Department of Gastrointestinal Surgery, Abdominal Center
Helsinki University Hospital

Doctoral Programme in Clinical Research
University of Helsinki

SEVERE ACUTE PANCREATITIS:

MORTALITY, COMPLICATIONS, AND SURGICAL TREATMENT

Henrik Husu

ACADEMIC DISSERTATION

To be presented for public examination with the permission of the Faculty of Medicine of the University of Helsinki, in Lecture Hall 2, Biomedicum Helsinki 1, on 30 September 2022, at 12 o'clock noon.

Helsinki, 2022

Supervisors

Adjunct Professor Panu Mentula, MD, PhD
Department of Gastrointestinal Surgery
Abdominal Center
Helsinki University Hospital
Helsinki, Finland

Professor Ari Leppäniemi, MD, PhD
Department of Gastrointestinal Surgery
Abdominal Center
Helsinki University Hospital
Helsinki, Finland

Reviewers

Adjunct Professor Anne Kuitunen, MD, PhD
Department of Intensive Care
Tampere University and Tampere University Hospital
Tampere, Finland

Adjunct Professor Saila Kauhanen, MD, PhD
Department of Digestive Surgery
University of Turku and Turku University Hospital
Turku, Finland

Opponent

Professor Jan De Waele
Department of Intensive Care Medicine, Ghent University Hospital, Ghent, Belgium
Department of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium

The Faculty of Medicine uses the Ouriginal system (plagiarism recognition) to examine all doctoral disserations.

ISBN 978-951-51-8495-5 (paperback)
ISBN 978-951-51-8496-2 (PDF)

Unigrafia
Helsinki, 2022

To my dear family

ABSTRACT

Background. Acute pancreatitis (AP) is a common inflammatory disease with a mostly benign course of disease. For unknown reasons, 3–12% of individuals impacted develop persistent organ failure (OF), namely, severe acute pancreatitis (SAP), often coupled with necrosis of the pancreas and its surrounding areas (necrotizing pancreatitis, NP). The mortality risk for SAP ranges from 22–52%. Local necrotic complications increase the need for invasive interventions, such as drainage and debridement (necrosectomy). However, roughly two-thirds of necrotic collections remain sterile and rarely require invasive intervention. Less than 5% of all patients with AP will require an invasive intervention for complicated pancreatic necrosis. Traditionally, invasive treatments were undertaken aggressively and early, whereas contemporary management protocols favor downstaging and delaying procedures until demarcation of necrotic collections (walled-off necrosis, WON) occurrs. Moreover, indications for interventions have also changed, with most interventions today directed towards infected pancreatic necrosis (IPN). Furthermore, a fraction of patients with SAP experience multiple OFs quite early. These patients are at risk of developing abdominal compartment syndrome (ACS), which ultimately requires surgical decompression of the abdomen (open abdomen [OA] treatment) if lowering the intra-abdominal pressure (IAP) conservatively fails.

Aim. The primary aim of this study was to evaluate mortality in patients with SAP. Secondarily, we analyzed patient outcomes following the surgical treatment of local complications in NP. Thirdly, we investigated the risk factors and related outcomes of infectious complications in necrotizing SAP, and attempted to identify the risk factors for death following more than one week of ICU treatment among patients with necrotizing SAP. Finally, we examined the risk factors of OA treatment and the subsequent consequences for patients with SAP.

Methods. This thesis comprises four clinical studies based on a retrospective cohort of consecutively treated patients with SAP. Patients were treated at Helsinki University Hospital (HUH) during a 20-year period. In study I, we investigated the 90-day (short-term) mortality and mortality for the entire follow-up period (long-term) in 435 patients with SAP, focusing specifically on short-term mortality risk factors and causes of death. Study II evaluated the outcomes following open necrosectomy for complicated NP among 109 patients. In study III, we studied the risk factors and consequences of IPN in 163 patients with severe NP, and risk factors associated with death following more than one week of ICU treatment. Study IV investigated the risk factors

of OA treatment in SAP comparing 47 patients who underwent OA treatment with 47 conservatively treated matched peers, specifically analyzing factors affecting outcomes following OA.

Results. The results of study I demonstrated that short-term survival after SAP reached 90% in patients under 60 years of age, 60% in patients aged 60–69, and 43% in patients ≥70 years. Independent short-term mortality risk factors included an age of 60–69 years (odds ratio [OR] 5.1), age ≥70 (OR 10.4), female sex (OR 2.0), preexisting comorbidities (heart disease [OR 2.9] and chronic liver failure [OR 12.3]), OA treatment (OR 4.4), and sterile necrosectomy within four weeks (OR 14.7). The ten-year survival estimate following SAP was 68% in paitents <60 years and 28% in patients ≥60 years. Finally, the long-term causes of death were alcohol related in 57% of patients, all of whom experienced alcoholic SAP.

The results from study II revealed that 90-day mortality after open necrosectomy was 23%, falling to 11% if necrotic collection was walled off and an open necrosectomy could be postponed for four weeks. The multivariable regression analysis identified the following risk factors for 90-day mortality: age ≥60 years (OR 19.4), preexisting comorbidities (OR 16.9), prolonged or deteriorating OF as an indication for necrosectomy (OR 10.4), necrosectomy within 28 days (OR 6.5), and multiple OF (MOF) (OR 12.2), or a white blood cell (WBC) count >23 x 10^9/L (OR 21.4) at the time of the index open necrosectomy. Open necrosectomy resulted in no mortality when at most one of these risk factors was present. Conversely, any combination of these risk factors resulted in a 90-day mortality risk exceeding 50%. Following the index necrosectomy, new-onset persistent OF occurred within one week in 21% of patients, pancreatic fistula in 39%, and 48% required a reoperation.

Study III demonstrated that a wider spread of necrotic collections (distant from the pancreas [OR 5.7] or widespread [OR 21.8]), postinterventional etiology of pancreatitis (OR 13.5), preceding bacteremia (OR 4.8), and OA treatment (OR 3.6) increased the risk of IPN in necrotizing SAP. We found that mortality in IPN and sterile necrosis were 15% and 19%, respectively. In IPN, intensive care unit (ICU) and the overall length of a hospital stay were longer (median 31 vs. 8 days, $P < 0.001$ and median 69 vs. 21 days, $P < 0.001$), the use of necrosectomy increased (92% vs. 5%, $P < 0.001$), and ICU readmissions were more common (33% vs. 1%, $P < 0.001$) when compared with patients with sterile necrosis.

In study IV, we found that oliguria (OR 5.0) and ACS (OR 4.6) independently associated with OA treatment in SAP. Mortality following OA treatment was 43%, compared with 17% in matched controls ($P = 0.012$). Moreover, 34% of patients who underwent OA treatment eventually presented with visceral ischemia (6% in matched controls, $P = 0.002$), associated with

63% mortality. Post-hoc evaluation identified no clinically meaningful variables that could have predicted the development of ischemia in these patients.

Conclusions. Young and previously healthy patients experience a good short-term survival after SAP. Beyond patient age, an early open necrosectomy for sterile necrosis, OA treatment, female sex, and comorbidities appear to increase the short-term mortality risk. Due to alcohol-related deaths, long-term survival remains poor even among young patients following SAP. Moreover, preoperative risk factors determine mortality following an open necrosectomy. When no more than one preoperative risk factor is present, an open necrosectomy can be performed without an increasing risk for mortality. In addition, the postinterventional etiology of AP, bacteremia, a wider spread of necrotic collections, and OA treatment increase the risk of IPN in severe NP. A significantly higher likelihood of a morbid outcome associates with IPN compared with sterile necrosis. Finally, oliguria and ACS independently predict OA treatment in SAP, and intra-abdominal ischemia is common in OA-treated patients with SAP. No predictive clinical parameters of ischemia were identified among this group of patients.

TIIVISTELMÄ

Tausta. Akuutti haimatulehdus on tavallinen ja yleensä itsestään parantuva tulehdustila haimassa. Vaikea taudinkuva kehittyy epäselvästä syystä 3–12 %:lle akuuttiin haimatulehdukseen sairastuneista. Siihen liittyy määritelmällisesti pysyvä elinhäiriö, ja pääsääntöisesti kyseessä on haiman ja sen ympäristön kuoliota aiheuttava (nekrotisoiva) tautimuoto. Kuolleisuus vaikeaan akuuttiin haimatulehdukseen on huomattavaa (22–52 %). Paikalliset nekroottiset kertymät lisäävät toimenpiteiden, kuten nekroosikertymän kanavoinnin (eli dreneerauksen) ja poiston (nekrosektomia) tarvetta. Noin kahdella kolmasosalla nekroosikertymä ei infektoidu, jolloin toimenpiteitä ei yleensä tarvita. Kaikista akuuttiin haimatulehdukseen sairastuneista vain noin 5% tarvitsee kajoavan toimenpiteen komplisoituneen nekroosin vuoksi. Kajoavat toimenpiteet olivat aiemmin yleisiä ja niihin päädyttiin jo hoidon varhaisvaiheessa. Nykyisin kaikkia toimenpiteitä pyritään välttämään ja viivästyttämään, kunnes nekroosikertymä on rajautunut ympäristöstään. Tärkein syy kajoaville toimenpiteille on haimanekroosin infektio. Osalla vaikeaan haimatulehdukseen sairastuneista kehittyy taudin alkuvaiheessa monielinhäiriö. Erityisesti näillä potilailla on riski vatsaontelon ylipaineoireyhtymän kehittymiselle, joka voi vaatia vatsaontelon aukaisun ja avomahahoidon, mikäli konservatiiviset vatsaontelopaineen hoitomuodot eivät ole tehonneet.

Tarkoitus. Tutkimuksen päätarkoitus oli tutkia vaikean akuutin haimatulehduksen kuolleisuutta. Toisena tarkoituksena oli tutkia haimanekroosin kirurgisen hoidon tuloksia. Kolmantena tarkoituksena oli analysoida infektoituneen haimanekroosin kehittymisen riskitekijöitä ja verrata steriilin ja infektoituneen haimanekroosin vaikutusta sairastuvuuteen. Lisäksi selvitettiin ensimmäisen tehohoitoviikon jälkeistä kuolleisuutta nekrotisoivassa vaikeassa akuutissa haimatulehduksessa. Neljänneksi selvitettiin avomahahoidon riskitekijöitä ja tuloksia vaikeassa akuutissa haimatulehduksessa.

Potilaat ja menetelmät. Tutkimukset perustuvat taannehtivaan potilasaineistoon 20 vuoden ajalta Helsingin yliopistollisessa keskussairaalassa hoidetuista potilaista. Ensimmäisessä osatyössä tutkittiin lyhyen aikavälin (90 vuorokautta) ja pitkän aikavälin (seuranta-ajan keskiarvo 6 vuotta) kuolleisuutta 435 potilaalla, joita oli hoidettu teho-osastolla vaikean akuutin haimatulehduksen vuoksi. Tutkimme lyhyen aikavälin kuolleisuuden riskitekijöitä sekä pitkän aikavälin kuolinsyitä. Toisessa osatyössä selvitettiin hoidon tuloksia 109 nekrosektomialla hoidetun potilaan aineistossa. Kolmannessa osatyössä tutkittiin infektoituneen haimanekroosin riskitekijöitä ja seurauksia 163 potilaalla, joilla oli nekrotisoiva vaikea akuutti

haimatulehdus. Lisäksi analysoitiin ensimmäisen tehohoitoviikon jälkeisen kuolleisuuden riskitekijöitä. Neljännessä osatyössä tutkittiin avomahahoidon riskitekijöitä vaikeassa akuutissa haimatulehduksessa vertaamalla 47 avomahahoidettua potilasta 47 kaltaistettuun verrokkipotilaaseen.

Tulokset. Ensimmäisen osatyön tulokset osoittivat, että 90 vuorokauden eloonjäämisennuste on 90% alle 60-vuotiailla, 60% 60-69-vuotiailla ja 43% ≥ 70-vuotiailla potilailla vaikean akuutin haimatulehduksen jälkeen. Lyhyen aikavälin kuolleisuuden riskitekijöitä oli 60-69 vuoden ikä (vetosuhde [odds ratio, OR] 5.1), ≥ 70 vuoden ikä (OR 10.4), naissukupuoli (OR 2.0), sydänsairaus (OR 2.9), maksakirroosi (12.3), avomahahoito (OR 4.4) ja nekrosektomia ei-infektoituneen haimanekroosin vuoksi (OR 14.7). Kymmenen vuoden eloonjäämisennuste < 60-vuotiailla oli 68 % ja ≥ 60-vuotiailla 28%. Pitkän aikavälin seurannassa menehtyneillä potilailla perus-, välitön- tai myötävaikuttava kuolinsyy liittyi alkoholin haitalliseen käyttöön 57% potilaista, ja kaikilla näillä potilailla oli taustalla sairastettu alkoholiperäinen vaikea haimatulehdus.

Toisessa osatyössä selvisi, että 90-vuorokauden kuolleisuus avoimen nekrosektomian jälkeen oli 23%. Kuolleisuus oli 11%, mikäli nekrosektomiaa tehtiin vasta neljän viikon kuluttua taudin alusta rajautuneen nekroosikertymän vaiheessa. Monimuuttujamallissa kuolleisuuden riskitekijöitä olivat ≥ 60 vuoden ikä (OR 19.4), perussairaudet (OR 16.9), mikäli leikkauksen indikaatio oli pitkittynyt tai vaikeutunut elinhäiriötilanne (OR 10.4), nekrosektomia < 28 vuorokautta taudin alusta (OR 6.5), monielinvaurio (OR 12.2) ja leukosytoosi > $23x10^9$/L (OR 21.4). Mikäli näitä riskitekijöitä oli korkeintaan yksi, ei kuolleisuutta ollut seurannassa. Jos taas riskitekijöitä oli useampia, yli puolet potilaista kuoli 90 vuorokauden seurannassa. Avoimen nekrosektomian jälkeen 21% kehittyi pysyvä uusi elinhäiriö viikon sisällä toimenpiteestä, 39% haimafisteli ja 48% tarvitsi jonkin uusintaleikkauksen puolen vuoden sisällä.

Kolmannessa osatyössä havaittiin, että nekroosikertymän laajuus (haimasta etäällä oleva kertymä [OR 5.7] ja laaja-alaisesti levinnyt kertymä [OR 21.8]), endoskooppisen tai kirurgisen toimenpiteen jälkeinen taudin etiologia (OR 13.5), bakteremia (OR 4.8) ja avomahahoito (OR 3.6) lisäsivät infektoituneen haimanekroosin riskiä nekrotisoivassa vaikeassa akuutissa haimatulehduksessa. Steriilin nekroosikertymän ollessa kyseessä, mortaliteetti oli 19%, ja infektoituneessa haimanekroosissa 15%. Potilailla, joilla oli infektoitunut nekroosi, oli pidempi tehohoito- (mediaani 31 ja 8 vuorokautta, $P < 0.001$) ja sairaalassaoloaika (mediaani 69 ja 21 vuorokautta, $P < 0.001$), sekä enemmän uusintahoitojaksoja teho-osastolla (33% ja 1%, $P < 0.001$) verrattuna ei-infektoituneeseen nekroosiin. Nekrosektomia tehtiin useammin jos potilaalla oli infektoitunut haimanekroosi verrattuna steriiliin nekroosiin (92% ja 5%, $P < 0.001$).

Neljännen osatyön monimuuttuja-analyysissä ilmeni, että vähävirtsaisuus (OR 5.0) ja vatsaontelon ylipaineoireyhtymä (OR 4.6) lisäsivät merkitsevästi avomahahoidon riskiä vaikeassa akuutissa haimatulehduksessa. Mortaliteetti oli 43% avomahahoidetuilla potilailla ja 17% konservatiivisesti hoidetuilla potilailla (P = 0.012). Avomahahoidettujen ryhmässä 34%:lla todettiin leikkauksessa vatsaontelonelinten iskemia (6% kaltaistetuilla verrokeilla, P = 0.002), ja mortaliteetti avomahahoidettujen iskemiapotilaiden alaryhmässä oli 63%. Tutkimuksessa ei löydetty kliinisesti merkitseviä iskemiaa ennustavia riskitekijöitä.

Johtopäätökset. Lyhyen aikavälin ennuste nuorilla ja terveillä potilailla on hyvä vaikean akuutin haimatulehduksen jälkeen. Iän lisäksi, varhainen ei-infektoituneen nekroosin vuoksi tehty nekrosektomia, avomahahoito, naissukupuoli ja litännäissairaudet lisäävät lyhyen aikavälin kuolleisuuden riskiä. Pitkän aikavälin ennuste sairastetun vaikean akuutin haimatulehduksen jälkeen on nuorillakin potilailla huono johtuen alkoholinkäyttöön liittyvästä kuolleisuudesta. Kuolleisuus avoimen nekrosektomian jälkeen riippuu toimenpidettä edeltävistä riskitekijöistä. Mikäli useita riskitekijöitä ei ole, voidaan toimenpide tehdä ilman kuolleisuutta. Toimenpiteen jälkeinen etiologia, bakteremia, nekroottisen kertymän laaja-alaisuus ja avomahahoito lisäävät haimanekroosin infektion riskiä nekrotisoivassa vaikeassa akuutissa haimatulehduksessa. Haimanekroosin infektoitumiseen liittyy merkittävää sairastuvuutta verrattuna ei-infektoituneeseen tulehtumattomaan nekroosiin. Vähävirtsaisuus ja vatsaontelon ylipaineoireyhtymä lisäävät avomahahoidon riskiä vaikeassa akuutissa haimatulehduksessa. Vatsaonteloelimen iskemia on tavallinen löydös avomahahoidetuilla potilailla mutta iskemiaa ennustavia riskitekijöitä ei tutkimuksessa löydetty.

TABLE OF CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The following publications serve as the basis for this thesis:

I Husu HL, Leppäniemi AK, Lehtonen TM, Puolakkainen PA, Mentula PJ. Short- and long-term survival after severe acute pancreatitis: A retrospective 17 years' cohort study from a single center. *Journal of Critical Care* 2019 Oct; 53: 81–86.

II Husu HL, Kuronen JA, Leppäniemi AK, Mentula PJ. Open necrosectomy in acute pancreatitis-obsolete or still useful? *World Journal of Emergency Surgery* 2020 Mar 17; 15(1): 21.

III Husu HL, Valkonen MM, Leppäniemi AK, Mentula PJ. Occurrence and Risk Factors of Infected Pancreatic Necrosis in Intensive Care Unit-Treated Patients with Necrotizing Severe Acute Pancreatitis. *Journal of Gastrointestinal Surgery* 2021 Sep; 25(9): 2289–2298.

IV Husu HL, Leppäniemi AK, Mentula PJ. Who Would Benefit from Open Abdomen in Severe Acute Pancreatitis? – A Matched Case–Control Study. *World Journal of Emergency Surgery* 2021 Jun 10; 16(1): 32.

The publications are referred to in the text by their Roman numerals, and are reproduced with the permission of the copyright holders.

ABBREVIATIONS

AAP	Acute alcoholic pancreatitis
ABP	Acute biliary pancreatitis
ACS	Abdominal compartment syndrome
ALAT	Alanine aminotransferase
ANC	Acute necrotic collection
AP	Acute pancreatitis
APACHE II	Acute Physiology and Chronic Health Evaluation II
APFC	Acute pancreatic fluid collection
ASA	American Society of Anesthesiologists Physical Status Classification System
BMI	Body mass index
CECT	Contrast-enhanced computed tomography
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
DGE	Delayed gastric emptying
DPDS	Disconnected pancreatic duct syndrome
EPI	Extrapancreatic infection
ERCP	Endoscopic retrograde cholangiopancreatography
GI	Gastrointestinal
GOO	Gastric outlet obstruction
HAPS	Harmless acute pancreatitis score
HUH	Helsinki University Hospital
IAH	Intra-abdominal hypertension
IAP	Intra-abdominal pressure
ICD-10	International Classification of Diseases, tenth edition
ICU	Intensive care unit
IL-6	Interleukin-6
IPN	Infected pancreatic necrosis
IQR	Interquartile range
MAP	Mean arterial pressure
MOF	Multiple organ failure
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NP	Necrotizing pancreatitis
OA	Open abdomen
OF	Organ failure
OR	Odds ratio
PCD	Percutaneous catheter drainage

PCT	Procalcitonin
PEP	Post-ERCP pancreatitis
RAC	Revised Atlanta classification
SAP	Severe acute pancreatitis
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequence organ failure assessment
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVT	Splanchnic vein thrombosis
TEN	Total enteral nutrition
US	Ultrasonography
WBC	White blood cell
WON	Walled-off necrosis

1 INTRODUCTION

Acute pancreatitis (AP) is a common inflammatory disorder of the pancreas (Xiao et al., 2016). Arising from a variety of etiologies, AP in the Finnish population predominantly follows excessive alcohol consumption and results from biliary stones obstructing the pancreatic duct outflow (Jaakkola & Nordback, 1993; Karjula et al., 2019; Khan et al., 2013). Initiating mechanisms of AP are linked to a pancreatic acinar cell injury, causing premature activation of pancreatic enzymes leading to autodigestion (Grady et al., 1996; Hofbauer et al., 1998; Rao et al., 1976; Saluja et al., 1999). Subsequent cellular events attract immune cells promoting (local) pancreatic inflammatory cascades with the potential for inordinate systemic (distant) inflammatory responses (Bhatia et al., 2005; Lee & Papachristou, 2019). A systemic inflammatory response syndrome (SIRS) is the clinical manifestation of these distant inflammatory responses, potentially leading to various degrees of organ dysfunctions and ultimately multiple organ dysfunction syndrome associated with a considerable mortality (Garg & Singh, 2019; Mayer et al., 2000; Norman et al., 1997).

A majority of patients with AP suffer from mild, self-limiting disease with a negligible mortality (Berger et al., 2020; Párniczky et al., 2016; Sternby et al., 2019). An estimated 10–20% of patients develop organ failure (OF), the most important predictor of mortality (Acevedo-Piedra et al., 2014; Choi et al., 2014; Sternby et al., 2019). Notably, persistent OF is characteristic of severe acute pancreatitis (SAP) (Banks et al., 2013), with a mortality in SAP of 22–52% (Choi et al., 2014; Padhan et al., 2018; Schepers et al., 2019; Sternby et al., 2019; Zubia-Olaskoaga et al., 2016). About 10–20% of AP patients develop necrotizing pancreatitis (NP), a subgroup of patients more likely to have SAP (Ashley et al., 2001; Beger et al., 1997; Besselink, van Santvoort, Boermeester, et al., 2009; Choi et al., 2014; Sternby et al., 2019). Patients with interstitial edematous AP develop severe disease only in conjunction with preexisting comorbidities (Singh et al., 2011). In 21–43% of all patients with NP, a necrosis becomes infected (infected pancreatic necrosis, IPN), a sequela known to increase mortality (Ashley et al., 2001; Beger et al., 1997; Büchler et al., 2000; Hartwig et al., 2002; Lariño-Noia et al., 2021; Perez et al., 2002; Petrov et al., 2010; Schepers et al., 2019; Sternby et al., 2019). Moreover, at least half of patients with SAP suffer from intra-abdominal hypertension (IAH), and 9–56% develop abdominal compartment syndrome (ACS) at some point during their intensive care (Al-Bahrani et al., 2008; Bhandari et al., 2013; Chen et al., 2008; Dambrauskas et al., 2009; Davis et al., 2013; de Waele et al., 2005; Ke et al., 2012; Keskinen et al., 2007; Kurdia et al., 2020; Smit et al., 2016). When conservative management aimed at decreasing intra-abdominal pressure (IAP) fails, candidacy for surgical decompression of the abdomen

(laparostomy) with subsequent open abdomen (OA) treatment is weighed against an anticipated morbid outcome (Kirkpatrick et al., 2013).

Treatment of SAP constitutes around 1% of all intensive care unit (ICU) admissions (Harrison et al., 2007). Estimated annual aggregate cost of AP treatment exceeded US$2.6 billion in the US alone in 2014 (Peery et al., 2019). Despite these costs, few studies have examined long-term outcomes following SAP (Appelros et al., 2001; Karjula et al., 2019). The management strategy of SAP has shifted, from early surgical treatment towards delaying and downstaging interventions (Boxhoorn et al., 2020). Interestingly, reports documenting discouraging results following open surgical necrosectomy primarily originate from premillennial studies relying on the implementation of early necrosectomy (Mier et al., 1997). Currently, a step-up treatment strategy is customary for the demarcation of necrotic collections occurring before interventions. Additionally, the management of critically ill patients has also changed. Notably, infected pancreatic necrosis (IPN) in AP is associated with an increased mortality (Petrov et al., 2010). Thus, establishing the risk factors for developing IPN in severe NP remains clinically important. No comparative data are available regarding patient selection for OA treatment due to refractory ACS in SAP.

As such, this thesis aimed to determine the mortality, complications, and surgical management of patients with SAP. The study material comprised a 20-year retrospective cohort of consecutive patients with SAP treated in the ICU at Meilahti Hospital, a part of the Helsinki University Hospital (HUH). The primary aim focused on investigating the short- and long-term mortality among patients with SAP. Specifically, the short-term mortality risk factors and long-term causes of death were evaluated. Secondarily, this research aimed to analyze the outcomes following open necrosectomy for complicated necrotic collections in NP. As such, the mortality and morbidity risk factors following open necrosectomy were investigated. The third aim was to evaluate IPN risk factors and outcomes following IPN in patients with severe NP. Moreover, this study also aimed to separately evaluate mortality risk factors following one week of ICU treatment for necrotizing SAP. The fourth aim focussed on identifying the risk factors of OA treatment in SAP and identifying the subsequent outcomes.

