Acute pancreatitis - severity classification, complications and outcome

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ACUTE PANCREATITIS

Severity Classification, Complications and Outcome

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This thesis is dedicated to my family

"Everything should be made as simple as possible, but not simpler."
Albert Einstein

Contents

List of publications

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

I. Andersson B, Olin H, Eckerwall G, Andersson R. Severe acute pancreatitis – outcome following a primarily non-surgical regime. Pancreatology 2006;6:536-541.

II. Andersson B, Andersson R, Ohlsson M, Nilsson J. Prediction of severe acute pancreatitis at admission to hospital using artificial neural networks. Submitted.

III. Andersson B, Nilsson E, Willner J, Andersson R. Treatment and outcome in pancreatic pseudocysts. Scand J Gastroenterol 2006;41:751-756.

IV. Andersson B, Andrén-Sandberg Å, Andersson R. Survey of the management of pancreatic pseudocysts in Sweden. Scand J Gastroenterol 2009;44:1252-1258.

V. Andersson B, Pendse M-L, Andersson R. Pancreatic function, quality of life and costs long-term after acute pancreatitis. Submitted.

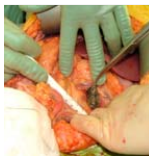
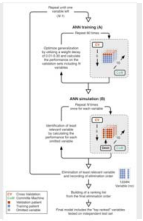
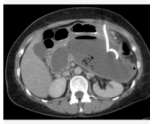
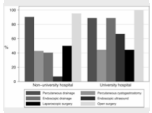
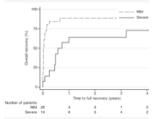
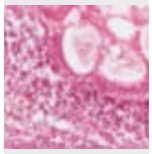
VI. Andersson B, Ansari D, Andersson E, Persson S, Anderson R. Fatal acute pancreatitis occurring outside the hospital – clinical and social characteristics. Submitted.

Summary

Acute pancreatitis, with an annual incidence of approximately 35 per 100 000 inhabitants in Sweden, is in most cases mild and self-limiting. Severe acute pancreatitis, affecting 10-15% of the cases is, however, associated with severe complications and even death. The optimal management of acute pancreatitis includes accurate early prediction of the disease severity. The aims of this thesis were to investigate early severity classification, complications and outcome in acute pancreatitis patients, with special regard to patients developing the severe form of the disease.

The results of the studies were: I) Two early risk factors for death were identified: increasing age and hypotension at admission. Deaths were to a high extent related to multiple organ dysfunction. Early recurrence after biliary acute pancreatitis was common. II) A model for early prediction of severity in acute pancreatitis with artificial neural networks was developed, identifying 6 risk factors. The ROC area for the model was 0.92, and it performed significantly better than the APACHE II score. III) Patients with pancreatic pseudocysts were found to be resource demanding in regard to recurrences and repeated hospital visits. Even larger pancreatic pseudocysts could be managed successfully with conservative treatment. IV) In a national Swedish survey, the treatment of patients with pancreatic pseudocysts appeared to be heterogeneous, with different treatment options available and varying local traditions. V) In long-term follow-up after acute pancreatitis, impairment was mainly seen in the endocrine pancreatic function, and especially after severe disease. The time to rehabilitation and return to work and normal life was long, and the costs for the society high. The quality of life years after the disease was, however, as good as in the normal population. VI) A survey of patients dying in acute pancreatitis without reaching the hospital showed that this group represents a substantial part of all deaths from the disease. The dominating aetiology was alcohol. Pulmonary injury was the most common organ manifestation outside the pancreas. To reduce mortality due to acute pancreatitis it is important to target also the patients that never reach hospital.

Thesis at a glance

	Question	Patients and Methods	Results		Conclusion
I	What is the outcome in SAP, and can risk factors for death be identified?	175 patients with SAP selected from 839 patients, 1994-2003.	Pancreatic surgery was performed in 14 patients (8%). Sixteen (9%) died during the hospital stay, 14 (88%) due to MODS.		Age and hypotension (systolic blood pressure <100 mm Hg) are predictive factors for death.
II	Can an ANN model predict severity in AP at admission to hospital?	Constructed on 139 patients, 2002-2005. Validated on 61 patients, 2007-2009. A five-fold cross-validated feed-forward ANN was created and trained.	The discriminatory power for the progression to a severe course, determined from the ROC curve, was 0.92 for the ANN, 0.84 for LR, and 0.63 for APACHE II.		Six risk variables available at admission were identified. A model with superior severity classification compared to APACHE II was achieved.
III	What is the efficacy and outcome concerning pancreatic pseudocysts, regarding treatment regimes and pseudocyst size?	Forty-four patients with pancreatic pseudocyst, 1994-2003.	Recurrence was seen in 1 instance (0-4) and repeated hospital admissions 3 times (0-16). LOS was 12 (0-141) days. Six patients (14%) had complications. Three (7%) died due to the disease.		Least risk of recurrence was noted after surgery. Larger (> 8 cm) pseudocysts do not imply a higher recurrences risk.
IV	How are pancreatic pseudocysts managed in Sweden today?	Questionnaire to all surgical departments; 51/58 (88%) answered.	Four (0-25) patients per hospital are treated annually. Endoscopic drainage is more common in university hospitals.		Heterogeneity in the choice of treatment was seen. Multidisciplinary team conferences and a tailored therapeutic approach are suggested.
V	Is the pancreatic function and quality of life impaired in the long-term after AP and SAP? What are the hospital costs?	Forty patients were followed-up after 42 (36-53) months. Laboratory tests, OGTT, a questionnaire and quality of life (SF-36) were evaluated.	DM or IGT were more common after SAP (11/14 versus 11/25). Sick leave and time to recovery were longer after SAP and hospital costs were higher.		Impairment in endocrine pancreatic function, especially after SAP was seen. QOL was as good as in an age- and gender-matched reference population, even after severe disease.
VI	Can patients dying from AP outside hospital be characterized regarding the incidence and medical and social conditions?	Fifty patients from the department of forensic medicine 1994-2008.	50/292 of all deaths due to AP in the region. Alcohol was the most common aetiology and pulmonary changes were common.		This group represents a substantial part of all deaths in AP. The incidence seems to decline. Patients were often in a vulnerable social situation.

Populärvetenskaplig sammanfattning

(Summary in Swedish)

Akut bukspottkörtelinflammation är en sjukdom som drabbar ungefär 35 per 100 000 invånare i Sverige årligen. Förloppet innebär i flertalet fall ett komplikationsfritt tillfrisknande. Cirka 20% drabbas dock av en allvarlig form som kräver stora sjukvårdsresurser och innebär avsevärd sjuklighet, inkluderande risk för vävnadsdöd i bukspottkörteln, lokala och spridda infektioner, ansamlingar av var i bukhålan, svikt av ett eller flera vitala organ, bildning av ”falska” cystor och även död (i närmare 20% av de svårt sjuka patienterna). Dödsfall i det tidiga förloppet (första veckan) är främst förknippade med svikt i ett eller flera organ. Senare dödsfall beror även på detta, men ofta med tillägg av infektion eller blodförgiftning, främst beroende på infektionshärdar i områdena med vävnadsdöd. Sjukdomen ses företrädelsevis hos vuxna men förekommer i alla åldrar och hos båda könen. De bakomliggande orsakerna till insjuknandet domineras av förekomst av gallsten eller alkoholintag (80-90%).

En förändring av handläggningen av svår sjukdom har skett över tiden, till en mer konservativ, organunderstödjande och icke kirurgisk attityd. Tidig uttalad vätskebehandling kan minska effekterna av otillräckligt blodflöde till vävnaden (ischemi) och vävnadsskada i samband med blodåterflöde (reperfusionsskada). Eventuell kirurgi riktat mot bukspottkörtelinflammationen kommer sent i förloppet. Att operativt avlägsna gallstenar när de gett upphov till bukspottkörtelinflammationen är däremot viktigt, då risken för återfall annars är stor. Detta skall göras under eller i omedelbar anslutning till det akuta vårdtillfället, med individuell bedömning av tidpunkten för kirurgi efter svår sjukdom samt hos multisjuka patienter.

Tidig bedömning av svårighetsgraden av bukspottkörtel-inflammationen för varje patient är väsentlig för att kunna sätta in snabb och korrekt understödjande behandling. Trots att det första riskbedömningssystemet publicerades redan 1974 (Ranson kriterierna) och att det sedan dess presenterats en uppsjö av morfologiska

markörer, laboratorieparametrar, samt riskbedömningsmodeller (såväl specifika för akut bukspottkörtelinflammation som mer generella), saknas ännu ett riktigt bra system. Det är fortfarande svårt att bedöma den enskilda patientens risk; flera av systemen inkluderar många parametrar och är därmed tidsödande att använda, och framförallt finns inget specifikt etablerat system som kan användas redan vid patientens ankomst till sjukhuset. En modell för tidig förutsägning av sjukdomens svårighetsgrad är artificiella neurala nätverk, en form av ”artificiell intelligens” som utnyttjar avancerad datorteknologi.

”Falska” cystbildningar, så kallade pseudocystor, är den vanligaste komplikationen efter svår sjukdom och diagnosticeras i 10-15% av patienter med genomgången akut bukspottkörtelinflammation. Symtomen beror på läge och storlek. En mer avvaktande behandlingsattityd har i takt med radiologins utveckling visat sig möjlig och flera olika behandlingsmodaliteter är idag tillgängliga. Svår och lätt akut bukspottkörtelinflammation skiljer sig inte bara åt under den akuta sjukdomsperioden, utan också i uppföljningen och återhämtningen.

Slutligen dör en del patienter i akut bukspottkörtelinflammation utan att ha sökt sjukhusvård. Denna grupp är viktig att identifiera då den utgör en betydande del av det totala dödstalet i sjukdomen.

I delarbete I gjordes en retrospektiv genomgång av 175 patienter som klassificerats som drabbade av moderat till svår akut bukspottkörtelsjukdom, från en ursprunglig grupp av 839 fall. Resultaten visade på en låg operationsfrekvens (8%) och mortalitet (9%). Hälften av dödsfallen inträffade under första veckan, och av dessa var 14/16 associerade med multipel organsvikt. Av registrerade inkomstparametrar var ålder och lågt blodtyck (hypotoni, definierat som systoliskt blodtryck <100 mmHg) riskfaktorer för död. Inom tre månader drabbades 24% av de med akut bukspottkörtelsjukdom förorsakad av gallsten av återfall i sjukdomen, vilket understryker vikten av adekvat åtgärd av gallstenssjukdomen.

I delarbete II utvecklades en algoritm för prognostisering av svårighetsgraden för akut bukspottkörtelinflammation med hjälp av artificiella neurala nätverk (ANN). ANN är en avancerad datoriserad optimeringsmodell som inspirerats av den mänskliga hjärnas funktion och som kan användas inom medicinen för analys av komplexa

samband. Riskfaktorer som är tillgängliga redan vid ankomst till sjukhus och som bidrar till svårighetsgraden i akut bukspottkörtelinflammation identifierades och rangordnades. En modell togs fram som hade en bättre prediktion än den hittills ofta använda modellen APACHE II, och som även var bättre än en linjär regressionsmodell.

I delarbete III kartlades alla patienter som diagnosticerats med pseudocystor i bukspottkörteln i Lund under en tioårsperiod. Totalt rörde det sig om 44 patienter och totalt 88 behandlingstillfällen. I resultaten noterades att gruppen var resurskrävande, med en stor risk för återfall. Ingen skillnad sågs avseende återfallsfrekvensen eller pseudocyststorleken när man jämförde konservativt behandlade patienter mot interventionellt åtgärdade. Större pseudocystor (≥ 8 cm) skilde sig inte avseende behandlingsval, vårdtid och återfall från mindre pseudocystor. Det fanns dock en tendens till mer komplikationer.

I delarbete IV undersöktes aktuellt nationellt omhändertagande av pseudocystor i bukspottkörteln, med hjälp av en enkätstudie riktad till Sveriges kirurgiska kliniker. Svarsfrekvensen var 88%. Val av behandlingsmodalitet skiljde sig mellan sjukhusen. Tydligast noterades detta för endoskopisk dränering, som var vanligare vid universitetssjukhusen för symtomatiska såväl icke-infekterade som infekterade pseudocystor. Bristen på evidens speglar heterogeniciteten i behandlingsvalen, som till stor del förefaller styras av lokala behandlingstraditioner och tillgång till specifika resurser. Ett nationellt vårdprogram skulle vara av värde.

I delarbete V efterforskade vi genom en noggrann uppföljning av 40 patienter deras tillstånd flera år efter sjukdomsepisoden med genomgången svår respektive mild akut bukspottkörtelinflammation, gällande såväl bukspottkörtelns funktion, olika aspekter på återhämtningen, samt livskvaliteten. Resultaten visar på en påverkan av bukspottkörtelfunktionen, framförallt den endokrina, med hög frekvens av diabetesutveckling i gruppen med genomgången svår bukspottkörtelinflammation. Återhämtningen var lång hos flera, och några personer från båda grupperna kände sig vid uppföljningen ännu inte helt återställda. Sjukhuskostnaderna associerade med den akuta bukspottkörtelinflammationen var höga. Livskvalitén var däremot lika

god som hos en matchad kontrollgrupp vid uppföljningen även efter svår sjukdom, vilket är en viktig information att sprida för att inge hopp till patienter och anhöriga när de går igenom den krävande sjukdomsperioden och rehabiliteringen.

I delarbete VI kartlade vi patienter som dör i sjukdomen, utan att varit i kontakt med någon vårdinrättning. Dessa patienter utgör en betydande del av de som dör av sjukdomen, i denna genomgång uppgick de till 17% av totala dödstalet i bukspottkörtelinflammation i aktuell region. Från det studerade rättsmedicinska materialet framgick det att lungskada var den vanligaste organskadan utanför bukspottkörteln. En överrepresentation av män noterades, flertalet överkonsumerade alkohol och detta bedömdes också vara den dominerande orsaken till sjukdomen. Flera hade psykisk sjukdom och vid genomgång av tillgängliga handlingar visade sig många vara socialt utsatta och ensamma. Några var hemlösa, andra levde i eget boende under miserabla yttre omständligheter. Ett fåtal hade välordnade förhållanden.

Sammanfattningsvis visar denna avhandling att både svårighetsklassificering och identifiering av riskfaktorer för död är möjliga redan vid patientens ankomst till sjukhuset. Förbättring i behandlingen av patienter med pseudocystor i bukspottkörteln föreslås. Även patienter med svår akut bukspottkörtelsjukdom har en god livskvalitet vid långtidsuppföljning. Det är väsentligt att försöka identifiera även de patienter som dör i akut bukspottkörtel-inflammation utan att ha sökt sjukhusvård, då gruppen utgör en betydande del av totala dödstalet i sjukdomen.

Abbreviations

ALAT	alanine aminotransferase
ALP	alkaline phosphatase
ANN	artificial neural network
AP	acute pancreatitis
APACHE II	acute physiology and chronic health evaluation II
ASA	American Society of Anesthesiologists
ASAT	aspartate aminotransferase
BMI	body mass index
CAPAP	procarboxypeptidase B activation peptide
CARS	compensatory acute response syndrome
CI	confidence interval
CRP	C-reactive protein
CT	computed tomography
DM	diabetes mellitus
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
GGT	gamma-glutamyltransferase
Hb	haemoglobin
HbA1C	glycosylated haemoglobin A1c
HOMA-IR	homeostasis model assessment – insulin resistance
ICD	International Classification of Diseases
ICU	intensive care unit
IGT	impaired glucose tolerance
K	potassium
LOS	length of stay

MODS	multiple organ dysfunction syndrome
MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreatography
N/A	not available
Na	sodium
OGTT	oral glucose tolerance test
ROC	receiver operating characteristic
SaO_2	saturation level of oxygen
SAP	severe acute pancreatitis
SD	standard deviation
SF-36	standard short form 36
SIRS	systemic inflammatory response syndrome
SOFA	sepsis-related organ failure assessment
TAP	trypsinogen activation peptide
UK	United Kingdom
US	ultrasonography
VAS	visual analogue scale
WBC	white blood cell count
WHO	World Health Organization
QOL	quality of life

Chapter 1

Introduction

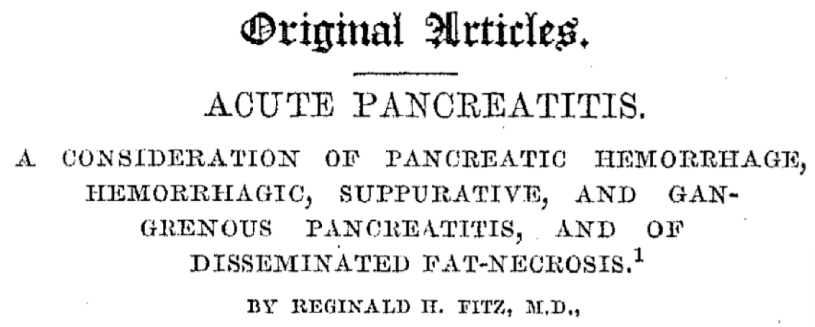
> "Acute pancreatitis is the most terrible of all the calamities that occur in connection with the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it, all render it the most formidable of catastrophes"
>
> Lord Moynihan, 1925

1.1 Historical notes

Did Alexander the Great die of acute pancreatitis? This theory has been suggested in a recent publication[1]. True or not, history offers many examples of disorders that might have been acute pancreatitis. Nicolaes Tulp (1593-1674), a Dutch physician and anatomist, published in 1652 the first clear description of acute pancreatitis.

Reginald Huber Fitz (1843-1913), an American pathologist and professor at Harvard Medical School, who had studied in Berlin under Rudolf Virchow, presented the first systematic analysis of acute pancreatitis in 1889 with the title "Acute pancreatitis: a consideration of pancreatic haemorrhage, hemorrhagic, suppurative and gangrenous pancreatitis, and of disseminated fat-necrosis"[2], with detailed clinical characteristics of fifty-three patients (Figure 1.1). Fitz's systematic clinical and bedside observations lead him to proclaim "an operation … in the early stages of this disease, is extremely hazardous". Fitz subsequently abandoned this conservative stance, and in 1903 he proposed "in cases of acute pancreatitis … laparotomy in an increasing number of cases has proven the most satisfactory method of treatment, and, like most abdominal operations for the relief of

acute symptoms, is the more helpful the earlier in the course of the disease it is performed". During the 20th century there have been different theories and trends concerning whether surgery or conservative treatment is to prefer. In the 1930s there was a change to a more conservative approach due to observations of high mortality rates after surgical interventions. During the 1960s and 1970s surgery again generally became more popular, including blunt necrosectomy for necrotizing pancreatitis.



Original Articles.

ACUTE PANCREATITIS.

A CONSIDERATION OF PANCREATIC HEMORRHAGE, HEMORRHAGIC, SUPPURATIVE, AND GANGRENOUS PANCREATITIS, AND OF DISSEMINATED FAT-NECROSIS.[1]

BY REGINALD H. FITZ, M.D.,

Figure 1.1. Title page of Dr Fitz's initial paper on pancreatitis, published on February 21, 1889 in the Boston Medical and Surgical Journal[2].

Fitz was mistaken concerning the underlying pathophysiological cause of acute pancreatitis. Hans Chiari (1851-1916), Professor of pathology in Prague, postulated only a few years later, in 1896, that the mechanism of the disease was pancreatic autodigestion, meaning that the pancreas "succumbs to its own digestive properties".

Giovanni Battista Morgagni (1682-1771), the Italian anatomist celebrated as the father of the modern anatomical pathology, made the first description of pancreatic pseudocysts in 1761. The first surgical treatment of a pancreatic cyst, probably a pseudocyst, was performed in 1862 with punction and drainage. Rudolf Jedlicka (1869-1926) from Bohemia performed in 1921 internal drainage with cystogastrostomy. Until the 1980s open surgery with internal drainage continued to represent the principal treatment for pancreatic pseudocysts.

Claude Bernard (1813-1878), the French physiologist, demonstrated the power of pancreatic secretion in the digestion of protein, carbohydrates and fat. Bernard concluded: "The presence of fat (in stool) is pathognomonic of the failure of pancreatic juice to reach the intestine". This was the starting shot for pancreatic exocrine replacement therapy.

Even if the history of research concerning acute pancreatitis and its complications is long and successful, many issues still remain to be discovered and developed.

1.2 The natural course of acute pancreatitis

Acute pancreatitis is an inflammatory process of the pancreas, with variable involvement of peripancreatic tissues and remote organ systems. In 80% of the cases the disease is mild, with interstitial oedema, and leads to recovery within days or weeks[3, 4]. Severe forms, characterized by local or systemic complications, may on the other hand be very demanding and are associated with severe morbidity and even death, in up to 15-20%[4, 5]. Early deaths, within the first week, are due to persistent systemic inflammatory response syndrome (SIRS), including pyrexia, tachycardia, tachypnea and leucocytosis, with subsequent single or multiple organ dysfunction. Late mortality is usually a consequence of organ dysfunction and local or systemic infections, including infected pancreatic necrosis[6].

