

Heikki Karjula

DIAGNOSIS, TREATMENT
AND PROPHYLAXIS OF
PANCREATIC FISTULAS
IN SEVERE NECROTIZING
PANCREATITIS AND THE LONG-
TERM OUTCOME OF ACUTE
PANCREATITIS

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL



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HEIKKI KARJULA

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PANCREATITIS**

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Abstract

Acute infected necrotizing pancreatitis (ANP) is a very complex disease with a high risk of complications and death. ANP is difficult to treat and is often associated with poor outcomes. Despite the increasing data on the technical details required to perform a mini-invasive necrosectomy for walled-off necrosis (WON), relatively few studies have focused on the presence and consequences of pancreatic duct disruption in the context of APN. Moreover, the long-term prognosis of patients with acute pancreatitis (AP) is scant.

The aim of this study was to examine the diagnosis, treatment and prophylaxis of pancreatic fistulas (PFs) associated with APN. In addition, the long-term prognosis of AP was evaluated.

The study population consists of the patients with AP treated at Oulu University Hospital, Finland (Studies I–IV) and Copenhagen University Hospital, Denmark (Study II) during 1995–2015.

In the first part of the study, all consecutive patients following open necrosectomy for infected ANP were demonstrated to have PF. Endoscopic transpapillary pancreatic stenting (ETPS) was attempted and proven to be an effective and safe treatment for patients with PF.

In Study II, prophylactic pancreatic stenting in the early stage of the disease was tested in a randomized controlled trial to the patients with ANP to prevent PFs associated with the disease. However, the study showed that the patients with ANP did not benefit from early prophylactic pancreatic ductal stenting (PPDS); instead, it seemed to be harmful for the patients.

The results of Study III showed that single drain amylase level measurement after surgical necrosectomy is unreliable. According to this study, serial measurements are recommended to diagnose PFs after necrosectomy.

Study IV including 1644 patients showed that AP, especially alcohol AP, was associated with a high long-term mortality. On the other hand, AP without an alcohol aetiology had a minimal impact on survival.

In conclusion, in patients with infected ANP, a PF has to be considered in treatment, but the prevention of ductal leak with PPDS is not recommended. In addition, the poor long-term outcome among alcohol AP patients was due to alcohol-related diseases.

Keywords: acute necrotizing pancreatitis, long-term outcome, necrosectomy, pancreatic fistula, pancreatic stenting, postoperative pancreatic fistula

Karjula, Heikki, Nekrotisoivaan haimatulehdukseen liittyvän haimafistelin diagnostiikka, hoito ja profylaksia sekä akuutin haimatulehduksen pitkäaikaisennuste.

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Tiivistelmä

Akuutti nekrotisoiva haimatulehdus ja erityisesti siihen liittyvä bakteeri-infektio on sairaus, johon liittyy korkea komplikaatio- ja kuolleisuusriski. Tautia usein komplisoi infektion lisäksi nekroosiin liittyvä haimafisteli, joka tekee hoidosta entistä haasteellisemmän. Viime aikaisissa tutkimuksissa on käsitelty runsaasti mini-invasiivista nekrosektomiaa, mutta suhteellisen vähän on tutkimuksia nekrotisoivaan haimatulehdukseen liittyvästä fisteliongelmasta. Haimatulehduspotilaiden pitkäaikaisennuste on myös epäselvä.

Tämän väitöskirjatutkimuksen tavoitteena oli selvittää nekrotisoivaan haimatulehdukseen liittyvän haimafistelin yleisyyttä, diagnostiikkaa, ehkäisyä ja hoitoa. Lisäksi tarkasteltiin akuuttiin haimatulehdukseen sairastuneiden potilaiden pitkäaikaisennustetta.

Ensimmäisessä osatyössä ilmeni, että kaikille potilaille, joille suoritettiin haiman nekrosektomia kehittyi fisteli ja endoskooppinen transpapillaarinen haimateiden stenttaus (ETPS) osoittautui hyväksi ja turvalliseksi hoidoksi fistelin hoidossa.

Toisessa prospektiivisessä randomoidussa kontrolloidussa osatyössä tutkittiin profylaktista haimateiden stenttausta nekrotisoivassa haimatulehduksessa. Tutkimus osoitti, etteivät potilaat hyötäneet stenttauksesta: toimenpiteestä oli enemmän haittaa kuin hyötyä. Tämän tutkimuksen mukaan protetisointia ei suositella tehtäväksi taudin alkuvaiheessa.

Kolmannessa osatyössä selvitettiin haiman nekrosektomian jälkeisen haimafistelin diagnoosintia. Tutkimustuloksen mukaan haimafistelin osoittamiseksi dreeneritteen amylaasitasoa mittaamalla tarvitaan useita mittauksia, koska yksittäisen mittauksen sensitiivisyys on matala.

Neljännessä osatyössä analysoitiin Oulun yliopistollisessa sairaalassa 1995–2012 akuutin haimatulehduksen sairastaneiden työikäisten potilaiden pitkäaikaisennustetta ja kuolinsyitä. Noin kymmenen vuoden seurannassa tutkimusryhmän (n = 1 644) kuolleisuus oli yli nelinkertainen verrattuna ikä- ja sukupuolivakioituihin verrokeihin (n = 8 220). Merkittävin kuolleisuutta lisäävä tekijä oli alkoholi.

Tutkimuksemme osoitti, että infektoituneen haimanekroosiin liittyvä haimafisteli on huomioitava hoidossa. Varhaisesta profylaktisesta haimateiden protetisoinnista ei tutkimuksessa osoitettu olevan hyötyä. Alkoholin aiheuttaman haimatulehduksen pitkäaikaisennusteen mortaliteetti on korkea johtuen alkoholin käytöstä ja siihen liittyvistä sairauksista.

Asiasanat: ennuste, fisteli, haimatiehytproteesi, haimatulehdus, nekroosi, nekrosektomia

*To my wife Sari
and Maria, Topias, Tuomas, Martta, Markus,
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Oulu, October 2019

Heikki Karjula

Abbreviations

ABP	Acute biliary pancreatitis
ACS	Abdominal compartment syndrome
ANC	Acute necrotic collection
ANP	Acute necrotizing pancreatitis
AP	Acute pancreatitis
APFC	Acute peripancreatic fluid collection
AUDIT	Alcohol use disorders identification test
APACHEII	Acute physiology and chronic health evaluation; A scoring system for the severity of illness
BISAP	Bedside index of severity in acute pancreatitis
BL	Biochemical leak
CARS	Compensatory anti-inflammatory response syndrome
CBD	Common bile duct
CECT	Contrast-enhanced computed tomography
CI	Confidence interval
CP	Chronic pancreatitis
CTSI	Computed tomography severity index
DPDS	Disconnected pancreatic duct syndrome
ERCP	Endoscopic retrograde cholangio-pancreatography
ERP	Endoscopic retrograde pancreatography
ESGE	European Society of Gastrointestinal Endoscopy
EST	Endoscopic sphincterotomy
ETPS	Endoscopic transpapillary pancreatic stenting
EUS	Endoscopic ultrasonography
EXPAN	Extrapancreatic necrosis
HAPS	Harmless acute pancreatitis score
ICU	Intensive care unit
LOS	Length of hospital stay
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangio-pancreatography
MRI	Magnetic resonance imaging
MOF	Multiorgan failure
MODS	Multiorgan distress syndrome
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pancreatic duct

PEP	Post-ERCP pancreatitis
PF	Pancreatic fistula
PFC	Pancreatic fluid collection
POPF	Postoperative pancreatic fistula
PPDS	Prophylactic pancreatic duct stenting
PCT	Percentile
RAP	Recurrent acute pancreatitis
RCT	Randomised controlled trial
SAP	Severe acute pancreatitis
SIRS	Systemic inflammatory response syndrome
TPN	Total parenteral nutrition
US	Ultrasonography
VARD	Video-assisted retroperitoneal debridement
WON	Walled off necrosis

Original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

- I Karjula, H., Saarela, A., Vaarala, A., Niemelä, J., Mäkelä, J. (2015). Endoscopic transpapillary stenting for pancreatic fistulas after necrosectomy with necrotizing pancreatitis. *Surgical Endoscopy*, 29(1), 108–112. <https://doi.org/10.1007/s00464-014-3645-0>
- II Karjula, H., Nordblad Schmidt, P., Mäkelä, J., Liisanantti, J. H., Ohtonen, P., Saarela, A. (2019). Prophylactic pancreatic duct stenting in severe acute necrotizing pancreatitis: a prospective randomized study. *Endoscopy*. Mar 20. <https://doi.org/10.1055/a-0865-1960>
- III Karjula, H., Saarela, A., Mäkelä, J., Liisanantti, J. H. Does drainage fluid amylase reflect pancreatic ductal leakage after necrosectomy? Manuscript submitted.
- IV Karjula, H., Saarela, A., Ohtonen, P., Ala-Kokko, T., Mäkelä, J., Liisanantti, J. H. (2019). Long-term Outcome and Causes of Death for Working-age Patients Hospitalized Due to Acute Pancreatitis With a Median Follow-up of 10 Years. *Annals of Surgery*, 269(5), 932–936. <https://doi.org/10.1097/SLA.0000000000002612>

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1 Introduction

Acute pancreatitis (AP) is one of the most frequent reasons for hospital admissions and causing a major burden for patients, the healthcare system and the society. Increasing costs and the need for resources invariably introduce the question of prioritization especially alcohol-induced pancreatitis, which can be considered self-induced disease (Halonen et al., 2003). Worldwide, the incidence has increased significantly, but mortality has decreased mainly due to improvements in care and diagnostics.

Wadhwa et al. showed that the national bill in the US caused by AP increased by 365 % in the study period from 1997 to 2012. Up to 70 % with AP were found to be younger than 65 years and there was a 200 % increase in admissions due to AP among people younger than 45 (Wadhwa et al., 2017).

In the US alcohol is the third-largest preventable cause of death after tobacco and obesity (Berger & Bradley, 2015). In Finland, a recent study showed that up to one third of the patients admitted to the intensive care unit (ICU) had excessive alcohol use or alcohol-related disease (Hietanen et al., 2017). Furthermore, over 40 % of trauma patients with lethal injuries have tested positive for drugs, alcohol or both (Demetriades et al., 2004).

Approximately 80 % of AP patients will experience a mild course of the disease without significant morbidity, whereas 20 % will develop acute necrotizing pancreatitis (ANP) with high mortality (10–85 %) along with a prolonged hospital stay among patients undergoing a pancreatic necrosectomy (Beenen, Brown, & Connor, 2011; Zarem, 2014).

The severity of AP determines the likelihood of pancreatic duct (PD) damage (Larsen & Kozarek, 2014). Most necrotic areas are bathed in amylase-rich fluid, not necessarily from glandular destruction, but from a ductal leak (Lau, Simchuk, Kozarek, & Traverso, 2001). It has been shown that up to 78 % of patients with ANP will experience PD leakage (Kozarek, Attia, & Traverso, 2000). The majority of patients with ANP develop acute necrotic collection (ANC), and of these, about half develop walled off pancreatic necrosis (WON) (Manrai et al., 2018; Sarathi Patra et al., 2014). WON is a typical situation that frequently involves a PD leak, and WON patients have been shown to have disconnected pancreatic duct syndrome (DPDS) in 35–70 % of cases (Larsen & Kozarek, 2014).

Infected pancreatic necrosis is nearly always an indication for intervention (van Santvoort et al., 2010). Almost all patients with an open necrosectomy will develop

some kind of complication and 3–72 % of those will experience a pancreatic fistula (PF) after necrosectomy (Connor et al., 2005).

However, it is unclear how often the complications are directly related to PF. In the literature, a PF is defined as an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid (Bassi et al., 2005).

In the past decade, a minimally invasive approach has replaced open surgery as the standard treatment of infected pancreatic necrosis and the results have been encouraging. These results are explained by the absence of general anaesthesia and surgical exploration with a reduction of surgical stress and surgery associated complications, such as PFs (van Brunschot, van Grinsven et al., 2018).

Interestingly, only a few studies have reported long-term survival after AP, even though up to 75 % of the patients will experience hospital admission due to AP and a huge effort is placed on treatment to cure patients (McNabb-Baltar et al., 2014). Poor long-term survival after an initial AP episode has been related to age over 70, continuing alcohol abuse, male sex, unemployment and diabetes (Appelros, Lindgren, & Borgstrom, 2001; Nojgaard et al., 2011). Moreover, specific data on mortality and causes of death post AP are scarce.

The aim of the present thesis was to identify PD leakages associated with severe pancreatitis and especially after surgical necrosectomy. In more detail, we evaluated whether PD disconnection can be prevented by inserting a pancreatic stent in the early stage of ANP. Theoretically, early prophylactic placement of a bridging pancreatic stent could help maintain PD continuity and prevent the complications associated with amylase-rich fluid leakages. Additionally, the accuracy of drain amylase analysis after necrosectomy to detect was analysed. Finally, the long-term survival and causes of death post AP were investigated.

2 Review of the literature

2.1 Epidemiology

AP has increasingly become one of the most important acute gastrointestinal disorders throughout the world, including Europe, Asia and North America (Roberts et al., 2017; Spanier, Dijkgraaf, & Bruno, 2008). Multiple hypotheses have been generated to explain the increase in incidence. The reported incidence of AP among 17 European countries varies from 4.6 to 100 per 100 000 inhabitants per year. The incidence is highest in eastern and northern Europe. Differences in the incidence and aetiology between and within the countries reflect differences in the risk factor prevalence (Yadav & Lowenfels, 2006b). The difference in alcohol consumption or in the incidence of gallstone disease may explain part of the divergence. It is also suggested that increasing AP is related to global epidemic of obesity, which in turn promotes gallstone formation and can result in biliary AP (Ogden et al., 2006). The increase in incidence can also be attributed to more frequent diagnosis of milder cases of AP, which might also explain why the mortality seems to be decreasing (Vidarsdottir, Moller, Vidarsdottir, Thorarinsdottir, & Bjornsson, 2013).

In Finland, the incidence of AP has doubled over the last four decades, mainly due to increased alcohol consumption, reaching the level of 73.4 per 100,000 inhabitants per year (among men up to 113.4/100 000) (Jaakkola & Nordback, 1993; Sand, Valikoski, & Nordback, 2009).

2.2 Aetiology

The two main aetiologies of AP are alcohol and gallstones, and they account approximately 60–90 % of all cases, although this varies between countries and age groups. In Finland up to 70 % of cases are caused by alcohol followed 20% of gallstone disease. Alcohol AP is highest among young or middle-aged groups around 35–44 years and gallstone AP is highest in older people (Jaakkola & Nordback, 1993; Roberts et al., 2017). In the US, it is presumed that gallstone-related disorders are a more probable cause of AP, given the rise in obesity and an increasingly aging population (Yadav & Lowenfels, 2006a), while alcohol consumption has decreased in the US (Lowenfels, Sullivan, Fiorianti, & Maisonneuve, 2005).

2.2.1 Acute alcohol-related pancreatitis

The association between alcohol consumption and AP has been recognized for over 100 years (Sand, Lankisch, & Nordback, 2007). However, it is still unclear why some people develop AP and others do not. At the individual level, the risk of acute or chronic pancreatitis (CP) increases remarkably along with alcohol consumption. In addition, the accurate detection of alcohol consumption is challenging, as self-reports of drinking habits and laboratory tests are unreliable. To improve the evaluation, structured questionnaires, such as the alcohol use disorders identification test (AUDIT) are recommended when the aetiology of AP is being determined (Chick & Kempainen, 2007). Moreover, alcohol consumption is a risk factor for pancreatitis with no safe threshold and the risk increases considerably with increased alcohol consumption. Abstinence is the only protection from alcoholic pancreatitis (Nordback, Sand, & Andren-Sandberg, 2007).

2.2.2 Gallstone pancreatitis

Worldwide gallstones are the most common cause of AP. In Europe and the other developed countries, up to 20 % of the adult population suffer from gallstones, being the etiologic factor in 40–50 % of the recorded pancreatitis cases (Lammert et al., 2016; van Dijk et al., 2017). In 4–8 % of patients with gallbladder stones, stones migrate into the main bile duct causing AP as they pass into the duodenum or impact in the sphincter of Oddi (Lammert et al., 2016). The known risk factors include advanced age and female gender, obesity, rapid weight loss, chronic hemolytic disorder and race (Glambek, Kvaale, Arnesjö, & Sbreide, 1987). The risk of biliary pancreatitis in patients with asymptomatic gallstones is approximately 2 % at 20–30-year follow-up (Lankisch et al., 2009).

2.2.3 Other causes

Hypertriglyceridemia (HTG) is a well-known but underestimated cause of acute AP, seen in 2–4 % cases. Triglyceride levels should be taken at admission from all patients, and it must be remembered that triglyceride levels fall rapidly because of fasting (Yadav, Agarwal, & Pitchumoni, 2002). Pancreatitis secondary to HTG is typically associated with uncontrolled diabetes, alcoholism, medications and pregnancy. An elevated triglyceride level $> 1.00 \text{ mg/dl}$ ($\geq 13 \text{ mmol/l}$) indicates a

high degree of suspicion of hypertriglyceridemia-induced AP (Scherer, Singh, Pitchumoni, & Yadav, 2014).

Hypercalcemia caused by e.g. hyperparathyroidism, sarcoidosis, an overdose of vitamin D or calcium and malignant diseases is associated with AP. Therefore, serum calcium should be routinely measured at admission in all patients with AP (Kemppainen & Puolakkainen, 2007).

