical minimally invasive necrosectomy.

The PANTER trial compared a surgical step-up approach with primary open necrosectomy. As a result, percutaneous drainage as first step of treatment has become the new golden standard for treatment of patients with infected necrosis. However, a good comparison of minimally invasive necrosectomy techniques with open necrosectomy has never been performed. Hence, open necrosectomy is still performed as second step of treatment after initial percutaneous drainage in many centers around the world. To investigate the difference between a minimally invasive necrosectomy (both surgical and endoscopic) and traditional open necrosectomy and to support our plea for minimally invasive necrosectomy as the treatment of choice, we conducted an individual patient data meta-analysis (IPDMA) in **chapter 9**. An important advantage of an IPDMA in this 'rare' group of patients is that by combining multiple cohorts and thus a large number of patients, mortality could be chosen as primary end point. The difference between an IPDMA and a systematic review is that for an IPDMA the individual patient data are used and not the data on group level. For this IPDMA we have selected all published cohorts of patients who have undergone some form of necrosectomy. The authors and principal investigators of selected studies were contacted to join this project and requested to provide the original data of these cohorts at the level of the individual patient. This appeared to be possible for 13 published and 2 unpublished cohorts. For some studies this included additional unpublished data. With a total of 1980 patients, from 51 hospitals and 8 different countries, this has become the largest international cohort of necrosectomy patients. 1167 Patients underwent open necrosectomy and 813 a minimally invasive surgical (N=467) or endoscopic (N=346) necrosectomy. There was a lower risk of mortality after both minimally invasive surgical and endoscopic necrosectomy compared to open necrosectomy. After propensity score matching with risk stratification, a minimally invasive surgical necrosectomy was associated with a lower risk of mortality than open necrosectomy in the very high-risk group. Endoscopic necrosectomy was associated with a lower risk of mortality than open necrosectomy both in the high risk and very high risk group. In conclusion, minimally invasive surgical or endoscopic necrosectomy is associated with a lower mortality than open necrosectomy in high risk patients with necrotizing pancreatitis.

The combined results of Dutch series collected by the DPSG and previously published cohort studies suggest that an endoscopic approach may further reduce major complications and mortality compared to a surgical approach.[21-23] To further investigate these promising results, we conducted the randomized multicenter TENSION trial (**chapter 10**). In this study, we compared an endoscopic step-up approach with the surgical step-up approach from the PANTER trial in patients with infected necrosis. The endoscopic approach consisted of endoscopic transluminal drainage as first step, followed if necessary by endoscopic transluminal necrosectomy. The surgical approach of percutaneous catheter drainage, if necessary followed by minimally invasive surgical necrosectomy (VARD). The primary end point was a composite of mortality and major complications within 6 months after randomization. In addition, the occurrence of pancreatic fistula, exo- and endocrine pancreatic insufficiency, hospital stay and costs were studied. In TENSION, the primary end point occurred in 43% of patients in the endoscopy group and 45% of patients in the surgery group (p=0.88). There were no significant differences in the individual components of the primary end point. Mortality was 18% compared to 13%, p=0.50, respectively. The number of pancreatic fistulas was lower in the endoscopy group (5% vs. 32%; p=0.001) and total hospital stay shorter (average 53 days vs. 69 days; p=0.01). In the endoscopy group, 41% of patients compared with 49% in the surgical group, did not require an additional necrosectomy after initial drainage (p=0.43). Finally, the total mean costs were € 13.655 lower (but non-significantly) in the endoscopy group. In conclusion, the TENSION trial shows that the endoscopic step-up approach is not superior to the surgical step-up approach in reducing mortality and major complications in patients with infected necrosis. However, the endoscopic approach significantly reduced total hospital stay and the number of pancreatic fistulas. In addition, TENSION demonstrates that endoscopic drainage as first step of treatment also prevents additional necrosectomy in many patients.

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CHAPTER 12

General discussion and future perspectives

The research presented in this thesis has contributed significantly in answering most of the questions that were raised at the start of this PhD project. Our results will lead to changes in management of patients with acute pancreatitis and improve outcome. Furthermore, they will be implemented in international treatment guidelines. In this final chapter, we will discuss the latest developments and findings of the research in this thesis and put these into the perspective of future research directions. We will also discuss the impact of the answers to the questions we have raised in the introduction of this thesis.

Has the revised version of the Atlanta classification improved the interobserver agreement and, if so, has this improved generalizability of results in the literature on diagnosis and outcome of patients with acute pancreatitis?
The international interobserver study described in chapter 3 showed that the revision of the Atlanta classification has improved the interobserver agreement for type of acute pancreatitis and for peri-pancreatic collections from overall poor in the original 1992 Atlanta classification to good in the revised version. Even non-expert clinicians scored moderate to good agreement. So, the revision of the Atlanta classification represents a substantial progress in uniform application of the classification of acute pancreatitis and the use of uniform definitions in clinical practice and research. We are convinced that the use of uniform definitions based on the revised Atlanta classification on a broader basis, will lead to more uniform reporting, improved comparability of research results and hopefully a better outcome for patients with acute pancreatitis in the future. Future reviews of the literature on acute pancreatitis will show whether this simplified use of the international classification is indeed applied on a broader basis and actually improves clinical practice and generalizability of results.

Is the Dutch nationwide expert panel on acute pancreatitis helpful for the trea ting physician in a local hospital during the treatment of acute pancreatitis? In other words, are classification of disease and treatment advice feasible and helpful on an E-consultation basis?
The evaluation in chapter 4 shows that an expert panel is feasible within the Dutch health care setting and is considered to be an accessible and valuable tool for treating clinicians. However, the effect on outcome of acute pancreatitis is unclear since no clinical outcome data was available for patients evaluated. An important offspring of our expert panel is that in fact 'the whole country is consulted' to discuss diagnosis and treatment of notoriously difficult cases. It is in fact a form of an electronic second opinion, with all medical

disciplines aboard. Asking 15 experts for their opinion will sometimes result in 15 different advices. Fortunately, complete diversity is rare and only concerns the most difficult cases in which an unanimous advice is just simply impossible. The threshold for consultation of the expert panel is low. This low threshold and a broad awareness of its existence will probably increase the number of clinicians asking for advice and hopefully further improve outcome. In accordance with our expert panel, more national panels of expertise are established. For example, the Dutch Pancreatic Cancer Group, Chronic Pancreatitis Study Group and the Dutch Initiative on Crohn's Disease and Ulcerative Colitis. A comparable expert panel system can be easily and inexpensively implemented in other national and international health care settings and for other rare and complex diseases. Future prospective research in this field is necessary, primarily in order to directly relate the consultation and treatment advice given to the effect on outcome.

What is the natural course of encapsulation and gas formation within necrotic collections in time?