2 REVIEW OF THE LITERATURE

2.1 THE PANCREAS AND ACUTE PANCREATITIS

The pancreas is an unpaired retroperitoneal organ. Situated behind the stomach, the pancreatic head is encircled by the duodenum at the root of the transverse colon mesentery, the neck overlaying the superior mesenteric vessels, with the body passing over the aorta covering the splenic vessels, and the tail positioned ventral to the left kidney in close proximity to the splenic hilum. A dual blood supply originating from the branches of the celiac and superior mesenteric arteries nourishes the pancreas, whereas venous outflow occurs via the branches towards the splenic and superior mesenteric veins, which unite into the portal system (Bertelli et al., 1995; Mourad et al., 1994). We can functionally distinguish between the endocrine and exocrine pancreatic glandular tissue. Endocrine Langerhans cells function in hormone homeostasis via secretion of insulin, glucagon, and somatostatin into the blood stream (Henderson et al., 1981; Sarles, 2010; Slack, 1995). Exocrine acinar and ductal structures, however, are responsible for the secretion of digestive enzymes (e.g., trypsin, amylase, lipase, and RN/DNases), water, and bicarbonate into the growing pancreatic ductal system, which empties primarily via the ampulla Vateri (or major duodenal papilla) into the second part of the duodenum. The sphincter of Oddi refers to the neuromuscular structure at the duodenal entry point of the distal biliary and pancreatic duct confluence.

AP is a necroinflammatory pancreatic disorder with various etiologies. More than a century of acquired knowledge has unraveled this disease, although the precise pathogenetic mechanisms remain unexplained (Wang et al., 2009). A pancreatic acinar cell injury with subsequent premature activation of its zymogen content, particularly trypsinogen, leads to the autodigestion of the pancreas, resulting in local and potentially uncontrolled systemic inflammatory reactions (Lankisch et al., 2015; Lee & Papachristou, 2019). Clinically, this translates into a broad spectrum of disease, ranging from a mild, spontaneously resolving upper gastrointestinal (GI) pain to a deadly sepsis-like state of inflammation. For unknown reasons, the disease progresses into a milder interstitial edematous AP or NP with a predominantly more severe course of disease. Several different pharmacological compounds have been evaluated in randomized controlled trials as treatment for AP. To date, none of these interventions have resulted in mortality benefits or other consistent clinical benefits (Moggia et al., 2017). Basic research has, however, identified several potential therapeutic target pathways for possible future drug research (Lee & Papachristou, 2019). At present, treatments remain organ-supportive and focused on managing complications.

2.2 EPIDEMIOLOGY

The reported annual incidence of AP ranges from 3 to 143 per 100 000 person-years (Iannuzzi et al., 2022; Roberts et al., 2017; Xiao et al., 2016; Yadav & Lowenfels, 2006). In Europe, incidence is typically highest in the northern and eastern regions, whereas southern European countries report lower incidence rates (Roberts et al., 2017). In Finland, incidence is as high as 75 per 100 000 person-years based on late 20th century studies (Jaakkola & Nordback, 1993). Interstudy population selection variability, diverging diagnostic criteria, and different inclusion criteria for recurrent AP attacks may partially explain the wide range of incidence rates reported between studies. However, results appear indicative of differences in AP incidence between different populations (Roberts et al., 2017; Yadav & Lowenfels, 2013).

Several studies have reported an increasing AP incidence over time in Europe and North America, whereas incidence in Asian populations appears rather consistent over time (Hamada et al., 2014; Iannuzzi et al., 2022; Roberts et al., 2017; Shen et al., 2012; Xiao et al., 2016; Yadav & Lowenfels, 2006). In addition to improved diagnostic imaging, several factors, such as an increasing alcohol consumption, obesity, and population age, have been proposed to explain this possible increase in AP incidence. Some investigators have, however, reported contradictory findings (Bertilsson et al., 2017; Jaakkola & Nordback, 1993; O'Farrell et al., 2007; Roberts et al., 2013; Sand et al., 2009). Interestingly, limited contemporary data suggest that incidence in Finland might have decreased (Nikkola et al., 2020).

2.3 ETIOLOGY

Worldwide, the most common AP etiologies are biliary (41%) and alcohol related (32%) (Lankisch et al., 2001). The remainding AP cases result from a variety of toxic, metabolic, iatrogenic, genetic, autoimmune, and traumatic factors. Furthermore, AP is in some cases deemed idiopathic.

2.3.1 ACUTE ALCOHOLIC PANCREATITIS (AAP)

Alcohol use impacts all organ systems with the pancreas being no exception. The observation that an association might exist between alcoholism and pancreatic disorders was first identified more than two centuries ago and has been actively studied since then (Fleischman, 1815; Friedreich, 1878). Today, the association between alcohol misuse and pancreatitis is undisputable.

Excessive alcohol consumption is either the leading or the second most common etiology for AP depending on the population studied. The proportion of acute alcoholic pancreatitis (AAP) cases is highest in Eastern and Nordic

European countries, as well as in South Africa, although reports vary between countries with most reports originating in the Western world (Appelros & Borgström, 1999; Roberts et al., 2017; Zilio et al., 2019). In North America, reported AAP incidence is highest among the Black population, suggesting a higher susceptibility to disease rather than actual differences in alcohol consumption (Frey et al., 2006; Yang et al., 2008). In addition, AAP is less common among women than men (Dufour & Adamson, 2003). Morever, a positive relationship between socioeconomic deprivation and AAP incidence has also been established (Ellis et al., 2009).

AAP develops in only a fraction (2–3%) of people who misuse alcohol, indicating that other factors likely trigger disease onset (Lankisch et al., 2002). The notion that AAP development requires a "coenzyme" or an underlying susceptibility combined with alcohol exposure is supported by observations that alcohol consumption does not differ between heavy drinkers who do and do not develop AAP (Juliusson et al., 2018; Wilson et al., 1985). The toxicity threshold of alcohol consumption in relation to AAP risk remains unknown. However, the relationship between alcohol exposure and incidence of AP has been established, and increased amounts of alcohol consumption appear to precede the development of AAP (Kristiansen et al., 2008; Lindkvist et al., 2008; Nordback, Pelli, Lappalainen-Lehto, Järvinen, et al., 2009). In addition, prolonged chronic heavy alcohol exposure associates with a higher risk of chronic pancreatitis (Yadav et al., 2009). For instance, in experimental models, chronic alcohol consumption combined with binge alcohol exposure induces a more severe pancreatic injury compared with chronic or binge alcohol exposure alone (Ren et al., 2016). It remains unclear, however, whether binge alcohol exposure causes AAP in the absence of underlying chronic excessive alcohol misuse (DiMagno, 2011). Results suggesting differences in AAP risk depending on consumed beverage types are contradictory (Kristiansen et al., 2008; Sadr Azodi et al., 2011).

2.3.2 ACUTE BILIARY PANCREATITIS (ABP)

Acute biliary pancreatitis (ABP) refers to AP caused by biliary tree calculus migrating through the sphincter of Oddi into the duodenum (Acosta & Ledesma, 1974). ABP is the leading cause of AP in most populations (Iannuzzi et al., 2022; Lankisch et al., 2001; Roberts et al., 2017). Globally, the risk of ABP has increased, which might result from risk factors associated with gallstone disease, such as age and obesity (Iannuzzi et al., 2022). In general, patients with ABP are older than patients with AAP, and ABP is associated with being female (Appelros & Borgström, 1999; Lankisch et al., 2001). Smaller sized (<5 mm) and a higher number of gallbladder stones, and the dilation of the cystic or common bile ducts increase the risk of ABP (Armstrong et al., 2005; Kelly, 1984).

2.3.3 OTHER CAUSES

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) occurs in 3–7% of patients undergoing ERCP (Andriulli et al., 2007; Frank & Adler, 2006; Rainio et al., 2017). Several well-known risk factors for PEP exist, including a younger age, female gender, and a difficult pancreatic duct cannulation (Andriulli et al., 2007). The use of rectal nonsteroidal anti-inflammatory drugs has proven efficacious in preventing PEP in several studies, although some conflicting reports of its effectiveness have emerged at centers with low PEP incidence (Rainio et al., 2017). PEP remains primarily mild throughout the course of disease, allowing discharge within the first postprocedural days. However, 0.3–0.6% of patients develop severe PEP (Andriulli et al., 2007).

The definition of **postoperative AP following pancreatic surgery** is under debate, with its relationship to postoperative pancreatic fistula being actively studied (Andrianello et al., 2021; Connor, 2016; Kühlbrey et al., 2017; Partelli et al., 2020; Räty et al., 2006, 2007; Yoo et al., 2021). Postoperative AP occurs in 53–68% of patients following pancreatic surgery (Andrianello et al., 2021; Chen et al., 2020). The latest definition of postoperative AP is that following pancreatic surgery a transiently elevated serum amylase or lipase over the normal upper limit develops on postoperative day 0–1 or urinary trypsinogen-2 >50 μg/L on postoperative day 1–2. An aforementioned transient amylase elevation combined with C-reactive protein (CRP) level >180 mg/L on postoperative day 2 predict pancreas-specific complications in two-thirds of patients (Connor, 2016).

Several other surgical procedures both in close proximity to the pancreas and in more remote locations have historically been associated with a risk of **postoperative AP**. Such surgeries include cardiopulmonary bypass surgery and surgeries targeting the aorta, abdominal vasculature, esophagus, and spine, as well as some bariatric procedures (Achouh et al., 2006; Blom et al., 1993; Burkey et al., 2000; Feng et al., 2018; Kumaravel et al., 2014; Lefor et al., 1992; Ramsey & Podratz, 1999; Reilly et al., 1994).

A myriad of other less common etiologies of AP have also been identified. For instance, metabolic conditions, such as **hypertriglyceridemia and hypercalcemia**, represent known potential etiologies. Specifically, hypertriglyceridemia may account for up to 5% of AP cases, possibly occurring in conjunction with alcoholism, obesity, diabetes, and pregnancy (Yang & McNabb-Baltar, 2020). To date, more than 500 drugs have been listed that may precitate AP as an adverse event, whereby AP has been identified as drug-induced in 0.1–2% of cases (Balani & Grendell, 2008; Lankisch, Dröge, et al., 1995; Nitsche et al., 2012). Additionally, blunt and penetrating **trauma** to the pancreas, which occurs in less than 10% of all abdominal injuries, are known initiators of AP (Sharbidre et al., 2020). **Benign or malign obstructive**

causes (such as neoplasia) can cause AP. According to one register study, NP may be attributable to coexisting pancreatic ductal adenocarcinoma in 0.8% of patients (Lewellen et al., 2020). Other anatomical and physiological variations, such as **pancreas divisum, duodenal diverticulae, and sphincter Oddi dysfunction,** are potential causes of AP, although the relevance of some of these entities remains disputed (Kwak et al., 2009). Other rare etiologies of AP include various **infections** (viral, bacterial, fungal, and parasitic) (Imam et al., 2020; Parenti et al., 1996; Rawla et al., 2017), and a specific **genetic susceptibility** to AP has also been identified (Kanth & Reddy, 2014). Following a careful etiological work-up, the cause of AP remains unknown in up to 10% of patients, comprising **idiopathic** AP (Vila, 2010). Finally, biliary **microlithiasis** may occur in 50–75% of patients with idiopathic AP (Lee et al., 1992; Räty et al., 2015; Ros et al., 1991).

2.4 PATHOGENESIS AND PATHOPHYSIOLOGY

Several changes to the pancreatic cell functions and signalling cascades related to AP pathophysiology have been identified, although the precise mechanism(s) precipitating an acinar cell injury remains incompletely understood (Criddle et al., 2007; Lee & Papachristou, 2019). Once the trigger for AP occurs, the premature intracellular activation of digestive enzymes via the primordial activation of trypsinogen, which may occur due to the fusion of trypsinogen-containing zymogen granules with lysosomes that contain trypsinogen-activating enzyme cathepsin B, initiate autodigestive cellular mechanisms. This in turn attracts the host immune system, leading to necroinflammation (Lee & Papachristou, 2019). Following an acinar cell injury, digestive enzymes leak into the acinar cell surroundings and enter circulation.

Many theories explaining the advent of AAP have emerged. For instance, the direct toxic effects induced by alcohol on the pancreatic cells are implicated as playing at least some role in the pathogenesis of AAP. The metabolism of alcohol in acinar cells precipitates a cellular injury via oxidative (resulting in free oxygen radicals) and nonoxidative pathways (involving free fatty acid ethyl esters) (Clemens et al., 2016; Lankisch et al., 2015; Tsai et al., 1998; Werner et al., 2001). Moreover, alcohol has the potential to increase the production of digestive and lysosomal enzymes in the acinar cells, a process illustrated via experimental animal models (Apte et al., 1995). An overt increase in the intracellular calcium concentration seemingly precedes the premature activation of these enzymes in their cytosolic storage units (called zymogen granules), igniting an acinar cell injury and subsequent necroinflammatory cell death (Lankisch et al., 2015). Some of the primary hypotheses regarding the mechanism of action of alcohol in AAP are as follows (Apte et al., 1998, 2010; Clemens et al., 2016; Lankisch et al., 2015):

(1) The direct toxic-metabolic effects of alchol on acinar cells (yielding metabolites, such as reactive oxygen species, which destabilize the acinar cell). A co-occurring increase in intracellular levels of digestive and lysosomal enzymes results in an aggravated risk of intracellular contact between these enzymes due to the destabilized cell organs.

(2) The effects of alcohol on protein precipitation in the pancreatic secretions via an alteration in the nondigestive pancreatic juice components. In the acinar cell, alcohol potentially induces an increase in the production of a highly precipitable lithostatine, and an increase in the secretion of self-aggregating glycoprotein G2, which may be result in the blockage of small pancreatic ducts by protein plugs. This could eventually cause ductal cell damage, further duct obstruction, and atrophy.

(3) The potential spasmogenic effects of alcohol on the sphincter of Oddi functioning, causing biliary reflux through a common distal pancreatobiliary channel with subsequent toxic effects from the biliary juice on the acinar cells. Experimental models have reported an increase in a sphincter Oddi tone following alcohol exposure, although such studies in humans remain contradictory.

(4) An increase in pancreatic juice secretion alongside an increase in the sphincter of Oddi pressure resulting in cellular injury via elevated pancreatic duct secretion pressure.

ABP develops following gallstone passage through the major duodenal papilla (papilla of Vateri) (Acosta & Ledesma, 1974). Our current understanding of ABP pathogenesis is that a temporary pancreatic duct obstruction via compression of an impacted stone at the level of a major duodenal papilla can cause a transiently increased pancreatic duct pressure enabling pancreatic juice to cause an injury to the pancreas (Sakorafas & Tsiotou, 2000).

2.5 DIAGNOSIS

Studies and guidelines generally adhere to the principle of fulfilling two out of three of the following criteria in order to diagnose AP: typical clinical symptoms of acute, severe persistent pain in the epigastrium possibly radiating to the back; laboratory elevation of amylase/lipase exceeding a value at threefold the upper normal limit; and/or signs of pancreatitis on imaging studies. AP can be diagnosed through clinical presentation and laboratory markers only, and imaging is not routinely indicated for diagnostic purposes. Likewise, diagnosis may follow imaging and laboratory testing alone despite a lack of typical clinical symptoms (Banks et al., 2013; Besselink et al., 2013).

2.5.1 CLINICAL PRESENTATION

Typically, AP presents with mild to severe epigastric pain, possibly radiating to the back or feeling band-like, and may be accompanied by nausea, vomiting, and pyrexia (Banks et al., 2006). Clinical traits may at times be more occult, with only a general unwellness and tachycardia, or symptoms may be absent altogether, especially among the elderly (Donhauser & Bigelow, 1958; Hamada et al., 2014; Hendrickson & Naparst, 2003; Lankisch et al., 1991; Lankisch, Mahlke, et al., 1995). For instance, in a study among patients during their first ABP event, 58% endured previous biliary pain colics ("warning signs") before developing their actual first ABP (Besselink, Venneman, et al., 2009). In AAP, symptoms typically develop within 48 hours (h) following the cessation of drinking (Nordback, Pelli, Lappalainen-Lehto, & Sand, 2009). Half of patients with AP present in the emergency department within 24 h of pain onset, although one-third seek care more than two days later, while others wait week(s) following symptom onset (Phillip et al., 2013).

The first 2–4 days following symptom onset in AP are characterized by a hypovolemic state, and as many as one-quarter of patients might develop signs of OF (Beger & Rau, 2007). Clinical signs of hypoperfusion/shock include hypotension, tachycardia, and tachypnea, as well as signs of hypoperfusion, such as skin changes (a cool pallor, moist skin, cyanosis, mottling, and a prolonged capillary refill time), an altered mental status, and a lower urine output (Cecconi et al., 2014; Evans et al., 2021). Determining the possibility of OF in AP requires assessing respiratory, cardiovascular, and renal organ system functions (Banks et al., 2013). The definition and classification of OF in AP are described below (see Chapter 2.6).

Several cutaneous ecchymoses related to AP have been described, including Grey–Turner's sign (flanks), Cullen's sign (umbilicus), Fox's sign (proximal thigh), and Bryant's sign (scrotum). These evolve from blood dissecting across the retroperitoneal planes, with none specific to AP (Dickson & Imrie, 1984; Jacobs et al., 1977; Lankisch et al., 2009; Miulescu et al., 2020). Grey–Turner's or Cullen's signs appear in 1–3% of AP cases, more often among patients experiencing worse outcomes (Bosmann et al., 2009; Dickson & Imrie, 1984; Jacobs et al., 1977; Lankisch et al., 2009).

2.5.2 LABORATORY TESTS

Three pancreatic acinar cell–derived enzymes (amylase, lipase, and proenzyme trypsinogen) are well-established biochemical markers utilized to diagnose AP. Venous and lymphatic drainage obstruction, capillary leakage, and possible peritoneal absorption of amylase are mechanisms thought to lead to an elevation of serum amylase in AP (Vissers et al., 1999). The measurement of serum (or plasma) amylase or lipase is a common diagnostic test for AP (Clavien et al., 1989). In addition, amylase clearance via urine also allows for

its urinalysis in suspected AP. The pancreatic acinar cell–produced proenzyme trypsinogen (isoform) type 2 is elevated both in the serum and urine following AP (Kemppainen et al., 1997; Yadav et al., 2002). The recommended cutoff is a threefold increase in the concentration of serum amylase or lipase, while a cutoff of 50μg/L is applied to urinary trypsinogen type 2 (also with a commercially available dipstick test) (Besselink et al., 2013; Clavien et al., 1989; Kemppainen et al., 1997; Rainio et al., 2021; Rompianesi et al., 2017; Yadav et al., 2002). An increase in the amylase concentration occurs within hours of symptom onset and the amylase concentration falls to normal within 3–5 days irrespective of the clinical progression of disease (Matull et al., 2006; Tenner et al., 2013). The total amylase concentration is affected by salivary gland production, as well as factors such as renal function impairment, obesity, hypertriglyceridemia, and alcohol use (Nakajima, 2016). Serum lipase remains elevated for 1–2 weeks following AP, providing a possible diagnostic benefit when patients seek medical attention following a moderate delay. In 2017, a Cochrane analysis of published studies demonstrated that the diagnostic sensitivity and specificity of serum amylase, serum lipase, and urine trypsinogen type 2 related to AP were similar. One conclusion was that a diagnostic elevation in these laboratory markers is not present in 20–30% of patients with AP, and that false-positive results are found in around 10% of patients without AP (Rompianesi et al., 2017).

Upon admission to hospital, laboratory tests, including analyzing liver function, as well as calcium, triglycerides, blood count, electrolytes, creatinine, blood urea nitrogen, and CRP levels, should be performed (Besselink et al., 2013; Lankisch et al., 2015). Utilizing CRP combined with interleukin-6 (IL-6) may be useful in predicting nonmild AP (Sternby et al., 2017). A threefold increase in the alanine aminotransferase (ALAT) level carries a 95% positive predictive value in identifying ABP. However, ALAT is normal in 11% of patients with ABP, and a threefold ALAT increase is absent in half of patients with ABP (Dholakia et al., 2004; Tenner et al., 1994).

2.5.3 IMAGING

Several imaging modalities are available for detecting AP, but the gold standard has thus far remained contrast-enhanced computed tomography (CECT) given its ready availability and diagnostic precision (Strömberg et al., 2007). In AP, CECT is primarily used in cases involving diagnostic uncertainty or when a patient's condition fails to improve, deteriorates, or other clinical traits suggest complications of AP, and when planning invasive interventions for AP (Besselink et al., 2013; Paola et al., 2020; Tenner et al., 2013). Optimally, if imaging is deemed necessary, CECT is postponed for at least 3–4 days from symptom onset to allow for the accurate radiological evaluation, since the appearance of imaging features of pancreatic parenchymal necrosis are delayed in 20% of patients with NP (Balthazar et al., 1990).

Magnetic resonance imaging (MRI) can be also used as a tool in the primary diagnosis of AP; however, its suitability is restricted by its availability, the longer duration for imaging required compared with CECT, and a diminished applicability in critically ill patients. Yet, magnetic resonance cholangiopancreatography (MRCP) provides a noninvasive alternative for the imaging of the biliary tree in suspected choledocholithiasis and cholangitis. Gadolinium-enhanced MRI appears to be at least as sensitive as CECT in detecting pancreatic necrosis and might outperform CECT in evaluating the contents of necrotic collections. Furthermore, secretin-enhanced MRCP can provide additional information related to a possible disconnected pancreatic duct (Maher et al., 2004; Paola et al., 2020). Endoscopic ultrasonography appears more sensitive than MRCP in the detection of microlithiasis (Somani et al., 2017).

Diagnostic imaging with ultrasonography (US), CECT, or MRI combined with MRCP is recommended when a biliary etiology of AP is suspected, and screening for the possibility of gallstones using US is included in the workup of AP etiology (Besselink et al., 2013; Leppäniemi et al., 2019; Tenner et al., 2013). When suspected cholangitis accompanies ABP, urgent ERCP is recommended (within 24 h) (Besselink et al., 2013; Tenner et al., 2013). Guidelines recommend ERCP when ABP is accompanied by obstructing common bile duct stones, although the urgency of ERCP in these instances remains somewhat contested (Besselink et al., 2013; Leppäniemi et al., 2019; Schepers et al., 2020; Tenner et al., 2013).

2.6 CLASSIFICATION

2.6.1 SCORING INDICES

Several scoring systems can be used to predict and evaluate AP severity. The Acute Physiology and Chronic Health Evaluation II (APACHE II), the sequential organ failure assessment (SOFA) score, and the multiple organ dysfunction score are indices developed to predict mortality among critically ill patients. Although not specifically developed for AP, these indices are utilized to identify patients likely to experience an increased severity and mortality risk in AP (Cho et al., 2015; Khanna et al., 2013; Knaus et al., 1985; Marshall et al., 1995; Vincent et al., 1996; Wu et al., 2008). A modification to the multiple organ dysfunction score, resulting in the modified Marshall score, serves as the basis for OF classification in AP based on guideline recommendations (see Chapter 2.6.2) (Banks et al., 2013).

Examples of severity assessment tools developed specifically for AP include the Ranson score, the bedside index of severity in AP, and the computed

tomography (CT) severity index in AP. These were developed for predicting the severity of the course of disease in AP (Balthazar et al., 1990; Banks et al., 2013; Ranson et al., 1974; Singh et al., 2009). In **Table 1**, the scoring indices are summarized with their predictive value for SAP and mortality.

A stratification tool for the identification of a nonsevere outcome has also been proposed (the harmless acute pancreatitis score, HAPS). This utilizes only elementary data available for all patients with AP upon admission (abdominal guarding/rebound tenderness, hematocrit [>43% men, >40% women], and creatinine [>177 μmol/L]). In the absence of these three measurements, HAPS shows a 97–98% positive predictive value in identifying a nonsevere course of disease in AP (Lankisch, Weber-Dany, Hebel, et al., 2009; Ma et al., 2020; Maisonneuve et al., 2021; Teng et al., 2021).

Table 1 *Scoring indices and their predictive value* (Balthazar et al., 1990; Khanna et al., 2013; Knaus et al., 1985; Ranson et al., 1974; Senapati et al., 2014; Singh et al., 2009; Vincent et al., 1996; Wu et al., 2008).