Acute onset of upper abdominal pain with radiation to the back, nausea and vomiting, local peritonitis located in the epigastrium and sometimes an effect on the circulatory system, in combination with elevated pancreatic enzymes in blood or urine, are the typical findings in acute pancreatitis. Upper abdominal pain is, however, characteristic of several other acute disorders such as gastric and duodenal ulcers, cholecystitis, cholangitis, ruptured aortic aneurysm, ileus, and even pneumonia and myocardial infarction. Even if elevated serum pancreatic amylase has a high sensitivity and specificity for acute pancreatitis, a slight rise in serum pancreatic amylase can be seen in the other abdominal conditions mentioned. A rise to a level >3 times the expected is however not always seen in acute pancreatitis, e.g. due

to a duration of the acute pancreatitis >48 hours, hypertriglyceridemia, or depleted acinar cell mass[7]. Increased serum lipase may be preferable for diagnosis because it remains normal in some nonpancreatic conditions that increase serum amylase, including macroamylasemia. The level of lipase also remains increased longer than that of serum pancreatic amylase[8].

The often-mentioned signs of Cullen (periumbilical bruising) and Grey-Turner (flank bruising) are rare[9], and may arise in any disease that causes retroperitoneal haemorrhage. Diagnosis of acute pancreatitis can be difficult, shown by the large number of cases diagnosed first at autopsy[10].

The incidence of acute pancreatitis varies between geographic regions, mostly due to different frequencies of gallstone disease and alcohol consumption, and is approximately up to 30-35 per 100 000 inhabitants annually in Sweden[11, 12]. Reports from many countries have suggested a tendency to an increasing incidence of acute pancreatitis over the past decades, including in a Swedish population[13, 14]. Despite an increase in the incidence of acute pancreatitis, the total mortality seems to be stable, due to a downward trend in case-fatality[15].

The most important aetiological factors for acute pancreatitis are either biliary tract stone disease or alcohol, which account for approximately 75-80% of all cases of acute pancreatitis[16]. Other causes are infrequent and include a variety of infections, hypertriglyceridaemia, hypercalcaemia, hypothermia, pancreatic and ampullary tumours, exposure to a variety of pancreatotoxic drugs and hereditary pancreatitis. Acute pancreatitis can also be a consequence of trauma (including iatrogenic damage such as abdominal surgery and ERCP)[17]. Cases without an obvious cause are referred to as idiopathic and should account for less than 20% of all cases, according to guidelines[18].

Even if chest X-ray and abdominal plain X-ray may show indirect signs of acute pancreatitis, such as pleural effusion and the "colon cut-off sign", the current golden standard for prediction of severity, detection of complications, follow-up, but also for diagnosis in unclear cases, is computed tomography (CT)[19]. Diagnostic CT signs include pancreatic swelling, peripancreatic infiltrates, peripancreatic fluid collections, and areas of nonenancement of the pancreas (Figure

1.2). Ultrasonography (US) plays no role in the diagnosis or staging, but is useful in the determination of gallstone aetiology by demonstration of stones in the gallbladder or common bile duct dilatation[20], and in the follow-up of pancreatic pseudocysts. Magnetic resonance imaging (MRI) is not as established and not that frequently used, but carries the ability to predict severity and outcome, and has an advantage over CT in the ability to detect bile duct lithiasis and pancreatic hemorrhage[21]. Magnetic resonance cholangio-pancreatography (MRCP) is a non-invasive alternative to diagnostic ERCP.

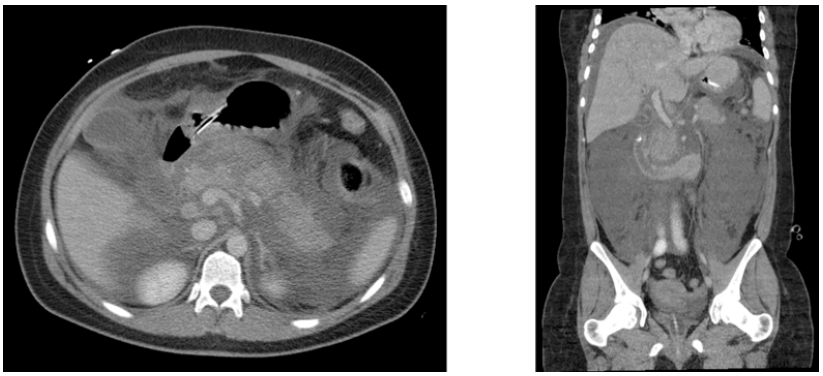


Figure 1.2. Computed tomography of a patient with severe acute necrotizing pancreatitis. There are signs of partly absent perfusion of the pancreas, especially in the head and body. Pronounced peripancreatic and retroperioneal edema and fluid collections.

1.3 The human pancreas and the development of acute pancreatitis

The human pancreas is located retroperitoneally in the upper abdomen, behind and below the stomach, and is connected to the intestinal tract by the duct of Wirsung, the major pancreatic duct. This joins the common bile duct prior to the ampulla of Vater, after which the common duct perforates the medial side of the second portion of the duodenum at the major duodenal papilla[22]. In order to understand different courses in acute pancreatitis and the development of

complications knowledge of pancreatic physiology and pathophysiology is essential.

1.3.1 Physiology

The human pancreas consists of two parts, the exocrine and the endocrine pancreas. The exocrine part consists of acinar and ductal cells, and comprises approximately 85% of the mass of the pancreas. The acinar cells produce proteolytic enzymes, lipolytic enzymes, amylolytic enzymes and nucleases needed for digestion of food. The digestive enzymes are secreted as inactive proenzymes including trypsinogen, chymotrypsinogen, proelastase, phospholipase A_2 and procarboxypeptidase A and B[22, 23]. Lipase and amylase alone require no activation and do not appear to have the capability of damaging pancreatic tissue. In health, enterokinase in the duodenum activates trypsinogen to trypsin, and the trypsinogen activation peptide (TAP) is cleaved off. Trypsin itself has the capability of activating trypsinogen, but is more effective in activating proteolytic enzymes and phospholipases, yielding active proteases as well as corresponding activation peptides, such as procarboxypeptidase B activation peptide (CAPAP). Protease inhibitors located in the intestinal mucosa protects the mucosa from harmful effects of the proteases[24]. The ductal cells produce electrolytes, and serve at least three important functions: to neutralize gastric acid, facilitate for pancreatic enzymes to reach the duodenum, and to aid in liquefaction of pancreatic enzymes and solubilization of pancreatic glycoproteins. The fluid containing digestive enzymes and bicarbonate is secreted in a volume of 600-1200 ml/day into the duodenal lumen. Pancreatic secretion is under both hormonal and nervous control. It is stimulated by secretin, cholcystokinin, and cholinergic influence. Secretion occurs during the cephalic phase (25-50%), the gastric phase (10%), and the intestinal phase (at least 50%)[22, 23].

The endocrine part, composed only of 2% of the pancreatic mass, is scattered as islets in the pancreas, termed the islet of Langerhans, with α cells that secrete glucagon, β cells secrete insulin and amylin, δ cells secrete somatostatin and PP cells that secrete pancreatic polypeptide. The endocrine pancreas is involved in the regulation of glucose in the blood. It responds to glucose levels and secretes

glucagon (a catabolic hormone) and insulin (an anabolic hormone) into the blood stream[23].

The remainder of the pancreas, accounting for approximately 13% of the mass, is composed of connective tissue, nerves and blood vessels.

1.3.2 Pathogenesis and pathophysiology

The pathogenesis of acute pancreatitis is only partially known. Two possible main mechanisms out of several others described are duct obstruction and acinar cell injury, for initiating of gallstone and alcoholic pancreatitis. The passage of gallstones through the common bile duct can cause transient obstruction of the pancreatic duct. This obstruction of the pancreatic duct raises the hydrostatic pressure within the pancreatic duct, causing blockage of pancreatic secretion and subsequent activation of pancreatic enzymes within the pancreas[25]. In alcoholic pancreatitis it is postulated that ethanol, its metabolites and oxidant stress exert a number of toxic effects on the pancreatic acinar cells which predispose the gland to autodigestive injury[25].

There are still much to learn about pathophysiological mechanisms explaining activation and release of pancreatic enzymes, and the progression from an initially localized disease to a systemic inflammatory response and potential multiple organ failure. Most investigators agree that premature activation within the pancreatic gland of the pancreatic proenzyme trypsinogen to the active enzyme trypsin is the central event in the pathogenesis of acute pancreatitis[26]. There are only three known ways of activation of trypsinogen: by enterokinase, cathepsin B and auto activation. Trypsin activates other pancreatic proenzymes and proinflammatory cascade systems (including the complement system, the kinin system, the coagulation system, the fibrinolytic system, and macrophages)[22]. Premature activation leads to autodigestion of pancreatic tissue, histologically characterized by acinar cell necrosis and parenchymal inflammatory infiltrat, as well as systemic effects from circulating enzymes, a severe inflammatory reaction and production of several acute phase reactants.

In the severe form of pancreatitis, the local injury rapidly leads to a generalized hyperinflammation, SIRS, associated with potential failure of distant organs. SIRS is defined as two or more of: high or low body temperature (<36 or >38°C), elevated heart rate (>90 beats per minute), tachypnea (respiratory rate >20 breaths per minute, or carbon dioxide <4.3 kPa), high or low WBC (<4 x 10^9 or >12 x 10^9 cells/L, or >10 % immature neutrophils)[27]. This may in turn progress to organ dysfunction. The hypoinflammatory state i.e. the compensatory anti-inflammatory response syndrome (CARS) may follow during the course of critical illness[28]. Hypothetically, the patients may be more vulnerable to e.g. bacterial translocation or the trauma added by surgical intervention during CARS. This could lead to the combination of MODS and sepsis[29, 30] (Figure 1.3).

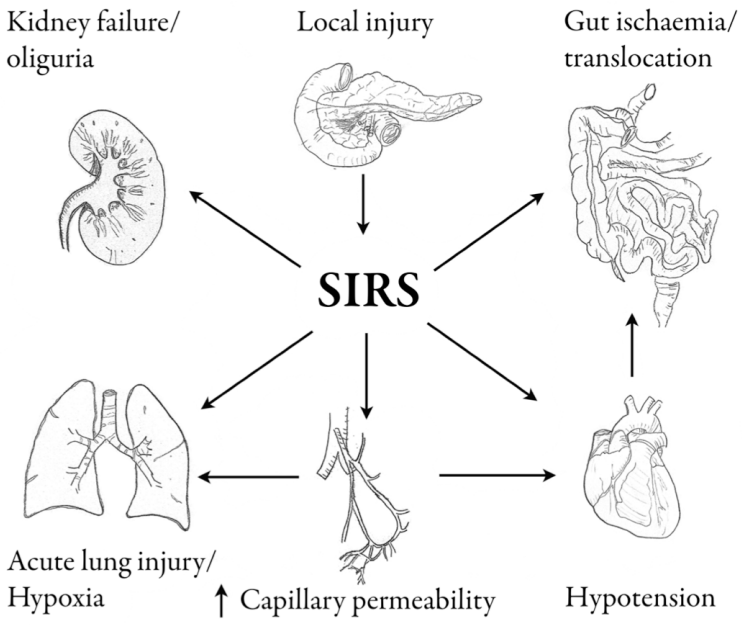


Figure 1.3. Acute pancreatitis and examples of the effect on distant organs and organ dysfunction. Other potential effects are e.g. liver failure, encephalopathy and coagulopathy.

Hypovolemia is common in severe disease and is a result of a substantial fluid loss to the retroperitoneal space, due to local inflammation, as well as remote organ capillary endothelial leakage and vasodilatation. Hypoxia and hypotension contribute to organ dysfunction, including respiratory failure, circulatory collapse, renal insufficiency and intestinal ischemia, which in turn may lead to endotoxin absorption and possibly also bacterial translocation across the intestinal wall[27, 31]. This leads to further activation of macrophages and circulating neutrophils, production and release of different cytokines, proteases and other inflammatory mediators, and an activation of the complement cascade[32].

It remains still to be clarified why some cases progress to the necrotizing form of acute pancreatitis and develop multiple organ failure, whereas others will only suffer from milder forms.

1.4 Severity classification in acute pancreatitis

In the ambition to give each patient the best possible treatment early severity classification is most important. Patients that are at risk of complications must be identified in order to initiate effective preventive management as soon as possible, prior to the development of complications. It is also important to be able to correctly categorize groups of patients according to severity in order to allow comparison of published series and to define groups at risk of complications for clinical trials.

1.4.1 Background

Initial assessment of the clinical progression of acute pancreatitis alone has been inadequate in identifying patients who develop a severe disease[33]. An ideal prognostic system or marker does not exist, and there are two ways onward: either the prognostic systems and markers need to be used in a more intelligent way, or by the discovery of new markers that measure key aspects of outcome.

A prognostic system or marker should be available at admission, be simple, quick, cheap to measure and reproducible. Further, it should not be affected by concomitant disorders, but be able to identify the risk of the individual patient. Challenges in the work

towards a good prognostic instrument include: different prevalence rates and definitions of severe acute pancreatitis; patients present at the hospital at different times after the onset of symptoms; and that organ failure as well as mortality has a bimodal distribution with early and late onset[28].

Identifying severe cases are important and can play a significant role in decision support and aid in development of treatments reducing the morbidity and mortality associated with severe acute pancreatitis. Accurate and simple severity stratification is also important when conducting clinical research.

1.4.2 Validation of prognostic systems

It is important to accurately evaluate the performance of a prognostic system. The cornerstone of clinical decision analysis, the 2x2 contingency table, is the starting point. It is commonplace to quote sensitivities and specificities, positive and negative predictive values and accuracy. There are two ways to combine sensitivity and specificity into a single measure, and both of these are particularly useful when comparing prognostic markers and systems[34, 35]. The ROC curve (plotting sensitivity against 1-specificity) allows the comparison of different tests by calculating the area under the curve (as used in this thesis). It is also useful in defining the optimal cut-off for that particular test, and is a measure of the overall performance of a model. An area of 1.0 under the ROC curve indicates perfect discrimination, whereas an area of 0.50 indicates complete absence of discrimination. Any intermediate value is a quantitative measure of the ability of the risk predictor model to distinguish between a positive or a negative outcome[36]. Sensitivity and specificity are independent of the number of cases with a specific outcome; consequently, so is the ROC analysis[37].

The second way is to calculate likelihood ratios, but this method was not used in this thesis.

1.4.3 The Atlanta classification

The Atlanta Classification from 1992[38] is accepted worldwide as the first clinical reliable classification system of acute pancreatitis. According to the classification, the mild form is associated with minimal organ dysfunction and an uneventful recovery, and lacks the

described features of a severe course. The severe disease is, on the other hand, associated with organ failure and/or local complications, such as necrosis, abscess, or pseudocysts. According to UK guidelines, organ failure that presents within the first week, but which resolves within 48 hours, should not be considered as an indicator of a severe attack of acute pancreatitis[18]. Three or more Ranson criteria[39] or eight or more APACHE II points[40] further characterize severe acute pancreatitis. A delayed progression from mild to severe acute pancreatitis is rare.

Despite that the Atlanta classification is probably the most widely used and of many considered as the "golden standard", it has several drawbacks. The main disadvantage is the lack of clear distinction between predicted and actual severity of severe acute pancreatitis. A significant proportion of patients who present with predicted severe acute pancreatitis do not develop a severe disease. It has further been proposed that the classification should be revised to include a patient group defined as "moderately severe acute pancreatitis", i.e. patients currently classified as severe acute pancreatitis but without organ failure[41]. Organ failure has been recognized as a more important determinant of survival than the extent of pancreatic necroses. The SOFA criteria[30] for systemic organ dysfunction are by some authors considered more reliable for clinical decision making than the Atlanta criteria[4]. In addition, although the Atlanta criteria incorporate clinical and morphological definitions of local complications of acute pancreatitis, no exact radiological criteria for these complications are provided. This leads to the Atlanta definitions for acute pancreatitis being used inappropriately[42] and alternative definitions are frequently applied, especially relating to peripancreatic fluid collections[43]. Concerning the terminology, several terms abandoned by the Atlanta classification are frequently used, and new terms have emerged that describe manifestations in acute pancreatitis that were not specifically addressed during the Atlanta symposium[44]. A revision of the Atlanta classification is desirable.

1.4.4 Severity classification – different scoring systems

Two general types of scoring system have been applied to pancreatitis: systems specific to pancreatitis, and systems that correlate non-specific physiological variables with outcome, Table 1.1.

The first risk stratification model developed in acute pancreatitis was the Ranson criteria from 1974[39]. From 43 clinical and laboratory variables, 11 factors were found to be predictive for morbidity and mortality; 5 of these can be measured on admission and a further 6 during the ensuing 48 hours. The model was developed and validated in patients with alcoholic pancreatitis. Despite almost four decades of evaluation in severity scoring systems for acute pancreatitis, only marginal improvements in the accuracy has occurred. Imrie proposed a modification of the Ranson criteria, called the Glasgow score[45]. The original system used 9 data elements. This was subsequently modified to 8, by the removal of the contribution of transaminase levels. This model has the same shortcomings as the Ranson score, in that it cannot be applied fully until 48 hours after admission.

No adequate specific scoring model in clinical use is available at admission, which is a major deficiency. The present scoring systems also consist of multiple factors, implying time-consuming calculations. The Balthazar score, originally introduced in 1985, is based on CT changes. It divides patients into five classes (A-E), according to the anatomical changes of the pancreatic and peripancreatic tissues, and carries the same disadvantage as mentioned above since CT changes associated with pancreatic necrosis take a minimum of 48 hours to develop[19].

APACHE II is a classification system designed to measure the severity of a disease for adult patients admitted to the intensive care unit[40]. The point score is calculated from the sum of the age points, the chronic health points (assigned if the patient has a history of severe organ system insufficiency or is immunocompromised) and the acute physiology score obtained from the points assigned to 12 routine physiological measurements (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrite, white blood cell count, and Glasgow coma score). Previous limitations of the APACHE II score were that it was complicated and time consuming to calculate, and required arterial blood gas measurements. Easy-to-use inline calculators are now available, and the venous bicarbonate level and the oxygen saturation can be substituted for the arterial pH and oxygen partial pressure. APACHE II provides a general measure

of severity of disease, appears to reflect any continuing disease activity, and proves a useful means to monitor the course of the illness and response to therapy in acute pancreatitis[46]. In the Atlanta symposium in 1992, and the Santorini consensus conference in 1999, the APACHE II score was proposed as the best score in assessment of severity[38, 47]. It has been shown to perform as well at 24 hours as the Ranson or Glasgow score at 48 hours[48]. Obesity has been shown to be an independent predictor of death and the development of severe acute pancreatitis. A modification to the APACHE II scoring system has been proposed that includes a factor for obesity, the APACHE-O scale, but this has not been employed in any major prospective study[49].

Table 1.1. Classification systems of severity in acute pancreatitis.

Classification system	Author and year	Number of parameters	Comments	SAP at score
Ranson score*	Ranson et al, 1974[39]	11	Requires assessment 48 h after admission Can not be repeated	≥3
Glasgow score*	Imrie et al, 1978[45]	8	Requires assessment 48 h after admission Can not be repeated	≥3
Balthazar score*	Balthazar et al, 1990[19]	Appearance on CT (A-E) and necrosis (percentage)	Of decreasing interest	
APACHE II	Knaus et al, 1985[40]	14	Can be used repeatedly	≥8
Marshall	Marshall et al, 1995[29]	6	Based on organ failure Can be used repeatedly	#
SOFA	Vincent et al, 1996[30]	6	Based on organ failure Can be used repeatedly Of increasing interest	#

*Specifically developed for acute pancreatitis, #different cut-off levels have been described.

Sepsis-related organ failure assessment (SOFA) score and Marshall score are designed not to predict outcome but to describe a sequence of complications in the critically ill to assess organ dysfunction/failure[29, 30]. Recently these scores have also been evaluated and used in severity prediction in acute pancreatitis.

Several new scoring models specific for acute pancreatitis have been published, but none has gained wide acceptance and use[50-56].

Recently, a simple clinical algorithm for rapid initial identification of patients with a first attack of acute pancreatitis that do not require intensive care, the Harmless Acute Pancreatitis Score (HAPS)[57], was presented.

1.4.5 Severity classification – single prognostic factors

During recent years, many variables have been proposed as early single tests for severity prediction in acute pancreatitis. These include clinical features, markers of the inflammatory response, and markers of pancreatic injury. Some of these factors have been tested in clinical use, but many have so far been studied only in a research setting.

The inflammatory process

Tests that are markers of severity of the inflammatory reaction, such as acute phase reactants and other mediators of the inflammatory process, include granulocyte elastase, tumour necrosis factor (TNF), interleukin-1, -6, -8 and -10, and C-reactive protein (CRP). Cellular markers of systemic inflammation and immunosuppression also belong to this group. CRP is the single most popular and widely available marker of SAP in use today[16]. At 48 hours after onset of symptoms it has even been shown to have an accuracy similar to that of the APACHE II score[46]. The drawback is that the value can be normal on admission, as raised CRP levels are dependent on hepatic synthesis secondary to circulating cytokines[58]. The peak in serum level is usually not maximal until about three days after the onset of pain. A cut-off level of 150 mg/L to distinguish between mild and severe disease are described[47]. Advantages are that the marker can be used to monitor the clinical course of the disease, and that it is a common clinically used test.

IL-6 is the principal cytokine mediator of the synthesis of different acute-phase proteins, including CRP. Serum levels within 24 hours have been shown to provide good discrimination between mild and severe acute pancreatitis[59, 60]. Also IL-8 is raised in the course of acute pancreatitis, and correlate with severe outcome[60]. The anti-inflammatory cytokine IL-10, has been shown to reduce the inflammatory response in experimental pancreatitis and also predict organ failure in humans[53]. The proinflammatory markers IL-1 and TNF-α correlates with severity in some studies, but are difficult to measure because of their short half life in blood and the variable and phasic release of TNF-α[61]. Polymorphonuclear (PMN) elastase also appears to be a valuable early marker of severity[62]. Compared to CRP the problem with the above-mentioned test is that assays suitable for routine clinical use or near patient assessment are not yet in use.