The main findings of the study presented in chapter 5 are that onset of gas configurations can occur in every phase of the disease. Although the walling-off of necrosis develops over time, over 40% of patients already have clear radiological signs of encapsulation around areas of necrosis within the first 3 weeks of disease. This has therapeutic implications because the presence of early encapsulation might justify earlier invasive intervention in this subset of patients with infected necrosis. This stands in contrast to earlier conviction and current international guidelines, which advice to postpone invasive intervention for at least 4 weeks and until walled-off necrosis is present. This is primarily based on studies in which outcome is worse in patients who underwent early necrosectomy. However, standard treatment of infected necrosis is no longer primary necrosectomy but involves catheter drainage as first step. It is suggested that catheter drainage does not require full encapsulation. Therefore, patients may benefit from earlier drainage which results in an improved outcome and possibly reduced need for necrosectomy. This hypothesis is currently being studied in a new multicenter randomized controlled trial in the Netherlands (POINTER trial, ISRCTN33682933). In this study, early drainage is compared with 'delayed' drainage in patients with infected necrosis. If this hypothesis is confirmed, the treatment paradigm of catheter drainage aiming at 'relieving pus under tension to prevent sepsis originating from the infected collection' needs to be questioned and probably replaced by a new paradigm.

Can early complications of acute pancreatitis be reduced by early enteral feeding?
In our large multicenter randomized trial including 208 patients, early nasoenteric tube feeding did not prevent complications such as infections or death, as compared with an oral diet after 72 hours in patients with acute pancreatitis at high risk for complications. These findings in chapter 6 result in the restriction of tube placement to patients who cannot tolerate an oral diet. Thereby reducing discomfort and costs in a substantial group of patients. The hypothesis of this trial, that early nasoenteric feeding reduces (the risk of) bacterial translocation and remote infection like infected necrosis, could not be confirmed. Therefore we have to move on and perform further studies on other topics (e.g. Early Endoscopic Retrograde Cholangiography in patients with predicted severe acute biliary pancreatitis and optimal fluid therapy in the early phase) in order to reduce systemic inflammatory complications in the early phase of acute pancreatitis.

The second part of this thesis was dedicated to improve treatment and thereby outcome of patients with severe acute pancreatitis. The research questions we asked ourselves at the start were as followed.

What do we know about the incidence, clinical course, treatment, and outcome of abdominal compartment syndrome (ACS), as a rare and often fatal complication of acute pancreatitis?
Our systematic review in chapter 7 shows that the incidence of ACS in acute pancreatitis varies greatly (from 9% to 36%) and was associated with a mortality rate of 49%. Surgical decompression lowers the intra-abdominal pressure (IAP) considerably. However, it is not possible to relate this decrease in IAP to clinical outcome from the available literature. The studies that were performed on this topic are sparse and of low methodological quality. It therefore remains unknown if and when invasive intervention should be performed for ACS and which method is most effective. Large prospective studies with accurate measuring of IAP and registration of most important clinical end points are necessary to adequately correlate interventions for ACS and the associated lowering of IAP to clinical outcome.

Can the results of a minimally invasive step-up approach through the retroperitoneum be further improved by an endoscopic transluminal approach for patients with infected necrosis?
The studies in our review of current literature on endoscopic necrosectomy were small and methodological quality was low, but they showed promising

results of endoscopic treatment. In addition to this study, we performed an individual patient data meta-analysis (IPDMA) comparing open necrosectomy with minimally invasive necrosectomy (i.e. surgical and endoscopic). Results showed that both a minimally invasive surgical and endoscopic necrosectomy reduced the risk of mortality compared with open necrosectomy. Moreover, we also compared an endoscopic step-up approach with a minimally invasive surgical step-up approach within the randomized controlled TENSION trial in chapter 10. The primary end point of major complications and death was comparable for both treatment options. However, an important clinical advantage of the endoscopic approach is the reduction in external pancreatic fistulas and hospital stay. In summary, the research in this thesis has demonstrated that drainage (i.e. percutaneous or endoscopic) should always be the first step of treatment. In case necrosectomy is required after drainage, this should be performed minimally invasive (i.e. surgical or endoscopic). Furthermore, both a minimally invasive surgical step-up approach and endoscopic step-up approach are valid treatment options. Altough there is an advantage of endoscopic treatment as the first step in management of patients with infected necrosis based on the reduction of pancreatic fistula and hospital stay. As mentioned, subject to further investigation is early drainage of infected collections. Furthermore, during the course of the TENSION trial, lumen-apposing metal stents were introduced and gained popularity in endoscopic treatment. The larger diameter may improve drainage and lead to diminished need for necrosectomy. However, up until now, there is no firm evidence of significant benefit of metal stents over plastic pigtail stents. In the Netherlands, the TENSION trial will be succeeded by a new study comparing metal stents in a case-control format to the pigtail stent results in TENSION.

In conclusion

Severe acute pancreatitis is relatively rare and associated with high morbidity and mortality. Treatment of patients with infected necrosis is complex and should be performed in tertiary referral centers by multidisciplinary teams where gastroenterologists, interventional radiologists and pancreato-biliary surgeons work closely together, because a combined and tailored approach leads to the best outcome. Given the data in this thesis, and further developments in endoscopic treatment, we predict that endoscopic step-up treatment will become the first line therapy, with additional percutaneous drainage or surgical treatment reserved for patients in whom endoscopic therapy either failed or is technically not possible. We believe that in time an individual tailored approach, based on patient characteristics, location of collections, and degree

of encapsulation, will become the new standard.

The research in this thesis answered several important questions in the field of severe acute pancreatitis, but more remains unanswered. The Dutch Pancreatitis Study Group will continue its research and hopefully perform many more nationwide multicenter studies in the coming years.