AP is also associated with **invasive procedures**. The incidence of AP after endoscopic retrograde cholangio-pancreatography (**ERCP**) in unselected patients is 3.5 %; it is of mild or moderate severity in approximately 90 % of cases (Dumonceau et al., 2014a). **Dysfunction of the sphincter of Oddi**, young age, female gender and prolonged procedure time are well-known independent risk factors for post-ERCP pancreatitis (PEP) (Dumonceau et al., 2014a; Swahn et al., 2013). In addition, AP is associated with the **postoperative phase of surgery, abdominal trauma and operations** (Kemppainen & Puolakkainen, 2007).

It is known that a history of pancreatitis is associated with **pancreatic cancer**. It is suggested that the main pathway could be chronic inflammation or the tumour itself causing tumour-associated ductal obstruction (Duell et al., 2012). For patients over 40 years of age with unknown AP aetiologies, pancreatic cancer should be considered in the differential diagnosis (Tenner, Baillie, DeWitt, Vege, & American College of Gastroenterology, 2013).

Over 100 drugs have been implicated by case reports as causing acute pancreatitis (Tenner, 2014). A few retrospective studies have estimated the rate of **pharmaceutical products** as a cause of AP to be between 0.3–5.3 %, but drugs as an aetiological factor might be under-reported (Vidarsdottir et al., 2013). Traditionally, studies have claimed an association between the use of statins and the development of AP, but there is a great deal of controversy over the role that statins can play in AP (Badalov et al., 2007; Ruiz-Rebollo, Munoz-Moreno, Mayo-Iscar, Udaondo-Cascante, & Nistal, 2019).

Finally, the aetiology of AP is unknown in many cases and is defined as **idiopathic**. According to guidelines, no more than 20–25 % of AP cases should be classified as idiopathic (Garg, Tandon, & Madan, 2007; Raty et al., 2015). However, up to 50 % to 75 % of idiopathic AP may be due to microlithiasis, which is undetectable by conventional imaging methods (Garg et al., 2007; Raty et al., 2015).

2.3 Diagnosis and pathophysiology of AP

2.3.1 Diagnosis of AP

AP is defined by at least two of the following three features: (1) abdominal pain suggestive of pancreatitis (acute onset of epigastric pain radiating to the back); (2) serum amylase or lipase activity levels at least three times greater than the upper limit of normal; and (3) characteristic findings on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) or transabdominal ultrasonography (US). If the diagnosis of AP is based on typical abdominal pain and an increase in the serum pancreatic enzyme activity, imaging is not usually required for diagnosis on admission to the hospital (Banks et al., 2013; Tenner et al., 2013).

Imaging

Abdominal US is the gold standard for the diagnosis of gallstones in the gallbladder. It is non-invasive, safe, widely available, repeatable and cheap. The sensitivity of US for gallstones is > 90 % in acute situations, and > 95 % when symptoms have resolved (Johnson & Levy, 2010). US should be performed on all patients with AP due to the high prevalence of gallstone disease and the importance of preventing recurrent disease (Tenner et al., 2013).

CECT is not usually required for diagnosis on admission, but it is indicated where there is diagnostic uncertainty. However, CECT is recommended if patients fail to improve after 48–72 hours and/or evaluation of possible complications in the later course of the disease is needed (Arvanitakis et al., 2018a; Banks et al., 2013).

MRI may be used in patients with contraindications to CECT. MRI is beneficial four weeks post onset when invasive interventions are considered because the contents (liquid vs. solid) of pancreatic collections are better characterised by MRI and the evaluation of PD integrity is possible (Arvanitakis et al., 2018a; Kamal et al., 2015).

2.3.2 Early pathogenesis

Early pathophysiological events in AP are thought to be a local inflammatory process starting from premature intrapancreatic activation of digestive enzymes

within acinar cells. The leading mechanism is the premature activation of trypsinogen to trypsin, which leads to autodigestion of the tissue and release of proinflammatory mediators by acinar cells and macrophages (Sutton, Robert et al., 2003).

Alcohol is known to have toxic effects on the pancreatic cells, but it does not exert adverse events alone. It is known that only a few drinkers develop overt disease, prompting the conclusion that additional insult is needed for precipitating pancreatitis. There is consistent evidence that the effect of alcohol on acinar cells and small PDs themselves play some part in alcohol-induced pancreatitis (Apte, Pirola, & Wilson, 2010). Alcohol increases pancreatic secretions and the formation of protein plugs within PD. Experimental studies have also shown that alcohol increases digestive and lysosomal enzyme content within acinar cells and thereby increases potential contact between these enzymes enabling premature activation. These effects are probably a result of toxic metabolites of alcohol (Lankisch, Apte, & Banks, 2015).

In gallstone-induced pancreatitis, the obstruction of common biliopancreatic duct is caused by migrated gallstones in the sphincter Oddi. The block of the efflux of pancreatic zymogens leads to increased pressure in the duct and leads to bile reflux into the PD and activation of trypsinogen to trypsin and pancreatic autodigestion (Wang, P. et al., 2009).

2.3.3 Development of pancreatitis

After the initial insult to the acinar cell, the progression of the disease is multifactorial. One of the earliest detectable events in pancreatitis is that elevated intracellular calcium can lead to premature activation and secretion of digestive enzymes from the acinar cells (Kambhampati, Park, & Habtezion, 2014; Sutton, R. et al., 2003). That leads to acinar cell injury, which stimulates an inflammatory response (infiltration of macrophages, neutrophils and release of cytokines interleukins 1, 6, 8 and tumour necrosis factor). Initially, proinflammatory cytokines are produced in the pancreas but also in the liver, lungs and spleen in progressive disease (Minkov, Halacheva, Yovtchev, & Gulubova, 2015). The systemic release of proinflammatory mediators in AP leads to a generalized inflammatory response at remote sites from the initial injury and gives rise to systemic inflammatory response syndrome (SIRS). It is suggested that uncontrolled activation of inflammatory cascade leads to early systemic complications during AP (Phillip, Steiner, & Algul, 2014). The evolution of systemic inflammation and

subsequent development of multi-organ failure (MOF) may occur rapidly, within the first few days or even hours (McKay & Buter, 2003). Patients with severe AP usually develop SIRS during the first day of hospitalisation, whereas almost all patients without SIRS have mild AP (Singh, Wu, Bollen, Repas, Maurer, Mortelet et al., 2009).

Simultaneously with the proinflammatory response, the secretion of anti-inflammatory mediators (such as interleukin-10) suppress the synthesis and effect of proinflammatory cytokines. This counterregulatory phenomenon is called compensatory anti-inflammatory response syndrome (CARS). This anti-inflammatory reaction may overcompensate and inhibit the immune response, rendering the host at risk for local complications and sepsis in the late phase of the disease (Kylanpaa, Rakonczay, & O'Reilly, 2012; Phillip, Steiner, & Algul, 2014). The immune system is downregulated in the phase of CARS and this is likely the reason infections usually do not occur earlier in the early phase of the disease (Besselink et al., 2009).

The interplay of these two contrasting phenomena determines the behaviour of the disease and requires an individualised therapeutic approach (Hoque, Malik, Gorelick, & Mehal, 2012). The model of the inflammatory responses is shown in Figure 1.

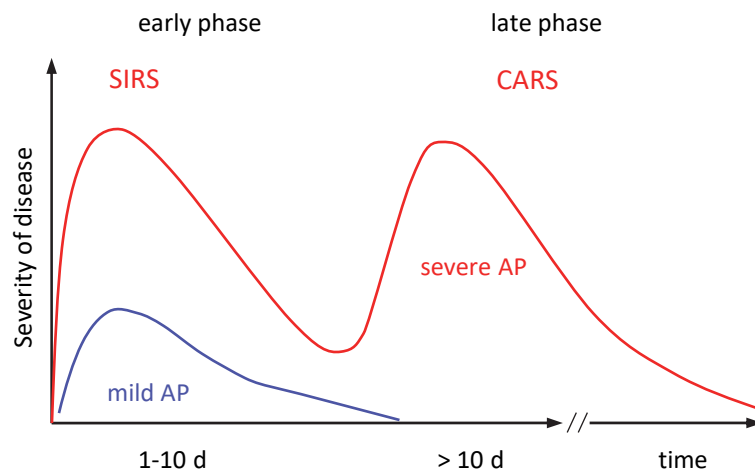


Fig. 1. Two phases of acute pancreatitis, early and late (modified from Philip et al. 2014, Early phase of AP, World J Gastrointest Pathophysiology, permission for publication obtained). Abbreviations: CARS: Compensatory anti-inflammatory response; SIRS: Systemic inflammatory response syndrome.

2.4 Classification of AP

The Atlanta conference established a classification system of AP in 1992 and the updated and revised classification 2012 (Atlanta classification, Figure 2). Recent classification defines criteria for the diagnosis of AP, identification of early and late phase of AP, classifies the clinical severity of AP into three categories (mild, moderate and severe), differentiates the two radiological types of AP (interstitial oedematous pancreatitis and necrotizing pancreatitis) and defines the fluid collection (pancreatic and peripancreatic collections) seen on imaging (Banks et al., 2013).

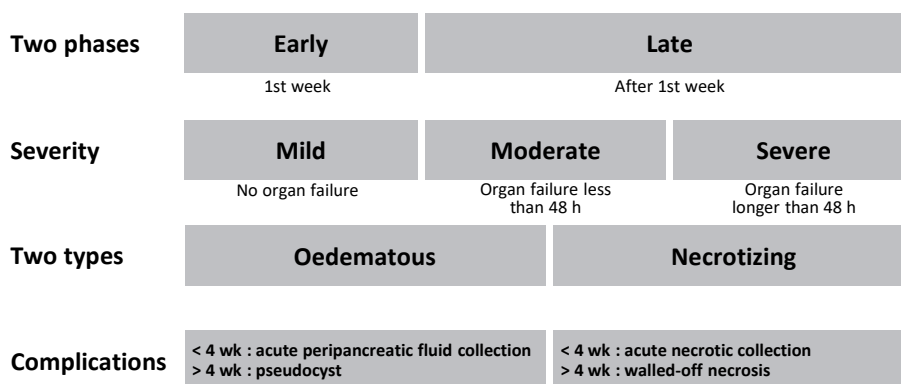


Fig. 2. Atlanta classification of acute pancreatitis.

2.4.1 Early and late phases of AP

AP is a dynamic process. During disease, we can distinguish two distinct phases with two peaks of mortality: early and late. The early phase usually occurs within the first week of onset of AP and the late phase takes place thereafter and may extend for weeks to months; it is characterised by necrosis, multiple organ failure and infection.

The duration of SIRS and organ failure during the first week of predicted severe AP is strongly associated with the risk of death or local complications. The resolution of organ failure within 48 hours suggests a good prognosis; persistent organ failure is a marker for subsequent local complications or death. About one third to half the deaths in AP occur during the first week due to progressive organ

failure (Buter, Imrie, Carter, Evans, & McKay, 2002; Johnson, C. D. & Abu-Hilal, 2004; Mofidi et al., 2006).

The late phase is characterised by the persistence of signs of systemic inflammation and/or by the presence of local complications. The late phase occurs in patients with moderately severe or severe pancreatitis and local complications evolve during that period (Banks et al., 2013). Local complications should be suspected if patient has persistent or recurrence of abdominal pain, increasing signs of sepsis and/or organ dysfunction. The second peak of mortality in AP during the late phase is mainly due to local complications. The complications may manifest systemically when necrotic tissue becomes infected and patients develop bacteraemia and sepsis. The mortality among patients with infected ANP is high, whereas mortality rates for sterile necrosis remain relatively low, 5–10 % (Besselink et al., 2009; Petrov, Shanbhag, Chakraborty, Phillips, & Windsor, 2010; Zerem, 2014). The type of treatment depends on the morphological findings seen on CECT and clinical conditions (Zerem, Imamovic, Omerovic, & Imsirovic, 2009; Zerem, Imamovic, Latic, & Mavija, 2013).

2.4.2 Clinical severity of AP and correlation in imaging findings

Clinically, AP can be divided into three groups: mild, moderately severe and severe pancreatitis.

Mild pancreatitis is characterised by the absence of organ failure. Patients do not develop any local or systemic complications and can be discharged during the early phase of the disease.

Pancreatitis with transient (less than 48 hours) organ failure is classified as moderate severe pancreatitis. Patients may develop local complications without persistent organ failure.

Severe pancreatitis is characterised by persistent organ failure, which can be single or multiple. Patients usually develop one or more local complications.

Radiologically, AP can be classified as interstitial oedematous and necrotizing pancreatitis.

In patients with interstitial oedematous pancreatitis, CECT demonstrates relatively homogenous enhancement in the pancreatic parenchyma and in the peripancreatic tissue some inflammatory changes without necrosis (Figure 3). The clinical symptoms usually resolve within a couple of weeks.

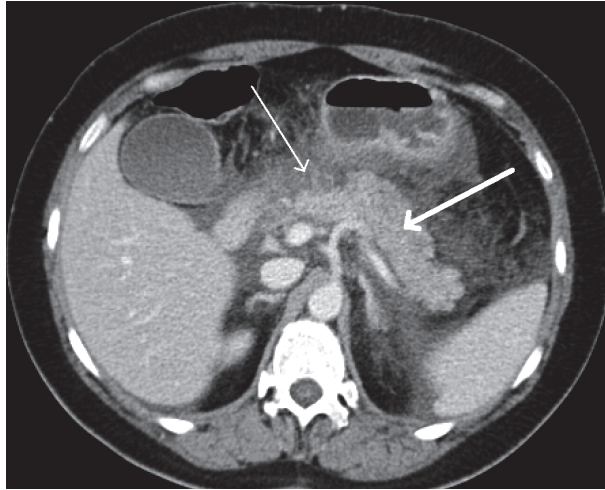


Fig. 3. Patient with mild course of acute pancreatitis. CECT showed interstitial oedematous pancreatitis with enhancing pancreatic parenchyma (thick arrow) surrounded with peripancreatic oedema (thin arrow) without necrosis.

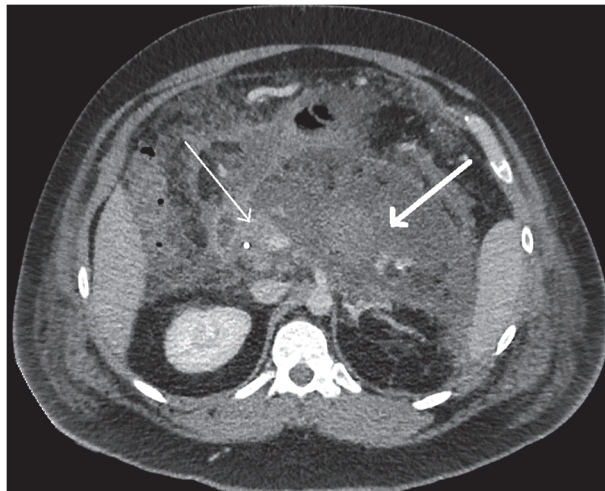


Fig. 4. CECT image of a patient with ANP demonstrating extensive pancreatic and peripancreatic necrosis (thick arrow). In the head of the pancreas, a part of the tissue is vital with enhancement in the CECT (thin arrow).

Approximately 10–20 % of the patients with AP develop necrosis (Figure 4) in the pancreatic parenchyma, the peripancreatic tissue or both (Pezzilli et al., 2010). The

initial CECT taken on admission often underestimates the degree of necrosis and shows only inflammatory changes. The necrotic signs develop over several days after the onset, and therefore the ideal time to address the extent of necrosis is the week after the onset of symptoms (Spanier et al., 2010; Thoeni, 2012).

2.4.3 Pancreatic and peripancreatic fluid collections

The acute fluid collections are acute peripancreatic fluid collection (APFC), pancreatic pseudocysts, acute necrotic collection (ANC) and WON. In the new classification, an important distinction is made between collections that arise of fluid alone without necrosis (APFC and pseudocysts) versus those that are composed of necrosis and contain solid components (ANC and WON) with varying amounts of fluid. The important factor in this classification is time. APFC occurs in patients with interstitial oedematous pancreatitis and some of these will develop pancreatic pseudocyst as a delayed complication (usually > 4 weeks). Patients with necrotizing pancreatitis initially (under 4 weeks) present with ANC, which will be surrounded by a radiologically identifiable capsule after a month from the onset of the disease (Figure 5). This matured collection is called WON (Banks et al., 2013).

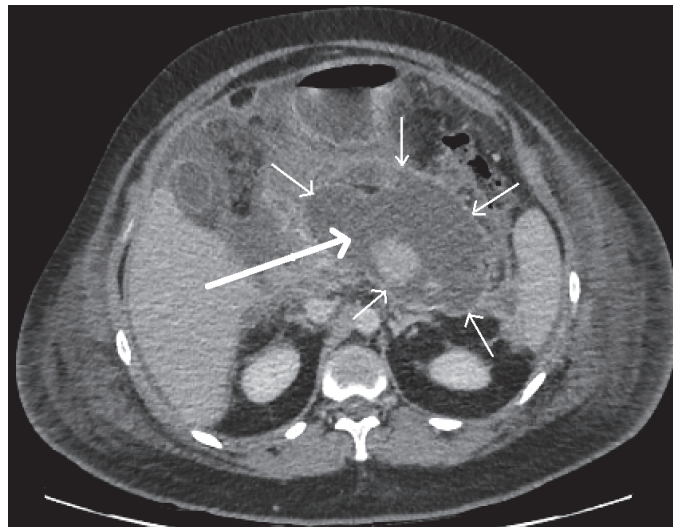


Fig. 5. Patient with ANP and CECT taken four weeks after the onset of the disease. CECT demonstrates WON (thick arrow), which is encapsulated by a thin membrane, pseudocapsule (thin arrows).