Procalcitonin, the inactive propeptide of the active hormone calcitonin, can be used as a marker of severe sepsis and has been assessed as a potential marker for predicting severity in acute pancreatitis on admission[63].

Trypsinogen activation

Since trypsin is the activator of the earliest pathophysiological events in acute pancreatitis, variables that measure trypsinogen activation or trypsin-induced events are hypothezised to indicate the severity of an attack of acute pancreatitis. Markers of trypsinogen activation appear very early after the onset of disease, with maximum levels 1-2 days after the onset of pain, and then decrease quickly[64]. Trypsinogen activation peptide (TAP) is the most thoroughly studied variable, and raised plasma and urinary levels correlate well with severity[65]. Other markers are carboxypeptidase B and trypsin-α-1-protease inhibitor[66, 67]. These are not currently available for routine laboratory use and require further evaluation.

Other potential risk factors

In patients, an admission haematocrit exceeding 47% has been shown to be a reliable predictor of the development of severe acute pancreatitis, and failure of the admission haematocrit value to decrease after resuscitation or within the first 24 hours predicts the development of local and systemic complications[68]. Obesity (BMI >30

kg/m^2) is a risk factor for development of local and systemic complication, and also for mortality[69].

Elevated creatinine and low calcium levels are examples of other risk factors included in present scoring models, that seem to have an ability to predict severe course or death, as single parameters[39, 40, 70].

Phospholipase A_2, produced in the pancreas, but also by neutrophil activation, may represent an early marker of severity[71]. Leakage of certain pancreatic enzymes from the pancreatic gland, such as pancreatic amylase, lipase, trypsinogen 2 and elastase are, however, better to use as for diagnosis than for a diagnostic purpose[39, 72, 73]. Gender is no independent risk factor for the severity and outcome of acute pancreatitis[74].

1.4.6 Artificial neural networks

ANNs are data analysis algorithms, designed to resemble biological nervous systems. They consist of a set of processing units that simulate neurons and are interconnected via a set of weights, analogous to synaptic connections, in a way that allows signals to travel through the network in parallel as well as serially. The weighted sum of the signals is compared with a threshold. If the threshold is exceeded the node fires; otherwise it remains inactive. Computational power in a neural network does not derive from the complexity of each processing unit, but from the density and complexity of the interconnections[75]. The feed forward neural networks, multilayer perceptron (MLP) (Figure 1.4) use one or more hidden layers of nodes with an activation function. The learning is usually achieved by minimizing an error function of the input and target data. The best network architecture for a particular task must be developed by experimentation

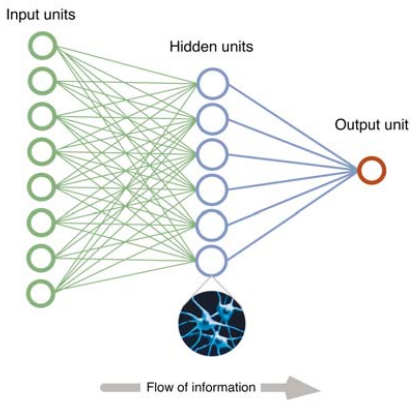


Figure 1.4. Schematic diagram of a multi-layer perceptron ANN.

and observation. ANNs use computer iteration to look for patterns in different variables associated with outcome, and are far less affected by low frequencies in the variables than traditional statistical methods[76, 77]. Furthermore, ANNs work in a nonlinear fashion, which may better describe the interaction between health risk factors (Figure 1.5). ANNs have found medical applications, such as predicting the outcome of terminal liver disease[78] and mortality risk scoring in cardiac surgery[79]. Some studies in clinical medicine have demonstrated superiority of the prediction by ANNs compared with other statistical methods[80].

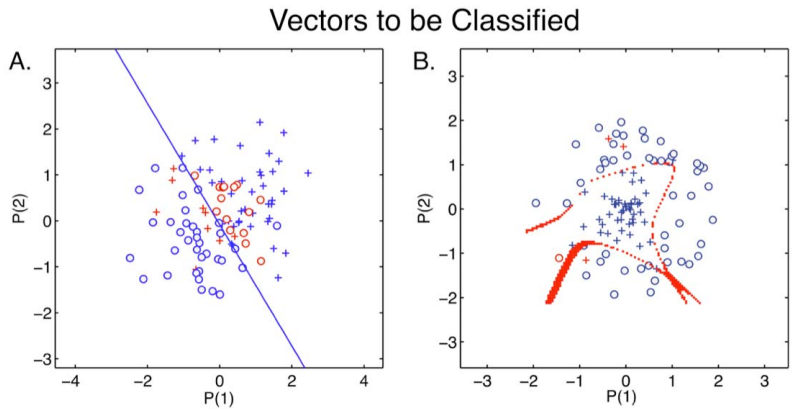


Figure 1.5. Solution of a two-dimensional classification problem. (A) Poor linear separation of a non-linear classification problem, performed by a linear model. (B) An almost complete non-linear separation of the two classes, using a bio-statistical method based on a non-linear model such as an ANN with six hidden nodes.

The predictive validity of a model is a measure of how well it performs on a data set other than the one from which it was developed. Numerous techniques are available to make an internal (on the original data) validation. The data may be randomly split into a development set and a validation set. Alternatively, more sophisticated techniques may be used: K-fold cross validation, leave-one-out cross validation and bootstrapping[75].

The accuracy of a model may be evaluated in several ways. The first property is termed "variability" and is a measure of the performance of the risk-adjusted model[81]. The second property is

termed "calibration" and is defined as the ability of the model to assign an appropriate risk to the patients upon whom the model is based[82]. A third property relating to the accuracy of a model is termed "discrimination" and is defined as the ability of the model to distinguish between those patients having and those not having the outcome of interest (e.g. ROC curve)[35]. The fourth property, "reliability", refers to the statistical term precision, i.e. the ability to repeat the observations using similar input variables and similar statistical techniques, with resultant similar outcome findings[83].

Conventional linear models may have limitations in terms of prediction of severity and death in complex medical diseases such as acute pancreatitis. Since ANNs work in a non-linear fashion, they may better describe the interactions between health risk factors and can be used on available data without delay. They are appealing alternatives to the traditional scoring systems. Several authors have used ANNs to develop predictive models for the assessment of patients with acute pancreatitis, with varying degrees of success[84-88].

In the future it is possible that ANNs will be a decision support aid for early identification of patients with severe disease.

1.5 Treatment strategies

There is no specific therapy for patients with severe acute pancreatitis directed at underlying pathophysiological mechanisms. Initial fluid resuscitation and organ supportive therapy may be potentially life saving and regulate the concomitant course of disease and the magnitude of severity.

1.5.1 Fluid resuscitation

Fluid must be aggressively replaced to balance the massive interstitial fluid loss that occurs during the early inflammatory phase due to an increase in the endothelial barrier permeability, to maintain microcirculation and potentially decrease ischemia and reperfusion injury. Intravascular volume depletion can develop rapidly and result in tachycardia, hypotension, and renal failure. It may also impair the blood flow to the pancreas and worsen necrosis development. There

is evidence that early and aggressive fluid management may result in the resolution of organ failure, and that this is associated with a reduced risk of mortality from acute pancreatitis. It is difficult to detect patients at risk for complications early on, and it may be wise to treat every patient aggressively until disease severity has been established[89]. According to a recent publication, patients with severe acute pancreatitis who do not receive at least one third of their initial 72-hour cumulative intravenous fluid volume during the first 24-hours are at risk for higher mortality than those who are initially resuscitated more aggressively[90].

1.5.2 Organ support and specific medical treatment

Despite initial encouraging results, anti-inflammatory agents (such as lexipafant), antiproteases (such as gabexate) and antisecretory agents (such as somatostatin analogues and octreotide) have all proven disappointing[91]. To date, there are also no clinical studies available that support the use of corticosteroids specifically in acute pancreatitis. Monitoring of the state of consciousness, the respiratory and cardiovascular system, and urinary output is important in the initial management, as is fluid replacement and pain control. Pulmonary dysfunction is the most frequent distant organ problem, followed by cardiovascular, renal and liver failure[92], and optimal intensive care monitoring and support of failing organs are vital in severe cases.

Antibiotics

The uses of prophylactic antibacterial drugs in patients with severe acute pancreatitis have gradually changed towards a more selective utilization. Earlier studies indicated an improved outcome in severe necrotizing acute pancreatitis when antibiotics were used[93]. Since then several studies, including two double blind placebo controlled trials, have not supported the use of prophylactic antibiotics[94, 95]. A recent meta–analysis consequently concludes that antibiotic prophylaxis of SAP does not reduce mortality or protect against infected necrosis or the need for surgical intervention[96].

Parenteral and enteral nutrition

Severe acute pancreatitis is initially a hyperinflammatory state with a pronounced catabolic state, where the catabolic processes may be aggravated by insufficient nutritional supplementation during the

acute phases. Traditionally, nutritional management has been in favour of the concept "putting the pancreas at rest", i.e. the use of parenteral fluid and nutrition until laboratory and clinical findings are normalized. An increasing number of studies, however, indicate positive results from providing patients with early enteral nutrition. A recently published Cochrane review concludes that there are significant benefits favouring enteral over parenteral nutrition by decreasing mortality, multiple organ failure, systemic infection and operative interventions. In addition, there is a trend to a decreased LOS and fewer local septic complications[97]. Immediate oral feeding is feasible and safe in mild acute pancreatitis and may accelerate recovery[98]. No data supports the use of immunonutritional supplements, and probiotics should be avoided in acute pancreatitis[99].

1.5.3 Endoscopic and radiological interventions

In recent years both endoscopic and radiological techniques have developed, and are nowadays important as tools in the treatment of acute pancreatitis.

Endoscopic treatment

Given the pathogenesis of biliary pancreatitis, the use of ERCP has been considered for decompression of the pancreatic ductal system through the removal of retained stones. Present guidelines in the management of acute gallstone-induced pancreatitis, based on three randomized trials, conclude that urgent therapeutic ERCP should be performed in patients who fulfil the criteria for predicted or actual severe acute pancreatitis, or when cholangitis, jaundice, or a dilated common bile duct is present[18]. The procedure is best carried out within 72 hours after the onset of pain[18]. This recommendation has now been challenged. ERCP is definitely indicated in acute pancreatitis when there is evidence of biliary obstruction or cholangitis. However, absent these indications, its role is less clear, with several experts arguing that a great proportion of stones will pass spontaneously and that ERCP-related complications might overweight the benefits. In a recent publication early ERCP was associated with a significantly reduced risk of clinically relevant complications in patients with predicted severe acute biliary pancreatitis, with

concurrent cholestasis. In patients without biliary obstruction there were no beneficial effects associated with early ERCP[100].

Elective ERCP for suspected retained stones is recommended for those who are poor candidates for surgery.

Radiological interventions

It is important to differentiate between sterile and infected pancreatic necrosis, since the outcome and need for intervention are different. While sterile pancreatic necrosis should be managed conservatively, infected pancreatic necrosis requires debridement and drainage supplemented by antibiotic therapy.

There is controversy over the roles of radiological drainage and surgical necrosectomy in the management of infected pancreatic necrosis. Surgery is the standard, but has been challenged by retrospective studies describing good outcome in patients managed by percutaneous drains[101]. Currently there is an ongoing randomised controlled study evaluating minimally invasive "step-up approach" (starting with drainage, followed, if necessary, by videoscopic assisted retroperitoneal debridement) versus maximal necrosectomy in patients with acute necrotising pancreatitis (the PANTER trial). Both procedures are followed by continuous postoperative lavage[102].

1.5.4 Surgery

There has been a change in the surgical management of acute pancreatitis over the past 20 years. This change has been away from early aggressive surgical intervention towards more conservative management. Most patients with acute pancreatitis do not require surgical treatment of the pancreatic disease. However, intervention is necessary in cases with infected pancreatic necrosis. In gallstone-induced acute pancreatitis the risk of recurrence is high without cholecystectomy.

Pancreatic surgery

The choice of surgical technique for necrosectomy depends on individual features and locally available expertise. Traditionally the abdomen may be closed over drains, packed and left open, or closed over drains and the pancreatic cavity irrigated. There is no clear evidence to favour any of these approaches[103]. Even if surgical

necrosectomy is the traditional approach, less invasive techniques (retroperitoneal or laparoscopic necrosectomy or computed tomography-guided percutaneous catheter drainage) may be equally effective[104, 105]. Open necrosectomy is depicted in Figure 1.6.

Cholecystectomy

Patients with gallstones should undergo definitive treatment in order to prevent recurrence of pancreatitis. There is a significant risk of further episodes of acute pancreatitis after the first attack[106]. Treatment of gallstones will usually be by cholecystectomy, either laparoscopic or open, with intra-operative cholangiography. For unfit patients, endoscopic sphincterotomy may be an adequate treatment. Definitive management of gallstones should in mild cases be performed during the initial hospital admission, or within the next two weeks[18, 91, 107]. In severe acute pancreatitis, signs of lung injury or other systemic disturbances have to resolve before treatment[108].

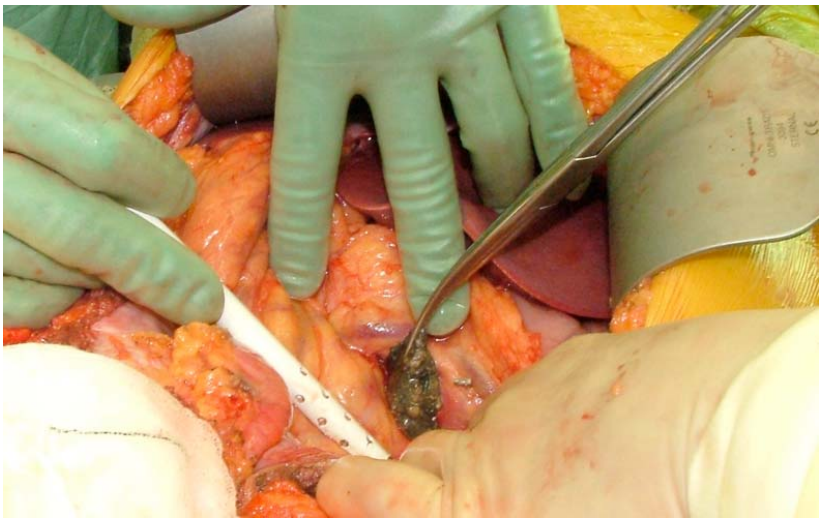


Figure 1.6. A necrotic pancreas exposed during open surgery due to pancreatic pseudocyst and infected pancreatic necrosis.

1.6 Pancreatic pseudocysts

Pancreatic pseudocysts may occur as a consequence of both acute and chronic pancreatitis. In the following section the focus is mainly on the acute aetiology, termed acute pseudocyst. Patients that develop an acute pancreatic pseudocyst have by definition suffered from severe acute pancreatitis, according to the Atlanta classification[38].

1.6.1 Definition and clinical characteristics

A pseudocyst presents as a cystic cavity connected to the pancreatic duct system, either directly or via the pancreatic inflammatory tissue. It contains a collection of pancreatic juice, usually sterile, is rich in pancreatic enzymes, and enclosed by a well-defined non-epithelialized wall of fibrous or granulation tissue. Formation of a pancreatic pseudocyst requires four or more weeks from the onset of acute pancreatitis[38]. Acute fluid collections are not surrounded by a wall, and occur early after acute pancreatitis. Infected pancreatic pseudocysts with pus are more correctly classified as pancreatic abscesses (Table 1.2).

Pancreatic pseudocysts are caused by pancreatic ductal disruption following increased pancreatic ductal pressure, either due to stenosis, protein plugs or calculi obstructing the main pancreatic ductal system, or as a consequence of pancreatic necrosis following an attack of acute pancreatitis[109, 110]. Trauma and chronic pancreatitis are other possible pathogeneses. A classification of pancreatic pseudocysts, published in 1991 and based on the underlying aetiology of pancreatitis (acute or chronic), the ductal anatomy, and the presence of communication between the cyst and the pancreatic duct, is still valid[111].

The pseudocyst size ranges from very small to more than 25 cm in diameter[112, 113]. Most commonly only one pseudocyst is present after acute pancreatitis. The symptoms depend on the size and location of the pseudocyst and may include pain, nausea and vomiting. Less frequent are gastric outlet and/or bile duct obstruction, bleeding and rupture[114]. Occasionally, the pseudocyst is palpable, but most often it is discovered by imaging techniques. US and CT are most important in the diagnostics and follow-up (Figure 1.7). Modalities such as ERCP, MRCP and EUS are also of value.

Table 1.2. Terminology in acute pancreatic disease according to the Atlanta classification[38].

Pathology	Characteristics and definitions
Acute fluid collections	- occur early in the course of AP - located in or near the pancreas - always lack a defined wall
Acute pseudocyst	- develops as a consequence of acute or chronic pancreatitis or pancreatic trauma - collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue - require four or more weeks from the onset of AP
Pancreatic abscess	- develops as a consequence of AP or pancreatic trauma - a circumscribed intra-abdominal collection of pus, containing little or no necrosis - occurs late in the course of SAP

Pancreatic pseudocysts are diagnosed in 10-15% of patients after acute pancreatitis[115, 116]. Even if no comprehensive cohort study has been conducted to evaluate the true incidence of pseudocysts, it is approximated to be 0.5-1 per 100 000 adults annually[117].

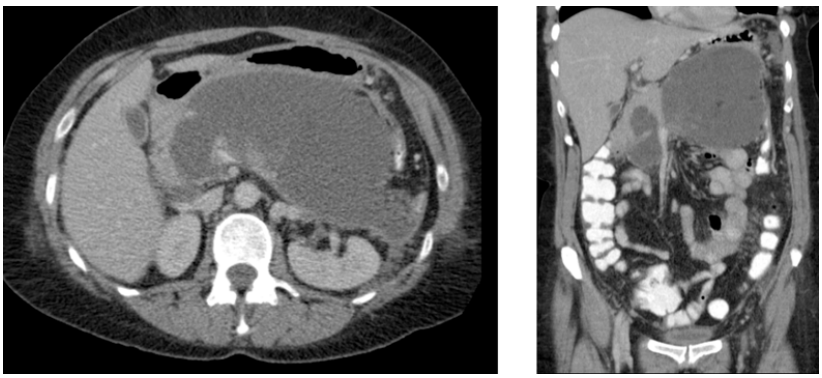


Figure 1.7. A large pancreatic pseudocyst diagnosed by contrast enhanced CT scan in a patient recovering from severe acute pancreatitis. The stomach is dislocated ventrally.

1.6.2 Treatment strategies

The patient's medical history, laboratory findings and imaging results must all be taken into consideration when deciding on the treatment regime in pancreatic pseudocysts, and pancreatic ductal anatomy correlates with outcome after different treatment regimens[111, 118]. The two main indications for invasive drainage are persistent symptoms and complications. Percutaneous drainage, endoscopic drainage and surgery are the available treatment strategies[119]. These techniques have not been directly compared in high-quality prospective randomized studies, and the preferred approach varies. There have been fruitful attempts to evaluate the evidence for management of pancreatic pseudocysts[120].

Conservative treatment

Conservative treatment, meaning "observation", is based on the knowledge that spontaneous resolution can occur[113, 121]. It is suitable in patients without symptoms, with unaltered or diminishing pseudocyst size. In case of symptoms, increasing pseudocyst size, or infection, invasive treatment must considered to reduce the risk of serious complications. The old rule that pseudocysts of more than 6 cm in size that do not decrease during a 6-week observation period should be actively treatmented[114, 115] has been changed. Some still advocate treatment in asymptomatic pseudocysts resulting from biliary pancreatitis, and associated with pancreatic necrosis, before complications develop[122]. Today most researchers, however, agree that conservative follow-up is possible in cases of larger and mainly asymptomatic pseudocysts[113, 119, 121]. Not only size but also aetiology, the presence of main pancreatic duct disruption, and the existence of more than one pseudocyst are factors that should influence the choice of treatment and subsequent outcome[111, 118, 123, 124].

Percutaneous puncture and drainage

Percutaneous puncture with US or CT guidance can give instant pain relief and the possibility to fluid bacterial culture, but the recurrence rate is high. Percutaneous drainage, on the other hand, can be a good treatment choice, especially in cases with normal anatomy and no communication between the pseudocyst and the pancreatic duct. The drainage can be external or internal with percutaneous

cystogastrostomy[125]. External drainage carries a high risk of infection. Resolution of the pseudocyst is seen in 42-94% of the cases after percutaneous drainage[111, 115, 118, 126]. Unsuccessful drainage is usually caused by large ductal leaks or obstruction of the main pancreatic duct[126].