APPENDICES

Dutch Summary
(NEDERLANDSE SAMENVATTING)

Acknowledgements
(DANKWOORD)

List of publications

PhD portfolio

Curriculum Vitae

Dutch Summary

(NEDERLANDSE SAMENVATTING)

Achtergrond

Acute pancreatitis is een veel voorkomende acute ontsteking van het pancreas. Meestal verloopt de ziekte mild (in 80% van de patiënten) met buikpijnklachten die binnen een week spontaan herstellen.[1] Echter, 20% van de patiënten ontwikkelt een ernstige pancreatitis. Hierbij treedt orgaanfalen op of ontwikkelt zich necrose van het pancreas.[2] Dit is geassocieerd met een hoog risico op complicaties en sterfte. De voornaamste doodsoorzaak in deze groep patiënten is, naast het ontwikkelen van orgaanfalen, het optreden van een secundaire bacteriële infectie van de necrose. Geïnfecteerde necrose treedt op in ongeveer 30% van de patiënten met pancreas necrose, en gaat gepaard met een aanzienlijke stijging van het risico op complicaties en sterfte, een verlengde ziekenhuisopname en hoge kosten.[3] Geïnfecteerde necrose is vrijwel altijd een indicatie voor invasieve interventie. Hoewel er de laatste 20 jaar veel is veranderd in de behandeling van patiënten met een necrotiserende pancreatitis, blijft het risico op sterfte bij geïnfecteerde necrose hoog met 12% tot 39%.[3-5] De huidige standaard behandeling is de chirurgische stapsgewijze benadering bestaande uit percutane (retroperitoneale) katheter drainage als eerste stap, indien nodig gevolgd door een minimaal invasieve chirurgische necrosectomie.[5]

Het aantal patiënten met geïnfecteerde necrose dat per jaar wordt opgenomen in het ziekenhuis is laag.[6] Hierdoor is het als individuele specialist en als individueel centrum moeilijk om voldoende kennis en ervaring op te doen, en te behouden, met de behandeling van deze complexe aandoening. Dit besef heeft ertoe geleid de ervaringen met de gecompliceerde vorm van acute pancreatitis te gaan bundelen. Hiervoor werd in 2002 de Pancreatitis Werkgroep Nederland (PWN) opgericht. De PWN streeft er naar om, door het uitvoeren van wetenschappelijk onderzoek, meer inzicht te verkrijgen in het ziektebeeld acute pancreatitis. Dit leidt tot het verbeteren van diagnostiek en behandeling, evenals de preventie van complicaties. Huidig proefschrift bevat het resultaat van 8 jaar intensief klinisch wetenschappelijk onderzoek binnen de PWN.

Dit proefschrift begint in **hoofdstuk 2** met een overzicht van de standaard behandeling van patiënten met een necrotiserende pancreatitis, zowel conservatief als invasief.

DEEL I

Diagnostiek, identificatie en preventie van ernstige pancreatitis

Acute pancreatitis is een complexe aandoening waarbij het van belang is correcte terminologie en heldere definities te gebruiken. Dit is met name belangrijk bij het stellen van de juiste diagnose, voor de communicatie tussen artsen en het rapporteren van uitkomsten van klinisch onderzoek. Om een meer uniform en correct gebruik van terminologie te bevorderen werd in 2012 de reeds bestaande Atlanta classificatie gereviseerd.[2] Een belangrijke aanpassing in deze herziene classificatie is het onderverdelen van patiënten met een necrotiserende pancreatitis in patiënten met necrose van het pancreasparenchym met of zonder necrose van het extra-pancreatische vetweefsel, en patiënten met alleen necrose van het extra-pancreatische vetweefsel, zonder necrose van het pancreasparenchym (EXPN). Uit recent onderzoek blijkt dat patiënten met EXPN een lager risico lopen op complicaties en sterfte.[7] Daarnaast geeft de gereviseerde classificatie duidelijke handvatten voor de morfologische beschrijving van het type pancreatitis en extra-pancreatische vochtcollectie. Zo spreekt men van interstitiële oedemateuze of necrotiserende pancreatitis afhankelijk van het aanwezig zijn van necrose. In de vroege fase (tot 4 weken en zonder afkapseling) worden collecties beschreven als respectievelijk acute vochtcollectie, of acute necrotische collectie wanneer necrose wordt waargenomen op de CT scan. In de late fase (na 4 weken en met afkapseling) spreken we van een pseudocyste, bij afwezigheid, of 'walled-off necrose', bij aanwezigheid van necrose. De matige interobserver overeenkomst voor dit specifieke onderwerp in de originele 1992 Atlanta classificatie was een bijkomende reden om de oorspronkelijke classificatie te reviseren. In **hoofdstuk 3** hebben wij de interobserver overeenkomst voor de gereviseerde Atlanta classificatie onderzocht. Hiervoor werden CT scans beoordeeld door een groep ervaren en onervaren radiologen, chirurgen en MDL-artsen. Concluderend is de interobserver overeenkomst onder alle reviewers goed, zowel voor het beschrijven van het type acute pancreatitis als het type extra-pancreatische collectie. De beste interobserver overeenkomst is tussen ervaren radiologen, terwijl onervaren clinici de laagste interobserver overeenkomst hebben. Dit betekent dat er aanzienlijke vooruitgang is geboekt vergeleken met de 1992 versie van de Atlanta classificatie.

Het diagnosticeren van geïnfecteerde necrose, de keuze voor interventie en het type interventie vormen een uitdaging. Om hierin te ondersteunen, de expertise te doen toenemen en de behandeling te verbeteren, is in 2006 het pancreatitis expert panel opgericht. Dit betreft een landelijk online en multidisciplinair adviesorgaan dat 24/7/365 beschikbaar is en binnen 24 uur een vrijblijvend behandeladvies geeft. Op het moment van studie bestond het expert panel uit 15 experts (7 chirurgen, 4 MDL-artsen en 4 radiologen) op het gebied van acute pancreatitis. De werkwijze van dit expert panel en een systematische evaluatie van haar functioneren is beschreven in **hoofdstuk 4.** Deze evaluatie laat zien dat het gebruik van het expert panel haalbaar is in Nederland en door de geraadpleegde behandelaars als makkelijk toegankelijk en waardevol wordt beschouwd. Ondanks de klinische heterogeniteit van necrotiserende pancreatitis en het feit dat de adviserende experts de patiënt niet zelf kunnen beoordelen, kan in een ruime meerderheid van het aantal consultaties (89%-97%) een duidelijk en bruikbaar advies worden gegeven.

Het besluit tot invasieve interventie bij geïnfecteerde necrotiserende pancreatitis wordt gebaseerd op de combinatie van klinische tekenen van infectie en radiologische bevindingen. Onder radiologische bevindingen vallen gasbellen in de collectie en afkapseling van collecties op een CT-scan. Gasvorming in collecties wordt beschouwd als pathognomonisch voor infectie van necrose en interventies worden over het algemeen uitgesteld tot er sprake is van vrijwel volledige afkapseling van de collectie (zgn. 'walled-off necrose'). Hoewel vaak wordt vermeld dat beide entiteiten zich meestal pas rond 4 weken na start van symptomen ontwikkelen, mist hiervoor onomstotelijk bewijs. Om die reden hebben wij in **hoofdstuk 5** het natuurlijk beloop van extra-pancreatische collecties, de timing van afkapseling en vorming van gas in deze collecties in de tijd onderzocht. Hiervoor werden alle CT scans, gemaakt gedurende de opname van patiënten met een necrotiserende pancreatitis, uit een eerder beschreven prospectief cohort verzameld.[3] De CT scans werden gecategoriseerd per week (week een tot en met acht sinds start symptomen) en beoordeeld door een ervaren pancreas radioloog. Anders dan gedacht is het merendeel van de collecties al na 3 weken afgekapseld en ontwikkelt maar 50% van de patiënten daadwerkelijk gas in de collectie.