	Prediction of severe acute pancreatitis	Prediction of mortality
General scoring indices:		
Acute Physiology and Chronic Health Evaluation II* *Evaluates potential deviations for 12 physiological variables with a score of 0–4 per variable (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, acid–base balance, sodium, potassium, creatinine, hematocrit, white blood cell count, and Glasgow coma scale) Additionally, this scoring system considers age and chronic health status* → ***Score range: 0–71***	***Score ≥ 8***: Sensitivity 80–81% Specificity 63–83%	***Score ≥ 8***: Sensitivity 100% Specificity 58–64%
Sequential Organ Failure Assessment Score* *Evaluates potential deviations for physiological variables from six organ systems (respiratory, cardiovascular, renal, coagulation, liver, and central nervous system) with a score of 0–4 for each organ system* → ***Score range: 0–24*** *(see* ***Table 3****)*	**Score ≥ 7**: Sensitivity 14% Specificity 100%	**Score ≥ 7**: Sensitivity 50% Specificity 99%
Scoring indices for acute pancreatitis:		
Ranson score* *Evaluates the following 11 physiological variables (1 point per variable) (for non-gallstone pancreatitis) Upon admission: Age >55 years, white blood cell count >16 000 / mm^3, lactate dehydrogenase >350 U/L, aspartate aminotransferase >250 U/L, and blood glucose >11 mmol/L At 48 hours: hematocrit decrease >10%, blood urea nitrogen increase >1.7 mmol/L, serum calcium <2.0 mmol/L, arterial partial O_2 pressure <60 mmHg, base deficit >4 mEqL, and fluid loss >6 L* → ***Score range: 0–11***	***Score ≥ 3***: Sensitivity 84–93% Specificity 52–78%	***Score ≥ 3***: Sensitivity 100% Specificity 47–59%
Bedside index of severity* *Each of the following are scored with 1 point: Blood urea nitrogen >8.9 mmol / L Impaired mental status (disorientation, lethargy, somnolence, or coma) Systemic inflammatory response syndrome criteria fulfilled Age >60 years Pleural effusion on imaging* → ***Score range: 0–5***	***Score ≥ 2***: Sensitivity 74% Specificity 68% ***Score ≥ 3***: Sensitivity 25–94% Specificity 77–95%	***Score ≥ 2***: Sensitivity 89% Specificity 56% ***Score ≥3***: Sensitivity 25–92% Specificity 76–93%
Computed tomography severity index *Grading of acute pancreatitis (Balthazar score): Normal pancreas (0 points), enlarged pancreas (1 point), pancreatic abnormalities with peripancreatic inflammation (2 points), single fluid collection (3 points), 2 or more collections, or gas (4 points) Pancreatic necrosis: None (0 points), <30% (2 points), 30–50% (4 points), and >50% (6 points)* → ***Score range: 0–10***	***Score ≥ 5***: Sensitivity 65% Specificity 50%	***Score ≥ 5***: Sensitivity 71% Specificity 45%

*Score calculated within 24 h of admission.

2.6.2 THE REVISED ATLANTA CLASSIFICATION

In this thesis, the grading of AP is based on the revised Atlanta classification (RAC) score. Disease severity is characterized by the presence of OF and local complications (see Chapter 2.7.1). However, RAC acknowledges OFs of the respiratory, cardiovascular, and renal organ systems only. A score equal to or exceeding 2 based on the modified Marshall scoring system defines OF (**Table 2**) (Banks et al., 2013).

Table 2 *Modified Marshall scoring system. Modified from* Banks et al., 2013.

Organ system	Score				
	4	3	2	1	0
Respiratory* PaO2/FiO2	≤101	101–200	201–300	301–400	>400
Cardiovascular† Systolic blood pressure	<90, pH < 7.2	<90, pH < 7.3	<90, not fluid responsive	<90, fluid responsive	>90
Renal‡ Creatinine	>439	311–439	170–310	134–169	≤134

Score >2 for any of these organ systems indicates an organ failure.
*PaO2/FiO2, ratio of partial arterial oxygen pressure (mmHg) to fractional inspired oxygen (expressed as a percentage).
†Systolic blood pressure (mmHg) in the absence of supportive vasoactive drugs.
‡Serum creatinine (µmol/l). In patients with chronic renal failure, this score depends on a worsening renal function from baseline, but no formal correction for this exists.

Since the modified Marshall scoring system does not take into account organ-specific supportive treatment, the SOFA score remains the preferred method for OF assessment in patients treated in ICU (**Table 3**) (Banks et al., 2013; Vincent et al., 1996). However, in the context of defining OF according to RAC in ICU-treated patients, only respiratory, cardiovascular, and renal OFs are considered.

Table 3 *Sequential organ failure assessment score. Modified from* Vincent et al., 1996.

Organ system	Score			
	4	3	2	1
Respiratory PaO2/FiO2, mmHg*	<100†	100–199†	200–299	<400
Cardiovascular‖ Hypotension	Dopamine >15 Norepinephrine >0.1	Dopamine >5 Norepinephrine ≤0.1	Dopamine ≤5	MAP <70 mmHg
Renal Creatinine (µmol/L) **or** Urine output (ml/day)	>440 <200	300–440 <500	171–299	110–170
Coagulation Platelets x 10^9/L	<20	<50	<100	<150
Liver Bilirubin (µmol/L)	>204	102–204	33–101	20–32
CNS Glascow coma scale	<6	6–9	10–12	13–14

*PaO2/FiO2, ratio of partial arterial oxygen pressure (mmHg) to fractional inspired oxygen (expressed as a percentage).
†With respiratory support.
‖Adrenergic medications are expressed as µg/kg per min.
Abbreviation: MAP, mean arterial pressure.

2.6.2.1 Mild acute pancreatitis

Based on RAC, no OF or local complications accompany mild acute pancreatitis. At least 65–84% of patients with AP suffer from mild disease (Acevedo-Piedra et al., 2014; Choi et al., 2014; Kwong et al., 2016; Sternby et al., 2019).

2.6.2.2 Moderately severe acute pancreatitis

Transient OF (lasting less than 48 h) or the presence of local complications define moderately severe AP based on RAC (Banks et al., 2013). Local complications (see Chapter 2.7.1) include liquefied or necrotic acute pancreatic and/or peripancreatic collections, splanchnic venous thrombosis (SVT), and colonic necrosis (Banks et al., 2013). The rate of moderately severe AP reaches 10–40% (Choi et al., 2014; Kwong et al., 2016).

2.6.2.3 Severe acute pancreatitis (SAP)

Persistent respiratory, cardiovascular, or renal OF (lasting longer than 48 h) defines SAP (Banks et al., 2013). The reported incidence of SAP is 5.9 per 100 000 per year (Sarri et al., 2019). In published series, SAP occurrence ranges from 3–12% of patients with AP (Acevedo-Piedra et al., 2014; Choi et al., 2014; Kwong et al., 2016; Sternby et al., 2019; Teng et al., 2021).

2.7 COMPLICATIONS

2.7.1 LOCAL COMPLICATIONS

Local complications in AP include fluid-filled collections or collections containing necrotic debris within or adjacent to the pancreatic parenchyma, or both. These collections can be classified according to their demarcation (walling off) from the surrounding structures. Other local complications include SVT, the involvement of the stomach, small bowel, colon, or biliary tree, and disconnected pancreatic duct syndrome (DPDS).

2.7.1.1 (Peri-) pancreatic fluid collections

Peripancreatic fluid collections primarily occur in patients with interstitial edematous AP (**Table 4**). Within the first four weeks, they are defined as acute peripancreatic fluid collections (APFCs) and later as pseudocysts (Banks et al., 2013). APFCs occur in 9–43% of patients with AP and in half of patients with SAP, with a considerable rate of spontaneous resolution (Lenhart & Balthazar, 2008; Manrai et al., 2018; Maringhini et al., 1999; Pá Rniczky et al., 2016;

Sarathi Patra et al., 2014; Sternby et al., 2019). A contemporary definition of a true pancreatic pseudocyst should consist of a (nonepithelial) walled-off amylase-rich fluid-filled collection (devoid of necrosis) within or adjacent to the pancreatic parenchyma (Banks et al., 2013). Pseudocysts occur in 0–15% of patients following AP (Kim & Kim, 2012; Manrai et al., 2018; Maringhini et al., 1999; Sarathi Patra et al., 2014). Since adopting RAC in 2013, classifying collections as pseudocysts following AP has become rare, given that mature collections following AP commonly contain varying amounts of necrosis (**Table 4**) (Manrai et al., 2018; Sarathi Patra et al., 2014). Furthermore, pseudocysts related to AP tend to decrease in size or resolve within six months in at least 70% of patients (Kim & Kim, 2012).

2.7.1.2 (Peri-) pancreatic necrosis

NP affecting only a pancreatic parenchyma is relatively rare (3–26%), with 23–49% of patients involving peripancreatic necrosis only, and 47–64% impacting both pancreatic and peripancreatic necrosis (**Table 4**) (Bakker et al., 2013; Rana et al., 2015; Sakorafas et al., 1999b; Sternby et al., 2019; van Grinsven et al., 2018). Acute necrotic collections (ANCs) are immature deposits of necrosis occurring in and around the pancreas without visible walling off (Banks et al., 2013). Based on consensus definitions, demarcation of necrotic collections occurs four weeks from symptom onset, however, the process presumably occurs in a more dynamic fashion in each patient (van Grinsven et al., 2018). The reported incidence of ANC in NP ranges from 90–100% (Kumar et al., 2021; Manrai et al., 2018; Sarathi Patra et al., 2014). Furthermore, the demarcation of necrotic collections is estimated to occur in 50–90% of patients with ANC, whereupon collection is referred to as walled-off necrosis (WON, **Table 4**) (Kumar et al., 2021; Manrai et al., 2018; Sarathi Patra et al., 2014).

Table 4 *Definition of (peri-) pancreatic collections (*Banks et al., 2013*).*

		Type of acute pancreatitis	
		Edematous	**Necrotizing**
Time	**<4 weeks**	**APFC:** Peripancreatic fluid No necrotic debris No encapsulation	**ANC:** Intra- and/or extrapancreatic Varying degree of necrosis and fluid No encapsulation
	>4 weeks	**Pseudocyst:** Only liquid content Usually located peripancreatically Round or oval shape Encapsulated	**WON:** Intra- and/or extrapancreatic Varying degree of necrosis and fluid Encapsulated

Abbreviations: ANC, acute necrotic collection; APFC, acute peripancreatic fluid collection; WON, walled-off necrosis.

2.7.1.3 Infected pancreatic necrosis (IPN)

Several potential pathways leading to IPN have been proposed: via hematogenous bacterial spread due to an impaired gut barrier dysfunction of the small bowel, via bacterial transmural migration directly or indirectly (via ascites/lymphatics/hematogenous) from the colon, or via bacterial spread from the biliary tree or duodenum through the main pancreatic duct (MPD) (Beger & Rau, 2007; Besselink, van Santvoort, Renooij, et al., 2009; Fritz et al., 2010; Schmid et al., 1999; Wu et al., 2014). IPN occurs in 21–43% of NP, usually 2–4 weeks following symptom onset (Ashley et al., 2001; Beger et al., 1997; Büchler et al., 2000; Hartwig et al., 2002; Lariño-Noia et al., 2021; Perez et al., 2002; Petrov et al., 2010; Schepers et al., 2019; Sternby et al., 2019). Early enteral nutrition reduces the risk of IPN in patients with suspected SAP (Petrov et al., 2008). Persistent OF, the extent of pancreatic parenchymal necrosis, and bacteremia in patients with pancreatic parenchymal necrosis are associated with an increased IPN risk (Besselink, van Santvoort, Boermeester, et al., 2009; Padhan et al., 2018; Rau et al., 2006; Tao et al., 2004). A recent meta-analysis reported that an older age, a gallstone etiology, more than 50% of pancreatic parenchymal necrosis, delayed enteral nutrition, multiple or persistent OF, and invasive mechanical ventilation all associated with IPN in NP or SAP (Tran et al., 2022).

Clinically, IPN may be difficult to distinguish since infectious symptoms are reminiscent of SAP symptoms. Late new-onset OF coupled with a fever and a persistent increase in inflammatory markers (CRP or procalcitonin) is suspicious of IPN in patients with NP (Chen et al., 2017; Mofidi et al., 2009; Müller et al., 2000). Visible gas in necrotic collections on CECT suggests IPN, although gas in necrotic collections is present in only 17–56% of patients with IPN (Paola et al., 2020; Rodriguez et al., 2008; van Baal et al., 2014; van Grinsven et al., 2018). Thus, diagnosis may be achieved through microbiological culturing of fine-needle aspirates from necrosis, although 12–25% of patients have false-negative and 2–10% have false-positive results (Rau et al., 2003; Rodriguez et al., 2008; van Baal et al., 2014). Microbiological sampling of necrotic debris obtained via percutaneous or endoscopic drainage and/or (index) necrosectomy procedures may also confirm a diagnosis. In one-fifth of patients, the treatment of IPN must be initiated based on clinical suspicion alone (Rodriguez et al., 2008). An IPN suspicion accompanied by septic shock warrants immediate administration of intravenous antibiotics regardless of the possibility of microbiological sampling of necrosis (Garret et al., 2020). Elevated levels of lactate and a quick SOFA determiniation (developed to identify patients at an increased risk of mortality) could be used as a screening tool for sepsis or septic shock, which could help guide the immediate initiation of antibiotic treatment for clinically suspected IPN-associated sepsis. When two or more of the following parameters are present, quick SOFA determiniation is considered positive: systolic blood pressure

<100 mmHg, respiratory rate ≥22 per minute, or an altered mental status (Glasgow coma scale <15) (Evans et al., 2021).

2.7.1.4 Other local complications

Splanchnic vein thrombosis (SVT). Splanchnic vein thrombosis (SVT) is defined as a thrombus located in the splenic, mesenteric, and/or portal veins. SVT is a recognized complication of AP, occurring in up to half of all patients with NP, colocalized in the vicinity of the pancreatic necrosis (Easler et al., 2014; Roch et al., 2019). SVT manifests in the splenic vein only in 40–50% of cases, whereas the portal vein is affected in 25–50% of patients (Gonzelez et al., 2011; Roch et al., 2019). According to prospective register-based data from nearly 5 000 admissions for AP, SVT occurs in 1% of patients within 30 days of discharge (Robbins et al., 2021). In AP cohorts from tertiary referral centers or in patients treated with necrosectomy, SVT occurs in 5–15% of patients, predominantly among patients with SAP (Connor et al., 2005; Gomatos et al., 2016; Gonzelez et al., 2011).

Stomach. Only a few studies have evaluated delayed gastric emptying (DGE) and gastric outlet obstruction (GOO, i.e., DGE due to mechanical obstruction) in patients with AP. GOO in AP results primarily from an outside compression of the necrotic collections, although in 15% of cases it develops due only to severe bowel wall edema (Qu et al., 2021). Between 4–8% of patients with AP and pancreatic collections or who need ICU treatment experience GOO (Qu et al., 2021; Sugimoto et al., 2018; Zhang et al., 2015). GOO generally occurs 1–3 months following symptom onset, whereas DGE manifests earlier, at around two weeks into the course of disease (Zhang et al., 2015). Between 60–80% of patients with GOO also experience a biliary obstruction(Qu et al., 2021; Sugimoto et al., 2018).

Small bowel. A rare serious complication of NP affecting the pancreatic head is the perforation of the duodenal wall resulting from necrosis, with only a few cases reported in the literature (Archer et al., 1991; Sakorafas et al., 1999a). Duodenal fistulas occur more frequently, accounting for 33% of NP-associated fistulas, whereas jejunal and ileal fistulas account for only 8% of cases (Jiang et al., 2016).

Main pancreatic duct. DPDS (also referred to as disconnected pancreatic tail syndrome or disconnected left pancreatic remnant) is characterized by a disruption of the MPD due to pancreatic necrosis (of at least 2 cm), a viable distal pancreatic remnant, and leakage from the MPD upon pancreatography (Sandrasegaran et al., 2007). Anatomically, the pancreatic neck seems particularly liable to the complete loss of MPD continuity (Howard et al., 2001). The reported occurrence of DPDS is 16–23% in patients with fluid collection or a suspected pancreatic fistula upon imaging, and 50% in patients

with NP (Lawrence et al., 2008; Maatman, Roch, et al., 2020; Sugimoto et al., 2018). Clinically, the accumulation of pancreatic juices into WON always progresses, and spontaneous healing has not been reported.

Biliary tract. Extrahepatic biliary strictures occur weeks or months after AP onset. These affect 16% of tertiary referral center patients with NP (as defined by a 75% narrowing) and are increasingly associated with factors such as IPN, SVT, necrosis located in the pancreatic head, and previous necrotic collection interventions (Maatman, Ceppa, et al., 2020). Biliary strictures occur in around 6% of patients with AP-associated pancreatic collections (fluid or necrosis) and in patients undergoing surgical necrosectomy (minimally invasive/open) for NP (Chaudhary et al., 2001; Connor et al., 2005; Sugimoto et al., 2018). GOO coexists with biliary strictures in 30% of cases (Sugimoto et al., 2018).

Colon. Colonic involvement in AP is defined as ischemia, strictures, perforation, and fistulas of the colon, occuring in 1–5% of AP patients, predominantly in moderately severe AP and SAP (6–40%) (Maatman, Nicolas, et al., 2020; Mohamed & Siriwardena, 2008; Nakanishi et al., 2016; van Minnen et al., 2004). The occurrence of colonic fistulas increases to up to 20% in NP, primarily in patients with IPN (Gao et al., 2020; Jiang et al., 2016; Wei et al., 2016). The possible underlying mechanisms for colonic injury appear to result from the direct contact of pancreatic enzymes due to (peri-) pancreatic necrosis compressing the colon, following hemodynamic shock with subsequent insufficient colonic perfusion, or due to pressure necrosis from drainage tubes (van Minnen et al., 2004). In clinical practice, the presenting symptoms among these patients may be difficult to distinguish from other symptoms of SAP, since pain and symptoms of inflammation resemble unremarkable events. Thus, one-tenth of colonic complications in AP are diagnosed postmortem (Mohamed & Siriwardena, 2008). Colonic complications occur on average within weeks following symptom onset, and clinical presentation may include occlusive and GI-bleeding symptoms (beyond infectious symptoms and pain).

Bleeding. Vascular involvement (other than SVT) in AP remains relatively rare. Prolonged exposure to pancreatic enzymes may lead to a weakening of the vasculature wall and bleeding, although bleeding may also occur due to an iatrogenic injury following invasive interventions for NP (Flati et al., 2003). Bleeding complications occur a median one month following presentation, with an estimated occurrence range of 1–6% (Balthazar & Fisher, 2001; Sharma et al., 2008). Specifically, bleeding occurs in the retroperitoneum, gastrointestinal tract, or the peritoneal cavity. In cases of arterial bleeding, the site of bleeding is the splenic artery in up to half of all cases, followed by bleeding from the gastro- and pancreaticoduodenal arteries (Evans et al., 2017; Flati et al., 2003; Zyromski et al., 2007). In 60% of patients, a ruptured

pseudoaneurysm causes bleeding, whereas in 20% of patients, bleeding originates from the pseudocyst without a visible pseudoaneurysm, and in 20% from the capillary, venous, or other small vessels (Evans et al., 2017).

2.7.2 SYSTEMIC COMPLICATIONS

2.7.2.1 Organ failure

In AP, an acinar cell injury with subsequent autodigestion is followed by local recruitment and activation of inflammatory cells. The resulting inflammatory responses exacerbate local tissue damage, leading to further upregulation of pro- and anti-inflammatory chemokine production (Bhatia et al., 2005). The amplification of these inflammatory responses initiates an overwhelming systemic inflammatory response symdrome (SIRS) and may ultimately lead to multiple organ dysfunction syndrome (Garg & Singh, 2019; Mayer et al., 2000; Norman et al., 1997). These mechanisms fuel the early development of OF and mortality, whereas late OF is related to septic inflammation following an inflammatory response to pathogen-associated molecular patterns (Garg & Singh, 2019). However, a binary division as early (due to SIRS) or late (due to infection) OF (Padhan et al., 2018) simplifies the clinical picture, since the release of inflammatory mediators associated with SIRS are not confined to the earliest stages of AP, and infectious complications may also occur early (Besselink, van Santvoort, Boermeester, et al., 2009; Moran et al., 2022).

In NP, 38% of patients develop persistent OF (Schepers et al., 2019), developing within the first week of symptom onset in more than 50% of patients with SAP (Schepers et al., 2019; Shi et al., 2020; Sternby et al., 2019). Half of patients who develop persistent OF present with signs of OF upon hospital admission (Buter et al., 2002; Johnson et al., 2001; Johnson & Abu-Hilal, 2004; Padhan et al., 2018). Respiratory failure occurs in 92% of patients with SAP, followed by cardiovascular failure in 16–80% of patients and renal failure in 18–44% of patients (Schepers et al., 2019; Shi et al., 2020). In these two studies, persistent OF was defined as a cardiovascular or renal SOFA or a modified Marshall score ≥2, or a respiratory SOFA or modified Marshall score ≥3, which lasted longer than 48 h. In SAP, patients experience a median of 19, 7, and 10 days of persistent respiratory, cardiovascular, and renal failure, respectively (Schepers et al., 2019). Age, comorbidities, and a higher percentage of pancreatic parenchymal necrosis are associated with the risk of developing OF (Schepers et al., 2019). In patients with extrapancreatic necrosis only, persistent OF develops in 21% and persistent multiple OF (MOF) in 15%, compared with 45% and 36%, respectively, in pancreatic parenchymal necrosis ($P < 0.001$) (Bakker et al., 2013). The CRP level at 48 h after hospital admission correlates with the development of OF according to the multiple organ dysfunction score (Mofidi et al., 2006). Among the

predictive indices, the SOFA score and 48-h Ranson score predict the development of persistent OFs, and persistent SIRS for 48 h after admission predicts the development of multiple organ dysfunction syndrome (Baey et al., 2021; Mofidi et al., 2006; Teng et al., 2021).

2.7.2.2 Extrapancreatic infections

The rate of extrapancreatic infections (EPIs) in AP is about 15–32%, manifesting mainly as respiratory (5–9%), urinary tract (2–4%), or biliary infections (3%), as well as bacteremia (1–8%) (Brown et al., 2014; Marstrand-Joergensen et al., 2020). Some tertiary referral centers report EPI in more than half of all patients with NP, whereas other series with moderately severe AP and SAP show fewer cases of pneumonia, bacteremia, urinary, and gastrointestinal tract infections (13%, 5%, 3%, and 4%, respectively) (Lu et al., 2019; Xue et al., 2009). On average, EPI occurs earlier than IPN, primarily within the first two weeks (Besselink, van Santvoort, Boermeester, et al., 2009; Lu et al., 2019; Xue et al., 2009).

2.7.2.3 Abdominal compartment syndrome

Intra-abdominal hypertension (IAH) is defined as a sustained or repeated intra-abdominal pressure (IAP) exceeding 12 mmHg, whereas abdominal compartment syndrome (ACS) is defined as a sustained IAP exceeding 20 mmHg in combination with a new or worsening existing organ dysfunction (Kirkpatrick et al., 2013). One in five or six patients with AP experience IAH (Aitken et al., 2014). Moreover, IAH develops in more than 50% of patients treated in a high dependency unit or ICU, and ACS develops in 9–56% of patients with SAP (Al-Bahrani et al., 2008; Bhandari et al., 2013; Chen et al., 2008; Dambrauskas et al., 2009; Davis et al., 2013; de Waele et al., 2005; Ke et al., 2012; Keskinen et al., 2007; Kurdia et al., 2020; Smit et al., 2016). One hypothesis proposes that massive edema due to permeability disturbances in AP predispose patients to ACS, possibly exacerbated by excessive fluid resuscitation, the formation of ascites, APFCs, and gastric or bowel obstruction (van Brunschot, Schut, et al., 2014). A positive initial 24-h fluid balance, the number of fluid collections, and serum calcium levels independently associate with IAH in SAP (Ke et al., 2012).

2.7.2.4 Ischemia

A small number of patients with SAP develop intra-abdominal ischemia, which is associated with ACS, but also rarely occurs in patients with IAH (Smit et al., 2016). Patients with ACS in SAP often experience severe hemodynamic shock, which possibly predisposes intra-abdominal organs to develop ischemia via mechanisms similar to those found in nonocclusive mesenteric ischemia

(Trompeter et al., 2001). The reported occurrence of nonocclusive mesenteric ischemia in AP is 0.5%, climbing to 5–13% in nonmild AP (Hirota et al., 2003; Reichling et al., 2020).

2.7.3 LONG-TERM MORBIDITY

In the longer term, chronic structural changes of the pancreas are observed in half of all patients following an attack of AAP, predominantly among patients with a more severe course of disease and recurrent attacks of AP (Nikkola et al., 2014). Recurrent pancreatitis occurs in 32–46% of patients following AAP, especially in younger patients, and in one-quarter of patients following SAP (Appelros et al., 2001; Halonen et al., 2003; Pelli et al., 2000). Persistent drinking after experiencing (moderate or severe) AP results in a 58% and 75%, respectively, risk of recurrent and chronic AP (Shimosegawa et al., 2006). Pancreatic exocrine insufficiency occurs in up to one-third of patients following AP, predominantly after NP and AAP (Boxhoorn et al., 2021; Hollemans et al., 2018; Huang et al., 2019). Within six months among patients treated invasively due to a suspected or verified IPN, one in five patients experience pancreatic endocrine insuffiency (diabetes mellitus) and 35–50% from pancreatic exocrine insufficiency. During long-term follow-up, the risk of diabetes affects 41–54% of patients after SAP, among whom half require insulin treatment (Doepel et al., 1993; Halonen et al., 2003). Among survivors following SAP, the quality of life seems comparable to that among healthy matched peers, with almost 90% eventually able to return to work (Doepel et al., 1993; Halonen et al., 2003; Soran et al., 2000).

