OUTCOME PREDICTION AND QUALITY OF LIFE IN SEVERE ACUTE PANCREATITIS

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Academic Dissertation

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7th May

Helsinki 2004

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ISBN 952-91-7167-6 (paperback)
ISBN 952-10-1831-3 (PDF)
http://ethesis.helsinki.fi
Helsinki 2004
Helsinki University Printing House

To my children Sara, Niko and Leevi

CONTENTS

1. ABSTRACT

Prognosis in severe acute pancreatitis (SAP)

Background. Acute pancreatitis (AP) is a common abdominal disorder with a severity varying from mild to fatal disease. Survival of patients with AP, and particularly in severe acute pancreatitis (SAP), is related to a combination of therapy-associated and patient-related factors. Predicting an individual patient's outcome remains problematic. There are only a few relevant methods for predicting mortality among patients with acute pancreatitis. The factors which cause death in most patients with SAP seem to be related specifically to the multiple organ dysfunction (MOD) syndrome. In the early phase of SAP multiple organ failure (MOF) seems to be caused by the same cytokine and inflammatory mediators as in septic shock. There are numerous ways to define and score MOD. There are three more recent scores: the MOD score, the Sequential (former Sepsis-related) Organ Failure Assessment (SOFA) score, and the Logistic Organ Dysfunction (LOD) score. These scores are designed to assess the severity and development of MOD as a single score. With an increasing number of patients surviving SAP more attention has been directed towards quality of life and long-term outcome, especially in patients with alcohol-induced disease. In studies with a small number of patients, quality of life and outcome after SAP have been good. However, only two of these studies have used generic multidimensional measures.

Aims. The first aim was to analyze a large consecutive series of patients with SAP to identify factors releted to the risk of dying during hospital treatment. Secondly, to construct a novel model to predic a fatal outcome in the early phase of SAP and to compare this model with current predictive models. Thirdly, to compare the MOD, SOFA, and LOD scores as predictors of hospital mortality, and to use one of these scores to assess the incidence and the prognostic usefulness of organ dysfunction/failure in patients with SAP treated in a general ICU. A further aim was to define the overall long-term post-discharge outcome after SAP.

Patients and methods. The total number of episodes of AP in the study during the 10 years study period was 1539 of which 317 (21%) were SAP. A consecutive series of 270 patients with SAP was included to study the factors related to a fatal outcome by univariate and multivariate analyses.

In addition, 234 patients with sufficient data were included to construct five logistic regression models and three artificial neural network (ANN) prognostic models to be applied on data from patients in the early phase of SAP. Two of these models were tested in an independent prospective validation set of 60 consecutive patients with SAP and compared with current predictive systems.

113 consecutive patients with SAP treated in a general intensive care unit (ICU) were studied for assessment of MOD/MOF. Their clinical and laboratory data were collected during a period of 35 days. Their Acute Physiology and Chronic Health Evaluation (APACHE) II, MOD score, SOFA score and LOD score were calculated and compared with regard to hospital mortality. In addition, a daily maximum score and a total maximum score (the sum of the highest values for each organ dysfunction) were calculated for all three

scores. The area under the receiver operating characteristic curve (AUC) was used as a measure of the accuracy of the scores.
Of the 283 patients with SAP, 211 survived. During follow-up for a mean period of 66 months an additional 27 patients died. The Rand 36-item Health Survey with accessory questions was mailed to 174 eligible patients. The final study population comprised 145 patients (the response rate was 83%). The study population was compared Finnish population scores matched for age and sex; accessory questions were analyzed separately.
Main results By univariate survival analysis advanced age, a history of previous chronic medication, patient transfers from other hospitals, a high BMI, respiratory or renal failure, a need of pressor support and a need of abdominal surgery were factors that significantly predicted inpatient mortality. By multivariate stepwise logistic regression analysis, such factors were need of pressor support, renal failure requiring dialysis, advanced age, history of previous chronic medication and need of abdominal surgery.
Out of five logistic regression and three artificial neural network models, the one prediction model considered optimal was a logistic model with four variables: age, highest serum creatinine value within 60 - 72 h of primary admission, need for mechanical ventilation, and chronic health status. In the validation set, the predictive accuracy, determined by the AUC-value, was 0.86 for the chosen model, 0.85 for the ANN model using eight variables, 0.82 for APACHE II, 0.78 for MOD score, 0.66 for Ranson, and 0.54 for Imrie scores. Among the patients treated in a general ICU accuracy was highest with daily maximum scores of AUC 0.85 for the SOFA score, 0.84 for the MOD score, and 0.84 for the LOD score. According to the maximum SOFA score, the highest mortality was associated with liver (83%, $p<0.001$) and renal (63%, $p<0.001$) failure. The mortality ratio in subgroup of patients who had failures of two organ system ranged from 50% to 91%. The highest mortality rate (91%) occurred among patients who had a combination of hepatic and renal failure. By multiple logistic regression analysis, only hepatic, renal, cardiovascular failure, and previous cardiovascular medication were independent risk factors for hospital mortality. There were no clinically significant differences regarding long-term HRQL between the study and the general population. Of the 145 patients 87% returned to work, 27% had recurrent pancreatitis, and 43% developed diabetes. Of the 113 patients with alcohol-induced SAP 30% were abstinent and 28% were problem drinkers, alcohol-dependent, or alcoholics at follow-up.
Conclusions. Previous chronic medication, advanced age, need of dialysis, mechanical ventilator support and pressor support are factors that independently predict the death of SAP patient. In SAP, Ranson and Imrie scores are inaccurate predictors of mortality. A novel predictive model based on four variables performs at least as well as the APACHE II system with 14 variables. In patients with SAP, organ dysfunction scores (MOD, SOFA, LOD) are accurate in comprasion with APACHE II for predicting death during hospital treatment. The maximum daily organ dysfunction scores were simple and useful for assessing MOD and for predicting hospital mortality of patients with SAP. Up to 13% of the SAP patients surviving initial hospitalization die within a few years. Among the survivors, long-term HRQL seems to be comparable to that of the general population, the majority returns to work and reduce their alcohol consumption markedly. The cost of treatment of SAP patients is high, but according to this study maximal treatment of these patients seems to be justified.

2. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles. They will be referred to by their Roman numerals.

I Halonen K, Leppäniemi A, Puolakkainen P, Lundin J, Kemppainen E, Hietaranta A, Haapiainen R. Severe acute pancreatitis – prognostic factors in 270 consecutive patients. *Pancreas* 21:266-271, 2000.

II Halonen K, Leppäniemi A, Lundin J, Puolakkainen P, Kemppainen E, Haapiainen R. Predicting fatal outcome in early phase of severe acute pancreatitis by using novel prognostic models. *Pancreatology* 3:309-315, 2003.

III Halonen K, Pettilä V, Leppäniemi A, Kemppainen E, Puolakkainen P, Haapiainen R. Multiple organ dysfunction associated with severe acute pancreatitis. *Crit Care Med* 30:1274-1279, 2002.

IV Halonen K, Pettilä V, Leppäniemi A, Kemppainen E, Puolakkainen P, Haapiainen R. Long-term health-related quality of life (HRQL) in survivors of severe acute pancreatitis. *Intensive Care Med* 29:782-786, 2003.

3. ABBREVIATIONS

ANN	Artificial neural network
ANN4	Artificial neural network model with 4 variables
ANN5	Artificial neural network model with 5 variables
ANN8	Artificial neural network model with 8 variables
AP	Acute pancreatitis
APACHE	Acute Physiology and Chronic Health Evaluation
AUC	Area under receiver operating curve
BMI	Body-mass index
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreaticography
HRQL	Health-related quality of life
IAP	Intra-abdominal pressure
ICU	Intensive care unit
IL	Interleukin
LOD	Logistic organ dysfunction
LR4	Logistic regression model with 4 variables
LR5	Logistic regression model with 5 variables
LR8	Logistic regression model with 8 variables
MOD	Multiple organ dysfunction
MOF	Multiple organ failure
MRI	Magnetic resonance imaging
OR	Odds ratio
QOL	Quality of life
RH	Relative hazard
SAP	Severe acute pancreatitis
SD	Standard deviation
SE	Standard error
SOFA	Sequential (former sepsis-related) Organ Failure Assessment

4. INTRODUCTION

Acute pancreatitis (AP) is a common disease and its incidence is increasing (Thomson et al. 1987, Wilson and Imrie 1990, Jaakkola and Nordback 1993). AP is severe among 10–30% of the patients. Biliary disease is the most common cause of AP in the United States, Asia and mos of Western Europe (Steinberg 1994). In contrast, up to 80% of the episodes of AP in Finland are alcohol-induced (Mero 1982, Puolakkainen et al. 1987, Jaakkola and Nordback 1993). The overall mortality rate among AP patients varies from 2% to 16%, and in severe acute pancreatitis (SAP) from 7% to 47% (Tenner et al. 1997).

The factors which cause death in most patients with SAP seems to be related specifically to multiple organ dysfunction (MOD) syndrome. SAP-associated MOD resembles the MOD seen in other clinical settings such as sepsis, major trauma, and thermal injury (Miskovitz 1998). In the early phase of SAP, multiple organ failure (MOF) seems to be caused by the same cytokine and inflammatory mediators as in septic shock, although pancreatic necrosis is sterile (Wilson et al 1998a). Early deaths caused by SAP are commonly associated with the MOD syndrome; these deaths account for 40 to 60% of in-hospital deaths in all age groups, and over the past decade this proportion has not declined (McKay et al 1999).

Patients with SAP consume considerable health care resources, reguire prolonged hospital treatment, and the in-hospital mortality remains high. There is need for collaboration between many medical specialties, general practitioners, and social workers when SAP patients are treated, because these patients have a wide range of medical problems while being treated in the hospital and after being discharge, such as requirement of intensive care unit (ICU) treatment, infection problems, need of dialysis, surgical and radiological procedures, diabetes, symptoms of polyneuropathy, recurrent pancreatitis, continual abdominal pain, and often medico-social problems.

The rising costs of ICU treatment and the ability to prolong the life of critically ill patients creates a need to identify early those patients who will benefit from intensive care and who will not (Atkinson et al. 1994). Several classification systems have been presented to assess the severity of AP. However, there are only a few practical methods for predicting if outcome in AP is fatal or not. Scores such as the Ranson (Ranson et al. 1974 and 1976, Ranson 1982), the Glasgow (Imrie et al. 1978a), the Blamey (Blamey 1984) and the Acute Physiology and Chronic Health Evaluation (APACHE) II scores (Knaus et al. 1985a) are practical for assessing the severity of the disease but they are not sufficiently well validated for predicting mortality. Survival in AP and particularly in SAP is related to therapy-associated as well as patient-associated factors. Several isolated factors related to mortality in AP have been identified but there is currently no model to prognosticate a fatal outcome in SAP which would take all these single predictors into account.

Much attention has been paid to quality of life and long-term outcome of patients surviving SAP, and especially to alcohol-induced SAP (Fenton-Lee and Imrie 1993, Orlando 3rd 2000). Comments regarding the futility of treating patients with SAP, especially those with alcohol-induced SAP and MOF, are commonplace in clinical work.

In studies including only a small number of patients, the quality of life (QOL) and outcome after SAP have been shown to be good (Doepel et al. 1993, Fenton-Lee and Imrie 1993, Broome et al. 1996, Soran et al. 2000). However, only two studies on QOL assessment after SAP have used generic multidimensional measures (Broome et al. 1996, Soran et al. 2000).

The purpose of this study was to identify the prognostic factors related to hospital mortality and to construct a new model for predicting a fatal outcome of patients in the early phase of SAP. In addition, the aim was evaluate the clinical usefulness of assessing multiple organ failure associated with SAP in relation to hospital mortality. Furthermore, the aim was to define the overall long-term post-discharge outcome of patients after SAP.

5. REVIEW OF THE LITERATURE

Moynihan described AP in 1925 in these words: " It is the most terrible of all calamities that occur in connection with abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it, all render it most formidable of catastrophes."

The name of the pancreas (Greek: pan=all, kreas=flesh) was first recorded in about 100 A.D. by Rufus of Ephesus, but the first description of this organ had been documented 400 years earlier by Herophilus of Chalkaidon (Fitzgerald 1980).

The pancreas secretes daily about 2500 ml isosmotic alkaline (pH > 8) fluid containing about 20 enzymes and zymogens. The pancreatic secretion contains the enzymes needed for the major digestive activities of the gastrointestinal tract and provides an optimum pH for the function of the digestive enzymes (Case 1998). The endocrine function of the pancreas is mediated by glucagon, insulin, and somatostatin. The endocrine cells mainly localized in the islets of Langerhans produce these hormones (Nauck 1998).

AP is an acute inflammatory process of the pancreas that may involve the peripancreatic tissue and various remote organ systems (Bradley 1993). The final key mechanism operating in AP is related to autodigestion of tissues by the proteolytic enzymes of the pancreas itself. Evidence suggests that some cytokines [e.g., tumor necrosis factor-α, interleukin-1 (IL-1), IL-6 and IL-8], endotoxin and inflammatory mediators (e.g., platelet activating factor and phospholipase A_2) are important in the development of the complications and MOF in SAP and sepsis (Wilson et al. 1998).

The severity of AP is graded by the development of local complications and/or distant organ dysfunction. Common findings in SAP are abdominal pain, nausea, vomiting, paralytic ileus, fever, abdominal tenderness, abdominal distension, and tachycardia which are seen in 65 to 95 % of patients. Less frequently patients have jaundice, tachypnea, respiratory insufficiency, hypovolemia, shock, pleural effusion, cardiac failure, renal failure, and abdominal mass (Z'graggen et al. 1998).

5.1 Epidemiology of AP and SAP

AP is a common disease in the developed countries and incidence is increasing (Svensson et al. 1979, Thomson et al 1987, Steinberg and Tenner 1994, Mckay et al. 1999). Pancreatitis is severe in 10–30% of the patients. In Finland, the incidence of AP has risen from 47/100 000/year in 1970 to 73 in 1989, but the proportion of SAP did not increase in relation as much as did the incidence of mild AP (Jaakkola and Nordback 1993). In Scotland the incidence has increased from 26/100 000/year in 1985 to 42 in 1995 (McKay et al. 1999). In Finland 80% of AP the patients are male and the incidence of AP among males increased greatly between 1970 and 1989 (Jaakkola and Nordback 1993). A recent study from the Netherlands reports that the number of incidents has grown from 12/100000/year in 1985 to 16 in 1995 and the incidence of AP has increased by 198% among males and 103% among

females from 1969 to 1995 (Eland et al. 2000). In children AP is usually associated with trauma (37% of cases); traumatic AP has been considered the most serious form of pancreatitis (Yeung et al. 1996).

A nationwide survey in Finland showed that the incidence of AP among men grew markedly from 1984 to 1989 and that this was the case especially in the age group 25-44. This increase may be caused by the growing alcohol consumption in Finland (Jaakkola and Nordback 1993). However, in the Netherlands the number of incidents has grown while the total amount of alcohol consumed per inhabitant decreased during the study period. The increase in the incidence of AP in Netherlands was explained by the growing incidence of gallstone disease and of endoscopic procedures to the pancreatic and bile ducts (Eland et al. 2000). Some of the change may be explained by improved diagnostic accuracy (Wilson and Imrie 1990).

5.2 Pathogenesis of AP and SAP

There are three classic theories to explain the pathogenesis of AP caused by gallstones:

1) The *flow/reflux theory* chaims that there is reflux of duodenal contents into the pancreatic ductal system due a direct effect of the passage of a gallstone through the sphincter of Oddi or an effect of alcohol which reduces its tonus, relaxing the sphincter (McCutcheon 1968). 2) According to the *bile reflux theory* an impacted gallstone obstructs the distal duct and creates a common channel between the bile and pancreatic ducts (Singh and Simsek 1990). 3) The *obstruction theory*, states that the bile stones obstruct the pancreatic duct and with continued secretion there is hypertension in the pancreatic duct which causes extravasation of pancreatic fluid into the parenchyma (Steer 1992).

Further theories include the *toxic metabolic hypothesis* which postulates that ethanol has a direct toxic effect on pancreas leading to AP, the *trypsinogen activation hypothesis*, the *ischemia/reperfusion theory* and the *hereditary pancreatitis/gene mutation theory* (Noronha et al.1981, Singh and Simsek 1990, Bettinger and Grendell 1991, Gullo et al. 1996, Whitcomb et al. 1996 a and b).

There are many similarities between SAP, sepsis syndrome and septic shock. Evidence suggests that cytokines (tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-8 etc.), endotoxin and inflammatory mediators (platelet activating factor phospholipase A_2 etc.) are important in the development of complications and in the development of MOF, something that occurs in both SAP and sepsis (Wilson et al. 1998).

Despite more than 100 years of experience and thousands of experimental, animal and clinical studies, the pathogenesis of AP and SAP is not well understood. Only a minority of patients with stones in the common bile duct or alcohol abusers gets AP. Perhaps the factors predisposing to SAP are multifactorial and explain our fragmentary understanding of the pathogenesis of SAP.

5.3 Etiology of SAP

AP and SAP are probably caused by the same etiological factors. In this review of the literature all published etiological factors associated with SAP are discussed. Ethanol and gallstones cause 70-90% of the episodes of SAP. Endoscopic retrograde cholangiopancreaticography (ERCP), surgery and trauma are the next common causes. Other causes of SAP are rare.

5.3.1 Ethanol and other toxins

The association between alcohol abuse and pancreatitis was first described by Symmers (1917). According to Schenker and Montalvo (1998) the alcohol-related triggering mechanism or mechanisms leading to the autodigestion of pancreatic tissue have not been elucidated. The most persuasive concepts are the toxic-metabolic hypothesis, oxidative stress-induced specific production of free radicals and membrane lipid alteration (Schenker and Montalvo 1998). In addition, genetic factors may also play a role. Only 5% of alcohol abusers have clinical evidence of pancreatitis, but at autopsy changes consistent with chronic pancreatitis have been reported in up to 75% of the alcohol abusers (Singh and Simsek 1990, Schenker and Montalvo 1998).

As far as other toxins are concered, methanol poisoning can cause a fatal form of SAP (Hantson and Mahieu, 2000), as may organophosphate poisoning (Panieri et al. 1997).

5.3.2 Obstructive causes

Opie (1901) was the first to describe the association between gallstones and pancreatitis. Gallstones are the most common obstructive cause of AP. According to the study of Steinberg and Tenner (1994), more women than men are affected, and the peak incidence age is between 50-60 years. In Finland gallstones are an etiological factor in only 10-20% of the attacks of AP, but when only females are considered, gallstones are the most common cause of AP (Mero 1982, Puolakkainen et al. 1987, Jaakkola and Nordback 1993)

Rare causes of SAP have been reported related to ascariasis (Choi and Wang 1984), choledochal cysts (Goldberg et al. 1980), papilla Vater´s adenoma, papilla Vater´s carcinoma (Sato et al. 1999), pancreatic ductal adenocarcinoma (Zyromski et al. 2001), impacted papilla minor stone in pancreas divisum (Renzulli et al. 1999), pancreatic carcinoma (Mujica et al. 2000), and metastases (Gutman et al. 1993)

5.3.3 ERCP, posttraumatic and iatrogenic causes

Althougt the cause of AP is obvious in patients who have undergone ERCP, stent placement, or sphincterectomy, the mechanism indicing AP is not clear (Bank and Indaram 1999). 1% to 3% of patients undergoing ERCP get fatal SAP (Fung et al. 1997). According to the study of Räty et al. (2001) 3 patients out of 315 (1 %) developed SAP as a complication of ERCP. Furthermore, the results suggested that the routine use of

prophylactic antimicrobial drugs reduces the incidence of AP following ERCP. Moreover, blunt or penetrating trauma to the pancreas can lead to an attack of SAP (Pollock 1959, Imrie et al. 1978b)

Post-operative SAP may occur after many different surgical procedures. Most attacks of post-operative SAP are caused by abdominal surgery (White et al. 1970, Imrie et al. 1978b), transplantation surgery (Fernandez-Cruz et al. 1989, Camargo et al. 1995, Krokos et al. 1995) or thoracic surgery (Adiseshiah et al. 1983, Fernandez-del Castillo et al. 1990, Lefor et al. 1992). Post-operative SAP is most likely induced by severe pancreatic ischemia leading to acinar cell injury (Gullo et al. 1996). Post-operative pancreatitis was found to be highly lethal (49% mortality) in a study involving 644 AP patients (Berman et al. 1961)

Invasive medical procedures or treatments such as percutaneous biopsy of the pancreas (Mueller et al. 1988), manometry of the sphincter Oddi (Albert et al. 1988), extracorporeal shock wave lithotripsy of kidney stones (Abe et al. 2000), laser treatment of periampullary adenoma (Maunoury et al. 1993), peritoneal dialysis, and hemodialysis (Bruno et al. 2000) have also been associated with the development of SAP.

5.3.4 Drugs and metabolic causes

There are numerous reports on an association between drugs and AP. Rűnzi and Layer (1996) point out that the course of drug-induced AP is usually mild and self-limited. Nonetheless, SAP has anecdotally been reported to be associated with the use of nelfinavir (Di Martino et al. 1999) and meglumine antimoniate (Delgado et al. 1999) in HIV infection, with the use of propofol (Metkus et al.1996), enalapril (Gonzales Ramallo et al. 1992), and L-asparaginase (Garrington et al. 1998).

Hypertriglyceridemia is associated with SAP (Toskes 1990, Ohmoto et al. 1999), whereas hyperparathyroid adenoma can cause hypercalcemia and this may in some cases lead to SAP (Shimizu and Kodama 1996).

5.3.5 Infection and hereditary causes

The following infections have been reported to cause SAP: hepatitis A (Davis and Keeffe 1992), Coxsackie B4 (Kennedy et al. 1986), Coxsackie B5 (Gooby Toedt et al. 1996), parotitis virus (Feldstein et al. 1974), HIV (Parithivel et al.1999), and some parasites (Choi and Wong1984).

Hereditary pancreatitis was described by Comfort in 1952 (Comfort 1952). It is a rare condition characterized by acute and chronic pancreatitis transmitted as an autosomal dominant trait in chromosome 7q35 (Whitcomb et al. 1996a and b, Sossenheimer et al. 1997). In general, the attacks of hereditary AP are mild, but very seldom female have attacks of SAP during pregnancy and menstruation (Gates et al. 1999).

5.3.6 Other causes

Pregnancy has been reported to be associasted with SAP; in most cases both biliary stones and biliary sludge are found in patients with AP in pregnancy and the postpartum period (Maringhini et al. 1993, Ramin et al. 1995, Maringhini et al. 2000). Necrotizing pancreatitis has also been reported in connection with polyarteritis nodosa (Flaherty and Bradley 1999), systemic amyloidosis in rheumatoid arthritis (Oishi et al. 2000) and primary sclerosing cholangitis (Goldin et al. 1990).

5.3.7 Idiopathic SAP

The cause of SAP cannot be established in from 2% to 40% of patients (Kemppainen et al. 1996, Fernandez-del Castillo et al.1998, Gloor et al. 2001, Johnson et al. 2001, Buter et al. 2002).

5.4 Diagnosis of AP

The diagnosis of AP and SAP is based on clinical, laboratory, radiological, surgical, and pathological findings. In the early 20th century, the diagnosis was only based on clinical, surgical and pathological findings (Moynihan 1925), but as laboratory methods developed, the importance of laboratory assessment has increased in diagnosis of AP. After 1985 imaging procedures have established a central role in the diagnosis and classification of AP (Kivisaari et al. 1983 and Balthazar et al. 1985).

Elman (1929) was the first to describe the association between elevated serum amylase activity and AP. The serum amylase activity has been the cornerstone in the diagnosis of AP. The serum amylase activity increases within hours of the onset of AP symptoms and is regularly normalized within 3-5 days. The normalization can sometimes occur very rapidly if the pancreatic tissue is extensively necrotic and may result in normoamylasemia already by the time the patient is admitted (Kemppainen et al. 1998a). Urine amylase activity increases later than the serum amylase. It has been shown that pancreatic amylase isoenzyme measurement (i.e, excluding the amylase activity from the salivary glands and other tissue) is more specific than total serum amylase measurement (Lin et al. 1989, Sternby et al. 1996).

Lipase originates mainly from the pancreas. Consequently the serum lipase activity may be more specific and more sensitive than amylase levels for detecting AP (Ranson 1997). By using a cut-off level of serum lipase and amylase activities > 3 times normal, the diagnostic accuracy is improved for differentiating nonpancreatic abdominal pain from AP. The sensitivity of an enhanced amylase activity for diagnosing AP is 52-95% and the specificity is 86-98%, and for lipase 74-100% and 34-100%, respectively (Wong et al. 1993). These values are generally considered unsatisfactory.

Trypsin is secreted from the pancreatic acinar cells as the proenzyme (zymogen) trypsinogen. Trypsinogen is activated in the duodenum by enterokinase. Trypsinogen-1 and trypsinogen-2 are the two major isoenzymes and constitute 20 % of the pancreatic secretion

proteins (Kimland et al. 1989). These isoenzymes, their inhibitors (α_2-macroglobulin and α_1-antitypsin) and their complexes can be measured by radioimmuno- and immunofluorometric assays. These assays have been reported to be useful for detecting AP, but none of them are used clinically (Itkonen et al. 1990, Hedström et al. 1994, 1996 b, c). However, a rapid urinary trypsinogen-2 test strip has proven to be useful for the screening of AP (Hedström et al. 1996a, Kemppainen et al. 1997, Kylänpää-Bäck et al. 2000).

5.5 Severity assessment of AP

The first one to classify AP was Fitz in 1889. The classification suggested three types of disease: hemorrhagic, gangrenous and suppurative (Moynihan 1925). During the following decades the classification of SAP was based on categorizing patients on the basis of etiology. The first international attempt to classify and define pancreatitis, which was mainly based on morphological criteria, was made at the Marseille meeting in 1963 (Sarles 1965). Three additional international attempts at classification were made. The first one in Cambridge 1983 (Sarner and Cotton 1984), the second one in Marseille 1984 (Singer et al. 1985) and the third one in Marseille-Rome 1988 (Sarles et al. 1989). A new, clinically based classification system for AP and its complications were proposed in Atlanta in 1992 (Bradley 1993). It adopted the following eight distinct clinical and morphological entities related to AP: mild and severe AP, interstitial edematous pancreatitis, sterile and infected necrotizing pancreatitis, fluid collections, pseudocyst and pancreatic abscess.

5.5.1 Laboratory evaluation of SAP

Amylase and lipase

The levels of amylase or lipase do not correlate with the severity of AP, nor do they have any prognostic value. Therefore, they should not be used for the follow-up or for the severity classification of patients with AP (Nordback 1985a).

Trypsin- based methods

In assessment of the severity of AP the concentration of trypsinogen-2 (Hedström et al.1996b) and the trypsin-2-α_1-antitrypsin complex (Hedström 1996c) have been reported to be useful. Trypsinogen activation peptide is released from trypsinogen when it is activated to trypsin during SAP (Formela et al. 1995). The measurement of trypsinogen activation peptide from plasma (Heath et al. 1994, Gudgeon et al. 1990) and urine samples (Neoptolemos et al. 2000) seems to be useful for staging AP.

Inflammatory mediators

C-reactive protein (CRP) is most widely documentated among the inflammatory mediators for the differentiation of severe and mild AP. The prognostic role of CRP in early AP is limited because of CRP values peak rather slowly; the delay may be 48 to 72 hours before peak levels are achieved. If peak CRP values, are over 150-120 mg/L 48 hours after

admission SAP is possible (Puolakkainen et al. 1987, Puolakkainen 1989, Isenmann et al. 1993, Heath et al. 1995, Paajanen et al. 1995).

The peak concentration of interleukin-6 (IL-6) occurs 24-48 hours before the rise of CRP values but otherwise the plasma profile increase parallels that of CRP. Interleukin-6 predicts SAP already at the time the patient is admitted (Leser et al. 1991, Viedma et al. 1992, Heath et al. 1993, Windsor et al. 1993, Inagiki et al. 1997, Ikei et al. 1998). Recently, many other proinflammatory cytokines (e.g., tumor necrosis factor ά, IL-1, IL-8, IL-18) and anti-inflammatory cytokines (IL-10, IL-1Ra, IL-11, serum IL-2 Ra) have been reported to be markers for SAP (Norman et al. 1994, Pezzilli et al. 1994, Norman 1998, Chen et al. 1999, Hynninen et al. 1999, Osman and Jensen 1999, Hirota et al. 2000, Opal and Depalo 2000, Rau et al. 2001).

The measurement of polymorphonuclear elastase and neopterin in serum as a marker of granulocyte activation has been used in the staging of AP (Gross et al. 1990, Domingues-Munoz et al. 1991, Viedma et al. 1994, Schölmerich et al. 1996, Uomo et al. 1996b, Widdison and Cunningham 1996, Ikei et al 1998, Kaufman et al. 1998).