Tenslotte wordt in het eerste deel van dit proefschrift ingegaan op het voorkómen van complicaties als infecties (d.w.z. geïnfecteerde necrose, bacteriëmie, pneumonie) waarvan bekend is dat dit de prognose van patiënten negatief beïnvloedt.[8,9] Er zijn klinische en dierexperimentele aanwijzingen dat dergelijke infecties mede veroorzaakt worden door een combinatie van bacteriële overgroei secundair aan verstoorde darm motiliteit en een toename van

de mucosale permeabiliteit.[9-11] Omdat enterale voeding de intestinale motiliteit stimuleert wordt aangenomen dat bacteriële overgroei wordt geremd. Daarnaast stimuleert enterale voeding de intestinale bloedtoevoer waardoor mogelijk de integriteit van de darmwand beter in stand blijft.[12-14] **Hoofdstuk 6** beschrijft een gerandomiseerde multicentrische studie waarin bovenstaande hypothese wordt getest door het vroeg starten van enterale sondevoeding te vergelijken met een normaal dieet 72 uur na klinische presentatie. Voor deze studie werden patiënten met een acute pancreatitis en een verhoogd risico op complicaties (zgn. 'voorspeld ernstige pancreatitis') geselecteerd. In deze PYTHON studie, werden patiënten gerandomiseerd voor sondevoeding binnen 24 uur na randomisatie (vroege groep) of een normaal dieet, 72 uur na presentatie (on-demand groep). De laatste groep kreeg alleen sondevoeding wanneer een normaal dieet niet werd verdragen. Het primaire eindpunt betrof een samengesteld eindpunt van infecties (d.w.z. geïnfecteerde necrose, bacteriemie of pneumonie) en sterfte binnen 6 maanden na randomisatie. In totaal zijn 208 patiënten gerandomiseerd. Het primaire eindpunt verschilde niet tussen beide groepen (30% in de vroege groep en 27% in de on-demand groep; p=0.76). Evenmin waren er verschillen tussen de groepen in infecties (25% vs. 26%; p=0.87) of sterfte (11% vs. 7%, p=0.33). In de on-demand groep tolereerde 69% van de patiënten een normaal dieet en had geen indicatie voor sondevoeding. Concluderend toont de PYTHON studie bij patiënten met voorspeld ernstige acute pancreatitis niet aan dat vroege enterale sondevoeding superieur is in het verminderen van het aantal infecties en sterfte in vergelijking met een normaal dieet gestart 72 uur na presentatie. De start van een normaal dieet na 72 uur, in plaats van routinematig gebruik van sondevoeding, zorgt echter wel voor een significante reductie in patiënt ongemak en kosten.

DEEL II

Behandeling van ernstige pancreatitis

Het tweede deel van dit proefschrift focust zich op het verbeteren van de behandeling van patiënten met een ernstige acute pancreatitis.

Een van de meest dodelijke complicaties van een ernstige acute pancreatitis is het optreden van een abdominaal compartiment syndroom (ACS). ACS kan lijden tot een verminderde perfusie en ischemie van intra-abdominale organen met een toename van orgaanfalen als gevolg.[15-17] Aangezien acute pancreatitis een bekende risico factor is voor ACS, adviseert de 2013 World Society of the Abdominal Compartment Syndrome (WSACS) richtlijn het routinematig meten van de intra-abdominale druk bij kritiek zieke acute pancreatitis patiënten.[18] De

diagnose ACS bij patiënten met een ernstige pancreatitis is lastig definitief te stellen aangezien de symptomen overlap vertonen met die van andere complicaties als systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), geïnfecteerde necrose en multi organ dysfunction syndrome (MODS).[17] Zowel in de internationale literatuur als de 2013 WSACS richtlijn wordt percutane katheter drainage als eerste stap van behandeling van ACS geadviseerd om zo potentieel een operatie te voorkomen.[18-20] De laatste jaren zijn er verschillende observationele cohort studies gepubliceerd op het gebied van ACS bij acute pancreatitis. Er blijft echter veel onbekend over de incidentie, diagnose, het klinisch beloop en de optimale behandeling. Het evalueren van alle gepubliceerde cohort studies op het gebied van ACS bij acute pancreatitis was het doel van de studie beschreven in **hoofdstuk 7**. Hierbij kijkend naar de methodologische kwaliteit en beperkingen, de verschillen in patiënt populatie, behandel strategieën en uitkomsten. Na een uitgebreid literatuuronderzoek werden slechts 7 studies geïncludeerd. Deze studies waren relatief klein en hadden methodologische tekortkomingen. De meerderheid van patienten onderging een decompressie laparotomie als eerste stap van de behandeling. Binnen de studies was ACS duidelijk geassocieerd met een toename van sterfte bij patiënten met een acute pancreatitis.

In de, eerder door de PWN uitgevoerde, gerandomiseerde multicentrische PANTER en PENGUIN studies werden meerdere invasieve behandel methodes vergeleken bij patiënten met geïnfecteerde necrose. De PANTER studie vergeleek een minimaal invasieve chirurgische stapsgewijze benadering met de conventionele primaire open necrosectomie.[5] De stapsgewijze benadering bestond uit percutane katheter drainage, indien nodig, gevolgd door een minimaal invasieve chirurgische necrosectomie (VARD). De resultaten van de PANTER studie toonden aan dat de chirurgische stapsgewijze benadering het aantal ernstige complicaties en sterfte, significant vermindert ten opzichte van een primaire open necrosectomie bij patiënten met geïnfecteerde necrose. Dit werd voornamelijk toegeschreven aan een verschil in orgaanfalen in het voordeel van de stapsgewijze benadering. De PANTER studie liet tevens zien dat 35% van de gedraineerde patiënten geen aanvullende necrosectomie nodig had. Hoewel het aantal ernstige complicaties significant werd verminderd door het gebruik van de stapsgewijze benadering, gaat de behandeling nog steeds gepaard met een gecombineerd risico op sterfte en ernstige complicaties van 40%.[5] Ten tijde van de PANTER studie werd in steeds meer centra wereldwijd een nieuwe behandeling toegepast. Deze zogenaamde endoscopische transluminale necrosectomie is ontwikkeld om het aantal ernstige complicaties en sterfte verder te verminderen. Algehele narcose is niet langer noodzakelijk en abdominale incisies, met