2.8 TREATMENT

AP treatment relies primarily on organ support and symptom relief. Early goal-directed fluid resuscitation, monitoring for incipient OF, treatment of existing OF, and early enteral nutrition when tolerated are the mainstays of AP treatment (Besselink et al., 2013; Leppäniemi et al., 2019; Tenner et al., 2013). Additionally, sufficient pain management according to local pain management protocols is recommended, since no evidence indicates the use of one analgesic (or administration route) over another (Stigliano et al., 2017). Prophylactic antibiotics have not demonstrated a significant clinical benefit to patients with AP (Villatoro et al., 2010). On-demand antibiotics are often needed for patients with SAP for sepsis, IPN, and EPI/nosocomial infections (de Waele et al., 2014; Montravers et al., 2019). Moroever, organ-supportive treatment and monitoring depend on the OF status, and include **inotropic medication** for cardiovascular failure, noninvasive and **mechanical ventilation** for respiratory failure, and ultimately **renal replacement therapy** for renal failure (Jaber et al., 2006; Nassar & Qunibi, 2019). The

routine monitoring of IAP is recommended at least in mechanically ventilated patients (Besselink et al., 2013; Leppäniemi et al., 2019).

At a minimum, ERCP with biliary sphincterotomy and stone retrieval is indicated in patients with ABP and suspected cholangitis (urgent, within 24 h), as well as in ABP without cholangitis, but persistent obstructive jaundice due to obstructive common bile duct calculi (Arvanitakis et al., 2018; Besselink et al., 2013; Oría et al., 2007; Schepers et al., 2020; Tenner et al., 2013; Tse & Yuan, 2012). To reduce the risk of further biliary complications, same-admission cholecystectomy is recommended for patients with mild ABP who are fit for surgery. In NP of a biliary origin, cholecystectomy within eight weeks is recommended provided that (peri-) pancreatic collections have resolved by that time (Banks et al., 2013; Besselink et al., 2013; da Costa et al., 2015; Hallensleben et al., 2021; Tenner et al., 2013). When interventions toward necrotic collections are deemed necessary, it is best to delay them until necrosis walling off has occurred if a patient's condition allows for it (Arvanitakis et al., 2018; Besselink et al., 2013; Isaji et al., 2015; Leppäniemi et al., 2019; Tenner et al., 2013).

Table 5 summarizes some of the landmark studies regarding the clinical evaluation and management of complicated AP.

Table 5 *Landmark clinical studies (Balthazar et al., 1990; Baron et al., 1996; Boxhoorn et al., 2021; Bradley & Allen, 1991; da Costa et al., 2015; Horvath et al., 2001; Kalfarentzos et al., 1997; Mier et al., 1997; Ranson et al., 1974; Runzi et al., 2005; van Brunschot, van Grinsven, et al., 2018; van Santvoort et al., 2010).*

Study	Primary result
Ranson, 1974	11 clinical variables (at admission and at 48-h follow-up) that predict a severe course of disease in acute pancreatitis Provided an understanding of the importance of severity risk stratification
Balthazar, 1990	A stratification tool based on a contrast-enhanced CT scan evaluating pancreas morphology and the percentage of parenchymal necrosis to predict a severe course of disease
Bradley, 1991	Reporting the notion that patients with sterile necrosis may be treated without debridement
Baron, 1996	The first description of an endoscopic transluminal drainage of collection with organized necrotic content
Kalfarenzos, 1997	Enteral nutrition leading to fewer septic complications in severe acute pancreatitis suggesting it as a first-line choice for nutrition
Mier, 1997	Established the harmfulness of very early necrosectomy in severe necrotizing pancreatitis
Horvath, 2001	Described a technique of minimally invasive surgical necrosectomy following the route of a previously placed percutaneous drainage
Runzi, 2005	Established the idea that not all patients with infected pancreatic necrosis require urgent surgery, since antibiotics may adequately treat some patients
van Santvoort, 2010	Established the concept that a step-up treatment algorithm is superior to immediate necrosectomy, and that 35% of patients with a verified or suspected infected pancreatic necrosis only require percutaneous drainage
Da Costa, 2015	Same admission cholechystectomy reduces the rate of recurrent gallstone complications following mild acute biliary pancreatitis
van Brunschot, 2018	Endoscopic step-up approach is not superior compared with surgical step-up approach regarding the study's primary endpoint of major complications or death within six months The endoscopic step-up group experienced fewer pancreaticocutaneous fistulas and had shorter length hospital stays
Boxhoorn, 2021	Immediate (endoscopic or percutaneous) drainage of suspected or confirmed infected pancreatic necrosis is not superior to delayed drainage Postponing drainage leads to fewer total interventions (drainage or necrosectomy) Postponing drainage leads to successful conservative antibiotic treatment only in one-third of patients

2.8.1 EARLY SEVERITY STRATIFICATION

The hopes of improving outcomes in SAP rely on developing accurate tools for predicting the risk of a subsequent early OF (Isenmann et al., 2001; Johnson et al., 2001; Padhan et al., 2018; Singh, Wu, Bollen, Repas, Maurer, Mortele, et al., 2009; Sternby et al., 2019). Retrospective analysis of scoring indices revealed that APACHE II ≥8, a bedside index of severity in AP ≥2, a Ranson score ≥3, and a CT severity index ≥5 served as the optimal cutoff values for predicting SAP (Khanna et al., 2013). According to the guidelines for the management of SAP, CRP ≥150 48 h after admission associated with SAP (Leppäniemi et al., 2019). An optimal stratification tool would accurately guide the early choice for the management of patients with potentially evolving

SAP, since the treatment of incipient or existing OF is best accomplished in ICU due to the high patient acquity (Besselink et al., 2013; Leppäniemi et al., 2019). Presently, clinical and radiological scoring systems perform this task equally well. Thus, early imaging is not indicated from a severity prediction perspective alone (Bollen et al., 2012). Recognizing SIRS is important in the early assessment of patients with AP since persistent SIRS increases the risk of developing OFs, while succesful alleviation associates with improved outcomes (Mofidi et al., 2006). A positive quick SOFA should raise awareness of the potential need for ICU treatment (Evans et al., 2021). Furthermore, the hemoconcentration at admission and/or inadequate early (<24 h) fluid resuscitation associate with developing OF and NP (Baillargeon et al., 1998; Brown et al., 2000, 2002).

2.8.2 FLUID RESUSCITATION

Generally in AP, early but optimized fluid resuscitation with repeated monitoring of hemodynamic targets is warranted in order to counter hypovolemia and maintain sufficient tissue perfusion (Besselink et al., 2013; Leppäniemi et al., 2019). Limited evidence recommends the use of Ringer's lactate for fluid resuscitation in patients with AP (Besselink et al., 2013; Leppäniemi et al., 2019). This recommendation stems from findings that SIRS occurs less often in patients resuscitated with Ringer's lactate than with saline, a result supported by a systematic review and meta-analysis(Iqbal et al., 2018; Lipinski et al., 2015; B. U. Wu et al., 2011). The timeframe for action is crucial, since about half of patients with SAP already suffer from ongoing organ dysfunction when admitted to hospital (Buter et al., 2002; Johnson et al., 2001; Johnson & Abu-Hilal, 2004). However, excessive fluid resuscitation also carries undesired consequences. In SAP, endothelial dysfunction leads to the accumulation of fluids in the third space, a vicious cycle worsened by fluid overload, leading ultimately to increased risks of acute respiratory distress syndrome, impaired renal function, coagulopathy, and ACS (Hines & Pandol, 2019). Thus, fluid therapy should depend not only upon AP itself, but also tailored according to each patient (considering factors such as age, weight, sex, and cardiovascular health) and guided by rigorous monitoring. When a patient's status mandates large volume crystalloids, it should be combined with the use of albumin (Evans et al., 2021). Ultimately, fluid resuscitation is initially guided by changes in the pulse rate, the mean arterial pressure (MAP), and urine output, as well as biochemical markers of the volemic state and tissue perfusion (hematocrit, blood urine nitrogen, creatinine, and lactate). It is difficult to determine whether traditional clinical checkpoints, such as MAP and urine output are sufficient guides for fluid management in AP (Jin et al., 2018). In ICU, more invasive and advanced hemodynamic monitoring measurements are recommended depending upon the patient's specific needs

(Antonelli et al., 2007; Besselink et al., 2013; Leppäniemi et al., 2019; Martin et al., 2020).

2.8.3 INFECTION PREVENTION

2.8.3.1 Prophylactic antibiotics

Findings indicate that the breeding grounds for IPN in SAP might be soiled during the early intestinal bacterial translocation rendering the use of antibiotic prophylaxis a compelling focus of research (Runkel et al., 1991). As such, numerous studies have addressed the issue of prophylactic antibiotic use in AP, resulting in conflicting findings (Dellinger et al., 2007; García-Barrasa et al., 2009; Isenmann et al., 2004; Nordback et al., 2001; Pederzoli et al., 1993; Røkke et al., 2007; Sainio et al., 1995; Schwarz et al., 1997). Study protocols, the number of patients, and the outcomes measured have differed between these studies. However, a common denominator has been the insufficient power of each study to detect the potential effects of prophylactic antibiotics in SAP (Howard, 2007). Published data have been pooled and processed in several systematic reviews and meta-analyses, along with a Cochrane review published in 2010 (Dambrauskas et al., 2007; Ding et al., 2020; Mazaki et al., 2006; Villatoro et al., 2010; Wittau et al., 2011; Yao et al., 2010). In summarizing existing evidence, the effects on IPN risk, mortality, or other relevant endpoints have not been provided for antibiotic prophylaxis in AP, NP, or SAP. Thus, guidelines widely recommend not using prophylactic antibiotics in AP regardless of disease severity (Arvanitakis et al., 2018; Baron et al., 2020; Besselink et al., 2013; Isaji et al., 2015; Leppäniemi et al., 2019).

The use of antibiotics should be reserved for verified or suspected infection. However, distinguishing infections from the inflammatory symptoms of SAP remains tricky. Audit studies demonstrate that the inappropriate use of antibiotics in AP and SAP is common (Baltatzis et al., 2016; Barrie et al., 2018; de Waele et al., 2014; Talukdar et al., 2014). Although heterogeneous treatment between healthcare centers exists, several studies have confirmed that most patients with SAP receive antibiotics during ICU treatment (Baltatzis et al., 2016; de Waele et al., 2014; Montravers et al., 2019; Talukdar et al., 2014). This likely depicts the interrelationship between infections and SAP, as well as the diagnostic dilemma between inflammatory and infectious symptoms. Incorporating procalcitonin (PCT) into algorithms aiming to distinguish between infections and to guide antibiotic therapy in patients with SAP represents a promising tool. As yet, no high-quality prospective studies have been published on the implementation of such algorithms (Hochreiter et al., 2009; Mofidi et al., 2009).

2.8.3.2 *Early enteral nutrition*

Observations from experimental models of severe thermal injury revealed that enteral nutrition might decrease host susceptibility to microbial translocation across the gut barrier. Thus, clinical studies demonstrated that total enteral nutrition (TEN) diminished septic complications in critically ill trauma patients (Inoue et al., 1989; Kudsk et al., 1992). These findings led researchers to explore the effects of TEN among patients with AP and SAP. In the late 1990s, landmark studies were published laying the groundwork for a shift in the treatment paradigm: instead of bowel rest, clinicians strove for TEN when treating patients with AP (Kalfarentzos et al., 1997; McClave et al., 1997; Windsor et al., 1998). Since then, reports indicated that TEN conveys immunomodulatory responses, alleviates SIRS, and diminishes infectious complications in patients with SAP (Gramlich et al., 2004; Kalfarentzos et al., 1997; Marik & Zaloga, 2004; McClave et al., 1997; Petrov et al., 2008; Shen et al., 2017; Windsor et al., 1998). Oral feeding is recommended early during mild AP if the patient is not experiencing severe pain and when bowel obstruction symptoms are absent (Eckerwall et al., 2007; Moraes et al., 2010). In critically ill patients with SAP, TEN is administered via a nasogastric or nasojejunal tube feeding, however, the latter is preferred in patients experiencing DGE or GOO (Besselink et al., 2013; Kumar et al., 2006; Nally et al., 2014; Qu et al., 2021; Singh et al., 2012). Routine early nasoenteral tube feeding does not decrease infectious complications in patients at a higher risk for AP complications compared to those for whom an oral diet is initiated 72 h after admission and on-demand nasoenteric feeding only when oral intake is not tolerated (Bakker et al., 2014). Thus, even in nonmild AP patients, an oral diet may be initiated if the patient tolerates it.

2.8.4 TREATMENT OF (PERI-) PANCREATIC COLLECTIONS

Selecting patients for invasive interventions of necrotic collections remains inaccurately defined. Very early interventions are harmful and should be avoided (de Beaux et al., 1995; Mier et al., 1997). At present, the most common indication for interventions targeting necrotic collections is a suspected or confirmed IPN (Banks et al., 2006; Besselink et al., 2013; Leppäniemi et al., 2019). A step-up approach is encouraged (van Santvoort et al., 2010) and urgent interventions are warranted in cases involving clinical deterioration. Diagnostic uncertainties of an actual infection in necrotic collections may result in treatment upstaging, such as with fine-needle aspiration, external or endoscopic drainage, and even (minimally invasive or surgical) necrosectomy (Rodriguez et al., 2008; van Baal et al., 2014).

2.8.4.1 Acute (peri-) pancreatic fluid collections (APFCs) and pseudocysts

Since most APFCs resolve by themselves, there is generally no incentive to intervene in their natural course (Lenhart & Balthazar, 2008). Mature pseudocysts upon follow-up imaging have a tendency towards spontaneous regression, which may occur at up to six months' follow-up (Kim & Kim, 2012; Lankisch et al., 2012; Manrai et al., 2018; Maringhini et al., 1999; Sarathi Patra et al., 2014). In a minority of patients with persistent symptomatic (e.g., pain or compressive symptoms of neighboring structures) or complicated (infection or bleeding) pseudocysts following AP, interventions are justified when spontaneous healing is no longer anticipated. The preferred treatment of pancreatic pseudocysts relies on endoscopic (endoscopic ultrasound guided, when needed) transmural and/or transpapillary drainage. However, if these pseudocysts are intraluminally unreachable, percutaneous drainage, and rarely surgery may be warranted (Akshintala et al., 2014; D'Egidio & Schein, 1991; Dumonceau et al., 2019; Gurusamy et al., 2016; Habashi & Draganov, 2009).

2.8.4.2 Sterile necrosis

Necrosis remains sterile in 57–79% of patients with NP (Ashley et al., 2001; Beger et al., 1997; Büchler et al., 2000; Hartwig et al., 2002; Lariño-Noia et al., 2021; Perez et al., 2002; Petrov et al., 2010; Schepers et al., 2019; Sternby et al., 2019). Several studies suggested a good prognosis when refraining from necrosectomy for sterile necrosis even when OF is present (Bradley & Allen, 1991; Büchler et al., 2000; Hartwig et al., 2002; le Mée et al., 2001). Thus, conservative treatment of sterile necrosis has been widely accepted as the treatment of choice. Assessing the need for invasive interventions for sterile necrotic collections is necessary in specific clinic scenarios, presented in **Table 6** (Besselink et al., 2013).

Table 6 *Indications for invasive interventions in sterile necrosis according to International Association of Pancreatology/American Pancreatic Association guidelines. Reprinted with the permission of Elsevier* (Besselink et al., 2013).

1.	Ongoing gastric outlet, intestinal, or biliary obstruction due to the mass effect of walled-off necrosis (i.e., arbitrarily >4–8 weeks after the onset of acute pancreatitis)
2.	Persistent symptoms (e.g., pain, 'persistent unwellness') in patients with walled-off necrosis without signs of infection (i.e., arbitrarily >8 weeks after the onset of acute pancreatitis)
3.	Disconnected pancreatic duct syndrome with persistent symptoms (e.g., pain, obstruction), collection(s) with necrosis without signs of infections (i.e., arbitrarily >8 weeks after the onset of acute pancreatitis)

2.8.4.3 Infected pancreatic necrosis (IPN)

Currently, IPN is not an absolute indication for invasive interventions. A suspicion of or confirmed IPN in a hemodynamically stable patient is treated with antimicrobial therapy alone, since some of these patients recover without invasive interventions (Mouli et al., 2013). The indications for invasive interventions in IPN are summarized in **Table 7**. A step-up treatment algorithm is preferred when clinically feasible (van Santvoort et al., 2010). Thus, clinically stable patients are first subjected to less-invasive interventions. Repeat or upstaged treatments are resorted to only if a patient does not improve.

Table 7 *Indications for invasive interventions for suspected or documented infected necrotizing pancreatitis according to International Association of Pancreatology/American Pancreatic Association. Reprinted with the permission of Elsevier* (Besselink et al., 2013).

1. Clinical suspicion of or documented infected necrotizing pancreatitis with clinical deterioration (preferably walled-off necrosis)
2. In the absence of confirmed infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis (preferably walled-off necrosis)

Antibiotic treatment only

Empirical antibiotic treatment in suspected or verified IPN should be directed at treatment for common gut-derived pathogens, covering both the aerobic and anaerobic spectrum, and common gram-positive and gram-negative species. Antibiotics with a known penetration to the pancreas, such as carbapenems and piperacillin/tazobactam, as well as fluoroquinolones and third-generation cephalosporins combined with metronidazole, may be used initially (Büchler et al., 1992; Leppäniemi et al., 2019; Wolbrink et al., 2020). Regional bacterial ecology and the development of a known antibiotic resistance also impact the choice of antibiotic treatment. Routine empirical antifungal therapy is not recommended, although it may later be combined in treatment. Conservative antibiotic treatment in IPN may be considered only in clinically stable patients (Besselink et al., 2013). The reported range of success with antibiotic treatment alone in IPN is 5–50%, with a reported mortality of 0–25% (Boxhoorn et al., 2021; Jain et al., 2020; Lariño-Noia et al., 2021; Lee et al., 2007; Runzi et al., 2005; van Santvoort et al., 2011; Zerem et al., 2011). De-escalation of the antimicrobial spectrum is guided by infectious disease specialists according to results from bacterial cultures from the necrosis. A recent review suggested continuing antibiotic treatment for a minimum of 5–7 days following source control of IPN (Wolbrink et al., 2020).

Drainage

Percutaneous catheter drainage (PCD). The success rate of necrotic collection treatment relying on percuataneous catheter drainage (PCD) may reach as high as 35–55% (Boxhoorn et al., 2021; Freeny et al., 1998; van Baal

et al., 2011; van Santvoort et al., 2010). The combined effects of antibiotic only treatment and antibiotics with PCD treatment result in a more than 60% success rate according to a systematic review and meta-analysis (Mouli et al., 2013). If a patient is not cured through PCD, such treatment may serve as a bridge to necrosectomy, enabling surgery postponement for two or three weeks (van Baal et al., 2011). A male sex, MOF, an increased proportion of pancreatic parenchymal necrosis, and a heterogenous content of necrotic collection all negatively impact the success of PCD as the only treatment for necrotic collections (Hollemans et al., 2016).

Endoscopic drainage. An endoscopic transgastric or transduodenal drainage approach to treat symptomatic necrotic collections in stable patients was reported in 1996 by Baron (Baron et al., 1996). Originally, transmural drainage was maintained with pigtail stenting relying on routine nasopancreatic lavage. Today, advanced endoscopic instrumentation allows for the use of, for instance, lumen-apposing metal stenting, enabling repeat endoscopic entry into the necrotic cavity facilitating gradual debridement (Arvanitakis et al., 2018).

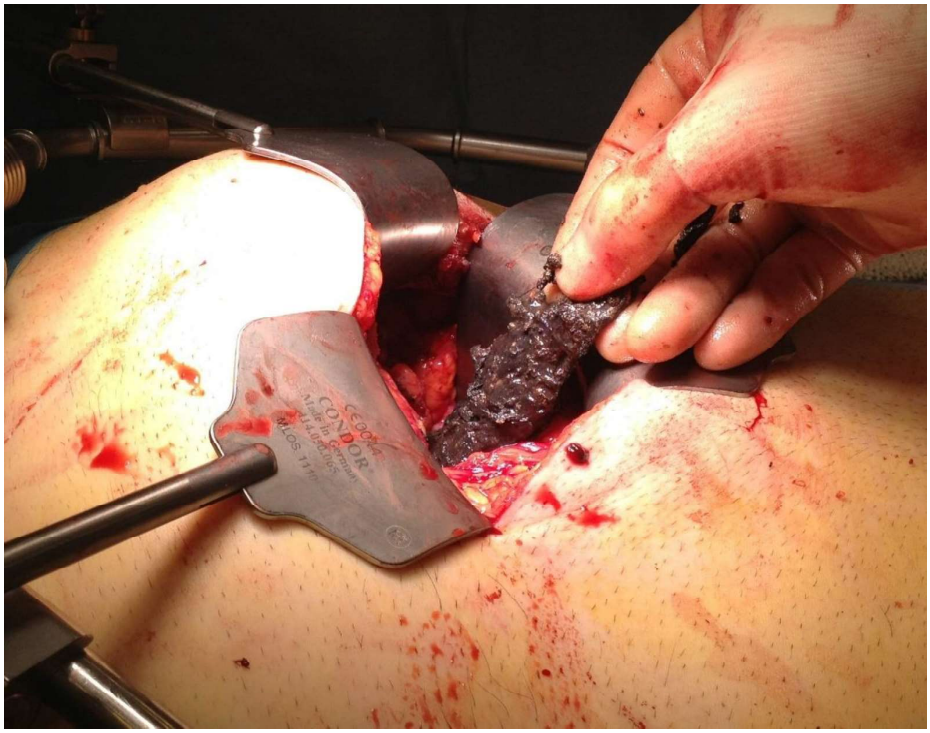
Few studies have compared endoscopic drainage alone with percutaneous drainage. In the limited number of patients who underwent prospective evaluation of an endoscopic or percutaneous step-up approach for IPN or IPN suspicion, drainage alone was sufficient for 43–65% of patients in the endoscopic arm (Bang et al., 2019; van Brunschot, van Grinsven, et al., 2018). The advantage of endoscopic step-up therapy is a lower occurrence of pancreaticocutaneous fistulas, and possibly a lower occurrence of new onset OF compared with a percutaneous step-up treatment approach (Darrivere et al., 2018; Haney et al., 2020). Endoscopic access is, however, limited to collections adjacent to the gastric or duodenal wall, whereas PCD is better suited to lateral collections. A combination of both these approaches is often necessary, whereby a tailored approach for each patient is recommended (Gluck et al., 2010; Haney et al., 2020). In patients with suspected or confirmed IPN, urgent drainage procedures (percutaneous or endoscopic) do not appear beneficial compared with drainage delayed until necrosis walling off. Instead, early drainage increases the total number of procedures required (Boxhoorn et al., 2021).

2.8.4.4 Necrosectomy (debridement)

Open necrosectomy via laparotomy (Picture 1). Open necrosectomy is performed via a subcostal or midline laparotomy. Access to the necrotic cavity is gained either by entering the omental bursa through the gastrocolic ligament or via a transmesocolic approach (Castillo et al., 1998; Werner et al., 2005). Since its proposal in the late 19th century (Fitz, 1889), the treatment of choice for NP has been an early open surgical debridement, accompanied by a

resulting increase in morbidity and mortality (Leach et al., 1990; Mier et al., 1997). A challenge to this surgical dogma has led to postponing and downstaging interventions, as well as narrowing down those patients allocated to invasive treatments (Bradley & Allen, 1991).

Both the harms associated with early necrosectomy and consensus regarding all patients with NP (independent of infectious status) do not need open necrosectomy are well established (de Beaux et al., 1995; Gomatos et al., 2016; Mier et al., 1997; Pascual et al., 2013; Tu et al., 2013). In select patients, an open necrosectomy provides good clearance of necrosis in a single session, whereas minimally invasive methods might require repeat procedures possibly via different approaches (Haney et al., 2020; Raraty et al., 2010; Seifert et al., 2009). Furthermore, open necrosectomy is an endpoint of step-up procedures, necessary in patients with other simultaneous complications warranting abdominal access (such as bowel ischemia or colonic perforation), and justified when intravascular treatment for bleeding complications fails (Besselink et al., 2013; Leppäniemi et al., 2019; Tenner et al., 2013).



Picture 1 Removal of necrotic pancreas parenchyma during an open necrosectomy (image courtesy of Panu Mentula, Department of Gastrointestinal Surgery, Helsinki University Hospital, 2013).

Open transgastric necrosectomy. In a highly select group of patients with complicated necrotic collections, open necrosectomy via gastric transmural access represents a possible debridement method with the potential benefits of open surgery (good exposure with the possibility of extensive debridement) combined with the benefits of internal drainage of a WON cavity (Boland et al., 2010; Driedger et al., 2020).

Minimally invasive necrosectomy. Several different minimally invasive strategies for treating complicated necrotic collections have been proposed. Anatomically, minimally invasive necrosectomy techniques fall into transperitoneal, retroperitoneal, and intraluminal approaches. From a technical point-of-view, these procedures may be grouped based on laparoscopic or endoscopic techniques.