Pancreatic phospolipase A_2 has been suggested to play a key role in the pathogenesis of pancreatic tissue injury in AP. Group I phospolipase A_2 clinical value in the diagnosis of AP. Group II phospolipase A_2 is thought to play an important role in the development of the systemic inflammatory response and organ complications (Puolakkainen et al. 1987, Grönroos and Nevalainen 1992, Viedma et al. 1994, Grönroos et al. 1998, Hietaranta et al. 1999, Nevalainen et al. 1999)

Among the inflammatory mediators, only CRP is used in a clinical routine, but IL-6 and Il-10 measurements and the trypsinogen dipstick test are also available commercially.

It may be too optimistic to think that there is a single laboratory test to identify the attack of SAP. Instead, a combination of tests (testpanels) may be needed to predict SAP and the systemic complications of SAP (Windsor 2000).

Others laboratory assessments

In some studies pancreatitis-associated protein has shown to predict SAP (Kemppainen et al. 1998b), although controversial results have been reported (Pezzilli et al. 1997). Hepatocyte growth factor levels have also shown to be closely related to SAP (Ueda et al. 1997). According to two recent studies the levels of endogenous plasma ascorbic acid are related to show SAP (Bonham et al. 1999, Abu-Zidan et al. 2000). The markers of oxidative stress (thiobarbituric acid reactive substances, myeloperoxidase, protein carbonyls and ascorbic acid) predict SAP (Abu-Zidan et al. 2000). Procalcitonin and granulocyte colony stimulating factor may also be useful for predicting SAP (Müller et al. 2000) as well is case for, amylin and serum amyloid A concentration (Phillips et al. 2000, Mayer et al. 2002). The level of procarboxypeptidase B in serum and urine has been shown to be valuable to detecting SAP (Appelros et al. 1998).

5.5.2 Clinical presentation

SAP has usually a rapid onset. It is manifested by upper abdominal pain, vomiting, fever, tachycardia, leukocytosis, and elevated serum levels of pancreatic enzymes (Baron and Morgan 1999).

The other clinical manifestations can be classified by the Atlanta classification or by subcutaneous manifestations.

Atlanta classification: organ failures, hypovolemia, abdominal mass, pericardial effusion, cardiac tamponade, hematemesis, melena and hypocalcemia (Bradley 1993).

Subcutaneous manifestations: Periumbilical lividity (Cullen's sign) was described by Cullen in 1918 in association with a ruptured ectopic pregnancy and may present in SAP. Gray Turner's sign described in 1919 in patients with SAP is defined periumbilical discoloration and discoloration in the flanks. Neither Cullen's sign nor Grey Turner's sign is specific for AP, since these signs are also seen in patients with perforated ulcer, liver disease, rupturated aortic aneurysm and ectopic pregnancy. Fox's sign is defined as ecchymosis of the penis or below inguinal ligament and Walzel's sign is livedo reticularis. Blauvert was first to describe subcutaneous fat necrosis in 1946 associated with AP. In patients with AP fat necrosis can be found in variety of extra-abdominal locations including the mediastinum, pericardium, myocardium, pleura, bone marrow, lower extremity joints, periarticular tissue, adrenal, and ovaries. (Cullen 1918, Grey Turner 1919, Blauvert 1946, Sigmund 1954, Scarpelli 1956, Jacobs et al. 1977, Wilson et al. 1983, Dickson and Imrie 1984, Francombe et al. 1995, Bem and Bradley 1998)

SAP patients may have ascites, septicemia, duodenal obstruction, portal vein thrombosis, massive intra-abdominal hemorrhage, encephalopathy, and sudden blindness (Z'graggen et al. 1998). Most of these manifestations develop late in the course of SAP and may be rare (except for those in the Atlanta classification). The symptoms described above are related to SAP, but their prognostic value regarding mortality has not been evaluated.

The clinical presentation in early SAP has only limited value. The sensitivity of the clinical presentation is poor, but the specificity seems to be good. SAP can be predicted correctly only in 34 to 39% of patients on admission by experienced clinicians (McMahon et al. 1980, Wilson et al. 1990).

5.5.3 Imaging

Plain abdominal and chest x-rays are important to identify pleural effusions, pneumonic infiltrations and abdominal emergencies. Pleural effusions are strongly associated with SAP (Lankisch et al. 1994, Maringhini et al. 1996, Heller et al. 1997). In the study carried out by Talamini et al. (1999) the serum creatinine concentration and chest radiography were useful for identifying, within 24 hours from admission, a group of SAP patients.

Sonography has only limited value in the diagnostics of SAP, since overlying bowel gas often obscures the pancreas. However, sonography is of more value in detecting or excluding gallstones and in the diagnosis and follow-up of established pancreatic fluid collections and abscesses (McKay et al. 1982).

Dynamic contrast-enhanced CT is the diagnostic "golden standard" for objective verification of pancreatic necrosis (Kivisaari et al. 1983, Balthazar et al. 1985 and 1990, Block et al 1986). In necrotic areas the contrast density fails to exceed 30-50 Hounsfield units (normal range 50-150) after intravenous administration of contrast medium (Kivisaari et al. 1983, Balthazar et al. 1990). However, it should be remembered that identifying viable pancreas tissue on contrast-enhanced CT does not exclude SAP. In a recent study, 19% of the patients with necrotizing pancreatitis did not have pancreatic parenchymal necrosis on contrast-enhanced CT (Sakorafas et al. 1999). Intravenous contrast medium may be detrimental to the kidneys, but in a recent study performing a contrast-enhanced abdominal CT did not aggravate the severity of the disease in patients with SAP (Hwang et al. 2000).

Kivisaari and Schröder developed a scoring system for extra-pancreatic findings, which correlated with the severity of AP (Kivisaari et al. 1983, Schröder et al. 1995). The extra-pancreatic findings included edema in part of the pancreas, edema of the entire pancreas, peritoneal fluid, perirenal fat edema, mesenteric fat edema, pleural effusion and bowel paralysis. Each of these findings scores one point. A total score < 4 suggests mild AP, and a score ≥ 4 suggest SAP. This scoring system is practical even among patients with renal dysfuntion or failure when no intravenous contrast medium agents can be administered.

Balthazar et al. (1985) published a scoring system based on the presence of pancreatic enlargement, peripancreatic edema, and fluid collections on computed tomography (CT). This system was further refined to include data on nonperfused and presumably necrotic pancreas in contrast-enhanced CT (Balthazar et al. 1990). The advantages of the Balthazar system are that it can be applied immediately and at any point during the patient's hospitalization. In addition, it provides information about local complications. The CT-based system has similar sensitivity and specificity rates as the APACHE II, Ranson and Glasgow systems have (Balthazar et al. 1990).

At present, the routine use of CT scanning to differentiate between interstitial and necrotizing pancreatitis is controversial (Banks 1997). A recent study suggests that a contrast-enhanced CT on admission correlates significantly with the severity of the disease and cannot be replaced by conventional laboratory prognostic scores (Ranson/Imrie) (Lankisch et al. 2001). According to Kemppainen et al. (1996) early localization of necrosis by contrast-enhanced CT can predict the outcome in patients with SAP. In that study necrosis in the head of pancreas was associated with a poorer outcome than necrosis located in the tail of the pancreas. However, there are no randomized studies documenting an improved outcome when a CT scan is performed early in the course of an attack of AP. In the early phase of AP, an abdominal CT scan seems to be indicated if there are differential diagnostic problems (e.g., suspicion of intestinal perforation and pancreatic trauma) (Yousaf et al. 2003).

Contrast-enhanced magnetic resonance imaging (MRI) is an alternative primary imaging technique for detecting SAP in patients with AP. MRI and CT are concordant in distinguishing viable pancreatic tissue from areas of necrosis. MRI appears to be more precise than CT in characterizing the content of fluid collections and in demonstrating gall stones, although CT is better in detecting gas and calcifications (Piironen et al. 1997 and 2000, Ward et al. 1997, Robinson and Sheridan 2000).

Technetium-99^{m}-hexametyl propylene amine oxine leukocyte scintigraphy may be useful in identifying SAP patients from other AP patients (Schölmerich et al. 1991, Papos et al. 1997, Werner et al. 1998). However, this method has not achieved widespread use.

Vesentini and coworkers introduced a system based on the extent of pancreatic necrosis in CT alone and reported a good correlation with clinical outcome (Vesentini et al. 1993).

5.5.4 Scoring systems

Ranson and Glasgow

Ranson et al. (1974) developed the first scoring system for all AP patients and later for patients with gallstone pancreatitis (Ranson 1982). The Ranson criteria have an estimated sensitivity of 72% and specificity of 76%. Their positive predictive value is around 51% and the negative predicting value 89% (Steinberg 1990).

The Glasgow criteria were developed in the late 1970s (Imrie et al. 1978a). Since then the criteria have been modified three times (Osborne et al. 1981, Blamey et al. 1984, Corfield et al 1985). The Glasgow criteria have an estimated sensitivity of 63%, a specificity of 84%, a positive predictive value of 52%, and a negative predictive value of 89% (Steinberg 1990).

Both criteria include clinical and laboratory variables during the initial 48 hours of admission and thus the differentions between severe or mild AP is made at this time point. These criteria are not valid for repeated measurements beyond 48 hours.

Atlanta classification

According to the Atlanta classification SAP is associated with systemic and local complications (Bradley 1993).

The systemic complications are:

- *organ failure* [shock (systolic blood pressure < 90 mm Hg), pulmonary failure (PaO_2 ≤ 60 mm Hg), renal failure (creatinine level > 177 µmol/L after rehydration), or gastrointestinal bleeding (>500 ml/24 hours)]
- *systemic fibrionolysis* [disseminated intravascular coagulation (platelets ≤ 100 000/ mm^3, fibrin split products > 80µg/mL)] and *severe metabolic disturbance* (serum calcium level ≤ 1.87 mmol/L).

The local complications are:

- *pancreatic necrosis* (an area of more than 3 cm diameter or involving more than 30 % of pancreas in CT and contrast density increase < 50 Hounsfield units in the area of necrosis after intravenous administration of contrast medium. In addition, pancreatic necrosis or peripancreatic necrosis defined at surgery characterize SAP)
- *acute fluid collections* (occur early in the course of AP, and are located in or near the pancreas, and always lack a wall of granulation or fibrous tissue)
- *abscess* (a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of AP or pancreatic trauma)
- *pseudocyst* (a collection of pancreatic fluid enclosed by a wall of fibrous or granulation tissue, which arises as a consequence of AP, pancreatic trauma, or chronic pancreatitis)

The Atlanta classification for SAP is broad since it includes also patients whose risk of death is not high (e.g., patients developing uncomplicated necrosis, pseudocyst or abscess). It is also retrospective (e.g., the development of a pseudocyst takes over 4 weeks). In the literature the definitions of SAP have been confusing before the Atlanta classification but also after it. For example, when predicting the outcome of a patient with SAP, some studies use the Atlanta classification of SAP whereas other studies include only a part of their SAP patients for assessment of prognosis (e.g., patients with pancreatic necrosis, infected necrosis, and organ or multiple organ failure).

APACHE II

APACHE II was developed as a general measure for ICU patients to estimate the severity of a disease, but it was quickly recognized for its potential for staging of patients with AP (Knaus et al. 1985a, Larvin and McMahon 1989, Wilson et al. 1990). Unlike the Ranson and Imrie criteria, the APACHE II system is a valid method for the prediction of the severity of AP on admission. The APACHE II system have comparable sensitivity and specificity rates to the Ranson and the Imrie criteria. The APACHE II system with its 14 variables and 96 alternatives is more complicated and cumbersome than the Ranson and the Imrie criteria. APACHE II and the Simplified Acute Physiology Score (SAPS) systems are of limited clinical utility in the early prognostic evaluation of AP (Domínguez-Muňoz et al. 1993). However, according to Khan et al. (2002) a deterioring APACHE II score at 48 hours after admission may identify patients who have a poor outcome.

Artificial neural network

Artificial neural networks (ANN) have been used to predict the duration of hospital stays in AP (Pofahl et al. 1998). ANNs have been successfully used for pattern recognition and survival prediction in several clinical settings (Dybowski et al. 1996, Golub et al. 1998, Lundin et al. 1999). ANNs offer a way of capturing nonlinearities and complex interactions between prognostic factors in a multivariable model (Burke 1996).

Other scoring systems

Diagnostic peritoneal lavage was successful in 95% of the AP patients who had free peritoneal fluid and the lavage fluid was useful for prediction of SAP (McMahon et al. 1980). However, lavaging is invasive and it cannot be justifieably carried out in all patients with AP. Bank et al. (1983) have also described an criteria for prediction of SAP. Fan et al. (1989) found that serum urea (>7.4 mmol/L) and plasma glucose (>11.0 mmol/L) on admission predicted SAP and that the predictive powers of these assessments were comparable with the Glasgow multifactor scoring system (Hong Kong criteria). Obesity may predispose to SAP (Suazo-Baráhona et al. 1998). The risk of SAP in AP patients is increased if the patients has an age greater than 55 years, male sex, AP of unknown origin or alcohol-related (Pezzilli et al. 1998). A high hematocrit (≥44%) on admission and a failure of the hematocrit to fall during the first 24 hours in hospital was the best binary predictors of necrotizing pancreatitis according a study by Brown et al. (2000). None of these systems are widely used.

5.6 Treatment of SAP

In most Finnish hospitals most patients with AP – whether of the mild or severe form – are treated in surgical wards or ICUs. The Department of Gastroenterological and General Surgery, at Meilahti hospital, has a long tradition of research and treatment of AP in Finland (Kivilaakso et al. 1984, Puolakkainen et al. 1987, Kemppainen et al. 1997, Sainio et al.1997), and serves as a tertiary referral center for a population of about 1.3 million inhabitants. The basic principles of treatment of AP have remained the same during the study period. Adequate initial resuscitation (fluid replacement up to 10 liters or more on the first day of treatment) is followed by aggressive nonoperative management with invasive monitoring and organ system support in an ICU, including treatment with early antibiotics for infection prophylaxis and prophylaxis for stress ulcers and thromboembolism. Necrosectomy is performed usually at the end of the third to fourth week in patients who have infected peripancreatic necrosis and worsening MOD (Leppäniemi 2003 and Uhl et al. 2003).

5.6.1 Conservative treatment

The conservative management of SAP is based on the two-phased nature of the disease. The first phase can continue for 14 days and is characterized by a systemic inflammatory response syndrome maintained by the release of various inflammatory mediators. As a result of this inflammatory mediators may lead to single or multiorgan failure (Norman et al. 1998, Gloor et al. 2001a). Surgery during the first phase of SAP does not seem to be appropriate (Büchler et al. 2000). The second phase is dominated by infectious sepsis related complications. During the second phase infection of pancreatic necrosis may occur.

General ICU management

The principles of ICU management in SAP include treatment of secondary causes of organ failure, such as hypovolemia, hypoxemia and tissue hypoperfusion. To achieve this,

adequate monitoring (e.g., arterial catheterization, pulmonary arteria catheterization for measuring pulmonary capillary wedge pressure, central venous catheterization for measuring central venous pressure) and aggressive support of ventilation and the cardiovascular system are necessary.

Rapid intravenous fluid therapy to correct dehydration is crucial for successful resuscitation of patients with SAP. In the early phase of SAP, the need of colloid and crystalloid fluid can be very high [1-3 L/hour and up to 10 L/day or more for normal weight (70 kg) patient]. Meta-analyses suggest that the use of human albumin to patients with a critical illness may increase mortality, and thus human albumin is not recommended (The albumin reviewers 2001). Fluid resuscitation can be considered successful if a pulmonary capillary wedge pressure of 12-16 mmHg or a central venous pressure of 8-12 mg is achieved.

If fluid resuscitation is not sufficient to achieve the targets (mean arterial pressure >65 or more), the use of one drug or combining vasoactive drugs [dopamine (2-10µg/kg/min), doputamine (2-10µg/kg/min), dopexamine, norepinephrine (0.05-3.0 µg/kg/min) or epinephrine] are needed. With the help of pulmonary capillary wedge pressure measurements, we can achieve the lowest loading stage of cardiac stroke volume and cardiac volume to ensure sufficient tissue oxygen import and transport. The target is to achieve at least mean arterial pressure of at least 65 mmHg and mixed venous oxygen saturation of 65% (Pettilä 2002).

Insufficient ventilation is initially diagnosed on the basis of blood-gas analyses, ventilation frequency, and oxygen saturation. Treatment consists of supplemental oxygen through an oxygen mask, CPAP (continuous positive air pressure) or mechanical ventilation. The markers of tissue oxygen hypoxia consist of low mixed venous oxygen concentration, high lactate concentration and metabolic acidosis (Pettilä 2002).

If acute renal failure develops in spite of rapid intravenous fluid therapy, continuous replacement of renal function should be started without delay to ensure optimal fluid and metabolic control and to ensure unlimited nutritional support without hemodynamic instability. Early hemodiafiltration has been shown to be more effective than late hemodiafiltration in patients with sepsis (Bellome and Ronco 1999). Continuous veno-venous hemofiltration tends to cause less hemodynamic instability than intermittent hemodialysis (Forni and Hilton 1997).

Increased intra-abdominal pressure (IAP), which may lead to the abdominal compartment syndrome is a known complication of SAP (Gecelter et al. 2002). A high IAP is manifested clinically by increased airway pressures, decreased cardiac output, oliguria, decreased visceral perfusion and increased cerebrospinal pressure and may lead to MOF (Gecelter et al. 2002). The IAP may be estimated by a validiated bladder measurement technique as is nowadays done at Meilahti hospital with ICU treated SAP patients (Fusco et al. 2001). In patients with a high IAP and the abdominal compartment syndrome decompressive laparotomy may be considered (Gecelter et al. 2002). However, the value of a decompressing lapartomy will have to be investigated by a randomized controlled trial before any general recommendations can be made (Sugrue 2002, Z'graggen and Gloor 2002).

Sufficient analgesics are mandatory to reduce the metabolic stress and to reduce the patients' discomfort. Conventionally SAP patients treated in ICU´s consist of high doses of opioids, often combined with sedatives. A German study has shown that epidural anesthesia provides good pain relief and can be safely used in patients with SAP (Niesel at al. 1991). The main advantage of epidural analgesia in patients with SAP is that side effects of high doses sedatives can be avoided, and usually patients are more awake, and are frequently able to breathe spontaneously (Sigurdsson 1998).

Patients who are treated in ICU and have a hemoglobin level of 70-90 g/L have a similar prognosis as patients with levels over 100g/L (Hebert et al. 1999). Thus low hemoglobin values should be appropiately considered when blood transfusions are planned for patients with SAP.

Intensive insulin therapy to maintain blood glucose between 4 to 6 mmol/l may reduce morbidity and mortality among critically ill patients (Van den Berghe et al. 2001), and thus optimal glucose control should also be considered for patients with SAP.

Infection prophylaxis

Bacterial translocation from the gut is the main cause of secondary infection of necrotic pancreatic tissue (Runkel et al. 1991, Widdison et al. 1994, Moody et al. 1995). Percutaneous sonographical or CT-guided aspiration samples for bacteriological studies are the cornerstone of identification of infected pancreatic necrosis in patients with SAP (Gerzof et al. 1987, Paye et al. 1998, Rau et al. 1998).

In two controlled and uncontrolled studies using selective gut decontamination (oral and rectal norfloxacin, colistin and amphotericin: and intravenous cefotaxime 500 mg every 8 hours) lower mortality, lower gram-negative pancreatic infection, and lower gram-negative intestinal colonization was achieved (Luiten et al. 1995, 1998). In a prospective randomized trial study carried out by Sainio et al. (1995) lower mortality and fewer infectious complications was achieved among patients with alcohol-induced necrotizing pancreatitis by using intravenous cefuroxime versus patients who received no antibiotic. In two studies in which intravenous imipenem was used the results indicated a lower incidence of pancreatic necrosis infection and a trend toward reduced mortality was achieved (Pederzolli et al. 1993, Ho et al. 1997). Decreased pancreatic and extrapancreatic infection rates were found in a randomized study by using imipenem comparing to pefloxacin, though mortality was similar (Bassi et al. 1998). However, all of these studies were underpowered and their results do not allow any definitive conclusion to be made.

A recent meta-analysis suggested that the use of prophylactic antibiotic reduces sepsis and mortality in patients with acute necrotizing pancreatitis (Sharma and Howen 2001). Prophylactic antibiotic administration seems to be beneficial, and as a result of this significant body of evidence, clinicians in charge with treating AP in the United Kingdom and Ireland now use antibiotic prophylaxis in the initial treatment of patients with a risk of SAP (Powell et al. 1999).

The need for surgery in patients with SAP is reduced if prophylactic antibiotic therapy (imipenem-cilastin) is started early rather than on-demand (Nordback et al. 2001). Räty et al. (1998) pointed out that in patients with alcohol-induced SAP gram-positive bacteria were found more often in infected pancreatic necrosis, and in patients with biliary SAP Gram-negative bacteria were more common.

Gram-negative rods are the main cause for early pancreatic necrosis infection. In a recent study (Büchler et al. 2000), the use of early antibiotic (imipenem/cilastin) changed pancreatic infection to predominantly gram-positive and fungal infections and the time when infection occurred was later than in earlier studies (Beger et al. 1986a and 1989, Büchler et al. 1992, Pederzoli et al 1993, Luiten et al. 1995, Sainio et al. 1995).

Fungal intra-abdominal infections in patients with SAP may complicate the disease and increas mortality (Hoerauf et al. 1998, Grewe et al. 1999). Early fungicide antibiotics should be considered for patients with SAP who are treated in an ICU (Gloor et al. 2001b).

Nutritional management

Traditionally, patients with SAP were treated with total parenteral feeding because enteral feeding was thought to stimulate the pancreas and worsen pancreatic injury (Feller et al. 1974, Kalfarentzos et al. 1991). On the contrary, recent data suggest that enteral feeding is actually well tolerated and does not affect recovery of the pancreas. Some prospective studies suggest that early enteral nutrition may result in fewer total and septic complications, and enteral nutrition may, in fact, significantly improve the acute phase responses and the severity scores of the disease. If this is case generally, costs will be reduced as patients may not need parenterial nutrition as much as has been customary. (Kalfarentzos et al. 1997, McClave et al.1997, de Beux et al. 1998, Windsor et al.1998).

A randomized controlled study (Sax et al. 1987) showed that there is no added advantage of using parenteral nutrition vs no nutritional support, and another study concluded that there is no evidence of an improved outcome SAP patients who have received early enteral nutrition vs parenterial nutrition (Powell et al. 2000).

Clearly, larger, well conducted trials that include only patients with SAP and that stratify patients by disease severity, nutritional status and etiology of pancreatitis before randomization are needed before any clear position on the benefits of nutritional support on outcome can be taken (Lobo et al. 2000). Enteral feeding through a nasojejunal (Windsor et al.1998) or nasogastric (Eatock et al. 2000) tube is current practise used at Meilahti hospital in the treatment of patients with SAP.

Specific medical treatment

Besides antibiotics, no single pharmacological therapy has proven to be effective with regard to the outcome of SAP or MOF. Many drugs have been tried, but the vast majority of these studies are inadequately powered to assess mortality.

Two prospective case-control studies suggested a beneficial effect of octreotide in patients with SAP (Fiedler et al. 1996, Paran et al. 2000), but the majority of trials showed no benefit at all (Planas et al. 1998, Uhl et al. 1999). The use of somatostatin or its analogues has been reported to be useful in preventing the formation of pseudocysts (Büchler et al. 1994). In a study conducted by Leese et al. (1987) low volumes of fresh frozen plasma were used in the treatment of AP, but this did not translate into a statistical difference in mortality.

Glucagon, calcitonin, fluorouracil, and atropin have also been in controlled studies in an attempt to reduce mortality, but these drugs have not affected mortality (Cameron et al. 1979, Goebell et al 1979, Kronborg et al. 1980, Saario 1983).

According to Büchler et al. (1993) gabexate mesilate was not effective in preventing complications and mortality in AP. However, a recent study showed that early intravenous gabexate mesilate infusion resulted in improved survival in SAP patients with organ dysfunctions (Chen et al. 2000).

Platelet-activating factor antagonist (Lexipafant®) reduces organ dysfunction according to a phase II trial, but the results from a phase III multicenter trial were disappointing: there was no reduction in the incidence of organ failure in patients on lexipafant treatment. It seems that the antagonism of platelet-activating factor activity does not influence the course of organ failure in SAP (Kingsnorth et al. 1995, Mckay et al. 1997, Johnson et al. 2001).

5.6.2 Operative options

Indications of surgery

In the early 20th century early surgical intervention to treat SAP was widely regarded as unnecessary and conservative management was favored (Moynihan 1925, Paxton and Payne 1948). In the mid-20th century Pollock (1959) and Trapnel (1966) began to reassess the role of surgery in patients with SAP. In 1963, Watts started a period of aggressive surgical treatment and this approach became widely accepted in a number of European countries. After the mid-1980´s aggressive surgery for all SAP patients was found to be unnecessary (Beger et al.1985) and only some subgroups of patients with SAP should be operated on by late necrosectomy (Beger et al. 1986a, Mier et al. 1997). Currently only infected peripancreatic necrosis is a generally accepted indication for operation (Büchler and Reber 1999, Uhl et al. 2003, Yousaf and al. 2003).

Pancreatic resection and pancreatectomy

Excision of the irreversibly damaged part of pancreas or total pacreatectomy was suggested as the appropriate treatment in some studies from 1960 to 1985 (Watts 1963, Kyösola and Fock 1975, Alexandre and Guerrieri 1981, Kivilaakso et al. 1981 and 1984, Aldridge et al. 1985). However, since pancreatic resection causes many complications and does not affect organ failures beneficially (Nordback et al. 1986, Teerenhovi et al. 1988), it should be avoided.

Peritoneal lavation

Peritoneal lavage was suggested as a treatment of SAP in some studies (Wall 1965, Stone and Fabian 1980, Ranson and Berman 1990). In a controlled clinical study conducted by Mayer et al. (1985) peritoneal lavage did not carry any advantage over conservative treatment.

Debridement, necrosectomy and drainage

Penrose/sump drainage was first reported as surgical treatment of SAP in 1963 (Altemeier and Alexander). This method had a mortality rate between 3% and 82% (Allardyce 1987, Wilson et al. 1988b, Howard 1989).

Careful, late-phase finger necrosectomy via a midline, subcostal or transverse abdominal incision is the basic surgical approach to manage patients with SAP. Here, multiple drainage tubes are placed intraperitoneally and post-operative lavage should be considered (Beger et al 1988, Beger and Isenmann 1999).

Necrosectomy and open packing as well as planned re-operation has been used in some centers in the USA as a surgical treatment of SAP (Bradley 1987, Bradley and Allen 1991, Margulies and Akin 1996, Bosscha et al. 1998). Necrosectomy and closed packing with or without a zipper technique, and planned reoperation is a method of surgical treatment in other centers (Branum et al. 1998, Tsiotos 1998).

Debridement and closed packing via laparotomy with penrose or Mikulicz drains and closed suction drains is an alternative choice for surgical treatment of SAP (Fernandez-del Castillo et al. 1998, Paye et al. 1999). Some centers use the retroperitoneal approach to operate on necrosis (Fagniez et al. 1989, Villazón et al.1991). Debridement can also be done endoscopically through a short lumbotomy (Gambiez et al. 1998) or laparoscopically (Alverdy et al. 2000, Hamad and Broderick 2000).

ERCP

In suspected biliary SAP ERCP within 72 hours and, if present, extraction of common bile duct stones should be considered. In patients with icterus or cholangitis, the extraction of stones is a necessity (Neoptolemos et al 1988, Fan et al. 1993, Fölsch et al 1997).

An intrapancreatic nasopancreatic lavage catheter and double pigtail catheters may be placed endoscopically to treat organized pancreatic necrosis (Baron et al. 1996, Baron et al. 1999b). However, infection can occur after endoscopic decompression of pseudocysts, if the pancreatic necrosis in the pseudocysts is unrecognized (Hariri et al.1994). Disruption of the main pancreatic duct by ERCP was observed in 31% of the cases in patients with biliary SAP. Moreover, disruption of the main pancreatic duct was not generally an absolute indication of surgery in patients with sterile necrosis (Uomo et al. 1998)

Interventional radiology

Percutaneous CT-guided insertation for drainage is one way to treat infected necrosis (Echenique et al. 1998, Freeny et al. 1998). There is, however, a risk of persistent pancreaticocutaneous fistula after percutaneous drainage of pancreatic fluid collections (Fotoohl et al. 1999). Percutaneous necrosectomy can also be done laparoscopically under CT-guidance (Douzinas et al. 1997, Carter et al.2000).

5.6.3 Future treatment options

A vascular access system for arterial infusion of a protease inhibitor and antibiotics in patients with SAP has been developed with promising results (Anai et al. 1999, Ganaha et al. 1999). The use of the physiological anticoagulants antitrombin III and activated protein C reduces mortality in patients with sepsis (Eisele et al. 1998, Bernard 2001), but no trial among patients with SAP has been reported with these drugs. There is some preliminary information on using extracorporeal membrane oxygenation for acute respiratory failure secondary to SAP (Peek et al. 1998).