2.5 Management of AP

In the early phase, the management of AP is mainly supportive and largely dependent on the degree of organ failure. Local findings in the pancreas and peripancreatic region have minimal impact on the first-line treatment unless the patient will develop abdominal compartment syndrome (ACS). In the later phase, the treatment of local complications starts to play a significant role in patients with severe AP.

2.5.1 Fluid therapy

Fluid therapy is a cornerstone of the initial management of AP to prevent hypovolemia, hypoperfusion and complications. However, the evidence basis for optimal fluid therapy in AP is obscure. Rapid infusion of crystalloid very early in the course of AP may be beneficial, but rapid fluid infusion later in the course of the disease may be deleterious (Mao et al., 2009; Thomson, 2018). It has been suggested that some patients with ANP die due to ACS caused by massive fluid resuscitation (Leppaniemi, 2008). According to guidelines Ringer's lactate is recommended for fluid resuscitation in AP. Goal directed therapy with 5–10 ml/kg/h intravenous fluids should be used initially until hemodynamic stability is reached and signs of hypovolaemia are absent. In most patients, a total of 2 500–4 000 ml of intravenous fluids will suffice to reach resuscitation goals within the first 24 hours (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).

2.5.2 Nutrition

In the past, a nil per os regimen was based on the hypothesis that oral intake will stimulate the secretion of pancreatic enzymes leading to increase of intrapancreatic enzyme activation and thus increase pancreatic tissue damage (Stigliano, Sternby, de Madaria, Capurso, & Petrov, 2017). However, gut-barrier dysfunction may occur in patients with ANP, and it is thought to lead to bacterial translocation and infection of pancreatic necrosis (Wu, Sankaran, Plank, Windsor, & Petrov, 2014). It is hypothesised that enteral nutrition stimulates intestinal motility and thereby reduces bacterial overgrowth and maintains mucosal gut integrity. A review of 11 randomized controlled trials (RCTs) showed that early enteral nutrition is superior to parenteral nutrition; it is associated with a reduced risk for MOF, pancreatic infectious complications and mortality (Petrov et al., 2009).

According to guidelines, enteral nutrition should be administered following the initial period of volume resuscitation and control of nausea and pain. Patients with mild AP should receive a normal oral diet. In patients with severe AP, enteral nutrition may be provided by the gastric or jejunal route if oral intake is not possible (Bakker et al., 2014; Marik, 2009).

2.5.3 Antibiotics

The use of prophylactic antibiotics has been a controversial issue for decades, even though one of the most lethal complications of AP is a secondary infection of pancreatic or peripancreatic necrosis (Bradley, 1989). Bacterial translocation from the gut is thought to be the reason for infection (Ammori et al., 1999). However, according to recent guidelines, prophylactic antibiotics are not recommended for the prevention of infectious complications in AP (Crockett et al., 2018; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). Antibiotics are only indicated when an infection is either proven or clinically highly suspected. In addition, probiotics are not recommended for prophylaxis in AP (Besselink, M. G. et al., 2008). Studies have shown increased rates of mortality in patients receiving probiotics, and their usage is considered contraindication in the treatment of severe AP.

2.5.4 Management of local fluid collections

Local complications with AP include fluid collections, gastric outlet dysfunction, biliary obstruction, splenic and portal vein thrombosis and colonic necrosis.

The clinical outcome (Figure 6) and treatment of pancreatic fluid collections (PFCs) is determined by their behaviour over time. The majority of APFCs resolve spontaneously and only a minority transform into pseudocysts, whereas significant proportion of ANC transforms into WON (Manrai et al., 2018; Sarathi Patra et al., 2014). Acute collections (APFC and ANC) do not usually need any interventions, but a substantial number of symptomatic pseudocysts and WON require percutaneous, endoscopic or surgical drainage (Nabi, Basha, & Reddy, 2017; Tyberg et al., 2016).

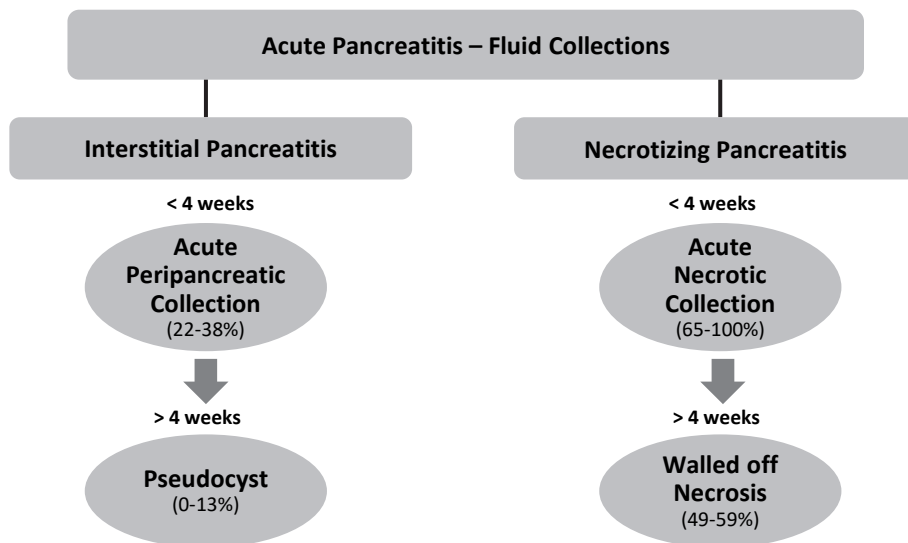


Fig. 6. Outcome of acute collections after acute pancreatitis.

According to guidelines (Besselink, Marc et al., 2013), indications for intervention involving local fluid collections (radiological, endoscopic or surgical) in ANP are:

1. documented or clinical suspicion of **infected necrotizing pancreatitis** with clinical deterioration, preferably when necrosis has become walled-off.
2. in the absence of infected necrotising pancreatitis, **ongoing organ failure for several weeks** after the onset of AP,
3. sterile necrosis, if (rarity)
 - a) ongoing biliary, intestinal or gastric outlet obstruction due to WON (> 4–8 weeks after onset of AP)
 - b) **persistent symptoms** (e.g. pain) in patients with WON (i.e. > 8 weeks after onset of AP)
 - c) **DPDS** with persisting symptomatic collections (i.e. > 8 weeks after onset of AP)

2.6 Pancreatic necrosis

The treatment of ANP has changed significantly over the last 20 years. First, the indication for intervention has changed from sterile necrosis to infected necrosis (Tenner et al., 2013). Historically, most patients with sterile necrosis underwent a

necrosectomy, but now it is accepted that sterile necrosis should be managed conservatively (van Santvoort et al., 2011). The only exceptions for intervention are patients with hepatobiliary or gastrointestinal obstruction for several weeks and perhaps very few patients with progressive SIRS and organ failure despite maximal therapy (Uhl et al., 2002; van Brunschot et al., 2014).

Necrotic collections (ANC and WON) become infected in about one third of patients and infection is nearly always an indication for intervention (van Santvoort et al., 2011).

Small cohort studies and a recent meta-analysis suggest that very selective and clinically stable patients with infected pancreatic necrosis might be managed conservatively with prolonged, targeted antibiotics (Adler, Chari, Dahl, Farnell, & Pearson, 2003; Mouli, Sreenivas, & Garg, 2013; Runzi, Niebel, Goebell, Gerken, & Layer, 2005). However, the exact subgroup of these patients has not been clearly defined.

Second, the timing of intervention has shifted from early phase to around 3–4 weeks after the onset of symptoms in the disease course. Historically, patients with ANP underwent early laparotomy and necrosectomy. This was associated with high morbidity (34 % to 95 %) and mortality (6 % to 25 %) rates, likely because these severely ill patients could not tolerate the extra hit of surgical trauma (Besselink, van Santvoort, Witteman, Gooszen, & Dutch Acute Pancreatitis Study Group, 2007; Mier, Leon, Castillo, Robledo, & Blanco, 1997; Raraty et al., 2010). Due to this finding, the current guidelines advocate for delaying interventions until the stage where an capsule around the fluid collections has been developed (Navaneethan, Vege, Chari, & Baron, 2009; Tenner et al., 2013). Moreover, when an infection is suspected, a broad spectrum of antibiotics is indicated, and antibiotics are mainly used to support patients until collections become encapsulated (WON). This is thought to promote safer interventions with fewer complications (van Dijk et al., 2017). However, some experts have disputed this and suggest immediate catheter drainage (van Grinsven et al., 2016).

2.6.1 Step-up approach

A step-up approach consisting of percutaneous catheter or endoscopic drainage of necrotic collection is now often the first step in treatment prior to a necrosectomy. In the PANTER trial (Table 1), which can be regarded as one of the landmark studies on the step-up approach in the treatment of infected necrotizing pancreatitis,

patients with infected necrotizing pancreatitis were randomized between an open necrosectomy or a step-up approach, which consisted of percutaneous drainage followed by a minimally invasive necrosectomy (VARD; video-assisted retroperitoneal debridement) if needed. The step-up approach reduced the major complication rate from 69 % to 40 %, and up to the third of the patients could be treated with catheter drainage only without necrosectomy (van Santvoort et al., 2010). The step-up approach is now considered the standard treatment for patients with infected pancreatic necrosis and been introduced in all major guidelines (Tenner et al., 2013).

2.6.2 Necrosectomy

The minimally invasive surgical necrosectomy and the even less-invasive endoscopic necrosectomy techniques are gradually replacing the traditional open surgical necrosectomy (Gomatos et al., 2016; van Brunschot et al., 2018; Wang et al., 2018; Wronski et al., 2017). In the minimally invasive surgical necrosectomy, patients usually undergo US or CT-guided drainage as the first step. The most preferred route is through the left retroperitoneum, as this route is the shortest and thereby often the safest (Bakker et al., 2012). In addition, the drain is retroperitoneal and does not infect the intra-abdominal space. If drainage is unsuccessful, VARD is performed (van Santvoort et al., 2007).

In the endoscopic necrosectomy approach, the initial drainage can also be performed endoscopically in a step-up approach without percutaneous drainage. The initial procedure is endoscopic ultrasound (EUS)-guided drainage to the gastric lumen or duodenum (transmural approach). A necrosectomy is performed via cystogastrostomy endoscopically if the patient fails to improve.

A minimally invasive necrosectomy is thought to be worthwhile by reducing surgical stress compared to open surgery and thereby lowering the proinflammatory response (measured with IL-6 levels) in already critically ill patients (Bakker et al., 2012). Another advantage is the avoidance of large abdominal incisions (van Brunschot, Hollemans et al., 2018).

Table 1. Randomised controlled trials (Landmark studies) of a necrosectomy in ANP.

Study	no patients	Aim of the study	Result
van Santvoort et al., 2010 (PANTER)	88	Compare complications between a minimally invasive step-up approach (percutaneous +/- VARD) vs an open necrosectomy	A minimally invasive step-up approach, compared with an open necrosectomy, reduced major complications or death among patients with infected necrotizing pancreatitis
Bakker et al., 2012 (PENGUIN)	22	Compare inflammatory response and complications between an endoscopic transgastric vs surgical necrosectomy (VARD +/- open necrosectomy) for infected necrotizing pancreatitis	An endoscopic necrosectomy reduced the proinflammatory response as well as major complications and death compared with a surgical necrosectomy.
van Brunschot et al., 2018 (TENSION)	98	To determine whether the endoscopic step-up approach is superior to a minimally invasive surgical step-up approach (percutaneous +/- VARD) in terms of clinical and economic outcomes	Endoscopic step-up approach was not superior to the minimally invasive 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.
Hollemaans et al., 2019	73	Compare complications and needs for reinterventions between a minimally invasive step-up approach (percutaneous +/- VARD) vs an open necrosectomy in long-term follow-up	The minimally invasive step-up approach for necrotizing pancreatitis was superior to open necrosectomy, without an increased risk of reinterventions.
Bang et al., 2019	66	Compare minimally invasive surgery vs endoscopic approaches	An endoscopic approach reduced major complications, lowered costs, and increased the quality of life compared to minimally invasive surgery

However, an endoscopic step-up approach is a potentially less-invasive alternative method compared to others (van Brunschot et al., 2018). An endoscopic necrosectomy has shown encouraging results in reducing complications in several studies (van Brunschot et al., 2018). These results might be explained by the reduction of surgical stress and the absence of general anaesthesia. Following the PANTER trial, the same Dutch group also performed the TENSION trial where they compared the endoscopic step-up approach with a minimally invasive step-up approach (VARD). The study failed to show any difference in major complications or death, but the rate of PFs and the length of hospital stay (LOS) was lower in the endoscopy group. The outcome of the trial will perhaps result in a shift to the endoscopic step-up approach as the preferred treatment (van Brunschot et al., 2018).

However, ANP is a very heterogenous disease and different invasive treatment strategies need to be considered in each individual patient, without ruling out the option of an open necrosectomy, especially in cases of large solid infected pancreatic necrosis (Gou et al., 2013; Hollemans et al., 2019; Rana, Bhasin, Sharma, Kathiresan, & Gupta, 2014). An open intraperitoneal necrosectomy should be considered a maximally invasive procedure that is generally performed as a substitute when other treatments have failed (Hackert & Buchler, 2016).

A pancreatic necrosectomy needs considerable healthcare resources. Any intervention that can reduce complications associated to ANP is likely to be cost-effective. However, data on this issue are very limited. Thus far, minimally invasive techniques have not been proven to be cost effective compared to open surgery (Beenen et al., 2011). On the other hand, an endoscopic transluminal approach has been reported to reduce costs for patients with necrotizing pancreatitis compared with minimally invasive surgery due to the reduced complication rate (Bang et al., 2019). The recent randomised controlled trials of the methods to perform necrosectomy in ANP are presented in Table 1.

2.7 ERCP in AP

The role of ERCP in AP is mainly related to the management of choledocholithiasis (Tenner et al., 2013). Although ERCP can be used to identify PD disruption in patients with severe AP, a consensus has never emerged as to whether ERCP should be performed routinely for this purpose (Tenner, 2004).

2.7.1 ERCP and acute biliary pancreatitis

According to the current guidelines, early ERCP (under < 24 hours) is indicated with AP if there is clinical suspicion of concomitant cholangitis, but not for those with cholestasis alone (Arvanitakis et al., 2018; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). However, diagnosing cholangitis in patients with severe AP, who are also suffering from SIRS, can be challenging (van Dijk et al., 2017). These clinical situations easily lead to the overdiagnosis of acute cholangitis in pancreatitis and potentially exposing patients to unnecessary ERCP procedures (Takada et al., 2013).

However, there is no strong evidence regarding the optimal timing of ERCP in patients with biliary pancreatitis without cholangitis. It has been shown that urgent ERCP had no impact on critical outcomes, such as mortality and morbidity, and it is reasonable to wait 24–48 hours for the spontaneous improvement of biliary obstruction (Crockett et al., 2018; Petrov et al., 2008; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). However, the European Society of Gastrointestinal Endoscopy (ESGE) recommends ERCP to be performed within 72 hours in patients with ongoing biliary obstruction (Arvanitakis et al., 2018).

Early ERCP with an endoscopic sphincterotomy (EST) is not recommended for patients with mild biliary AP, as the procedure-related risks outweigh the potential benefits; this is because common bile duct (CBD) stones may pass into the duodenum spontaneously, in which case ERCP with EST is unnecessary and even harmful (van Dijk et al., 2017).

2.7.2 ERCP and post-ERCP pancreatitis

PEP appears unavoidable, even in the hands of expert endoscopists, and it is the most common complication of ERCP, occurring typically 2–4 % of cases and even 20 % of certain high-risk procedures and patients (Badalov, Tenner, & Baillie, 2009; Freeman, 2016). Patients with suspected sphincter Oddi dysfunction, young females and those with a lack of obstructive jaundice are at higher risk of PEP (Wang, P. et al., 2009). Interestingly, patients for whom conventional ERCP is least indicated are at the highest risk of PEP. Procedure-related factors include: difficult cannulation, PD instrumentation, PD injection, precut sphincterotomy, pancreatic sphincterotomy and balloon dilatation of an intact sphincter (Dumonceau et al., 2014).

The most effective method for the prevention of PEP in patients with high- and low-to-mixed risk is proven to be the placement of pancreatic stents (Dubravcsik et al., 2012; Freeman, 2007). The incidence has reduced by 60–80 % with pancreatic stents (Mazaki, Mado, Masuda, & Shiono, 2014).

Second, the administration of rectal NSAIDs reduces the risk of PEP 50–60 %, but does not seem to replace the need for a PD stent in prevention (Freeman, 2016; Tenner et al., 2013). The ESGE recommends routine rectal administration of 100 mg of diclofenac or indomethacin immediately before or after ERCP in all patients without contraindications (Dumonceau et al., 2014).

In addition, the recent randomised controlled trial showed that combining sublingual nitrate and rectal diclofenac seems to reduce the overall incidence of PEP compared with a diclofenac suppository alone (Tomoda et al., 2019).