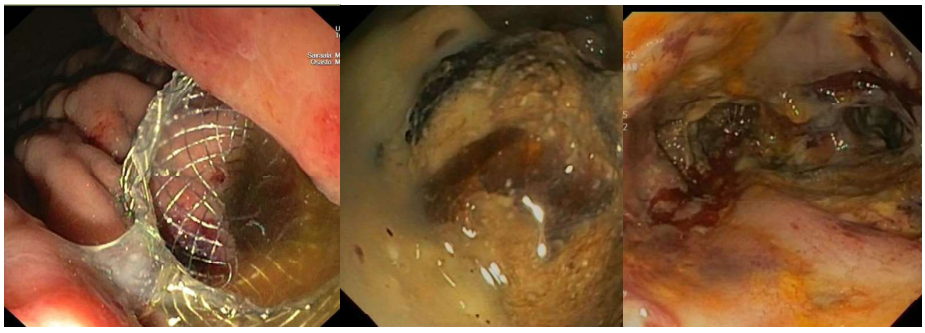
Numerous reports on the adoption of minimally invasive surgical or endoscopic necrosectomy techniques have been published along with a pooled analysis of published studies (Abu Dayyeh et al., 2018; Bakker et al., 2012; Bausch et al., 2012; van Brunschot, Hollemans, et al., 2018; van Brunschot, van Grinsven, et al., 2018; van Santvoort et al., 2010, 2011). Minimizing the trauma to patients during therapeutic procedures may relieve inflammatory responses resulting in less postoperative organ dysfunction and wound-related morbidity (Bakker et al., 2012; Darrivere et al., 2018). However, existing evidence on necrosectomy techniques primarily rely on retrospective series from specialized treatment centers, with only a few prospective randomized studies appearing in the literature (Bakker et al., 2012; Bang et al., 2019; van Brunschot, van Grinsven, et al., 2018). Specific reports suggest an increased utilization of invasive interventions after endorsing minimally invasive necrosectomy techniques (Gomatos et al., 2016). Yet, adopting minimally invasive necrosectomy techniques might also increase the number of required interventions and may be ill-suited for treating anatomically widespread necrosis or when liquefaction of necrosis is poor (Papachristou et al., 2007; Rana et al., 2014; van Brunschot, van Grinsven, et al., 2018).

Video-assisted retroperitoneal debridement. Video-assisted retroperitoneal debridement was originally reported in 2001 by Horvath (Horvath et al., 2001). The technique is based on percutaneous direct retroperitoneal access to the cavity, and thus is best suited for lateral (mostly left-sided) IPN collections. Along with preoperative imaging, preceding a PCD, which serves as a guide for entry, a 4–5 cm incision is made through the fascial plane. Next, the retroperitoneum is bluntly entered, and following port placement necrosectomy is performed using laparoscopic instruments (Horvath et al., 2001; van Santvoort et al., 2007).

Laparoscopic necrosectomy. Several reports since 2006 have described and adopted utilizing laparoscopic transperitoneal and transgastric (and even

combined endoscopic–laparoscopic) techniques for necrosectomy (Fischer et al., 2008; Kulkarni et al., 2015; Parekh, 2006; Simo et al., 2014; Zyromski, 2013).

Endoscopic necrosectomy. Endoscopic necrosectomy, a type of natural orifice transluminal surgery, is performed transgastrictly or transduodenally with a flexible upper-GI endoscope (Seifert et al., 2000). Endoscopic drainage precedes endoscopic necrosectomy (Baron et al., 1996). Retroperitoneal access may be gained via multiple pigtail stenting, fully covered self-expanding metal stents, and lumen-apposing metal stents (**Picture 2**) (Feng et al., 2021). Endoscopic necrosectomy is limited to collections adjacent to the gastric and duodenal wall and might be ill-suited to collections with a high percentage of solid necrosis and anatomically wide-spread necrosis (or require combined multimodal drainage/debridement). However, the incidence of clinically significant fistulas is low following endoscopic necrosectomy, and endoscopic necrosectomy might abate the risk of OFs (Bakker et al., 2012; van Brunschot, Hollemans, et al., 2018; van Brunschot, van Grinsven, et al., 2018).



Picture 2 Transgastric entry to the necrotic cavity may be facilitated by placing a lumen-apposing metal stent (in this case, Hot AXIOS™, Boston Scientific, left picture). An initial endoscopic view of the necrotic cavity: solid necrosis and liquefied content (middle picture). Endoscopic view inside the necrotic cavity upon follow-up endoscopic necrosectomy (right picture). (Images courtesy of Marianne Udd, Department of Gastrointestinal Surgery, Helsinki University Hospital, 2022.)

2.8.5 TREATMENT OF OTHER COMPLICATIONS

2.8.5.1 Splanchnic vein thrombosis (SVT)

A relative paucity of evidence has examined whether anticoagulation for SVT in AP is beneficial or not. The rationale for treating SVT focuses on achieving recanalization and preventing chronic thrombosis complications (e.g., ascites, varices, splenomegaly, and even rarely intestinal ischemia) (Valeriani et al., 2019). Thus, patients should be evaluated for esophageal varices, ascites formation, and splenomegaly, although all patients at risk for sinistral

hypertension may not present with any of these findings (Besselink, 2011). One-third of patients are asymptomatic, with a 9–25% spontaneous recanalization rate reported (Butler et al., 2011; Easler et al., 2014; Gonzelez et al., 2011). In a limited number of reported patients, anticoagulative treatment has led to a recanalization rate of 50–73% (Gonzelez et al., 2011; Lemma et al., 2020). Anticoagulation may, however, increase the bleeding risk. Hence, it is important to identify (e.g., liver chirrhosis) and treat (e.g., esophageal varices) the possible underlying risks of bleeding. Considering anticoagulative treatment in at least symptomatic (pain, nausea, vomiting, anorexia, ascites, and bleeding) patients with SVT is recommended when treatment-related risks are manageable (Valeriani et al., 2019). However, the optimal length of SVT treatment also remains poorly understood. Thus, thrombus resolution is best evaluated through control imaging.

2.8.5.2 Foregut complications

Patients with GOO are primarily managed conservatively with the insertion of a nasojejunal tube to maintain enteral feeding (Qu et al., 2021). When symptoms persist despite conservative management, treating necrotic collections responsible for compression symptoms may be considered. Most patients treated for persistent GOO have first undergone PCD, while some have also been treated with endoscopic and open necrosectomy, and a minority with endoluminal stenting (Qu et al., 2021; Sugimoto et al., 2018; Zhang et al., 2015). In accordance with guidelines, step-up invasive treatment in GOO should be considered only after 4–8 weeks following disease onset (Besselink et al., 2013; Leppäniemi et al., 2019).

Due to severe inflammatory conditions, aiming for primary definitive surgical treatment for duodenal necrosis due to NP might be precarious. Thus, local source control by means of intra- and extraluminal drainage with the aim of a controlled fistula might be a preferred surgical management strategy (Archer et al., 1991; Sakorafas et al., 1999a). Small bowel fistulas are primarily treated nonsurgically (Jiang et al., 2016).

More than 90% of patients with DPDS require some type of drainage for pancreatic duct leakage, resulting in an 80–90% success rate according to reported series (Chong et al., 2021; Sugimoto et al., 2018). However, the definition of DPDS varies greatly between studies, with most studies not adhering to the criteria proposed by Sandregesan (see Chapter 2.7.1.4), and some not even reporting the criteria used to define DPDS (Chong et al., 2021; Sandrasegaran et al., 2007). In general, surgery for DPDS is ideally postponed for quite some time following AP in order to allow the inflammation to resolve, which often requires a lengthy PCD as a bridge to surgery. Based on a large cohort of patients with NP, two-thirds of patients with DPDS required surgery aimed specifically at DPDS (Maatman, Roch, et al., 2020). This consisted of

internal surgical drainage in almost 55% of cases (i.e., cystgastrostomy, cystjejunostomy, pancreaticojejunostomy, pancreaticogastrostomy, and pancreaticoduodenectomy) and distal pancreatic resection in 45% of cases.

Patients with biliary obstruction are, when possible, primarily treated with ERCP and stenting, which results in an 80% success rate within a median of six months' treatment, with only a minority of patients requiring biliary tract surgery (Maatman, Ceppa, et al., 2020).

2.8.5.3 Colonic complications

Necrosis, perforation, and strictures of the colon are primarily treated using surgical resection and a diverting ostomy. Conventional therapy for colonic fistulas following NP also relies on surgical resection and fecal diversion, although other options may be considered for stable, nonseptic patients (Jiang et al., 2016). Examples of such strategies include drainage with possible step-up necrosectomy, along with a possible proximal intestinal diversion and awaiting the spontaneous closure of a fistula (Gao et al., 2020). Endoscopic management strategies, such as a closure of the fistula outlet with over-the-scope clip application combined with pancreatic necrosis drainage, have also been used in a limited number of patients with varying results (Hwang et al., 2010; II & Mullady, 2012; Ito et al., 2013).

2.8.5.4 Other vascular complications

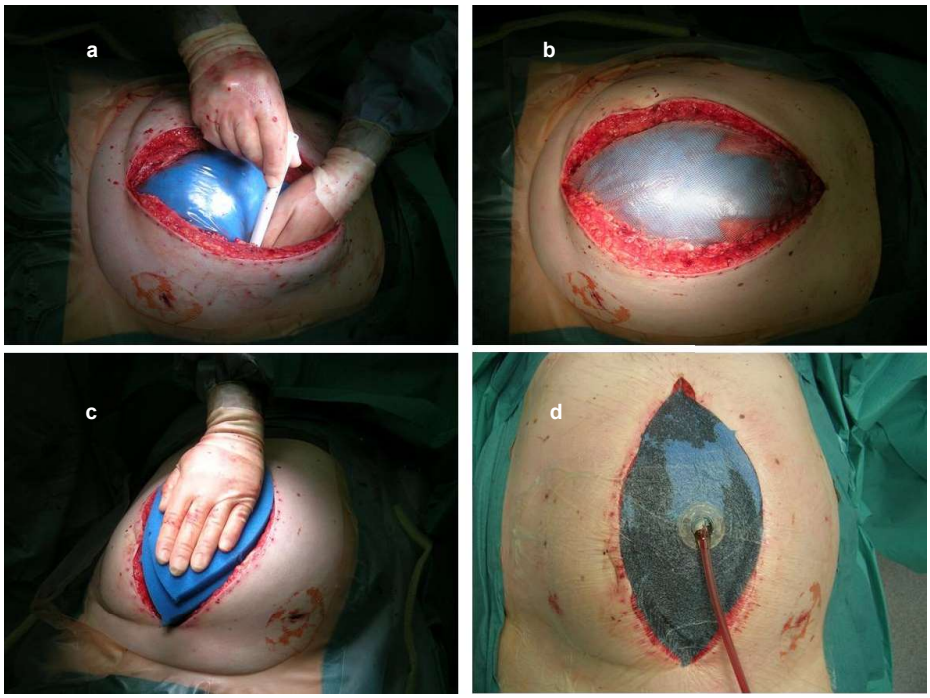
The primary management of bleeding due to a visceral pseudoaneurysm following AP remains angiography with intravascular embolization if a patient's hemodynamic condition allows for this procedure. If the bleeding patient is unstable or when intravascular attempts to control pseudoaneurysmal bleeding fail, open surgery becomes necessary (Evans et al., 2017). Roughly 74–96% of patients with a bleeding pseudoaneurysm can undergo an angiographic evaluation (Bergert et al., 2005; Zyromski et al., 2007). A failure to visualize the site of the pseudoaneurysm on angiography or an inability to access the site of bleeding for embolization occurs in 4–39% of patients. The success rate of the primary embolization lies between 83–94% when attempted (Bergert et al., 2005; Nykänen et al., 2017; Udd et al., 2007; Zyromski et al., 2007).

2.8.6 TREATMENT OF ABDOMINAL COMPARTMENT SYNDROME (ACS)

ACS in SAP is primarily treated conservatively (Coccolini et al., 2018; Kirkpatrick et al., 2013; Leppäniemi et al., 2019). Such treatments include optimized fluid management (avoiding fluid overload), adequate sedation and

analgesia, neuromuscular blockage, evacuation of intraluminal contents, and drainage of intra-abdominal and peripancreatic collections (de Keulenaer et al., 2015). Ascite drainage in SAP lowers IAP by a median of 2–4 mmHg (Al-Bahrani et al., 2008; Bai et al., 2007). Persistent ACS after conservative management is considered an indication for surgical decompression of the abdomen and leaving the abdomen open (Kirkpatrick et al., 2013; Leppäniemi et al., 2019). In persistent ACS, PCD is attempted as the first-line treatment in 13% of patients, whereas 87% undergo surgical decompression. Three-quarters of patients with attempted PCD to alleviate ACS eventually end up undergoing open abdomen (OA) treatment (van Brunschot, Schut, et al., 2014). Surgical decompression of ACS in SAP lowers IAP a median of 15 mmHg, although IAP might be sustained in a fraction of patients even following decompression (Davis et al., 2013; Mentula et al., 2010; Smit et al., 2016; van Brunschot, Schut, et al., 2014). OA treatment is, however, a morbid condition carrying risks of complications, such as a frozen abdomen and fistula formation (Cirocchi et al., 2016; Coccolini et al., 2018; Kirkpatrick et al., 2013). Weighing these risks against the imminent risks of persistent ACS is complicated, and the literature provides largely circumstantial evidence to inform clinical decision-making. Moreover, surgical decompression is mostly performed via midline laparostomy, although the use of a bilateral subcostal incision and minimally invasive decompression methods have also been described (Coccolini et al., 2018; Kirkpatrick et al., 2013; Leppäniemi et al., 2006; Smit et al., 2016; van Brunschot, Schut, et al., 2014). The OA wound can be managed through vacuum-assisted closure, and a delayed abdominal closure is primarily achieved by gradually opposing fascial edges utilizing mesh-mediated traction (**Picture 3**) (Petersson et al., 2007; Rasilainen et al., 2012).

In patients with IAH in SAP, the repeated use of intramuscular neostigmine results in the significantly faster reduction of IAP and increased stool volume compared with conventional treatment (He et al., 2022). Limited cohort studies regarding ACS in SAP found that a minority of patients experience respiratory, hemodynamic, and/or renal function improvements following the surgical decompression of ACS. Thus, evidence from the surgical decompression of ACS due to various etiologies suggests organ function improvements (Boone et al., 2013; Mentula et al., 2010; Smit et al., 2016; van Damme & de Waele, 2018).



Picture 3 Maintaining an open abdomen via vacuum assistance with mesh-mediated fascial traction. Following a midline laparotomy: a) a visceral protective layer is positioned intra-abdominally; b) a polypropylene mesh is sutured to the fascial edges; c) a wound-shaped foam is placed on top of the mesh; and d) the foam is protected with an adhesive sheet and a suction pad for the vacuum device is applied. The patient is returned to the operating room for dressing changes at 2–4-day intervals. The mesh is cut in half during the first dressing change to achieve abdominal access. The fascial edges are gradually re-approximated by tightening the half-cut mesh with a monofilament suture. (Images courtesy of Ari Leppäniemi, Department of Gastrointestinal Surgery, Helsinki University Hospital, 2017.)

2.9 OUTCOMES

According to classification. Outcomes based on the RAC are summarized in **Table 8**. As we see, outcomes are excellent for mild AP, with morbidity increasing primarily for moderately severe AP, and both morbidity and mortality high for SAP.

According to the presence of organ failure. Persistent OF represents the most important predictor of outcomes, specifically for early occurring persistent OF and multiple organ dysfunction syndrome, associating with an increased mortality in AP (Hamada et al., 2014; Kamal et al., 2017; Shen et al., 2012). Mortality based on OF status is presented in **Figure 1**.

Among working-age adult patients, a fivefold increase in mortality is observed over the long-term following AAP compared with matched peers (Karjula et al., 2019). In another study examining long-term follow-up data, early organ

dysfunction (multiple organ dysfunction score ≥2 within one week) independently associated with premature deaths in the long-term compared with patients without early organ dysfunction (mean survival, 10.0 vs. 11.6 years, $P = 0.001$) even after excluding in-hospital mortality. Age, alcohol, and idiopathic etiology also independently associated with long-term mortality (Skouras et al., 2014).

Table 8 *Outcomes according to the revised Atlanta classification* (Appelros et al., 2001; Choi et al., 2014; Padhan et al., 2018; Schepers et al., 2019; Sternby et al., 2019; Zubia-Olaskoaga et al., 2016).

	Mild	Moderately Severe	Severe
Median length of ICU stay, in days	0	3	7–22
Median length of hospital stay, in days	6–7	10–11	37–64
Invasive interventions	0%	7–22%	37–48%
Short-term mortality	0%	2–3%	22–52%
Long-term survival	≥94%* 80%†	unknown	~60%‡

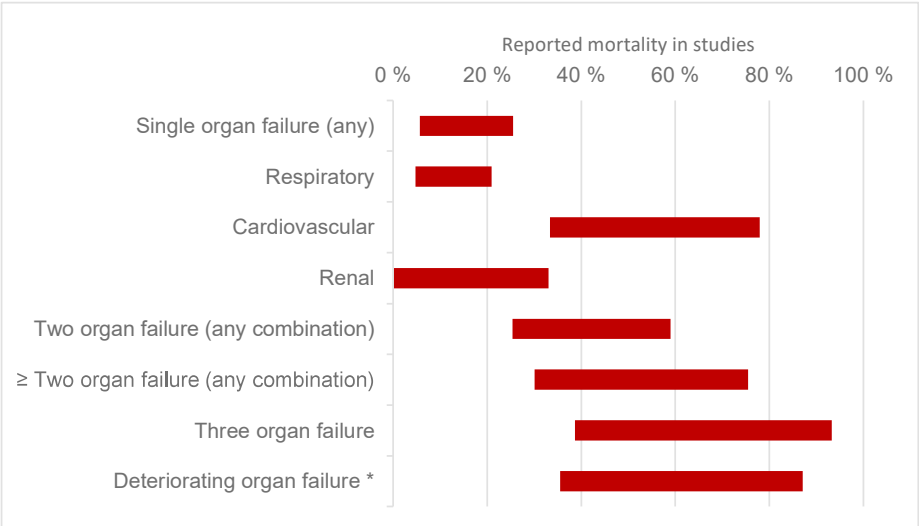
*10-year survival among working-aged (18–64 years) patients with nonalcoholic acute pancreattis (Karjula et al., 2019).
†10-year survival among working-aged patients with alcoholic acute pancreatitis (Karjula et al., 2019).
‡10-year survival among working-aged patients with alcoholic severe acute pancreatitis or 7-year survival among all patients across age groups with moderately severe or severe acute pancreatitis of mixed etiologies (Andersson et al., 1999; Appelros et al., 2001; Karjula et al., 2019).

According to comorbidities and other risk factors. Age and previous comorbidities are among the most important preexisting risk factors of a worse outcome in AP (Frey et al., 2007). In a case–control study of SAP, in-hospital mortality among patients >70 years was 21%, whereas it was 7% in patients <70 years (Gardner et al., 2008). Type 2 diabetes and obesity have also been associated with an increased mortality in AP (Huh et al., 2018; Martínez et al., 2006).

According to complications following AP. Extrapancreatic necrosis results in a mortality rate of 8–9%, whereas mortality climbs to 16–20% in patients with pancreatic parenchymal necrosis (Bakker et al., 2013; Rana et al., 2015; Sternby et al., 2019). The risk of complications and mortality increases with an increasing proportion of pancreatic parenchymal necrosis (Jain et al., 2020). Low mortality (0–10%) is observed in patients with sterile necrosis, although early death (within 7–10 days) is often excluded from the analysis in these studies (Bradley & Allen, 1991; Büchler et al., 2000; Jain et al., 2020; le Mée et al., 2001; Sternby et al., 2019; van Santvoort et al., 2011). According to a meta-analysis from 2010, mortality reached 32% in patients with IPN, which (along with OF) independently increased mortality in AP (Petrov et al., 2010). Recently, some individual publications have challenged the existing consensus of IPN as an independent risk factor of mortality when adjusting for existing OFs (Schepers et al., 2019; Shi et al., 2020; Sternby et al., 2019). The association between EPI and AP severity or mortality has yet to be established (Brown et al., 2014).

In patients with SAP, higher mean and maximal IAP values associate with an increased mortality (Ke et al., 2011; Keskinen et al., 2007). IAH upon admission strongly predicts 30-day mortality in AP, and the mortality rate in patients with IAH was 37% compared with 2% in patients without IAH in a single-center observational study ($P < 0.001$) (Aitken et al., 2014). According to a meta-analysis among patients primarily with SAP, the mortality rate in the presence of ACS was 49%, falling to 11% in patients without ACS ($P = 0.03$). In nonocclusive mesenteric ischemia related to AP, the mortality rate lies between 60–100% (Hirota et al., 2003; Reichling et al., 2020). Finally, the overall mortality rate among patients who experience bleeding complications in AP reaches 30–35% (Flati et al., 2003; Sharma et al., 2008).

Effect of treatments. Fluid overload in AP may be associated with a worse outcome, whereby goal-directed fluid therapy is currently advocated (de-Madaria et al., 2011; Mao et al., 2009). Early enteral nutrition reduces mortality in patients with suspected SAP (Petrov et al., 2008). At present, differences regarding mortality have not been observed between different necrosectomy modalities (endoscopic, minimally invasive surgical, or open) (Bakker et al., 2012; Bang et al., 2019; Gurusamy et al., 2016; van Brunschot, van Grinsven, et al., 2018). The mortality rate lies at around 50% in patients who require OA treatment due to ACS in SAP; yet, if OA is initiated early (within the first four days from disease onset), it might result in a better outcome (Boone et al., 2013; Mentula et al., 2010; Smit et al., 2016). In patients with intra-abdominal ischemic complications in SAP, mortality may exceed 80% (Smit et al., 2016).



Persistent (≥48 h) organ failure, refers to the organ failure of respiratory, cardiovascular, or renal organ system according to the revised Atlanta classification (Banks et al., 2013).
*Progression of multiple organ dysfunction score during the first week of follow-up.

Figure 1 The impact of persistent organ failure on mortality (Buter et al., 2002; Schepers et al., 2019; Shi et al., 2020; Sternby et al., 2019; Thandassery et al., 2013).

3 THE PRESENT INVESTIGATION

3.1 STUDY AIMS

The primary aim of this thesis was to investigate mortality in SAP. The specific aims were as follows:

(1) To study short-term mortality and short-term mortality risk factors in SAP (study I).

(2) To investigate long-term mortality and cause of late death following SAP (study I).

(3) To examine mortality and morbidity following open necrosectomy (study II).

(4) To evaluate IPN risk factors, outcomes following IPN, and mortality risk factors following one week of ICU treatment for necrotizing SAP (study III).

(5) To analyze risk factors associated with OA treatment in severe acute pancreatitis and to study the outcomes following this treatment (study IV).

3.2 MATERIALS AND METHODS

This reseach project was carried out at Helsinki University Hospital (HUH). Each individual study included consecutively treated patients treated in the ICU at Meilahti Hospital within HUH. In addition, study II included all patients treated with an open necrosectomy, whereby some were treated on a regular surgical ward only. Data were retrieved and the analyses were completed retrospectively. The data gathered for each study were collected via specific databases. By replacing the patient identity using a running numbering system, patient anonymity was protected. Institutional review board approval was not required due to the observational retrospective nature of this project. The Department of Gastrointestinal Surgery at HUH approved the protocol for each study. In addition, separate permission was granted from Statistics Finland, enabling the retrieval of cause of death information for patients in study I. All studies adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist (von Elm et al., 2007).

3.2.1 PATIENT DATA

This thesis comprised a 20-year retrospective consecutive cohort study of adult patients with SAP treated in the ICU at HUH. The only exception was study II, which (in addition to patients with SAP and open necrosectomy) also included patients with moderately severe AP (treated on the surgical ward) if they underwent an open necrosectomy. Based on the data collected, four individual studies with separate endpoints were conducted.

All datasets included variables consisting of basic patient characteristics, preexisting comorbidities, the number of previously endured AP, AP etiology, the date of AP symptom onset, the RAC score during the hospital stay, the length of the hospital stay, the length and timing of an ICU stay, the utilization and timing of OA and open necrosectomy, the infection status of necrosis, and survival information. For each study, separate appendices listing the variables collected were established prior to data collection.

Data were gathered from hospital electronic patient and ICU databases, daily ICU monitoring sheets, an imaging study database, radiological reports, laboratory results, and (when applicable) indirect knowledge from the Finnish Population Information System. For long-term survival and cause of death information, data were provided by Statistics Finland (study I) where appropriate. The populations investigated for each individual study are described in **Table 9**.