5.7 Prognostic factors for fatal outcome in SAP

Among patients with AP each factor that predicts SAP is also a predictor of death, because mortality in mild AP is very low and mortality in SAP is 10 to 30 times higher. Thus, when studies which search for the prognostic factor in AP are avaluated, it must be kept in mind that a prognostic factor among all patients with AP may not be a prognostic factor for death among patients with SAP.

5.7.1 Prognostic factors on admission

Advanced age is a negative prognostic indicator in AP (Ranson and Pasternack 1977, Blamey et al. 1984, Williamson 1984, Roumen et al. 1992), but this has not been the case in all reports (Fan et al.1988, Lankisch et al.1996)

Several studies have identified a number of outcomes depending on the underlying etiologic factors related to AP (Imrie 1974, Ranson et al. 1976, Frey 1981). However, the cause of the AP was not associated with mortality in a report of 190 patients (Uhl W et al. 1996).

The influence of admission-related factors was evaluated in a study of DeBeux and coworkes (1995) with 279 patients with AP. The mortality rate was 2% among those patients who were directly admitted to the study hospital, but it was 10-fold higher for patients referred from another hospital.

Diabetic patients have an increased risk dying of AP compared to non-diabetic patients (Renner et al. 1985).

According to Enquist et al. (1958), the incidence of obesity among the patients with pancreatitis who died was much higher than the incidence of obesity among control patients. In another study obesity was associated with extensive peripancreatic and septal necrosis

(Nordback et al. 1985b). The role of obesity has been pointed out as a prognostic factor for AP (Lankisch et al.1990. Porter and Banks 1991, Funnell et al. 1993, Martínez et al. 1999). However, the mortality rate was not higher for obese patients among 320 patients with AP, but obese patients did have a higher risk of local complications in the course of AP (Tsai 1998).

5.7.2 Laboratory tests

Only few laboratory tests predict of a fatal outcome in SAP. In a recent study, a high hematocrit (≥44%) on admission and failure of the admission hematocrit to decrease during 24 hours were the best binary predictors of necrotizing pancreatitis and organ failure (Brown et al. 2000). Hypocalcemia predisposes to death among SAP patient (Shader et. al. 1966).

5.7.3 Organ failure and multiple organ dysfunction/failure

Single and multiple organ failure have been identified as prognostic factors related to a fatal outcome of patients with AP and SAP (Allardyce et al. 1987, Lumsden and Bradley 1990, McFadden 1991, Karimgani et al. 1992, De Beaux et al. 1995 and 1996, Uomo et al. 1996a, Tenner et al. 1997).

Fulminant hepatic failure and chronic liver disease increase mortality in patients with AP (Kuo et al. 1998). In a study of 267 patients with AP the mortality rate of patients with acute renal failure was 81%, and in another study with 14 patients the mortality rate was 71% (Frost et al. 1990, Tran et al. 1993b).

On admission 30% of patients with SAP had organ failure and their mortality rate was 42% (Isenmann et al. 2001). In another study 44% of the patients with SAP had organ failure on admission and, contrariwise, 97% of the patients who died had organ failure within the first week of admission (Johnson et al. 2001). In a recent study by Buter et al. (2002) it was shown that worsening of organ dysfunction during the first week of admission was associated with death in 11 patients of 20 (55%) with SAP.

5.7.4 Infection

Infected pancreatic necrosis develops in 40-70% of the patients with necrotizing pancreatitis (Schmid et al. 1999). Beger et al. (1986b) reported a postoperative mortality rate of 39% in patients with peripancreatic necrosis and bacteriological positive findings, whereas the mortality rate was 9% in bacteriologially negative patients. Bacterial infection of pancreatic necrosis correlates with the incidence of organ failure in patients with SAP (Isenmann et al. 1999). In a study by Armengol-Carrasco et al. (1999) the CRP levels and the APACHE II score were related to the development of peripancreatic necrosis infection in patients with SAP.

5.7.5 Scoring systems

Ranson and Glasgow

The Ranson and Glasgow scores have been developed for predicting the severity of acute pancreatitis, but they have also been used for predicting fatal outcome (Ranson et al. 1974, and 1976, Corfield et al. 1985). However, a recent meta-analysis demonstrated that the Ranson criteria have a poor predictive power for a fatal outcome in SAP (De Bernardinis et al. 1999). In contrast, a recent study by Eachempati et al. (2002) found the Ranson score was a valid predictor of mortality among SAP patients in an ICU setting. In this study, the critically ill SAP patients who were treated in the medical ICU were not included.

APACHE II and logistic regression models

The current prognostic models are usually based on statistical regression analysis, as is the case for the APACHE II score (Knaus et al. 1985a), the Nottingham prognostic index of breast cancer (Haybittle et al. 1982), and a proposed model of survival for patients with primary melanoma (Schuchter et al. 1996). The APACHE II system is of only limited clinical utility for early prognostic evaluation of patients with SAP (Domínguez-Muňoz et al. 1993).

Artificial neural networks

Artificial neural networks (ANN) have been successfully used for pattern recognition and survival prediction in several clinical settings (Lundin et al. 1999, Dubowski et al. 1996, Golub et al. 1998). ANNs offer a way of capturing nonlinearities and complex interactions between prognostic factors in a multivariable model (Burke 1996). Figure 1 shows the basic structure of a multilayer ANN (Lundin1998).

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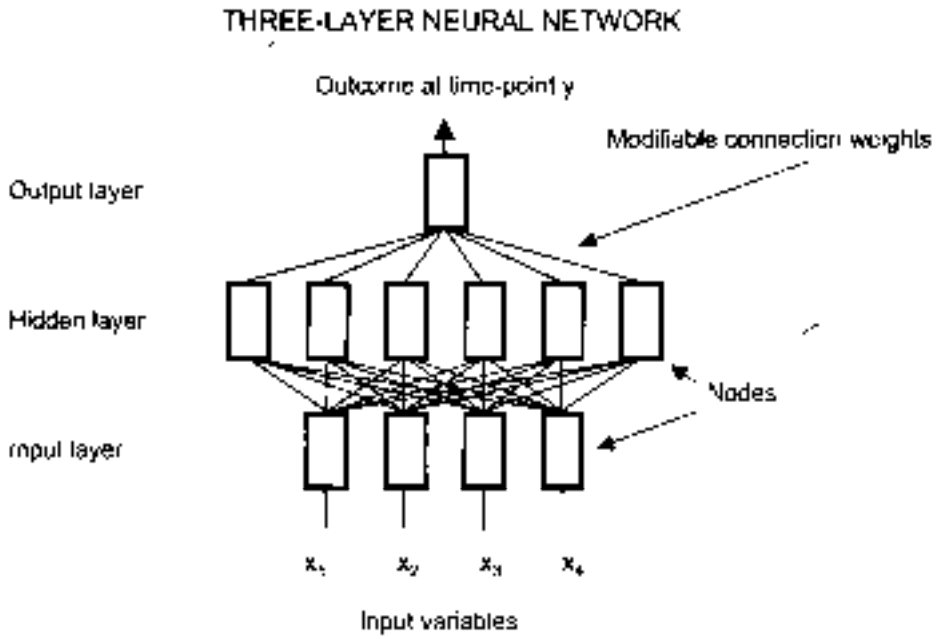


Figure 1 Basic structure of multilayer backpropagation neural network (multilayer perception) for outcome prediction (Lundin 1998)

5.7.6 Other prognosticators

The presence of retinopathy indicates a poor prognosis in patients with SAP (Hollo et al. 1994). Some studies have shown that the gastric mucosal pH to predicts death in SAP (Bonham et al. 1997, Hynninen et al. 2000).

5.7.7 Local complications of SAP

Local complications increase the morbidity of SAP patients and may also increase the risk of a fatal form of SAP. Many of these complications occur in the late phase of the disease and are often treated conservatively.

Intestinal

It has been reported that SAP causes duodenal obstruction. However, total parenteral nutrition is associated with a good prognosis in patients with these lesions (Chen et al. 2001). Ischemic strictures may form in the small intestine (Kato et al. 1998). Colon necrosis and strictures have also been described during SAP. Early detection and prompt surgery of lesions of the colon have been shown to improve patient outcome (Aldridge et al. 1989,

Kriwanek et al. 1996 and 1997, Fernández-Cruz et al. 1997, Umeno et al. 2000). Gastrointestinal fistulas are common in SAP patients who have undergone operative treatment of SAP (Ho et al. 1995, Kriwanek 1999).

Vascular

A variety of vascular complications have been reported in patients with SAP, including thrombosis of the portal vein (Dörffel et al. 2000). Pseudoaneurysm is a severe complication and carries a high risk of death. However, it can usually be treated with angiographic embolization or open operation with pancreas resection (Savastano et al. 1993, Sand et al. 1997, De Perrot et al.1999). Patients with SAP may also develop arteriovenous fistulas, which can be treated surgically or using angiographic embolization (Raat et al. 1999). The percutaneous placement of a transgastric catheter for a pancreatic pseudocyst increases the risk of splenic artery pseudoaneurysms (Quinn et al. 1988).

Pseudocysts

Pseudocysts need treatment only if complications develop. Most pseudocysts disappear spontaneously; this is the case for 92% of the small cysts and the ones located in the pancreas tail (Maringhini et al. 1999). A pseudocyst can also cause obstructive jaundice (Fujita et al. 1996). Hastings et al. (1978) reported intrasplenic pancreatic pseudocysts in patients with SAP.

Complicated pseudocysts can be treated with endoscopic, percutaneous or surgical procedures (Cooperman 2001a). Endoscopic management includes cystogastrostomy, cystoduodenostomy, cystojejunostomy, and transpapillary stenting (Vidyarthi and Steinberg 2001).

If pancreatic necrosis in a pseudocyst is unrecognized, infection can occur after radiological and endoscopic decompression of the pseudocyst (Hariri et al.1994). Complicated pseudocysts have previously been operated by pseudocystojejunostomy via open laparotomy (Bradley et al. 1979, Cooperman 2001b). Endoscopic (pseudocysto-gastrostomy) and laparoscopic treatments of pseudocysts have also been reported (May et al. 1994, Oria et al. 2000, Schacter et al. 2000). Percutaneous catheter drainage is a well-established method for treating pseudocysts and abscesses. Drainage of a cyst by a single-step needle drainage carries a recurrence rate of 70% or even more (Barkin et al. 1981, Neff 2001). Also, fistulas may form after percutaneous drainage (Cooperman et al. 2001a). At Department of Gastroenterological and General Surgery, Meilahti hospital, the primary treatment of complicated pseudocysts is endoscopic (pseudocystogastrostomy or duodenostomy and, as required, stenting of ductus wirsingianus). If this treatment is unsuccessful, open surgery is needed (Baron et al. 2002).

Other complications

As a consequence of AP, perisplenic adhesions may form and cause spontaneous rupture of the spleen (Lukash 1967). Generalized heterotopic ossification has also been descibed in patients with SAP (Jacobs et al. 1999).

Various neurophysiological abnormalities may complicate the outcome of ICU treated patients (Coakley et al. 1998). Critical illness polyneuropathy (CIP) is defined as mixed motor and sensory disturbance. CIP may cause prolonged ICU and hospital stay and prolonged need of mechanical ventilation and it may increase the in-hospital mortality of septic patients with MOD syndrome requiring mechanical ventilation (Garnacho-Montero et al. 2001). CIP occurs frequently in patients with ICU treated SAP. But there are, no studies concerning the prognostic value of CIP in relation to hospital mortality in SAP patients.

5.8 Hospital mortality of AP and SAP patients

5.8.1 Mortality of AP patients

The mortality rates of patients with AP vary from 2 to 9% (Mann et al. 1994, Grönroos et al. 1999). According to the studies of Wilson et al. (1988a) and Appelros et al. (1999), pancreatitis was diagnosed only at necropsy in 42% to 52 % of the patients with fatal AP, while Mann et al. (1994) found that a diagnosis of pancreatitis can be established in 88% of patients with AP before death. Early mortality from AP was high in reports from Scotland and USA (Renner et al. 1985, McKay et al. 1999). However, in a recent study early deaths of patients with SAP were rare: nine out of the ten deaths occurred later than 3 weeks after disease onset (Gloor et al. 2001).

In studies in Turku covering the period 1971 to 1991 (Grönroos et al. 1999) and in Rotterdam 1985 to 1995 (Eland et al. 2000) the mortality trend of patients with AP did not decrease, while Bank et al. (2002) reported a reduction of mortality rates from 14% in 1978-1982 to 4% in1998-2001 in New York.

5.8.2 Mortality in SAP

It is not feasible to compare the reported mortality rates in SAP, because most studies involve only a part of the SAP patients (e.g., patients with pancreatic necrosis, infected necrosis, sterile necrosis, with ICU treatment and organ or multiple organ failure). Also some studies include patients with a low risk of death.

The mortality rate of patients with SAP has declined in the Meilahti hospital from 69-96% in 1967-1973 to 22-47% in 1979-1983 (Kivilaakso et al. 1981 and 1984). Rau et al. (1995) reported an overall mortality of 10% in a series of 172 patients with sterile necrosis in SAP; mortality was13% in the operatively treated group and 6% in the nonoperatively treated group. In a series of 30 patients with severe AP requiring treatment at an ICU, the mortality rate was 30% (Malcynsky et al. 1996). The survival of patients with necrotizing pancreatitis may be improving (Oleynikov et al. 1998, Kalfarentos et al. 1999). According to a recent study the mortality rates among SAP patients decreased from 50-58% in 1978-1982 to 12-18% in 1993-1997 (Bank et al. 2002).

5.9 Long-term outcome after SAP

5.9.1 SAP-related diseases

Among patients who have recovered from necrotizing pancreatitis no less than 80-85% have persistent global or decreased pancreatic exocrine function (Bozkurt et al 1995) to an extent that varies with the degree of pancreatic parenchymal necrosis (Tsiotos et al. 1998). In earlier studies, 83-100% of the patients developed diabetes after distal resection of the pancreas for surgical treatment of pancreatic necrosis (Nordback and Auvinen 1985c, Schröder et al. 1990, Doepel et al. 1993). In the study of Büchler et al. (1987) half of the patients developed subclinical or overt diabetes mellitus after necrosectomy or closed lavation. Two studies have reported neuropathy symptoms in patients who have survived an attack of SAP. Occasionally, neuropathy persists and the patient becomes work-incapacitated (Nordback and Auvinen 1985c, Gross et al. 1988).

5.9.2 Quality of life

In studies with a small number of patients, the quality of life (QOL), and outcome after SAP have been to be good (Doepel et al. 1993, Fenton-Lee and Imrie 1993, Broome et al. 1996, Soran et al. 2000). However, only two studies regarding QOL assessment after SAP have used generic multidimensional measures. Two telephone surveys were carried out using the 36-item short-form general health survey. The first one consisted of 22 SAP patients who were operated on and the second one of 21 patients who were treated in an ICU. The results showed no statistically significant impairment in health-related quality of life (HRQL) (Broome et al. 1996, Soran et al. 2000).

The Rand 36-item Health Survey is a generic multidimensional health-related quality of life (HRQL) measure considered to be an objective and reproducible instrument for the assessment of HRQL (Hays et al. 1993, VanderZee et al. 1996). The 15D instrument is a generic, comprehensive, 15-dimensional, standardized and validated measure of HRQL, developed in Finland. The 15D instrument is highly reliable and sensitive (Sintonen 2001). The 15D instrument has not been used in patients with SAP, while the Rand36 survey has been shown to have excellent psychometric properties in other populations and diseases and has also been evaluated in the measurement of long-term outcome of critically ill patients (Essink-Bot et al. 1997, Heyland et al. 2000, Pettilä et al. 2000).

5.9.3 Return to work

Doepel et al. (1993) recorded that, 24 of 31 (77%) ICU treated SAP patients returned to work. Similarly, in another Finnish study 19 of 24 (79%) SAP patients with pancreatic resection returned to work (Nordback and Auvinen 1985c).

6. PRESENT INVESTIGATION

6.1 Aims of the study

The general aim of this clinical study was to evaluate the outcome and quality of life of patients with SAP.

The specific aims of this study were:

1. To identify prognostic factors for hospital mortality in SAP by analyzing a large consecutive series of patients with SAP in a tertiary referral center.

2. To construct multivariable predictive models to predict hospital mortality during the early phase of SAP, and to compare these models prospectively to previously reported predictive systems such as Ranson, Imrie, APACHE (Acute Physiology and Chronic Health Evaluation) II and Multiple Organ Dysfunction (MOD) score.

3. To compare the MOD score, the Sequential (former Sepsis-related) Organ Failure Assessment (SOFA) score, and the Logistic Organ Dysfunction (LOD) score as predictors of hospital mortality, and to use one of these scores to assess the incidence and prognostic significance of organ dysfunction/failure in patients with SAP treated in a general intensive care unit (ICU).

4. To assess the long-term health-related quality of life (HRQL) after SAP with the RAND 36-item Health Survey, and to compare the HRQL of patients with SAP and some subgroups of SAP with that of the general population. An aim was also to define the overall long-term post-discharge outcome of patients after SAP.

6.2 Patients

The total number of episodes of AP in the study hospital during the 10 years study period was 1539 of which 317 (21%) were SAP. Patients with SAP who were admitted to the Second Department of Surgery at the Helsinki University Central Hospital from January 1989 through December 1998 were included in the study. The study periods and the characteristics are presented in Table 1. The demographic and clinical characteristics of the overall study population and patients in studies III-IV are shown in Table 2.

6.2.1 Definition of SAP

1) Low contrast enhancement of the pancreas (below 50 Hounsfield units) on contrast-enhanced computed tomography (Kivisaari et al. 1983 and Balthazar et al.1985, 1990, 1994) and CRP concentration above 120 mg/L within 48 h of admission (Büchler et al. 1986, Puolakkainen et al. 1987, Wilson et al. 1989)

2) Necrotizing pancreatitis at autopsy

3) Histologically confirmed necrosis discovered during surgery

4) Respiratory and renal organ failure requiring mechanical ventilation and dialysis, respectively, with hyperamylasemia (3 times the upper limit of the reference range) and CRP over 120mg/L within 48 h of admission

At least one of the criteria above had to be fulfilled for inclusion of a patient in the study. All patients in my study fulfilled the Atlanta criteria for SAP (Bradley 1993).

6.2.2 Definitions of causes of SAP

Alcohol-related disease was assumed if there was a clear history of frequent alcohol consumption or alcohol excess immediately before the attack of AP and when no other etiologic factors were identified. Gallstone-related disease was based on the identification of gallstones by radiological examinations (sonography, ERCP, computed tomography or magnetic resonance imaging). Post-operative and post-ERCP pancreatitis was assumed if the disease occurred within a week after the procedure.

6.2.3 Study patients

In study I, 270 consecutive patients admitted to study hospital from January 1989 through October 1997 with SAP were included in to the study.

In study II, the hospital records of 253 patients with SAP admitted to the study hospital from January 1989 through April 1997 were retrospectively analyzed for constructing the predictive models. Nineteen patients had insufficient data on one or more of the variables and were excluded, leaving 234 eligible patients to the test set. An independent validation set consisted of prospectively collected data during the first 72 hours of 60 consecutive SAP

patients with primary or transferral admission to the study hospital from May 1997 through December 1998. The patient characteristics in the test and validation sets are shown in Study II, table 1 page 311. 73% of the patients in the test set and 75% of the patients in the validation set were admitted within less than 24 h after the first symptoms of AP and a maximum delay of 48 h from onset of symptoms to admission was recorded in 88% of the patients in both sets. The number of operated patients in the test and validation set was 84 (36%) and 16 (27%), respectively. The mortality rates in these groups were 41% and 50%, respectively. No significant difference was found between the test and validation sets.

In study III, the hospital records were retrospectively analyzed for 178 consecutive patients with SAP admitted to the study hospital from January 1994 through December 1998. Of these, 113 were treated in a 10-bed general intensive care unit (ICU). The criteria for general ICU treatment were progressive organ dysfunction. Of the 65 patients with SAP not treated in the general ICU, but in the surgical ICU, only four died (6%). The characteristic of these patients are shown in study III, page 1275.

In study IV, the hospital records of 283 consecutive patients with SAP admitted to study hospital from January 1989 to December 1997 were analyzed retrospectively. Of these 72 (25%) died during hospitalization and 27 (10%) died 7-115 months after discharge during the follow-up period (mean 66). A causes of death were recorded from the Central Statistical Bureau of Finland and are shown in study IV, page 783. Seven patients with unknown addresses and three with limited cultural or mental abilities to complete the questionnaire were excluded, and thus questionnaires were sent to 174 patients. Of these, 145 returned the questionnaires (83% response rate) and comprised the final study population. The characteristics of all survivors of SAP are presented in Study IV, in table 1 (page 783).

Table 1 **Study characteristics of episodes of severe acute pancreatitis (SAP)**

	Number of episodes of SAP	Time period	Inclusion criteria	Number of included episodes
I Study	270	1/1989 to 10/1997	SAP	270
II Study	317	1/1989 to 12/1998	SAP and sufficient data	294
Test set	253	1/1989 to 4/1997		234
Validation set	64	5/1997 to 12/1998		60
III Study	178	1/1994 to 12/1998	SAP and ICU treatment	113
IV Study	283	1/1989 to 12/1997	SAP and alive 8/1999	174[a]

[a]Excluded 7 patients with unknown addresses and 3 patients with limited linguistic or mental abilities to complete the questionnaire. ICU = intensive care unit.

Table 2	Demographic data for 317 consecutive episodes of severe acute pancreatitis (SAP)			
	All	Study III	Study IV Survey[a]	No Survey
Number of episodes of SAP	317	113	145	39
Male sex (%)	265 (84)	100 (89)	120 (83)	35 (90)
Mean age (range)	46 (16-83)	46 (16-83)	44 (20-78)	43 (21-83)
Alcohol etiology (%)	245 (77)	90 (80)	113 (78)	35 (90)
Mean length of hospital stay, days (range)	38 (2-212)	45 (2-208)	39 (10-212)	29 (10-144)
Mean length of ICU stay [b], days (range)	19 (0-149)	26 (1-77)	17 (0-94)	14 (0-74)
Required general ICU treatment (%)	194 (61.2)	113 (100)	76 (52)	18 (46)

[a] Fulfilled Finnish version of the Rand 36-item Health Survey 1.0 questionnaire. ICU = intensive care unit.
[b] Include both surgical and general ICU.

6.3 Methods and data collection

6.3.1 Assessments of multiple organ dysfunction

The MOD syndrome was first described as a sequential system failure in 1973 (Tilney et al. 1973). The mortality rate has ranged from 20 to 100%, depending on the number of organ involved, severity, duration, type, and combination of organ failures, as well as definition (Knaus et al. 1985b, Tran et al. 1993a, Zimmerman et al. 1996).

There are indeed numerous ways to define and score MOD (Fry et al. 1980, Pine et al. 1983, Goris et al. 1985, Knaus et al. 1985b, Fagon et al. 1993, Hebert et al. 1993). The three more recent scores are the Multiple Organ Dysfunction (MOD) score (Marshall et al. 1995), the Sequential (formerly termed Sepsis-related) Organ Failure Assessment (SOFA) score (Vincent et al. 1996 and 1998), and the Logistic Organ Dysfunction (LOD) score (Le-Gall et al. 1996) which are designed to assess the severity and development of multiorgan dysfunction as a single score. A comparison of the values of Multiple Organ Dysfunction Score (MODS), Logistic Organ Dysfunction System (LOD), and Sequential System Assessment (SOFA) are shown in table 3.

Table 3. Comparison of values of Multiple Organ Dysfunction Score (MODS), Logistic Organ Dysfunction System (LOD), and Sequential System Assessment (SOFA)

Organ system /score	0	1	2	3	4	5
Respiratory						
PO_2/FIO_2, mmHg						
SOFA	>400	300-399	200-299	100-199[a]	<100[a]	
MODS	>300	226-300	151-225	76-150	<76	
LOD						
On MV[b]or CPAP[c]		≥150		<150		
	No Vent[d] and No CPAP[c] No IPAP[e]					
Renal						
Serum creatinine, µmol/L						
SOFA	<110	110-170	171-299	300-440	>440	
Or urine output, L/day				or <0.5	or <0.2	
MODS	≤100	101-200	201-350	351-500	>500	
LOD	<106 and	106-140		≥141		
Serum urea, mmol/L	<6 and	or 6-9.9		or 10-19.9		≥20
Urine output, L/day	0.75-9.99			or >10		<0.5
Serum urea nitrogen mmol/L	and <6	or 6-9.9		or 10-19.9		≥20
Hepatic						
Serum bilirubin, µmol/L						
SOFA	<20	20-32	33-101	102-204	>204	
MODS	≤20	21-60	61-120	121-240	>240	
LOD	<34.2 and	≥34.2 or				
And protombin time%	≥25%	<25%				
Cardiovascular						
SOFA						
Mean arterial pressure, mmHg	>70	< 70				
Adrenergic agents, µg/kg/min[f]			Dop[g] <5	Dop[g] 5-15	Dop[g] >15	
Or			Dob[h]ny dose	Epinep[i] <0.1	Epinep[i] >0.1	
Or				Norep[j] <0.1	Norep>0.1	
MODS						
PAR[k]	≤10.0	10.1-15.0	15.1-20.0	20.1-30.0	>30.0	
LOD						
Heart rate, beats/min	30-139 and	>140 or				<30 or
Systolic blood pressure, mmHg	90-239	70-89 or 240-269		40-69 or ≥270		<40
Hematologic						
Platelet count x 10^9/L						
SOFA	>150	100-150	50-99	20-49	<20	
MODS	>120	81-120	51-80	21-50	≤20	
LOD	≥50 and	≤50 or				
White blood cell count x 10^9/L	2.5-49.9	1.0-2.4 or ≥50.0		<1.0		
Neurologic						
Glasgow Coma Scale						
SOFA	>14	13-14	10-12	6-9	< 6	
MODS	15	13-14	10-12	7-9	≤6	
LOD	14-15	9-13		6-8		3-5

[a] with respiratory support. [b] mechanical ventilation. [c] continuos positive airway pressure. [d] ventilation. [e] intermittent positive airway pressure. [f] adenergic agents administered for at least one hour. [g] dopamine. [h] dobutamine. [I] epinephrine. [j] norepinephrine. [k]=heart rate x right atrial or central venous pressure / blood pressure

6.3.2 Definition of organ and multiple organ failure

Organ failures were defined as a SOFA score of any organ of ≥3 of 4; PaO_2/FiO_2 <200 (mm Hg) for respiratory failure, platelets x 10^9/L <50 for coagulation, bilirubin >102 (µmol/L) for liver, epinephrine or norepinephrine administered for ≥1h or dopamine administered for ≥1h at >5µg/kg· min for cardiovascular, Glasgow coma scale <10 for central nervous system, and creatinine >300 (µmol/L) or urine output <500 mL/day for renal failure (Vincent et al. 1996). MOF was defined as the failure of at least two organs in the SOFA score for any organ of ≥3 of 4.

6.3.3 Assessment of quality of life

The Rand 36, a generic multidimensional HRQL measure, consists of 36 questions divided into eight domains, each measured by responses to groups of two to ten items on a scale from 0 (poorest) to 100 (best). Rand 36 and its Finnish version are based on the Medical Outcomes Study 36-item short-form health survey (SF-36) (Machorney et al. 1993, Aalto et al. 1999). This questionnaire includes questions related to physical and to mental health. Questions regarding physical health include physical functioning, role limitations because of physical problems, bodily pain, and general health. Mental health variables include vitality, social functioning, role limitations because of emotional problems, and mental health. The items, scoring rules, and permission to use the Rand 36 questionnaire are readily available in English via the Internet. (http://www.rand.org/health/surveys/sf36item/) (Anonymous 2002).

6.3.4 Data collection

Retrospective data collection included: age, gender, etiology (alcohol/nonalcohol), history of previous AP (first/recurrent), chronic medication, primary or referral admission, height and weight on admission for body-mass-index (BMI) calculation, need of mechanical respiration support, use of vasoactive drugs, renal failure, abdominal surgery performed during hospitalization, length of hospital stay and length of stay in the general or surgical ICU.

In study II the highest leukocyte value, the highest CRP value, the lowest hemoglobin value and the highest hemoglobin value during the first 72 hours were also collected. The serum creatinine value was measured within 60-72 h of admission to make adequate fluid replacement for dehydration possible.

In study III the data collection on the 113 patients who had general ICU treatment included also the presence of intra-abdominal infection, infection of pancreatic necrosis, white blood cell and platelet counts, plasma potassium and sodium concentration, blood gas analysis, blood hemoglobin, hematocrit, prothrombin time, temperature, Glasgow coma scale, respiratory rate, inspiratory oxygen fraction, blood pressure, mean arterial pressure, heart rate, central venous pressure, daily urine output, serum creatinine, urea, albumin, and

bilirubin concentrations. In study IV the presence of diabetes, diarrhea, abdominal pain, recurrent pancreatitis, symptoms of polyneuropathia, and MOF were also collected.