2.8 Pancreatic duct disruption in AP

PD disruption can occur as a consequence of several different types of injuries to the pancreas, including AP, CP, pancreatic surgery and abdominal trauma (Das et al., 2016). A normal PD with a minor leak from a small side branch may heal spontaneously, whereas a persistent leak from disruption of main pancreatic duct (MPD) is often complicated by the development of local pancreatic fluid collection, internal or external PF formation (Mutignani et al., 2017; Varadarajulu, Rana, & Bhasin, 2013).

The likelihood of PD damage in AP is determined by the severity of the disease (Larsen & Kozarek, 2014). In severe AP, the necrosis of pancreatic parenchymal and ductal epithelial cells may lead to the extravasation of pancreatic juice and the formation of pancreatic fluid collections, but not in those with interstitial oedematous pancreatitis (Lau et al., 2001; Neoptolemos, London, & Carr-Locke, 1993). In addition, the disruption of PD is often associated with extensive necrosis (> 50 %) and central full-thickness glandular necrosis (Kamal et al., 2015; Sandrasegaran et al., 2007; Tann et al., 2003).

Neoptolemos et al. (1993) showed that PD disruptions and/or leaks may be common in the severe AP form of this disease, whereas in the mild form the PD remains intact. Patients with necrosis and MPD injury had an increased likelihood of surgical intervention, whereas patients with pancreatic necrosis, but without local complications had intact MPD and did not require surgery (Neoptolemos et al., 1993).

In a retrospective series, Lau et al. (2001) demonstrated that the presence of a PD leak is associated with pancreatic necrosis and a prolonged LOS and suggested that endoscopic retrograde pancreatography (ERP) should be performed in cases where conservative therapy fails (Lau et al., 2001).

DPDS is the most severe form of a pancreatic leak, which occurs in the settings of necrotizing pancreatitis and trauma. DPDS is an often-overlooked complication and is seen up to 50 % of the patients with ANP-associated WON (Larsen & Kozarek, 2016). It is characterised by the complete disruption of the MPD resulting in a variable portion of the upstream pancreas becoming isolated from the MPD downstream to the duodenum (Bang et al., 2018). The disconnected segment remains functional, resulting in a persistent PFC, nonresolving pancreaticocutaneous fistula or pancreatic ascites (Tann et al., 2003).

In the analysis of a prospective multicentre database of 639 patients with APN, the need for intervention was lower in patients with only extrapancreatic necrosis (EXPAN) than in patients with parenchymal necrosis with or without EXPAN (18 % vs. 57 %; $p < 0.001$) (Bakker et al., 2013). One reason might be that ductal disruption, which may occur with parenchymal necrosis, causes more complications, although the database did not include data on PF. Ductal leaks could facilitate a bacterial invasion of pancreatic tissue. In this study, patients with pancreatic necrosis developed an infection significantly more often (47 % vs 16 %).

Only a few studies have focused on PFs exclusively after ANP, although the incidence of pancreatic leaks following ANP has been reported as high as 78 % (Kozarek et al., 2000). The reported variation (31–78 %) in the incidence illustrates the difficulties in diagnosing fistulas associated with ANP (Jang et al., 2016; Kozarek et al., 2000; Uomo et al., 1998). PD disruption in AP seems to be more common than previously realised in ANP (Neoptolemos et al., 1993).

Pancreatic duct disruption post necrosectomy

Despite the expanding literature on the technical details required to perform a mini-invasive necrosectomy for WON, relatively few studies have focused on issues surrounding the presence and outcome of MPD disruption in the context of APN (Freeman et al., 2012; Jang et al., 2016; Tenner et al., 2013). The PF post necrosectomy is due to the disease itself, but the development of fistulas can also be iatrogenic (Figure 7). Local trauma during a necrosectomy may play a role in the fistula formation as well (Doberneck, 1989; Orlando, Welch, Akbari, Bloom, & Macaulay, 1993; Tsiotos, Smith, & Sarr, 1995).

PFs are often associated with considerable morbidity, such as nutritional and metabolic disturbances, prolonged LOS and even mortality (Tsiotos et al., 1995).

The estimated incidence of PFs post intervention for necrotizing pancreatitis varies from 17 to 76 % (Bakker et al., 2011). The wide variation in the incidence indicates differences in the definition of a PF as well as patient and treatment heterogeneity (Connor et al., 2005). In addition, patients with ANP undergoing an open necrosectomy will experience complication rates of 34–95 % and mortality of 11–39 % (Connor et al., 2005; Freeman et al., 2012; Howard et al., 2007; Rau, Bothe, & Beger, 2005; Rodriguez et al., 2008). However, it is unclear how many of the complications are caused by a PF itself.

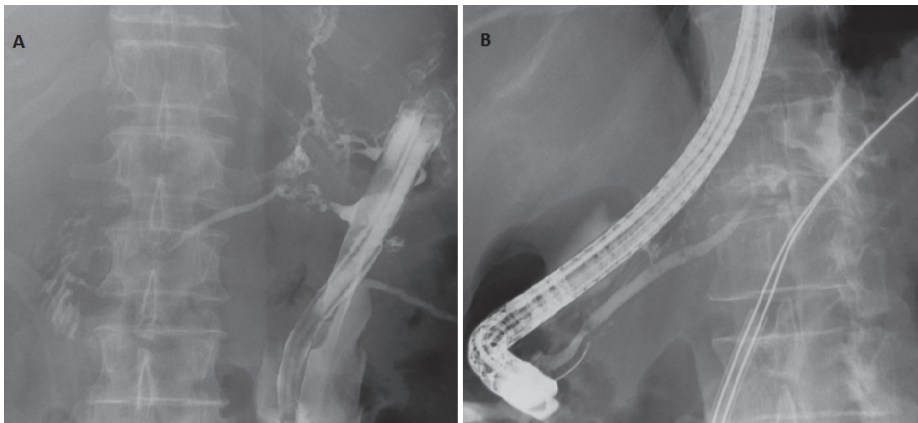


Fig. 7. Fistulography and ERP demonstrate a PF post necrosectomy. Contrast medium has been injected through abdominal drains to the operated area (infected WON), and injected contrast material is seen in the fistula tract (PD leakage) and finally reaches the duodenum (A). ERP shows the disconnection of MPD in the corpus of the pancreas and (B).

2.8.1 Diagnosis of a pancreatic duct leak in AP

Diagnosing an MPD disruption in APN can be challenging. In acute settings, CECT is accepted as the imaging procedure of choice to diagnose the disease, but sensitivity is limited to show PD integrity (Arvanitakis et al., 2004). ERCP has been regarded as a gold standard in diagnosing of PD leaks. However, even ERCP have been reported to fail to reveal PD disruptions in up to 25 % of pancreatic trauma patients (Costamagna et al., 2001). MRCP can be strongly recommended for

detecting PD leaks as an initial modality because of its non-invasive nature (Jang et al., 2016), but sensitivity is limited in detecting small PD disruptions (Wu & Banks, 2013).

2.8.2 Postoperative pancreatic fistulas

A postoperative pancreatic fistula (POPF) is one of the most serious complications in pancreatic surgery with increased mortality and morbidity. This condition might be related to either a leak of a pancreatic-enteric anastomosis or, alternatively, originating from traumatised, raw pancreatic surface resulting from nonclinically relevant to severe systemic complications requiring major invasive procedures (Bassi et al., 2017; Pulvirenti et al., 2017).

The incidence of POPF following elective pancreatic resections is still between 3–45 % despite all the developed technical modifications (Molinari et al., 2007). One reason for the variation in incidence might be due to heterogenous classification and differences in the methods to diagnose POPF.

In 2005, the International Study Group of Pancreatic Fistula (ISGPF) developed a definition and grading of POPF that has become the gold standard in classification. The classification was updated by ISGPS in 2016, and POPF is redefined as the drain output of any measurable volume of fluid with an amylase level over three times the upper limit of normal serum amylase activity, associated with clinically relevant condition related directly to the POPF (Bassi et al., 2017). Although the PF definition remains unchanged, the criteria for its diagnosis has undergone a radical change. The increase in drain amylase content alone is no longer sufficient to define POPF, but it has to be associated with an impaired clinical condition (Pulvirenti, Ramera, & Bassi, 2017). Grade A POPFs no longer exist; they have been replaced by a new term ‘biochemical leaks’ (BLs), which are asymptomatic leaks and no longer refer to a true PF (Bassi et al., 2017).

A Grade B POPF requires a change in the management, drains are kept in place over three weeks or repositioned through percutaneous or endoscopic procedures and signs of infection without organ failure. A Grade C POPF refers to a fistula that requires reoperation or leads to organ failure and/or mortality (Bassi et al., 2017).

In the recent ISGPS consensus report, the basis for the definition of POPFs is the measurement of an amylase level via an intraoperatively placed or postoperatively inserted fluid output, and grading (BL, B and C) is based on clinical conditions. Interestingly, the classification is mainly based on the literature after sterile and elective pancreatic resections (pancreaticoduodenectomies and distal

pancreatic resections), but there are few studies on POPFs post necrosectomy. In an elective and clean operation, the drains are inserted in sterile field without necrosis, but after necrosectomy the drained area is nearly always a mixture of infected material and pancreatic juice. In cases of POPF, biochemical analysis alone may not always be sufficient for diagnosing PFs (Pratt, Callery, & Vollmer, 2009). However, after interventions for necrotizing pancreatitis, up to 72 % will experience POPFs (Bakker et al., 2011).

2.8.3 Management of pancreatic duct leakage in AP

Traditionally, PFs are most often treated conservatively, although the time for a fistula to resolve spontaneously usually takes more than three months and in some cases over a year (Sikora et al., 2005). The initial management using conservative treatment involves total parenteral nutrition (TPN) with complete bowel rest, antibiotic administration and possibly octreotide medication (Larsen & Kozarek, 2016). The majority of low volume leaks are easily controlled with drains and spontaneous closure of fistulas is seen over days to weeks (Li-Ling & Irving, 2001). However, refractory cases are common and historically were treated surgically, but in the recent decades endoscopically (Varadarajulu et al., 2013).

Over the years, several studies have proposed ETPS as an alternative strategy for the management of PD injuries, especially if conservative treatment fails (Bakker et al., 2012; Halttunen, Weckman, Kemppainen, & Kylanpaa, 2005; Kozarek et al., 1997). ETPS decreases intraductal pressure, which facilitates the drainage of pancreatic fluid to the duodenum instead of a fistula. Studies investigating the efficacy of PD stent placement therapy for PFC show that pancreatic ductal anatomy determines the major complications resulting from pancreatitis (Larsen & Kozarek, 2014; Nealon et al., 2009). Endoscopic therapy using a transpapillary stent for partial ductal disruption has been shown to be more successful than total disruption with poor outcomes (Das et al., 2016; Varadarajulu, Noone, Tutuian, Hawes, & Cotton, 2005). Telford et al. (2002) demonstrated that inserting a PD stent to bridge the disruption is associated with PD disruption resolution (Telford et al., 2002). In patients where bridging was not achieved (a stent either entered the disruption or a short stent crossed only the papilla) the resolution PD leak was unlikely. Moreover, over the years, ETPS has been reported to be safe and effective, especially in the absence of complete ductal disruption (Das et al., 2016).

A MEDLINE search was performed for studies reporting the results of transpapillary stenting in ANP. Search terms were ‘transpapillary stenting’ AND ‘necrotizing pancreatitis’. Only study populations with ANP were included. Studies reporting simultaneous percutaneous and endoscopic drainage with transpapillary stenting were included. The results of the search are presented in Table 2. The fistula rate of the study population varies between 38–100 % Concomitant procedures (percutaneous, transmural and nasopancreatic drainage) were performed in most patients (75–100 %). The complication rate associated to transpapillary stenting is low and the success rate of fistula closure is high.

Disconnected pancreatic duct syndrome

Unlike pseudocysts, WON with necrotic material is more difficult to drain. If necrosis becomes infected, the morbidity is high and is associated with mortality rates up to 40 % (Bang et al., 2018; Baron, Harewood, Morgan, & Yates, 2002). The situation is even more challenging if DPDS is also present in patients with WON (Figure 8). Early recognition of DPDS and WON and the implementation of appropriate treatment improve clinical outcomes (Nadkarni, Kotwal, Sarr, & Swaroop Vege, 2015). In patients with DPDS who are not responding to conservative management, percutaneous drainage alone should be avoided due to high risk of development of a pancreaticocutaneous fistula (Larsen & Kozarek, 2016). DPDS is not also amenable to a transpapillary approach. The isolated part of the pancreas cannot be reached from the papilla and therefore the leak cannot be bridged endoscopically (Varadarajulu et al., 2005). However, data on endoscopic treatment of PFCs in the settings of DPDS is scant.

In patients with DPDS secondary to ANP, the main concern is typically the treatment of WON, and the management of DPDS is secondary (Larsen & Kozarek, 2016). However, in these patients, treatment must be targeted on both necrosis and DPDS-associated fistula at the same time. Optimal management of these patients often requires a multidisciplinary team of therapeutic endoscopists, interventional radiologists and surgeons (Lankisch et al., 2015). An endoscopic necrosectomy and dual modality drainage (transmural and percutaneous drainage) are good endoscopic options for these patients, as they both involve transmural drainage, which is the mainstay of endoscopic treatment for DPDS (Larsen & Kozarek, 2016).

Table 2. Literature review on transpapillary stenting and necrotizing pancreatitis.

Study	Number of SAP patients	ERP ²	Fistula rate in ERP	Number of transpapillary stenting/total patients	Additional treatment	Fistula resolution rate / days (d)	Stent-related complications	Mortality (number of patients)	Additional intervention due to treatment failure during follow-up
Trevino, Tamhane, & Varadarajulu, 2010	110	77/110	70 (90.9 %)	40/110	TMD ³ (100 %)	39/40 (97.5 %) / < 56 d	3 bleeding 2 stent migration 1 infection	1 2 SN 4 ETPS ⁷	
Bakker et al., 2010	24	19/24	19 (100 %)	19/24	SN ⁶ + PCD ⁴ (100 %)	16/19 (84.2 %) / 71 d	4 migration 2 stent clogging 1 clinical deterioration	2 4 SN	2 TMD
Yokoi, Kikuyama, Kurokami, & Sato, 2016	15	13/15	13/13 (100 %)	11/15	NPD ⁵ + PCD (100 %)	10/11 (90.9 %) / 45 d	1 NPD clogging	1	none
Jang et al., 2016	84	44/84	32/44 (72.7 %)	17/84	PCD + TMD + SN (78 %)	ND ¹	ND	1	4 SN 5 PCD 2 ETPS
Rana, Sharma, & Gupta, 2018	12	12/12	12/12 (100 %)	3/12	TMD (75 %)	3/3 (100 %) / 47 d	1 infection	0	none

¹ not determined, ² endoscopic retrograde pancreatography, ³ transmural drainage, ⁴ percutaneous drainage, ⁵ nasopancreatic drainage, ⁶ surgical necrosectomy, ⁷ endoscopic transpapillary pancreatic stenting

After the transmural drainage, long-term indwelling transluminal stents are indicated to prevent recurrence (Arvanitakis et al., 2007). However, combining transmural drainage with routine transpapillary drainage does not seem to be beneficial (Yang et al., 2016).

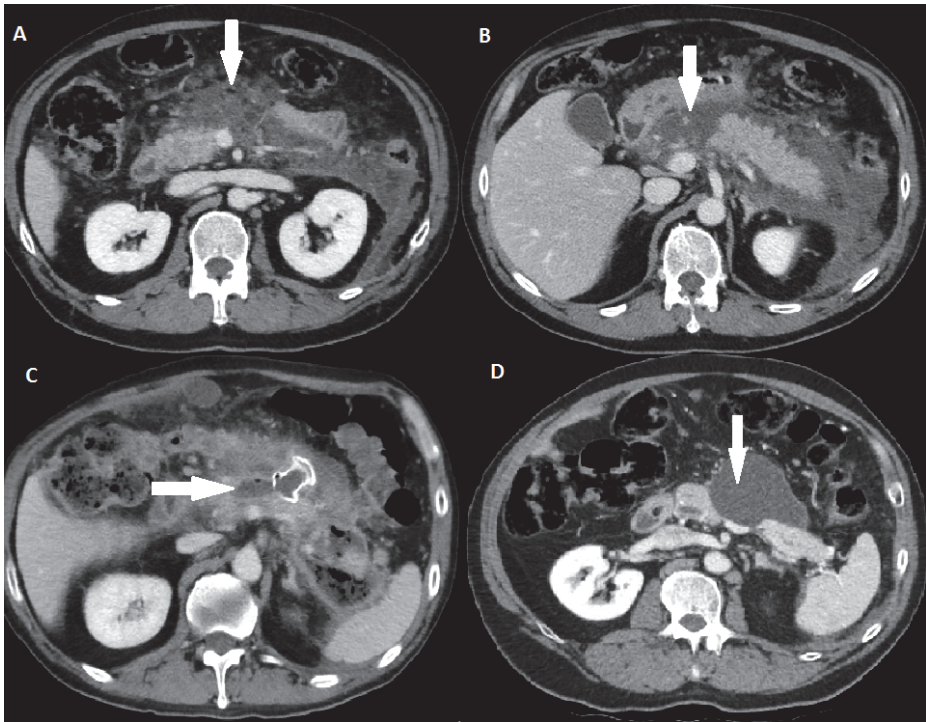


Fig. 8. CECT images demonstrate full-thickness necrosis in the neck of the pancreas in a patient with ANP (thick arrows in pictures A and B). One month after the onset of AP, the patient developed infected WON, which was drained through a cystogastrostomy stent to the ventricle (C). DPDS was overlooked and the stent was removed three months after. Four weeks later, the patient developed an infected collection in the same region due to DPDS (D).