Table 9 *Patient selection and aims for each study.*

Study	Years (n)	Study population	Study aim
I	1999–2015 (n = 435)	Consecutive ICU-treated patients with SAP	- Short-term (≤90 day) mortality risk factors - Long-term mortality (>90 day) and cause of death
		***Exclusion criteria**:* not SAP, loss to follow-up	
II	2006–2017 (n = 109)	Consecutive patients treated with open necrosectomy	- Outcome following open necrosectomy
		***Exclusion criteria**:* first necrosectomy in other hospital, minimally invasive necrosectomy	
III	2010–2018 (n = 163)	Consecutive patients with necrotizing SAP	- IPN risk factors and outcomes - Mortality risk factors following the first week of ICU treatment
		***Exclusion criteria**:* not SAP, not treated in the ICU at HUH within 7 days of hospital admission, edematous SAP, chronic pancreatitis, transplant pancreatitis, initial treatment abroad, loss to follow-up or lack of sufficient ICU data	
IV	2009–2019 (n = 47 + 47)	Study patients: consecutive OA-treated patients with SAP Matched controls managed conservatively*	- Risk factors for OA - Outcome following OA
		Matching at a 1:1 ratio. All matched controls were treated for SAP, but avoided OA treatment. In order of importance, matching was based on 1) maximal (within 72 h) SOFA score ± 2; 2) age ± 10 years; 3) preceding comorbidities; and 4) year of treatment* ***Exclusion criteria:* ICU admission after 10 days or OA treatment after 4 weeks from hospital admission	

Abbreviations: HUH, Helsinki University Hospital; ICU, intensive care unit; IPN, infected pancreatic necrosis; OA, open abdomen; SAP, severe acute pancreatitis; SOFA, sequential organ failure assessment score.

Study I

All patients treated in the ICU at Meilahti Hospital within HUH under the International Classification of Diseases tenth edition (ICD–10) codes K85.X or K86.X were manually screened for eligibility (n = 610). We excluded patients without SAP according to RAC, as well as patients lost to follow-up. In total, 435 patients were included in the study.

In addition to variables collected for all four studies (described previously, see above), specifically for this study we also collected information related to the underlying, immediate, and contributing causes of death for patients who died during follow-up. Survival data were gathered until the time of data collection–that is, between April and June 2016. Patients were grouped according to year of treatment into two groups: group 1 were treated between 1999 and 2007 and group 2 were treated between 2008 and 2015. Patient characteristics are summarized in **Table 10**.

Table 10 *Characteristics of patients in study I (n = 435).*

	Number of patients (%)
Median age, in years (IQR)	48 (39–58)
<60 years	342 (79)
60–90 years	63 (14)
≥70 years	30 (7)
Male sex	355 (82)
Etiology	
alcoholic	335 (77)
biliary	51 (12)
other	49 (11)
Any comorbidity*	145 (33)
Recurrent acute pancreatitis	99 (23)
Year of treatment	
1999–2007 (group 1)	231 (53)
2008–2015 (group 2)	204 (47)

*Any heart or pulmonary disease, chronic renal insufficiency, liver chirrhosis, chronic pancreatitis, and/or diabetes.
Abbreviations: IQR, interquartile range.

Study II

All patients receiving a Nordic Medico-Statistical Committee classification with a surgical procedure code JLC50 and an ICD-10 code K85.X were manually screened for open necrosectomy. In addition, we also reviewed the patient records for all patients with AP either treated for >10 days in the hospital or who died during the hospital treatment period for possible open necrosectomy. Altogether, our search yielded 116 patients potentially eligible for analysis, among whom 7 were excluded (3 did not meet the inclusion criteria and 4 met an exclusion criterion). The patients included in this study either suffered from moderately severe AP or SAP. A single radiologist re-evaluated the CECT studies preceding the first open necrosectomy for all patients. Access to the necrotic collection was gained primarily via a subcostal transverse laparotomy and through the gastrocolic ligament (with or without mobilization of the colonic flexures). In cases where a bowel resection or adhesiolysis was anticipated, or in the case of an existing OA treatment for ACS, access to the necrotic collection was gained via a midline laparotomy.

For this specific study, we collected information on preoperative necrosis management, findings on preoperative imaging and laboratory tests, an indication of necrosectomy, OF (as defined in **Table 14**, see Chapter 3.2.2) within 24 h from the first necrosectomy, intraoperative findings and simultaneous procedures during necrosectomy and reoperations, and postoperative morbidity outcomes. Renecrosectomies and reoperations within six months, and endoscopic interventions within the first year following the first necrosectomy were collected. **Table 11** provides the patient characteristics at the time of the index necrosectomy.

Table 11 *Characteristics of patients in study II at the time of the index open necrosectomy (n = 109).*

	Number of patients (%)
Median age, in years (IQR)	52 (42–61)
Male sex	96 (88)
Etiology	
alcoholic	62 (57)
biliary	25 (23)
other	22 (20)
Any comorbidity*	43 (39)
Acute pancreatitis severity classification before the index necrosectomy (according to RAC, for the entire treatment period)	
moderately severe	39 (36)
severe	70 (64)
Preoperative contrast-enhanced CT	63 (58)
Reason for utilizing CT without contrast enhancement	
renal insufficiency (acute/chronic)	37 (34)
emergency laparotomy due to shock	4 (4)
unknown reason	4 (4)
preceding magnetic resonance imaging	1 (1)
Findings upon preoperative imaging	
pancreatic parenchymal necrosis	
unassessable	45 (41)
<30%	31 (28)
30–50%	11 (10)
≥50%	22 (20)
walled-off necrosis	91 (84)
distant necrosis†	98 (90)
widespread necrosis‡	66 (61)
disconnected pancreatic duct syndrome	34 (31)
Treatment in ICU at the time of the index necrosectomy	44 (40)
OF within 24 h from necrosectomy	
none	64 (59)
single	12 (11)
multiple	33 (30)
Indication for surgery	
verified or suspected infected pancreatic necrosis	82 (75)
prolonged OF or deterioration of existing OF	18 (17)
prolonged pain	6 (6)
bleeding, GOO, or suspicion of colonic necrosis	3 (3)
Open abdomen at the time of necrosectomy	14 (13)
Time since symptom onset, in days (IQR)	36 (22–59)
≥4 weeks	69 (63)
Step-up treatment§	40 (37)

*Any heart or pulmonary disease, chronic renal insufficiency, liver chirrhosis, chronic pancreatitis, and/or diabetes.
†Distant necrosis refers to left and/or right paracolic gutter and/or retromesenteric area.
‡Widespread necrosis extending to both paracolic gutters or the paracolic gutter and the retromesenteric area.
§Preceding drainage procedure of necrotic collection before the index necrosectomy.
Abbreviations: CT, computed tomography; GOO, gastric outlet obstruction; ICU, intensive care unit; IQR, interquartile range; OF, organ failure; RAC, revised Atlanta classification.

Study III

An initial search identified all patients admitted to the ICU at Meilahti Hospital within HUH with the ICD-10 diagnosis codes K85.X and K86.X (n = 465), among whom 203 did not meet the inclusion criteria. Furthermore, 99 patients met the exclusion criteria eliminating them from analysis. Thus, 163 patients were included in study III.

The specific variables examinined for this study included the timing and type of infections acquired, results from imaging studies, body mass index (BMI), tertiary referral status, scores from various predictive indices, OF (as defined in **Table 14**, see Chapter 3.2.2) within the first 24 h of ICU admission, interventions targeted at necrotic collections, and ICU readmission status. An infectious disease specialist reviewed all cases of pneumonia and all uncertain cases of other infectious complications to insure the correct diagnosis was registered. Given the institutional protocol, all patients received a five-day intravenous antibiotic prophylaxis (1.5-g cefuroxime thrice daily) beginning on day 0 in ICU. The patient characteristics are summarized in **Table 12**.

Table 12 *Comparison of demographic data at baseline between the study groups in study III (n = 163).*

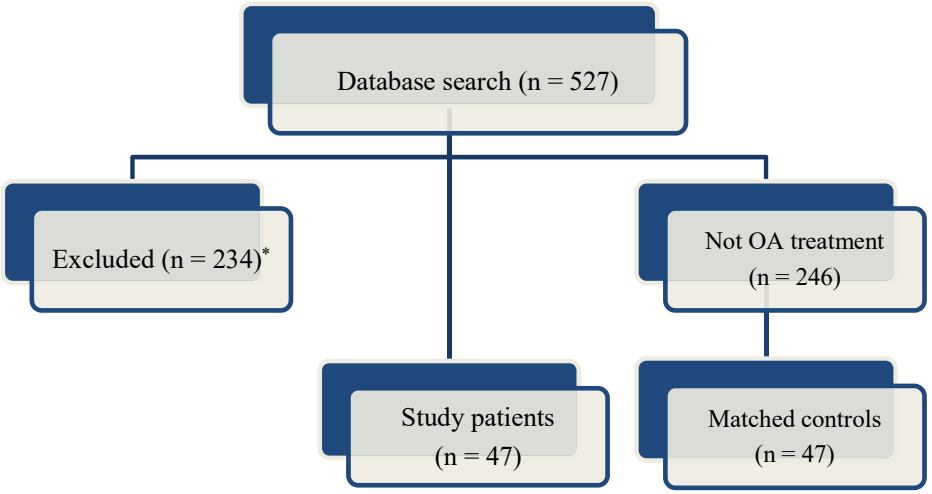
	No IPN (n = 116)	IPN (n = 47)	*P*
Median age, in years (IQR)	50 (18–82)	51 (25–66)	0.682
Mean body mass index ± SD, kg/m2	30 ± 5	29 ± 4	0.560
Male sex	93 (80)	40 (85)	0.512
Any comorbidity*	37 (32)	11 (23)	0.345
Alcoholic etiology	80 (69)	31 (66)	0.714
biliary	23 (20)	5 (11)	0.178
other	11 (10)	3 (6)	0.759
postoperative or post-ERCP	2 (2)	8 (17)	0.001
Tertiary referral	36 (31)	20 (43)	0.203
ASA ≥3	61 (53)	25 (53)	1.000
Maximum SOFA <72 h (IQR)†	9 (6–11)	10 (7–13)	0.086
APACHE II <24 h (IQR)†	16 (13–23)	19 (12–23)	0.968
Multiple organ failure <24 h (IQR)†	70 (60)	32 (68)	0.378
Preceding open abdomen treatment	21 (18)	18 (38)	0.008
Preceding bacteremia	8 (7)	7 (15)	0.136
Preceding pneumonia	17 (15)	3 (6)	0.191
Necrotic collection location			
central (around the pancreas)	56 (48)	5 (11)	<0.001
distant‡	35 (30)	12 (26)	0.703
widespread§	25 (22)	30 (64)	<0.001
>50% pancreatic parenchymal necrosis¶	9 (13)	5 (20)	0.514

Data are presented as the number of patients and percentage of patients in parenthesis unless stated otherwise.
*Any heart or pulmonary disease, chronic renal insufficiency, liver chirrhosis, and/or diabetes.
†From ICU admission.
‡Distant necrosis in the left or right paracolic gutter or retromesenteric area.
§Widespread necrosis extending to both paracolic gutters or the paracolic gutter and the retromesenteric area.
¶Data were missing for 70 patients (22 with IPN); thus, n = 93 for this variable
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II scoring system; ASA, American Society of Anesthesiologists physical status classification system; ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; IPN, infected pancreatic necrosis; IQR, interquartile range; SD, standard deviation; SOFA, sequential organ failure assessment score.

Study IV

Hospital databases were searched for eligible patients for analysis. The search included all patients treated at HUH's Meilahti Hospital ICU with an ICD-10 diagnosis code of K85.X or K86.X. Subsequently, patient records were manually screened for OA treatment. Patients with SAP treated with OA were selected for inclusion. Matching peers were drawn from patients with SAP, but who did not undergo OA treatment during their hospital stay. The daily SOFA

score (including all six organ system categories) for the first 72 h following ICU admission was calculated. The highest SOFA score within these three days was selected as the primary matching criteria. In case more than one possible matched control based on the primary matching criteria was identified, patients were secondarily matched according to (in order of importance): 1) age, 2) existence of comorbidities, and 3) the year of treatment. Based on our protocol, we allowed a maximal deviation for the 72-h SOFA score of ±2 and age ±10 years. For each study patient, a matched control was chosen in a 1:1 fashion. Data for the matched-control patient were collected for as long as their peer study patient was treated until surgical decompression. The flow chart (**Figure 2**) depicts the selection of patients in study IV.



*Not SAP (n = 220), primarily OA in another hospital (n = 3), OA >28 days after hospitalization (n = 7), insufficient data (n = 2), initial treatment abroad (n = 1), and pancreas transplant pancreatitis (n = 1).
Abbreviation: OA, open abdomen.

Figure 2 Flow chart of study and control patients in study IV.

The information specifically collected for this study included the timing and type of infections acquired, results from imaging studies, body mass index, tertiary referral status, scores from various predictive indices, the worst and best values for physiological parameters (such as IAP, mean arterial pressure, etc.) at 12-h intervals and laboratory tests at daily intervals preceding OA treatment (or the same time period for matched controls), endured ACS time (hours) until OA treatment commenced (or the same time period for matched controls), intraoperative findings at the index operation, additional surgical interventions within 90 days, intraoperative findings from any potential additional surgical interventions, and the timing and method of an abdominal closure.

Study group patients were primarily managed with a midline laparotomy for the surgical decompression of the abdomen. In a majority of cases, vacuum-assisted wound closure with mesh-mediated fascial traction (2–4 days of gradual approximation) was used to maintain the OA, aiming for a delayed primary fascial closure. In some cases, a Bogota bag temporary closure was utilized. Due to an otherwise insufficient number of control patients, violations of the predetermined matching criteria were made in three cases: one control patient with a SOFA score of 16 was matched with a study patient with a SOFA score of 19, and an 11-year age difference between the study and control group patients were allowed in two cases. A univariate comparison of study and control group patient characteristics appear in **Table 13**.

Table 13 *Comparison of demographic data at baseline between patient groups for study IV.*

	OA treatment (n = 47)	**Matched controls (n = 47)**	***P***
Median age, in years (IQR)	49 (38–56)	50 (40–60)	0.456
Mean BMI ± SD, kg/m2	30 ± 5	30 ± 5	0.991
Male sex	42 (89)	41 (87)	1.000
Any comorbidity*	14 (30)	16 (34)	0.825
Alcoholic acute pancreatitis	40 (85)	34 (72)	0.207
Tertiary referral	18 (38)	16 (34)	0.830
ASA ≥3	32 (68)	25 (53)	0.205
Maximum SOFA <72 h (IQR)†	13 (11–14)	12 (10–15)	0.876
APACHE II <24 h (IQR)†	23 (17–29)	18 (15–26)	0.056
Time between hospital and ICU admission, in hours (IQR)	23 (8–33)	28 (12–40)	0.318

Data are presented as the number of patients and percentage in parentheses unless stated otherwise.
*Any heart or pulmonary disease, chronic renal insufficiency, liver chirrhosis, chronic pancreatitis, and/or diabetes.
†From ICU admission.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II scoring system; ASA, American Society of Anesthesiologists physical status classification system; BMI, body mass index; IQR, interquartile range; OA, open abdomen; SD, standard deviation.

3.2.2 DEFINITIONS

We used a consensus definition of AP, indicated as fulfilling two out of three of the following criteria: typical clinical upper- GI pain symptoms; an elevated amylase at least three times the upper margin; and/or signs of acute pancreatitis upon imaging (most often via CT scan) (Besselink et al., 2013; Isaji et al., 2015; Leppäniemi et al., 2019; Tenner et al., 2013).

The grading of AP severity was based on RAC. A failure of the respiratory, cardiovascular, or renal organ systems indicted OF. Accordingly, in studies I, III, and IV, only patients with persistent OF of at least one of these three organ systems were included, whereby patients with AP requiring ICU treatment due to delirium alone were excluded from further analysis. Study II included patients who underwent an open necrosectomy (patients with moderately

severe AP and SAP). The definitions for OF and AP severity in studies I–IV are summarized in **Table 14**.

Table 14 *Definitions of organ failure and acute pancreatitis severity in studies I–IV.*

Respiratory	PaO2/FiO2 < 300 **or** A need for mechanical ventilation
Cardiovascular	Systolic blood pressure <90 mmHg and not responsive to fluid resuscitation **or** A need for inotropic medication (catecholamines)
Renal	Creatinine >170 µmol/L **or** Daily diuresis <500 ml **or** A need for renal replacement therapy
Transient organ failure	<48 h
Persistent organ failure	>48 h
Multiple organ failure	Two or three of the abovementioned organ failures occurring on the same day
Moderately severe acute pancreatitis	Transient organ failure **or** Local complications related to acute pancreatitis (see Chapter 2.7.1)
Severe acute pancreatitis	Persistent organ failure

Hypoperfusion was categorized based on consensus. The clinical presentation includes hypotension (systolic blood pressure <90 mmHg), often but not always present in association with signs of inadequate tissue perfusion. Signs of inadequate tissue perfusion can appear in the perifery (as cold, pale, cyanotic, or mottled skin changes), as a decreased urine output (<0.5 mL/kg/h), and as signs of an altered mental status, as well as other markers of hypoperfusion, such as a hyperlactatemia (>2 mmol/L) (Cecconi et al., 2014).

Pancreatic or peripancreatic nonenhancement areas on CECT (within the treatment period or within three months of discharge and follow-up at the outpatient clinic), or evidence of necrosis during an invasive intervention were considered evidence of NP. Necrosis extending beyond the vicinity of the pancreas was regarded as distant necrosis. Widespread necrosis (also referred to as "complex" in the original publication) consisted of a necrotic collection spread into the paracolic gutters bilaterally or its spread into the paracolic gutter and the retromesenteric area. A positive microbiological culture from a fine-needle aspirate, the first drainage, or necrosectomy procedure characterized IPN. The time to necrosectomy was determined as the number of days from symptom onset. DPDS constituted a large intrapancreatic nonenhancement combined with a viable distal pancreatic remnant alongside MPD leakage upon imaging (or an MPD discontinuity directly visualized during surgery) (Sandrasegaran et al., 2007).

IAP measurements were obtained via a bladder foley catheter as follows: IAP <12 mmHg was defined as normal, IAP ≥12 mmHg was defined as IAH, and IAP persistently exceeding 20 mmHg in association with a new OF or a worsening existing OF was defined as ACS (Kirkpatrick et al., 2013).

Irreversible necrosis (found intraoperatively or upon obduction) of a viscera was considered ischemia. In an attempt to quantify exposure to ACS (study IV), we summarized the gross exposure time to ACS for each patient.

In study I, short-term follow-up was defined as 90 days from hospital admission and long-term follow-up represented the entire follow-up period. In study II, survival was reported at 90 days, reoperations at 6 months, and endoscopic interventions at 1 year after the first necrosectomy. In studies III and IV, survival was reported at 90 days from admission to ICU. A separate analysis of the mortality risk factors between days 8 and 90 after admission ("late death") to ICU was conducted in study III.

3.2.3 STATISTICAL ANALYSES

All statistical analyses were performed using SPSS (IBM Corp., Armonk, NY, USA), STATA (StataCorp, College Station, TX, USA), and Excel (Microsoft Corp., Redmond, WA, USA). In all studies, we applied an alpha level set to 5%.

In **study I**, short-term and long-term survival analyses were conducted utilizing the Kaplan–Meier analysis. Survival differences were compared using the log-rank test. Short-term mortality risk factors were evaluated by performing an univariate analysis of prespecified variables utilizing binary logistic regression models, calculating the odds ratios (ORs), and 95% confidence intervals (CIs). Statistically significant variables in the binary logistic regression models along with clinically important variables were entered into a multivariable logistic regression model. Proportions were compared utilizing the Pearson's chi-square test (or Fisher's exact two-sided test if $n \leq 5$).

In **study II**, 90-day survival in patients with WON and ANC were evaluated by means of the Kaplan–Meier analysis, and survival differences were compared using the log-rank test. The potential short-term mortality risk factors following necrosectomy were evaluated by means of an univariate analysis of prespecified variables utilizing binary logistic regression models, calculating the ORs and 95% CIs. The Fisher's exact two-sided test and the Mann–Whitney U test were used to evaluate differences in proportions and continuous variables, respectively. For continuous variables, we converted values to dichotomous variables guided by a receiver operating characteristic analysis. The pre- and intraoperatively known variables with $P < 0.010$ in binary logistic regression models were entered into a multivariable binary logistic regression model. The variables with statistically significant results from the multivariable model were further evaluated, testing the effect on mortality of each combination of these independent risk factors. The risk of renecrosectomy and reoperations were evaluated by means of an univariate

analysis of prespecified variables utilizing binary logistic regression models, calculating the ORs and 95% CIs.

In **study III**, IPN risk was investigated through an univariate analysis of prespecified variables utilizing binary logistic regression models, calculating the ORs and 95% CIs. The Fisher's exact two-sided test and the Mann–Whitney U test were performed to compare differences in proportions and continuous variables, respectively. All variables with $P < 0.05$ were entered into a multivariable binary logistic regression model. The Kaplan–Meier estimates of survival in patients with and without IPN were calculated. Risk factors of a late death (between day 8 and 90 from ICU admission) were analyzed through the univariate analysis of prespecified variables utilizing binary logistic regression models, calculating the ORs and 95% CIs.

In **study IV**, the risk of allocation to OA treatment was evaluated through an univariate analysis of prespecified variables utilizing binary logistic regression models, calculating the ORs and 95% CIs. The Fisher's exact two-sided test and the Mann–Whitney U test were performed to compare differences in proportions and continuous variables, respectively. For continious variables, we converted the data in dichotomous variables guided by a receiver operating characteristics analysis. Clinically relevant variables with a statistical significance in the univariate analysis were entered into a multivariable logistic regression analysis. The outcomes from the univariate analysis between OA and conservatively treated patients were evaluated utilizing the log-rank test, the Fisher's exact two-sided test, and the Mann–Whitney U test, as appropriate. The post-hoc univariate analysis of the available potential risk factors for visceral ischemia in the OA group of patients was performed using binary logistic regression models, calculating the ORs and 95% CIs.

3.3 RESULTS

The main findings from this thesis project are summarized in **Table 15**.

Table 15 *Main findings from studies I–IV.*

Study	Results	
I	**Short-term survival** - Overall: 82% - Age <60: 90% - Age ≥60: 55% **Independent short-term mortality risk factors**: age 60–69, age ≥70, female sex, heart disease, liver cirrhosis, OA treatment, necrosectomy <4 weeks for sterile necrosis	**10-year survival estimate** - Age <60: 68% - Age ≥60: 28% **Long-term death causes** - Alcohol-related: 57%
II	**90-day mortality after open necrosectomy** - Overall: 23% - Walled-off necrosis >4 weeks: 11% **Independent mortality risk factors**: leukocytosis ≥23 x 10^9, age ≥60, comorbidities, multiple organ failure, prolonged/deteriorating organ failure as the indication for open necrosectomy, necrosectomy ≤28 days <2 risk factors present → mortality: 0% ≥2 risk factors present → mortality: more than 50%	**Postoperative morbidity** - Transient organ failure: 14% - Persistent organ failure: 21% - Reoperation: 48% - Renecrosectomy: 25% - Pancreaticocutaneous fistula: 39%
III	**90-day mortality after ICU admission** - IPN: 15% - Sterile necrosis: 19% **Independent IPN risk factors:** postintervention etiology, wider anatomical spread of necrotic collection, bacteremia, OA treatment	**Morbidity** - Longer length of hospital and ICU stays in IPN - Higher ICU readmission rate in IPN - Higher risk for a necrosectomy **Risk factors for death at days 8–90:** related to previous health status and disease severity
IV	**90-day mortality after ICU admission** - OA treatment: 43% - Matched controls: 17% **Independent OA treatment risk factors:** abdominal compartment syndrome, oliguria	**Morbidity** - More visceral ischemia in OA - Necrosectomy more often in OA - Longer length of stay in OA **Delayed primary fascial closure** - Achievable in 97%

Abbreviations: ICU, intensive care unit; IPN, infected pancreatic necrosis; OA, open abdomen; OF, organ failure.

3.3.1 SURVIVAL AFTER SEVERE ACUTE PANCREATITIS (STUDY I)

Overall short-term (<90-day) survival was 82%. Short-term survival was 90% in patients under 60 years, 60% in patients aged 60–69 years, and 43% in patients aged 70 or more ($P < 0.001$). Independent risk factors for mortality included both being 60–69 years of age (OR 5.1) and ≥70 years age (OR 10.4) compared with patients younger than 60. The other independent risk factors were being female (OR 2.0), preexisting comorbidities (heart disease: OR 2.9; liver chirrhosis: OR 12.3), OA treatment (OR 4.4), and necrosectomy within four weeks due to a sterile necrosis compared with patients who did not undergo a necrosectomy (OR 14.7).

The ten-year (long-term) survival estimate was 68% for patients under 60 years of age and 28% for patients over 60. We observed no significant differences in survival when dividing patients under 60 years into age groups (<40 years, 40–49 years, and 50–59 years; $P = 0.680$). AP was listed as the cause of death for 26% of cases that died later than 90 days from hospital admission. Alcohol was an immediate or contributing factor for death (e.g., alcohol intoxication, alcohol-related trauma, or alcohol-related chronic disease) in 57% of late deaths. All of these patients experienced AAP, whereas alcohol-related late deaths did not occur in patients without AAP ($P < 0.001$). The pattern from the Kaplan–Meier long-term survival estimates were different in patients who endured alcoholic SAP compared with etiologies other than alcohol. An initially better survival for alcoholic SAP was followed by an increasing mortality risk during the follow-up period, whereas patients with nonalcoholic SAP experienced a seemingly worse early survival within the first year of follow-up, followed by a plateau. As an example of this pattern, the Kaplan–Meier curve for patients under 60 appears in **Figure 3**. In this age group, patients with alcoholic SAP were a median of 7 years younger than patients with etiologies other than alcohol ($P = 0.001$).