For analysis, the patients with alcohol-induced AP formed one group and the patients with non-alcohol AP another group. My definition of a patient having a comorbid disease was the need for chronic medication. Patients were assumed to have comorbid disease when a prescription for chronic medication had been made before admission to the hospital regardless of whether they used the medication or not. In study II the history of chronic medication was subdivided into different groups according to underlying diseases [asthma, diabetes, prophylaxis for thromboembolism, cardiovascular disease (e.g., diuretics, antihypertensive drugs, digoxin), other diseases and disease combinations].

The body-mass index (BMI) was calculated as weight (kg)/height^2 (m^2). In study I eight patients with inadequate data on height and/or weight were excluded from multivariate and univariate analysis on BMI. Mechanical ventilation (except for anesthesia required for surgery), dialysis, or need of vasoactive pressor drugs at any time during hospitalization was considered positive for that these respective variables. Abdominal surgery during hospitalization included both early explorative laparotomy for acute abdomen as well as planned procedures for AP.

The presence of infected necrosis was determined by culture of computed tomography-guided percutaneous aspiration (Gerzof et al. 1987) or pancreatic tissue derived at surgery. The presence of intra-abdominal infection was considered positive if there was infected necrosis or positive culture from specimens taken from an abdominal drainage tube or from abdominal ascites.

6.3.5 Study methods

In study I, univariate and multivariate logistic regression analysis was performed using hospital mortality as the end-point. Univariate analysis was performed with 11 variables. Multivariate logistic regression analysis was performed on the data from 262 patients for all variables as well as the variables available on admission (age, gender, etiology, number of previous AP, previous medication history, type of admission and BMI).

In study II, univariate logistic regression analysis was performed on the test set to evaluate single prognostic factors for hospital mortality during the first 72 h (results are seen in Study II, table 2, page 311). The information from the test set analyses of single prognostic factors was used to create five logistic regression and three ANN prediction models (LR4, ANN4, LR4*, LR5, LR5*, ANN5, LR8, and ANN8 which are shown in study II, in table 3, page 312. Three prediction models (LR5, LR5*, and ANN5) were first constructed with all independent prognostic factors. The admission variable was considered too unreliable and dependent on local circumstances and was, therefore, excluded. The predictive power of the need for mechanical ventilation and the need for pressor support were almost equal. However, the predictive accuracy of the former was statistically more significant and was chosen for the LR4, ANN4, LR4*, LR8, and ANN8 models. Two prediction models (ANN8 and LR4) were chosen to generate survival estimates in an independent validation set. The

ANN8 model with eight variables had the highest accuracy. The LR4 model had almost the same accuracy as ANN8 and was the simplest with four variables. These two models were compared for predictive accuracy with the established prognostic systems Ranson (1982), Imrie (Blamey et al. 1984), APACHE II (Knaus et al. 1985a, Wilson et al. 1990), and MOD score (Marshall et al. 1995).

In study III, the APACHE II score (Knaus et al. 1985a, Wilson et al. 1990) was calculated from the data from the first 24 hours spent in the general ICU's. Missing data were considered to be normal. The organ dysfunction scores (MOD, SOFA, LOD) were calculated for the first 24 h of general ICU stay and for days 3, 7, 14, 21, 28, and 35 after primary admission to the hospital. If a laboratory value was missing, the previous day's value was used, and if that value was not available, the next day's value was used. If both of these were missing, the value was considered missing data and calculated as a normal value. Organ dysfunction scores were calculated until the patient died or was transferred without any organ dysfunction to a surgical ward. For all scores, the Glascow coma scale was considered to be normal in sedated patients, if there was no known cause for abnormality. In order to achieve better comparability among SOFA, MOD, and LOD scores, the scores were calculated for each day by use of the worst single values for that day, not the worst value for the entire hospital stay, which has been validated in previous studies (Marshall et al. 1995). Maximum scores for daily values and total maximum scores (sum of the highest values for each organ dysfunction) were calculated for all three organ dysfunction scores. To assess the incidence and the prognostic usefulness of organ dysfunction/failure, I calculated individual organ scores separately by using the SOFA score for first 24 h of general ICU stay and for days 3, 7, 14, 21, 28, and 35 after primary admission to the hospital. The highest value on these days was considered as the maximum organ dysfunction score.

In study IV, the validated Finnish version (Aalto et al. 1999) of the Rand 36-item Health Survey 1.0 (Hays et al. 1993) questionnaire with accessory questions regarding subjective overall assessment of professional status, symptoms, medication, and living status, was mailed to patients for self-administration. If there was no initial response to the questionnaire, the patients were contacted twice again by mail or by phone, and the questionnaire was resent to ensure a maximal response rate. Readmissions and outpatient visits until August 1999 was reviewed from the hospital records. Further analysis was performed with the following subgroups: patients with or without MOF, with or without general ICU treatment and those having undergone abdominal surgery or not treated operatively.

6.4 Statistical analyses

In study I, age and BMI were analyzed as continues variables, and the other variables were dichotomous. Univariate and multivariate logistic regression analysis (Stat View; SAS Institute, Cary, N.C., USA) was performed using hospital mortality as the end-point. A χ^2-test was used to test for associations between variables. A p-value less than 0.05 was considered statistically significant. In the tests for associations between variables, the cut-off for age was 43.5 years (median) and for BMI 28.

In the study II, the area under the receiver operating characteristic curve (AUC) was used as a measure of accuracy of the predictor models in separating survivors from nonsurvivors (Metz 1978). In the logistic regression analyses (Stat View; SAS Institute, Cary, N.C., USA), a p-value of 0.05 was adopted as a limit for significance and inclusion of a covariate.

The artificial neural networks were constructed using a freely available computer program (Nevprop 4, www.scsr.nevada.edu/nevprop/; Dr. Philip Goodman, University of Nevada, Reno, Ne.V., USA). All three ANN models were feed-forward three-layer models with a learn rate of 0.01 and weight decay –0.001.The chosen ANN8 model had eight hidden nodes. A pure gradient descent, globally adaptive learning rule was used to optimize the network. Sigmoid transfer functions were used in the hidden layer and in the output layer. Network output ranged from 0 to 1. The log likelihood (cross-entropy) was used as the error function and train criterion for the input. A holdout data set of 40 % of the patients and a five-fold cross-validation were used to assess the error criterion of the model during the process of optimization. The data set was bootstrapped 50 times to estimate the optimistic bias due to overtraining and to correct the accuracy measures accordingly.

In study III, data are presented as mean ± SE or median (range). In all comparisons, $p< 0.05$ (two-tail) was considered significant, and the Mann-Whitney rank sum test was used. Predictive values for the various scores regarding hospital mortality were evaluated. AUC (SE) served as a measure of discrimination (ability to distinguish between patients who die and those who survive) of organ dysfunction scores. Multiple logistic regression analysis was performed regarding hospital mortality. Statistical tests were performed with the BMDP 1.1 version for Windows (BMDP Statistical Software, Cork, Ireland), SPSS 9.0 for Windows (SPSS, Chigaco, IL, USA), and GraphROC 2.0 for Windows [Turku, Finland (Kairisto and Poola 1995)].

In study IV, the results were expressed as means ± SD (median). For comparisons, the norms of the Finnish population were adjusted for distribution by age and sex of the study patients and separately for the subgroups. These scores were compared with the study population by the non-parametric Mann-Whitney U test. Results of HRQL were also converted to Z scores (standard deviation unit), in which the Z score is the patient mean score minus the adjusted Finnish population score divided by the standard deviation for the Finnish population (Weinert et al. 1997). If the means differed by more than 10 and the Z score more than 2, these were considered clinically significant (Pettilä et al. 2000). Multiple linear regression analysis was performed to identify variables independently associated with HRQL domains.

6.5 Results

6.5.1 Hospital mortality in SAP

The overall hospital mortality rate for the patients with 317 episodes of SAP was 26%. The mortality rate of patients treated in the general and surgical ICU was 25%, and for those treated with general ICU alone 36%. The mortality rates of patients with MOF and early

MOF were 49% and 64%, respectively. The mortality rates in the different subgroups are presented in table 4.

6.5.2 Prognostic factors for hospital mortality in SAP

As shown by table 1 and 2, in study 1, in pages 268-269 the independent prognostic factors for hospital mortality were advanced age, history of continuous medication, renal, respiratory or cardiovascular failur, while gender, etiology, first vs multiple episodes of AP, type of admission, BMI or abdominal surgery were not. The independent prognostic factors according to logistic regression analysis for variables available on admission were referral admission, advanced age and chronic medication (results are shown in Study I, in table 3, page 269). The numerous associations between variables are shown in Study I, in table 4, page 270.

The statistically most significant combination of medication variables by univariate survival analyses in study II was the history of chronic cardiovascular and/or anticoagulation medication (relative hazard RH 4.510, confidence interval CI 2.314-8.791, $p<0.0001$). By multivariate logistic regression analysis in the test set in study II, the independent prognostic factors turned out to be advanced age, history of chronic cardiovascular and/or anticoagulation medication, high serum creatinine value within 60-72 h of admission, transferal admission, and either a need for mechanical ventilation during the first 72h of admission or a need for vasoactive pressor drugs during the first 72 h of admission. Results from multivariate logistic regression analysis are seen in Study II, in table 3, page 312.

Table 4 **Comparison of mortality of different subgroups during a 5-year period of patients wih 317 episodes of severe acute pancreatitis (SAP)**

	1989-1993		1994-1998		1989-1998		
	Number of episodes of SAP	Mortality %	Number of episodes of SAP	Mortality %	Number of episodes of SAP	number of deaths	Mortality %
	139	25	178	26	317	81	26
Gender							
Male	116	22	149	26	265	64	24
Female	23	35	29	31	52	17	33
Age							
Over 60 years	15	47	31	48	46	22	48
Under 60 Years	124	22	147	22	271	59	22
Etiology							
Alcohol	112	21	133	25	245	57	23
Non-alcohol	27	37	45	31	72	24	33
Type of admission							
Hospital transfer	84	33	110	32	194	63	33
Primary admission to study hospital	55	11	68	18	123	18	15
History of cardiovascular medication							
Yes	34	53	58	43	92	43	47
No	105	15	120	18	225	38	17
Organ failure							
Yes	82	42	111	29	193	79	41
No	57	0	67	3	124	2	2
Single organ failure	21	0	13	8	34	1	3
Multiple organ failure							
Yes	60	57	98	45	158	78	49
No	79	0	80	4	159	3	2
Early* organ failure							
Yes	47	62	74	46	122	64	53
No	92	5	104	13	195	18	9
Early* multiple organ failure							
Yes	34	74	50	58	84	54	64
No	105	9	128	14	233	27	12
Abdominal infection#							
Yes			48	56			
No			130	15			
Peripancreatic necrosis infection¤							
Yes			28	46			
No			150	23			
Abdominal operation	48	35	61	49	109	47	43
Emergency operation	14	50	16	38	30	13	43
Planned local peripancreatic	40	33	52	52	92	40	44
Emergency operation+planned oper.	8	38	10	40	18	7	39
No operation	91	19	117	15	208	34	16

Organ failures were defined as a SOFA score for any organ of $\geq$3 of 4. Multiple organ failure was defined as the failure at least two organs in the SOFA score for any organ of $\geq$3 of 4. * before 72 hours from admission. # infected necrosis or positive culture from abdominal drainage tube or ascites. ¤ positive culture from percutaneous aspiration or pancreatic tissue debrided at surgery.

6.5.3 New models to predict a fatal outcome in SAP

The two new models (LR4 and ANN8) had a better predictive performance than the Ranson, Imrie, Apache II, and MOD scores. There were statistically significant differences in predictive accuracy between my two models and the Ranson and Imrie scores, as is seen in table 5. The LR4 model had a better accuracy than the ANN8 model and was chosen as the optimal model.

Table 5. Predictive values of the novel prediction models in the prospective validation set compared with Ranson, Imrie, APACHE II and MODS system in 60 consecutive patients with severe acute pancreatitis

	LR4[a]	ANN8[b]	Ranson	Imrie	APACHE[c] II	MODS[d]
Mean (±SD)	0.34(0.27)	0.38(0.33)	5(1.8)	4(1.7)	10(10.4)	6(5.7)
Sensivity (%)[e]	88	82	65	94	65	59
Specificity (%)[e]	88	88	70	28	91	91
AUC[f] (accuracy)	0.86	0.85	0.66	0.54	0.82	0.78
CI 95%[g]	0.76-0.96	0.74-0.95	0.50-0.81	0.36-0.71	0.70-0.93	0.66-0.90
Spec at 88 sens[h]	88	74	79	28	42	40
Sens at 88 spec[i]	88	82	24	6	65	65
P-values LR4 vs[j]		0.74	0.01	0.001	0.46	0.22

[a]logistic regression predictive model with 4 variables. [b]artificial neural network predictive model with 8 variables. [c]Acute Physiology and Chronic Health Evaluation. [d]Multiple Organ Dysfunction Score. [e]model's sensivity and specifity in best spot. [f]area under curve. [g]confidence interval at 95%level. [h]systems specifity at 88% sensivity level. [i]systems sensivity at 88% specifity level. [j]2-tailed (p)-value comparing the novel logistic regression prediction model's AUC values to other systems.

The chosen logistic regression model (LR4) has four variables: age (RH 1.05, $p<0.004$), history of chronic cardiovascular and/or anticoagulation medication (RH 2.545, $p<0.021$), need for mechanical ventilation during the first 72 h (RH 2.973, $p<0.005$) and highest serum creatinine value within 60-72 h of admission (RH 1.006, $p<0.0001$).

The regression equation for the LR4 model is:

Logit (p) = -4.77 + 0.045 x age + 0.934 x history of chronic cardiovascular and/or anticoagulation medication + 1.090 x mechanical ventilation during the first 72 h of admission + 0.006 x highest serum creatinine value between 60-72 h of admission

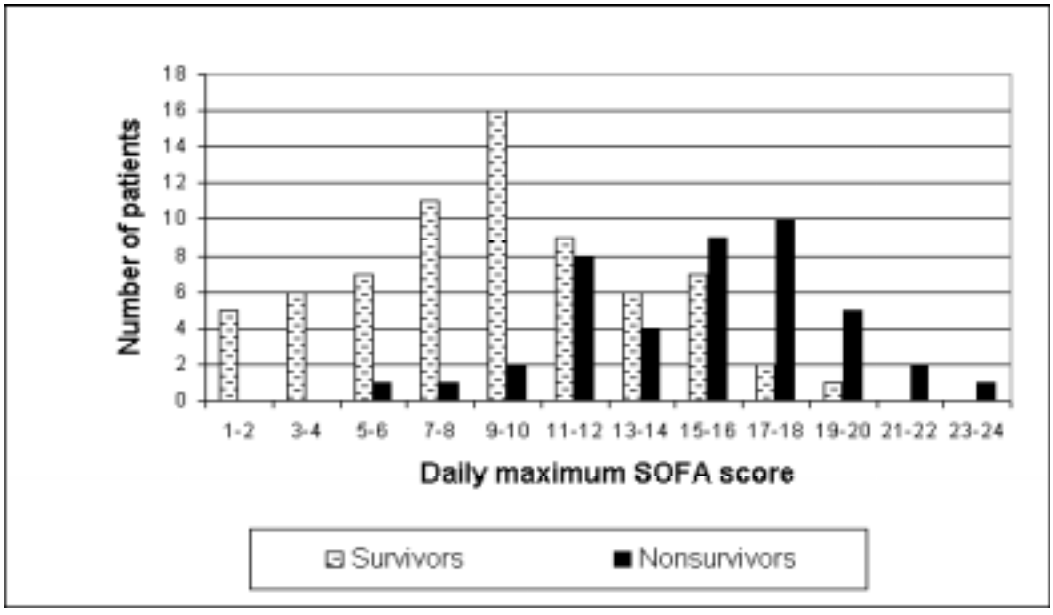
Example: A 61-year-old man with antihypertensive medication, mechanical ventilation from the second day after admission and a serum creatinine value of 350 µmol/l 72 h after admission would have the following probability of death: Logit (p) = $\log_e [p/(1-p)]$ = -4.765 + 0.045 x 61 + 0.934 + 1.090 + 0.006 x 350 = 2.104. $p=e^{logit(p)}/(1+e^{logit(p)})$ = 0.89. Thus, the patient has an 89% risk of dying from this episode of SAP.

6.5.4 Multiple organ dysfunction associated with SAP

In study III, 41 of 43 nonsurvivors died of MOF. The other two patients died of cerebral infarction with respiratory failure, and myocardial infarction with respiratory failure, respectively. The median APACHE II score for the first 24 hours at the general ICU was 11 (range 0-32) and the AUC value for the APACHE II score in predicting hospital mortality was 0.773 (SE 0.1).

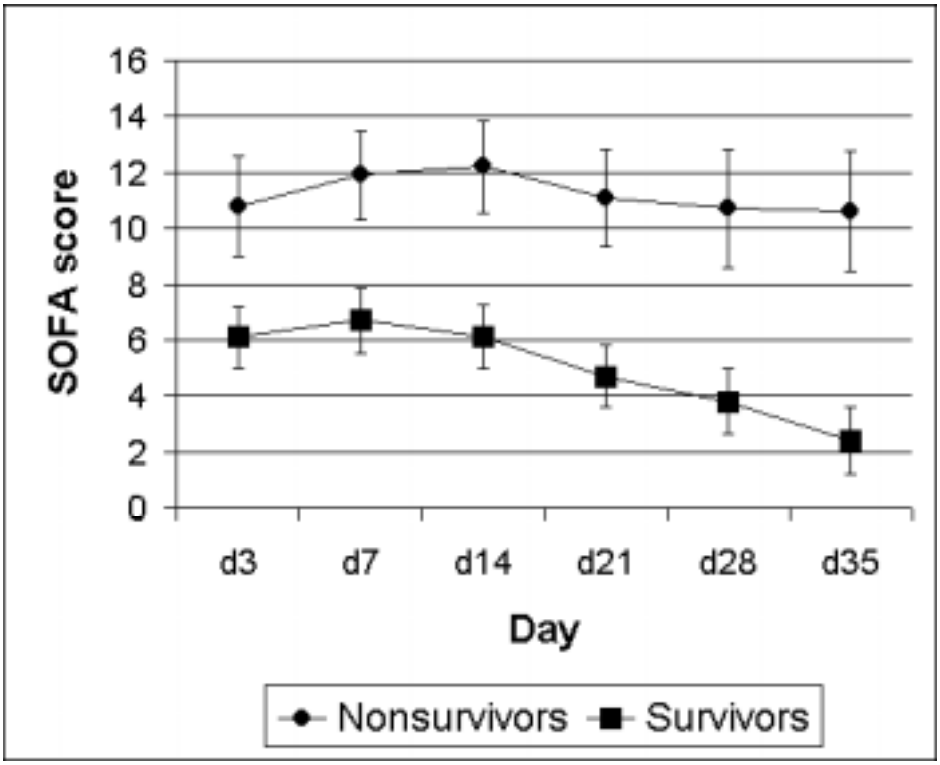
Daily maximum SOFA scores of survivors and nonsurvivors among 113 patients with SAP treated in intensive care unit are shown in Figure 2.

Figure 2 The daily maximum SOFA scores of the survivors and nonsurvivors among 113 patients with severe acute pancreatitis treated in an intensive care unit



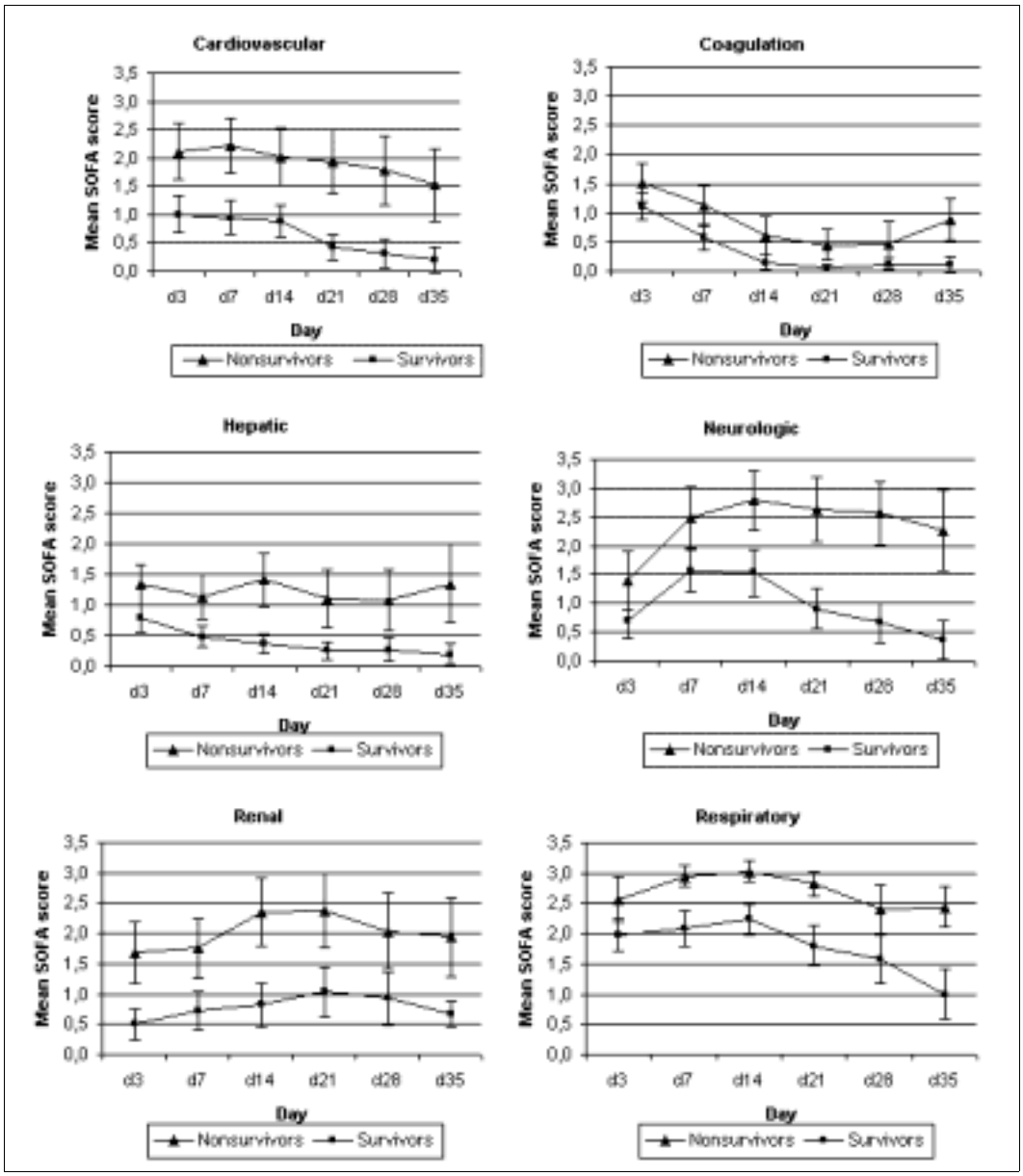
The results of the SOFA, MOD and LOD scores for predicting hospital mortality and daily maximum values are presented in Study III**,** in Figure 1, page 1276**.** The SOFA scores had the highest discrimination values and the daily organ maximum scores the highest discrimination. Survivors achieved the maximum mean daily SOFA score on day 7 (6.7, SE 6.7) and nonsurvivors on day 14 (12.2, SE 4.8)**.** Figure 3 shows how the mean daily SOFA scores changed in these subgroups.

Figure 3. Mean (CI 95%) daily Sequential Organ Failure Assessment (SOFA) score in 113 patients with severe acute pancreatitis treated in an intensive care unit



The mean maximum neurological (2.0, SE 1.7), renal (1.3, SE 1.7), and respiratory (2.5, SE 1.0) dysfunction scores were reached on day 14. The maximum mean of scores for cardiovascular (1.4, SE 1.6), coagulation (1.3, SE1.0), and liver (1.0, SE 1.1) organ dysfunction were reached on the third day (Figure 4).

Figure 4 Development of organ dysfunction by mean (95% CI) Sequential Organ Failure Assessment (SOFA) scores (range 1-4) in 113 patients with severe acute pancreatitis treated in an intensive care unit



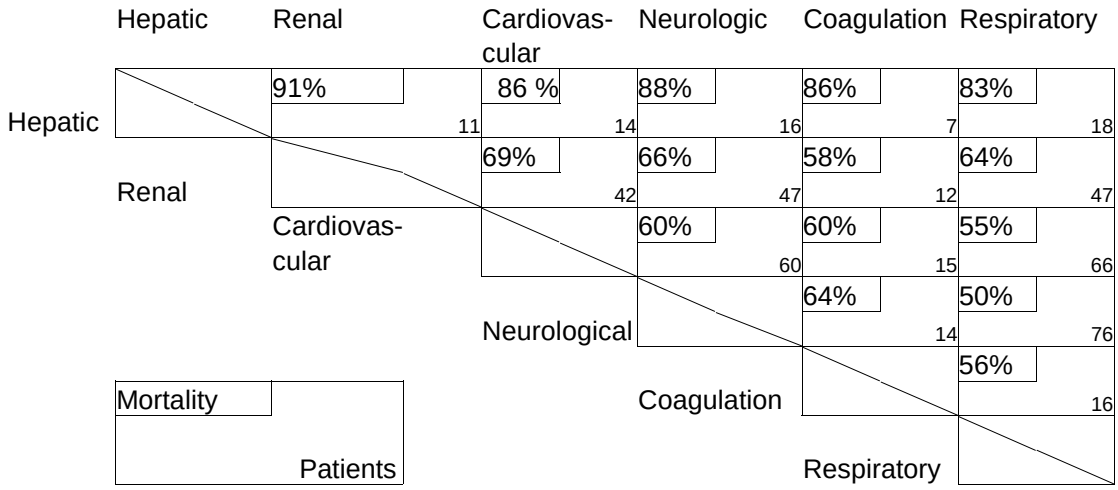
Mortality rates for patients with single maximum organ dysfunction in the subgroups of no dysfunction (SOFA 0), mild dysfunction (SOFA 1 or 2), and organ failure (SOFA 3 or 4) were highest when associated with hepatic (83%, p<0.001) and renal (63%, p<0.001) failures (Figure 5). The prevalence rates of patients without organ failure, with only one organ failure, with 2 to 3 organ failures and with 4 to 6 organ failures were 12%, 10%, 35%, and 43%, and the mortality rates 0%, 18%, 20%, and 69%, respectively.

Figure 5 Maximum SOFA organ score (from d3, d7, d14, d21, d28 and d35 values) and hospital mortality for 113 patients with severe acute pancreatitis treated in an intensive care unit

		Hepatic	Renal	Coagu-lation	Cardio-vascular	Neuro-logic	Respira-tory
SOFA 0	Mortality	22%	6%	28 %	5%	0%	0%
	Patients	36	48	25	21	18	2
SOFA 1-2	Mortality	34%	56%	38%	20%	19%	13%
	Patients	69	16	72	25	16	15
SOFA 3-4	Mortality	83%	63%	56%	55%	51%	43%
	Patients	18	49	16	67	79	96

Regarding the hospital mortality rates for different combinations of two organ system failures, mortality was highest (91%) among patients with a combination of hepatic and renal failures (Figure 6). By multiple logistic regression analysis, only hepatic failure (OR 13.0), renal failure (OR 5.6), previous chronic cardiovascular medication (OR 4.7), and cardiovascular failure (OR 4.7,) were associated independently with hospital mortality. In contrast to the overall results of this study, this model (Nagelkerke R^2 0.53; Goodness of Fit 0.10) did not identify age, etiology, respiratory failure, coagulation failure, neurological failure or infection of pancreatic necrosis as independent risk factors for hospital mortality.

Figure 6 Hospital mortality rates for different combinations of two organ system failure (maximum organ SOFA score 3 or 4) for 113 patients with severe acute pancreatitis treated in an intensive care unit



Patients with a history of chronic cardiovascular and/or anticoagulation medication had a mortality rate of 62% ($p<0.001$), and all patients in this category with a daily maximum SOFA >15 died (12 patients). Twenty patients had a history of chronic cardiovascular and/or anticoagulation medication and had renal dysfunction on day 3 and a mortality rate of 85% ($p<0.001$); 14 of these patients with SOFA scores from 2 to 4 died. The mortality rates for the patients with infected pancreatic necrosis (27 patients) and intra-abdominal infection (46) were 48% (NS) and 54% ($p<0.003$), respectively.

Age had an AUC value of 0.65 (SE 0.15) for hospital mortality. The mortality rates for patients with SAP who were <45 years old and had a daily maximum SOFA score <10 (28 patients), a SOFA score between 10 and 15 (15), and a SOFA score >15 (13) were 0%, 20%, and 85%, respectively. Of patients >60 yrs old, nine had daily maximum SOFA scores >10, with a mortality rate of 100%, and eight had daily maximum SOFA scores <10, with a mortality rate of 38%.

6.5.5 Long-term health-related quality of life of survivors from SAP

The HRQL measured by the Rand 36 survey of patients after SAP is presented in table 6. Of the 145 patients, 76 (52%) stated that their general health was about the same or better than before SAP. There was no clinically significant difference between the study group or subgroups (patients with vs. without general ICU treatment, MOF, and surgery), and an the general Finnish population matched for age and sex.