While endoscopic therapy for DPDS is the first option, it is not uncommon after a failed endoscopy to perform surgery as a more definitive solution. In DPDS patients, the main disadvantage of surgical intervention is the significant morbidity (0–14 %) and mortality (0–8 %), although the success rate is high (80 %) (Murage et al., 2010).

2.8.4 Prevention of complications associated with a pancreatic duct leak in ANP

Because a significant percentage of patients with necrotizing pancreatitis have a high risk of developing a PD leak in the early course of the disease, ductal anatomy imaging (MRCP/ERCP) might be useful for determining whether the MPD is disrupted or disconnected (Jang et al., 2016). Although ERCP can be used to identify PD disruptions in patients with severe AP, a consensus has not been reached as to whether ERCP should be performed routinely for this purpose (Tenner, 2004). The greatest concern is that ERCP carries the risk of infection of sterile necrosis when contrast material is injected with nonphysiological pressure exacerbating a leak (Jang et al., 2016; Varadarajulu et al., 2005). In addition, performing an endoscopic intervention in a critically ill patient with ANP and concomitant papillary oedema, PD or duodenal obstruction may be technically challenging and may potentially even worsen the clinical outcome (Bakker et al., 2011).

However, data from previous studies have not confirmed the potential risk of pancreatic stenting in ANP (Kozarek et al., 2000; Lau et al., 2001; Neoptolemos et al., 1993). Interestingly, no studies have tested the possible benefit of early ERP and prophylactic stenting, although prophylactic placement has been constantly shown to be effective in reducing the risk of PEP. In addition, temporary small-calibre PD stent placement may even offer sufficient drainage to reverse the process of acute AP (Dubravcsik et al., 2012b; Freeman, 2007; Kerdsirichairat et al., 2014). In their study of 3 216 ERCPs, Kerdsirichairat et al. (2014) reported 64 PEPs (2 %), which was diagnosed according Cotton consensus criteria (abdominal pain and serum amylase level at least three times greater than the upper limit of normal serum level after ERCP, and requiring more than one night of hospitalisation (Cotton, Garrow, Gallagher, & Romagnuolo, 2009) Patient with PEP urgent salvage ERCP and pancreatic stenting was performed within 2–48 hours after onset of the symptoms with the rapid resolution of clinical pancreatitis with no necrotizing pancreatitis or late complications (Kerdsirichairat et al., 2014).

A case-control study by Madacsy et al. (2009) also demonstrated that during the early course of PEP, rescue ERCP and the placement of a PD stent could reverse the further evolution of the inflammatory process and prevent complications (Madacsy et al., 2009). Neoptolemos et al. showed in their study that MPD disruption occurred over four days after the onset of ANP (Neoptolemos 1993).

These results suggest that early prophylactic pancreatic stents could be helpful in severe AP, as a significant number of the patients with necrotizing pancreatitis will develop PD leaks during the disease. Theoretically inserting a prophylactic pancreatic stent in ANP early could maintain PD continuity and even prevent peripancreatic fluid leakage and the evolution of DPDS-associated complications.

2.9 Short- and long-term outcomes of AP

Short-term mortality

The short-term mortality (Figure 9) in hospitalised patients with AP has been reported in several studies: the overall mortality of AP is 2–5 %, but it reaches about 20–30 % in severe cases (Pavlidis et al., 2013; Singh, Wu, Bollen, Repas, Maurer, Johannes et al., 2009). Because high mortality is associated with severe AP, several scoring systems have been established to assess the severity of the disease as early as possible and accurately identify patients who will need more aggressive interventions and thereafter reduce morbidity and mortality.

There are many different predictive scoring systems for AP (e.g. APACHE II, Harmless AP score (HAPS), Ranson, Bedside Index of Severity in AP (BISAP), and modified Glasgow score), including single serum markers (C-reactive protein, haematocrit, procalcitonin, blood urea nitrogen) and radiological images (CT severity index = CTSI), but none are clearly superior or inferior to (persistent) SIRS (Papachristou et al., 2010). Although the presence of SIRS during the initial 24 hours has a high sensitivity for predicting organ failure and mortality, the presence of SIRS lacks specificity for severe cases of the disease (41 %). The lack of specificity is since the presence of SIRS is not as important as its persistence (Johnson & Abu-Hilal, 2004; Tenner et al., 2013). SIRS as a marker for predicting severe AP over the other scoring systems is recommended due its simplicity, widespread familiarity and practicality (Singh, Wu, Bollen, Repas, Maurer, Mortelet, & Banks, 2009; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).

Patient-related risk-factors for short-term mortality include age, chronic diseases and a high body mass index (Halonen et al., 2003; Ikeura et al., 2017). Disease-specific risk-factors for short-term mortality include signs of hypovolemia, such as an elevated creatinine and an elevated haematocrit, the presence of pleural effusions and/or infiltrates and altered mental status (Johnson, C. D. & Abu-Hilal, 2004; Tenner et al., 2013).

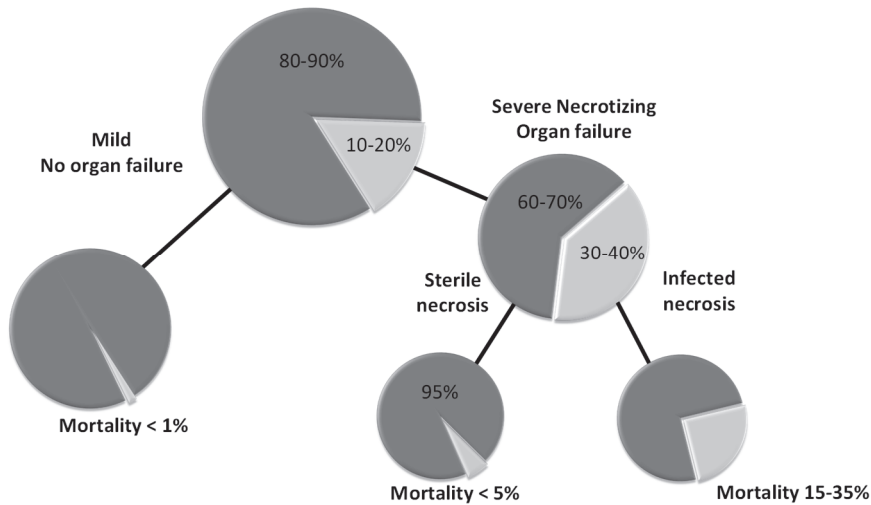


Fig. 9. Short-term mortality of acute pancreatitis.

Recurrent pancreatitis

Approximately half of the patients with alcohol AP will have a recurrence (Pelli, Sand, Laippala, & Nordback, 2000). Younger patients seem to be at the highest risk. The risk for recurrence is also increased in patients if the first episode of alcohol-associated AP is mild (Appelros & Borgstrom, 1999; Pelli et al., 2000). This finding is in line with the finding that ANP is linked to a low rate of recurrence (Tzovaras, Parks, Diamond, & Rowlands, 2004). One potential reason might be that a severely damaged pancreas no longer can produce an acute attack (Pelli et al., 2000). In addition, the quality of life in survivors of severe pancreatitis seems to be comparable to that of the normal population (Halonen et al., 2003). Progression to CP usually occurs in patients with recurrent pancreatitis, alcohol abuse and smoking (Yadav, O'Connell, & Papachristou, 2012).

In patients with biliary pancreatitis, a cholecystectomy will reduce the risk of recurrence. The current guidelines recommend a cholecystectomy during the same hospital admission, but in severe AP delayed operation is preferred (Crockett et al., 2018; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).

Long-term mortality and causes of death

Although AP is one of the most common gastroenterological diseases, its natural course is not well known, and the limited number of reports on long-term outcomes are conflicting (Lankisch et al., 2009). The data concerning long-term mortality, consequences of recurrent AP and causes of death are scarce. The previous studies have been criticised because of major variations in outcomes, follow-up times and control groups, which make comparison of studies very difficult (Lund, Tonnesen, Tonnesen, & Olsen, 2006).

The reported long-term mortality after an episode of AP has varied between 4 % and 83 % during follow-up times of four to 30 years (Castoldi et al., 2013; Nojgaard et al., 2011). In addition, mortality rates are rarely evaluated in comparison to a defined population; instead, most studies report the number of patients with AP treated at a specific hospital (Appelros & Borgstrom, 1999).

Poor long-term survival after the first AP has been related to continuing alcohol abuse, being over 70 years old, diabetes, unemployment and male gender (Appelros & Borgstrom, 1999; Nojgaard et al., 2011). However, the causes of death are poorly reported in the literature and the problem with the studies is the low number and low rate of autopsies.

The risk for recurrent acute pancreatitis after the first acute pancreatitis episode also seems to be highly dependent on the level of continuing alcohol consumption. Abstaining from alcohol may prohibit recurrent acute pancreatitis and reduce pain in CP (Berger & Bradley, 2015; Nordback et al., 2007; Sand et al., 2009). Nordback et al. (2007) showed a decreased rate of recurrent AP in a randomised control trial after a multiple-intervention program. Patients were helped to reduce their alcohol consumption and recognise the consequences of alcohol abuse (Nordback et al., 2007).

3 The aims of the study

The main aim of the study is to examine the diagnosis, treatment and prevention of pancreatic fistulas associated with acute necrotizing pancreatitis and the long-term prognosis of acute pancreatitis. The specific aims of the study are as follows.

1. To investigate the pancreatic fistula rate after surgical necrosectomy.
2. To study the feasibility of endoscopic transpapillary pancreatic stenting after necrosectomy,
3. To examine the use of early prophylactic pancreatic duct stenting in acute necrotizing pancreatitis to prevent local complications.
4. To evaluate the accuracy of the drained fluid amylase measurement following surgical necrosectomy as an indicator of pancreatic ductal leakage.
5. To examine the long-term outcome and causes of death of acute pancreatitis in working-age patients.

4 Materials and methods

4.1 Patients

The patients in studies I, II and IV have been treated in the Oulu University Hospital. Study II was conducted in the Oulu University Hospital and in the Copenhagen University Hospital Hvidovre (Hvidovre, Denmark). The study protocols were accepted by the hospital administrations and study II was also approved by the ethical committees of both hospitals. The aims of the study and inclusion criteria are introduced in Table 3.

Table 3. Aim of the study and inclusion criteria.

Study	Aim of the study	Inclusion criteria
I	To assess prospectively the rate of POPF after necrosectomy and the feasibility and results of ETPS in patients with POPF following necrosectomy.	All consecutive patients (n = 29) who underwent an open necrosectomy and postoperative ERP and ETS from January 2009 to December 2012 were enrolled in the study.
II	Prospective randomized bi-centre control study to test the feasibility and safety of PPDS in ANP and to compare PPDS with conservative treatment.	Patients (n = 154) 18–75 years of age who were diagnosed with ANP on admission between February 2011 and July 2015 were enrolled in the study. These patients were prospectively randomised to receive PPDS or conservative treatment. PPDS was performed as soon as possible after randomisation.
III	Retrospective analysis to investigate the sensitivity of drainage fluid amylase levels in detecting PD leakage after necrosectomy.	Between January 2009 and December 2013 all patients (n = 21), who had postoperative drain amylase analysis and POPF confirmed on ERP after necrosectomy were included in the study. Samples were taken after the first necrosectomy and ERP. The correlation between ERP findings and drain amylase measurements was analysed.
IV	Retrospective register-based analysis of long-term survival and causes of death among working-age patients with AP compared with the normal population.	All patients (n = 1 644) with AP aged 18–64 years admitted to Oulu University Hospital in 1995 to 2012 were included to study. Patient data were compared with data from 8,220 age- and sex-matched controls that resided in the hospital district area.

4.2 Methods

4.2.1 Study I

All consecutive patients following an open necrosectomy for infected ANP from January 2009 to December 2012 in Oulu University Hospital were included in the study (n = 29). Patients who had any measurable volume of postoperative drainage with an increased amylase level (> three times to reference value the serum amylase, 360 IU/l) were planned for ERP and possible ETPS, if needed.

ERP and ETPS procedures were performed under sedation. Contrast media was injected after successful PD cannulation. In the presence of leakage or disruption, adequate PD stent length, with or without pancreatic sphincterotomy over the guide wire, was inserted to bridge the area of leakage. If bridging was not achieved, the secondary aim was to drain the pancreatic juice collection with a pancreatic stent. Finally, if bridging or drainage was unsuccessful, a transpapillary stent was introduced to reduce the intraductal pancreatic pressure gradient towards the duodenum. Early and late ERCP-related complications were recorded.

All patients were followed up monthly until the closure of fistulas. Repeated ERP with stent replacement and preferably to a larger calibre stent was performed, if fistula output was not reduced and/or occlusion of the stent and/or infection was suspected. After fistula closure, a control ERP was performed in 3–6 months' time and the stent was removed if the pancreatic duct was normal. In the case of leakage, stricture or pseudocyst, a new stent was inserted. Fistula closure was defined as complete resolution of fistula output after the removal of percutaneous drains and without the need for any additional radiological, endoscopic or surgical intervention.

The aim of the study was to evaluate the rate of PFs after necrosectomy and the feasibility and effectivity of early ETPS in the treatment of POPE.

4.2.2 Study II

This trial was a two-centre, randomised, superiority clinical trial designed to test the feasibility and safety of prophylactic pancreatic duct stenting (PPDS) in ANP, and to compare PPDS with conservative treatment. The trial was conducted at the Oulu University Hospital (Finland) and at the Copenhagen University Hospital Hvidovre (Denmark).

All patients between 18 and 75 years of age admitted to participating hospitals with CECT-diagnosed ANP were evaluated for the study. CECT showing an area of non-enhancing pancreatic parenchyma was thought to represent necrosis. CECT was repeated after one week, if necrosis was not observed on initial CECT in suspected cases. The patient was enrolled in the study, if CECT revealed 20–30 % parenchymal necrosis affecting the main PD or pancreatic necrosis affecting over 30 % of the head, neck, or body of the pancreas.

The exclusion criteria were pregnancy, isolated necrosis of the pancreatic tail, inability to give informed consent, or the patient was unfit to tolerate endoscopy and suspicion of abdominal tumour on CECT or MRI. Patients were also excluded if experienced ERCP therapeutic pancreaticobiliary endoscopists were not available. An advanced therapeutic pancreaticobiliary endoscopist should have at least 10 years of experience with 300 ERCPS annually, with approximately one third including pancreatic stent placement. Informed consent was taken from all participants prior to randomisation in both written and oral forms and patients were randomised to two groups: PPDS or conservative treatment group.

For patients who were randomised to the PPDS group, ERP was scheduled as soon as possible after admission—if possible before the end of the first week after symptom onset and before potential ductal disruption. Informed consent was obtained from all participants prior to randomisation in both written and oral forms. ERP was performed after preparation and sedation to patients, as is standard practice at both participating centres. The PD was cannulated and opacified during ERP. Regardless of whether leakage was seen, an adequate length of a PD stent (5–10 Fr) was inserted to bridge the area of necrosis, with or without pancreatic sphincterotomy. The second attempt was planned for within one week if the first ERP procedure was unsuccessful. Patients in the PPDS group were called for stent removal or replacement at two months after the primary ERP, or earlier if needed. If the control ERP did not show leakage, the stent was removed. In cases of persistent leakage, a new stent was inserted, and ERP was repeated at two-month intervals until the cessation of leakage without ductal stricturing. The other treatment was identical with a conservative group and was done according to reported international guidelines (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).

The primary endpoint for the study was the rate of endoscopic, percutaneous, laparoscopic or open surgical drainage and/or debridement one year after randomisation.

The secondary endpoints included LOS, persistent PFC, other local complications, new onset of endocrine or exocrine insufficiency and mortality within one year after the randomisation.

The study was conducted in accordance with the Declaration of Helsinki and the principles of the ICH-GCP guidelines. The trial was registered at Clinical Trials.com (NCT01767233).

4.2.3 Study III

All consecutive patients who underwent an open surgical necrosectomy due to infected pancreatic necrosis between January 2009 and December 2013 were identified from the prospective database in the Oulu University Hospital. All patients who had postoperative drain amylase levels measured and ERP-confirmed POPF were included to the study. The analysis was performed between the first primary surgical necrosectomy and the first ERP.

Exclusion criteria were ERP, and pancreatic stenting was performed before a necrosectomy (pancreatic stenting performed before a necrosectomy might cause duodenal reflux into the necrotic cavity giving false-positive results), and a patient had a complex fistula, e.g. a pancreatico-cutaneous-intestinal fistula.

The primary outcome measure was to analyse the sensitivity of drainage fluid amylase levels in diagnosing PD leakages after surgical necrosectomy. Drain amylase activity was compared to ERP findings.

The secondary outcome measure was to analyse the significance of the distance of PD leaking sites from abdominal drains (which was inserted to the WON cavity during a necrosectomy) and its correlation to measured. The distance of abdominal drains to PD leaking sites were measured from the first ERP image (demonstrating the leak) and CT taken after PD stent was inserted. Patients with re-necrosectomies and/or re-insertions of abdominal drains, the localisation of reinserted drains were measured from recent CT.

Data were retrieved from the discharge registry of the Oulu University Hospital and individual medical records.

4.2.4 Study IV

This retrospective, case-control, registry-based study was carried out in Oulu University Hospital, which serves 411 856 (2017) inhabitants of Northern Finland.