Endoscopic drainage

Endoscopic techniques to drain pseudocysts are possible, but as in all drainage techniques, except percutaneous catheter drainage, it is important to allow the wall of the pseudocyst to mature. Endoscopic transpapillary drainage with ERCP is suitable in pseudocysts complicating chronic pancreatitis, which communicate with the ductal system[127]. Endoscopic transmural drainage is a second technique that via a transgastric or transduodenal approach is used when the pseudocyst is directly adjacent to the gastrointestinal wall. The principle is to establish a communication between the pseudocyst and the stomach or duodenum via a stent. The endoscopic approach has been dependent upon the presence of a bulge into the gastrointestinal lumen. In combination with EUS it can, however, be a safe minimally invasive method also in cases with a less prominent, non-bulging, pseudocysts[128]. EUS has become important in order to determine the size, location and thickness of the pseudocyst wall. A distance between the gastric or duodenal wall and the cyst wall of more than 1 cm, or the presence of large intervening vessels or varices are relative contraindications for endoscopic drainage[129]. The potential complications are severe bleeding and perforation[130]. Endoscopic treatment has been shown to be as equally effective as open surgery[131]. The technique is, however, presently available only in some of the centres that take care of this patient group. It avoids the need for an external drainage, is less invasive than open surgery and has a high long-term success rate[132]. The technique is also under constant development[133].

Surgery

Even if the trend is towards primary minimally invasive treatment, open surgery with internal drainage to the gastrointestinal tract is a well-established and safe choice with good results, but also associated with significant morbidity and mortality in some cases[113, 116, 124, 126, 134, 135]. Some patients are primarily best suited for surgical intervention,

e.g. in the case of a thick pseudocyst-wall (which can rule out percutaneous or endoscopic treatment), when concomitant necrosis is present, in multiple pseudocysts, as an alternative in recurrences, in chronic pancreatitis, and when malignancy is confirmed or suspected. By providing a communication between the pseudocyst cavity, and the stomach or small bowel, the pseudocyst is drained. The surgical stoma should be placed in the most dependent portion of the cystic cavity in order to maximize the chances of complete drainage. The stoma usually remains patent and functional for several months. Laparoscopic surgery is a less invasive alternative to open surgery, which in trained hands has shown good results[136, 137].

A proposed algorithm for treatment of pancreatic pseudocysts is presented in Figure 1.8.

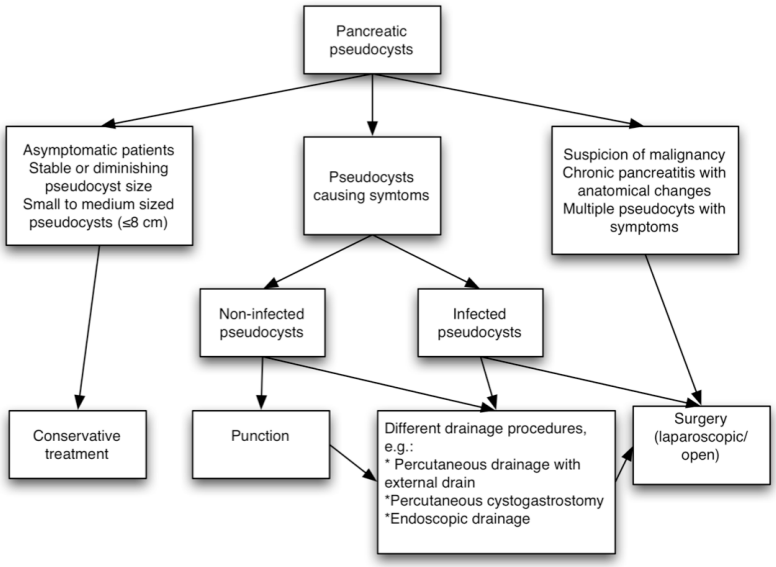


Figure 1.8. Treatment algorithm for pancreatic pseudocysts according to Andersson B, et al[138].

1.6.3 Differential diagnosis

Pseudocysts due to pancreatitis are the most common cystic lesion in the pancreas, but other cystic processes such as benign serous cystadenomas, pre-malign mucinous cystadenomas and malignant cystadenocarcinoma are important to recognize, since early surgery can cure these patients[139]. A careful patient history, including history of pancreatitis or trauma, but also radiological investigation, is important[140].

1.7 Long-term results after acute pancreatitis

Acute pancreatitis can be mild and self-limiting or severe and very resource demanding in the acute phase. At long-term follow up the outcome concerning pancreatic function and general recovery can also differ within a wide range. Nowadays, critical assessment of outcome with respect to quality of life and the financial resources spent is also required for a management to be considered successful.

1.7.1 Pancreatic dysfunction

At the Marseilles symposium on pancreatitis in 1963 it was stated that after recovery, complete restitution of the pancreas is the rule[141]. This point of view has subsequently changed. The extent of recovery varies in different studies. Complete restitution has been described[142], but some dysfunction is the usual scenario, especially after severe disease with necrosis[143-147]. According to JPN guidelines, about one-third to one-half of acute pancreatitis patients develop functional disorders of both the endocrine system and the exocrine system (diabetes mellitus and fatty stool)[148].

Endocrine dysfunction

Endocrine dysfunction with glukosuria and elevated blood sugar levels is common during the acute phase of acute pancreatitis, but usually resolves in parallel with the pancreatitis. Endocrine dysfunction with diabetes mellitus and impaired glucose tolerance are, however, more common with time. The dysfunction can be due to loss of β-cell function, with decreased insulin secretion. Insulin resistance has also

been shown to be a prominent feature in patients after pancreatic resection[149], implying that β-cell loss and hyperinsulinaemia may coexist[150, 151]. The pathophysiological mechanisms involved are not clarified.

Incidence figures for diabetes mellitus after acute pancreatitis vary widely in the literature, from 14 to 92%[143, 144, 152, 153]. It is more common after severe than mild disease[153], and correlates also with increasing extent of necrosis[147]. It has been suggested that it is the pancreatic surgery, and not the pancreatitis per se, that is the main reason for the development of diabetes after severe disease[151]. However, a pronounced effect on the glucose metabolism is seen also in cases with necrotizing acute pancreatitis not subjected to surgery [150]. Acute pancreatitis due to alcohol is more often followed by impaired glucose tolerance and diabetes mellitus than acute pancreatitis due to other aetiologies[153].

Exocrine dysfunction

Evaluation of exocrine pancreatic insufficiency is difficult, particularly when non-invasive methods are used; invasive tests are nowadays only used for research and not in clinical care. Examples of direct function tests are the secretin-cholecystokinin or secretin-caerulein test. These have the highest sensitivity and specificity for the detection of exocrine pancreatic dysfunction[154]. Direct pancreatic function tests, however, have various practical disadvantages: they are invasive, uncomfortable, expensive, time consuming, not standardized, and require fluoroscopic tube placement. Several simple indirect pancreatic function tests for clinical practice have been established[154]. However, these have limited sensitivity in mild and moderate exocrine pancreatic insufficiency. Pancreatic insufficiency is often not obvious until 90% of the gland structure is destroyed and exocrine insufficiency is not necessarily clinically relevant.

Exocrine pancreatic function has mainly been studied after SAP, with divergent results. In mild, oedematous-interstitial cases of acute pancreatitis, the pancreas can recover completely. After SAP, however, morphological changes may often remain and functional recovery is not always complete[143, 144, 147, 152]. Acute pancreatitis with alcohol as the aetiological factor may carry a higher risk of exocrine impairment[155], though this has not been confirmed by others[147].

The pancreatic insufficiency is also related to the degree of necrosis. Normal pancreatic function was noted in one study with up to 27% extension of necrosis[147].

After surgical treatment a persistent insufficiency can be seen in up to 80-85%, although a recovery is noted over time[144, 152]. Damaged pancreatic acinar cells may recover and improve pancreatic function[144]. Exocrine pancreatic secretory impairment seems to improve gradually, following a time-course mainly depending on the severity of the pancreatitis[144, 156, 157].

Dysfunction in both the endocrine and exocrine system

The endocrine and exocrine pancreas are closely linked together, both anatomically and physiologically. As previously mentioned, exocrine dysfunction is common after severe disease and related to the extension of necrosis, but it is also correlated to the degree of concomitant endocrine dysfunction[152]. Other studies present similar results, showing that an impairment in the exocrine parenchyma may cause impairment of the endocrine function, and vice versa[153]. Patients with diabetes mellitus have a significantly higher incidence of severe exocrine dysfunction[143].

Most patients recover after acute pancreatitis and regain good health. This is especially true for patients after mild disease. The 15-20% suffering from severe disease may, however, suffer from permanent morphological changes with incomplete functional recovery.

1.7.2 Recovery and quality of life

When interviewing patients having a history of acute pancreatitis a few years earlier, some patients have to remind themselves that they really had been ill, while others still have not recovered. This reflects the wide variety in the disease, not only in the acute phase, but also at long-time follow-up. Reports on when patients return to daily activity and work after an attack of acute pancreatitis are limited; only one previous publication has dealt with this topic. The finding was that patients who were working in the year before the onset of severe acute pancreatitis returned to work in 84%[158].

One of the mostly used quality of life assays is the Short Form 36 (SF-36). This is a question form consisting of in 8 scales, examining

social and physical function, physical and emotional well-being, bodily pain, vitality, mental health and overall general health perception. This can be summarized as health-related quality of life (HRQL)[159]. Swedish normative data from age-matched controls are available.

Quality of life after acute pancreatitis has received increased interest during the last 10 years. Most researchers (with few exceptions[160, 161]) focus on patients with severe disease. In severe cases a tendency to or a statistically proven impairment is a common finding[162-165]. There are, however, also results showing an excellent long-term quality of life, even as good as in the normal population[146, 166-168]. After debridement for pancreatic necrosis, quality of life has been shown to vastly exceed that noted in patients with other severe medical diseases, such as congestive heart failure and severe hypertension[166]. The influence of aetiology should be further evaluated, but in one study infected pancreatic necrosis due to alcohol was associated with a lower quality of life compared with biliary aetiology[169].

1.7.3 Costs

Cost analyses in acute pancreatitis are very sparse. In a study from the United Stated the estimated total annual cost for acute pancreatitis admissions was estimated to be $2.2 billion, with a mean cost per hospitalization of $9870[170]. Older patients had disproportionately high hospitalization rates. In two European studies, including patients with severe disease, mean hospital costs were higher in non-survivors[146, 171]. Hospital-acquired infections in acute pancreatitis, which are not that well studied, imply significantly increased hospital charges[172].

There is no published report on total hospital cost, also including costs of hospital care after discharge, and subsequent economical burden for the society. Since sick leave may be long and rehabilitation can be necessary after severe disease not only the hospital cost, but also the costs due to loss of production can be massive.

1.8 Fatal outcome

In patients contracting severe acute pancreatitis the risk of dying is 15-20%[4]. Mortality from acute pancreatitis follows a bimodal distribution. Early deaths in acute pancreatitis are usually defined as occurring within the first 7 days. Pronounced SIRS with organ failure, including MODS, without apparent infection is the most common early cause of death[173]. Mortality during the first week is usually reported to account for about 40 % of the total number of deaths[6]. Late deaths are most often the result of MODS, combined with infection/sepsis, frequently caused by secondary infection of pancreatic tissue or peripancreatic necrosis[5, 58, 173]. Regardless of the timing, death in patients with acute pancreatitis is closely associated with the number of failing organs, as well as the severity and reversibility of organ failure. Different risk factors for a fatal course in patients with acute pancreatitis have been presented, including elevated serum creatinine and blood glucose, obesity, and diabetes mellitus[6, 69].

Acute pancreatitis in patients dying in hospital is sometimes not diagnosed until the post-mortem examination. In modern literature this has been reported to be as frequent as 12-42% of deaths caused by acute pancreatitis[10, 12, 174, 175]. Several of the patients do not seem to have abdominal pain; in one report, 46/53 patients undiagnosed in life before death had no abdominal pain, explaining the difficulties is achieving a correct diagnosis[176]. In a review of 1000 consecutive autopsies of individuals dying of natural causes, two were due to acute pancreatitis[177].

Death in acute pancreatitis in patients never admitted to hospital has been analyzed in a few studies, investigating forensic materials[12, 178-180]. Up to one-third of patients dying from acute pancreatitis has been reported to die outside hospital[178].

Chapter 2

Aims of the Thesis

The general aim of this thesis was to increase the knowledge of acute pancreatitis, especially concerning early severity classification, outcome and long-time function, as well as treatment strategies for the complication of pancreatic pseudocysts. The purpose of the work is to achieve a higher quality of treatment and improve the outcome for this patient group, with special regard to the severe form.

The specific aim for each paper was to:

I. evaluate treatment, outcome, and risk factors for death in severe acute pancreatitis in a centre with a restrictive attitude to surgery;

II. systematically evaluate the accuracy and performance of ANNs to select and rank the most important early risk factors for a severe course of acute pancreatitis, and develop a severity classification model, by using high performance computer clusters;

III. evaluate the treatment efficacy and complications for patients with pancreatic pseudocysts after different management regimes;

IV. identify current treatment strategies in the management of pancreatic pseudocysts in Sweden;

V. evaluate pancreatic endocrine and exocrine function, quality of life and costs, long-term after acute pancreatitis;

VI. investigate the incidence of patients dying from acute pancreatitis outside the hospital, as well as the medical and social circumstances.

Chapter 3

Material and Methods

3.1 Study population

Lund University Hospital, Sweden, serves a primary population of approximately 285 000 inhabitants, and the Department of Surgery provides care for patients from 15 years of age (*Study I-III* and *V*).

The Department of Forensic Medicine, Lund, Sweden, covers a population of about 1.5 million inhabitants from the southern parts of Sweden (*Study VI*).

Studies I and III

All patients (≥15 years old) admitted to the Department of Surgery between 1994 and 2003 with the diagnosis acute pancreatitis or pancreatic pseudocysts, according to the International Classification of Disease (ICD-9 until 1996, thereafter ICD-10), were identified from the hospital records, aided by a computer search. From 839 patients admitted to the hospital with acute pancreatitis, 185 severe cases (22%) were selected for further analysis in *Study I*. Patients referred from another hospital or included in a nutritional study were excluded. Finally, 175 patients were included.

Sixty-four patients with the diagnosis pancreatic pseudocyst were identified in Study III. The definition of pseudocysts was according to the Atlanta Classification[38]. Patients not fulfilling the Atlanta Classification criteria for acute pancreatic pseudocyst, or patients primarily treated at another hospital, were excluded. Primary referrals were included. Finally, 44 patients formed the study group.

Studies II and V

Case records from patients with acute pancreatitis, prospectively evaluated for the participation in two nutritional studies (2002-2005)[98, 181], were examined.

In *Study II,* 139 prospectively included patients were evaluated and included in the developmental part. In the validation part, 61 patients were included. These patients for validation were not prospectively collected, but identified by computer search as performed in *Studies I* and *III*, from a different period (2007-2009).

In *Study V* exclusion criteria were dementia, malignancy, an additional episode of severe acute pancreatitis, or chronic pancreatitis. Fifteen patients with severe and 30 with mild disease were invited to the follow-up survey. Finally, 14 patients with a history of severe and 26 cases with a history of mild disease agreed to be included.

Study IV

A questionnaire comprising 12 questions concerning management of pancreatic pseudocysts was e-mailed, in the spring of 2008, to the head surgeons in all hospitals in Sweden that possibly could treat patients with acute pancreatitis (n=63). Reminders were sent by e-mail, surface mail or via telephone calls. Five hospitals were excluded because they no longer treated this particular patient category. Finally, 51/58 (88%) of the hospitals treating pancreatic pseudocysts in Sweden answered the questionnaire. Nine of ten university hospitals reported, with a primary catchment area of 150 000-360 000 persons (median: 290 000), and 42/48 non-university hospitals, with 23 000-580 000 inhabitants per hospital (median: 120 000). In total, 24 non-university hospitals had a primary catchment area of less than 150 000 persons. Data were collected from the answers.

Study VI

A total of 60 patients with the diagnosis acute pancreatitis were identified, aided by computer search, from the 13468 adults (age ≥18 years) undergoing autopsy at the department of Forensic Medicine during the period 1990-2008. Six had been admitted to hospital and four did not have acute pancreatitis as their main cause of death, and were therefore excluded. Finally, 50 patients were included in the study.

3.2 Study design and data collection

In *Studies I, III* and *VI* the design was retrospective clinical surveys. The patient materials in *Studies II* and *V* consisted of prospectively included patients. In *Study II* the material was retrospectively supplemented. *Study IV* was based on information collected via a national questionnaire study.

Study I, III

Demographic data, aetiology, length of hospital stay, recurrent disease, laboratory parameters, cultures, medical treatment, fluid resuscitation, radiological investigation, interventions, complications, and death were registered from the case records. The radiological investigations were in unclear cases re-evaluated by a specialist in radiology to determine pseudocyst size.

Study II

From the prospectively included patients (n=139) and available data, the addition of possible risk factors at the time of admission to hospital was collected from case records. These were included in the ANN training. Missing values were replaced using the probability imputation technique before the ANN was trained. The probability imputation technique substitutes conditional probabilities for missing covariate values when the covariate is qualitative[182]. A temporal validation of the final ANN risk model was performed on a second dataset, including 61 patients treated during a more recent time period.

Study IV

A questionnaire, consisting of 12 questions designed specifically to obtain information on management and treatment options of pancreatic pseudocysts, was created (Figure 3.1).

Pancreatic pseudocysts – treatment and follow-up:

1. Are there guidelines concerning treatment of pancreatic pseudocysts at your hospital?
Yes [ ] No [ ]
2. Which treatment options are available at your hospital?

Treatment	Yes	No
Percutaneous punction and drainage		
Percutaneous cystogastrostomy		
Endoscopic drainage (transmural and transpapillary)		
EUS-assisted endoscopic drainage		
Laparoscopic surgery		
Open surgery		

3. Are multidisciplinary team conferences held for patients with pseudocysts at your or another hospital? Yes [ ] No [ ]
Comments: …
4. Do you refer some of these patients to another hospital for investigation/treatment?
Yes [ ] No [ ]
Comments: …
5. Are complicated cases of pancreatic pseudocysts referred to your hospital?
Yes [ ] No [ ]
Comments: …
6. Do you have different treatment strategies for treatment of pseudocysts after acute or chronic pancreatitis? Yes [ ] No [ ]
Comments: …
7. Roughly how many patients with pseudocysts are treated yearly with any of the treatment options?
8. Which treatment option (including conservative) is your first choice in the clinical situations presented below:

- A large (>8 cm) but asymptomatic pancreatic pseudocyst after acute pancreatitis?
- A symptomatic non-infected pancreatic pseudocyst after acute pancreatitis?
- A symptomatic infected pancreatic pseudocyst after acute pancreatitis?
- Multiple pancreatic pseudocysts in chronic pancreatitis?
- A 5 cm large pancreatic cyst in the tail of the pancreas without a history of acute or chronic pancreatitis?

Figure 3.1. Questionnaire concerning pancreatic pseudocysts, originally written and used in the Swedish language.

Study V

A thorough physical and physiological investigation was performed on every patient at the outpatient clinic. Blood samples were taken in the fasting state and during a 75g-2 hour oral-glucose tolerance test (OGTT). The homeostasis model assessment (HOMA) for evaluating insulin resistance (HOMA IR = fasting insulin (mIE/ml) x fasting glucose (mmol/L) / 22.5) was calculated. A faecal sample was collected. All patients completed a questionnaire examining current pancreatic function, medication, abdominal surgical interventions, eating and drinking habits, readmissions for pancreatitis, ability to return to normal daily activity, and time until the patient had recovered from the acute episode of pancreatitis. The patient's ability to work was noted. Quality of life forms were completed. Several aspects of the patients' current condition were evaluated, using a visual analogue scale (VAS: 0-100).

The Swedish version of Standard Short Form 36 (SF-36), a widely used general quality-of-life questionnaire that has been validated in a variety of medial settings, was used[159]. The SF-36 examines 8 areas consisting of physical function (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (RE), and mental health (MH). Swedish normative data of age-matched controls were used for comparison. An exact gender and age matched reference group (n=84) was randomly selected for the severe group from the Swedish SF-36 norm database (n=8930). Seven referent persons were used for each patient (quota=6:1). The numbers of referent persons were decided from the lowest available number representing one study patient (female, 83 years old). The corresponding figures for mild acute pancreatitis was a referent group of 182 persons, and a quota of 7:1, decided from the lowest available number representing one study patient (male, 79 years old).

Costs, obtained from the Department of Economics at the hospital, were calculated as total hospital costs per patient at the primary hospital stay, including expenses at the ward, ICU stay, anaesthesia and operating costs, radiological and clinical physiology expenses and costs for laboratory analysis and blood products. Subsequent costs, both for in-hospital stay and outpatient care, directly related to the primary acute pancreatitis episode, was further

analysed. Sick leave days were retrieved from the patient's medical records and from the patients at follow-up visits.

Study VI

Data was based on police records and a complete forensic autopsy that was performed in all cases. This includes collection and analyses of blood samples. The abdomen, thorax and cerebral spaces are opened and gross findings from all organs are noted. Tissue specimens are collected from the pancreas, liver, lung, heart and kidney for histological examination. Specimens are fixed in 4 % formalin and embedded in paraffin, and sections are then stained with haematoxylin and eosin for histological studies.

From available documents a number of factors including sex, age, circumstances of death, social background of the deceased, blood alcohol concentration at the time of death, BMI, aetiology, autopsy findings and histopathology was collected.

3.3 Definitions

Acute pancreatitis was defined as an increase in serum pancreas amylase to at least three times the upper normal level, in association with typical symptoms of the disease.

The definitions for severe acute pancreatitis and organ failure in *Study I* were according to Table 3.1 and in *Study II* and *VI* according to a modification of the Atlanta Classification definitions (including organ failure and or local complications - pancreatic necrosis, pancreatic pseudocyst or pancreatic abscesses). Solely clinical manifestations, such as APACHE II≥8 or fluid collections was not considered enough for being a severe disase[38].