Table 6 **Health-related quality of life according the RAND 36 test (mean) for 145 patients with severe acute pancreatitis (SAP) compared with the age- and sex-matched general population (POP)**

	GH		PF		BP		RP		VI		SF		RE		MH	
	SAP	POP	SAP	POP	SAP	POP	SAP	POP	SAP	POP	SAP	POP	SAP	POP	SAP	POP
All (145 patients)	51	60	83	83	73	74	69	72	60	65	76	81	68	75	68	74
Median	50	65	90	87	76	73	81	82	70	65	80	77	100	76	100	75
SD	21	8	22	12	22	3	28	5	23	6	28	7	38	14	39	8
p-value[a]	<0.001		0.23		0.53		0.72		0.34		0.39		0.11		0.14	
Z-score[b]	1.16		0.08		0.10		0.23		0.76		1.0		0.89		1.73	

GH= general health. PF= physical functioning. BP= bodily pain. RP= role limitations because of physical problems. VI= vitality. RE= role limitations SF= social functioning because of emotional problems. MH=mental health. SD= standard deviation. [a] Man-Whitney U test. [b]patient mean score minus adjusted Finnish population score divided by standard deviation of the Finnish population.

The HRQL domains were not independently associated with follow-up time, cause, gender, general ICU treatment, duration of general ICU stay, MOF or operating status by multivariate regression analysis. On the other hand, the working status before SAP was independently associated with physical functioning (p=0.04), social functioning (p=0.04), vitality (p=0.04), role limitations because of physical problems (p=0.005), and role limitations because of emotional problems (p=<0.001). Age at time of analysis was independently associated with physical functioning (p=<0.001) and with role limitations because of physical problems (p=0.010).

Of all survivors, 175 patients had the opportunity to return to work (patients >63 yrs old and those who were known to be retired before SAP were excluded). Of these, 61% did return to work. Of the 145 patients in the study population, 68 % were working during the year before onset of SAP; 69% of them returned to work and 60% were working at the time of the study. Of the patients who were working during the year before onset of SAP, 87%

returned to work and 70% were working at the time of the study. There were no statistically significant differences between the subgroups.

The long-term morbidity after SAP is presented in table 7. 37% of the patients developed diabetes during hospitalization for a SAP attack. During the follow-up period, 47% of the patients developed diabetes. The rate for developing diabetes among the 8 patients with pancreatic resection and the 31 with digital necrosectomy was 100% and 52%, respectively. By posthoc subanalysis, patients with diabetes did not differ significantly with respect to any HRQL domain from the patients with no diabetes. During the study period, 43% of the patients had diabetes, 45% of them had also numbness in their lower or upper limbs, compared to the 40% with alcohol-induced SAP. Polyneuropathia symptoms among the other subgroups are presented in table 7.

Table 7 Complications and symptoms (%) of 145 patients who survived severe acute pancreatitis (SAP)

	Recurrent pancreatitis	Diabetes[a]	Neuropathy[b]	Diarrhea[c]	Abdominal Pain[c]
All (145 patients)	27	41	39	11	15
ICU treatment[d] (76)	29	45	41	13	16
MOF[e] (53)	17	47	42	11	17
No MOF (92)	33	37	37	11	14
Operation[f] (43)	26	52	35	9	5[g]
No operation (102)	28	35	40	12	20

[a]oral antidiabetic agents and/or insulin treatment. [b]numbness in lower or upper limbs. [c]at least twice a week. [d]general intensive care unit. [e]at least two organs' failure in the Sequential Organ Failure Assessment score (SOFA) for any organ >2. [f]any kind of abdominal operation. [g]operation versus no operation p-value 0·02 (from 2-tail Fischer test). Other differences non-significant.

Of the 145 patients answering the questionnaire 113 had had alcohol-induced SAP. 30% of them did not use alcohol, 42%, used less than 280 g (190 g for women) absolute alcohol per week, and the remaining 28%, were problem drinkers (over 280 g pure alcohol per week for men and over 190 g for women), alcohol dependent or alcoholics (Sillanaukee 1996).

6.6 Discussion

6.6.1 Hospital mortality among patients with SAP

The overall mortality rate in the present study was 26%. The total mortality was similar between the two 5-year periods (1989-1993 and 1994-1998). In a series of 172 AP patients with sterile necrosis where the classification of severity was similar to the present one the overall mortality rate was 10% (13% in the operatively treated group and 6% in the

nonoperatively treated group) (Rau et al. 1995). In a series of 30 patients requiring ICU admission due to SAP, the mortality rate was 30% (Malcynsky et al. 1996).

Improved survival of patients with necrotizing pancreatitis has been reported (Oleynikov et al. 1998, Kalfarentos et al. 1999). In the present study (table 4) mortality decreased in some subgroups of patients with SAP during the periods 1989-1993 and 1994-1998. The mortality of patients with SAP during the same five-year periods was with organ failure (42% and 29%), early organ failure (62% and 46%), MOF (57% and 45%), and early MOF (74% and 58%).

The proportion of elderly SAP patients (age over 60 years) increased from 13% during the first 5-year period to 21% during the second period. Similarly the proportion of elderly patients among nonsurvivors almost doubled. This may explain the finding in this study that the total mortality did not change between the periods.

Previous studies have recorded mortality rates between 40–80% for patients with infected necrosis (Renner et al. 1985, Allardyce 1987, Bradley 1989, Lumsden and Bradley 1990, Pederzoli et al. 1993, Ranson et al. 1997). According to this study the mortality rate during the second 5-year period for patients with infected peripancreatic necrosis was 46%, and 56% if there was abdominal infection. However, only 28 % the patients who died (13 of 47) had infected peripancreatic necrosis and 57% of them (27 of 47) had abdominal infection. 79% of the patients with SAP who underwent abdominal surgery had also an intra-abdominal infection.

6.6.2 Prognostic factors available on admission for hospital mortality in SAP

Previous chronic medication is an indicator of patients' overall health prior to the onset of the disease. This variable has not previously been reported to be a significant prognostic factor for fatal outcome in SAP. However, in study I multivariate logistic regression analysis showed that it was an independent prognostic factor for death in SAP. There were statistically significant associations between previous chronic medication and high age, high BMI and the need of pressor support and less significant association with etiology, which may explain the higher risk for fatal organ failure in this subset of patients. A history of chronic cardiovascular or anticoagulation medication is a new prognostic factor and it should alert clinicians for a potentially unfavorable outcome of patients with SAP (Study II).

Advanced age has been identified as a negative prognostic indicator in AP (Ranson and Pasternack 1977, Blamey et al. 1984, Williamson 1984), although controversial results have been reported (Fan et al. 1988, Lankisch et al. 1996). In the present study, age was associated with BMI, etiology, history of previous medication and respiratory failure. However, advanced age proved to be an independent prognostic factor by univariate and multivariate survival analysis.

BMI. The role of obesity has been emphasized as a prognostic factor in AP (Lankisch et al. 1990, Porter and Banks 1991, Funnell et al. 1993). In a series of 320 patients with AP the mortality rate was not higher in obese patients, but obese patients had a higher risk for

developing local complications in the course of AP (Tsai 1998). The present study (Study I) identified BMI as a prognostic factor in SAP in univariate analysis but it was not an independent factor by multivariate logistic regression analysis. BMI was associated with several other prognostic variables, such as age and history of chronic medication, first episode of AP, development of renal and respiratory failure and need of pressor support. According to this study these multiple associations explain largely the unfavorable outcome of patients with a high BMI.

Etiology. Several studies have shown different outcomes depending on the etiology of AP (Imrie 1974, Ranson et al. 1976, Frey 1981), although in a report of 190 patients, the cause of the AP was not associated with mortality (Uhl et al. 1996). This is keeping with this study results; neither univariate nor multivariate analysis identified etiology as an independent prognostic factor. However, the early identification of biliary AP remains of outmost importance, because this condition requires in some case adequate early endoscopic treatment.

Type of admission. In a study with 279 patients with AP, the mortality rate was 2% among patients who were directly admitted to the study hospital and it was 10-fold higher among the patients referred from another hospital (De Beux et al. 1995). This is in accordance with findings in this study (Study I and II): the prognosis of patients transferred from other hospitals was poorer, even to the extent that in the study II in my first models constructed for the test set the referral admission was a significant prognostic variable. There was a strong association between admission and respiratory, renal and cardiovascular organ failure, and this indicates that the referred patients were clinically in a more severe condition, which may be related to suboptimal early treatment or more severe disease. The poorer prognosis of the referred patients explains the relatively high total mortality in the present study. I recommend emergency transfer of patients with SAP within the first 72 hours of admission to primary a hospital to a hospital with expertise in the treatment of SAP and this is especially important for those who have advanced age, a history of chronic cardiovascular or anticoagulation medication and organ failure. The same conclusion was drawn in a study on patients with alcohol-induced acute pancreatitis and incipient organ failure (Lankisch et al. 1999).

6.6.3 Organ dysfunction associated with SAP

Single and multiple organ failure is known to predict the outcome of SAP patients (Lumsden and Bradley 1990, Karimgani et al. 1992, De Beaux et al. 1995 and 1996, Uomo et al. 1996a, Tenner et al. 1997). Studies I-III add evidence that organ failure is indeed an important prognostic factor in SAP. Consequently, every effort to reduce the risk of organ system dysfunction improves the chance of survival.

In studies I and II the need for mechanical ventilation or the need of vasoactive drugs in the early phase of SAP were identified as important prognostic factors. The most significant factor predictive of inpatient death early in SAP was the highest serum creatinine value within 60 to 72 hours of admission. This variable indicates frank renal failure, or incipient renal failure and thus every effort to protect the kidneys may improve the chances of

survival. The present study shows that organ failures in the early phase of SAP are independent prognostic factors, and the same conclusion was drawn in a study by Isenmann et al. (2001). In a recent study, early organ dysfunction in AP resolves and does not seem to have a significant impact on mortality. In contrast, worsening of organ dysfunction is associated with death (Buter et al. 2002).

According to study III, the respiratory organ failure was more common than failure in the other organs. However, the mortality rate in the respiratory failure group was 43% which is lower than for the other organ failure groups. Hepatic system failure was associated with the highest mortality (83%). This is keeping with the findings of SOFA-group work (Vincent et al. 1996). In a study involving 267 patients with AP, the mortality rate among patients with acute renal failure was 81%, compared to 83% with cardiovascular failure and 72% with hematological failure (Tran et al. 1993b). In my study, mortality rates of patients with SAP and renal, cardiovascular and coagulation organ failure were 63%, 55%, and 56%, respectively. This difference in mortality can, in part, be caused by the different criteria for definition of organ failure. In my study, multiple logistic regression analysis showed that failure, only of the hepatic, renal, and cardiovascular systems was an independent inpatient mortality risk factor, whereas failure of the respiratory, coagulation, and neurologic systems was not. The prognostic value of neurologic failure was lower in my study than in the SOFA-group work (Vincent et al. 1998). In study I, respiratory failure was identified as an independent inpatient mortality risk factor. Dissimilar study populations may explain this difference. In study I, 50 % of patients needed mechanical ventilation, whereas in study III 85% needed mechanical ventilation.

The highest SOFA score for the individual organ systems was reached at different time points. The mean maximum SOFA score for the cardiovascular, hepatic, and coagulation systems was reached on day 3, for the respiratory and neurologic systems at the 14th day and for the renal system on day 21. These findings differ from those of the SOFA-group, who reported the shortest time to the mean maximum SOFA score for the respiratory system and the longest for the hepatic system (Vincent et al. 1998).

6.6.4 Multiple organ dysfunction associated with SAP

The present study demonstrated that organ dysfunction scores (MOD, LOD, and SOFA) predict well hospital mortality in patients with SAP. To my knowledge, this is the first study in which organ dysfunction scores have been used to predict hospital mortality in patients with SAP. SOFA scores had the highest discrimination values, but there was no statistically significant difference between organ dysfunction scores regarding AUCs. A good discrimination power is achieved when the daily maximum score of all organ dysfunction scores is recorded. The AUC values of the SOFA scores increased from the day 3 value to day 35 value. The AUCs of the organ dysfunction scores were better than APACHE II score in predicting of hospital mortality.

The mortality rate associated with a maximum daily SOFA score of more than 15 was lower than the one reported by the SOFA (Vincent et al. 1996). The present study (Figure 6) found a mortality of 50%-91% among SAP patients with failure of two organ system; this compares favorable with range of 48%-73% reported by the SOFA group (Vincent et al. 1998). According to the present study, the range of mortality is wider than the one reported by the SOFA group (Vincent et al. 1996). The highest mortality rate (91%) in my study was recorded for the combination of hepatic and renal failure in SAP patient. Two studies have shown mortality rates between 80 and 86% for patients with AP and a combination of acute renal and hepatic failure (Tran et al. 1993b, Ljutic et al. 1996). In these two studies the criteria for hepatic failure differ slightly from those of the SOFA group.

Throughout the duration of the hospital stay, mean daily SOFA scores were significantly higher for the nonsurvivors than for the survivors. According my study, the development of the daily SOFA score after day 14 seems to distinguish between SAP patients who will survive and who will not.

6.6.5 Multifactorial models to predict mortality in patients with SAP

The Ranson and Imrie scores have been developed for predicting the severity of AP but they have also been used for predicting hospital mortality (Ranson et al. 1974 and 1976, Corfield et al. 1985). Study II demonstrated that the Ranson and Imrie scores are not accurate predictors of a fatal outcome of patients with SAP. My study supports the conclusions of a meta-analysis regarding the predictive power of the Ranson score (De Bernardinis et al. 1999). According to a recent study the Ranson score is as a valid predictor of mortality among SAP patients who are treated in a surgical ICU; the study excluded critically ill SAP patients who were treated in the medical ICU (Eachempati et al. 2002).

The APACHE II and MODS systems have been used for predicting the outcome of severely ill patients. In the study II, these systems had a much higher accuracy than Ranson and Imrie scores, but a lower accuracy than my study new models. Both chosen models in my study (study II) resulted in higher AUC values (accuracy) than APACHE II and MODS, but the difference was not statistically significant. The main advantage of the novel LR4 model is that it is simple as compared with APACHE II and MODS. The LR4 model uses only four variable which are readily available and these four variables yield a higher accuracy than the 14 variables and 96 alternatives in APACHE II. The four variables of the LR4 model are age, history of cardiovascular or anticoagulation medication, need for mechanical ventilation and highest serum creatinine value within 60-72 h from admission.

ANN has been used to predict the duration of hospital stay of AP patient (Pofahl et al. 1998), but not for survival prediction. To my knowledge, this is the first study to use ANN to predict death in patients with SAP. It turned out that ANN did not offer any advantages over a logistic regression model. The ANN8 model with its eight variables had almost the same accuracy as the logistic model (LR4) with four variables. The four variables of LR4 were also tested in a neural network model (ANN4), but accuracy was not affected. This indicates

that there are only few nonlinearities or complex interactions between these four variables (Baxt 1994, Burke 1996).

From these findings I conclude that the four variables in the LR4 model are independent predictors of hospital mortality early in SAP.

Patients' age and history of chronic medication were identified as factors to predict a fatal outcome (studies I and II). The organ dysfunction scores do not take into account these two confounding factors. Study III shows that in patients >60 yrs old, a SOFA score over 10 indicates an extremely poor prognosis (mortality100 %). In that study, age was not an independent risk factor for death by in multiple regression analysis. Perhaps the multiple regression model used in study III as well as the small number of elderly patients treated in the general ICU underestimated the prognostic value of age. All 12 patients with a history of chronic cardiovascular medication and a SOFA score over 15 died. Early renal dysfunction in patients with a history of cardiovascular medication is also a sign of a poor prognosis. 20 patients had early renal dysfunction (SOFA scores 1-4) and 14 of them had SOFA scores of 2-4 on the day 3. The mortality rates in these two groups were 85% and 100%, respectively. This study shows that renal failure and a history of chronic cardiovascular medication are independently associated with a fatal outcome in this patient population. Apparently these patients have deficient physiological reserve for surviving.

In 1973, Tilney suggested that, in patients with a ruptured abdominal aneurysm, the superimposition of pre-existing chronic cardiovascular disease on the mechanical and metabolic consequences of the surgical procedure leads to a high mortality. In patients with a history of cardiovascular medication, cytokines and inflammatory mediators in the early phase of SAP may initiate a vicious cycle and leads inevitably to death. Two studies have suggested that supranormal hemodynamic performance is needed by critically ill patients for survival from shock-related organ failures (Bishops et al. 1993, Shoemaker et al. 1993), and in patients with advanced age and cardiovascular disease, these values may be difficult to achieve. These findings may explain the poor outcome in these subgroups, because SAP can cause shock, which demands of a patient the ability to achieve these supranormal values.

6.6.6 Long-term health-related quality of life in survivors after SAP

The findings in study IV show that patients with long-term survival following SAP have a good quality of life, which seems to be comparable to that of the general population, as assessed with the Rand 36-item Health Survey. Although the difference in the general health domain was statistically significant, the Z score was below 2 and the differences between means was <10, and this indicates that the difference was not clinically significant (Pettilä et al. 2000).

A study by Pettilä et al. (2000) demonstrated impairment in several domains of HRQL of ICU patients 1 year after discharge. Two studies used the 36-item short-form general health survey and found no statistically significant difference in HRQL between 22 SAP patients who were operated on and 21 others who had been treated in ICU (Broome et al. 1996, Soran

et al. 2000). The present study revealed no clinically significant difference in the HRQL when subgroups of patients with MOF or undergoing ICU or surgical treatment were analyzed.

Multiple regression analysis showed that only the employment status before SAP and the age during the study period were independently associated with some HRQL domains. Follow-up time, etiology of SAP, gender, ICU treatment, duration of ICU stay, MOF and need for abdominal operation did not affect adversely the HRQL among long-term survivors of SAP.

6.6.7 Long-term outcome in survivors of SAP

This study found that 87% of the patients who were working the year before the onset of SAP returned to work, which confirms the results of a previous Finnish study showing that 77% of ICU treated SAP patients returned to work (Doepel et al. 1993).

The overall incidence of diabetes in my study was 47%. Previous studies have reported an incidence of 83-100% after distal resection of the pancreas required for treatment of SAP (Nordback et al. 1985c, Schröder et al. 1990, Doepel et al. 1993). Büchler et al. (1987) found that one-half of the patients developed subclinical or overt diabetes after necrosectomy or closed lavation. The incidence of diabetes in this study among eight patients with pancreatic resection was 100% and among the 31 who underwent digital necrosectomy 52%. This study adds evidence that pancreas-preserving necrosectomy is associated with a lower risk of diabetes. However, the follow-up period in my study may have been too short to assess the impact of diabetes on HRQL, if any.

The mortality rate in this study was 25%. This figure is comparable to the one reported from other tertiary referral center (De Beaux et al. 1995). According this study (study IV), an additional 10% of patients died within a few years, mostly from alcoholism and pancreas-related diseases, mainly diabetes. This has not been published previously. In the present study, 78% of the patients had alcohol-induced pancreatitis, and it was encouraging that 30% of them became totally abstinent and that 42% reduced their alcohol intake to a reasonable level.

6.6.8 Study limitations

Several limitations of this study should be addressed. Firstly, data collection was retrospective in study III and partly retrospective in studies I and II. However, the proportion of missing values in study III {most frequently serum bilirubin [21 missing values out of 678 (3.1%)]} was fairly small [total missing values was 52 out of 8249 (0.6%)]. Statistically, the missing data did not have any notable affect on the results. Secondly, the scores compared in study III were not published at the time of the beginning of the study period, and MOD scores are based on efficient registration of routine laboratory values and vasoactive medication. Thirdly, because I collected data over only 7 days during a period of 35 days in study III, I may have missed some valuable information on the maximal values. Fourthly, because this study was partly retrospective, I was not able to estimate the prognostic value with regard to survive of serum calcium, the amount of pancreatic necrosis and the value of

early prophylactic antibiotic in the treatment of SAP. Fifthly, I was not able to include the variable infected pancreatic necrosis in the analyses of mortality (study I). Sixthly, the new prognostic models (study II) require 72 h of follow-up data as of admission and this time seems to be too long to allow starting some (e.g., anticytokine) therapies to treat AP and SAP. However, the models in this study were developed primarily for predicting hospital mortality and not to classify the severity of AP.

Seventhly, I had no baseline measurement for assessment of QOL with the Rand 36 tool (study IV); it is most difficult to obtain baseline data in all patients with SAP. Eightly, the Rand 36 survey is not validated nor has its reliability been tested in SAP patients. Furthermore, the assessment of the level of clinical relevance for any difference in QOL values is arbitrary and may well be criticized. Very few QOL studies have succeeded in meeting strict methodological criteria (Heyland et al. 1998). However, Rand 36 has been shown to be a valid and reliable measure of HQOL in critical ill patients with sepsis (Heyland et al. 2000).

6.6.9 Clinical implications

It is, in my opinion, of utmost clinical importance to increase the accuracy of prognostic systems, especially those related to hospital mortality. Early identification of high-risk patients with SAP may have several clinical consequences. These patients should be referred to a specialized unit swiftly. Clearly, there is a need to improve the treatment of this group since their outcome is not good. New types of immunosupportive and anticytokine therapies carry promise of improved treatment. The optimal target group of these therapies might be patients with a predicted poor prognosis. The novel LR4 model is feasible for enrolling patients with SAP in prospective trials focusing on hospital. The prognostic score generated by the LR4 model has been validated only in a relatively small population and mainly alcohol-induced SAP. However, my studies and earlier studis have not established the etiology of SAP as a significant prognostic factor for hospital mortality (Uhl et al. 1996). The model requires further validation before it may be recommended for use in the clinics. Also, an evaluation of how close the predictions are to the actual death rate (calibration) still needs to be corroborated.

The importance of study III lies in that it validates some organ dysfunction scores (MOD, LOD, and SOFA) in the target population of ICU treated SAP patients (Miskovitz 2002). According to this study, organ dysfunction scores are simple and useful for assessing MOD and for predicting a fatal outcome of patients with SAP. I recommed the routine use of one of them in clinical work.

Although the present study found that some subgroups have a very poor prognosis, it is underpowered to allow any definitive conclusions about the power to predict a poor outcome (as to support end-of-life decisions) in clinical practice. Large prospective studies are needed to confirm these findings.

This study (study IV) may have implications at the microeconomic level, where it can be used as a tool to encourage ICUs in hospitals to do follow-up surveys and assess the long-term efficiency of the treatment provided at the ICUs.

Whether the present results can be used to justify the management of SAP patients in general, is in my view, controversial. However, according to the present study it seems to be worthwhile to treat actively patients with SAP, although the cost of treatment is high. The long-term health-related quality of life of patients surviving a bout of SAP is comparable to that of the general population, and thus maximal treatment of these patients seems to be justified.

6.6.10 Future directions

Despite numerous studies AP is still a poorly understood disease. There is a large number of studies using univariate analysis to identify prognostic factors in AP. However, the outcome in SAP depends on multiple intermingled variables making the prediction unreliable, even by multivariate analysis.

To achieve a clinically acceptable accuracy for the predicting the outcome of patients with SAP, better prediction models than those currently available are required. One solution could be to identify separate prognostic factors as markers of severity of disease and of fatal outcome.

This study shows that 79% of patients who died had organ failure within 72 hours of admission and 67% of the patients who died had early MOF (within 72 hours of admisson). In study by Johnson et al. (2001) 44% of patients with SAP had organ failure on admission and 97% of the patients who died had organ failure within the first week of admission. To decrease hospital mortality in patients with SAP, it is important to predict early organ dysfunction/failure to allow immediate transfer of these patients to specialized units. High-risk SAP patients should be identified by a single or multifactorial testing on admission or during the early hours of an attack of AP to predict single or multiple organ failure. This is also needed for identification of patients that should be invited to participate in future trials.

Althoug there are no drugs, as yet, to prevent or cure MOF, the development of a new type of immunosupportive and anticytokine therapies is ongoing. Supraphysiological doses of hydrocortisone intravenously early (8-24h from start) during the course of septic shock (50-100 mg 3-4 times per day during 5 to 7 days) have been shown to reduce mortality (Bollaert et al. 1998, Briegel et al. 1999). This treatment should be considered also for patients with SAP who need vasoactive pressor support for a longer time (48 hours). Similarly, the use of physiological anticoagulants antitrombin III and activated protein C reduces mortality in patients with sepsis (Eisele et al. 1998, Bernard 2001) and thus this treatment should be also considered for SAP patients.

Morbidity and mortality among critically ill patients is reduced by intesive insulin therapy targeted at maintaining the blood glucose concentration between 4 to 6 mmol/L (Van den Berghe et al. 2001). This therapy should also be considered for patients with SAP.

Increased intra-abdominal pressure (IAP), which may lead to the abdominal compartment syndrome, is a known complication of SAP (Gecelter et al. 2002). Some patients may be treated by abdominal decompressive laparotomy (Gecelter et al. 2002), but the value of a decompressing laparotomy will have to be studied in a randomized controlled trial before any recommendations can be made (Sugrue 2002, Z'graggen and Gloor 2002).

6.7 Conclusions

1. The following independent prognostic factors for hospital mortality in patients with severe acute pancreatitis (SAP) were identified: advanced age, need of dialysis, need of mechanical ventilator support, need of pressor support and previous chronic medication (a marker of the overall health of the patient before the onset of SAP).

2. The novel logistic regression predicting model with four easily available variables has a higher accuracy as compared with 14 variables (12 physiological variables and points for age and chronic health) and 96 alternatives in APACHE II. According to our study Ranson and Imrie scores are inaccurate indicators of the mortality in SAP. Organ failures in the early phase of SAP are the best predictors of mortality. Age and comorbid diseases must be taken into account when predicting the survival of patients with SAP. The new four-variable predicting model identifies patients with a high risk of death early in SAP.

3. The SOFA, MOD, and LOD multiple organ dysfunction scores are effective predictors of hospital mortality among patients with SAP treated in a general ICU. The SOFA scores had the highest discrimination values, although the differences were not statistically significant. The maximum daily multiple organ dysfunction scores are simple and useful for assessing multiple organ dysfunctions and predicting hospital mortality rates in patients with SAP. Hepatic, renal, and cardiovascular failure and a history of chronic cardiovascular medication were independent risk factors for hospital mortality in this high-risk patients group.

4. A significant proportion of patients with mainly alcohol-induced SAP surviving initial hospitalization die within a few years from alcoholism and pancreas-related disease. HRQL among the survivors is comparable to that in the general population, and the majority returns to work and reduce their alcohol consumption markedly.

7. ACKNOWLEDGEMENTS

The present study was carried out at the Second Department of Surgery and Department of Gastroenterological and General Surgery at Meilahti Hospital, Helsinki University between 1997 and 2004.

I express my respect and gratitude to Professor Eero Kivilaakso for the opprtunity to carry out this study at the Second Department of Surgery.

I am most grateful to the supervisor of this thesis, Docent Ari Leppäniemi, for his unfailing guidance and encouragement in my study and work.

I express my sincere gratitude to the second supervisor Docent Reijo Haapiainen for his confidence in my work and for providing me with the opportunity to be a member of the pancreatitis research group in the Second Department of Surgery.

I owe my sincerest thanks to Docent Esko Kemppainen and Docent Pauli Puolakkainen for their friendly support and for their greatest advice in the scientific work and world.

I owe my warmest thanks to MD Ville Pettilä for his statistical advice and for his wide knowledge in the field of outcome prediction and treatment of intensive care unit patients.

I owe my warmest thanks to my co-authors MD Johan Lundin, Professor Seppo Sarna and Docent Antti Hietaranta for their kind collaboration during this work.

I express my sincere gratitude to Docent Isto Nordback from the Tampere University Central Hospital and Docent Tero Ala-Kokko from the Oulu University Central Hospital, for their prompt and professional criticism in reviewing this thesis.

I am grateful to Mrs Tuula Lehtinen for her assistance with data collection.

I express my deepest gratitude to the entire staff of the Surgical Department at the Helsinki University Central Hospital, for their positive attitude toward my clinical and research work.

The English language was revised by Docent Rober Paul, certifical Translater.

8. REFERENCES

Abe H. Nisimura T. Osawa S. Miura T. Oka F. Acute pancreatitis caused by extracorporeal shock wave lithotripsy for bilateral renal pelvic calculi. *Int J Urol* 7:65-8, 2000.

Abu-Zidan FM. Bonham MJ. Windsor JA. Severity of acute pancreatitis: a multivariate analysis of oxidative stress markers and modified Glasgow criteria. *Br J Surg* 87:1019-23, 2000.

Aalto A, Aro S, Aro AR, Mähönen M. Rand 36-Item Survey 1.0. Finnish version. *STAKES* (National Research and Development Centre for Welfare and Health), Helsinki, 1999.

Adiseshiah M. Wells FC. Cory-Pearce R. Wallwork J. English TAH. Acute pancreatitis after cardiac transplantation. *World J Surg* 7:519-21, 1983.

Albert MB. Steinberg WM. Irani SK. Severe acute pancreatitis complicating sphincter of Oddi manometry. *Gastrointest Endosc.* 34:342-5, 1988.