The study population consisted of all working-age patients (18–64 years) who were admitted with AP to the Oulu University Hospital from 1995 to 2012. Patients were retrieved from/identified in the computer database of hospital discharge records, based on ICD-10 codes, K85–K86.00. Patients were included when they had two of the following three features: (1) abdominal pain, (2) characteristic findings of AP on US, CT or MRI, and (3) a serum amylase level at least three times greater than the upper limit of normal.

The first admission for AP during the study period was classified as the first AP. We collected data on aetiology, age, gender, date of admission and ICU admissions. AP was considered severe when the patient died during the hospital stay or when the patient needed an ICU admission during the hospital stay.

Alcohol was considered the aetiological factor when the patient reported a regular and high intake of alcohol or when the patient reported considerable alcohol consumption preceding the onset of the disease. Aetiology of gallstones was based on a finding of stones in the gallbladder or in the bile ducts. In other cases, we performed an intensive search for rare aetiologies. The aetiology was considered idiopathic when no aetiology could be confirmed.

The hypothesis of our study was that mortality in the study population would be notably higher than that in an age- and sex-matched control population. For each patient with AP, we randomly selected five (5) control individuals from the Statistics Finland database. Criteria for matching each control to a given patient were the same gender, year of birth, and province of residence in Finland; alive on the date of the primary admission of the patient and a different social security number. The vital status (alive/dead) of controls at the end of year 2014 and the possible cause of death were received from the mortality database of Statistics Finland.

The primary outcome measure was to examine long-term outcome and causes of death among working-age patients with AP compared with the normal population.

4.3 Statistical analysis

The data were analysed using SPSS-software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) Continuous variables are presented in medians and percentiles or means and standard deviations. Proportional data are presented in number and percent. Continuous variables were

tested using Student's t-test and proportional data using Pearson's chi-square or Fisher's exact. P-values of $p < 0.05$ are considered significant.

In study II, analyses were performed primarily using the intention-to-treat (ITT) principal, and secondarily using the per protocol (PPT) principal.

For study III, summary measurements are presented as the mean or median and range. Wilson's 95 % confidence intervals (95 % CI) were calculated for sensitivity. For study IV, Kaplan-Meier survival curves were constructed, with the follow-up starting on the first day in hospital due to AP, and the follow-up ending on the day of death or on 31.12.2014. Statistical comparisons of survival data were performed with the log-rank test.

5 Results

Patients included the study and the main results of the present study are shown in Table 4.

Table 4. Main results of the study.

Study	Patients included the analysis	Main result
I	29 consecutive patients with severe AP and a necrosectomy were enrolled into this study. Five patients died before ETPS due to the rapid progress of the disease and were excluded. Therefore, the remaining 24 patients were included in the analysis.	All patients after surgical necrosectomy had pancreatic fistula and ETPS was an effective and safe method to treat POPF after necrosectomy. Fistulas were closed in all patients with successful ETPS.
II	24 patients were included in the analysis. These patients were prospectively randomised to receive PPDS (n = 11) or conservative treatment (n = 13) at two tertiary centres.	PPDS in ANP is associated with an unacceptably high risk of pancreatic necrosis infection. The study indicates that PPDS in ANP seems to increase the complication rate and is perhaps harmful for patients.
III	The total of 87 drain amylase samples (the mean of 4.2, range 1–9) were taken from 20 patients. Four samples (4.5 %) were so contaminated that the laboratory was not able to measure the amylase level. Therefore, the remaining 83 samples were used in the analysis.	The sensitivity of single-drain amylase levels in detecting POPF using measurement was 65.0 % (95 % CI 53.1–74.5 %).
IV	1 644 patients with AP aged 18–64 years admitted to Oulu University Hospital in 1995 to 2012 were included in the study. Patient data were compared with data from 8 220 age- and sex-matched controls who resided in the hospital district area.	The long-term mortality among patients (mainly alcohol-induced) with AP was four times higher than that in the control population. The significant difference in the causes of death between groups could be explained by alcohol-related diseases. Episodes of AP without an alcohol aetiology had a minimal impact on survival.

5.1 The rate of POPF after open necrosectomy (I)

From January 2009 to December 2012 twenty-nine consecutive patients with SAP and a necrosectomy in Oulu University Hospital were enrolled in this study. There were 25 men and four women, and the mean age was 51 years (range 27–71 years). Five patients died before ETPS due to the rapid progress of the disease and therefore were excluded.

All patients following surgical necrosectomy had POPF according to the definition of the International Study Group of Postoperative Pancreatic Fistula (ISGP) criteria (Bassi et al., 2017). 92 % of the fistulas were demonstrated in ERP.

5.2 Success of ETPS after open necrosectomy (I)

Initial ERP was performed after a median of 35 days (range 13–90 d) after the first surgical open necrosectomy. The first ERP was successful in 21 patients (88 %), in two patients on the second and one patient on the fifth attempt. The reason for repeated attempts and delays was duodenal obstruction due to oedema related to severe AP in all these cases.

The primary ETPS was achieved in 20 of 24 patients (83 %). Three patients needed a second attempt, and in one patient ETPS was impossible even after several attempts due to technical difficulties. A bridging stent was successful in two, an internal draining stent into the necrosectomy cavity in 12 and a transpapillary stent in nine patients.

ETPS was done a median of twice per patient (range 1–5) before the closure of the fistula. In three of the seven transpapillary stenting patients, stent replacement was upgraded to the internal drainage of the fluid collection, and in four cases two pancreatic stents were introduced instead of one stent.

Fistulas were closed in all 23 patients with successful ETPS. The median time to fistula closure was 82 days (2–210 days). Two patients without demonstrable contrast media leakage in ERP had PF closure in four and seven days after ETPS. One patient without successful ETPS still had a persistent pancreaticocutaneous fistula at the end of the study period.

During the short-term follow-up, none of the patients had major complications. Seven patients (32 %) experienced minor complications before the fistula closure. Stent clogging occurred in five of 23 patients. Clogging was diagnosed if the patients developed signs of infection and/or radiological examinations showed undrained collections with a suspected pancreatic origin in the abdomen or the fistula output did not decrease. Stent migration was identified in two patients. One patient developed abdominal pain and sepsis one day after ETPS and a re-necrosectomy was performed three times after ETPS. During the last operation, the pancreatic stent was also removed because of a suspicion of duodenal reflux through the stent to the necrotic cavity worsening infection. Six weeks later, a new ETPS was performed and the patient's recovery was uneventful.

5.3 Use of PPDS in ANP (II)

During the study, suspicion arose of an increased rate of harmful events in the stent group. The trial was prematurely stopped based on ethical concerns regarding a significantly higher rate of infected necrosis in the PPDS group after interim analysis.

Between February 2011 and July 2015, 25 patients with ANP were enrolled in the study. The inclusion flowchart is presented in Figure 10. According to the hospital discharge registry diagnosis codes, a total of 155 patients were admitted for ANP during the study period, and 25 (23.4 %) of them were enrolled in the study: 12 were randomised to the PPDS group and 13 to the conservative treatment group. One patient in the PPDS group was ruled out due to misdiagnosed pancreatic necrosis upon the initial CECT. Patients characteristics of the PPDS and conservative treatment groups were similar (Table 5).

Table 5. Patients characteristics in Study II.

Patient characteristics	Prophylactic stenting (n = 11)	Conservative treatment (n = 13)
Age; mean (range)	48.2 (23–69)	52.7 (38–68)
Male sex (%)	9/11 (81.8)	8/13 (61.5)
Cause of AP		
alcohol	8 (72.7)	8 (61.5)
gallstones	3 (27.3)	4 (30.8)
other		1 (7.7)
Localisation of pancreatic necrosis		
head-body	3 (27.3)	5 (38.5)
body-tail	3 (27.3)	2 (15.4)
all	5 (45.4)	6 (46.1)
Extent of necrosis		
< 30 %	2 (18.2)	5 (38.5)
30–50 %	4 (36.4)	3 (23.1)
> 50 %	5 (45.5)	5 (38.5)

There were no statistically significant differences between the study groups in the parameters ($p < 0.05$).

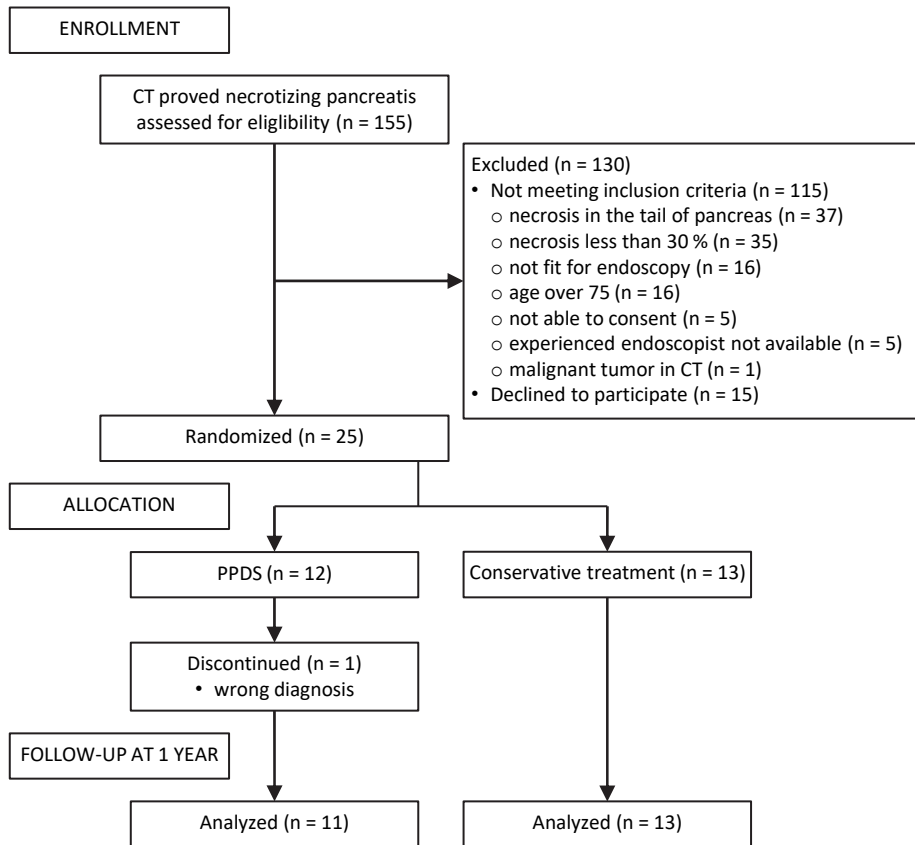


Fig. 10. Flow chart of participants in Study II. PPDS; prophylactic pancreatic ductal stenting.

Primary endpoint

According to intention to treat (ITT) analysis, 7/11 (63.6 %) in the PPDS group had infected pancreatic necrosis, compared to 3/13 (23.1 %) in the control group (difference between infection rate 40.6 %, 95 % CI 1.4 to 66.5 %, $p = 0.095$). Infected pancreatic necrosis developed in all five patients after successful PPDS. PPT analysis revealed significantly more frequent rate of infected necrosis among patients with successful PPDS (5/5, 100 %) than patients in the conservative treatment group (3/13, 23 %; difference between rates 76.9 %, 95 % CI 25.7–91.8 %, $p = 0.007$).

The composite primary endpoint of endoscopic, radiological or surgical intervention occurred in eight of the 11 patients (72.7 %) in the PPDS group at the one-year follow-up, compared to four of 13 (30.7 %) patients in the conservative treatment group (Table 6). The difference between intervention rates for the PPDS and conservative groups was 42.0 % (95 % CI 2.2 to 67.1 %, $p = 0.10$).

Table 6. Patient outcomes at the one-year follow-up.

Outcome	Prophylactic stenting (n = 11)	Conservative treatment (n = 13)	p-value
Major complication or death	8 (72.7)	4 (30.8)	0.1
- death	1 (9.1)	0	
- infection of necrosis	7 (63.6)	3 (23.1)	0.095
Patients requiring intervention	8 (72.7)	4 (30.8)	0.1
- necrosectomy (mini-invasive/open)	3 (27.3)	4 (30.8)	> 0.9
- drainage procedure	4 (36.4)	2 (15.4)	0.36
- other (additional ETPS)	2 (18.2)	0	0.082
Length of hospital stay; days; mean (range)	39.3 (9–81)	5 (38.5)	0.49
ICU admission during 1. admission	3 (27.3)	4 (30.8)	> 0.9
Readmission	7 (63.6)	6 (46.1)	0.095
Others after 1 year			
- fistula/collection	4 (36.4)	3 (23.1)	> 0.9
- stent in the pancreas	4 (36.4)	0	
- DM	4 (36.4)	4 (30.8)	0.68
- use of pancreatic enzymes	4 (36.4)	3 (23.1)	0.65

Secondary endpoint

During the one-year follow-up, the total LOS was 39.3 days in the PPDS group and 31.3 days in the conservative treatment group (difference between means 8.0 days, 95 % CI -15.5–31.7 days, $p = 0.49$). Seven of the 11 (64 %) patients in the PPDS group required readmission to the hospital, compared to two of the 13 patients (15 %) in the conservative treatment group, throughout the one-year follow-up. The average number of readmissions was 2.9 (1–6) in the PPDS group.

After one year, four of the 11 patients in the PPDS group still had a pancreatic stent due to persisting PFs or fluid collection (> 3 cm), including three patients with successful PPDS. In the conservative treatment group five of the 13 patients had WON, but none required pancreatic stents or other treatment. The study groups did not differ in their incidence of pancreatic exocrine insufficiency or new-onset diabetes.

5.4 Technical success of PPDS in ANP (II)

In the PPDS group, the average time from the onset of symptoms to PPDS was 4.6 days (range, 2–9 days). PD cannulation and pancreatogram was successful in seven of 11 patients (63.9 %). None of the patients showed complete disruptions, but partial PD leakage was observed in three patients. PPDS was achieved in five of 11 patients (45.5 %). A long bridging stent (5–7 Fr 12–15 cm) was successfully placed in two cases. In three cases, only a short non-bridging stent could be placed due to a stenotic PD. After successful cannulation, two patients exhibited a very narrow PD that precluded any stenting even with a 5 Fr stent.

Among the seven patients following successful cannulation, the average PD diameter was 2.0 mm (SD, 3.0–1.6 mm) in the head, 1.6 mm (2.0–1.3 mm) in the body, and 1.1 mm (1.3–1.0 mm) in the tail of the pancreas. In the four cases of cannulation failure, pronounced duodenal oedema prevented major papilla visualisation (three patients), and access to the second part of the duodenum (one patient). An additional attempt also failed in three of these cases. No pancreatic sphincterotomies were performed. None of the patients in the PPDS group experienced any immediate ERP or anaesthesia-related complications. Endoscopic findings and procedures in the PPDS group are shown in Table 7.

Table 7. Endoscopic findings and procedures in the PPDS group.

Pt	Timing (days) ¹	ERP achieved	ERP findings	PD diameter (mm) (head, corpus, tail)	PPDS	Reason for failure	Complication
1	9	yes	leakage, narrow PD	2.0, 1.9, 1.3	non-bridging		infection
2	7	yes	leakage, narrow PD	1.6, 1.5, 1.2	failed	1. duodenal oedema 2. PD too narrow	none
3	2	yes	no leakage, narrow PD	1.7, 1.4, 1.1	non-bridging		infection
4	5	no	not achieved		failed	duodenal oedema	None
5	7	yes	no leakage, narrow PD	1.6, 1.6, 1.3	failed	PD too narrow	none
6	3	no, only ERC + EPT	not achieved		failed	1. duodenal oedema 2. duodenal oedema	death
7	3	yes	no leakage, narrow PD	1.8, 1.4, 1.0	bridging		infection
8	3	no	not achieved		failed	duodenal oedema	infection
9	2	yes	no leakage, narrow PD	2.2, 1.3, 1.0	bridging		infection
10	8	yes	leakage, narrow PD	3.0, 2.0, 1.0	non-bridging		infection
11	4	no	Not achieved		failed	duodenal oedema	none

¹from the onset of symptoms to prophylactic pancreatic duct stenting

5.5 Sensitivity of drain amylase analysis to detect POPF (III)

Twenty of 34 consecutive patients met the inclusion criteria following an open necrosectomy for infected ANP. Fourteen patients were excluded for the following reasons: six patients died before ERCP, in six patients ERP and pancreatic stenting was performed before the necrosectomy and left in situ during the necrosectomy, in one patient ERP did not prove POPF and one patient had a complex fistula; a pancreato-duodeno-cutaneous-fistula.

Therefore, the remaining 20 patients were included in the study.

There were 16 male and four female patients and the median age of the patients was 48.7 years (range 27–66). The aetiology of AP was alcohol in 15 (75 %), gallstones in four (20 %) and statin medication in one (5 %).

ERP was performed after a median of 48.2 (range 13–188 days) days after the first necrosectomy. The primary ERP was successful in 20 patients (100 %), and ETPS was successful in 18 patients (90 %) in the same session. In addition, in two cases ETPS was achieved in the second ERCP.

Nineteen out of 20 leakages were in the MPD and one in the side branch. The localisations of the leak seen in ERP were: three in the head (15 %), 11 in the body (55 %) and five in the tail of the pancreas (25 %).

The total of 87 drain amylase samples (the mean of 4.2, range 1–9) were taken from 20 patients. Four samples (4.5 %) were contaminated by pus and amylase level analysis was not possible. Therefore, the remaining 83 samples were used in the analysis. All drain amylase analyses were taken a mean of 31.1 days after the necrosectomy (range 1–187 days).