The median length of stay in ICU was 13 (interquartile range [IQR] 6–25) days and the median length of hospital stay was 25 (IQR 15–45) days. Within a 90-day follow-up period, 71% were managed nonoperatively, while OA treatment and open necrosectomy were utilized in 16% and 24% of cases, respectively.

Patients in group 2 (treatment years 2008–2015) underwent OA treatment more often (21% vs. 11%, $P = 0.003$) than patients in group 1 (years 1997–2007). In group 2, open necrosectomy after 28 days from symptom onset was more common (39% vs. 18%, $P = 0.022$), and an open necrosectomy due to a sterile necrosis was less common (9% vs. 33%, $P = 0.003$) compared with patients in group 1 (years 1997–2007). We did not observe a significant difference in short-term survival between these groups (group 1: 81%, group 2: 84%; $P = 0.373$).

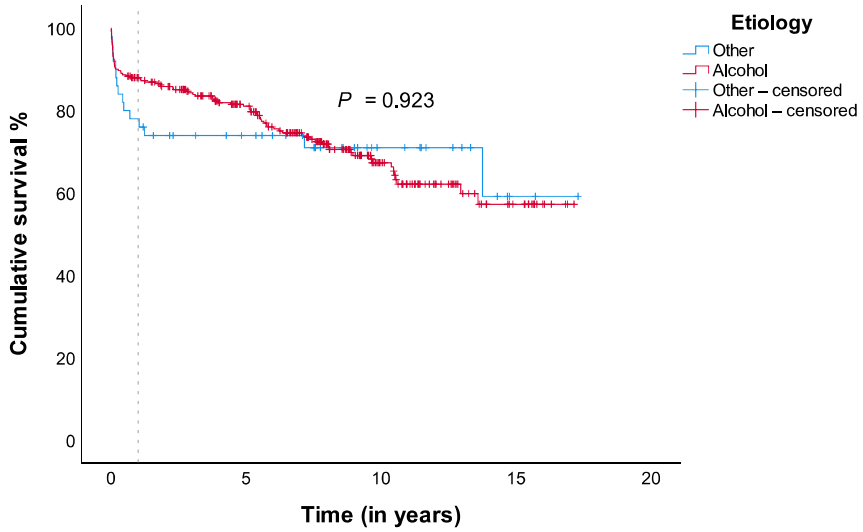


Figure 3 Long-term survival among patients under 60 years of age following SAP due to alcohol misuse or other etiologies. The dotted line indicates the timepoint for the first year of follow-up.

3.3.2 OUTCOMES AFTER OPEN NECROSECTOMY (STUDY II)

The overall 90-day mortality after an open necrosectomy was 23%. More specifically, mortality was 56% in patients with ANC upon preoperative imaging, falling to 16% in patients with WON ($P < 0.001$). If necrosectomy for WON could be delayed for 28 days from symptom onset, mortality fell further to 11%.

Independent preoperative risk factors for mortality included leukocytosis exceeding 23 x 10^9 (OR 21.4), age >60 (OR 19.4), any comorbidity (OR 16.9), MOF at the time of necrosectomy (OR 12.2), prolonged OF or deterioration as an indication for necrosectomy (OR 10.4), and a necrosectomy within 28 days (OR 6.5). Any combination of these risk factors resulted in a mortality exceeding 50% (**Table 16**). By contrast, around half of all patients (n = 52) exhibited only one or none of these risk factors, and experienced no mortality.

Within the week following an index open necrosectomy, new transient OF occurred in 14% and persistent OF in 21% of patients. Preoperatively existing OFs resolved within two days following an index necrosectomy in five (5%) patients.

Around half of patients underwent a reoperation and 25% had a renecrosectomy within six months. Any reoperation was significantly more

likely if a patient underwent an index necrosectomy within 28 days from symptom onset (68% vs. 36%, $P = 0.003$) or in the case of widespread necrosis (58% vs. 33%, $P = 0.012$). Within six months of follow-up, 21%, 19%, 18%, and 11% of patients underwent cholecystectomy, bowel resection, pancreatic resection, and splenectomy, respectively. Among patients with ABP, 60% underwent a synchronous cholecystectomy during an index necrosectomy procedure. Among all study patients, 40 (37%) had an intraoperative finding of DPDS or a preoperative suspicion of DPDS upon CECT. Among these patients, pancreatic resection was performed due to DPDS in 16 (40%) patients and 15 (38%) underwent endoscopic pancreatic duct stenting within 1 year following an index necrosectomy. A pancreaticocutaneous fistula following an open necrosectomy occurred in 39% of patients, and one-fifth of these patients were treated operatively.

The risk of renecrosectomy increased if the index necrosectomy occurred within four weeks (OR 3.5), the patient underwent OA treatment at the time of an index necrosectomy (OR 11.5) or postoperatively (OR 8.1), in the case of MOF within 24 h before index necrosectomy (OR 7.0), and if the patient had severe acute pancreatitis by the time of the first necrosectomy (OR 3.1).

In the univariate analysis of postoperative mortality predictors, OA treatment following necrosectomy (OR 7.6, $P < 0.001$) and reoperations other than renecrosectomy (OR 3.2, $P = 0.018$) (especially reoperations due to bleeding [OR 12.7, $P < 0.001$] or enteric fistula/ischemia [OR 4.9, $P = 0.003$]) associated with an increased mortality. New onset OF postoperatively (transient or persistent [$P = 0.152$, $P = 0.163$]) and renecrosectomies ($P = 0.186$), however, did not associate with an increased mortality risk.

Table 16 *Risk factor combinations and mortality.*

	Age >60 years	Comorbidity*	Indication	<28 days†	MOF	WBC >23	None
Age >60 years	**42%** 31						
Comorbidity*	**50%** 18	**33%** 43					
Indication	**86%** 7	**50%** 6	**67%** 18				
<28 days†	**62%** 13	**60%** 15	**89%** 9	**43%** 40			
MOF	**83%** 6	**75%** 8	**85%** 13	**52%** 21	**49%** 33		
WBC >23	**100%** 6	**80%** 10	**89%** 9	**77%** 13	**69%** 16	**63%** 24	
None	**0%** 6	**0%** 11	**0%** 2	**0%** 5	**0%** 2	**0%** 2	**0%** 24

Mortality (**bolded**) as a percentage and the number of patients (not bolded) for the specific risk factor combination in question.
*Chronic pancreatitis, diabetes, or any chronic heart, liver, pulmonary, or renal diseases.
†Necrosectomy within 28 days of symptom onset.
Abbreviations: MOF, multiple organ failure; WBC, white blood cell.

3.3.3 RISK FACTORS OF INFECTED PANCREATIC NECROSIS (STUDY III)

More than half of patients experienced an infection within 90 days. IPN occurred in 29%, bacteremia in 13%, and pneumonia in 13% of patients at a median of 4, 16, and 23 days, respectively, following ICU admission. The risk of IPN was highest during the first week (30%) and decreased by half by the end of the first month following ICU admission (**Figure 4**).

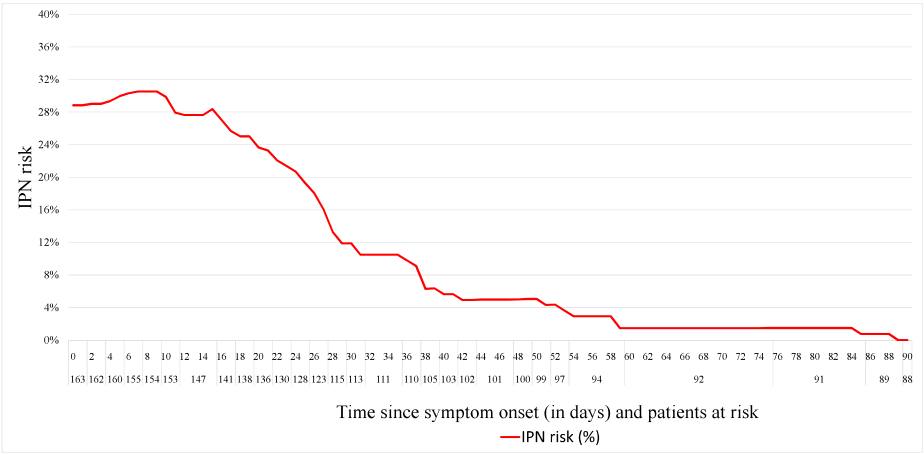


Figure 4 Risk of infected pancreatic necrosis within 90 days of symptom onset among patients with necrotizing severe acute pancreatitis.

The following variables independently associated with IPN risk: postintervention etiology (PEP or postoperative nonpancreatic surgery) compared with patients with AAP (OR 13.5), a wider anatomical spread of necrotic collection (distant [OR 5.7] and widespread [OR 21.8]) compared with local necrotic collections, preceding bacteremia (OR 4.8), and preceding OA treatment (OR 3.6).

In 153 (94%) patients, including all patients with IPN, enteral nutrition was initiated at a median on the first day (IQR 1–2, range 0–12) following ICU admission. Patients who did not receive enteral nutrition either died prior to its initiation (five died on ICU day 0–1 and three on ICU day 2) or recovered sufficiently early to tolerate oral intake (two patients).

In addition, 90-day mortality was 15% in IPN patients and 19% among patients without IPN. The Kaplan–Meier survival estimate among patients with and without IPN showed that the mortality risk inherently differed between these groups. Thus, patients had to survive the first days or weeks in order to develop IPN, and this survival bias rendered comparison of survival between groups inappropriate (data shown in the original study).

The length of stays in ICU (median : 31 vs. 8 days, $P < 0.001$) and hospital (median : 69 vs. 21 days, $P < 0.001$) were significantly longer in patients with IPN relative to patients without IPN. ICU readmission risk was 33% in patients with IPN compared with 1% in patients without IPN ($P < 0.001$). All patients with IPN underwent at least one intervention, whereas 15% of patients without IPN underwent an intervention ($P < 0.001$). In IPN and sterile necrosis, 91% and 5%, respectively, underwent an open necrosectomy ($P < 0.001$).

Statistically significant risk factors for death from day 8 to 90 following ICU admission are summarized in **Table 17**.

Table 17 *Univariate logistic regression analysis of statistically significant risk factors for death from day 8 through 90 following intensive care unit admission (n = 152).*

	Survivors (n = 134)	Nonsurvivors (n = 18)	OR (95% CI)	*P*
Any comorbidity*	34 (25)	11 (61)	4.62 (1.7–12.9)	0.004
ASA ≥3	63 (47)	16 (89)	9.02 (2.0–40.8)	<0.001
Hypoperfusion <24 h†	101 (75)	18 (100)	NA	0.013
Organ failure <24 h†				
cardiovascular	65 (49)	17 (94)	18.1 (2.3–139.5)	<0.001
renal	35 (26)	11 (61)	4.5 (1.6–12.4)	0.005
multiple	74 (55)	17 (94)	13.8 (1.8–106.6)	0.001
APACHE <24 h†	15 (12–20)	23 (21–28)	1.2 (1.1–1.3)	<0.001
Highest SOFA <72 h†	8 (5–11)	13 (8–17)	1.4 (1.2–1.6)	<0.001
Open abdomen treatment	26 (19)	12 (67)	8.3 (2.9–24.2)	<0.001

Data are presented as the number of patients and percentage in parenthesis unless stated otherwise.
*Any heart or pulmonary disease, chronic renal insufficiency, liver chirrhosis, and/or diabetes.
†From ICU admission.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II Scoring System; ASA, American Society of Anesthesiologists physical status classification system; SOFA, sequential organ failure assessment score; NA, not applicable.

3.3.4 UTILIZATION OF OPEN ABDOMEN (STUDY IV)

We compared 47 patients who underwent OA treatment with an equal number of matched controls. In doing so, we found that ACS (85% vs. 45%, $P < 0.001$) and oliguria (68% vs. 30%, $P < 0.001$), defined by an urine output <20 ml/h, occurred more frequently in OA-treated patients than in matched controls. An indication for surgical decompression of the abdomen was persistent ACS in 85% of patients, and in 15% of patients the abdomen was left open following an explorative laparotomy. Exposure time to ACS was similar in OA-treated patients and matched controls (median : 7 vs. 14 h, $P = 0.317$). Variables associated with OA treatment in the univariate analysis are summarized in **Table 18**. We found that oliguria (OR 5.0) and ACS (OR 4.6) associated with an increased risk of OA treatment in the multivariable analysis.

Overall mortality within 90 days was 43% among OA-treated patients and 17% in matched controls ($P = 0.012$). In addition, OA-treated patients experienced visceral ischemia more often than their matched peers (34% vs.

6%, P = 0.002), needed necrosectomy more often (55% vs. 21%, P = 0.001), and endured longer stays in ICU (median : 37 vs. 13 days, P < 0.001) and hospital in general (median : 73 vs. 30 days, P < 0.001). A post-hoc analysis identified no clinically meaningful risk factors predictive of visceral ischemia.

Furthermore, delayed primary fascial closure was feasible in 97% of patients who survived OA treatment. Abdominal wound closure was achieved within a median 20 days following the initiation of OA treatment; 15% needed an anterior separation of components, whereas 3% (one patient) required split-skin grafting for abdominal wound closure due to an enteroathmospheric fistula and a frozen abdomen.

Table 18 *Statistically significant predictors of open abdomen treatment from an univariate analysis.*

	OA treatment (n = 47)	Matched controls (n = 47)	*P*
MAP, mean ± SD, mmHg*	79 ± 8	85 ± 11	0.004
IAP, highest (24 h) ± SD, mmHg†	24 ± 4	21 ± 5	<0.001
IAP, mean ± SD, mmHg*	20 ± 3	17 ± 3	<0.001
APP, lowest (24 h) ± SD, mmHg†	46 ± 9	56 ± 13	<0.001
APP, mean ± SD, mmHg*	58 ± 9	68 ± 11	<0.001
Urine output, lowest (24 h) ± SD, ml/h†	19 ± 29	41 ± 36	<0.001
Urine output, mean ± SD, ml/h*	31 ± 31	72 ± 66	<0.001
Blood leukocyte count, mean ± SD, 10^9/L	16.0 ± 9.1	11.9 ± 6.1	0.016
Plasma bilirubin, highest (24 h) ± SD, umol/L†	45 ± 46	58 ± 51	0.041
Plasma lactate, mean ± SD, mmol/L*	4.5 ± 3.9	2.9 ± 2.6	0.014
Arterial pH, mean ± SD‡	7.22 ± 0.14	7.29 ± 0.10	0.016
Serum potassium, mean ± SD, mmol/l‡	5.3 ± 1.1	4.6 ± 0.9	0.001
Serum sodium, mean ± SD, mmol/l‡	127 ± 5	130 ± 6	0.008
Cumulative excess fluid balance ± SD, ml§	12 267 ± 7374	8616 ± 6888	0.020

IAP and APP had one missing value in the OA treatment group.
*Mean of all preceding values.
†Mean of the most divergent value within 24 h from a laparostomy (OA group) vs. mean of the most divergent value during the entire follow-up period (matched controls).
‡Mean of the most divergent values within 24 h from ICU admission.
§Between admission and OA treatment (and the corresponding time period for matched controls).
Abbreviations: APP, abdominal perfusion pressure; IAP, intra-abdominal pressure; MAP, mean arterial pressure; OA, open abdomen; SD, standard deviation.

3.4 DISCUSSION

3.4.1 SURVIVAL AFTER SEVERE ACUTE PANCREATITIS (STUDY I)

The management of patients with SAP resulted in good short-term survival if patients were younger than 60 years of age, albeit at the expense of considerable morbidity. Consistent with previous studies, an older age, preexisting comorbidities, and early necrosectomy increased the risk of mortality (Besselink, van Santvoort, Boermeester, et al., 2009; Frey et al.,

2007; Halonen et al., 2002; McKay et al., 1999; Rodriguez et al., 2008). In addition, OA treatment associated with an increased mortality, likely resulting from a more severe disease itself, corresponding with earlier reports of patients with SAP treated with OA (Boone et al., 2013; Mentula et al., 2010; Smit et al., 2016).

An independent association between female sex and poorer 90-day survival could be established. A similar finding was previously reported in a surgically treated cohort of patients with NP (Rodriguez et al., 2008). However, three potential confounders were identified which may have influenced this finding in the present study. Firstly, AAP occurred less frequently in female than male patients. Secondly, female patients were significantly older than their male counterparts. Finally, the number of female patients was quite low (on average, only five per year).

The present study was not designed to evaluate the management strategy of patients with NP complications, and thus the reasons why an open necrosectomy was utilized in each patient remain unclear. However, necrosectomy in patients with IPN later than 28 days became more common during the later years of this study. This could reflect the evolving implementation of updated treatment guidelines from 2013, indicating that interventions were postponed, and avoided in patients with sterile necrosis (Besselink et al., 2013).

Despite the encouraging short-term results in this study, long-term survival estimates remained disappointing even among younger patients. For instance, the 10-year survival estimates following an incident of SAP were less than 70% among patients under 40 years of age. Our results regarding long-term causes of death suggest that ongoing alcohol misuse contributes to a considerable reduction in life expectancy in patients following alcoholic SAP. These results mirror other epidemiological findings suggesting that alcohol is the primary risk factor for death in younger populations, accounting for almost 10% of deaths globally among individuals aged 15–49 (Griswold et al., 2018). Moreover, a recent Finnish study with a median 10-year follow-up period among working-aged patients with AP demonstrated that the mortality risk within the follow-up period increased fivefold among patients with a single incident of AAP compared with (age- and sex-matched) controls, and that long-term mortality was alcohol-related in 43% of patients following alcoholic AP (Karjula et al., 2019). These findings are consistent with the findings presented here.

The long-term survival pattern observed in the present study warrants consideration when treating patients with alcoholic SAP. Battling these long-term risks following an insult of alcoholic SAP could warrant repeat interventions intended to promote alcohol abstinence, previously associated

with lower AP recurrence rates (Nordback, Pelli, Lappalainen-Lehto, Järvinen, et al., 2009). It seems logical that any intervention aimed at decreasing alcohol consumption in the longer term would also improve outcomes after experiencing alcoholic SAP.

3.4.2 CONTEMPORARY OPEN NECROSECTOMY RESULTS (STUDY II)

The present study found that mortality risk following open necrosectomy may be attributable to several independent preoperative risk factors: age >60 years, previous comorbidities, necrosectomy within 28 days from symptom onset, MOF, prolonged or deteriorating OF as an indication for necrosectomy, and a markedly elevated WBC count (>23 x 10^9). Any combination of these risk factors resulted in at least a 50% mortality rate, whereas patients with none or only one of these risk factors experienced no mortality. Open necrosectomy 28 days following symptom onset when necrosis was demarcated (i.e., WON) resulted in around a 10% mortality rate, whereas more than half of patients died if they underwent an open necrosectomy before demarcation occurred. Despite these overall encouraging results regarding mortality, patients who underwent an open necrosectomy experienced significant morbidity. Almost half of the study patients underwent an additional operation, one-quarter requiring further necrosectomy and around 40% developing a pancreaticocutaneous fistula.

Mortality following an open necrosectomy in the present study is comparable to recently published results (Babu et al., 2010; Gomatos et al., 2016; Madenci et al., 2014; van Santvoort et al., 2010). In line with earlier studies, risk factors for mortality, such as age, early necrosectomy, and MOF, were also recognized as independent risk factors in the study reported here (Connor et al., 2005; de Waele et al., 2004; Gomatos et al., 2016; Madenci et al., 2014; Mofidi et al., 2007; Raraty et al., 2010). Specifically, this investigation revealed that the indication for open necrosectomy independently associates with mortality risk, which has not been extensively reported. In fact, in a previous cohort of 27 patients treated with an open necrosectomy based on a step-up algorithm, mortality reached 33% (4/12) if ongoing sepsis or a failure to thrive indicated the necrosectomy, and reached 50% (3/6) if the indication was a worsening sepsis. However, the authors did not include an indication for an open necrosectomy in their mortality risk factor analysis (Babu et al., 2013). Thus, the present study indicates that patients who underwent an open necrosectomy following a failure to thrive or deteriorating OFs experienced an increased mortality. In addition, WBC was previously associated with a more severe AP disease course, which corresponds with our findings (al Mofleh, 2008; de Campos et al., 2008; Kaya et al., 2007).

To our knowledge, our study is the first to demonstrate that combining these preoperative risk factors can be used to evaluate likely outcomes following an open necrosectomy in terms of mortality. Most combinations that involved a persistent or deteriorating OF as an indication for necrosectomy, age >60 years, MOF, and WBC count exceeding 23 x 10^9 /l resulted in 80–100% mortality. This mortality is exceptionally high, since, for instance, mortality in ICU-treated patients with acute respiratory distress syndrome ranges from 35–46% and renal replacement therapy for acute kidney injury from 47–60% (Bellani et al., 2016; Schiffl, 2006; Uchino et al., 2005). The only risk factors that can be manipulated are the timing and indication for an open necrosectomy. Among patients not clinically improving from OFs, it might be possible to downstage or delay the initiation of invasive procedures, which could potentially improve survival. Whether patients treated with an open necrosectomy for these indications would experience a better outcome after a minimally invasive necrosectomy, however, remains unknown. Yet, it seems that among patients deteriorating despite maximal supportive therapy, relying on minimally invasive treatment strategies may carry risks associated with delaying and/or misdiagnosing other complications related to severe NP. Certain complications, such as visceral perforations and ischemia, may be treatable during open surgery, thereby altering the outcome.

Study patients suffered from significant morbidity in terms of the need for repeat procedures. For instance, one-half needed an additional procedure within 90 days and one-quarter needed a renecrosectomy, findings which are also comparable to previous investigations (Babu et al., 2010; van Santvoort et al., 2010). They also endured complications, such as pancreaticocutaneous fistulae and required a prolonged hospitalization. The reported rate of pancreaticocutaneous fistulae of around 40% resembles previously published results following open and minimally invasive extraluminal methods (Bang et al., 2019; van Brunschot, van Grinsven, et al., 2018; van Santvoort et al., 2010).

The risk of repeated interventions was highest among patients who experienced a more severe disease, ongoing OA at the time of the index necrosectomy, an OA following necrosectomy, and when the necrosectomy was performed within 28 days of symptom onset. By contrast, although most patients experienced anatomically widely distributed necrosis, three-quarters did not require an additional necrosectomy. Because open necrosectomy provides the most comprehensive debridement during a single treatment session, some previous studies have advocated for its use in specific patients with extensive necrotic collections (van Brunschot, Hollemans, et al., 2018). However, minimally invasive necrosectomy might facilitate the need for a repeat and a combination of procedures (van Brunschot et al., 2013; van Brunschot, Fockens, et al., 2014; van Brunschot, van Grinsven, et al., 2018).

Based on the results from this study and clinical experiences, several situations occurred during which an open necrosectomy might have been a feasible debridement option. These included cases such as ongoing OA treatment in case of a simultaneous need for the treatment of DPDS (or other procedures such as cholecystectomy), in cases involving a wide anatomical spread of the necrotic collection, in cases involving a suspected or acknowledged other simultaneous complications requiring open surgery (e.g., colonic necrosis, persistent bleeding despite endovascular treatment), and in cases involving inadequate experience in providing minimally invasive necrosectomy techniques.

3.4.3 INFECTED PANCREATIC NECROSIS RISKS AND CONSEQUENCES (STUDY III)

Most patients with necrotizing SAP suffer from some type of infection within 90 days from ICU admission. Bacteremia and pneumonia generally occur earlier than IPN. The reported 29% occurrence of IPN we found is comparable to previous reports (Petrov et al., 2010). Higher rates have been reported primarily in cohorts among patients receiving parenteral nutrition (García-Barrasa et al., 2009; le Mée et al., 2001), while lower occurrences were reported primarily in cohorts experiencing milder AP (Dellinger et al., 2007; Gloor et al., 2001; Isenmann et al., 2004). In this study, TEN was included as a routine treatment for all patients. Only patients who died before its initiation or when patients improved and tolerated oral intake early did not receive enteral nutrition. Thus, the impact of enteral nutrition on IPN risk was not evaluated.

As previously shown, IPN generally occurs a few weeks after symptom onset (Besselink, van Santvoort, Boermeester, et al., 2009). The current study indicates that more than half of patients develop IPN in the four weeks from disease onset, primarily during the third and fourth weeks, which corresponds with previous studies (Petrov et al., 2011). Here, we observed a sharp decrease in IPN risk following the first month of treatment (**Figure 4**). It is worth emphasizing that most patients are diagnosed with IPN during the time period during which contemporary guidelines recommend postponing interventions when clinically possible (Besselink et al., 2013; Leppäniemi et al., 2019). Thus, interventions may become necessary before 28 days from disease onset in deteriorating patients with verified or suspected IPN.

A wider anatomical spread of necrotic collections, a postintervention etiology of pancreatitis, preceding bacteremia, and preceding OA treatment all independently predicted evolving IPN. Consistent with our findings, an extrapancreatic necrosis volume in AP, the number of necrotic collections in SAP, and bacteremia have previously been associated with an increased risk of

IPN (Besselink, van Santvoort, Boermeester, et al., 2009; Çakar et al., 2020; Ding et al., 2019; Meyrignac et al., 2015; Pamies-Guilabert et al., 2020).