In *Study I* and *III* the aetiology was considered to be of biliary origin when gallstones were found on radiological examination and/or ERCP and when the patients had no history of alcohol abuse or other disease that might affect the liver and pancreas. Alcohol was registered as the aetiological factor when there was a history of alcohol abuse. In the absence of gallstones or alcohol abuse, the classification was other/unknown. In *Study VI*, in presence of both alcohol abuse and gallstones, the exact aetiology was not settled unless the gallstones obviously had obstructed the main bile duct, in which case the aetiology was determined to be of biliary origin.

Table 3.1. Definition of severe acute pancreatitis and organ failure according to *Study I*.

	Definitions
Severe acute pancreatitis	• Organ failure and/or • Hospital stay more than 7 days, together with at least one of: o CRP>150 mg/L during the first 72 h after admission o Pancreatic necrosis, confirmed by CT o ICU treatment
Single organ failure	• respiratory failure (need for support by ventilator) • renal failure (<100ml urine/24 h) • circulatory failure (blood pressure <90mm hg and/or inotropic support).
MODS	Two or more failing organ systems

In *Study I* and *III* the aetiology was considered to be of biliary origin when gallstones were found on radiological examination and/or ERCP and when the patients had no history of alcohol abuse or other disease that might affect the liver and pancreas. Alcohol was registered as the aetiological factor when there was a history of alcohol abuse. In the absence of gallstones or alcohol abuse, the classification was other/unknown. In *Study VI*, in presence of both alcohol abuse and gallstones, the exact aetiology was not settled unless the gallstones obviously had obstructed the main bile duct, in which case the aetiology was determined to be of biliary origin.

Recurrence in pancreatic pseudocysts was defined as recurrence after initial resolution or regression, or failure of a chosen treatment, necessitating further intervention because of symptoms.

The guidelines and definitions established by the World Health Organisation (WHO) were followed concerning performance of the

OGTT and the definition of diabetes mellitus and impaired glucose tolerance[183]. This implies that fasting plasma glucose ≥7.0 mmol/l meets the criterion for diabetes mellitus and 6.1-6.9 mmol/l for impaired fasting glucose. OGTT plasma glucose values ≥11.1 mmol/l at 2 hours are defined as diabetes, and values between ≥7.8 and <11.1 mmol/l as impaired glucose tolerance.

All costs are given in 2008 price levels, inflated using the Swedish consumer price index. The costs have been converted from Swedish krona (SEK) to Euros (€) using the yearly average exchange rate for 2008 (9.6055 SEK to €1).

Classification of the pancreatic histopathological changes was performed according to the proposal by Enquist et al[184]: acute interstitial (oedematous) pancreatitis, acute pancreatic necrosis, acute pancreatic necrosis with haemorrhage, and acute pancreatic necrosis with suppuration.

3.4 Statistical Methods

Mean (±SD) or median (range in *Study I, II, IV* and interquartile range in *Study II, V, VI*) was used to describe continuous variables. For categorical data, absolute numbers in addition to percentages were given. Univariate analysis for continuous variables was conducted with the unpaired Student's t test (*Study I, II, III*) or the Wilcoxon test (*Study II*, IV-*VI*) or the Mann-Whitney test (*Study III*). Categorical variables were analyzed by the χ^2 test, except when expected frequencies were less than 5, in which case the Fisher's exact test was used.

3.4.1 Logistic regression

Multivariate analysis (*Study I, II, III*) was performed using stepwise logistic regression for categorical outcome and stepwise linear regression for continuous outcome. Inclusion criteria for the full model was $P<0.200$. The limit for stepwise backward elimination was $P<0.100$. A probability level of a random difference of $P<0.05$ was considered significant.

In *Study II* logistic regression analysis was performed to obtain the coefficients for the risk variables included in the logistic model, as described by Hosmer and Lemeshow[82].

3.4.2 Performance analysis

To compare the number of correctly classified patients by ANNs, the logistic regression model, and APACHE II, a proportion test were used. The confidence limits for the output from the ANN were calculated using bootstrap technique[75]. The Receiver Operating Characteristic (ROC) curves were used to describe the performance and predictive accuracy of the models[185]. The area under the curve, with 95% CI, was used as a quantitative measure of the ability to compare the number of correctly classified patients by ANNs, by logistic regression, and by the APACHE II model. To compare the areas under the resulting ROC curves, the non-parametric approach described by DeLong and co-workers[186] was used.

3.4.3 Time to event

In *Study V*, the Kaplan-Meier estimate was used to calculate time to event. The log-rank test was used to compare the difference between the groups.

3.4.4 Artificial neural networks – training and validation

An ensemble approach was used. Several ANNs were combined into a single prediction model. The individual members in the ensemble were standard multilayer perceptrons with 6 hidden layers and an output node used to encode the severity of acute pancreatitis[187]. Each multi-layer perceptron was trained using conjugate gradient descent applied to a mean square error function. To avoid over-training and improve the generalization performance, a weight decay regularization term was used. The calibration of the model was performed using a fivefold cross-validation procedure (Figure 3.2).

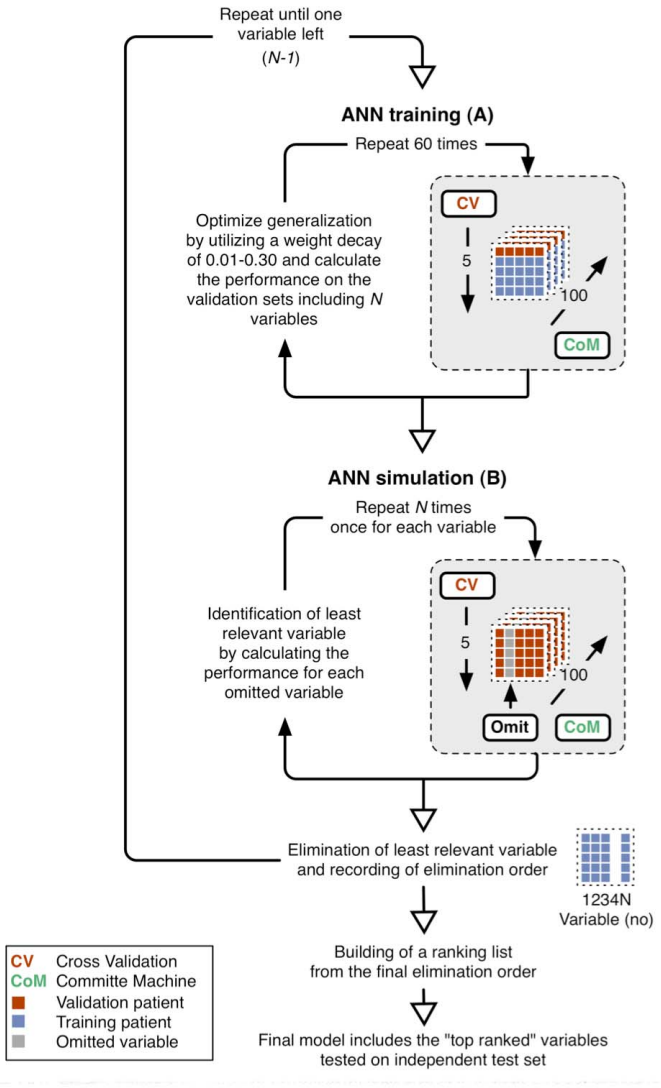


Figure 3.2. Schematic illustration of the variable-ranking process. A: Training the ANN model by fivefold cross-validation (CV), using a committee machine (CoM) with 100 samples. B: Simulation using the optimized ANNs (n=50) from (A) to rank the variables.

3.4.5 Risk factor identification

To select the most important risk variables and to minimize the number of variables included in the final model, a ranking of risk variables was performed. A baseline ROC area was created using all variables (N=23). The order of relevance was obtained by measuring the change in ROC area when one risk variable was omitted from the model. This procedure was repeated for each of the variables included. The least relevant variable corresponded to the largest increase in the ROC area when omitted from the model. To optimize the model, the bottom-ranked variable was eliminated and the ANNs were recalibrated, using N-1 variables, and a new identification procedure of the least relevant variable was performed. This procedure was repeated until only one variable remained (Figure 3.2). The final ranking list was constructed from the top-ranked variables, which improved performance of the model.

Effective odds ratios for the risk variables were determined as described by Lippmann and co-workers[77]. By changing the risk variable in a patient from absent to present and calculating the odds for the two conditions, an odds ratio for the specific risk variable of each patient could be determined. An effective odds ratio for the specific variable was obtained by computing the geometric mean of the odds ratios from all patients.

3.4.6 Bootstrapping

The 80% confidence intervals for both the output from the ANNs and the odds ratio were calculated using the bootstrap technique[77, 188]. From the original database, 200 bootstrap training data sets were created by resampling with replacement. These bootstrap training sets were then used to calibrate new ANN models with the same architecture and parameter settings as for the final ANN risk prediction model. Each ANN model generated a classification (percentage mortality risk) for each individual patient, resulting in 200 different classifications for each patient. Standard techniques[77, 188] were then used to extract the confidence intervals from these sets of risk predictions. The confidence intervals of the odds ratio for each risk variable were calculated in the same way.

3.4.7 ANN and statistical software

The ANN calibration and analyses were performed with MATLAB 2010a Distribution Computing Server (MathWorks, Natick, MA).

Statistical analyses were in *Study I-IV* performed with Intercooled Stata statistical package for Mac OS X (Stata Corporation, College Station, Texas, USA). In *Study V* and *VI* data were analysed using the R software (R Foundation for Statistical Computing, Vienna, Austria).

Chapter 4

Results

4.1 Study I - Severe acute pancreatitis – outcome following a primarily non-surgical regime

Of the included 175 patients with severe acute pancreatitis, the mean age was 61±17 years. The women were older than the men (65 versus 59 years, *P*=0.017). 107 patients (61%) were men and alcohol was more common as the aetiology for acute pancreatitis in men (38 versus 8, *P*<0.001). Patients with biliary pancreatitis (n=72) were older than subjects where alcohol was the cause (68 versus 48 years, *P*<0.001). Aetiology, surgical interventions and outcome are shown in Figure 4.1.

CT examination was performed in 145 patients (83%), and more frequently in men (96 versus 49, *P*=0.001). US were performed in 121 patients (69%), revealing biliary stones in 47 (39%).

Blood cultures were taken in 55 of the patients (31%), with growth of bacteria verified in 19 (35%). Pancreatic tissue or abdominal fluid was cultured in 24 of the patients (14%), with bacterial growth demonstrated in 21 (88%). Antibiotics were given to 150 patients (86%), starting 1 (1-12) days after admission.

Overall fluid resuscitation rate the first day was in mean 3100 ±1900 ml and during the first three days 10000±3700 ml, also including patients with very early deaths.

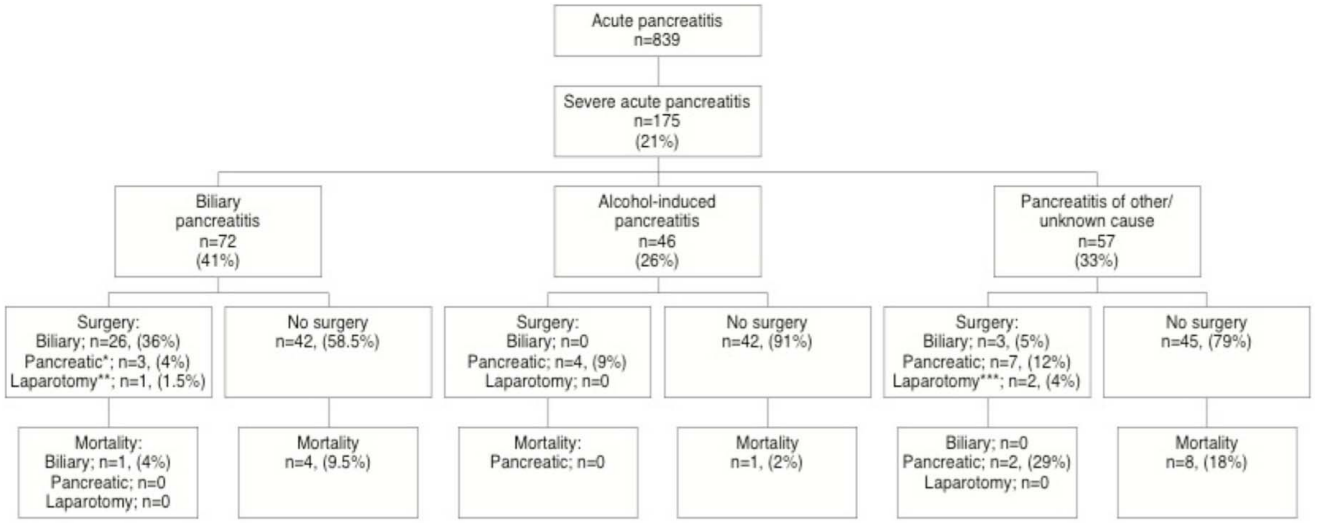


Figure 4.1. Figure illustrating aetiology, surgery and mortality for patients investigated. *Cholecystectomy was performed at the same operation as pancreatic necrosectomy in two patients, **explorative laparotomy performed as perforated duodenal ulcer could initially not be ruled out, cholecystectomy performed at a later operation, ***explorative laparotomy due to suspicion of bowel ischemia after cardiac surgery; and diagnostic laparoscopy and explorative laparotomy due to initial uncertain diagnosis.

The hospital stay was in median 13 (1-160) days. For length of hospital and ICU stays, pancreatic surgery was the only identified independent risk factor (both $P<0.001$).

Sixteen patients (9%) died in-hospital and 14 deaths (88 %) were associated with MODS. Half of the deaths occurred within 7 days after admission. One fourth died after more than 14 days, all due to MODS in combination with sepsis. Overall 14 (45%) of patients contracting MODS died.

Relapses of acute pancreatitis were common, occurring in 64 patients (37%). Of patients with biliary pancreatitis, 28 had a cholecystectomy performed during the primary hospital stay. 11/44 patients (26%) in the non-operated group with biliary-induced acute pancreatitis suffered from recurrence already within 3 months after discharge (Figure 4.2).

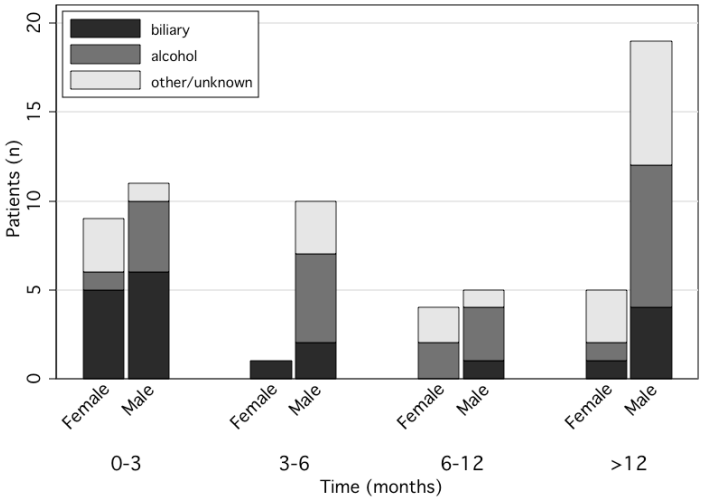


Figure 4.2. Recurrence of acute pancreatitis. The table illustrates time to recurrence and differences concerning sex and aetiology.

Data dividing the material in patients <65 and ≥65 years of age are presented in Table 4.1. Older patients had an increased mortality risk, but were not more frequently admitted to the ICU.

Table 4.1. Outcome following severe acute pancreatitis in patients less than 65 years of age or 65 years and older.

Variables	Age<65years	Age≥65years	*P* value
	n=93	n=82	
Mortality	3(3)	13(16)	0.004
Hypotension (systolic BP <100 mm Hg)	6(6)	9(11)	0.286
Surgery	24(26)	22(27)	0.878
Complications			
- MODS	14(15)	17(21)	0.326
- respiratory failure	17(18)	17(21)	0.682
- renal failure	5(5)	16(20)	0.004
- circulatory failure	11(12)	19(23)	0.047
ICU	23(25)	24(29)	0.499

Values in parentheses are percentages.

Of the potential risk factors for death possible to register already by the time of admission, age and hypotension (defined as systolic blood pressure <100 mm Hg) were identified by multivariate analysis as risk factors for death (Table 4.2).

Table 4.2. Independent predictors for death due to severe acute pancreatitis (n=175).

Variables	Odds ratio	*P* value
Age	1.05(1.01-1.09)	0.014
Hypotension at admission	5.42(1.42-20.75)	0.014

Values in parenthesis are 95 per cent confidence intervals.

4.2 Study II - Prediction of severe acute pancreatitis at admission to hospital using artificial neural networks

Twenty patients (14%) in the development set (n=139) fulfilled the criteria regarding severe acute pancreatitis. In the temporal validation set (n=61) 8 patients fulfilled the criteria for severe disease.

Different ANN models were validated using different ANN architectures. The final ANN model was constructed with one hidden layer containing six nodes, one output node and 100 individual members of the ensemble. This architecture was used in the selection of risk factors used for the severity prediction.

Parameters collected at admission and included in the model, and the risk factors, ranked in order of influence upon discriminatory power, are presented in Table 4.3.

The largest validation ROC area was achieved when the 6 top-ranked risk variables were selected (Figure 4.3). These included duration of pain until arrival at the emergency department, creatinine, haemoglobin, alanine aminotransferase (ALAT), heart rate, and white blood cell count. The logistic regression model selected four of the eight variables: creatinine, haemoglobin, heart rate, and duration of pain until arrival at the emergency department.

The discriminatory power (i.e. the area under the ROC curve) for severity stratification in AP was significantly greater for the final ANNs, at 0.92 (95% CI: 0.83-0.99) than for APACHE II, at 0.63 (95% CI: 0.50-0.76; χ^2=17.6; P<0.001) for the logistic model with four of the eight top-ranked risk variables, 0.84 (95% CI: 0.76-0.92; χ^2=4.6; P=0.031) (Fig. 4.4, Table 4.4).

At a sensitivity of 25%, 50%, and 75% the number of correctly classified patients with mild AP was 119, 118, and 111 for the ANN model; 109, 75 and, 40 for APACHE II; and 117, 103 and 90 for the logistic regression model. The difference between the ANNs and the APACHE II score was significant for all 3 sensitivity cut-off values (P=0.001, P<0.001 and P<0.001), and between the ANNs and the logistic regression model at 50% and 75% sensitivity cut-off (P=0.002 and P=0.002).

Table 4.3. Prevalence of risk factors in the study material, ranked in order of importance for the discriminatory power (ROC area) in classification of severe acute pancreatitis. The factors ranked 1-6 had a positive impact on the performance of the ANN model.

Rank No.	Risk variable	Mild (n=119)	SAP (n=20)	Odds Ratio
1	Duration of pain (h)	12 (6-24)	5 (2-14)	0.705
2	S-creatinine (μmol/L)	68 (56-81)	71 (62-86)	1.020
3	B-Hb (g/L)	140 (130-150)	146 (140-160)	1.389
4	S-ALAT (μkat/L)	3.1 (0.8-6.5)	1.1 (0.5-2.4)	0.710
5	Heart rate	80 (67-88)	83 (77-106)	1.247
6	B-WBC (10^9/L)	12 (9-14)	17 (11-19)	1.236
7	Systolic blood pressure (mmHg)	140 (125-160)	136 (113-160)	
8	Temperature (°C)	37 (37-38)	37 (36-38)	
9	P-CRP (mg/L)	11 (6-41)	14 (6-50)	
10	Female gender*	56 (47)	8 (40)	
11	BMI (kg/cm^2)	28 (26-32)	28 (25-30)	
12	First-time pancreatitis*	98 (82)	17 (85)	
13	SaO_2 (%)	96 (95-97)	96 (94-97)	
14	P-glucose (mmol/L)	7.0 (6.0-8.4)	8.1 (6.5-8.5)	
15	S-ASAT (μkat/l)	2.6 (0.8-6.4)	0.9 (0.6-2.7)	
16	Chronic illness*	56 (48)	8 (50)	
17	S-bilirubin (μmol/l)	26 (14-46)	16 (10-29)	
18	S-GGT (μkat/L)	4.1 (1.7-10)	1.8 (0.7-5.1)	
19	S-ALP (μkat/L)	5.8 (2.8-8.5)	3.2 (2.2-5.4)	
20	S-Na (mmol/L)	140 (138-142)	140 (136-143)	
21	S-pancreatic amylase (μkat/L)	18 (8-33)	19 (11,44)	
22	S-K (mmol/L)	3.8 (3.6-4.0)	3.7 (3.5-4.0)	
23	Age (years)	62 (48-76)	61 (42-76)	

Values in parentheses are median (interquartile range) except where *percentages.

To evaluate whether the final ANN risk prediction model was applicable to a patient cohort that had not been used in the development of the ANNs, a subset of patients, with no missing value in the 6 top-ranked variables, was used as a temporal validation set. In this cohort, the ROC area was 0.84 (95% CI: 0.72-0.96) for the ANNs.