bijbehorende potentiële complicaties zoals pancreasfistels, littekenbreuken en wondinfecties, worden voorkomen in deze al kritiek zieke groep patiënten. De geïnfecteerde necrose wordt hierbij endoscopisch via maag of duodenum verwijderd. Om te onderzoeken of deze, in opzet nog minder invasieve benadering, voor een betere uitkomst zorgt werd de PENGUIN studie uitgevoerd.[21] In deze kleine pilot studie is onderzocht of de post-procedurele pro-inflammatoire reactie (interleukine-6) en het risico op complicaties na endoscopische necrosectomie lager is dan na chirurgische, meestal open, necrosectomie. In beide studie armen werden 10 patiënten geïncludeerd. Endoscopische necrosectomie bleek gepaard te gaan met een lagere pro-inflammatoire reactie en een verbetering van de klinische uitkomst in vergelijking met een chirurgische necrosectomie bij patiënten met geïnfecteerde necrose. Als volgende stap naar een nieuwe gerandomiseerde studie, heeft **hoofdstuk 8** een overzicht gegeven van de resultaten van gepubliceerde studies over endoscopische necrosectomie. In deze systematische review van de literatuur werden alle gepubliceerde cohorten, tussen 2005 en 2013, van patiënten met een necrotiserende pancreatitis die een endoscopische necrosectomie hebben ondergaan geëvalueerd. Na uitgebreide screening werden 14 studies met in totaal 455 patiënten geïncludeerd. Deze studies waren klein, bijna altijd retrospectief en van lage methodologische kwaliteit. De gerapporteerde sterfte en het risico op complicaties was respectievelijk 6% en 36%, waarbij bloedingen de meest voorkomende complicaties waren. Concluderend lijkt een endoscopische necrosectomie inderdaad een veilig en mogelijk goed alternatief voor minimaal invasieve chirurgische necrosectomie.

De PANTER studie vergeleek een chirurgische stapsgewijze benadering met primaire open necrosectomie. Dit heeft er toe geleid dat percutane drainage, als eerste stap van behandeling van patiënten met geïnfecteerde necrose, de nieuwe gouden standaard is geworden. Echter een goed vergelijk van minimaal invasieve necrosectomie technieken met open necrosectomie is niet eerder uitgevoerd. Vandaar dat er wereldwijd soms nog steeds een open necrosectomie wordt verricht na initiële percutane drainage. Om het verschil tussen een minimaal invasieve necrosectomie (zowel chirurgisch als endoscopisch) en de traditionele open necrosectomie te onderzoeken, hebben wij een individual patiënt data meta-analysis (IPDMA) verricht (**hoofdstuk 9**). Een belangrijk voordeel van een IPDMA bij deze relatief zeldzame groep patiënten is dat, door het bundelen van meerdere cohorten en daarmee een groot aantal patiënten, sterfte als uitkomstmaat gekozen kon worden. Daarnaast wordt voor een IPDMA data op individueel patiënt niveau gebruikt, in tegenstelling tot de data per groep in een systematische review. Voor de IPDMA hebben wij

alle gepubliceerde cohorten van patiënten die een of andere vorm van necrosectomie hebben ondergaan geselecteerd. De auteurs en hoofdonderzoekers van geselecteerde studies werden benaderd om deel te nemen aan dit project en gevraagd om de originele data van deze cohorten, op het niveau van de individuele patiënt, beschikbaar te stellen. Dit bleek mogelijk voor 13 gepubliceerde en 2 nog niet gepubliceerde cohorten. Daarnaast betrof dit voor een aantal studies aanvullende ongepubliceerde data. Met in totaal 1980 patiënten, vanuit 51 ziekenhuizen en 8 verschillende landen, is dit het grootste internationale cohort van necrosectomie patiënten geworden. 1167 Patiënten ondergingen een open necrosectomie en 813 een minimaal invasieve chirurgische (N=467) of endoscopische (N=346) necrosectomie. Er bleek een lager risico op sterfte na minimaal invasieve chirurgische of endoscopische necrosectomie in vergelijking met open necrosectomie. Na propensity score matching met risico stratificatie bleef een minimaal invasieve chirurgische necrosectomie geassocieerd met een lager risico op sterfte dan een open necrosectomie in de zeer-hoog risico groep. Endoscopische necrosectomy was geassocieerd met een lager risico op sterfte dan open necrosectomie, zowel in de hoog risico als zeer-hoog risico groep. Concluderend, bij hoog risico patiënten met een necrotiserende pancreatitis gaat een minimaal invasieve chirurgische of endoscopische necrosectomie gepaard met een lagere sterfte dan open necrosectomie.

De gecombineerde resultaten van Nederlandse series verzameld door de PWN en eerder gepubliceerde cohort studies suggereren dat een endoscopische benadering de gecombineerde sterfte en ernstige complicaties verder kan verminderen ten opzichte van een chirurgische benadering.[21-23] Om deze veelbelovende resultaten verder te onderzoeken, hebben wij de gerandomiseerde multicentrische TENSION studie (**hoofdstuk 10**) uitgevoerd. In deze studie hebben wij een endoscopische stapsgewijze benadering vergeleken met de chirurgische stapsgewijze benadering uit de PANTER studie bij patiënten met geïnfecteerde necrose. De endoscopische benadering bestond uit endoscopische transluminale drainage als eerste stap, indien nodig gevolgd door endoscopische transluminale necrosectomie. De chirurgische benadering uit percutane katheter drainage, indien nodig gevolgd door minimaal invasieve chirurgische necrosectomie (VARD). Het primaire eindpunt betrof een samengesteld eindpunt van sterfte en ernstige complicaties binnen 6 maanden na randomisatie. Daarnaast werden het optreden van pancreasfistels, exo- en endocriene pancreasinsufficiëntie, de opnameduur en kosten onderzocht. Het primaire eindpunt trad op in 43% van de patiënten in de endoscopische groep en 45% van de patiënten in de chirurgische groep (p=0.88). Er waren geen significante verschillen in de individuele componenten van het primaire eindpunt. Sterfte was respectievelijk 18%

vs. 13%, p=0.50. Het aantal pancreasfistels was lager in de endoscopische groep (5% vs. 32%; p=0.001) en de totale opnameduur korter (gemiddeld 53 dagen vs. 69 dagen; p=0.01). In de endoscopische groep had 41% van de patiënten vergeleken met 49% in de chirurgische groep geen aanvullende necrosectomie nodig na initiële drainage (p=0.43). Tenslotte waren de totale gemiddelde kosten, niet significant maar wel, €13.655 lager in de endoscopische groep. Concluderend tonen de resultaten van de TENSION studie aan dat de endoscopische stapsgewijze benadering niet superieur is aan de chirurgische stapsgewijze benadering in het verminderen van sterfte en ernstige complicaties bij patiënten met geïnfecteerde necrose. Echter, de endoscopische benadering zorgt wel voor een significante vermindering van de totale opnameduur en het aantal pancreasfistels. Daarnaast bewijst TENSION dat ook endoscopische drainage als eerste stap van behandeling in veel patiënten een necrosectomie voorkomt.