Aldridge MC. Ornstein M. Glazer G. Dudley HA. Pancreatic resection for severe acute pancreatitis. *Br J Surg* 72:796-800, 1985.

Aldridge MC. Francis ND. Glazer G. Dudley HA. Colonic complications of severe acute pancreatitis. *Br J Surg* 76:362-7, 1989.

Alexandre JH. Guerrieri MT. Role of total pancreatectomy in the treatment of necrotizing pancreatitis. *World J Surg* 5:369-77, 1981.

Allardyce DB. Incidence of necrotizing pancreatitis and factors related to mortality. *Am J Surg.* 154:295-9, 1987.

Altemeier WA. Alexander JW. Pancreatic abscess. *Arch Surg* 87:80-9, 1963.

Alverdy J. Vargish T. Desai T. Frawley B. Rosen B. Laparoscopic intracavitary debridement of peripancreatic necrosis: preliminary report and description of the technique. *Surgery* 127:112-4, 2000.

Anai H. Sakaguchi H. Uchida H. Matsuo N. Tanaka T. Yoshioka T. Ohishi H. Murao Y. Miyamoto S. Continuous arterial infusion therapy for severe acute pancreatitis: correlation between CT arteriography and therapeutic effect. *J Vasc Intervent Radiol* 10:1335-42, 1999.

Anonymous. Rand-36 item health survey 1.0. Rand Health Program.
http://www.rand.org/health/surveys/sf36item/, 3 Jan, 2002

Appelros S. Borgstrom A. Incidence, aetiology and mortality rate of acute pancreatitis over 10 years in a defined urban population in Sweden. *Br J Surg.* 86:465-70, 1999.

Appelros S. Thim L. Borgstrom A. Activation peptide of carboxypeptidase B in serum and urine in acute pancreatitis. *Gut* 42:97-102, 1998.

Armengol-Carrasco M. Oller B. Escudero LE. Roca J. Gener J. Rodriguez N. del Moral P. Moreno P. Specific prognostic factors for secondary pancreatic infection in severe acute pancreatitis. *Dig Surg* 16:125-9, 1999.

Atkinson S. Bihari D. Smithies M. Daly K. Mason R. McColl I. Identification of futility in intensive care. Lancet. 344:1203-6, 1994.

Balthazar EJ. Ranson JH. Naidich DP. Megibow AJ. Caccavale R. Cooper MM. Acute pancreatitis: prognostic value of CT. *Radiology*. 156:767-72, 1985.

Balthazar EJ. Robinson DL. Megibow AJ. Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. *Radiology*. 174:331-6, 1990.

Balthazar EJ. Freeny PC. Van Sonnenberg E. Imaging and intervention in acute pancreatitis. *Radiology*. 193:297-306, 1994.

Bank S. Wise L. Gersten M. Risk factors in acute pancreatitis. *Am J Gastroenterol* 78:637-40, 1983.

Bank S. Indaram A. Causes of acute and recurrent pancreatitis. Clinical considerations and clues to diagnosis. *Gastroenterol Clin North Am* 28:571-89, 1999.

Bank S. Singh P. Pooran N Stark B. Evaluation of factors that have reduced mortality from acute pancreatitis over the past 20 years. *J Clin Gastroenterol* 35:50-60, 2002.

Banks P. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 92:377-86, 1997.

Barkin JS. Smith FR. Pereiras R. Jr. Isikoff M. Levi J. Livingstone A. Hill M. Rogers AI. Therapeutic percutaneous aspiration of pancreatic pseudocysts. *Dig Dis Sci* 26:585-6, 1981.

Baron TH. Thaggard WG. Morgan DE. Stanley RJ. Endoscopic therapy for organized pancreatic necrosis. *Gastroenterology* 111:755-64, 1996.

Baron TH. Morgan DE. Acute necrotizing pancreatitis. *N Engl J Med.* 340:1412-7, 1999.

Baron TH. Morgan DE. Vickers SM. Lazenby AJ. Organized pancreatic necrosis: endoscopic, radiologic, and pathologic features of a distinct clinical entity. *Pancreas* 19:105-8, 1999b.

Baron TH. Harewood GC. Morgan DE. Yates MR. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. *Gastrointest Endosc* 56:7-17, 2002.

Bassi C. Falconi M. Talamini G. Uomo G. Papaccio G. Dervenis C. Salvia R. Minelli EB. Pederzoli P. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. *Gastroenterology* 115:1513-7, 1998.

Baxt WG. Complexity, chaos and human physiology: the justification for non-linear neural computational analysis. *Cancer Letters*. 77:85-93, 1994.

Beger HG. Krautzberger W. Bittner R. Block S. Büchler. Results of surgical treatment of necrotizing pancreatitis. *World J Surg* 9:972-9, 1985.

Beger HG. Bittner R. Block S. Büchler M. Bacterial contamination of pancreatic necrosis. A prospective clinical study. Gastroenterology. 91:433-8, 1986a.

Beger HG. Bittner R. Buchler M. Hess W. Schmitz JE. Hemodynamic data pattern in patients with acute pancreatitis. *Gastroenterology* 90:74-9, 1986b.

Beger HG. Büchler M. Bittner R. Block S. Nevalainen T. Roscher R. Necrosectomy and postoperative local lavage in necrotizing pancreatitis. *Br J Surg* 75:207-12, 1988.

Beger HG. Surgical management of necrotizing pancreatitis. *Surg Clin North Am* 69:529-49, 1989.

Beger HG. Isenmann R. Surgical management of necrotizing pancreatitis. *Surg Clin North Am* 79:783-800, 1999.

Bellomo R. Ronco C. Continuous renal replacement therapy in the intensive care unit. *Intensive Care Med* 25:781-9, 1999.

Bem J. Bradley EL 3rd. Subcutaneous manifestations of severe acute pancreatitis. *Pancreas* 16:551-5, 1998.

Berman LG. Dunn E. Straehley CJ Jr. Survey of pancreatitis-central New York surgical society. *Gastroenterology* 40:94-108, 1961.

Bernard GR. Vincent JL. Laterre PF. LaRosa SP. Dhainaut JF. Lopez-Rodrigues A. Steingrub JS. Garber GE. Recombinant human activated protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 344:699-709, 2001.

Bettinger JR. Grendell JH. Intracellular events in the pathogenesis of acute pancreatitis. *Pancreas* 6:2-6, 1991.

Bishop MH. Shoemaker WC. Appel PL. Wo CJ. Zwick C. Kram HB. Meade P. Kennedy F. Fleming AW. Relationship between supranormal circulatory values, time delays, and outcome in severely traumatized patients. *Crit Care Med.* 21:56-63, 1993.

Blamey SL. Imrie CW. O'Neill J. Gilmour WH. Carter DC. Prognostic factors in acute pancreatitis. *Gut.* 25:1340-6, 1984.

Blauvert H. A case of acute pancreatitis with subcutaneous fat necrosis. *Br J Surg* 34:207-8, 1946.

Block S. Meier W. Bittner A. Büchler M. Identification of pancreatic necrosis in severe acute pancreatitis: imaging procedures versus clinical staging. *Gut* 27:1035-42, 1992.

Bollaert PE. Charpentier C. Levy B. Debouverie M. Audibert G. Larcan A. Reversal of late septic schock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 26:645-50, 1998.

Bonham MJ. Abu-Zidan FM. Simovic MO. Windsor JA. Gastric intramucosal pH predicts death in severe acute pancreatitis. *Br J Surg* 84:1670-4, 1997.

Bonham MJ. Abu-Zidan FM. Simovic MO. Sluis KB. Wilkinson A. Winterbourn CC. Windsor JA. Early ascorbic acid depletion is related to the severity of acute pancreatitis. *Br J Surg* 86:1296-301, 1999.

Bosscha K. Hulstaert PF. Hennipman A. Visser MR. Gooszen HG. van Vroonhoven TJ. Van den Werken C. Fulminant acute pancreatitis and infected necrosis: results of open management of the abdomen and "planned" reoperations. *J Am Coll Surg* 187:255-62, 1998.

Bozkurt T. Maroske D. Adler G. Exocrine pancreatic function after recovery from necrotizing pancreatitis. *Hepato-Gastroenterology* 42:55-8, 1995.

Bradley EL. Clements JL Jr. Gonzalez AC. The natural history of pancreatic pseudocysts: a unified concept of management. *Am J Surg* 137:135-41, 1979.

Bradley EL 3rd. Management of infected pancreatic necrosis by open drainage. *Ann Surg* 206:542-50, 1987.

Bradley EL 3rd. Antibiotics in acute pancreatitis. Current status and future directions. *Am J Surg*. 158:472-8, 1989.

Bradley EL 3rd. Allen K. A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. *Am J Surg* 161:19-25 1991.

Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg.* 128:586-90, 1993.

Branum G. Galloway J. Hirchowitz W. Fendley M. Hunter J. Pancreatic necrosis: results of necrosectomy, packing, and ultimate closure over drains. *Ann Surg* 227:870-7, 1998.

Briegel J, Frost H. Haller M. Schelling G. Kilger E. Kuprat G. Hemmer B. Hummel T. Lenhart A. Heyduck M. Stoll C. Peter K. Stress doses of hydrocortisone reverse hyperdynamic septic schock: A prospective, randomised, double-blind, single-center study. *Crit Care Med* 27:723-732, 1999.

Broome AH. Eisen GM. Harland RC. Collins BH. Meyers WC. Pappas TN. Quality of life after treatment for pancreatitis. *Ann Surg.* 223:665-70; discussion 670-2, 1996.

Bruno MJ. Van Westerloo DJ. Van Dorp WT. Dekker W. Ferwerda J. Tytgat GN. Schut NH. Acute pancreatitis in peritoneal dialysis and haemodialysis: risk, clinical course, outcome, and possible aetiology. *Gut* 46:385-9, 2000.

Brown A. Orav J. Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas* 20:367-72, 2000.

Burke HB. Statistical analysis of complex systems in biomedicine; *in Fisher D., Lenz H.J.(eds): Learning from data.* AI and Statistics V. Berlin, Springer, 1996, vol 112, pp 251-258.

Buter A. Imrie CW. Carter R. Evans S. McKay CJ. Dynamic nature of early dysfunction determines outcome in acute pancreatitis. *Br J Surg* 89:298-302, 2002.

Büchler M. Malfertheiner P. Schoetensack C. Uhl W. Beger HG. Sensitivity of antiproteases, complement factors and C-reactive protein in detecting pancreatic necrosis. Results of a prospective clinical study. *Int J Pancreatol.* 1:227-35, 1986.

Büchler M, Hauke A, Malfertheiner P. Follow-up after acute pancreatitis- morphology and function. *In Beger HG, Büchler M, editors. Acute pancreatitis-research and clinical management.* Berlin, Heidelberg: Springer-verlag, 1987 p. 367-374.

Büchler M. Malfertheiner P. Friess H. Isenmann R. Vanek E. Grimm H. Schlegel P. Friess T. Beger HG. Human pancreatic tissue concentration of bactericidal antibiotics. *Gastroenterology* 103:1902-8, 1992.

Büchler M. Malfertheiner P. Uhl W. Schölmerich J. Stöckmann F. Adler G. Gaus W. Rolle K. Beger HG. Gabexate mesilate in human acute pancreatitis. German Pancreatitis Study Group. *Gastroenterology* 104:1165-70, 1993.

Büchler MW. Binder M. Friess H. Role of somatostatin and its analogues in the treatment of acute and chronic pancreatitis. *Gut* 35:S15-9, 1994.

Büchler P. Reber HA. Surgical approach in patients with acute pancreatitis. Is infected or sterile necrosis an indication--in whom should this be done, when, and why?. *Gastroenterol Clin North Am* 28:661-71, 1999.

Büchler MW. Gloor B. Müller CA. Friess H. Seiler CA. Uhl W. Acute necrotizing pancreatitis: treatment strategy according to the status of
infection. *Ann Surg*232:619-26, 2000.

Camargo CA. Greig PD. Levy GA. Clavien P-A. Acute pancreatitis following liver transplantation. *J Am Coll Surg* 181:249-56, 1995.

Cameron JL. Mehigan D. Zuidema GD. Evalution of atropine in acute pancreatitis. *Surg Gynecol Obstet* 148:206-8, 1979.

Carter CR. McKay CJ. Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of nfected pancreatic necrosis: an initial experience. *Ann Surg* 232:175-80, 2000.

Case RM. Pancreatic exocrine secration: machanism and control In: Beger HG: et al. (ed). The Pancreas. London, Blackwell Science Volume 1:63-100, 1998.

Chen C-C. Wang S-S. Lu R-H. Chang F-Y. Lee S-D. Serum interleukin 10 and interleukin 11 in patients with acute pancreatitis. *Gut* 45:895-9, 1999.

Chen C-H. Lu C-L. Chang F-Y. Lee S-D. Duodenal lesions following severe acute pancreatitis: Review of 10 years' clinical experience. *Hepato-Gastroenterol* 48:869-71, 2001.

Chen HM. Chen JC. Hwang TL. Jan YY. Chen MF.
Prospective and randomized study of gabexate mesilate for the treatment of severe acute pancreatitis with organ dysfunction. *Hepato-Gastroenterol* 47:1147-50, 2000.

Choi TK. Wong J. Severe acute pancreatitis caused by parasites in the common bile duct. *J Tropical Med Hygien* 87:211-4, 1984.

Coakley JH. Nagendran K. Yarwood GD. Honavar M. Hinds CJ. Patterns of neurophysiological abnormality in prolonged critical illness. *Intensive Care Med* 24:801-7, 1998.

Comfort M. Steinberg A. Pedigree of a family with hereditary chronic relapsing pancreatitis. *Gastroenterology* 21: 54-63, 1952.

Cooperman AM. An overview of pancreatic pseudocysts. The emperor' new clothes revisited. *Surg Clinic North Am* 81:391-7, 2001a.

Cooperman AM. Surgical treatment of pancreatic pseudocysts. *Surg Clin North Am* 81:411-9, 2001b.

Corfield AP. Cooper MJ. Williamson RC. Mayer AD. McMahon MJ. Dickson AP. Shearer MG. Imrie CW. Prediction of severity in acute pancreatitis: prospective comparison of three prognostic indices. *Lancet.* 2:403-7, 1985.

Cullen TS. A new sign in ruptured extrauterine pregnancy. *Am J Obstet* 78:457, 1918.

Davis TV. Keeffe EB. Acute pancreatitis associated with acute hepatitis A. *Am J Gastroenterol* 87:1648-50, 1992.

De Beaux AC. Palmer KR. Carter DC. Factors influencing morbidity and mortality in acute pancreatitis; an analysis of 279 cases. *Gut.* 37:121-6, 1995.

De Beaux AC. Goldie AS. Ross JA. Carter DC. Fearon KC. Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis. *Br J Surg* 83:349-53, 1996.

De Beaux AC. O'Riordain MG. Ross JA. Jodozi L. Carter DC. Fearon KC. Glutamine-supplemented total parenteral nutrition reduces blood mononuclear cell interleukin-8 release in severe acute pancreatitis. *Nutrition* 14:261-5, 1998.

De Bernardinis M. Violi V. Roncoroni L. Boselli AS. Giunta A. Peracchia A. Discriminant power and information content of Ranson's prognostic signs in acute pancreatitis: a meta-analytic study. *Crit Care Med* 27:2272-83, 1999.

De Perrot M. Berney T. Bühler L. Delgadillo X. Mentha G. Morel P. Management of bleeding pseudoaneurysms in patients with pancreatitis. *Br J Surg* 86:29-32, 1999.

Delgado J. Macias J. Pineda JA. Corzo JE. Gonzalez-Moreno MP. de la Rosa R. Sanchez-Quijano A. Leal M. Lissen E. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodeficiency virus type-1-infected patients. *Am J Tropical Med Hygien* 61:766-9, 1999.

Dickson AP. Imrie CW. The incidence and prognosis of body wall ecchymosis in acute pancreatitis. *Surg Gyn Obst* 159:343-7, 1984.

Di Martino V. Ezenfis J. Benhamou Y. Bernard B. Opolon P. Bricaire F. Poynard T. Severe acute pancreatitis related to the use of nelfinavir in HIV infection: report of a case with positive rechallenge. *AIDS*. 13:1421-3, 1999.

Doepel M. Eriksson J. Halme L. Kumpulainen T. Höckerstedt K. Good long-term results in patients surviving severe acute pancreatitis. *Br J Surg*. 80:1583-6, 1993.

Dominguez-Munoz JE. Carballo F. Garcia MJ. de Diego JM. Rabago L. Simon MA. de la Morena J. Clinical usefulness of polymorphonuclear elastase in predicting the severity of acute pancreatitis: results of a multicentre study. *Br J Surg*. 78:1230-4, 1991.

Dominguez-Munoz JE. Carballo F. Garcia MJ. de Diego JM. Campos R. Yanguela J. de la Morena J. Evaluation of the clinical usefulness of APACHE II and SAPS systems in the initial prognostic classification of acute pancreatitis: a multicenter study. *Pancreas* 8:682-6, 1993.

Douzinas EE. Georgopoulou S. Karmpaliotis DI. Karavasilis J. Andrianakis I. Roussos C. Drainage tube endoscopy: a contribution to the management of severe acute pancreatitis? *Intensive Care Med* 23:1171-3, 1997.

Dybowski R. Weller P. Chang R. Gant V. Prediction of outcome in critically ill patients using artificial neural network synthesised by genetic algorithm. *Lancet*. 347:1146-50, 1996.

Dörffel T. Wruck T. Ruckert RI. Romaniuk P. Dörffel Q. Wermke W. Vascular complications in acute pancreatitis assessed by color duplex ultrasonography. *Pancreas* 21:126-33, 2000.

Eachempati SR Hydo LJ Barie PS. Severity scoring for prognostication in patients with severe acute pancreatitis: Comparative analysis of the Ranson score and the APACHE III. Arch Surg 137:730-6, 2002.

Eatock FC. Brombacher GD. Steven A. Imrie CW. McKay CJ. Carter R. Nasogastric feeding in severe acute pancreatitis may be practical and safe. *Internat J Pancreatol* 28:23-9, 2000.

Echenique AM. Sleeman D. Yrizarry J. Scagnelli T. Guerra JJ Jr. Casillas VJ. Huson H. Russell E. Percutaneous catheter-directed debridement of infected pancreatic necrosis: results in 20 patients. *J Vasc Intervent Radiol* 9:565-71, 1998.

Eisele B. Lamy M. Thijs LG. Keinecke HO. Schuster HP. Matthias FR. Fourrier F. Heinrichs H. Delvos U. Antithrombin III in patients with severe sepsis. A randomised, placebo-controlled, double-blind, multicenter trial plus a meta-analysis on all randomised, placebo-controlled, douple-blind trials with antithrombin III in severe sepsis. *Intensive Care Med* 24:663-72, 1998.

Eland IA. Sturkenboom CM. Wilson JHP. Stricker BH. Incidence and mortality of acute pancreatitis between 1985 and 1995. *Scand J Gastroenterol* 10:1110-16, 2000.

Elman R. Arneson N. Graham EA. Value of blood amylase estimation in the diagnosis of pancreatic disease: a clinical study. *Arch Surg* 19:943-67, 1929.

Enquist IF. Gliedman ML. Gross autopsy findings in cases of fatal pancreatitis. *Arch Surg* 77:985-991, 1958.

Essink-Bot ML. Krabbe PF. Bonsel GJ. Aaronson NK. An empirical comparison of four generic health status measures. The Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts, and the EuroQol instrument. *Med Care*. 35:522-37, 1997.

Fagniez PL. Rotman N. Kracht M. Direct retroperitoneal approach to necrosis in severe acute pancreatitis. *Br J Surg* 76:264-7, 1989.

Fagon JY. Chastre J. Novara A. Medioni P. Gibert C. Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the ODIN model. *Intensive Care Med*. 19:137-44, 1993.

Fan ST. Choi TK. Lai CS. Wong J. Influence of age on mortality from acute pancreatitis. *Br J Surg* 75:463, 1988.

Fan ST. Choi TK. Lai EC. Wong J. Prediction of severity of acute pancreatitis: an alternative approach. *Gut* 30:1591-5, 1989.

Fan ST. Lai EC. Mok FP. Lo CM. Zheng SS. Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med*. 328:228-32, 1993.

Feldstein JD. Johnson FR. Kallick CA. Doolas A. Acute hemorrhagic pancreatitis and pseudocyst due to mumps. *Ann Surg* 180:85-8, 1974.

Feller JH. Brown RA. Toussaint GPM. Thompson AG. Changing methods in the treatment of severe pancreatitis. *Am J Surg* 127:196-201, 1974.

Fenton-Lee D. Imrie CW. Pancreatic necrosis: assessment of outcome related to quality of life and cost of management. *Br J Surg* 80:1579-82, 1993.

Fernandez-Cruz L. Taragona EM. Cugat E. Alcaraz A. Oppenheimer F. Acute pancreatitis after renal transplantation. *Br J Surg* 76:1132-5, 1989.

Fernandez-Cruz L. Navarro S. Castells A. Saenz A. Late outcome after acute pancreatitis: functional impairment and gastrointestinal tract complications. *World J Surg* 21:169-72, 1997.

Fernandez-del Castillo C. Harringer W. Warshaw AL. Vlahakes GJ. Koski G. Zaslavsky AM. Rattner DW. Risk factors for pancreatic cellular injury after cardiopulmonary bypass. *N Engl J Med* 19:783-91, 1990.

Fernandez-del Castillo C. Rattner DW. Makary MA. Mostafavi A. McGrath D. Warshaw AL. Debridement and closed packing for the treatment of necrotizing pancreatitis. *Ann Surg* 228:676-84, 1998.

Fiedler F. Jauernig G. Keim V. Richter A. Bender HJ. Octreotide treatment in patients with necrotizing pancreatitis and pulmonary failure. *Intensive Care Med* 22:909-15, 1996.

Fitzgerald P. Medical anecdotes concerning some disease of the pancreas. In : Fitzgerald P.J. (ed). The Pancreas. Baltimore, William&Wilkins 1980:1-29.

Flaherty J. Bradley EL 3rd. Acute pancreatitis as a complication of polyarteritis nodosa. *Int J Pancreatol.* 25:53-7, 1999.

Fotoohl M. D'Agostino HB. Wollman B. Chon K. Shahrokni S. Van Sonnenberg E. Persistent pancreaticocutaneous fistula after percutaneous drainage of pancreatic fluid collections: Role of cause and severity of pancreatitis. *Radiology* 213:573-8, 1999.

Formela LJ. Galloway SW. Kingsnorth AN. Inflammatory mediators in acute pancreatitis. *Br J Surg* 82:6-13, 1995.

Forni LG. Hilton PJ. Continuous hemofiltration in the treatment of acute renal failure. *N Engl J Med* 336:1303-9, 1997.

Francombe J. Kingsnorth N. Tunn E. Case report. Panniculitis, arthritis and pancreatitis. *Br J Rheum* 34:680-3, 1995.

Freeny PC. Hauptmann E. Althaus SJ. Traverso LW. Sinanan M.
Percutaneous CT-guided catheter drainage of infected acute necrotizing pancreatitis: techniques and results. *AJR. American Journal of Roentgenology.* 170:969-75, 1998.

Frey CF. Gallstone pancreatitis. *Surg Clinic North Am* 61:923-38, 1981.

Frost L. Pedersen RS. Ostgaard SE. Hansen HE. Prognosis in acute pancreatitis complicated by acute renal failure requiring dialysis. *Scand J Urol Nephrol* 24:257-60, 1990.

Fry DE. Pearlstein R. Fulton RL. Polk HC. Multiple system organ failure: the role of uncontrolled infection. *Arch Surg* 115:136-140, 1980.

Fujita N. Matsumoto K. Shiga N. Nonaka A. Koya Y. Ogawa H. Tsuda T. Tomita M. Fukami T. Asahara M. Kinoshita Y. Hatani M. A rare case of severe acute pancreatitis complicated with pancreatic pseudocysts, obstructive jaundice and intraperitoneal hemorrhage. Int Med 35:785-90, 1996.

Fung AS. Tsiotos GG. Sarr MG. ERCP-induced acute necrotizing pancreatitis: is it a more severe disease? *Pancreas* 15:217-21, 1997.

Funnell IC. Bornman PC. Weakley SP. Terblanche J. Marks IN. Obesity: an important prognostic factor in acute pancreatitis. *Br J Surg*. 80:484-6, 1993.

Fusco MA. Martin RS. Chang MC. Estimation of intra-abdominal pressure by bladder pressure measurement: Validity and methodology. *J Trauma* 50:297-302, 2001.

Fölsch UR. Nitsche R. Ludtke R. Hilgers RA. Creutzfeldt W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med* 336:237-42, 1997.

Gambiez LP. Denimal FA. Porte HL. Saudemont A. Chambon JP. Quandalle PA. Retroperitoneal approach and endoscopic management of peripancreatic necrosis collections. *Arch Surg* 133:66-72, 1998.

Ganaha F. Yamada T. Yorozu N. Ujita M. Irie T. Fukuda Y. Fukuda K. Tada S. Vascular access system for continuous arterial infusion of a protease inhibitor in acute necrotizing pancreatitis. *Cardiovasc Intervent Radiol* 22:436-8, 1999.

Garnacho-Montero J. Madrazo-Osuna J. García-Garmendia JL. Ortiz-Leyba C. Jiménez-Jiménez FJ. Barrero-Almodóvar A. Garnacho-Montero MC. Moyano-Del-Estad MR. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. *Intensive Care Med* 27:1288-96, 2001.

Garrington T. Bensard D. Ingram JD. Silliman CC. Successful management with octreotide of a child with L-asparaginase induced hemorrhagic pancreatitis. *Medical & Pediatric Oncology* 30:106-9, 1998.

Gates LK. Ulrich CD. Whitcomb DC. Hereditary pancreatitis: Gene defects and their implications. *Surg Clin N Am* 79:711-22, 1999.

Gecelter G. Fahoum B. Gardezi S. Schein M. Abdominal compartment syndrome in severe acute pancreatitis: An indication for a decompressing laparotomy? *Dig Surg* 19:402-5, 2002.

Gerzof SG. Banks PA. Robbins AH. Johnson WC. Spechler SJ. Wetzner SM. Snider JM. Langevin RE. Jay ME. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. *Gastroenterology*. 93:1315-20, 1987.

Gloor B. Müller CA. Worni M. Martignoni E. Uhl W. Büchler. Late mortality in patients with severe acute pancreatitis. *Br J Surg* 88:975-9, 2001a.

Gloor B. Müller CA. Worni M. Stahel PF. Redaelli C. Uhl W. Büchler MW. Pancreatic infection in severe pancreatitis. The role of fungus and multiresistant organisms. *Arch Surg* 136:592-97, 2001b.

Goebell H. Ammaann R. Herfarth C et al. A double-blind trial of synthetic salmon calcitonin in the treatment of acute pancreatitis. *Scand J Gastroenterol* 14:881-9, 1979.

Goldin E. Libson E. Wengrower D. Antal S. Kovacs Z. Rachmilewitz D. Severe acute pancreatitis as the presenting symptom of primary sclerosing cholangitis: treatment by endoscopic insertion of a biliary stent. *Internat Surg* 75:58-60, 1990.

Goldberg PB. Long WB. Oleaga JA. Mackie JA. Choledochocele as a cause of recurrent pancreatitis. *Gastroenterology* 78:1041-5, 1980.

Golub R. Cantu R Jr. Tan M. The prediction of common bile duct stones using a neural network. *J Am Coll Surgeon* 187:584-90, 1998.

Gonzales Ramallo VJ. Muino Migues A. Torres Segovia FJ. Necrotizing pancreatitis and enalapril. *Eur J Med* 1:123, 1992.

Gooby Toedt DM. Byrd JC. Omori D. Coxsackievirus-associated pancreatitis mimicking metastatic carcinoma. *South Medical J* 89:441-3, 1996.

Goris RJ. te Boekhorst TP. Nuytinck JK. Gimbrere JS. Multiple-organ failure. Generalized autodestructive inflammation?. *Arch Surg.* 120:1109-15, 1985.

Grewe M. Tsiotos GG. Luque de-Leon E. Sarr MG. Fungal infection in acute necrotizing pancreatitis. *J Am Coll Surg.* 188:408-14, 1999.

Grey Turner G. Local discoloration of abdominal wall as a sign of acute pancreatitis. *Br J Surg* 7:394-5, 1919.

Gross MLP. Fowler CJ. Ho R. Russell RCG. Harrison MJG. Peripheral neuropathy complicating pancreatitis and major pancreatic surgery. *J Neurol Neurosurg Psych* 51:1341-4, 1998.

Gross V. Scholmerich J. Leser HG. Salm R. Lausen M. Ruckauer K. Schoffel U. Lay L. Heinisch A. Farthmann EH. Granulocyte elastase in assessment of severity of acute pancreatitis. Comparison with acute-phase proteins C-reactive protein, alpha 1-antitrypsin, and protease inhibitor alpha 2-macroglobulin. *Dig Dis Sci* 35:97-105, 1990.