In 54 out of the 83 drain amylase analyses (65.1 %), the measured amylase levels (426–350 360 IU/l) were above 360 IU/l, indicating fistulas seen also in ERP. In seven patients (35.0 %), all the measured amylase activity levels were above 360 U/l, whereas in 65 % of the patients at least one of the measured amylase levels was low (< 360 IU/l).

The sensitivity of drain amylase analysis to detect POPF using a single measurement was 65.0 % (95 % CI 53.1–74.5 %). The postoperative drainage fluid amylase levels are shown in Table 8.

Table 8. Postoperative drain amylase levels (IU/l) in 20 patients after necrosectomy and before ERP.

Patient	Number of samples/patients	Mean IU/l (range)	Samples taken on separate days + amylase level > 360 IU/l - amylase level < 360 IU/l	Distance from the abdominal drain to the leak (mm) ¹
1	0	30 (3–64)	-/-	195
2	4	699 (17–1 423)	-/-/+	55
3	3	9 449 (199–26 610)	+/-	75
4	5	1 231 (41–2 399)	+/-/-/+	NA ²
5	6	2 323 (34–13 260)	-/-/-/-	NA
6	2	2 750 (446–5 053)	+/+	NA
7	2	3 060 (3 018–3 101)	+/+	NA
8	4	24 465 (13–50 500)	+/+/-	58
9	2	27 933 (15 903–39 962)	+/+	10
10	6	4 857 (67–15 997)	+/-/+/+	NA
11	9	9 604 (10–34 120)	-/+/-/+/-/+/-	NA
12	3	112 845 (15–238 920)	-/+	10
13	3	74 463 (6 215–210 850)	+/+	6
14	4	115 624 (2 554–350 360)	+/+/+	NA
15	4	15 132 (312–59 520)	+/+/+	10
16	7	1 770 (21–5 700)	-/+/-/+	10
17	3	19 836 (157–24 470)	-/+	114
18	4	38 250 (30–54 900)	+/-/+	NA
19	1	3 311	+	5
20	8	6 318 (5–36 528)	+/-/-/-/-	50

¹distance was measured using CT imaging, ²not analysed (CT imaging was not done)

The impact of distance between the leak site and the abdominal drain (III)

The distance between the abdominal drain and the origin of the fistula was possible to measure in 12 of 20 patients. In eight patients, the measurement was impossible due to a lack of CT imaging.

In patients (n = 6) who had a distance (from the leak to the abdominal drain) less than 50 mm, 17/20 of the measured drain amylase levels were > 360 IU/l indicating fistulas seen in ERP. If the distance was more than 50 mm, only 10/22 drain amylase levels were > 360 IU/l (p = 0.011). For one patient with a distance of 195 mm, all drain amylase levels were < 360 IU/l (Table 7).

5.6 Long-term survival and causes of death of working-age patients (IV)

We identified 2317 admissions for AP during 1995–2012 in Oulu University Hospital discharge registry. Thirty-two (1.4 %) patients under 18 years old and 531 (23.9 %) patients over 64 years of age were excluded. The diagnostic inclusion criteria were not fulfilled by 99 patients, and the aetiology remained uncertain in 11 patients, which could not be classified as idiopathic. A total of 1644 cases (410 females; 24.9 %) were enrolled in the final study and they were compared with 8220 age- and gender-matched controls.

The mean age of the study group upon first admission was 45.3 years (SD 11.4 y). A total of 197 patients (11.9 %) were admitted to the ICU, due to one or multiple organ failures, and these were classified as cases of severe AP. A total of 614 of the 1644 patients (37.3 %) were re-hospitalised during the study period due to RAP.

Aetiology (IV)

The main aetiological factor of AP in the study group was caused by alcohol in 71.4 % of the cases, followed by biliary (13.2 %) and idiopathic (10.9 %) factors (Table 9). Patients were divided into subgroups based on whether the AP aetiology was alcohol-related or non-alcohol-related.

Table 9. Aetiological factors of AP in 1644 patients treated at Oulu University Hospital between 1995 and 2012.

Aetiology	Patients (N)	%
Alcohol	1 173	71.4
Biliary	217	13.2
Idiopathic	180	10.9
Drugs	31	1.9
ERCP	16	1.0
Tumour	12	0.7
Trauma	7	0.4
Hypertriglyceridemia	5	0.3
Pregnancy	3	0.2

5.6.1 Mortality (IV)

Of 1644 patients, 398 (24.2 %) in the study group and 519 of 8220 controls (6.3 %) died during the median follow-up time of 9.5 years (25th–75th PCT 5.4 to 14.5, range 0–20 y) from the primary admission ($p < 0.001$). The median age of death was 54 (range 47–61) years in the study group, compared to 61 (range 55–67, $p < 0.001$) years in the control group. In the AP group, long-term mortality rates were 27.1 % (335/1 234) among males and 15.4 % (63/410) among females ($p < 0.001$). In the alcohol-related AP subgroup, the median age at death was 54 (range 46–60) years, whereas in the non-alcohol-related AP subgroup the median age at death was 62 (range 55–74) years ($p < 0.001$).

The Kaplan-Meier survival curves of the study and control population are shown in Figure 11. Further, the study group was analysed according to alcohol and nonalcohol AP aetiology. In the study population, the survival curve of the alcohol AP subgroup started to fall linearly from the control group after the first episode of AP. The mortality of patients with alcohol-related AP (30.6 %) was significantly higher than that of the control group (6.3 %, $p < 0.001$). However, the survival of patients with non-alcohol-related AP did not differ from that of the control group.

The long-term survival after severe AP was significantly worse than after mild AP ($p < 0.001$). These survival curves started to separate immediately after the beginning of AP, but after a few months, the lines declined in parallel (Figure 12).

In the alcohol AP subgroup, 43.5 % of patients (510/1 173) were readmitted due to RAP during the follow-up time, whereas the corresponding rate was 22.1 % (104/471) in the nonalcohol subgroup ($p < 0.001$). The long-term survival curve with alcohol recurrent acute pancreatitis (RAP) starts to separate from that of patients without recurrence, after approximately in five years, but the difference failed to reach statistical significance ($p = 0.10$, Figure 13).

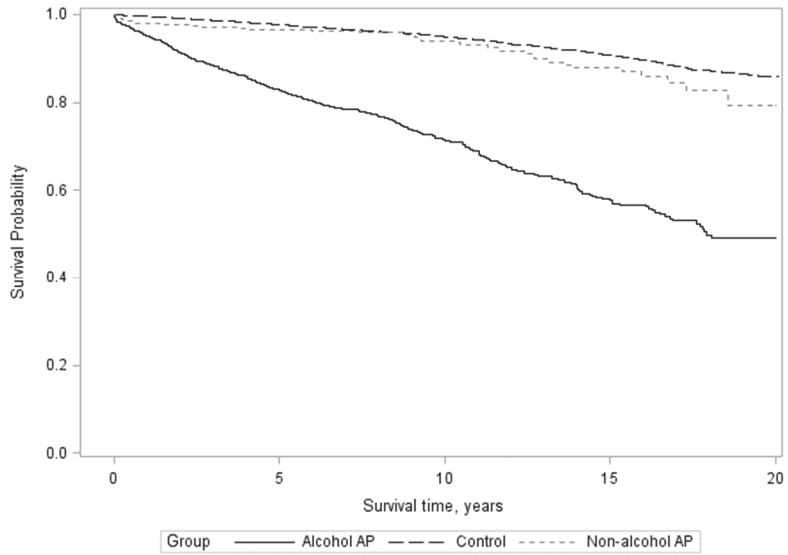


Fig. 11. Long-term survival after a first attack of AP compared with an age- and sex-matched control group (dashed line). The group of patients with AP is subdivided into those with alcohol AP (solid line) and those with nonalcohol AP (dotted line).

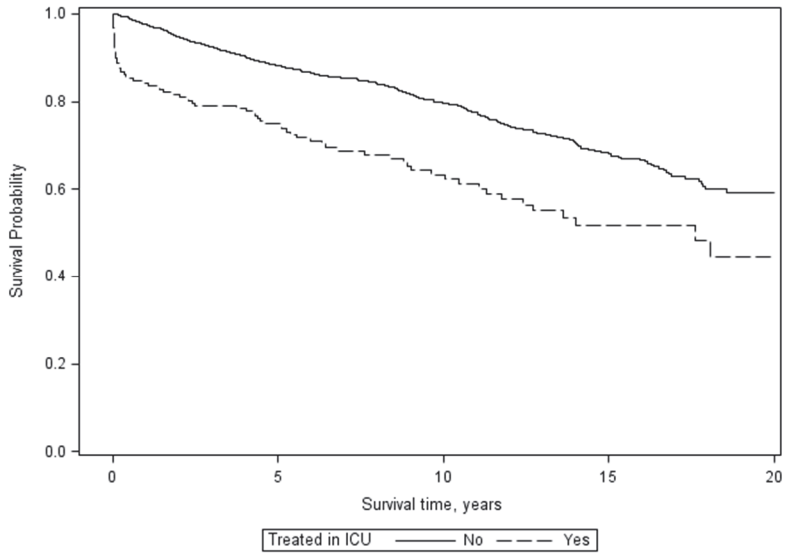


Fig. 12. Long-term survival in mild and severe AP.

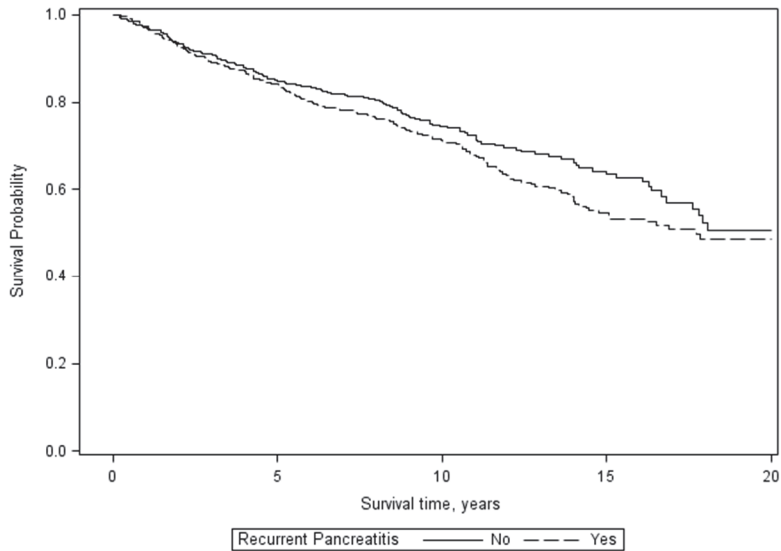


Fig. 13. Long-term survival of recurrent and nonrecurrent AP.

5.6.2 Causes of death (IV)

The cause of death was available in 99.7 % (397/398) of the study population and 98.7 % (512/519) of the control group. In nine cases (one in the study group and eight in the control group), the cause of death was lacking due to emigration. Autopsies were conducted in 259 of 398 (65.0 %) deceased individuals in the study group and 273 of 519 (52.6 %) deceased patients in the control group. The causes of death in the study population, control population and the AP aetiology subgroups are summarised in Table 10.

The main categories of causes of death differed significantly ($p < 0.001$) between the study and control groups and alcohol AP and nonalcohol AP patients ($p < 0.001$).

The most common cause of death in the study population was gastrointestinal disease, followed by cardiovascular and neoplastic diseases. AP comprised 59.1 % (65/110) of gastrointestinal diseases in the study group compared to 13.2 % (5/38) in the control group.

Mortality due to alcohol-related diseases (AP, poisoning and alcohol-related liver disease) was reported in 157/398 (39.4 %) patients in the AP study group and

in 154/359 (42.9 %) patients in the alcohol-related AP subgroup. Mortality due to alcohol-related diseases was only 87/519 (16.8 %) in the control population.

Pancreatic cancer was the most common cause of death (17.9 %, 7/39) in the non-alcohol-related AP subgroup, compared to 1.7 % (6/359) in the alcohol-related AP subgroup.

All except one patient in the non-alcohol-related AP group had tumour-induced AP pancreatitis. In the alcohol-related AP subgroup, 42.9 % (27/63) of deaths were related to recurrence.

Table 10. Causes of death in 1 644 patients (Study Group) treated for AP compared with the general population (control group). Study group has also been divided into subgroups (alcohol and nonalcohol AP).

Cause of death	Study group n = 1 644, n(%)	Control group n = 8 220, n(%)	Study group	
			Alcohol AP n = 1 173, n(%)	Nonalcohol AP n = 471, n(%)
All causes of death	398 (24.2)	519 (6.3)	359 (30.6)	39 (8.2)
Gastrointestinal	110 (27.6)	37 (7.1)	105 (29.2)	5 (12.8)
AP	65 (16.3)	5 (1.0)	63 (17.5)	2 (5.1)
Alcoholic liver disease	38 (9.6)	28 (5.4)	38 (10.6)	0 (0.0)
Cardiovascular	87 (21.9)	149 (28.7)	83 (23.1)	4 (10.3)
Ischemic heart disease	57 (14.3)	110 (21.2)	54 (15.0)	3 (7.7)
Other heart diseases	30 (7.59)	39 (7.5)	29 (8.1)	1 (2.6)
Neoplasm	58 (14.6)	137 (26.4)	39 (10.6)	20 (51.3)
Pancreatic cancer	13 (3.3)	20 (3.9)	6 (1.7)	7 (17.9)
Lung cancer	15 (3.8)	46 (8.9)	14 (3.9)	1 (2.6)
Poisoning	54 (13.6)	48 (9.2)	53 (14.8)	1 (2.6)
Trauma	52 (13.1)	54 (10.4)	50 (13.9)	2 (5.1)
Neurological	23 (5.8)	49 (9.4)	16 (4.5)	7 (17.9)
Respiratory	5 (1.3)	18 (3.5)	5 (1.4)	
Infection	2 (0.5)	3 (0.6)	2 (0.6)	
Other	6 (1.5)	17 (3.3)	6 (1.7)	
Unknown	1 (0.3)	7 (1.3)	1 (0.3)	

¹ Posture detection not applied in method, ND = not determined

6 Discussion

6.1 Main findings

The results of this study confirm that PFs are common in patients after a surgical necrosectomy and the diagnosis of a PF is challenging in infected situations. The results also confirm that ETPS is a good treatment for PFs after necrosectomy, but the prevention of pancreatic leaks with prophylactic ETPS in ANP seems to be harmful for patients. The long-term outcome of AP, particularly alcohol AP, was associated with high mortality.

This all indicates that for patients with infected ANP, a PF must be considered in the treatment, but the prevention of a ductal leak with prophylactic stenting cannot be recommended. In addition, long-term mortality among patients with AP (mainly alcohol-induced) was four times higher than within the age-and sex-matched control population.

6.2 PFs after necrosectomy (I)

This study showed that all 24 patients after surgical necrosectomy developed PFs. The population in this study included all consecutive patients after necrosectomy between 2009–2013. PFs were diagnosed according to international guidelines (Bassi et al., 2017) and fistulas were demonstrated in 92 % of the patients in ERP.

This result emphasises the importance to plan the optimal method to perform a necrosectomy. When considering a necrosectomy, a PF has to be considered. A necrosectomy itself might worsen the clinical condition by creating a PF. Therefore, for patients in need of a necrosectomy, it is not only the necrosis that needs to be removed but the treatment has to be targeted as well to possible pancreatic leaks associated with ANP (Larsen & Kozarek, 2016). In addition, PD disruption is commonly associated with central gland necrosis (Dhaka et al., 2018). The results of study I also support the current and preferred method to treat infected ANP. A minimally invasive transmural approach is a more than welcomed method to treat infected pancreatic necrosis because it also resolves the fistula problem associated with an open necrosectomy (Bakker et al., 2012; van Brunschot et al., 2018).

The present result is difficult to compare with other studies. In the settings of ANP, the literature often emphasises parenchymal necrosis and its consequences, such as WON, but studies on the PD disruptions associated with ANP are scarce

(Jang et al., 2016). Previous studies that have addressed this problem are limited by the heterogenous cohorts of patients with chronic pancreatitis, acute pancreatitis and post-surgical fistulas (Baron et al., 2002; Halttunen et al., 2005; Varadarajulu, Rana, & Bhasin, 2013).

There are only a few studies stressing the importance of PFs after necrosectomy in ANP (Bakker et al., 2011; Boerma et al., 2000; van Brunschot et al., 2018). However, the PF incidence post intervention for ANP in those studies cannot accurately detected, but it varies between 5–44 %.

In the retrospective study by Jagielski, Smoczynski and Adrych (2018), 226 patients with symptomatic WON after ANP was analysed. ERP was performed in 204/226 to assess the morphology and integrity of MPD and possible use of endoscopic treatment. In 164/204 (81.4 %), ERP showed a contrast flow outside the MPD, which is in comparable to our results.

6.3 Prophylactic pancreatic duct stenting (II)

In the present study, the main result was that PPDS in necrotizing pancreatitis is harmful. All patients with successful PPDS developed infected necrosis.

The theory behind the study was that the majority of patients with ANP will experience leakage from the disconnected pancreatic duct, resulting in intrapancreatic and/or peripancreatic fluid collections (Fischer, Gutman, Hughes, Trevino, & Behrns, 2014; Lau et al., 2001). Thus, it was reasonable to hypothesise that early PPDS placement might maintain PD continuity and thereafter decrease later morbidity (Kozarek, 2005).