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Beste Nicolien, jaren zaten we gezellig samen op een kamer en hebben we heel wat besproken. Jij bent echt altijd vrolijk en meer dan enthousiast. Daardoor lekker luidruchtig in ons kleine hokje, gelukkig heeft dit nooit tot irritaties geleid. Al bood onze zelfgemaakte en geïsoleerde Nicolien belbox wel uitkomst. Altijd op je fietsje met de laptop op je rug, snel stoppen als je gebeld werd en dan ter plekke op de meest onmogelijke plaatsen randomiseren. Onze weekendjes in Loenen zal ik ook niet vergeten. Geen enkel bereik midden in het bos, dus snel naar het hoogste punt om onze mails te downloaden en bekijken of we geen oproepen hadden gemist. Stiekem was dat ook wel eens heerlijk rustig. Bedankt voor de leuke tijd, we spreken snel weer wat af samen met Rein.

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List of publications

1. **van Brunschot S***, van Grinsven J*, Besselink MG, van Santvoort HC, Bollen TL, for the Dutch Pancreatitis Study Group. The natural history of computer tomography assessed gas configurations and encapsulation in patients with necrotizing pancreatitis.
   Submitted

2. van Eck van der Sluijs A, van Grinsven J, Abrahams A, Brema C, Bakker O, Bos W, van Santvoort H, Bruno M, van Goor H, **van Brunschot S** et al. Impact of intravenous fluid therapy in predicted severe acute pancreatitis: post-hoc analysis in a prospective multicenter cohort.
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17. **van Brunschot S**, Bakker OJ, Besselink MG, Bollen TL, Fockens P, Gooszen HG, van Santvoort HC, for the Dutch Pancreatitis Study Group. Treatment of necrotizing pancreatitis.
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19. Bakker OJ, van Santvoort HC, **van Brunschot S**, Geskus RB, Besselink MG, Bollen TL, van Eijck CH, Fockens P, Hazebroek EJ, Nijmeijer RM, Poley JW, van Ramshorst B, Vleggaar FP, Boermeester MA, Gooszen HG, Weusten BL, Timmer R, for the Dutch Pancreatitis Study Group. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis.
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20. **van Brunschot S**, van Santvoort HC, Gooszen HG, Fockens P. Endoscopic versus surgical treatment of infected necrotising pancreatitis: the TENSION study.
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21. Bakker OJ, van Santvoort HC, **van Brunschot S**, Ahmed Ali U, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Brink MA, Dejong CH, van Geenen EJ, van Goor H, Heisterkamp J, Houdijk AP, Jansen JM, Karsten TM, Manusama ER, Nieuwenhuijs VB, van Ramshorst B, Schaapherder AF, van der Schelling GP, Spanier MB, Tan A, Vecht J, Weusten BL, Witteman BJ, Akkermans LM, Gooszen HG, for the Dutch Pancreatitis Study Group. Pancreatitis, very early compared with normal start of enteral feeding (PYTHON trial): design and rationale of a randomised controlled multicenter trial.
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* *shared first author*

Collaborator

24. Schepers NJ, Besselink MG. New procedure for review of multicentre studies: procedure improved, implementation variable.
Ned Tijdschr Geneeskd. 2014;158:A7328.

25. Ahmed Ali U, Nieuwenhuijs VB, van Eijck CH, Gooszen HG, van Dam RM, Busch OR, Dijkgraaf MG, Mauritz FA, Jens S, Mast J, van Goor H, Boermeester MA, for the Dutch Pancreatitis Study Group. Clinical outcome in relation to timing of surgery in chronic pancreatitis: a nomogram to predict pain relief.
Arch Surg. 2012;147(10):925-32.

26. Ahmed Ali U, Bruno MJ, Issa Y, Gooszen HG, Fockens P, Boermeester MA, for the Dutch Pancreatitis Study Group. Better pain management in chronic pancreatitis through early surgery?
Ned Tijdschr Geneeskd. 2012;156(5):A4469.

Book Chapter

27. van Grinsven J, Besselink MG, Bakker OJ, **van Brunschot S**, Boermeester MA, van Santvoort HC. Retroperitoneoscopic Approaches for Infected Necrotizing Pancreatitis. In: C.E. Forsmark and T.B. Gardner (eds.), Prediction and Management of Severe Acute Pancreatitis.
Springer Media, New York. 2015, chapter 15, p 189-195.

PhD portfolio

PhD student: **Sandra van Brunschot**
PhD period: November 2009 - November 2017
PhD supervisor: Prof. dr. P. Fockens

PhD training

	Year	Workload (ECTS)
General courses		
Clinical Epidemiology	2013	0.75
BROK course - recertification	2013	0.20
Practical Biostatistics	2013	1.00
Project Management	2011	0.50
Clinical Data Management	2011	0.20
Evidence Based Searching	2010	0.10
SPSS course	2010	0.50
BROK course	2009	1.00
Specific courses		
Writing competitive FP7 collaborative projects	2012	0.50
Randomised Controlled Trials Course. Oriel College, Oxford	2010	2.00
Seminars, workshops and master classes		
Mini-symposium pancreatitis by Dutch Pancreatitis Study Group. Veldhoven, the Netherlands.	2014	0.10
Acute and chronic pancreatitis. NVGE&NV-MD, Veldhoven, the Netherlands.	2013	0.20
Writing articles, NWO talent class	2010	1.00
Presenting, NWO talent class	2010	0.50
Networking, NWO talent class	2010	0.50
Abdominal compartment syndrome: Diagnosis and treatment. United European Gastroenterology Week (UEGW). Barcelona, Spain.	2017	0.50