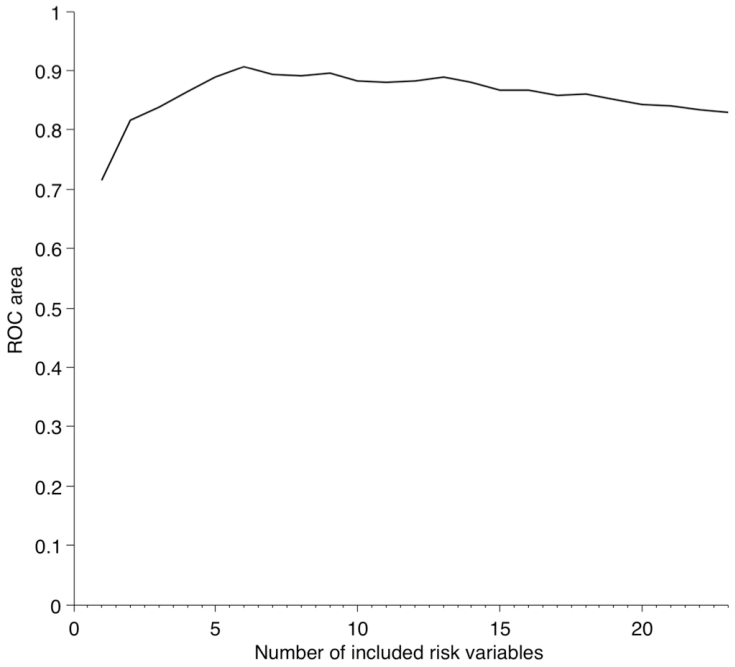


Figure 4.3. The solid line shows the validation ROC area (y-axis) from the ANNs with different numbers of risk variables included (x-axis).

Table 4.4. The receiver operating characteristic (ROC) area for different prediction models in the validation set.

Prediction model	ROC area (95% CI)	*P* value
Artificial neural network model	0.92 (0.85-0.99)	
Logistic regression model	0.84 (0.76-0.92)	0.031[a]
Apache II	0.63 (0.50-0.76)	0.001[b]

a The *P* value for the ANN model compared with the logistic regression model.

b The *P* value for the ANN model compared with the APACHE II model.

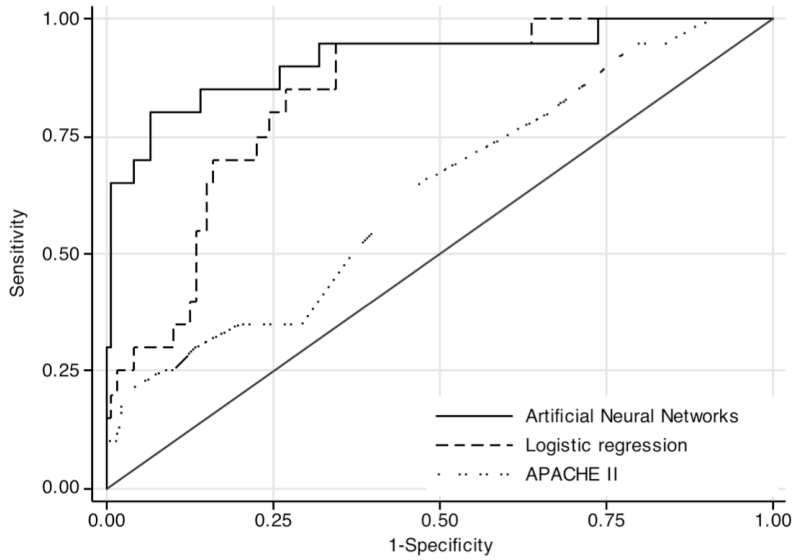


Figure 4.4. The receiver operating characteristic (ROC) curves from the validation data set: the ANN model (solid line), logistic regression model (dashed line), and the APACHE II (dotted line). The area under the curve for the ANN model (0.92) is greater than for the APACHE II (0.63), χ^2=17.6; *P*=0.001 and the Logistic regression model (0.84), χ^2=4.6; *P*=0.031.

4.3 Study III - Treatment and outcome in pancreatic pseudocysts

The mean age of included patients were 55±14 years and the majority (n=29, 66%) were men. Alcohol as aetiological factor was more common than biliary disease (21 versus 15, *P*=0.006). Thirty-four patients (77%) had a history of acute pancreatitis (seven of these had recurrent acute disease) and 10 chronic pancreatitis (23%). The size of the largest pseudocyst for each patient when diagnosed was in median 8 (1.5-40) cm. At diagnosis the patients presented with a mean of 1.4±0.9 (1-5) pseudocysts, without difference between acute and chronic disease (*P*=0.101).

Radiological or endoscopic investigations and treatment was performed as follows: US in 41 (93%) patients, CT in 40 (91%) patients, ERCP in 15 (34%) patients, gastroscopy in 13 (30%) patients, and angiography with embolisation in two patients, in one case due to a pseudoaneurysm of the splenic artery and in the other due to a pseudoaneurysm of the superior mesenteric artery.

Symptomatic pseudocysts were common and among symptoms at diagnosis of the pseudocyst, the following were registered: abdominal pain or back pain in 39 (89%), nausea/vomiting in 23 (52%), elevated temperature, defined as ≥37.8°C, in 20 (45%), palpable tumour in 12 (30%), abdominal distension/intestinal obstruction in 4 (9%) and sepsis in 3 (7%) patients.

Conservative treatment was more common as the initial treatment of choice for patients with acute pancreatitis as compared to chronic pancreatitis (P=0.046), though no difference was seen concerning recurrence rate. Eighteen patients in the entire group had no recurrence of the pseudocyst disease following initial treatment (41%). Recurrence overall occurred in a mean of 1.0±1.1 times (median 1; range 0-4) per patient. For the entire group, 88 different occasions with conservative (n=21) and interventional treatment (n=67) were seen. The total recurrence rate after treatment was 44 (50%), Table 4.5. Surgery tended to be associated with less recurrences than other interventions (P=0.062).

Table 4.5. Pancreatic pseudocyst size and recurrence with different treatment regimes.

Treatment	Pseudocyst size (cm)*	Treatment number (recurrence/total)					
		1	2	3	4	5	Total
Conservative	8.3±5	11/21	0	0	0	0	11/21
Percutaneous							
- puncture	7.4±4	6/8	6/8	2/3	0/2	0	14/21
- drainage	12±9	7/10	2/5	0/2	0/1	0/1	9/19
- cystogastrostomy	12±5	1/2	2/7	2/3	1/1	0	6/13
Surgery	7.1±3	1/3	1/6	2/3	0/2	0	4/14
Total	9.3±6	26/44	11/26	6/11	1/6	0/1	44/88

*Values are mean±S.D. before each treatment occasion.

Conservatively managed patients were heavier (*P*=0.021) and more often had acute pancreatitis (*P*=0.046) as compared to patients whose first treatment was interventional. In a multivariate analysis, no patient risk factor was shown to influence the risk of recurrence.

Treatment of pancreatic pseudocysts was resource demanding. The length of individual stay at the initial admission was in median 12 days (range 0-141) per patient, and in median 3 hospital stays (range 0-16) per patient was required. Eleven patients (25%) needed intensive care; 9 (82%) of these had a recurrence, and 5 (45%) complications after treatment. Complications were in total registered in six patients, including infection (3 patients), fistula (1 patient), and postoperative bleeding (2 patients). A total of ten (23%) patients died during the study period. Three (7%) of these deaths were directly related to the pseudocyst disease. Comparison of patient characteristics and outcome in pseudocysts < 8 cm and ≥8 cm in diameter are presented in Table 4.6.

Table 4.6. Comparison of different parameters for patients with pseudocysts <8 cm and ≥8 cm in diameter (size measured before treatment start).

	Pseudocysts <8 cm (n=21)	Pseudocysts ≥ 8 cm (n=23)	*P* value
CRP (mg/L)*	42(4-285)	101(5-411)	0.183
Weight (kg)#	74±12	77±20	0.503
Bilirubin (μmol/L)*	11(3-27)	11(4-256)	0.526
Acute pancreatitis	16(76)	18(78)	0.870
Nausea/vomiting	10(48)	13(57)	0.555
Pain: stomach and/or back	21(100)	18(78)	0.050
Pain at abdominal examination	19(90)	16(70)	0.089
Palpable tumour	2(10)	11(48)	0.008
Fever ≥ 37.8°C	8(38)	12(52)	0.349
Recurrence	12(57)	14(61)	0.802
Conservative treatment	11(52)	10(43)	0.555
Complications after treatment	1(5)	5(22)	0.101
LOS*	10(0-141)	12(0-60)	0.814

Values in parenthesis are percentages except where median(range)* and mean±S.D#.

4.4 Study IV - Survey of the management of pancreatic pseudocysts in Sweden

Pancreatic pseudocysts requiring treatment were estimated to occur in 232 patients per year among the 51 hospitals answering the questionnaire. When adjusting for missing and non-responders to the questionnaire, this was extrapolated to a total number of about 300 patients with pancreatic pseudocysts managed yearly in Sweden. University hospitals treated more patients, i.e. 7 (4-15) patients per hospital annually, versus 3 (1-25) patients in non-university hospitals (P=0.007). Five hospitals, of which one was a university hospital, had written guidelines for the management of patients with pancreatic pseudocysts.

In Figure 4.5 the treatment alternatives available at different hospitals are presented. The most striking difference was registered for EUS (more common in university hospitals, 6/9 versus 3/42; P<0.001) and endoscopic drainage (8/9 versus 17/42; P=0.008).

Treatment strategies for the management of pseudocysts after acute as compared to chronic pancreatitis were more frequently differentiated for hospitals with 150 000 persons or more in the primary catchment area (16/25) versus smaller hospitals (5/22; P=0.005). Multidisciplinary team conferences were regularly held in 75% of the hospitals, with no difference between hospital types.

Twenty-six departments (53%) reported that they probably would refer at least some patients to another hospital for treatment. However, six made a comment that this rarely happened. 4/22 (18%) of the hospitals with <150 000 persons in their primary catchment area stated that they never refer patients with pancreatic pseudocysts, not even in complicated cases. Fourteen (28%) of the hospitals regularly cared for patients referred from other hospitals.

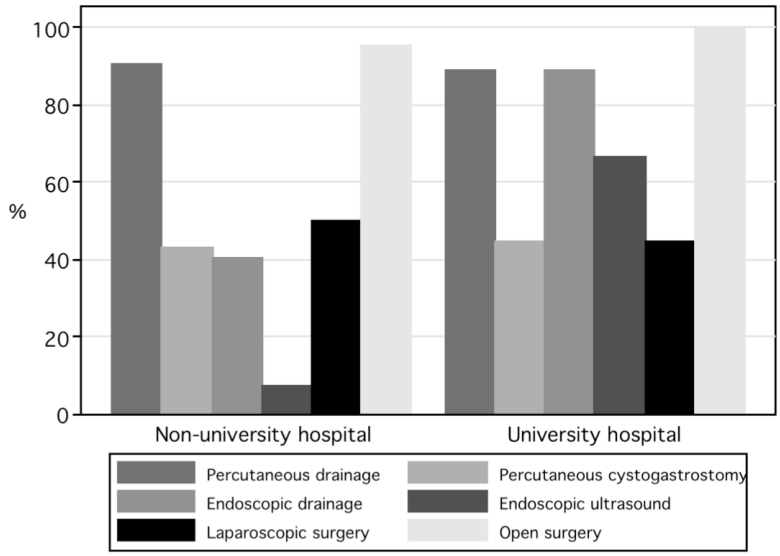


Figure 4.5. Presentation of treatment options for pancreatic pseudocysts available at university (n=9) and non-university hospitals (n=42).

Five clinical situations with pancreatic pseudocysts were presented in the questionnaire, asking for the primary choice of therapy, including conservative treatment. The first case was a large (>8cm), but asymptomatic pseudocyst after acute pancreatitis. The majority, 35 (74%), chose conservative treatment, but 12 (26%) wanted to perform an invasive procedure, with no difference depending on the primary catchment area or category of hospital (Figure 4.6).

When treating symptomatic non-infected pancreatic pseudocysts after acute pancreatitis, the vast majority of hospitals (36, i.e. 82%) chose an invasive approach. Endoscopic drainage was more common in university hospitals (4/8 versus 4/34; *P*=0.005). Eight hospitals (18%) preferred a conservative approach and 7 failed to answer (Figure 4.7).

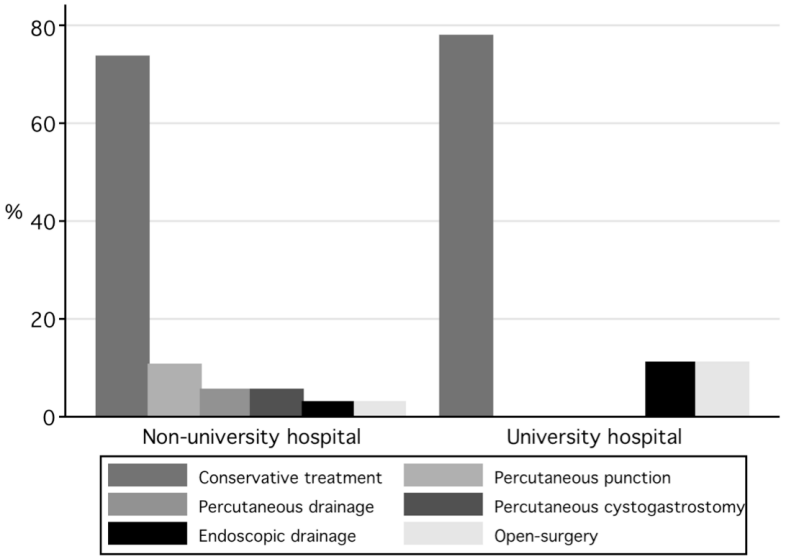


Figure 4.6. Presentation of the primary treatment option (including conservative) chosen in the clinical situation with a large (>8 cm), but asymptomatic pancreatic pseudocyst after acute pancreatitis in university and non-university hospitals.

None of the 44 answering departments advocated a conservative approach for a symptomatic and infected pancreatic pseudocyst. Percutaneous drainage was most commonly chosen, in 26 (59%), of which 3 preferred percutaneous cystogastrostomy. In one hospital, only percutaneous puncture was made. In 7 hospitals an endoscopic technique was used, more commonly in university hospitals (4/9 versus 3/33; *P*=0.004). Eight preferred open surgery and 2 referred the patients to another hospital (Figure 4.8).

The majority, 27 (59%) of the centres, preferred conservative treatment in the case of multiple pseudocysts in chronic pancreatitis. In addition, 7 chose a conservative approach, drainage or surgery depending on symptoms and 3 wanted further investigations. One centre preferred percutaneous drainage and in 4 centres the preference was to perform ERCP drainage. Four centres primarily referred these patients and 5 did not answer.

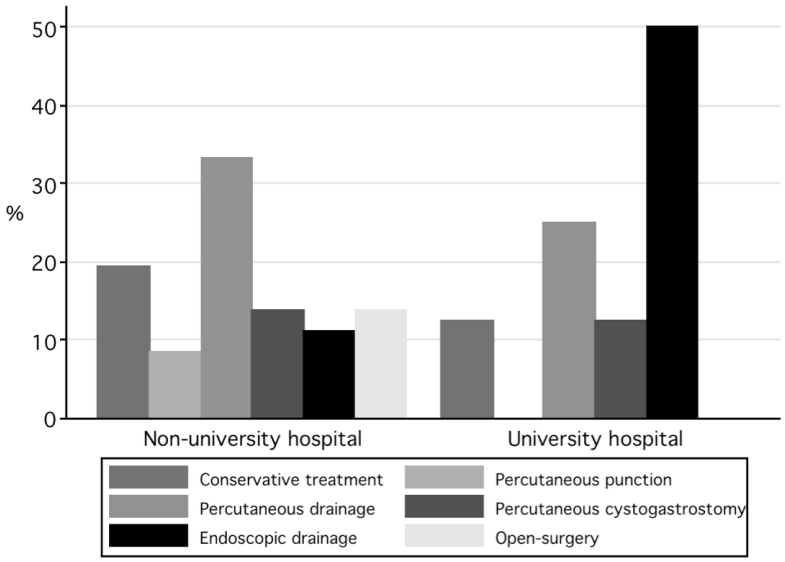


Figure 4.7. Presentation of the primary treatment option (including conservative) chosen in a situation with a symptomatic, non-infected pancreatic pseudocyst after acute pancreatitis, in university and non-university hospitals.

A pancreatic cyst in the pancreatic tail with a diameter of 5 cm, with no history of acute or chronic pancreatitis was a patient case that 34 (77%) centres wanted to follow-up, with the recognition that it could be a pre-malignant or even a malignant lesion. In 3 hospitals EUS was chosen as the next procedure and at 10 units cytological specimens would be the next step. In 6 hospitals surgery was chosen, more often in university hospitals (4/8 versus 2/36; P=0.011). Four centres (9%) would, however, practice a conservative approach and did not make any arrangements for follow-up. Seven centres failed to answer.

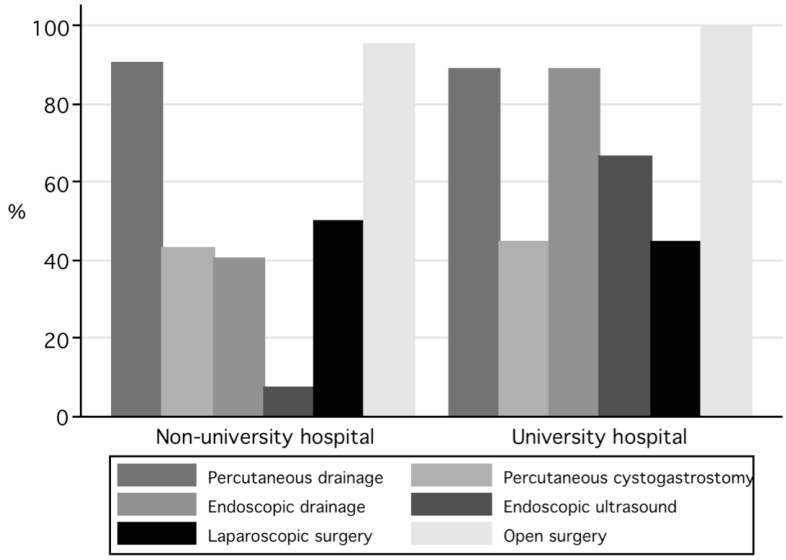


Figure 4.8. Presentation of the primary treatment option (including conservative) chosen in a situation with a symptomatic infected pancreatic pseudocyst after pancreatitis, in university and non-university hospitals.

4.5 Study V - Pancreatic function, quality of life and costs long-term after acute pancreatitis

This study finally included 40 patients; 16 (40%) were men. No difference was seen in routine laboratory parameters between patients with a history of mild and severe disease. Different patient characteristics and parameters are specified in Table 4.7.

There were no significant differences between the groups concerning steatorrea (1/14 versus 2/26), change in bowel habits (4/14 versus 10/25) or pancreatic enzyme supplementation (2/14 versus 1/26). Most patients had a weight-loss during the acute disease. 4/14 versus 5/26 still had a decreased weight at follow-up as compared to the situation before the disease, though without difference between the groups. A change in diet was more common after severe acute pancreatitis (6/26 versus 9/14, P=0.01). Faecal

elastase-1 was decreased only in one patient, having a history of severe disease.

Table 4.7. Patient characteristics and parameters at the follow-up after mild and severe acute pancreatitis.

Parameter	Mild acute pancreatitis (n=26)	Severe acute pancreatitis (n=14)	All patients (n=40)	Difference between groups
Time to follow-up (months)	41 (35-50)	47 (37-63)	42 (36-53)	*P*=0.14
Age (years)	61 (51-70)	58 (45-67)	61 (48-68)	*P*=0.72
BMI (kg/m^2)	27 (25-32)	29 (26-31)	28 (26-31)	*P*=0.82
ASA	2 (1-2)	1 (1-2)	1.5 (1-2)	*P*=0.68
S-pancreasamylase (μkat/L)	0.45 (0.37-0.53)	0.27 (0.18-0.43)	0.043 (0.27-0.52)	*P*=0.007
P-ALAT (μkat/L)	0.30 (0.23-0.47)	0.39 (0.33-0.54)	0.34 (0.29-0.50)	*P*=0.035
Sick-leave days	14 (7-30)	120 (70-165)	30 (14-97)	*P*<0.001
Time to activity (days)	10.5 (0-21)	90 (60-365)	21(2-60)	*P*<0.001
Time to recovered (days)	21 (14-60)	270 (180-*)	60 (14-365)	*P*=0.005

* Seven patients did not feel recovered at time for follow up.

Fasting P-glucose, as well as the P-glucose after the OGTT was higher in patients with a history of severe as compared to mild acute pancreatitis (*P*=0.055 and *P*=0.044, respectively; Figure 4.9), and a difference was also registered for HbA1C (*P*=0.041). Patients with a history of severe disease more frequently fulfilled the criteria for DM and/or IGT in either fP-glucose or 120min P-glucose, or both, (11/14 versus 11/25; *P*=0.037). There was no significant difference in the incidence of DM when comparing different aetiologies of acute pancreatitis. fP-C-peptide, as well as 120 min P-C-peptide, had a tendency to be lower in the severe acute pancreatitis group, though without statistical significance (Figure 4.9).

P-C-peptide was higher in patients fulfilling the criteria for DM, both fasting and after the OGTT, and a significant difference was also seen for S-Insulin (Table 4.8). Insulin resistance, expressed as HOMA-IR had, however, a tendency to be lower in patients with DM and/or IGT after severe disease.

Table 4.8. Endocrine parameters in patients classified as having diabetes (according to the definition by the World Health Organization) versus patients not fulfilling the criteria.