The previous studies have shown the efficiency of rescue ERCP and placement of a small-calibre PD during the early course of PEP (Kerdsirichairat et al., 2014; Madacsy et al., 2009). However, necrotizing pancreatitis was not demonstrated in those studies before rescue ERCP and placement of a temporary small-calibre PD stent may offer sufficient drainage to reverse the process of AP (Dubravcsik et al., 2012; Freeman, 2016; Kerdsirichairat et al., 2014; Madacsy et al., 2009).

In addition, several randomised trials have shown that placement of a small-calibre pancreatic stent in patients at a high risk for post-ERCP pancreatitis is effective by reducing the risk development and severity of PEP (Freeman, 2016; Mazaki et al., 2014).

The difference from other studies is that prophylactic stenting has not been tested before in patients with ANP. There are speculations as to whether ERP is safe to perform in the early stage of pancreatitis and especially the risk of delivering

infection to sterile necrosis by early PPDS (Nadkarni, Kotwal, Sarr, & Swaroop Vege, 2015; Tenner, 2004). On the other hand, studies investigating the efficacy of pancreatic stent therapy has shown that changes in PD anatomy determine the major complications resulting from pancreatitis (Nealon et al., 2009; Telford et al., 2002). Lau et al. (2001) demonstrated that a PD leak should be looked for to direct treatment in patients with AP (Lau et al., 2001). Bridging stent placement is associated with successful outcomes in cases of partial ductal disruption (Larsen & Kozarek, 2014; Varadarajulu et al., 2013).

However, after interim analysis, study II was prematurely terminated due to prophylactic PD stenting in ANP being associated with an unacceptably high risk of pancreatic necrosis infection. In ANP proven on CT, the inflammation is in the late phase and already irreversible. It seems that we are well over the prophylactic and therapeutic window and on that stage PPDS seems to be harmful for the patients and should be avoided.

6.4 Success and safety of ETPS in ANP (I and II)

Performing a duodenoscopy and ETPS in critically ill patients, with necrotizing pancreatitis and concomitant duodenal and papillary oedema, pancreatic ductal leak or obstruction, may be technically challenging and may potentially worsen the clinical outcome (Bakker et al., 2011). ETPS was performed in studies I and II, but the success rate was quite different. In both studies, all patients suffered from ANP and were critically ill.

In study I, the primary ETPS was successful in 88 % of the cases, which is comparable with other studies (Das et al., 2016; Halttunen et al., 2005). In contrast, ETPS was achieved only in 45 % of the cases in study II.

The difference can be explained by the timing of endoscopic intervention. In study I, an endoscopy was performed well after the onset of the disease and a necrosectomy, whereas in study II intervention was performed as early as possible after admission. In study II, the failure rate of ETPS was much higher if an endoscopy was performed very early of the disease (under four days), whereas in the later course of the disease pancreatic cannulation became easier. In study II, the main obstacle to cannulation of PD was extreme duodenal oedema, which prevented access to duodenum and prevented visualisation of the major papilla. Even if cannulation was achieved, successful bridging stenting was achieved only in one fifth of patients due to inflammation and oedema. In study I, all endoscopies were performed in the period when inflammation and oedema have settled.

In study I, 17 out of 24 patients had DPDS and bridging stenting was only achieved in two patients. In most of the cases, the pancreatic stent (internal) reached into the necrosectomy (WON) cavity. However, all fistulas healed even after this kind of stenting. This result differs from previous findings (Das et al., 2016; Larsen & Kozarek, 2016; Telford et al., 2002). The main difference is that all patients in study I had AP and had undergone a surgical necrosectomy. It might be that internal drainage is the realistic goal in ETPS when treating fistulas after a necrosectomy.

Study I showed that ETPS is a safe procedure in the later course of the disease. None of the patients experienced any complications associated with ETPS if procedure was performed in the late phase of the disease after necrosectomy. The main complications were associated with stent occlusion and migration. This is in line with other studies (Cremer, Deviere, Delhaye, Baize, & Vandermeeren, 1991; Kawaguchi et al., 2015; Price et al., 2009). In study II, all patients experienced complications when ETPS was performed in the early stage of the disease.

6.5 Drain amylase analysis (III)

This study showed the insensitivity of drain amylase levels to diagnose POPF, which was confirmed by ERP. In study III, the sensitivity of single-drain amylase levels for detecting POPF was 65 %, but by taking a serial measurement sensitivity approach approximating 100 %. Therefore, to diagnose POPF after necrosectomy, serial measurements are mandatory in diagnostics.

There are several potential explanations for this finding. In previous studies, the measurements of drain amylase contents were performed after elective and sterile pancreatic surgery (e.g. Whipple procedure), whereas in our study samples were taken after necrosectomy. All patients in this study had ERCP-proven POPF and the drained area was infected.

Pratt et al. (2009) described a term latent fistula after 405 consecutive Whipple operations; 107 patients (26 %) developed POPF and 56 of those were clinically relevant (grade B or C). 20 patients had latent fistulas (5 % of all resections, 19 % of all fistulas and 36 % of all clinically relevant fistulas) initially lacking amylase-rich effluent, but ultimately relevant (grades B or C) POPF.

Six days after the operation measured amylase activity was low (3–235 units/l), but the patients subsequently manifested clinically obvious POPF (abdominal pain, wound infection, radiographic evidence, sinister effluent, fever). After additional surgical or drainage of collections, subsequent amylase activity was markedly raised (median 18 270 IU/l, range 1 779–58 225 IU/l). This study demonstrated

that one third of patients had a latent clinically relevant PF. This finding is in line with our results. In both studies, the common factor for missed fistula was the presence of infection. Evident fistulas were typically sterile, whereas latent fistulas were twice as likely to be infected. It seems that biochemical analysis alone is not sufficient for diagnosing PFs (Pratt et al., 2009).

Study III also demonstrated that a longer distance from the drain to the origin of the leak increases the probability of a false-negative result. This finding is also in line with the study by Pratt et al. (2009), as during the primary elective operation (Whipple) the inserted drains were not necessarily close to the leak. Once a leak occurs and amylase-rich fluid is not drained, local fluid collection will develop probably close to the leak. When an additional drain was inserted to the collections, they were perhaps near the leak and therefore the measured amylase levels were high. Amylase-rich fluid dilution when the distance from the leak to the drain increases might also explain partly false-negative results.

Based on study III, achieving an accurate diagnosis of PFs in infected situation seems to be challenging and sometimes even impossible. This study also supports the current guidelines of treating infected necrosis. Based on the literature, a significant number of the patients with ANP have pancreatic leaks (Jang et al., 2016; Kozarek et al., 2000). Comparing different methods to perform a necrosectomy, the transluminal approach seems to limit the risk of occurrence of a pancreaticocutaneous fistula following traditional necrosectomy (Driedger et al., 2018). The outcome of the TENSION trial also supports a shift to the endoscopic step-up approach as the treatment preference in infected necrotizing pancreatitis, due to lower rate POPF compared to mini-invasive surgery (van Brunschot et al., 2018).

6.6 Long-term outcome and causes of death (IV)

This was the first study where the long-term outcome was compared with an age- and gender-matched control population, and it showed that long-term mortality among working-age patients with AP (24.2 %) was four times higher than that in control population during the approximately 10-year follow-up. The mortality in the alcohol AP subgroup was 30.6 %, whereas in the nonalcohol AP subgroup, mortality was comparable to controls. These results are difficult to compare with other studies because of major variations in follow-up times, outcomes and controls (Appelros & Borgstrom, 1999; Nojgaard, 2010; Yadav et al., 2012). The reported mortality has varied between 4 % and 83 % during follow-up times of four to 30

years. Mortality rates are rarely evaluated in comparison to the general population; instead, studies usually report the number of cases of AP treated at a certain hospital (Lankisch et al., 2009; Lund, Tonnesen, Tonnesen, & Olsen, 2006; Nojgaard et al., 2011).

RAP occurred in nearly half of the patients with alcohol AP, but rarely among patients with nonalcohol AP. RAP has been considered a relatively benign disease with low mortality (Appelros & Borgstrom, 1999; Appelros et al., 2001; Lund et al., 2006). However, the study IV also showed that AP was the most important cause of deaths in the study group and nearly half of the deaths were related to RAP during the approximately 10-year follow-up. The result conflicted the above-mentioned view of RAP as a relatively benign condition.

The study also showed that during the 10-year follow-up, patients with severe AP had high mortality compared to patients with mild AP, but after the first few months, the difference between the groups did not increase. However, the overall survival after an alcohol AP and especially after severe AP was dismal. The long-term survival (10 year) among patients with severe AP was about the same as survival among the patients with colorectal cancer (Klint et al., 2010; Morris et al., 2011).

The difference in the causes of death between patients with alcohol AP and controls differed significantly in this study. Alcohol-related liver diseases, pancreatitis and poisoning accounted for more than one-third of the deaths. About half of trauma-related deaths and suicides are influenced by alcohol according to a recent Finnish study (Raatinemi et al., 2016). In addition, alcohol consumption has been a significant risk factor for several cancers (Bagnardi, Blangiardo, La Vecchia, & Corrao, 2001). All these findings support the hypothesis that the high rate of deaths in this study was fully or partly caused by alcohol. In previous studies, poor long-term outcome of AP has been associated with age, alcohol abuse, male sex and unemployment (Appelros et al., 2001; Nojgaard et al., 2011), but exact causes of death are largely unknown.

All this indicates that alcohol consumption seems to be the most important risk factor that affects the long-term outcome in patients with alcohol AP. A study by Nordback et al. showed a decreased rate of RAP after a multiple-intervention program (Nordback et al., 2009). In this view, there is a great demand for prophylactic therapeutic implementations to improve long-term outcomes.

6.7 Clinical impact and generalisability of the results

ANP with infected necrotic tissue is a very complex disease associated with a high rate of complications and death. This disease is difficult to treat and is often associated with poor outcomes (Rosenberg, Steensma, & Napolitano, 2015). The challenge is not only infected necrosis, but also PD leaks are often associated with the disease (Larsen & Kozarek, 2016).

Our current studies have several clinical impacts and some can be generalised in daily practise. First, the study showed that patients with ANP do not benefit from early PPDS; instead, it seems to be harmful for them. Second, the study showed that after a surgical necrosectomy, the majority or even all patients develop a PF, and the third point is that diagnosing pancreatic leak after necrosectomy in infected situations is difficult and sometimes even impossible. Therefore, when considering a necrosectomy, a possible PF must be taken into consideration. The target of treatment-infected necrosis must be focused on the control of infection, the removal of infected necrosis with mini-invasive method and manage the possible PD leak. This requires a multi-disciplinary treatment strategy individualised for each patient. The fourth statement is that for patients with PFs after surgical necrosectomy, ETPS is a safe and effective treatment.

Finally, to improve the long-term outcome especially in patients with alcohol AP, prophylactic therapeutic intervention needs to be undertaken. It is also notable that, after the first hospitalisation in patients with severe AP, the long-term survival trend seems to be equal to patients with mild AP. Therefore, aiming the effort on secondary prevention is essential to improve outcome in all patients after alcohol AP.

6.8 Strengths and limitations of the study

Study I

The strength of this study is the prospective setting and homogenous group of patients. Between 2009 and 2013, for all consecutive patients with SAP and a necrosectomy, ETPS was performed prospectively. In previous studies, the results of ETPS for PF have been reported in very heterogenous groups of patients including patients with a PF after trauma, surgery after pancreatic tumour and CP (Bakker et al., 2011; Halttunen et al., 2005).

The shortcoming of this study was the lack of a conservative control group. There was also wide variation in the timing of ETS after pancreatic necrosectomy. The median fistula closure time was overestimated, as the control interval was long and in many cases the fistula had closed before the next control visit.

Study II

Study II was novel and clinically meaningful; PPDS seems to be harmful for patients with ANP and therefore should be avoided. In addition, PD stenting in such patients is challenging due to oedema. Our approach was also exceptional and to the best of our knowledge, a similar approach has not been used before. The prospective randomised control design can also be considered a strength of this study.

The limitation of the study was the small number of patients. Due to this, the conclusion can be expressed as exploratory rather than confirmatory. However, continuing the study after interim analysis was regarded as unethical.

Study III

The method to test accuracy of drain amylase levels to detect POPF after necrosectomy was exceptional. The classification of POPF is based on studies where the amylase activity has been compared to clinical condition after surgical resection. To our knowledge, the studies of drain amylase levels in relation to direct evidence of POPF seen in pancreatography with ERP are absent. In addition, the majority of the studies on the definition and grading of POPF are based on elective and sterile pancreatic surgery, but the literature on POPF after necrosectomy with infected APN is scant.

This study has limitations. First, there was a small number of patients and a relatively small number of samples analysed and a retrospective design. Second, we were not able to locate the inserted drains with 100 % accuracy. However, these results reflect the actual clinical situation and therefore the present results can be generalised in daily surgical practice.

Study IV

In the literature, long-term mortality is typically described in terms of case/cohort mortality, which limits their ability compare mortality with non-AP pancreatitis and

other studies (Appelros & Borgstrom, 1999; Nojgaard, 2010; Yadav et al., 2012). This study used age-and sex-matched controls from the general population to examine differences in causes of death and mortality. To our knowledge, this method has not been used before to report the long-term outcome in AP. In addition, the high autopsy rate (greater than 50 %) increased the reliability of the causes of death. There is always a possibility of errors in the registry data. The high number of patients limits the effect of possible errors in the results.

The limitation of this study is the retrospective design. On the other hand, a prospective setting with this number of patients is nearly impossible. The data on this study did not include reports of alcohol consumption levels for all patients and any data on the potential termination of alcohol use during follow-up.

6.9 Further studies and thoughts

In recent years, the minimally invasive surgical necrosectomy has gained popularity and is gradually replacing the open surgical necrosectomy. The endoscopic approach is gaining popularity due to its simplicity and causing less surgical trauma for patients. However, data on the ideal method of performing a necrosectomy in patients with large and infected solid necrosis is limited, and those cases are the most challenging and expensive to treat. This area needs more information and research.

In addition, it seems that whatever the method to perform a necrosectomy, patients often need multiple procedures, which increases complication rate, LOS and costs. Now, the endoscopic transluminal approach is a fairly easy method to reach the necrotic area. One of the main obstacles in these cases is the lack of ideal instrumentation, which is an interesting field of further studies.

The population of study IV was limited to working-age patients. But it also would be beneficial to investigate the long-term survival among elderly patients after the first episode of AP. The aetiology of AP and the causes of death might differ from working-age patients, but not necessarily from the age- and sex-matched controls.

Study IV showed poor long-term results among alcoholic AP patients. This is in line with the finding of the mortality registry of Statistics Finland (2007): the most common cause of death among the working age population in Finland is alcohol-related diseases (Tilastokeskus 2008). It is well known that the treatment of alcohol-related diseases is very challenging. In addition, society has changed considerably in recent decades. In the past, the responsibility of your own well-

being was based mainly on one's own activity. It seems that this responsibility has been shifted on the shoulders of society. In clinical practice, we can see more and more young patients with alcohol AP without vision and hope for the future. Do we actually recognise these patients or do we just close our eyes to such problems?

Our country puts significant effort into the healthcare system. Interestingly, there are clear guidelines on how to treat e.g. gallstone pancreatitis or how to follow up with patients who have undergone an operation for colorectal cancer. In cases of alcohol AP, do we just offer sick leave or medication without proper intervention to reduce alcohol consumption and alter drinking habits? I keep asking myself: Are we as doctors opening doors that are not good for the patients and thereafter for our country? Will the western world reach its limits?

Seventy years ago, after the second world war our fathers and grandfathers came home from the battlefield and they were badly hurt, internally and externally. They were not offered money, sick leave, retirement or even any kind of therapy. Our poor country had mainly two things to offer: work and hope for a better future. How did they survive? The story is a miracle. They built up a new country with all this welfare and prosperity, and they survived. I am sure that they lived through those historic and meaningful words that President Kennedy pronounced in his inauguration in 1961:

'Ask not what your country can do for you – ask what you can do for your country'.

However, after all is said and done, we all will face the truth:

'Today I am giving you a choice. You can choose life and success or death and disaster. Choose life'. (5. Moos. 30: 15, 19)

7 Conclusions

1. All the patients developed a PF after surgical necrosectomy.
2. ETPS is an effective and safe treatment for fistulas after necrosectomy.
3. Early PPDS may be harmful for the patients with ANP.
4. To diagnose POPF after necrosectomy, a serial drain amylase level measurement is recommended in diagnostics.
5. Patients with alcohol AP have a high mortality rate in long-term follow-up. Half of the deaths in AP are associated with alcohol abuse.

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Original publications

- I Karjula, H., Saarela, A., Vaarala, A., Niemelä, J., Mäkelä, J. (2015). Endoscopic transpapillary stenting for pancreatic fistulas after necrosectomy with necrotizing pancreatitis. *Surgical Endoscopy*, 29(1), 108–112. <https://doi.org/10.1007/s00464-014-3645-0>
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- III Karjula, H., Saarela, A., Mäkelä, J., Liisanantti, J. H.; Does drainage fluid amylase reflect pancreatic ductal leakage after necrosectomy? Manuscript submitted.
- IV Karjula, H., Saarela, A., Ohtonen, P., Ala-Kokko, T., Mäkelä, J., Liisanantti, J. H. (2019). Long-term Outcome and Causes of Death for Working-age Patients Hospitalized Due to Acute Pancreatitis With a Median Follow-up of 10 Years. *Annals of Surgery*, 269(5), 932–936. <https://doi.org/10.1097/SLA.0000000000002612>

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