	Year	Workload (ECTS)
Presentations		
Endoscopic versus Surgical Step-up Approach for Infected Necrotizing Pancreatitis. Pancreas Club. Chicago, USA.	2017	0.10
Endoscopic versus Surgical Step-up Approach for Infected Necrotizing Pancreatitis. Digestive Disease Week (DDW). Chicago, USA.	2017	0.20
Pitch TENSION trial residential plenary session of the ASGE. DDW. Chicago, USA.	2017	0.20
Endoscopic versus Surgical Step-up Approach for Infected Necrotizing Pancreatitis. American Pancreatic Association (APA). Boston, USA.	2016	0.20
Endoscopic versus Surgical Step-up Approach for Infected Necrotizing Pancreatitis. UEGW. Vienna, Austria.	2016	0.50
Endoscopic versus Surgical Step-up Approach for Infected Necrotizing Pancreatitis. Nederlands Vereniging voor Gastroenterologie (NVGE) najaarscongres. Veldhoven, the Netherlands.	2016	0.10
Endoscopic versus Surgical Step-up Approach for Infected Necrotizing Pancreatitis. Nederlands Vereniging voor Heelkunde (NVvH) najaarsdag. Ede, the Netherlands.	2016	0.20
Enteral feeding in acute pancreatitis. European Pancreatic Club (EPC)/ International Association of Pancreatology (IAP). Southampton, UK.	2014	0.50
Timing and route of feeding in acute pancreatitis. Pancreasdag, Utrecht, the Netherlands.	2014	0.50
Abdominal compartment syndrome in acute pancreatitis: a systematic review. APA. Miami, USA.	2013	0.20
Infected necrotising pancreatitis. Nederlandse Vereniging voor Intensive Care (NVIC) infectiedagen. Ede, the Netherlands.	2013	0.20
Abdominal compartment syndrome in acute pancreatitis: a systematic review. NVvH najaarsdag. 's-Hertogenbosch, the Netherlands.	2013	0.25
Acute Pancreatitis: an overview. NVGE voorjaarscongres. Veldhoven, the Netherlands.	2013	0.50
Treatment of infected pancreatic necrosis: Endoscopy. European-African Hepato-Pancreato-Biliary Association (E-AHPBA). Belgrade, Serbia.	2013	0.50
Endoscopic transluminal step-up approach versus surgical step-up approach in patients with infected necrotizing pancreatitis (TENSION): design and rationale of a randomized controlled multicenter trial. APA/IAP. Miami, USA.	2012	0.20

	Year	Workload (ECTS)
Presentations		
How to build and maintain a nationwide study group. Hungarian Pancreatic Association. Budapest, Hungary.	2012	0.50
Acute pancreatitis. Regioavond Maag-Darm-Leverziekten. Groningen, the Netherlands.	2012	0.20
Endoscopic transluminal step-up approach versus surgical step-up approach in patients with infected necrotizing pancreatitis (TENSION): design and rationale of a randomized controlled multicenter trial. Pancreas Club. San Diego, USA.	2012	0.50
Endoscopic transluminal necrosectomy in necrotizing pancreatitis: a systematic review. APA/IAP. Miami, USA	2012	0.20
Endoscopic transluminal necrosectomy in necrotizing pancreatitis: a systematic review. UEGW. Amsterdam, the Netherlands.	2012	0.20
Endoscopic transluminal step-up approach versus surgical step-up approach in patients with infected necrotizing pancreatitis (TENSION): design and rationale of a randomized controlled multicenter trial. EPC. Prague, Czech Republic.	2012	0.20
Endoscopic transluminal necrosectomy in necrotizing pancreatitis: a systematic review. EPC. Prague, Czech Republic.	2012	0.20
Endoscopic transluminal necrosectomy in necrotizing pancreatitis: a systematic review. DDW. San Diego, USA.	2012	0.50
Endoscopic transluminal step-up approach versus surgical step-up approach in patients with infected necrotizing pancreatitis (TENSION): design and rationale of a randomized controlled multicenter trial. Presentation in all Dutch participating centers.	2011-2012	2.00
Infected Pancreatic Necrosis. NVIC infectiedagen. Ede, the Netherlands.	2011	0.50
Acute Pancreatitis. Stichtsgenootschap. Harmelen, the Netherlands.	2011	0.10
Acute Pancreatitis. GESAP meeting. Rotterdam, the Netherlands.	2011	0.20
Acute Pancreatitis. Duamutef meeting. Zwolle, the Netherlands.	2011	0.50
How to feed in pancreatitis: how and when? 3e Nationale voedingscongres. Ede, the Netherlands.	2010	0.50
Pancreatitis, very early compared with normal start of enteral feeding (PYTHON trial): design and rationale of a randomised controlled multicenter trial. Presentation in all Dutch participating centers.	2010-2011	2.00

	Year	Workload (ECTS)
(Inter)national conferences		
United European Gastroenterology Week. Barcelona, Spain.	2017	1.00
European Pancreatic Club. Budapest, Hungary.	2017	0.75
Pancreas Club meeting. Chicago, USA.	2017	0.25
Digestive Disease Week. Chicago, USA.	2017	0.75
NVvH najaarsdag. Ede, the Netherlands.	2016	0.25
American Pancreatic Association. Boston, USA.	2016	0.75
NVGE najaarscongres. Veldhoven, the Netherlands.	2016	0.25
United European Gastroenterology Week. Vienna, Austria.	2016	0.75
NVvH Chirurgendagen. Veldhoven, the Netherlands.	2016	0.50
NVvH najaarsdag. Hilversum, the Netherlands.	2015	0.25
NVvH Chirurgendagen. Veldhoven, the Netherlands.	2015	0.50
NVvH najaarsdag. Utrecht, the Netherlands.	2014	0.25
European Pancreatic Club/ International Association of Pancreatology. Southampton, UK.	2014	0.75
Pancreasdag. Utrecht, the Netherlands.	2014	0.25
NVvH Chirurgendagen. Veldhoven, the Netherlands.	2014	0.50
NVIC infectiedagen. Ede, the Netherlands.	2013	0.25
NVvH najaarsdag. 's-Hertogenbosch, the Netherlands.	2013	0.25
NVGE najaarscongres. Veldhoven, the Netherlands.	2013	0.50
United European Gastroenterology Week. Berlin, Germany.	2013	0.75
European-African Hepato Pancreato Biliary Association. Belgrade, Serbia.	2013	0.75
European Pancreatic Club. Zurich, Switserland.	2013	0.75
Chronische pancreatitis dag. Zeist, the Netherlands.	2013	0.25
Pancreasdag. Utrecht, the Netherlands.	2013	0.25
NVvH Chirurgendagen. Veldhoven, the Netherlands.	2013	0.50
NVGE voorjaarscongres. Veldhoven, the Netherlands.	2013	0.50
Conference of the Hungarian Pancreatic Study Group. Szeged, Hungary.	2012	0.50
Dutch Highlights at International Hepato-Pancreato-Biliary Association (IHPBA) symposium. Zeist, the Netherlands.	2012	0.15
United European Gastroenterology Week. Amsterdam, the Netherlands.	2012	0.75
American Pancreatic Association/International Association of Pancreatology. Miami, USA.	2012	0.75
NVvH najaarsdag. Rotterdam, the Netherlands.	2012	0.25