Parameter	Diabetic patients (n=9)	Non-diabetic patients (n=30)	Difference between groups
fP-glucose, 0 min*	6.9 (6.0-7.3)	5.1 (4.6-5.5)	*P*<0.001
P-glucose, 120 min*	13 (12-14)	6.8 (5.5-8.2)	*P*<0.001
P-C-peptide 0 min+	1.7 (1.3-2)	0.72 (0.6-1.0)	*P*<0.001
P-C-peptide 120 min+	4.8 (4.1-5.9)	2.9 (2.2-4.4)	*P*=0.024
S-Insulin 0 min#	16 (13-17)	6 (4-9)	*P*=0.001
S-Insulin 120 min#	103 (79-126)	42 (28-60)	*P*=0.001
HOMA-IR	4.2 (3.7-5.4)	1.3 (0.9-2.2)	*P*<0.001
HBA1c	5.3 (5.0-5.6)	4.6 (4.5-4.8)	*P*<0.001

Values are given in median and in parentheses interquartile range. *P-Glucose in mmol/l, +P-C-peptide in nmol/L, #S-Insulin in mIE/L.

It was more common for patients with a history of severe acute pancreatitis to fulfil the WHO criteria for DM and/or IGT in either fP-glucose or 120min P-glucose, or both (11/14 versus 11/25, *P*=0.037).

Regarding quality of life, no significant differences were seen when comparing patients with a history of mild and severe disease in the eight SF-36 domains (Figure 4.10). When comparing each group with the respective reference group, no significant difference was identifiable; the results for the severe group are presented in Figure 4.11. Despite the excellent results in SF-36, the time to recovery was extensive for several patients, and at the end of the study period 7 patients (from both groups) still did not feel recovered (Figure 4.12).

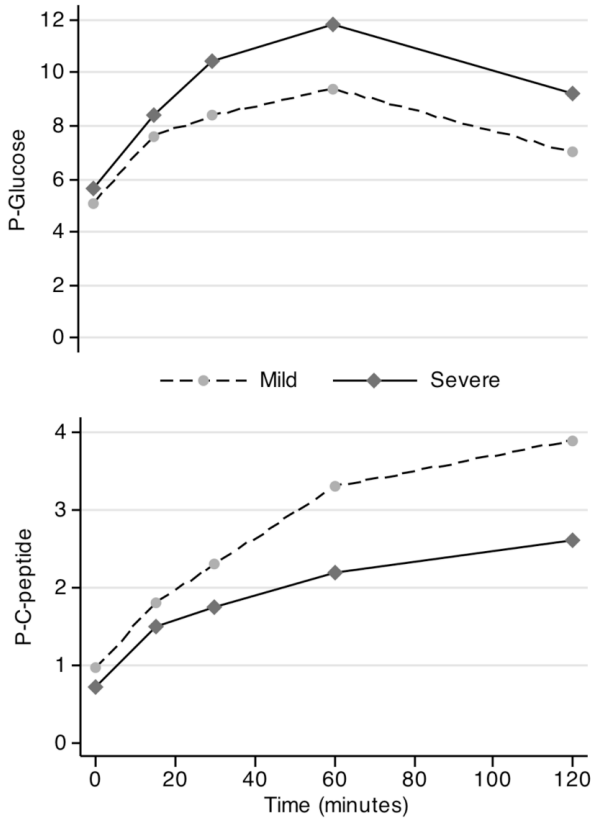


Figure 4.9. Relationship between mild and severe acute pancreatitis patients in the oral glucose tolerance test concerning glucose and C-peptide values (P-Glucose in mmol/l, P-C-peptide in nmol/L).

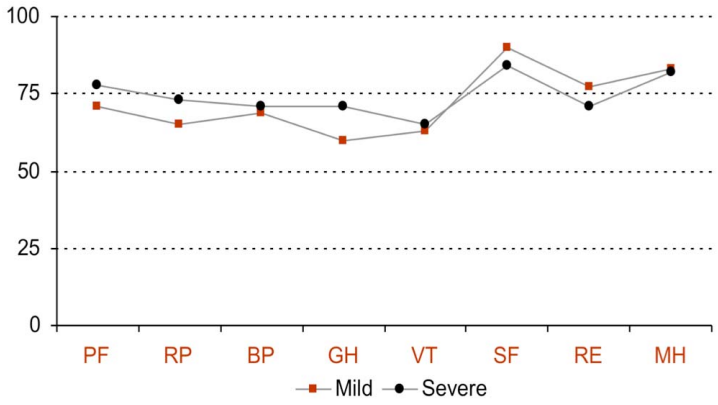


Figure 4.10. SF-36. Mean value for patients after mild acute pancreatitis and severe acute pancreatitis in the 8 SF-36 domains. For abbreviations, see page 39.

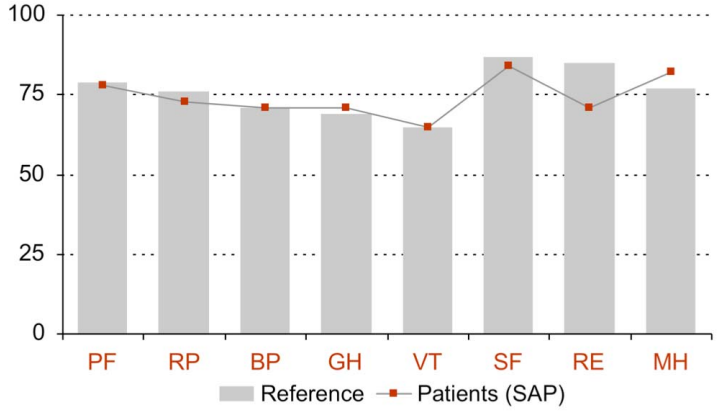


Figure 4.11. SF-36. Mean value for patients after severe acute pancreatitis compared with an age - and gender - matched control group in the 8 SF-36 domains. For abbreviations, see page 39.

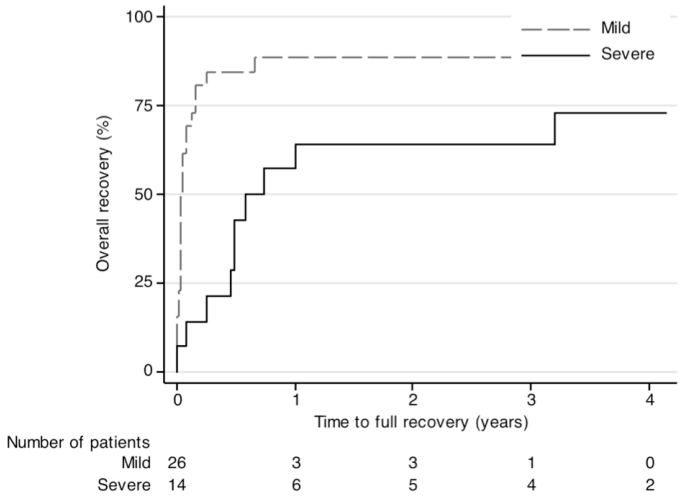


Figure 4.12. Log-rank test for time to recovery after acute pancreatitis, divided in mild (dashed line) and severe (solid line) acute pancreatitis.

There was a difference between severe and mild disease when comparing the median costs for the primary hospital stay (€15774 versus €3480, $P<0.001$), Figure 4.13. When including the total hospital cost, adding costs for follow-up (both including in-hospital stay and outpatient care), the difference was still pronounced (€5000 versus €16572, $P<0.001$), Figure 4.14. This means that the severe cases are 3.3 times more expensive concerning hospital costs.

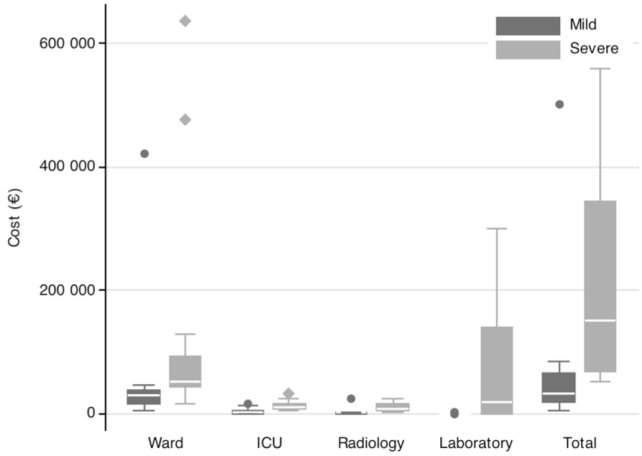


Figure 4.13. Specified in-hospital costs during the primary care for acute pancreatitis, divided in mild and severe acute pancreatitis groups. Box plots: the whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box and the dots and diamonds denote outliers.

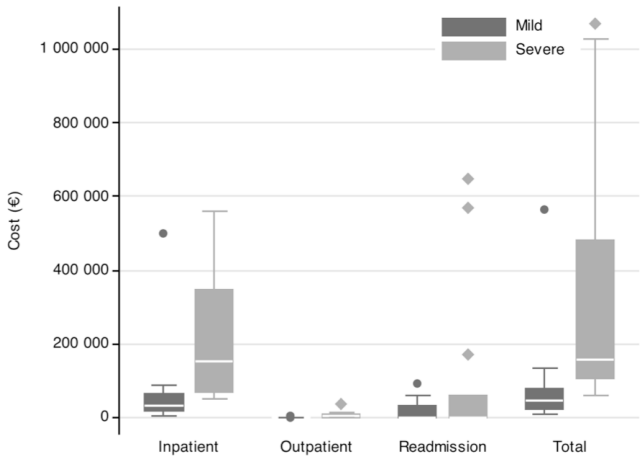


Figure 4.14. Total cost at follow-up including in-patient and out-patient expenses. Box plots: the whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box and the dots and diamonds denote outliers.

4.6 Study VI - Fatal acute pancreatitis occurring outside the hospital – clinical and social characteristics

The 50 patients dying from acute pancreatitis outside hospital during the 15-year study period had a mean age of 54 (47-60) years. Thirty-seven (74%) were men. According to death statistics, 292 patients (162 men and 130 women) died from acute pancreatitis in the southern part of Sweden during the same time period, and hence 50/292 (17%) of fatal pancreatitis cases never reached hospital. There was an overrepresentation of men in the forensic medicine material as compared to the entire acute pancreatitis death statistics: 37/50 versus 125/242, P=0.004.

From the records - with a risk of underestimation - at least 20 persons in the forensic medicine material had abdominal pain prior to death, with a median duration of 3.0 (1.6-6.2) days in evaluable cases. Furthermore, at least 20 patients had a chronic disease requiring medication, including 8 persons with diabetes mellitus. Five subjects had previously been treated for acute pancreatitis, 5 had ongoing drug abuse (other than alcohol) and 9 had gone through previous abdominal surgery. Nine patients had mental disorders.

Based on available information, the underlying assumed aetiological factors included alcohol in at least 35 patients (70%), gallstone disease in at least 3 patients (6%), drugs (codeine) in 1 patient (2%), unknown in 5 patients (10%) and alcohol or gallstone in an additional 6 cases (12%). A history of chronic alcohol consumption, based on information in police records, witness reports and documentation on lifestyle, could be established in all but one of the cases with the aetiological factor considered to be alcohol. The remaining case was a woman with a high blood alcohol concentration at autopsy. Toxicological analyses showed that 13 patients had an elevated level of ethanol in femoral blood, in median 0.77‰ (0.32-1.6‰) (770 mg/100ml). Death rates were lowest during autumn (September-November) with 6 patients expiring. No seasonal variation in death due to acute pancreatitis was otherwise seen.

The median BMI of the patients was 24 (21-30) kg/m^2. Twenty-six of the patients (52%) had a BMI within normal range. Twelve

patients (24%) were classified as obese (BMI > 30 kg/m^2). More than one-fourth was either underweight or obese (28%).

Gross pathology and histopathology examinations of the pancreas were in at least 20 cases difficult due to putrefaction. According to the proposed classification, 15 of the patients (30%) had interstitial (oedematous) changes in the gland and infiltration of polymorphonuclear leukocytes, but no pancreatic tissue necrosis. The remaining 35 patients all had pancreatic necrosis to various extents. Eighteen (36%) presented with necrosis without bleeding and infection, 12 (24%) had acute pancreatic necrosis with haemorrhage, and 5 (10%) had acute pancreatic necrosis with suppuration (and frequently haemorrhage). No malignancy was found. Characteristics of the patients and potential differences between the groups when divided in different histological changes can be seen in Table 4.9.

The lungs were the most common extrapancreatic organs damaged, including bronchopneumonia in 10 patients, right-sided pleural effusion in 15 patients, and left-sided in 17 patients. The diagnosis of pulmonary oedema was difficult to evaluate from the present records. Information on the existence of pulmonary foam was available from the last 26 patients, and was found in 22/26 (85%) cases, indicating that pulmonary oedema is a common finding. Also the weights of the lungs, median 590 g for the right lung and 685 g for the left lung in the entire material, are higher than in healthy persons.

Extrapancreatic findings also included fatty livers in all but 4 patients (n=46, 92%). Nine patients had liver cirrhosis. Moderate to severe coronary arterio-sclerosis was found in 21 patients, and as many patients also had myocardial fibrosis. Ulcerations of the oesophagus and stomach were seen in five patients, and one patient had a profuse bleeding.

When comparing the first and the second 7.5-year period of the study, no significant differences were noted between the groups among available parameters. Twenty-nine patients died during the first half and 21 patients during the second, a 28% decrease.

The majority, 35 patients, was found in their own home. Eight died indoors at other locations and four died outdoors. Many of the persons lived alone, and at least three persons were homeless.

Table 4.9. The histopathological classification of the pancreas related to patient characteristics.

Clinical characteristics	Acute interstitial pancreatitis (n=15)	Acute pancreatic necrosis (n=35)	Difference between groups, P value
Gender (female)	5 (33)	8 (23)	P=0.440
Age* (years)	55 (50-61)	54 (46-60)	P=0.840
Aetiology alcohol	9 (60)	26 (74)	P=0.312
BMI* (kg/m2)	21 (20-30)	25 (23-30)	P=0.086
Mental disorder	6 (50)	3 (9)	P=0.002
Chronic somatic disease	5 (45)	15 (52)	P=0.720
Diabetes mellitus	4 (31)	4 (13)	P=0.160
Ethanol in blood* (‰)	0.12 (0-0.32)	0	P=0.043
Hypertrophic cardiomyopathy+	2 (18)	11 (58)	P=0.034
Liver weight* (gram)	1580 (1330-2008)	2885 (2365-3095)	P=0.001
Ascites* (ml)	0	0 (0-150)	P=0.003

Values in parentheses are percentages or *25th and 75th percentiles, +measured in 30 of the patients. The analysis is based on available patient data.

Chapter 5

General Discussion

Acute pancreatitis may, depending on its severity, be everything from a mild and self-limiting disease to a severe and potentially life-threatening condition. Thus, acute pancreatitis can initiate SIRS, leading to local and distant organ damage and risk of a rapid and fatal course. Still, many issues are yet to be clarified, e.g. further clarification of pathophysiological mechanisms, and also regarding treatment alternatives that have to be conceived and evaluated. The dynamic nature of the disease makes it both interesting and terrifying, and motivates researchers around the world. The aim of the present thesis was to improve the knowledge of acute pancreatitis further and to - if possible - provide inspiration and tools for future research.

5.1 Methodological considerations – challenges in clinical studies

5.1.1 Study design

The goal when treating patients is to practice evidence-based medicine, i.e. apply the best available evidence gained from scientific methods, to medical decision-making. The evidence is based on publications, where evidence obtained from meta-analysis of randomised controlled trials is top-ranked and information obtained from expert committee reports, opinions or clinical experiences of respected authorities are considered to be bottom-ranked, with several different study designs ranked in-between. These evidence categories are summarized in a grading of recommendations, often A-C[3, 18]. Even if a retrospective study has its shortcomings, and only reaches the evidence category of III and a grading of B, a well designed study contributes to our knowledge, especially in areas less studied.

To facilitate good clinical research in acute pancreatitis, severity classification is essential. The results from *Study II* can hopefully be of help in the future when performing randomized controlled studies, which in turn can provide stronger evidence. Another appealing alternative to obtain information on acute pancreatitis is to set up a prospectively collected database. This is common in other fields, like in cardiology, but also available in i.e. gallstone disease, www.ucr.uu.se/gallriks/. In an abstract presented in the Swedish Surgical Week 2009, we reported the results from a national questionnaire. Of 46 responding surgical clinics in Sweden, 41 were interested in a Scandinavian database for acute pancreatitis, especially concerning the severe cases. Another study design is questionnaire surveys, that can yield information otherwise impossible to collect, e.g. concerning treatment regimes.

5.1.2 Inclusion of patients

In the present studies we rely on a correct ICD-9 and ICD-10 classification for inclusion of patients. No study has hitherto been performed to evaluate the number of correctly and incorrectly-classified patients for this diagnosis.

5.1.3 Definitions

In studies of acute pancreatitis, different definitions are often used concerning severity classification, definition of acute fluid collections, pancreatic pseudocyst and organ failure. This makes studies difficult to compare and evaluate.

Even if we think that our severity definition in *Study I* is good, taking known and available parameters of proven prognostic value into consideration, e.g. CRP, that has been suggested to be a simple alternative to the currently available severity scoring systems[16, 18], with an independent prognostic value[189], and organ failure, which has gained increasing interest as comes to definition of severity in acute pancreatitis[4], we also are aware of that it is not ideally to set up own definitions. This definition of severe acute pancreatitis may not only include "true" severe patients, but also patients with potentially more moderate but still clinically relevant disease, probably especially in the group with the combination hospital stay more than 7 days together with a short ICU stay.

The current "golden standard" for severity classification in acute pancreatitis – the Atlanta classification – has some drawbacks that have been discussed in section 1.4.3 in the present thesis. It has been proposed that the classification should be revised, for several reasons including that different interpretation of the Atlanta consensus document is possible and probably common[43].

Despite the shortcomings of the Atlanta classification, we chose to use the classification in our subsequent research since nothing more accurate is yet available. However, a modification was performed implying that the criteria under "Definition" had to be fulfilled in the classification, and acute fluid collections was not considered enough for fulfilling the criteria for a local complication. Uniformity may be more important than an ideal classification to be able to compare studies, and in the strive to create good clinical research. If we were to conduct *Study I* again, we might have chosen SOFA scores for definition of organ failure[30].

Concerning pseudocysts, we believe that current golden standard for classification is good and uncontroversial[38].

5.1.4 Collection of data

The retrospective study design may limit available information. For example, parameters like S-calcium and respiratory rate would have been of interest in *Study II*. There are different ways of handling missing data; we used the probability imputation technique[182] in *Study II*. ANNs is a model that is tolerant to missing data[77]. Also, prospective trials can be demanding when it comes to data collection. For instance in *Study V,* a concern was to obtain all the blood samples, especially during the OGTT, from the study patients. In questionnaire surveys, a high answering rate is crucial, since that often is the only quality rating that counts. Our 88% response rate, is a very satisfactory result, better than in similar studies[190].

5.2 Studies included in the thesis (I-VI)

5.2.1 Survey of patients with moderate to severe acute pancreatitis

In a previous study, the incidence, management and recurrence rate of acute pancreatitis over a 22-year period was evaluated[11]. In *Study I* the focus was on severe cases. During the last 2 decades, management of severe acute pancreatitis has changed from a more aggressive surgical intervention towards a more conservative approach, except when infected necrosis has been confirmed[3, 191, 192]. Our centre has practised a conservative attitude, with less patients undergoing surgery than in similar patient materials reported by other centres[143, 193]. Before the study, we also believed that we practiced an aggressive attitude to fluid replacement, but when analysing our results we became aware that an improvement was possible. This is information worth considering.

Broad-spectrum antibiotics were given to the vast majority of the patients. Meta-analysis of the role of antibiotics in acute pancreatitis had at that time concluded that patients with severe disease should be treated with broad-spectrum antibiotics in order to reduce the risk of complications[194]. Since then other studies, including two double-blind placebo-controlled trials, have shown an opposite result[94, 95]. Also, a recent meta–analysis concludes that antibiotic prophylaxis in severe acute pancreatitis does not reduce mortality or protect against infected necrosis or surgical intervention[96]. In current guidelines antibiotic prophylaxis is not recommended. This reflects the importance of awareness of the dynamic changes and improvements in the treatment.

Concerning gallstone-induced pancreatitis, the timing of cholecystectomy depends on the clinical condition of the patient. The current recommendation is to perform cholecystectomy, and clearance of potential bile duct stones, during the initial hospital stay and ideally within two weeks after onset of an attack of mild acute pancreatitis[3], in order to avoid recurrent attacks of pancreatitis[107]. After severe acute pancreatitis, cholecystectomy should be delayed until there is sufficient resolution of the inflammatory reaction and clinical recover[107, 108]. Recurrences of acute pancreatitis in the present study

was, as in other studies, more often due to alcohol-induced pancreatitis than biliary pancreatitis[11, 12]. However, recurrence of biliary pancreatitis was substantial, above all during the first three months, and a more active attitude to bile duct clearance would most likely have decreased the recurrence rate. This observation further supports current guidelines.