Grönroos J. Nevalainen T. Increased consentrations of synovial-type phospolipase A2 in serum and pulmonary and renal complications in acute pancreatitis. *Digestion* 52:232-236, 1992.

Grönroos JM. Hietaranta AJ. Kemppainen EA. Nevalainen TJ. Phospholipases A2--what are they and what is their clinical significance in acute pancreatitis? *Ann Chir Gyn* 87:196-9, 1998.

Grönroos JM. Nylamo EI. Mortality in acute pancreatitis in Turku University Central Hospital 1971-1995. *Hepato-Gastroenterol* 46:2572-4, 1999.

Gudgeon AM. Heath DI Hurley P. Jehanli A. Patel G. Wilson C. Shenkin A. Austen BM. Imrie CW. Hermon-Taylor J. Trypsinogen activation peptides assay in the early prediction of severity of acute pancreatitis. *Lancet* 335:4-8, 1990.

Gullo L. Cavicchi L. Tomassetti P. Spagnolo C. Freyrie A. D'Addato M. Effects of ischemia on the human pancreas. *Gastroenterology.* 111:1033-8, 1996.

Gutman M. Inbar M. Klausner JM. Metastases-induced acute pancreatitis: a rare presentation of cancer. *Eur J Surg Oncol* 19:302-4, 1993.

Hamad GG. Broderick TJ. Laparoscopic pancreatic necrosectomy. *J Laparoendosc Advanc Surg Techn* Part A. 10:115-8, 2000.

Hantson P. Mahieu P. Pancreatic injury following acute methanol poisoning. *J Toxicol - Clin Toxicol* 38:297-303, 2000.

Hariri M. Slivka A. Carr-Locke DL. Banks PA. Pseudocyst drainage predisposes to infection when pancreatic necrosis is unrecognized. *Am J Gastroenterol* 89:1781-4, 1994.

Hastings OM. Jain KM. Khademi M. Lazaro EJ. Intrasplenic pancreatic pseudocyst complicating severe acute pancreatitis. *Am J Gastroenterol* 69:182-6, 1978.

Haybittle JL. Blamey RW. Elston CW. Johnson J. Doyle PJ. Campbell FC. Nicholson RI. Griffiths K. A prognostic index in primary breast cancer. *Br J Cancer* 45:361-6, 1982.

Hays RD. Sherbourne CD. Mazel RM. The RAND 36-Item Health Survey 1.0. *Health Economics.* 2:217-27, 1993.

Heath DI. Cruickshank A. Gudgeon M. Jehanli A. Shenkin A. Imrie CW. Role of interleukin-6 in mediating the acute phase protein response and potential as an early means of severity assessment in acute pancreatitis. *Gut* 34:41-5, 1993.

Heath DI. Wilson C. Gudgeon AM. Jehanli A. Shenkin A. Imrie CW. TAP concentrations in peritoneal fluid of patients with acute pancreatitis and their relation to the presence of histologically confirmed pancreatic necrosis. *Gut* 35:1311-5, 1994.

Heath DI. Cruickshank A. Gudgeon AM. Jehanli A. Shenkin A. Imrie CW. The relationship between pancreatic enzyme release and activation and acute-phase protein response in patients with acute pancreatitis. *Pancreas* 10:347-53, 1995.

Hebert PC. Drummond AJ. Singer J. Bernard GR. Russell JA. A simple multiple system organ failure scoring system predicts mortality of patients who have sepsis syndrome. *Chest.* 104:230-5, 1993.

Hebert PC. Wells G. Blajchman MA. Marshall J. Martin C. Pagliarello G. Tweeddale M. Schweitzer I. Yetisir E. A multicentre, randomized controlled clinical trial of transfusion requirements in critical care (TRICC). *N Engl J Med* 340:409-17, 1999.

Hedström J. Leinonen J. Sainio V. Stenman U-H. Time-resolved immunofluorometric assay of trypsin-2 complexed with alpha1-antitrypsin in serum. *Clin Chem* 40:1761-5, 1994.

Hedström J. Korvuo A. Kenkimäki P. Tikanoja S. Haapiainen R. Kivilaakso E. Stenman U-H. Urinary trypsinogen-2 test strip for acute pancreatitis. *Lancet* 347:729-31, 1996a.

Hedström J. Sainio V. Kemppainen E. Haapiainen R. Kivilaakso E. Schröder T. Leinonen J. Stenman UH. Serum complex of trypsin 2 and alpha 1 antitrypsin as diagnostic and prognostic marker of acute pancreatitis: clinical study in consecutive patients. *BMJ* 313:333-7, 1996b.

Hedström J. Sainio V. Kemppainen E. Haapiainen R. Kivilaakso E. Schauman K-O. Stenman U-H. Urine trypsinogen 2 as a marker of acute pancreatitis. *Clin Chem* 42:685-90, 1996c.

Heller SJ. Noordhoek E. Tenner SM. Ramagopal V. Abramowitz M. Hughes M. Banks PA. Pleural effusion as a predictor of severity in acute pancreatitis. *Pancreas* 15:222-5, 1997.

Heyland DK. Guyatt G, Cook DJ, Meade M, Juniper E, Cronin L. Gafni A. Frequency and methodologic rigor of quality-of-life assessments in the critical care literature. *Crit Care Med* 26:591-8, 1998.

Heyland DK. Hopman W. Coo H. Tranmer J. McColl MA. Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. *Crit Care Medicine.* 28:3599-605, 2000.

Hietaranta A. Kemppainen E. Puolakkainen P. Sainio V. Haapiainen R. Peuravuori H. Kivilaakso E. Nevalainen T. Extracellular phospholipases A2 in relation to systemic inflammatory response syndrome (SIRS) and systemic complications in severe acute pancreatitis. *Pancreas* 18:385-91, 1999.

Hirota M. Nozawa F. Okabe A. Shibata M. Beppu T. Shimada S. Egami H. Yamaguchi Y. Ikei S. Okajima T. Okamoto K. Ogawa M. Relationship between plasma cytokine concentration and multiple organ failure in patients with acute pancreatitis. *Pancreas* 21:141-6, 2000.

Ho HS. Frey CF. Gastrointestinal and pancreatic complications associated with severe pancreatitis. *Arch Surg* 130:817-23, 1995.

Ho HS. Frey CF. The role of antibiotic prophylaxis in severe acute pancreatitis. *Arch Surg.* 132:487-93, 1997.

Hoerauf A. Hammer S. Muller-Myhsok B. Rupprecht H. Intra-abdominal Candida infection during acute necrotizing pancreatitis has a high prevalence and is associated with increased mortality. *Crit Care Med* 26:2010-5, 1998.

Hollo G. Tarjanyi M. Varga M. Flautner L. Retinopathy of pancreatitis indicates multiple-organ failure and poor prognosis in severe acute pancreatitis. *Acta Ophthalmol* 72:114-7, 1994.

Howard JM. Delayed debridement and external drainage of massive pancreatic or peripancreatic necrosis. *Surg Gynecol Obstet* 168:25-29, 1989.

Hwang TL. Chang KY. Ho YP. Contrast-enhanced dynamic computed tomography does not aggravate the clinical severity of patients with severe acute pancreatitis: reevaluation of the effect of intravenous contrast medium on the severity of acute pancreatitis. *Arch Surg* 135:287-90, 2000.

Hynninen M. Valtonen M. Markkanen H. Vaara M. Kuusela P. Jousela I. Piilonen A. Takkunen O. Interleukin 1 receptor antagonist and E-selectin concentrations: a comparison in patients with severe acute pancreatitis and severe sepsis. *J Crit Care* 14:63-8, 1999.

Hynninen M. Valtonen M. Markkanen H. Vaara M. Kuusela P. Jousela I. Piilonen A. Takkunen O. Intramucosal pH and endotoxin and cytokine release in severe acute pancreatitis. *Shock* 13:79-82, 2000.

Ikei S. Ogawa M. Yamaguchi Y. Blood concentrations of polymorphonuclear leucocyte elastase and interleukin-6 are indicators for the occurrence of multiple organ failures at the early stage of acute pancreatitis. *J Gastroenterol Hepatol* 13:1274-83, 1998.

Imrie CW. Observations on acute pancreatitis. *Br J Surg.* 61:539-44, 1974.

Imrie CW. Benjamin IS. Ferguson JC. McKay AJ. Mackenzie I. O'Neill.J. Blumgart LH. A single centre double blind trial of trasylol therapy in primary acute pancreatitis. *Br J Surg* 65:337, 1978a.

Imrie CW. McKay AJ. Benjamin IS. Blumgart LH. Secondary acute pancreatitis: aetiology, prevention, diagnosis and management. *Br J Surg* 65:399-402, 1978b.

Inagaki T. Hoshino M. Hayakawa T. Ohara H. Yamada T. Yamada H. Iida M. Nakazawa T. Ogasawara T. Uchida A. Hasegawa C. Miyaji M. Takeuchi T. Interleukin-6 is a useful marker for early prediction of the severity of acute pancreatitis. *Pancreas* 14:1-8, 1997.

Isenmann R. Buchler M. Uhl W. Malfertheiner P. Martini M. Beger HG. Pancreatic necrosis: an early finding in severe acute pancreatitis. *Pancreas.* 8:358-61, 1993.

Isenmann R. Rau B. Beger HG. Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. *Br J Surg* 86:1020-4, 1999.

Isenmann R. Rau B. Beger G. Early severe acute pancreatitis: Characteristics of a new suobgroup. *Pancreas* 22:274-8, 2001.

Itkonen O. Koivunen E. Hurme M. Alfthan H. Schröder T. Stenman U-H. Time-resolved immunofluorometric assays for trypsinogen-1 and 2 in serum reveal preferential elevation of trypsinogen-2 in pancreatitis. *J Lab Clin Med* 712-8, 1990.

Jaakkola M. Nordback I. Pancreatitis in Finland between 1970 and 1989. *Gut* 34:1255-60, 1993.

Jacobs JW. De Sonnaville PB. Hulsmans HM. van Rinsum AC. Bijlsma JW. Polyarticular heterotopic ossification complicating critical illness. *Rheumatol (Oxford)* 38:1145-9, 1999.

Jacobs ML. Daggett WM. Civette JM. Vasu MA. Lawson DW. Warshaw AL. Nardi GL. Bartlett MK. Acute pancreatitis: analysis of factors influencing survival. *Ann Surg* 185:43-51, 1977.

Johnson CD. Kingsnorth AN. Imrie CW. McMahon MJ. Neoptolemos JP. McKay C. Toh SK. Skaife P. Leeder PC. Wilson P. Larvin M. Curtis LD. Double blind, randomised, placebo controlled study of a

platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. *Gut* 48:62-9, 2001.

Kairisto V. Poola A. Software for illustrative presentation of basic clinical characteristics of laboratory tests--GraphROC for Windows. *Scand J Clin Lab Invest* 222:S43-60, 1995.

Kalfarentzos FE. Karavias DD. Karatzas TM. Alevizatos BA. Androulakis JA. Total parenteral nutrition in severe acute pancreatitis. *J Am Coll Nutr* 10:156-62, 1991.

Kalfarentzos F. Kehagias J. Mead N. Kokkinis K. Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg* 84:1665-9, 1997.

Kalfarentzos FE. Kehagias J. Kakkos SK. Petsas T. Kokkinis K. Gogos CA. Androulakis JA. Treatment of patients with severe acute necrotizing pancreatitis based on prospective evaluation. *Hepato Gastroenterol* 46:3249-56, 1999.

Kato T. Morita T. Fujita M. Miyasaka Y. Senmaru N. Hiraoka K. Horita S. Kondo S. Kato H. Ischemic stricture of the small intestine associated with acute pancreatitis. *Int J Pancreatol* 24:237-42, 1998.

Kaufmann P. Tilz GP. Demel U. Wachter H. Kreijs GJ. Fuchs D. Neopterin plasma concentrations predict the course of severe acute pancreatitis. *Clin Chem Lab Med* 36:29-34, 1998.

Karimgani I. Porter KA. Langevin RE. Banks PA. Prognostic factors in sterile pancreatic necrosis. *Gastroenterology*. 103:1636-40, 1992.

Kemppainen E, Sainio V, Haapiainen R, Kivisaari L, Kivilaasko E, Puolakkainen P. Early localization of necrosis by contrast-enhanced computed tomography can predict outcome in severe acute pancreatitis. *Br J Surg* 83:924-9, 1996.

Kemppainen EA. Hedstrom JI. Puolakkainen PA. Sainio VS. Haapiainen RK. Perhoniemi V. Osman S. Kivilaakso EO. Stenman UH. Rapid measurement of urinary trypsinogen-2 as a screening test for acute pancreatitis. *N Engl J Med* 336:1788-93, 1997.

Kemppainen E. Puolakkainen P. Leppäniemi A. Hietaranta A. Grönroos J. Haapiainen R. Diagnosis of acute pancreatitis. *Ann Chir Gyn* 87:191-4, 1998a.

Kemppainen EA. Hedström JI. Puolakkainen PA. Haapiainen RK. Stenman UH. Advances in the laboratory diagnostics of acute pancreatitis. *Ann Med* 30:169-75, 1998b.

Kennedy JD. Talbot IC. Tanner MS. Severe pancreatitis and fatty liver progressing to cirrhosis associated with Coxsackie B4 infection in a three year old with alpha-1-antitrypsin deficiency. *Acta Paediat Scand* 75:336-9, 1986.

Khan AA. Parekh D. Cho Y. Ruiz R. Selby RR. Jabbour N. Genyk YS. Mateo R. Improved prediction of outcome in patients with severe acute pancreatitis by the APACHE II score at 48 hours after hospital admission compared with the APACHE II score at admission. Acute Physiology and Chronic Health Evaluation. *Arch Surg.* 137:1136-40, 2002.

Kimland M. Russick C. Marks WH. Borgström A. Immunoreactive anionic and cationic trypsin in human serum. *Clin Chim Acta* 184:31-46, 1989.

Kingsnorth AN. Galloway SW. Formela LJ. Randomized, double-blind phase II trial of Lexipafant, a platelet-activating factor antagonist, in human acute pancreatitis. *Br J Surg* 82:1414-20, 1995.

Kivilaakso E. Fraki O. Nikki P. Lempinen M. Resection of the pancreas for acute fulminant pancreatitis. *Surg Gynecol Obstet* 152:493-8, 1981.

Kivilaakso E. Lempinen M. Mäkelainen A. Nikki P. Schröder T. Pancreatic resection versus peritoneal lavation for acute fulminant pancreatitis. A randomized prospective study. *Ann Surg* 199:426-31, 1984.

Kivisaari L. Somer K. Standertskjold-Nordenstam CG. Schröder T, Kivilaakso E. Early detection of acute fulminant pancreatitis by contrast-enhanced computed tomography. *Scand J Gastroenetrol* 18:39-41, 1983.

Knaus WA. Draper EA. Wagner DP. Zimmerman JE. APACHE II: a severity of disease classification system. C*rit Care Med* 13:818-29, 1985a.

Knaus WA. Draper EA. Wagner DP. Zimmerman JE. Prognosis in acute organ-system failure. *Ann Surg* 202:685-93, 1985b.

Kriwanek S. Armbruster C. Beckerhinn P. Dittrich K. Redl E. Improved results after aggressive treatment of colonic involvement in necrotizing pancreatitis. *Hepato Gastroenterol* 43:1627-32, 1996.

Kriwanek S. Armbruster C. Beckerhinn P. Dittrich K. Redl E. Improved results after aggressive treatment of colonic involvement in necrotizing pancreatitis. *Hepato Gastroenterol* 44:274-8, 1997.

Kriwanek S. Gschwantler M. Beckerhinn P. Armbruster C. Roka R. Complications after surgery for necrotising pancreatitis: risk factors and prognosis. *Eur J Surg* 165:952-7, 1999.

Krokos NV. Karavias D. Tsakis A. Tepetes K. Ramos E. Todo S. Fung JJ. Starzl TE. Acute pancreatitis after liver transplantation: incidence and contributing factors. *Transplant Int* 8:1-7, 1995.

Kronborg O. Bulow S. Joergensen PM. Svendsen LB. A randomized double-blind trial of glucagon in treatment of first attack of severe acute pancreatitis without associated biliary disease. *Am J Gastroenterol* 73:423-5, 1980.

Kuo PC. Plotkin JS. Johnson LB. Acute pancreatitis and fulminant hepatic failure. *J Am Coll Surg* 187:522-8, 1998.

Kylanpää-Bäck M. Kemppainen E. Puolakkainen P. Hedström J. Haapiainen R. Perhoniemi V. Kivilaakso E. Korvuo A. Stenman U. Reliable screening for acute pancreatitis with rapid urine trypsinogen-2 test strip. Br J Surg 87:49-52, 2000.

Kyösola K. Fock G. Fatal pancreatitis. A clinical and post-mortem study on 24 cases of acute pancreatitis with fatal outcome, with special reference to some clinical aspects of autopsy findings. *Ann Chir Gynaecol Fenniae* 64:91-5, 1975.

Lankisch PG. Schirren CA. Increased body weight as a prognostic parameter for complications in the course of acute pancreatitis. *Pancreas.* 5:626-9, 1990.

Lankisch PG. Droge M. Becher R. Pleural effusions: a new negative prognostic parameter for acute pancreatitis. *Am J Gastroenterol* 89:1849-51, 1994.

Lankisch PG. Burchard-Reckert S. Petersen M. Lehnick D. Schirren CA. Stockmann F. Kohler H. Etiology and age have only a limited influence on the course of acute pancreatitis. *Pancreas* 13:344-9, 1996.

Lankisch PG. Pflichthofer D. Lehnick D. Acute pancreatitis: which patient is most at risk? *Pancreas* 19:321-4, 1999.

Lankisch PG. Struckmann K. Assmus C. Lehnick D. Maisonneuve P. Lowenfels AB. Do we need computed tomography examination in all patients with acute pancreatitis within 72 h after admission to hospital for the detection of pancreatic necrosis? *Scand J Gastroenterol* 36:432-436, 2001.

Larvin M. McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. *Lancet* 2:201-5, 1989.

Leese T. Holliday M. Heath D. Hall AW. Bell PRF. Multicentre clinical trial of low volume fresh frozen plasma therapy in acute pancreatitis. *Br J Surg* 74:907-911, 1987.

Lefor AT. Vuocolo P. Parker FB Jr. Sillin LF. Pancreatic complications following cardiopulmonary bypass: factors influencing mortality. *Arch Surg* 127:1225-31, 1992.

Le Gall JR. Klar J. Lemeshow S. Saulnier F. Alberti C. Artigas A. Teres D. The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. *JAMA.* 276:802-10, 1996.

Leppäniemi A Necrosectomy for severe acute pancreatitis. In: Vincent J-L (ed). 2003 Yearbook of Intensive Care and Emergency Medicine, Springer-Verlag Berlin Heidlberg 838-46, 2003.

Leser HG. Gross V. Scheibenbogen C. Heinisch A. Salm R. Lausen M. Ruckhauer K. Andreesen R. Farthmann EH. Scholmerich J. Elevation of serum interleukin-6 concentration precedes acute-phase response and reflects severity in acute pancreatitis. *Gastroenterology* 101:782-785, 1991.

Lin X-Z. Wang S-S. Tsai Y-T. Lee S-D. Shiesh S-C. Pan H-B. Su C-H. Lin C-Y. Serum amylase, isoamylase, and lipase in the acute abdomen: their diagnostic value for acute pancreatitis. *J Clin Gastroenterol* 11:47-52, 1989.

Ljutic D. Piplovic-Vukovic T. Raos V. Andrews P. Acute renal failure as a complication of acute pancreatitis. *Ren Fail* 18:629-33, 1996.

Lobo DN. Memon MA. Allison SP. Rowlands BJ. Evolution of nutritional support in acute pancreatitis. *Br J Surg* 87:695-707, 2000.

Luiten EJ. Hop WC. Lange JF. Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. *Ann Surg* 222:57-65, 1995.

Luiten EJ. Hop WC. Endtz HP. Bruining HA. Prognostic importance of gram-negative intestinal colonization preceding pancreatic infection in severe acute pancreatitis. Results of a controlled clinical trial of selective decontamination. *Int Care Med.* 24:438-45, 1998.

Lukash WM. Complications of acute pancreatitis. Unusual sequelae in 100 cases. *Arch Surg* 94:848-52, 1967.

Lumsden A. Bradley EL 3rd. Secondary pancreatic infections. *Surg Gyn Obst* 170:459-67, 1990.

Lundin J. Artificial neural networks in outcome prediction. *Ann Chirg Gynaecol* 87:128-30, 1998

Lundin M. Lundin J. Burke HB. Toikkanen S. Pylkkänen L. Joensuu H. Artificial neural networks applied to survival prediction in breast cancer. *Oncology.* 57:281-6, 1999.

Malcynski JT. Iwanow IC. Burchard KW. Severe pancreatitis. Determinants of mortality in a tertiary referral center. *Arch Surg* 131:242-6, 1996.

Mann DV. Hershman MJ. Hittinger R. Glazer G. Multicentre audit of death from acute pancreatitis. *Br J Surg* 81:890-3, 1994.

Margulies AG. Akin HE. Marsupialization of the pancreas for infected pancreatic necrosis. *Am Surg* 63:261-5, 1997.

Maringhini A. Ciambra M. Baccelliere P. Raimando M. Orlando A. Tine F. Grasso R. Randazzo MA. Barresi L. Gullo D. Domenici MM. Pagliaro L. Biliary sludge and gaalstones in pregnancy: Incidenec, risk factors, and natural history. *Ann Int Med* 119:116-20, 1993.

Maringhini A. Ciambra M. Patti R. Randazzo MA. Dardanoni G. Mancuso L. Termini A. Pagliaro L. Ascites, pleural, and pericardial effusions in acute pancreatitis. A prospective study of incidence, natural history, and prognostic role. *Dig Dis Sci* 41:848-52, 1996.

Maringhini A. Uomo G. Patti R. Rabitti P. Termini A. Cavallera A. Dardanoni G. Manes G. Ciambra M. Laccetti M. Biffarella P. Pagliaro L. Pseudocysts in acute nonalcoholic pancreatitis: incidence and natural history. *Dig Dis Sci* 44:1669-73, 1999.

Maringhini A. Lankisch MR. Zinsmeister AR. Melton LJ III. Dimagno EP. Acute pancreatitis in the postpartum period: A population-based case-control study. *Mayo Clin Proc* 75:361-4, 2000.

Marshall JC. Cook DJ. Christou NV. Bernard GR. Sprung CL. Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 23:1638-52, 1995.

Martinez J. Sanchez-Paya J. Palazon JM. Aparicio JR. Pico A. Perez-Mateo M. Obesity: a prognostic factor of severity in acute pancreatitis. *Pancreas* 19:15-20, 1999.

Maunoury V. Brunetaud JM. Ghisbain H. Leroy B. Saudemont A. Cortot A. Quandalle P. Paris JC. Severe acute pancreatitis following laser treatment of periampullary villous adenoma.
Dig Dis Sci 38:382-3, 1993.

May LW. Legha P. Mori T. Laparoscopic pancreatic cystogastrostoma: The first operation in the new field of intraluminar laparoscopic surgery. *Surg Endosc* 8:235, 1994.

Mayer AD. McMahon MJ. Corfield AP. Cooper MJ. Williamson RC. Dickson AP. Shearer MG. Imrie CW. Controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis. *N Engl J Med* 312:399-404, 1985.

Mayer JM. Raraty M. Slavin J. Kemppainen E. Fitzpatrick J. Hietaranta A. Puolakkainen P. Beger HG. Neoptolemos JP. Serum amyloid A is a better early predictor of severity than C-reactive protein in acute pancreatitis. *Br J Surg* 89:163-71, 2002.

McClave SA. Snider H. Owens N. Sexton LK. Clinical nutrition in pancreatitis. *Dig Dis Sci.* 42:2035-44, 1997.

McCutcheon AD. Reflux of duodenal contents in the pathogenesis of acute pancreatitis. *Gut* 9:296-310, 1968.

McFadden DW. Organ failure and multiple organ failure in pancreatitis. *Pancreas* 1991; 6:S37-43, 1991.

McHorney CA. Ware JE Jr. Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 31:247-63, 1993.

McKay AJ. Imrie CW. O'Neill J. Duncan JG. Is an early ultrsound scan of value in acute pancreatitis? *Br J Surg* 69:369-72, 1982.

McKay CJ. Curran F. Sharples C. Baxter JN. Imrie CW. Prospective placebo-controlled randomized trial of lexipafant in predicted severe acute pancreatitis. *Br J Surg* 84:1239-43, 1997.

McKay CJ. Evans S. Sinclair M. Carter CR. Imrie CW. High early mortality rate from acute pancreatitis in Scotland, 1984-1995. *Br J Surg* 86:1302-1306, 1999.

McMahon MJ. Playforth MJ. Pickford IR. A comparative study of methods for the prediction of severity of attacks of acute pancreatitis. *Br J Surg* 67:22-5, 1980.

Mero M. Changing aetiology of acute pancreatitis. *Ann Chir Gynaecol* 71:126-9, 1982.

Metz CE. Basic principles of ROC analysis. *Seminars in Nuclear Medicine* 8:283-98, 1978.

Metkus AP. Trabulsy PP. Schlobohm RS. Hickey MS. A firefighter with pancreatitis. *Lancet* 348:1702, 1996.

Mier J. Leon EL. Castillo A. Robledo F. Blanco R. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg* 173:71-5, 1997.

Miskovitz P. Scoring of multiple organ dysfunction in patients with severe acute pancreatitis. *Crit Care Med* 30:1390-1, 2002.

Moody FG. Haley-Russell D. Muncy DM. Intestinal transit and bacterial translocation in obstructive pancreatitis. *Dig Dis Sci* 40:1798-1804, 1995.

Miskovitz P. Acute pancreatitis: further insight into mechanisms. *Crit Care Med* 26:816-7, 1998.

Moynihan B. Acute pancreatitis *Ann Surg.* 81:132-42, 1925.

Mujica VR. Barkin JS. Go VLW. And study group participants. Acute pancreatitis secondary to pancreatic carcinoma. *Pancreas* 21:329-32, 2000.

Mueller PR. Miketic LM. Simeone JF. Silverman SG. Saini S. Wittenberg J. Hahn PF. Steiner E. Forman BH. Severe acute pancreatitis after percutaneous biopsy of the pancreas. *AJR. Am J Roentgenol* 151:493-4, 1988.

Müller CA. Uhl W. Printzen G. Gloor B. Bischofberger H. Tcholakov O. Büchler MW. Role of procalcitonin and granulocyte colony stimulating factor in the early prediction of infected necrosis in severe acute pancreatitis. *Gut* 46:233-8, 2000.

Nauck MA. Physiology and pathophysiology of endocrine pancreatic secration.In: Beger HG: et al. (ed). The Pancreas. London, Blackwell Science Volume 1:101-37, 1998.

Neff R. Pancreatic pseudocysts and fluid collection. Percutaneous approaches. *Surg Clin North Am* 81:399-403, 2001.

Neoptolemos JP. Carr-Locke DL. London NJ. Bailey IA. James D. Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. *Lancet* 2:979-83, 1988.

Neoptolemos JP. Kemppainen EA. Mayer JM. Fitzpatrick JM. Raraty MG. Slavin J. Beger HG. Hietaranta AJ. Puolakkainen PA. Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide: a multicentre study. *Lancet* 355:1955-60, 2000.

Nevalainen TJ. Hietaranta AJ. Grönroos JM. Phospholipase A2 in acute pancreatitis: new biochemical and pathological aspects. *Hepato-Gastroenterol* 46:2731-5, 1999.

Niesel HC. Klimpel L. Kaiser H. Bernhardt A. Al-Rafai S. Lang U. Epidural blockade for analgesia and treatment of acute pancreatitis. *Regional Anaesthesia* 14:97-100, 1991.

Nordback I. Value of monitoring amylase activities in patients with pancreatitis. *Lancet*. I(8437):1092, 1985a.

Nordback I. Pessi T. Auvinen O. Autio V. Determination of necrosis in necrotizing pancreatitis. *Br J Surg* 72:225-7, 1985b.

Nordback IH. Auvinen OA. Long-term results after pancreas resection for acute necrotizing pancreatitis. *Br J Surg*. 72:687-9, 1985c.

Nordback I. Auvinen O. Pessi T. Autio V. Complications after pancreatic resection for acute necrotizing pancreatitis. *Acta Chir Scand* 152:49-54, 1986.

Nordback I. Sand J. Saaristo R. Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis – A single-center randomised study. *J Gastrointest Surg* 5:113-19, 2001.

Norman J. Franz M. Riker A. Fabri P. Gower W. Rapid elevation of systemic cytokines during acute pancreatitis and their origination within the pancreas. *Surg Forum* 45:148-50, 1994.

Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. *Am J Surg* 175:76-83, 1998.

Noronha M. Salgadinho A. Ferreira de Almeidea MJ. Dreling DA. Bordalo O. Alcohol and the pancreas. Clinical associations and histopathology of minimal pancreatic inflammation. *Am J Gastroenterol* 76:114-9, 1981.