	Year	Workload (ECTS)
(Inter)national conferences		
European Pancreatic Club. Prague, Czech Republic.	2012	0.75
Pancreas Club. San Diego, USA.	2012	0.25
Digestive Disease Week. San Diego, USA.	2012	0.75
NVvH Chirurgendagen. Veldhoven, the Netherlands.	2012	0.50
NVGE voorjaarscongres. Veldhoven, the Netherlands.	2012	0.50
NVIC infectiedagen. Ede, the Netherlands.	2011	0.25
NVvH najaarsdag. Ede, the Netherlands.	2011	0.25
NVGE najaarscongres. Veldhoven, the Netherlands.	2011	0.50
United European Gastroenterology Week. Stockholm, Sweden.	2011	0.75
European Pancreatic Club. Magdeburg, Germany.	2011	0.75
Pancreas Club. Chicago, USA.	2011	0.25
Digestive Disease Week. Chicago, USA.	2011	0.75
NVvH Chirurgendagen. Veldhoven, the Netherlands.	2011	0.50
NVGE voorjaarscongres. Veldhoven, the Netherlands.	2011	0.50
Dutch Highlights at IHPBA symposium. Zeist, the Netherlands.	2010	0.15
NVvH najaarsdag. Ede, the Netherlands.	2010	0.25
European Pancreatic Club. Stockholm, Sweden.	2010	0.75
NVvH Chirurgendagen. Veldhoven, the Netherlands.	2010	0.50
NVGE voorjaarscongres. Veldhoven, the Netherlands.	2010	0.50
Other		
Chair oral and poster session. United European Gastroenterology Week, Barcelona, Spain.	2017	0.40
Poster reviewer. United European Gastroenterology Week, Vienna, Austria.	2016	0.25
Member organising committee 'Pancreasdag' 2014. Utrecht, the Netherlands.	2013-2014	0.25
Chair poster session. European Pancreatic Club/ International Association of Pancreatology, Southampton, UK.	2014	0.25
Member PANAMA (data management system) project group. Radboud University Nijmegen.	2012-2013	1.00
Organising committee regional referee evening. Radboud University Nijmegen.	2011	0.50
Organising committee 'Chirurgencup' region VII 2011.	2010-2011	3.00
Columnist Pancreatief, Journal Dutch Pancreatitis Patient Association (Alvleeskliervereniging, AVKV).	2009-2012	3.00

Teaching

	Year	Workload (ECTS)
Lecturing		
Education medical students Radboud University Nijmegen	2010-2011	1.00
Sandwich course, Dutch Society of Radiology (NVvR)	2012	0.50
Education surgical residents and medical students Elisabeth-TweeSteden Hospital	2014-2016	1.00
Tutoring, Mentoring		
Y. Issa, PhD student	2011	0.50
N.J. Schepers, PhD student	2012	0.50
J. van Grinsven, PhD student	2013-2015	3.00
D.W. da Costa, PhD student	2013	1.00
M. Strijker, Master student AMC	2015-2016	1.00
A.J. Schut, Master student AMC	2013	1.00
Supervising		
V. Zeguers, research nurse	2009-2013	3.00
H. van der Eng, research nurse	2011-2012	2.00
A.J. Roeterdink, research nurse	2014-2015	1.00

Publications

See list of publications (page 301)

Parameters of Esteem

	Year
Grants	
Ministry of Health, Welfare and Sport (Ministerie van VWS)/ The Dutch Healthcare Institute (Zorginstituut Nederland, ZIN)/ Health insurers Netherlands (Zorgverzekeraars Nederland, ZN)/ The Netherlands Organization for Health Research and Development, Health Care Efficiency Research program (ZonMw, grant number 837004008), TENSION trial, €276.000	2013
Tramedico Ltd., General Research Grant Dutch Pancreatitis Study Group, €45.000	2013
Olympus Netherlands Ltd., TENSION trial, €5.000	2012
Tramedico Ltd., General Research Grant Dutch Pancreatitis Study Group, €15.000	2012
Fonds NutsOhra (grant number 1101-108), TENSION trial, €150.000	2011
The Dutch Digestive Disease Foundation (Maag Lever Darm Stichting, grant number WO 09-45), TENSION trial, €130.000	2010
Dutch Pancreatitis Patient Association (Alvleeskliervereniging, AVKV), General Research Grant Dutch Pancreatitis Study Group, €12.500	2010
Awards and Prizes	
Kenneth Warren Annual Research Award. Pancreas Club, Chicago, USA. $1.000	2017
Top Abstract Prize. United European Gastroenterology Week, Vienna, Austria. €10.000	2016
Travel Grant. United European Gastroenterology Week, Vienna, Austria. €1.000	2016
Best oral presentation. American Pancreatic Association, Boston, USA. $1.000	2016
Travel grant. American Pancreatic Association, Boston, USA. $500	2016
Best oral presentation. European Pancreatic Club, Prague, Czech Republic.	2012
Travel grant. European Pancreatic Club, Prague, Czech Republic.	2012
Travel grant. American Pancreatic Association, Miami, USA.	2012
The Dutch Health Care Inspectorate Prize (ZorgVeiligPrijs IGZ), 2nd prize.	2010

Curriculum Vitae

Sandra van Brunschot was born on April 29th 1983 in Breda, the Netherlands. She graduated from secondary school at the Titus Brandsma Lyceum in Oss in 2001. In the same year, she started medical school at the University of Amsterdam. In 2007, she graduated from medical school and started working at the department of surgery of the Flevo Hospital in Almere (dr. P.C.M. Verbeek), followed by the department of surgery of the Academic Medical Center in Amsterdam (prof. dr. D.J. Gouma). In November 2009, she joined the Dutch Pancreatitis Study Group as a PhD student and worked at the Academic Medical Center in Amsterdam, University Medical Center in Utrecht, and Radboud University Medical Center in Nijmegen. Her research was supervised by prof. dr. Paul Fockens, prof. dr. Hein G. Gooszen and dr. Hjalmar C. van Santvoort. For 4 years, she coordinated the activities and finances of the Dutch Pancreatitis Study Group including the PYTHON, PENGUIN and TENSION trials. She was also responsible for the establishment of the largest international cohort of patients with necrotizing pancreatitis who underwent an invasive intervention. In 2014 she started her training in general surgery at the Elisabeth-TweeSteden Hospital in Tilburg (dr. P.W.H.E. Vriens and dr. M.S. Ibelings). In 2018 she will continue her training at the University Medical Center in Utrecht (prof. dr. M.R. Vriens).

Sandra van Brunschot is (co-)author of over 25 peer reviewed articles and book chapters and presented her work at numerous large (inter-)national conferences. She received over €600.000 in research grants and several awards, including the Top Abstract Prize at the United European Gastroenterology Week 2016, the APA Young Investigator Award at the American Pancreatic Association 2016, and the Kenneth Warren Annual Research Award 2017.

She lives in Oss with her boyfriend Ben and their two children Sofie and Isa.