In severe cases SIRS develops within the first days. Early deaths (within the first 7 days) are usually due to pronounced SIRS and organ failure, including MODS, without apparent infection. Late deaths are most often the result of MODS combined with infection/sepsis, frequently caused by secondary infection of pancreatic or peripancreatic necrosis[191]. In our study, the majority of deaths were related to MODS. The total mortality rate was fairly low. Our attempt to determine risk factors for death, available at time of admission, revealed increasing age and hypotension at admission as prognostic factors in multivariate analysis. Age has previously been described as a risk factor for death[193, 195, 196]. Hypotension, without fulfilling the criteria for shock, as a risk factor in the early stage of the disease was previously reported by our group when conducting univariate analysis[11]. Laboratory parameters, such as elevated serum creatinine[6, 70, 193] and blood glucose[6, 70], have also all been shown to be determinants of mortality. Aetiology is another described risk factor[196], though this has not been supported by other studies[197], nor was this the case in the present material. Fatal outcome has been shown to correlate with the need for inotropic and/or vasopressor support[193], and the presence of respiratory insufficiency [195], as well as renal[193, 195] and organ failure in general[196]. Organ failure correlated with a higher risk of death also in the present study, but since our aim was to identify risk factors that potentially could influence our observance and treatment of the patients during the early stage of the disease, organ failure was not included in the analysis.

In summary, this study reinforces that early identification of patients at higher risk for fatal outcome is possible. We believe that patients at risk should immediately be monitored concerning vital parameters, and that active and aggressive circulatory resuscitation and haemodynamic management should be provided. However, there is

also a need for early identification of patients at risk of developing severe acute pancreatitis. This lead us to conduct *Study II*.

5.2.2 Severity prediction

Despite almost four decades of evaluating severity scoring systems for acute pancreatitis, only marginal improvements in the accuracy of prediction of severity have occurred. Clinical assessment alone has been shown to be a poor predictor of severity of the disease[33]. Of the scoring models in clinical use today, like Ranson and Glasgow scores, none are applicable at admission, which is a major deficiency.

In a review, we evaluated the use of Artificial Neural Networks in pancreatic disease[198]. Since ANNs work in a non-linear fashion, the model may better describe the interactions between health risk factors. Furthermore, ANNs use computer iteration to search for patterns in different variables associated with outcome, and they are far less affected by low frequencies in the variables[75]. The advantages of ANNs include the fact that less formal statistical variable transformation is required, that there is no need for *a priori* assumptions or knowledge of underlying frequency distributions, the ability to implicitly detect complex non-linear relationships between dependent and independent variables, and the availability of multiple training algorithms. ANNs are also robust and tolerant of missing data and input errors[77].

Only a few studies have investigated ANNs in the prediction of outcome in acute pancreatitis, with varying results and degree of usefulness[84-88]. The first article showing superiority of ANNs over linear models in predicting severe acute pancreatitis was a publication by Mofidi et al[86] in 2007. Their ANN model was also more accurate than APACHE II and the Glasgow severity (GS) score. That study had several strengths, above all due to the large number of patients and use of parameters that could be collected at an early stage, since all the values used as input variables were available within the first 6 hours of admission. Failure to respond to initial resuscitative measures was also introduced as a predictor of outcome. However, an ensemble approach was not used, and the ranking procedure had a weakness in the possibility the ANN model could be overtrained. The results encouraged further evaluation of ANNs in acute pancreatitis.

A crucial step is the selection of the most relevant variables for the final ANN model, as well as the number of variables. A large number of potential input variables are often available for a limited number of training and evaluation cases. No *a priori* variable selection, such as significance testing, was used in our study. Instead, the ANNs ranked every variable in order of its importance for the mortality prediction. In a second step, the total number of variables was minimized to include only variables with a positive contribution to the prediction of outcome. The largest ROC area was achieved when the top-ranked variables were included in the model. If more variables were included, the discriminatory power decreased. The ROC curve is currently one of the best developed statistical tools for describing performance[185].

Of the six selected input variables, all are available at admission to hospital, and already measured as part of routine clinical management. To our knowledge, the parameter "duration of pain until arrival at the emergency department" has never before been included in a risk model. This factor correlates with several others, not at least the inflammatory response, and is of great value when combining data in an ANN model. In the present study, patients with severe acute pancreatitis arrived earlier, which can be part of the explanation why CRP was not identified as a prognostic parameter. Creatinine and haemoglobin were both higher in the severe group, which may be an early sign of haemoconcentration due to fluid loss initiated in acute pancreatitis, by factors such as local inflammation, remote organ capillary endothelial leakage, and vasodilation. Also, the heart rate and WBC counts were higher in the severe acute pancreatitis group; both parameters are also systemic inflammatory response syndrome (SIRS) criteria[28]. Somewhat surprisingly, ALAT was one of the predictors identified, and a higher value was prognostic of a mild event. In the literature, there is evidence that the aetiology of alcohol-induced acute pancreatitis more often indicates a severe course[199]. ALAT has also been shown to be higher in biliary-induced acute pancreatitis than in alcohol-induced acute pancreatitis[21]. Since we chose not to include these aetiologies in the primary variables, due to the fact that they are often unknown at the time of admission, we propose that ALAT possibly acts as a surrogate marker for the aetiology.

In this study, the ROC curve for the ANN model was consistently above the APACHE II ROC curve, making direct comparison possible. It is important to maximize sensitivity so that patients with the potential for serious outcome are identified early, and appropriate therapy may be instituted. Specificity must also be acceptably high, so that patients who are not likely to progress to severe disease are not subjected to unnecessary interventions. ANNs performed significantly better than the APACHE II score at sensitivity cut-offs of 25%, 50%, and 75%, and also better than logistic regression analysis at 50% and 75%.

In the study, missing data was handled with multiple imputation technique, a large number of combinations of parameters in different ANN architectures were evaluated using high-performance computer clusters, and the final model was temporally validated in patients who were not included in the ANN training. All these factors contribute to make the present study solid. A larger group of patients, especially with severe disease, and more potential risk factors collected at admission, would possibly have further improved the study.

In summary, the risk variables achieved superior severity prediction in an ANN model than in APACHE II, and also performed better than in a logistic regression model. We conclude that ANNs have the capability of playing a significant role as decision support in the future management of patients with acute pancreatitis.

5.2.3 Pancreatic pseudocysts

The most common complication in severe acute pancreatitis is pancreatic pseudocysts. In our aim to learn more about acute pancreatitis, and especially the severe form, we designed one retrospective and one questionnaire study concerning pancreatic pseudocysts.

In the first study, different treatment regimes for pancreatic pseudocysts during a ten-year period were evaluated. Studies before 1993, prior to the Atlanta classification[38], usually include a much more heterogeneous group of patients; for instance, peripancreatic fluid collections could be regarded as pseudocysts[113]. We strictly used the Atlanta classification. As in other studies, alcohol was the most common aetiological factor[111, 135, 200]. Many patients had bodily

stigmata due to alcohol abuse, and a troublesome social situation was also overrepresented. These factors most likely influence outcome and adds to a higher risk for these patients, despite choice of treatment.

Large pseudocysts have been shown to more frequently require invasive therapy due to persistent symptoms or complications[113, 124], but the overall treatment results are not obviously influenced by the size of the pseudocyst[124]. In our study a palpable tumour, but not pain or other symptoms, was more common in the group with pseudocysts ≥8 cm. Patients with larger pseudocysts were not less often treated conservatively, and did not demonstrate more recurrences or need for longer hospital stay. More complications were, however, seen in this group, although the difference did not reach statistical significance. Fifty-two percent of the initially conservatively managed patients needed further treatment, but recurrences were not more common compared with other treatments. Two patients died in this group, one in a circulatory collapse due to bleeding from a pseudoaneurysm of the splenic artery. The other patient had a bleeding into the pseudocysts from a pseudoaneurysm in the gastroepiploic artery. This was initially controlled by angiography with embolization, but the patient developed circulatory and respiratory failure. Previous studies have reported more complications after conservative treatment[115], but later studies have shown that it is possible not only to treat small but also large pseudocysts with conservative treatment[113, 121], assuming that the overall clinical picture, including severity of symptoms, is taken into consideration.

The invasive procedures that were part of the treatment of the patients in *Study III* consisted of different percutaneous approaches, including puncture, drainage and cystogastrostomy, and also the most invasive: open surgery. The highest recurrence rate was associated with percutaneous puncture. This procedure is known to be an alternative to achieve diagnosis, but often results in recurrence, especially when a communication between the pseudocyst and the pancreatic duct is present[131]. Pancreatic ductal anatomy has been shown to correlate with outcome after different treatment regimes[118]. The best percutaneous alternative to achieve a low recurrence rate (4/14) in this study was cystogastrostomy. External drainage procedures render about similar results, with resolution in just over

half of the treated patients, comparable with results from other studies[111, 115, 118, 126]. The best treatment option to decrease the risk of recurrence of the pseudocyst was surgery. In accordance with other studies[113, 124, 126], surgical management of pancreatic pseudocysts seems to be a safe method with good results. To be able to make a safe internal drainage, a well-established pseudocyst wall is required, which in general is supposed to require at least six weeks after the acute episode of pancreatitis. Surgery was usually not the first treatment alternative. No individual patient risk factor was shown to influence recurrence.

A drawback in this study, in common with many others in the field, is that pseudocysts both after acute pancreatitis and as a consequence of chronic pancreatitis were included. At our current level of knowledge, we would have separated the two groups in the study.

In summary, we found complications and mortality rate to be limited, but recurrences were common, and hence resource utilization was high. An over-representation of alcohol consumption and social problems seen in the group could also have an influence on outcome. A gradual "step-up" in invasiveness of the treatment is possible.

The questionnaire survey aimed to investigate the availability and use of different treatment facilities for pancreatic pseudocysts, and to describe how pancreatic pseudocysts are managed today in Sweden. The individual hospitals are exposed to a very limited number of patients. Almost one half of the hospitals refer some or all patients with a pancreatic pseudocyst, but a substantial number of hospitals with 150 000 persons or less in their primary catchment area always treat all their patients, even complicated cases.

"Best clinical practice" has traditionally been used in the treatment of pancreatic pseudocysts, and there are no prospective randomized studies or evidence-based guidelines for the detailed management. The different treatment strategies, besides conservative treatment, include percutaneous and endoscopic drainage procedures and open surgery[117, 126-128, 201]. The lack of evidence probably explains why only 5 out of 51 hospitals in this survey have written guidelines for the management of pancreatic pseudocysts.

The choice of procedure depends on a number of factors, including the general condition of the patient. Also the size, number, and location of the pseudocysts, presence or absence of communication between the pseudocyst and the pancreatic duct, and presence or absence of infection constitutes crucial information for the decision-making. According to this survey, many hospitals (especially smaller units) did not have different strategies for the treatment of pseudocysts after acute pancreatitis as compared to pseudocysts associated with chronic pancreatitis.

Five clinical situations with pancreatic pseudocysts were presented in the questionnaire. Three remarkable findings were registered. A large but asymptomatic pseudocyst was invasively treated in almost one quarter of the hospitals. In cases with symptomatic pseudocysts, the chosen drainage procedure varied extensively, with endoscopic drainage being more common in university hospitals. One tenth chose a conservative attitude and did not make any arrangements for follow-up in a patient with a pancreatic cyst in the tail with a diameter of 5 cm, with no history of acute or chronic pancreatitis.

Comments on the findings are that size of the pseudocyst still seems to influence the chosen treatment, even in asymptomatic cases, although several studies has shown that it is possible to treat even the larger pseudocysts conservatively[124]**.** The heterogeneity of treatment emphasises the importance of working in multidisciplinary teams, including interventional radiologists, therapeutic endoscopists, gastroenterologists, and pancreatic surgeons, and that team conferences should be considered in all cases with pancreatic pseudocysts. Less than three quarters of the hospitals included in this survey stated that they regularly have these type of conferences. Even if pseudocysts are the most common cystic lesions of the pancreas, accounting for 75-80%, a cystic neoplasm with potential malignancy must never be forgotten as a differential diagnosis[139, 140].

In summary, this survey demonstrates that the number of patients with pancreatic pseudocysts that require some type of invasive treatment at an individual hospital is low, and that the treatment modalities available and used vary widely. Improved experience and comparisons between different possible treatment options are necessary. Interventions have to be performed in a limited number of

centres, ideally within clinical trials, working in a network and applying national or even international registries and guidelines when available.

5.2.4 Long-term follow-up

An ensemble approach was conducted to evaluate patients both with severe and mild disease at long-term follow-up.

Nowadays, most agree that endocrine and exocrine pancreatic dysfunction occurs during the initial stage after acute pancreatitis, but functional recovery of the gland is controversial. Full recovery has been described[142], but some dysfunction is the usual scenario, especially after severe disease with necrosis[143, 144, 146, 147]. After surgical treatment, a persistent exocrine insufficiency has been noted in up to 80-85%[144, 152]. In the present study, with only a few patients subjected to pancreatic surgery, only one patient had an objective exocrine insufficiency. When analysing the answers regarding change in stool habits, including frequency, a mild impairment was common with a fluctuation over time, but constant steatorrea at follow-up was uncommon. Medication with pancreatic enzyme supplements was used by a very limited number of patients. However, there is a "greyscale" concerning when and to what extent an exocrine dysfunction is present and of clinical relevance.

Endocrine dysfunction with glukosuria and elevated blood sugar levels is common during the acute phase of pancreatitis, but usually self-limiting and resolving. Endocrine dysfunction with diabetes mellitus and impaired glucose tolerance is, however, more common by time[147]. Diabetes mellitus is also known to occur more often after operative treatment[158]. We found diabetes and impaired glucose tolerance in 79% after severe acute pancreatitis and in 42% after mild acute pancreatitis. The result shows that not only loss of β-cell function was present, but also that insulin resistance is an additional and important explanation for the development of diabetes. The risk of diabetes and impaired glucose tolerance, especially after severe disease, was much higher than expected in the population. This indicates that endocrine insufficiency after acute pancreatitis may be an underestimated problem. When taking the risks of untreated diabetes with poor metabolic control into consideration, a follow-up of these patients may be more important than hitherto realized.

With an increasing number of patients surviving severe acute pancreatitis, more attention has been directed towards quality of life and long-term outcome. Quality of life as an outcome measure has sporadically been reported, with diverging results. Both tendencies to or statistically proven reduced quality of life respectively good quality of life after acute pancreatitis have been presented[146, 160, 163, 166]. In the present study SF-36 was used, and both patients with a history of severe and mild disease had a quality of life as good as an age- and gender-matched "normal" reference population.

Only a few reports on cost analyses in acute pancreatitis have been made, mainly focusing on severe cases[146, 171, 202]. In the present study, we calculated costs for the primary admission, being significantly more costly in severe cases, but with a wide spread. Additional hospital costs directly related to the pancreatitis episode was also investigated, showing that subsequent treatment of gallstone disease is costly. We believe that this treatment can be optimised.

Reports on when the patients return to daily activity and work are limited[158]. In the present study return to work in many cases took a long time after the severe disease, with the possibility that patients, despite surviving the acute disease, were never able to go back to normal life and work again. Overall, it took an extensive period for patients to feel entirely recovered, with several patients not being subjectively recuperated at the end of the study period, but still back to full-time work.

Generally, reports in the literature concerning follow-up after acute pancreatitis have limitations and have led to contradictory results. This is due to a number of factors, e.g. a limited number of patients, different severity classifications used, different criteria for impaired glucose tolerance and diabetes mellitus, different tests used to evaluate exocrine insufficiency, and different instruments to evaluate quality of life. The follow-up time also varies widely[203]. The weakness in our study is the limited number of patients. The strength is, however, strict definitions of SAP, DM and IGT and an attempt to make a complete follow-up concerning several important factors.

In summary, this study lead us to believe that a structured follow-up plan for patients that have suffered severe acute pancreatitis, dealing with physiological aspects including information on signs of

exocrine insufficiency and the possible benefits of controlling blood glucose levels, could be of great benefit. The good long-term quality of life is an important and encouraging result for patients, relatives and health care professionals taking care of this patient category.

5.2.5 Fatal acute pancreatitis

Sometimes, despite all possible hospital care, the patient with severe acute pancreatitis has a fatal outcome. What is less well studied are patients dying from acute pancreatitis, but never even reaching hospital. In this study, we wanted to examine the incidence and clinical characteristics of this group, in the hitherto largest report investigating death in acute pancreatitis in a forensic medicine material, and the only including only out-patient fatalities.

Previous studies have noted that up to one third of patients dying due to acute pancreatitis seemed to die outside hospital, while in our study it was 17%. Another conclusion from previous studies was that the progression of the disease seemed rapid, something we do not fully agree upon. In the present study, information about the patients' situation prior to death was available in several cases, and the duration of pain did not generally seem explicit short, but all deaths were early (within the first week after symptom). Today, we are aware of the importance of early fluid resuscitation in the initial treatment of severe acute pancreatitis[90]; since these patients stayed at home, probably often dehydrated, this can be a crucial factor contributing to the fatal course.

In the present patient series we noted that the number of fatal cases outside hospital decreased with 28%, comparing the first and the second time period. This trend is even stronger when comparing the incidence in a previous publication from the same region during the 1980´s, and an equal time period in the present study[178].

The occurrence of pulmonary complications is a frequent early feature of acute pancreatitis. In the present series, pulmonary changes were sometimes difficult to evaluate, mainly due to putrefaction and difficulties in interpreting the histological results, but lung injury was common. In a large autopsy series of patients dying from acute pancreatitis, Renner et al[204] found that pulmonary complications, including pulmonary oedema and congestion, appeared to be the most

significant factor contributing to death, occurring even in those cases where the pancreatic injury appeared to be of only moderate extent.

Several risk factors for severe disease and death are known, one of which is obesity[69]. In the present material, half of the cases had a BMI outside the normal range, including 24 % being obese.

Investigation of the patients' social network, lifestyle and circumstances of death in acute pancreatitis has not previously been done. A study by Ellis et al[205] is, to the best of our knowledge, the only previous publication touching this issue. In a comprehensive epidemiological study of acute pancreatitis, they found a clear relationship between socioeconomic deprivation and incidence of the disease, which was largely explained by a higher incidence of alcoholic aetiology.

In summary, patients dying from acute pancreatitis without reaching hospital, represent a substantial part of the total mortality encountered in the disease. Alcohol abuse is frequent, but mental disorders, drug abuse and a socially deprived position are also overrepresented. This group is important to target to prevent death from acute pancreatitis in the future.

5.3 Future perspectives

Many issues concerning acute pancreatitis are yet to be discovered, making research in this field inspiring and demanding.

Future studies connected to the present thesis

The present thesis presents an ANN model for pancreatitis severity prediction, which may be our most important result. A well validated severity prediction model, available at time for admission and with a high accuracy - is as mentioned earlier - very important and opens doors to facilitate future clinical studies, due to the higher number of correctly classified patients at study start. A prospective study to further develop this model would be desirable, with the possibility also of including new parameters. Preferably, the evolution would be in a multi-centre setting achieving a larger patient material.

As shown in the studies, an improvement in the management of pancreatic pseudocysts is possible. Scandinavian guidelines for the management of acute pancreatitis are scheduled to be published in the near future. It would be important to verify the possible changes in the management after the implementation with an additional survey.

The follow-up study raises questions concerning the pathogenesis for diabetes mellitus after acute pancreatitis. Despite it being so common, few studies have been performed, and more is yet to be discovered.

Even if costs related to hospital care were analysed by us, the total costs for acute pancreatitis, including costs for the society due to sick leave and loss of production, community healthcare, rehabilitation and deaths have never been estimated. Also, quality-adjusted healthcare cost is yet to be evaluated.

Future studies overall

A revision of the Atlanta classification is desirable, as mentioned earlier.

Evaluation of a fast-track concept for the improved management of acute pancreatitis, with endpoints like hospital stay, quality of life and costs, studied in a randomized controlled fashion, is interesting and relevant.

When evaluating treatment with regard to complications and outcome, large patient series in a multicenter setting and performed in a prospective randomized fashion is desirable, but not always achievable. We believe that a perhaps underestimated way to obtain information is through large, prospectively collected databases, and that this is going to be an increasingly important part of future medical research and quality control, including in acute pancreatitis.

We still have a lot to learn concerning the pathophysiology. The fact that we do not have any specific treatment for the disease is challenging, and makes acute pancreatitis an excellent area for translational research. "The sky is the limit!"

Chapter 6

Conclusions

The major conclusions reached in the studies included in this thesis were:

I. Two early risk factors for death, increasing age and hypotension at admission, were identified. Early recurrence in biliary induced acute pancreatitis was common, emphasizing the importance of cholecystectomy and bile duct clearance.

II. A model for early prediction of severity in acute pancreatitis with Artificial Neural Networks was developed, and showed high accuracy. This is promising for the ability to optimise future acute pancreatitis research and treatment.

III. Pancreatic pseudocysts proved to be resource demanding, due to recurrences and repeated hospital stays. Even larger pancreatic pseudocysts were possible to manage successfully with conservative treatment. The invasiveness can be increased stepwise. A tailored treatment approach is suggested.

IV. In a national survey the treatment of patients with pancreatic pseudocysts appeared to be heterogeneous, with different treatment options available and varying local traditions. Multidisciplinary team conferences and a centralisation of the treatment would be desirable. Guidelines would be of benefit.

V. Long-term follow-up after acute pancreatitis showed impairment mainly in the endocrine pancreatic function, and especially after severe disease. The time for rehabilitation and return to work and normal life was long, and the costs for the society high. The quality of life, however, was as good as in the normal population years after the acute disease.

VI. Patients dying in acute pancreatitis outside hospital represent a substantial part of all deaths from the disease. The dominating aetiology was alcohol, and lung injury was the most common extrapancreatic organ manifestation.

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