Ohmoto K. Neishi Y. Miyake I. Yamamoto S. Severe acute pancreatitis associated with hyperlipidemia: report of two cases and review of the literature in Japan.*Hepato-Gastroenterol* 46:2986-90, 1999.

Oishi K. Wada J. Nagake Y. Hida K. Hashimoto H. Hayakawa N. Kashihara N. Makino H. Fatal pancreatitis associated with systemic amyloidosis in a rheumatoid arthritis patient. *J Med* 31:303-10, 2000.

Oleynikov D. Cook C. Sellers B. Mone MC. Barton R. Decreased mortality from necrotizing pancreatitis. *Am J Surg* 176:648-53, 1998.

Opal S. Depalo V. Anti-inflammatory cytokines. *Chest* 117:1162-72, 2000.

Opie EL. The relation of cholelithiasis to disease of the pancreas and to fat necrosis. *Am J Med Sci* 121:27-43, 1901.

Oria A. Ocampo C. Zandalazini H. Chiappetta L. Moran C. Internal drainage of giant acute pseudocysts: the role of video-assisted pancreatic necrosectomy. *Arch Surg* 135:136-40, 2000.

Orlando R 3rd. Quality of life in intensive care unit survivors: a place for outcomes research in critical care. *Crit Care Med* 28:3755-6, 2000.

Osman MO. Jensen SL. Acute pancreatitis: the pathophysiological role of cytokines and integrins. New trends for treatment? *Dig Surg* 16:347-62, 1999.

Osborne DH. Imrie CW. Carter DC. Biliary surgery in the same admission for gallstone associated pancreatitis. *Br J Surg* 68:758-61, 1981.

Paajanen H. Laato M. Jaakkola M. Pulkki K. Niinikoski J. Nordback I. Serum tumour necrosis factor compared with C-reactive protein in the early assessment of severity of acute pancreatitis. *Br J Surg* 82:271-3, 1995.

Panieri E. Krige JE. Bornman PC. Linton DM. Severe necrotizing pancreatitis caused by organophosphate poisoning. *J Clin Gastroenterol.* 25:463-5, 1997.

Papos M. Takacs T. Farkas G. Lang J. Csernay L. Lonovics J. Prognostic role of 99mTc-HM-PAO-leukocyte scintigraphy in acute pancreatitis and in patients with pancreatic pseudocysts. *Pancreas* 14:9-15, 1997.

Paran H. Mayo A. Paran D. Neufeld D. Shwartz I. Zissin R. Singer P. Kaplan O. Skornik Y. Freund U. Octreotide treatment in patients with severe acute pancreatitis. *Dig Dis Sci* 45:2247-51, 2000.

Parithivel VS. Yousuf AM. Albu E. Kaul A. Aydinalp N. Predictors of the severity of acute pancreatitis in patients with HIV infection or AIDS. *Pancreas* 19:133-6, 1999.

Paxton JR. Payne JH. Acute pancreatitis: a statistical review of 307 established cases of acute pancreatitis. *Surg Gynecol Obstet* 86:69-75, 1948.

Paye F. Rotman N. Radier C. Nouira R. Fagniez PL. Percutaneous aspiration for bacteriological studies in patients with necrotizing pancreatitis. *Br J Surg* 85:755-9, 1998.

Paye F. Frileux P. Lehman P. Ollivier JM. Vaillant JC. Parc R. Reoperation for severe pancreatitis: a 10-year experience in a tertiary care center. *Arch Surg* 134:316-21, 1999.

Pederzoli P. Bassi C. Vesentini S. Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surg Gyn Obst* 176:480-3, 1993.

Peek GJ. White S. Scott AD. Hall AW. Moore HM. Sosnowski AW. Firmin RK. Severe acute respiratory distress syndrome secondary to acute pancreatitis successfully treated with extracorporeal membrane oxygenation in three patients. *Ann Surg* 227:572-4, 1998.

Pettilä V. Kaarlola A. Mäkelainen A. Health-related quality of life of multiple organ dysfunction patients one year after intensive care. *Int Care Med.* 26:1473-9, 2000.

Pettilä V. Sepsiksen hoito. *Suomen Lääkärilehti* 4:407-11, 2002.

Pezzilli R. Billi P. Gullo L. Beltrandi E. Maldini M. Mancini R.Incorvaia L. Miglioli M. Behavior or serum soluble interleukin-2 receptor, soluble CD8 and soluble CD4 in the early phase of acute pancreatitis. *Digestion* 55:268-73, 1994.

Pezzilli R. Billi P. Migliori M. Gullo L. Clinical value of pancreatitis-associated protein in acute pancreatitis. *Am J Gastroenterol* 92:1887-90, 1997.

Pezzilli R. Billi P. Morselli-Labate AM. Severity of acute pancreatitis: relationship with etiology, sex and age. *Hepato-Gastroenterol* 45:1859-64, 1998.

Phillips AR. Abu-Zidan FM. Bonham MJ. Cooper GJ. Windsor JA. Amylin and severe acute pancreatitis. *Pancreas* 20:105-6, 2000.

Piironen A. Kivisaari R. Pitkäranta P. Poutanen V-P. Laippala P. Laurila P. Kivisaari L. Contrast-enhanced magnetic resonance imaging for the detection of acute haemorrhagic necrotizing pancreatitis. *Eur Radiol* 7:17-20, 1997.

Piironen A. Kivisaari R. Kemppainen E. Laippala P. Koivisto AM. Poutanen VP. Kivisaari L. Detection of severe acute pancreatitis by contrast-enhanced magnetic resonance imaging. *Eur Radiol* 10:354-61, 2000.

Pine RW. Wertz MJ. Lennard ES. Dellinger EP. Carrico CJ. Minshew BH. Determinants of organ malfunction or death in patients with intra-abdominal sepsis. A discriminant analysis. *Arch Surg*. 118:242-9, 1983.

Planas M. Perez A. Iglesia R. Porta I. Masclans JR. Bermejo B. Severe acute pancreatitis: treatment with somatostatin. *Intensive Care Med* 24:37-9, 1998.

Pofahl WE. Walczak SM. Rhone E. Izenberg SD. Use of an artificial neural network to predict length of stay in acute pancreatitis. *Am Surg.* 64:868-72, 1998.

Pollock AV. Acute pancreatitis: analysis of 100 patients. *BMJ* :6-14, 1959.

Porter KA. Banks PA. Obesity as a predictor of severity in acute pancreatitis. *Int J Pancreatol* 10:247-52, 1991.

Powell JJ. Campbell E. Johnson CD. Siriwardena AK. Survey of antibiotic prophylaxis in acute pancreatitis in the UK and Ireland. *Br J Surg.* 86:320-2, 1999.

Powell JJ. Murchison JT. Fearon KC. Ross JA. Siriwardena AK. Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. *Br J Surg.* 87:1375-81, 2000.

Puolakkainen P. Valtonen V. Paananen A. Schröder T. C-reactive protein (CRP) and serum phospholipase A2 in the assessment of the severity of acute pancreatitis. *Gut*. 28:764-71, 1987.

Puolakkainen PA. Early assessment of acute pancreatitis. A comparative study of computed tomography and laboratory tests. *Acta Chir Scand.* 155:25-30, 1989.

Quinn SF. Finney R. Rosemurgy A. Pieck CG. Splenic artery pseudoaneurysm after placement of percutaneous transgastric catheter for a pancreatic pseudocyst. *AJR* 151:495-6, 1988.

Raat H. Stockx L. De Meester X. Van Steenbergen W. Marchal G. Percutaneous embolization of a splenic arteriovenous fistula related to acute necrotizing pancreatitis. Eur Radiol 9:753, 1999.

Ramin KD. Ramin SM. Richey SD. Cunningham FG. Acute pancreatitis in pregnancy. *Am J Obst Gynecol* 173:187-91, 1995.

Ranson JH. Rifkind KM. Roses DF. Fink SD. Eng K. Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. *Surg, Gynecol Obstet.* 139:69-81, 1974.

Ranson JH. Rifkind KM. Turner JW. Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. *Surg Gynecol Obstet* 143:209-19, 1976.

Ranson JH. Pasternack BS. Statistical methods for quantifying the severity of clinical acute pancreatitis. *J Surg Res.* 22:79-91, 1977.

Ranson JH. Etiological and prognostic factors in human acute pancreatitis: a review. *Am J Gastroenterol.* 77:633-8, 1982.

Ranson JHC. Berman RS. Long peritoneal lavage decreases pancreatic sepsis in acute pancreatitis. *Ann Surg* 211:708-16, 1990.

Ranson JH. Diagnostic standards for acute pancreatitis. *World J Surg* 21:136-42, 1997.

Rau B. Pralle U. Uhl W. Schoenberg MH. Beger HG. Management of sterile necrosis in instances of severe acute pancreatitis. *J Am Coll Surg* 181:279-88, 1995.

Rau B. Pralle U. Mayer JM. Beger HG. Role of ultrasonographically guided fine-needle aspiration cytology in the diagnosis of infected pancreatic necrosis. *Br J Surg* 85:179-84, 1998.

Rau B. Baumgart K. Paszkowski AS. Mayer JM. Beger HG. Clinical relevance of caspase-1 activated cytokines in acute pancreatitis: High correlation of serum interleukin-18 with pancreatic necrosis and systemic complications. *Crit Care Med* 29:1556-62, 2001.

Renner IG. Savage WT 3rd. Pantoja JL. Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. *Dig Dis Sci.* 30:1005-18, 1985.

Renzulli P. Muller C. Uhl W. Scheurer U. Büchler MW. Impacted papilla minor stone in pancreas divisum causing severe acute pancreatitis: a case for early ERCP in acute pancreatitis of unknown origin. *Digestion* 60:281-3, 1999.

Robinson PJ. Sheridan MB. Pancreatitis: computed tomography and magnetic resonance imaging. *Eur Radiology* 10:401-8, 2000.

Roumen RM. Schers TJ. de Boer HH. Goris RJ. Scoring systems for predicting outcome in acute hemorrhagic necrotizing pancreatitis. *Eur J Surg* 158:167-71, 1992.

Runkel NS. Moody FG. Smith GS. Rodriguez LF. LaRocco MT. Miller TA. The role of the gut in the development of sepsis in acute pancreatitis. *J Surg Res* 51:18-23, 1991.

Rünzi M. Layer P. Drug-associated pancreatitis: Facts and fiction. *Pancreas* 13:100-9, 1996.

Räty S. Sand J. Nordback I. Difference in microbes contaminating pancreatic necrosis in biliary and alcoholic pancreatitis. *Int J Pancreatol* 24:187-191, 1998.

Räty S. Sand J. Pulkkinen M. Matikainen M. Nordback I. Post-ERCP pancreatitis: Reduction by routine antibiotics. *J Gastrointest Surg* 5:339-45, 2001.

Saario IA. 5-Fluorouracil in the treatment of acute pancreatitis. *Am J Surg* 145:349-52, 1983.

Sainio V. Kemppainen E. Puolakkainen P. Taavitsainen M. Kivisaari L. Valtonen V. Haapiainen R. Schroder T. Kivilaakso E. Early antibiotic treatment in acute necrotising pancreatitis. *Lancet.* 346:663-7, 1995.

Sakorafas GH. Tsiotos GG. Sarr MG. Extrapancreatic necrotizing pancreatitis with viable pancreas: a previously under-appreciated entity. *J Am Coll Surg* 188:643-8, 1999.

Sand JA. Seppänen SK, Nordback IH. Intracystic hemorrhage in pancreatic pseudocysts: initial experiences of treatment protocol. *Pancreas* 14:187-91, 1997.

Sarles H. Proposal adopted ananimously by the participants of the symposium on acute pancreatitis at Marseille, 1963. *Bibl Gastroenterol* 7:VII-VIII, 1965.

Sarles H. Adler G. Dani R. Frey C. Gullo L. Harada H. Martin E. Norohna M. Scuro LA. The pancreatitis classification of Marseilles-Rome 1988. *Scand J Gastroenterol* 24:641-2, 1989.

Sarner M. Cotton PB. Classification of pancreatitis. *Gut* 25:756-9, 1984.

Sato T. Konishi K. Kimura H. Maeda K. Yabushita K. Tsuji M. Miwa A. Necrotizing acute pancreatitis caused by tiny carcinoma in adenoma in vater´s papilla. *Gastrointest Endoscp* 50:672, 1999.

Savastano S. Feltrin GP. Antonio T. Miotto D. Chiesura-Corona M. Castellan L. Arterial complications of pancreatitis: diagnostic and therapeutic role of radiology. *Pancreas* 8:687-92, 1993.

Sax HC. Warner BW. Talamani MA. et al. Early total parenteral nutrition in acute pancreatitis: Lack of beneficial effects. *Am J Surg* 153:117-124, 1987.

Scarpelli DG. Fat necrosis of bone marrow in acute pancreatitis. *Am J Pathol* 32:1077-87, 1956.

Schachter PP. Avni Y. Gvirz G. Rosen A. Czerniak A. The impact of laparoscopy and laparoscopic ultrasound on the management of pancreatic cystic lesions. *Arch Surg* 135:260-64, 2000.

Schenker S. Montalvo R. Alcohol and pancreas. *Recent Developments in alcoholism* 14:41-65, 1998.

Schmid SW. Uhl W. Friess H. Malfertheiner P. Buchler MW. The role of infection in acute pancreatitis. *Gut* 45:311-6, 1999.

Schröder T. Kivisaari L. Somer K. Strandertskjöld-Nordenstam CG. Kivilaakso E. Lempinen M. Significance of extrapancreatic findings in computed tomography (CT) of acute pancreatitis. *Eur J Radiol* 5:273-5; 1985.

Schröder T. Puolakkainen P. Rämö J. Nuutinen P. Kivilaakso E. Kiviluoto T. Haapsaari P. Kivisaari L. Long term results after pancreatic resection and peritoneal lavage for acute hemorrhagic pancreatitis. *Surg Res Comm* 7:145-9,1990.

Schuchter L. Schultz DJ. Synnestvedt M. Trock BJ. Guerry D. Elder DE. Elenitsas R. Clark WH. Halpern AC. A prognostic model for predicting 10-year survival in patients with primary melanoma. The Pigmented Lesion Group. *Annals of Internal Medicine*. 125:369-75, 1996.

Schölmerich J. Schümichen C. Lausen M. Gross V. Leser HG. Lay L. Farthmann EH. Gerok W. Scintigraphic assessment of leukocyte infiltration in acute pancreatitis using technetium-99m-hexamethyl propylene amine oxine as leukocyte label. *Dig Dis Sci* 36:65-70, 1991.

Schölmerich J. Interleukins in acute pancreatitis. *Scand J Gastroenterol* 31(Suppl 219):37-42, 1996.

Shader AE. Paxton JR. Fatal pancreatitis. *Am J Surg* 111:369-73, 1966.

Sharma VK. Howden CW. Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: a meta-analysis. *Pancreas* 22:28-31, 2001.

Shimizu H. Kodama A. Severe acute pancreatitis as a first symptom of primary hyperparathyroid adenoma: a case report. *J Laryngol Otol* 110:602-3, 1996.

Shoemaker WC. Appel PL. Kram HB. Hemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery. *Crit Care Med.* 21:977-90, 1993.

Sigmund WJ. Shelley WB. Cutaneous manifestations of acute pancreatitis, with special reference to livedo reticularis. *N Engl J Med* 251:851-3, 1954.

Sigurdsson GH. Necrotizing pancreatitis: Intensive-care measures. In: Beger HG: et al. (ed). The Pancreas. London, Blackwell Science Volume 1:466-71, 1998.

Sillanaukee P. Mäkelä R. Kiianmaa K. Seppä K. Alkoholin suurkulutus ja alkoholismi. *Duodecim* 112:1918-27, 1996.

Singer MV. Gyr K. Sarles H. Revised classification of pancreatitis. *Gastroenterology* 89:683-5, 1985.

Singh M. Simsek H. Ethanol and the pancreas: current status. *Gastroenterology* 98:1051-62, 1990.

Sintonen H. The 15D instrument of health-related quality of life: properties and applications. *Ann Med* 33:328-36, 2001.

Soran A. Chelluri L. Lee KK. Tisherman SA. Outcome and quality of life of patients with acute pancreatitis requiring intensive care. *J Surg Research.* 91:89-94, 2000.

Sossenheimer MJ. Aston CE. Preston RA. Gates LK Jr. Ulrich CD. Martin SP. Zhang Y. Gorry MC. Ehrlich GD. Whitcomb DC. Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype. The Midwest Multicenter Pancreatic Study Group (MMPSG). *Am J Gastroenterol* 92:1113-6, 1997.

Steer ML. How and where does acute pancreatitis begin. *Arch Surg* 127:1350-53, 1992.

Steinberg WM. Predictors of severity of acute pancreatitis. *Gastroenterol Clin North Am* 19:849-61, 1990.

Steinberg W. Tenner S. Acute pancreatitis. *N Engl J Med* 330:1198-210, 1994.

Sternby B. O'Brien JF. Zinsmeister AR. Dimagno EP. What is best biomechanical test to diagnose acute pancreatitis? A prospective clinical study. *Mayo Clin Proc* 71:1138-44, 1996.

Stone HH. Fabian TC. Peritoneal dialysis in the treatment of acute alcoholic pancreatitis. *Surg Gynecol Obstet* 150:878-82, 1980.

Suazo-Barahona J. Carmona-Sanchez R. Robles-Diaz G. Milke-Garcia P. Vargas-Vorackova F. Uscanga-Dominguez L. Pelaez-Luna M. Obesity: a risk factor for severe acute biliary and alcoholic pancreatitis. *Am J Gastroenterol* 93:1324-8, 1998.

Sugrue M. Intra-abdominal pressure: time for clinical practice guidelines? *Intensive Care Med* 28:389-391, 2002.

Svensson JO. Norbäck B. Bokey EL. Edlund Y. Changing pattern in aetiology of pancreatitis in an urban Swedish area. *Br J Surg* 66:159-61, 1979.

Symmers WSC. Acute alcoholic pancreatitis. *Dublin J Med Sci* 143:244-7, 1917.

Talamini G. Uomo G. Pezzilli R. Rabitti PG. Billi P. Bassi C. Cavallini G. Pederzoli P. Serum creatinine and chest radiographs in the early assessment of acute pancreatitis. *Am J Surg* 177:7-14, 1999.

Teerenhovi O. Nordback I. Isolauri J. Influence of pancreatic resection on systemic complications in acute necrotizing pancreatitis. *Br J Surg* 75:793-5, 1988.

Tenner S. Sica G. Hughes M. Noordhoek E. Feng S. Zinner M. Banks PA. Relationship of necrosis to organ failure in severe acute pancreatitis. *Gastroenterology*. 113:899-903, 1997.

The Albumin Reviewers (Alderson P. Bunn F. Lefebvre C Li Wan Po A. Li L. Roberts I. Schierhout G.). Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database of Systematic Reviews* 3, 2001.

Thomson SR. Hendry WS. McFarlane GA. Davidson AI. Epidemiology and outcome of acute pancreatitis. *Br J Surg* 74:398-401, 1987.

Tilney NL. Bailey GL. Morgan AP. Sequential system failure after rupture of abdominal aortic aneurysms: an unsolved problem in postoperative care. *Ann Sur.* 178:117-22, 1973.

Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am* 4:783-91, 1990.

Tran DD. Cuesta MA. van Leeuwen PA. Nauta JJ. Wesdorp RI. Risk factors for multiple organ system failure and death in critically injured patients. *Surgery.* 114:21-30, 1993a.

Tran DD. Oe PL. de Fijter CW. van der Meulen J. Cuesta MA. Acute renal failure in patients with acute pancreatitis: prevalence, risk factors, and outcome. *Nephrol Dial Transplant* 8:1079-84, 1993b.

Trapnell JE. The natural history and prognosis of acute pancreatitis. *Ann R Coll Surg Engl* 38:265-87, 1966.

Tsai CJ. Is obesity a significant prognostic factor in acute pancreatitis? *Dig Dis Sci* 43:2251-4, 1998.

Tsiotos GG. Luque-de Leon E. Soreide JA. Bannon MP. Zietlow SP. Baerga-Varela Y. Sarr MG. Management of necrotizing pancreatitis by repeated operative necrosectomy using a zipper technique. *Am J Surg.* 175:91-8, 1998.

Tsiotos GG. Luque-de Leon E. Sarr MG. Long-term outcome of necrotizing pancreatitis treated by necrosectomy. *Br J Surg* 85:1650-3, 1998b.

Ueda T. Takeyama Y. Hori Y. Nishikawa J. Yamamoto M. Saitoh Y. Hepatocyte growth factor in assessment of acute pancreatitis: comparison with C-reactive protein and interleukin-6. *J Gastroenterol* 32:63-70, 1997.

Uhl W. Isenmann R. Curti G. Vogel R. Beger HG. Buchler MW. Influence of etiology on the course and outcome of acute pancreatitis. *Pancreas.* 13:335-43, 1996.

Uhl W. Büchler MW. Malfertheiner P. Beger HG. Adler G. Gaus W. A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* 45:97-104, 1999.

Uhl W. Warshaw A. Imrie C. Bassi C. McKay CJ. Lankisch PG. Carter R. Di Magno E. Banks PA. Whitcomb DC. Dervenis C. Ulrich CD. Satake K. Ghaneh P. Hartwig W. Werner J. McEntee G. Neoptolemos JP. Buchler MW. IAP Guidelines for the Surgical Management of Acute Pancreatitis. *Pancreatology* 2:565-73, 2003.

Umeno Y. Otsuka J. Sasatomi E. Irie K. Development of colonic necrosis following severe acute pancreatitis. *Int Med* 39:305-8, 2000.

Uomo G. Visconti M. Manes G. Calise F. Laccetti M. Rabitti PG. Nonsurgical treatment of acute necrotizing pancreatitis. *Pancreas.* 12:142-8, 1996a.

Uomo G. Spada OA. Manes G. Feola B. Misso S. Cavallera A. Rabitti PG. Neopterin in acute pancreatitis. Scand J Gastroenterol 31:1032-6, 1996b.

Uomo G. Molino D. Visconti M. Ragozzino A. Manes G. Rabitti PG. The incidence of main pancreatic duct disruption in severe biliary pancreatitis. *Am J Surg* 176:49-52, 1998.

Van den Berghe G. Wouters P. Weekers F. Verwaest C. Bruyninckx F. Schetz M. Vlasselaers D. Ferdinande P. Lauwers P. Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 345:1359-67, 2001.

VanderZee KI. Sanderman R. Heyink J. A comparison of two multidimensional measures of health status: the Nottingham Health Profile and the RAND 36-Item Health Survey 1.0. *Quality of Life Research.* 5(1):165-74, 1996.

Vesentini S. Bassi C. Talamini G. Cavallini G. Campedelli A. Pederzoli P. Prospective comparison of C-reactive protein level, Ranson score and contrast-enhanced computed tomography in the prediction of septic complications of acute pancreatitis. *Br J Surg.* 80:755-7, 1993.

Vidyarthi G. Steinberg SE. Endoscopic management of pancreatic pseudocysts. *Surg Clin North Am* 81:405-10, 2001.

Viedma JA. Perez-Mateo M. Dominguez JE. Carballo F. Role of interleukin-6 in acute pancreatitis. Comparison with C-reactive protein and phospholipase A. *Gut.* 33:1264-7, 1992.

Viedma JA. Perez-Mateo M. Agullo J. Dominguez JE. Carballo F. Inflammatory response in the early prediction of severity in human acute pancreatitis. *Gut* 35:822-7, 1994.

Villazon A. Villazon O. Terrazas F. Rana R. Retroperitoneal drainage in the management of the septic phase of severe acute pancreatitis. *World J Surg* 15:103-7, 1991.

Vincent JL. Moreno R. Takala J. Willatts S. De Mendonca A. Bruining H. Reinhart CK. Suter PM. Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med.* 22:707-10, 1996.

Vincent JL. de Mendonca A. Cantraine F. Moreno R. Takala J. Suter PM. Sprung CL. Colardyn F. Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med.* 26:1793-800, 1998.

Wall AJ. Peritoneal dialysis in the treatment of severe acute pancreatitis. *Med J Aust* 2:281-3, 1965.

Ward J. Chalmers AG. Guthrie AJ. Larvin M. Robinson PJ. T2-weighted and dynamic enhanced MRI in acute pancreatitis: comparison with contrast enhanced CT. *Clinical Radiology* 52:109-14, 1997.

Watts GT. Total pancreatectomy for fulminant pancreatitis. *Lancet* ii:384, 1963.

Weinert CR. Gross CR. Kangas JR. Bury CL. Marinelli WA. Health-related quality of life after acute lung injury. *Am J Resp Crit Care Med.* 156:1120-8, 1997.

Werner J. Dragotakes SC. Fernandez-del Castillo C. Rivera JA. Ou J. Rattner DW. Fischman AJ. Warshaw AL. Technetium-99m-labeled white blood cells: a new method to define the local and systemic role of leukocytes in acute experimental pancreatitis. *Ann Surg* 227:86-94, 1998.

Whitcomb DC. Preston RA. Aston CE. Sossenheimer MJ. Barua PS. Zhang Y. Wong-Chong A. White GJ. Wood PG. Gates LK. Ulrich C. Martin SP. Post JC. Ehrlich GD. A gene for hereditary pancreatitis maps to chromosome 7q35. *Gastroenterology* 110:1975-80, 1996a.

Whitcomb D. Gorry M. Preston R. Furey W. Sossenheimer M. Ulrich C. Hereditary pancreatitis is caused by mutation in cationic trypsinogen gene. *Nat Genet* 14:141-5, 1996b.

White MT. Morgan A. Hopton D. Postoperative pancreatitis: a study of seventy cases. *Am J Surg* 120: 132-7, 1970.

Widdison AL. Karanjia ND. Reber HA. Routes of spread of pathogens into the pancreas in a feline model of acute pancreatitis. *Gut* 35:1306-10, 1994.

Widdison AL. Cunningham S. Immune function early in acute pancreatitis. *Br J Surg* 83:633-6, 1996.

Williamson RC. Early assessment of severity in acute pancreatitis. *Gut.* 25:1331-9, 1984.

Wilson HA. Askari AD. Neiderhiser DH. Johnson AM. Andrews BS. Hoskins LC. Pancreatitis with arthropathy and subcutaneous fat necrosis. Evidence for pathogenicity of lipolytic enzymes. *Arthritis and rheumatism* 26:121-6, 1983.

Wilson C. Imrie CW. Carter DC. Fatal acute pancreatitis. *Gut* 29:782-8, 1988a.

Wilson C. McArdle CS. Carter DC. Imrie CW. Surgical treatment of acute necrotizing pancreatitis. *Br J Surg* 75:1119-23, 1988b.

Wilson C. Heads A. Shenkin A. Imrie CW. C-reactive protein, antiproteases and complement factors as objective markers of severity in acute pancreatitis. *Br J Surg* 76:177-81, 1989.

Wilson C. Heath DI. Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems. *Br J Surg* 77:1260-4, 1990.

Wilson C. Imrie CW. Changing patterns of incidence and mortality from acute pancreatitis in Scotland, 1961-1985. *Br J Surg* 77:731-4, 1990.

Wilson PG. Manji M. Neoptolemos JP. Acute pancreatitis as a model of sepsis. *J Antimicrob Chemother* 41 Suppl A:51-63, 1998.

Windsor JA. Fearon KC. Ross JA. Barclay GR. Smyth E. Poxton I. Garden OJ. Carter DC. Role of serum endotoxin and antiendotoxin core antibody levels in predicting the development of multiple organ failure in acute pancreatitis. *Br J Surg* 80:1042-6, 1993.

Windsor AC. Kanwar S. Li AG. Barnes E. Guthrie JA. Spark JI. Welsh F. Guillou PJ. Reynolds JV. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 42:431-5, 1998.

Windsor JA. Search for prognostic markers for acute pancreatitis. *Lancet* 355:1924-5, 2000.

Wong ECC. Butch AW. Rosenblum JL. Ladensson JH. Scott MG. The clinical chemistry laboratory and acute pancreatitis. *Clin Chem* 39:234-43, 1993.

Yeung CY. Lee HC. Huang FY. Ho MY. Kao HA. Liang DC. Hsu CH. Hung HY. Chang PY. Sheu JC. Pancreatitis in children--experience with 43 cases. *Eur J Pediat.* 155:458-63, 1996.

Yousaf M. McCallion K. Diamond T. Management of severe acute pancreatitis. *Br J Surg* 90:407-20, 2003.

Z'graggen K. Wilson PG. Neoptolemos JP. Büchler MW. Diagnosis of acute pancreatitis: Clinical aspects. In: Beger HG: et al. (ed). The Pancreas. London, Blackwell Science Volume 1:466-71, 1998.

Z'graggen K. Gloor B. Invited commentary. *Dig Surg* 19:402-5, 2002.

Zimmerman JE. Knaus WA. Wagner DP. Sun X. Hakim RB. Nystrom PO. A comparison of risks and outcomes for patients with organ system failure: 1982-1990. *Crit Care Med* 24:1633-41, 1996.

Zyromski JN. Haidenberg J. Sarr M. Necrotizing pancreatitis caused by pancreatic ductal adenocarcinoma. *Pancreas* 22:431-32, 2001.