Interestingly, no previous studies mentioned an increased risk of IPN in SAP patients with a postintervention etiology compared with alcoholic SAP. Previous reports found that PEP seldom develops into SAP (<1%) (Kochar et al., 2015). Notably, our results indicated that bacterial infection often accompanies postintervention SAP. This suggests that bacterial infection might propel disease progression in these patients. The association between a preceding surgical decompression of the abdomen in SAP and the development of IPN was not previously reported. Based on IPN developmental theory, it makes sense that early worsening OFs in conjunction with a critically elevated IAP would result in an increased infectious susceptibility due to poor visceral perfusion and a dysfunctioning gut barrier.

Patients with IPN experienced significantly more morbidity in relation to a longer length of stay and as the need for invasive interventions increased compared with patients without IPN. All patients with IPN needed some type of invasive procedure. This finding differs from previously reported studies, which found that 5–50% of patients were treated conservatively for a suspicion of or verified IPN (Boxhoorn et al., 2021; Jain et al., 2020; Lariño-Noia et al., 2021; Lee et al., 2007; Runzi et al., 2005; van Santvoort et al., 2011; Zerem et al., 2011).

Due to the inherent survival bias related to patients with and without IPN, a comparison of mortality was considered inappropriate here. This bias resulted from the inclusion of patients who experienced early mortality due to MOF in the non-IPN group, whereas developing IPN generally required survival through this first stage of disease. Thus, although survival was comparable at the 90-day timepoint, the Kaplan–Meier analysis showed differing survival patterns. A large prospective register study presented similar findings whereby an increased mortality was not related to IPN (compared with sterile necrosis) when adjusting for existing OFs (Sternby et al., 2019).

3.4.4 UTILIZATION OF OPEN ABDOMEN AND ISCHEMIA (STUDY IV)

The present investigation revealed that the development of oliguria and ACS predicts the use of OA treatment in patients with SAP. Patients treated with OA experienced considerable morbidity and exhibited an increased mortality. Specifically, ischemic complications of intra-abdominal viscera commonly affect these patients, most often with devastating outcomes. Unfortunately, we could not identify which variables accurately predict the development of ischemic changes, posing a major clinical problem. Among patients surviving

OA treatment, an abdominal closure is generally achieved when a gradual closure approach with dynamic traction systems is utilized.

The timing and indication of OA treatment in patients with SAP remain controversial, posing challenges to clinical practice. The decision to decompress the abdomen always includes a level of uncertainty since the exact timepoint for when a new or worsening OF in conjunction with an elevated IAP justifies inaction remains unspecified. One problem lies in the fact that most patients with SAP suffer from an elevated IAP and as many as half have ACS, as we observed and as many others have as well (Al-Bahrani et al., 2008; Bhandari et al., 2013; Chen et al., 2008; Dambrauskas et al., 2009; Davis et al., 2013; de Waele et al., 2005; Keskinen et al., 2007; Kurdia et al., 2020; Smit et al., 2016). None of the available studies, however, provide an answer to the question, "What amount of storminess is acceptable before the abdomen should be opened?" Circumstantial evidence suggests benefits can be gained from early OA treatment for ACS in SAP, although no randomized controlled trials have been conducted (Mentula et al., 2010). The present study attempted to provide additional information to answer this question through the gross measurement of ACS time. However, we observed no group differences.

In experimental animal models of SAP, the reversibility of urine output extends to the point of oliguria, whereafter abdominal decompression no longer exerts reversible effects on urine output (Ke et al., 2013). This finding supports current practices implemented during the study period. A meta-analysis of OA-treated patients with mixed etiologies suggests that respiratory and renal improvements follow abdominal decompression (van Damme & de Waele, 2018). By contrast, the present study found that half of conservatively treated patients experienced ACS, one-third of whom were oliguric during the study period. In addition, patient survivial among the control group was significantly better compared with patients who underwent laparostomy.

The observed rate of 30% irreversible ischemic complications among patients with OA treatment primarily due to ACS is lower than previous reports. Ischemia was observed in 60% of 13 SAP patients who underwent surgical decompression for ACS (Smit et al., 2016). In mixed-etiology patients undergoing OA treatment, mortality related to ischemic complications was 15% (van Damme & de Waele, 2018). A mortality rate of 43% following OA treatment in our study was comparable to previous reports among adult ACS patients with different etiologies (50%) and among patients with ACS in SAP (60%) (Smit et al., 2016; van Damme & de Waele, 2018). Additionally, two-thirds of patients with ischemia died in our study, which is lower than rates reported from an earlier study with an 82% mortality rate following ischemia in SAP (Smit et al., 2016).

Our study confirmed that the diagnosis of ischemia in patients with SAP is extremely difficult. We were, unfortunately, unable to find clinically relevant physiological or biochemical parameters which can predict ischemic events. The clinical dilemma is that IAH and ACS commonly occur in SAP, persistent OF is a characteristic of SAP, and these generally occur within the first few days of disease onset. Similarly, irreversible ACS in SAP occurs within the first few days following disease onset, sometimes developing within hours. Therefore, distinguishing an abnormal early course of disease in SAP warranting OA treatment becomes quite difficult. Thus, the clinicians treating patients in our study performed well despite this diagnostic difficulty, since they were able to decompress most patients experiencing ischemia. Only 16% (3/19) of patients with ischemia were treated in the control group. It remains unknown whether an earlier laparostomy could have revered some ischemic events.

3.4.5 STRENGTHS AND LIMITATIONS

The strength of this thesis is that it consisted primarily of patients with SAP and only 30% of patients exhibited moderately severe AP in one of the four studies (study II). Another strength lies in the relatively large sample sizes for each study. Moreover, this thesis included consecutively treated patients applying relatively few, albeit warranted, exclusion criteria. Therefore, this thesis depicts well the current state of management of these patients. Predefined variable and statistical analyses, as well as adherence to the STROBE statement checklist, also represent strengths of the research summarized in this thesis. Reporting results from an academic teratiary center, with largely round-the-clock possibilities for the multidisciplinary contemporary management of SAP complications, should also be considered an additional strength to this study. Furthermore, despite being based on experience from a single institution, this research relied on a large catchment population extending to more than 1.5 million people.

The specific strengths of study I are that it represents the largest cohort of patients with long-term follow-up results following SAP, and included late causes of death. A specific strength of study II is that the number of open necrosectomy procedures did not increase during the study period. This depicts a constrained, highly conservative treatment approach during a relatively long time frame, as recommended by contemporary guidelines. A specific strength of study III is that infectious disease specialists were both involved in the actual management of patients with necrotizing SAP as well as a part of the actual study group, resulting in more reliable diagnoses of infectious complications. The strength of study IV is that it is one of the few attempts to study the topic of surgical decompression of ACS in SAP attempting to adjust for baseline confounders.

The primary limitation of this thesis is its retrospective nature. Thus, patients were investigated as treated and data were retrieved as reported, which possibly introduces selection and reporting biases in each study. Furthermore, the patient cohorts studied and their management might have changed during the study years. However, such changes remain speculative since the researchers were unaware of such changes. Furthermore, variables related to organ-specific supportive treatments in the ICU were not collected. Thus, the presence and effect of possible management changes could not be evaluated, representing another limitation to these studies. All individual studies are susceptible to confounding factors, such as different criteria for the allocation of patients to ICU treatment, along with any other management-related differences, since treatments were not standardized to a particular protocol specifically for the purposes of the study. Although each cohort of consecutive patients was quite large within the context of the specific studies, the absolute number of some events was quite low, depicted by the wide confidence intervals in some of the analyses. This might increase the effect attributed to random events. Although long-term follow-up data regarding mortality and cause of death were gathered for study I, no other long-term variables (such as pancreatic insufficiencies, chronic pain, recurring attacks of AP, incisional hernia, and quality of life) were evaluated in any of the studies, representing a limitation. In addition, the use of monocentric tertiary data limits their application in different instances and populations.

More specifically, a limitation of study I lies in the lack of a reference group consisting of age-, health-, and sex-matched patients for long-time survival. One limitation to both studies I and II is that the severity of organ dysfunctions was not continuously evaluated through the objective grouping of items, such as the SOFA or APACHE II scoring systems. In addition, one limitation related to study II is that patients potentially treated through minimally invasive techniques or with drainage alone were not included as a reference. Nevertheless, open necrosectomy served as the primary method of debridement during the study period at the institution in question. Another limitation of study II was that standardized multidisciplinary meetings were not implemented. The use of prophylactic antibiotics in study III is a limitation, since contemporary guidelines do not recommend such practices. Fortunately, the duration of administration of prophylactic antibiotics remained short-lived. Finally, the primary limitation of study IV is that, although we attempted to match patients based on baseline characteristics, patients in the study group were still more severely ill at baseline. As such, a larger number of control group patients (i.e., matching 1:2) may have decreased the potential bias introduced by variability. This would also have increased the chances of detecting baseline group differences and true effects. However, control group patients in study IV included the most severe cases with SAP not subjected to OA treatment at our institution, and a larger control group would have required a multicenter study population.

3.4.6 FUTURE PROSPECTS

Although several improvements to treatment for patients with SAP have emerged in recent decades, many obstacles remain for these patients. It seems that late mortality in SAP could be eliminated in the future following an increased undertanding of SAP patient complications and treatment. The expanding potential of minimally invasive treatment for complicated necrosis might further increase the use of such techniques, potentially decreasing the risk of worsening OF, pancreaticocutaneous fistulas, and pancreatic insufficiencies. However, an open necrosectomy will most likely remain necessary as a salvage technique and as treatment of simultaneously occurring complications of NP, such as intestinal perforation or ischemia, and in unstable patients who require urgent interventions. Whether its use will extend to specific subgroups of patients, such as those with widespread necrotic collections, is unclear at present. In summary, the future of patients with complicated necrosis seems to involve an even more personalized approach to each patient's problems. Thus, improving treatment results for late complications could include an increased centralization of multidisciplinary team decision-making for these difficult-to-treat patients.

Despite the advancements in treatment described here, many challenges have yet to be addresed. The early detection and treatment of incipient OF could result in even further improvements to outcomes. Clinicians and other personel who treat patients with AP need additional tools for the early and accurate identification of patients requring more rigorous monitoring and supportive treatment. Furthemore, patients with evolving SAP present irrespective of the hour and often at an initial delay. Any tool which improves the screening of incipient OFs, finetunes maintaining the management of organ function, or decreases treatment-related adverse events (such as fluid overload) might improve outcomes, since most deaths in SAP associate with the early occurrence of MOF. Furthermore, based on the current study's results, clinicians need to shift their perspective to extend beyond the initial hospitalization period, since any succesful preventive intervention targeted towards abstaining from alcohol following alcoholic SAP could result in better long-term outcomes among these patients.

Finally, as is the case with this thesis, the bulk of the existing literature is densely packed with retrospective research projects and precious few prospective studies. Since SAP is uncommon, the efficient coordination of multicenter prospective research projects represents the primary means for solving the many riddles related to the treatment of this fascinating disease. This includes the question of the correct allocation of decompression for ACS in SAP.

3.5 CONCLUSIONS

(1) Short-term survival following SAP reaches 90% in patients under 60 years of age, falling to 55% among patients over 60. Age, preexisting comorbidities, an early open necrosectomy for sterile necrosis, OA treatment, and being female all serve as independent short-term mortality risk factors.

(2) Long-term survival following SAP is poor even among young patients due to alcohol misuse.

(3) Mortality is around 10% when an open necrosectomy is performed for WON four weeks following symptom onset. The absence of multiple preoperative mortality risk factors results in virtually no mortality. Following an open necrosectomy, a new persistent OF occurs in 21% of cases, pancreaticocutaneous fistula in 39% of cases, and around half of patients need a reoperation.

(4) A wider spread of necrotic collections, a postintervention etiology, bacteremia, and OA treatment all represent independent risk factors for IPN among patients with necrotizing SAP. The length of stay and the risk of readmission to ICU increase following a pancreatic necrosis infection.

(5) ACS and oliguria independently increase the risk of OA treatment in SAP. Overall mortality is 43% following OA treatment. Visceral ischemia occurs in one-third of patients treated with OA, with an accompanying mortality reaching two-thirds among such patients.

ACKNOWLEDGEMENTS

This study was conducted between 2016 and 2021 in the Department of Gastrointestinal Surgery of the Abdominal Center at Helsinki University Hospital and the University of Helsinki. I am grateful to all the ingenius individuals who made my work on this study possible.

Financial support was provided by the Medical Society of Finland, the Perkléns Foundation, the Martti I. Turunen Foundation, the Helsinki University Library, the University of Helsinki Funds, and the Helsinki University Hospital Research Funds. All funding is gratefully acknowledged.

I thank Professor Pauli Puolakkainen for the possibility of carrying out this study and for the inspiring and encouraging scientific environment created within the Department of Gastrointestinal Surgery.

My deepest gratitude belongs to my supervisor, Docent Panu Mentula, for his thorough guidance during this study. His comprehensive and punctual support was quintessential and included but was not limited to his vast knowledge particularly of the scientific field in question, medical statistics, the publication process, and real-life clinical scenarios.

I am sincerely grateful to my esteemed supervisor, Professor Ari Leppäniemi, for the invaluable scientific guidance and personal encouragement he provided throughout this study. His extensive and impressive knowledge extends far beyond the topic of this research combined with an effortlessness to teaching have proved inspirational throughout these years.

I deeply appreciate my collaboration with each co-author. I especially value the prompt and insightful expert comments from Professor Pauli Puolakkainen, and the valuable contributions regarding patient data extraction and interpretation from Drs. Taru Lehtonen and Jouni Kuronen. I am sincerely grateful to Dr. Miia Valkonen for her participation, particularly her guidance in the field of infectious diseases and intensive care medicine, which taught me so much.

I am indebted to Anna But for her critical biostatistical review of study III.

I humbly express my gratitude to Vanessa Fuller, who punctually revised the English language in this thesis. I also thank Carrol Pelli and Jennifer Rowland for their language revisions of studies II and III.

I wish to warmly thank the official thesis reviewers, Docents Anne Kuitunen and Saila Kauhanen, for their encouraging comments, which improved this thesis considerably.

I am grateful to Dr. Anna-Maija Korhonen and Docents Leena Kylänpää and Hanna Seppänen for serving as the monitoring group of this study.

I am thankful to Dr. Pälvi Vento for supporting the earliest stages of my career in surgery at Kymenlaakso Central Hospital. I am grateful to my resident colleagues at Kymenlaakso Central Hospital at that time for all of their peer support and friendship extended during the earliest years of my surgical training, especially that provided by Nikola Fösel, Juha Virtanen, Jaakko Lommi, Allan Metsar, Alar Tuvikene, and Kai Zilliacus, among many others.

I extend my gratitude towards all of my colleagues at Helsinki University Hospital. I thank the directors of the Department of Gastrointestinal Surgery, Esko Kemppainen, Leena Halme, and Jukka Sirén, for their immense support in combining academic and clinical work. I express my earnest gratitude towards all of my senior colleagues at Jorvi Hospital for welcoming me so warmly in our daily work and as one of the newest members of the team. I also thank all of my mentors during the years of my residency. I am especially grateful to my fellow resident "team mates" during some tough but rewarding years of residency at Helsinki University Hospital, especially Timo Tarvainen, Tuomas Kaprio, Lauri Elonen, Artur Ojakäär, Anna Nieminen, Antti Turunen, and many others.

I extend my utmost gratefulness to my family and friends. I thank my parents, Sol-Britt and Raimo, for their love, support, and guidance to always continue challenging myself. I thank my brother, Riku, for the unwavering friendship and support throughout our lives. I express my gratitude to my in-laws, Juha, Mikko, and Heidi, for their wonderful contribution to my daily life. I especially thank my friends, Pauli and Andreas, for their endless supportive conversations during these strenuous most recent years of life.

I thank my dear boys, Daniel and Oscar, for every single precious shared moment together. Above all, I am grateful to my beautiful wife, Christa, for the endless love, support, and friendship. Thank you for experiencing the ups with me, but also for backing me up during these tough years of study. You are my partner-in-crime, my most dearest, imaginable friend, and the perfect mother for our children.

REFERENCES

Abu Dayyeh, B. K., Mukewar, S., Majumder, S., Zaghlol, R., Vargas Valls, E. J., Bazerbachi, F., Levy, M. J., Baron, T. H., Gostout, C. J., Petersen, B. T., Martin, J., Gleeson, F. C., Pearson, R. K., Chari, S. T., Vege, S. S., & Topazian, M. D. (2018). Large-caliber metal stents versus plastic stents for the management of pancreatic walled-off necrosis. *Gastrointestinal Endoscopy*, *87*(1), 141–149. https://doi.org/10.1016/J.GIE.2017.04.032

Acevedo-Piedra, N. G., Moya-Hoyo, N., Rey-Riveiro, M., Gil, S., Sempere, L., Martínez, J., Lluís, F., Sánchez-Payá, J., & De-Madaria, E. (2014). Validation of the determinant-based classification and revision of the Atlanta classification systems for acute pancreatitis. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *12*(2), 311–316. https://doi.org/10.1016/J.CGH.2013.07.042

Achouh, P. E., Madsen, K., Miller, C. C., Estrera, A. L., Azizzadeh, A., Dhareshwar, J., Porat, E., & Safi, H. J. (2006). Gastrointestinal complications after descending thoracic and thoracoabdominal aortic repairs: A 14-year experience. *Journal of Vascular Surgery*, *44*(3), 442–446. https://doi.org/10.1016/J.JVS.2006.05.018

Acosta, J. M., & Ledesma, C. L. (1974). Gallstone Migration as a Cause of Acute Pancreatitis. *New England Journal of Medicine*, *290*(9), 484–487. https://doi.org/10.1056/NEJM197402282900904

Aitken, E. L., Gough, V., Jones, A., & Macdonald, A. (2014). Observational study of intra-abdominal pressure monitoring in acute pancreatitis. *Surgery*, *155*(5), 910–918. https://doi.org/10.1016/J.SURG.2013.12.028

Akshintala, V. S., Saxena, P., Zaheer, A., Rana, U., Hutfless, S. M., Lennon, A. M., Canto, M. I., Kalloo, A. N., Khashab, M. A., & Singh, V. K. (2014). A comparative evaluation of outcomes of endoscopic versus percutaneous drainage for symptomatic pancreatic pseudocysts. *Gastrointestinal Endoscopy*, *79*(6), 921–928. https://doi.org/10.1016/J.GIE.2013.10.032

al Mofleh, I.-A. (2008). Severe acute pancreatitis: pathogenetic aspects and prognostic factors. *World Journal of Gastroenterology*, *14*(5), 675–684. https://doi.org/10.3748/wjg.14.675

Al-Bahrani, A. Z., Abid, G. H., Holt, A., McCloy, R. F., Benson, J., Eddleston, J., & Ammori, B. J. (2008). Clinical relevance of intra-abdominal hypertension in patients with severe acute pancreatitis. *Pancreas*, *36*(1), 39–43. https://doi.org/10.1097/MPA.0B013E318149F5BF

Andersson, R., Börjesson, A., Leveau, P., & Ihse, I. (1999). Long-term course following severe acute pancreatitis. *HPB*, *1*(3), 137–140. https://doi.org/10.1016/S1365-182X(17)30646-9

Andrianello, S., Bannone, E., Marchegiani, G., Malleo, G., Paiella, S., Esposito, A., Salvia, R., & Bassi, C. (2021). Characterization of postoperative acute pancreatitis (POAP) after distal pancreatectomy. *Surgery (United States)*, *169*(4), 724–731. https://doi.org/10.1016/J.SURG.2020.09.008

Andriulli, A., Loperfido, S., Napolitano, G., Niro, G., Valvano, M. R., Spirito, F., Pilotto, A., & Forlano, R. (2007). Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *The American Journal of Gastroenterology*, *102*(8), 1781–1788. https://doi.org/10.1111/J.1572-0241.2007.01279.X

Antonelli, M., Levy, M., Andrews, P. J. D., Chastre, J., Hudson, L. D., Manthous, C., Meduri, G. U., Moreno, R. P., Putensen, C., Stewart, T., Torres, A., Antonelli, M., Levy, M., Andrews, P. J. D., Hudson, L. D., Manthous, C., Meduri, G. U., Moreno, R. P., Putensen, C., … Torres, A. (2007). Hemodynamic monitoring in shock and implications for management. *Intensive Care Medicine 2007 33:4*, *33*(4), 575–590. https://doi.org/10.1007/S00134-007-0531-4

Appelros, S., & Borgström, A. (1999). Incidence, aetiology and mortality rate of acute pancreatitis over 10 years in a defined urban population in Sweden. *The British Journal of Surgery*, *86*(4), 465–470. https://doi.org/10.1046/J.1365-2168.1999.01049.X

Appelros, S., Lindgren, S., & Borgström, A. (2001). Short and long term outcome of severe acute pancreatitis. *The European Journal of Surgery = Acta Chirurgica*, *167*(4), 281–286. https://doi.org/10.1080/110241501300091462

Apte, M. v., Haber, P. S., Norton, I. D., & Wilson, J. S. (1998). Alcohol and the pancreas. *Addiction Biology*, *3*(2), 137–150. https://doi.org/10.1080/13556219872209

Apte, M. v., Pirola, R. C., & Wilson, J. S. (2010). Mechanisms of alcoholic pancreatitis. *Journal of Gastroenterology and Hepatology (Australia)*, *25*(12), 1816–1826. https://doi.org/10.1111/j.1440-1746.2010.06445.x

Apte, M. v., Wilson, J. S., Korsten, M. A., McCaughan, G. W., Haber, P. S., & Pirola, R. C. (1995). Effects of ethanol and protein deficiency on pancreatic digestive and lysosomal enzymes. *Gut*, *36*(2), 287–293. https://doi.org/10.1136/GUT.36.2.287

Archer, S., Levitt, S., & Drury, P. (1991). Duodenal necrosis and intramural haematoma complicating acute pancreatitis. *The Australian and New Zealand Journal of Surgery*, *61*(7), 542–544. https://doi.org/10.1111/j.1445-2197.1991.tb00286.x

Armstrong, C. P., Taylor, T. v., Jeacock, J., & Lucas, S. (2005). The biliary tract in patients with acute gallstone pancreatitis. *British Journal of Surgery*, *72*(7), 551–555. https://doi.org/10.1002/BJS.1800720718

Arvanitakis, M., Dumonceau, J. M., Albert, J., Badaoui, A., Bali, M. A., Barthet, M., Besselink, M., Deviere, J., Ferreira, A. O., Gyökeres, T., Hritz, I., Hucl, T., Milashka, M., Papanikolaou, I. S., Poley, J. W., Seewald, S., Vanbiervliet, G., van Lienden, K., van Santvoort, H., … van Hooft, J. (2018). Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. *Endoscopy*, *50*(5), 524–546. https://doi.org/10.1055/A-0588-5365

Ashley, S. W., Perez, A., Pierce, E. A., Brooks, D. C., Moore, F. D., Whang, E. E., Banks, P. A., & Zinner, M. J. (2001). Necrotizing pancreatitis: contemporary

analysis of 99 consecutive cases. *Annals of Surgery*, *234*(4), 572–579; discussion 579-80. https://doi.org/10.1097/00000658-200110000-00016

Babu, B. I., Sheen, A. J., Lee, S. H., O'Shea, S., Eddleston, J. M., & Siriwardena, A. K. (2010). Open pancreatic necrosectomy in the multidisciplinary management of postinflammatory necrosis. *Annals of Surgery*, *251*(5), 783–786. https://doi.org/10.1097/SLA.0B013E3181B59303

Babu, R. Y., Gupta, R., Kang, M., Bhasin, D. K., Rana, S. S., & Singh, R. (2013). Predictors of surgery in patients with severe acute pancreatitis managed by the step-up approach. *Annals of Surgery*, *257*(4), 737–750. https://doi.org/10.1097/SLA.0B013E318269D25D

Baey, S., Tan, T., Gunasekaran, S. K., Junnarkar, S. P., Low, J. K., Huey, C. W., & Shelat, V. G. (2021). Sequential Organ Failure Assessment (SOFA) Score Is Superior to Classical Prognostic Indices in Prediction of Severity, Intensive Care Unit Admissions and Mortality in Acute Pancreatitis. *HPB*, *23*, S48–S49. https://doi.org/10.1016/j.hpb.2020.11.116

Bai, Y., Liu, Y., Jia, L., Jiang, H., Ji, M., Lv, N., Huang, K., Zou, X., Li, Y., Tang, C., Guo, X., Peng, X., Fang, D., Wang, B., Yang, B., Wang, L., & Li, Z. (2007). Severe acute pancreatitis in China: Etiology and mortality on 1976 patients. *Pancreas*, *35*(3), 232–237. https://doi.org/10.1097/MPA.0B013E3180654D20

Baillargeon, J. D., Orav, J., Ramagopal, V., Tenner, S. M., & Banks, P. A. (1998). Hemoconcentration as an early risk factor for necrotizing pancreatitis. *The American Journal of Gastroenterology*, *93*(11), 2130–2134. https://doi.org/10.1111/J.1572-0241.1998.00608.X

Bakker, O. J., van Brunschot, S., van Santvoort, H. C., Besselink, M. G., Bollen, T. L., Boermeester, M. A., Dejong, C. H., van Goor, H., Bosscha, K., Ali, U. A., Bouwense, S., van Grevenstein, W. M., Heisterkamp, J., Houdijk, A. P., Jansen, J. M., Karsten, T. M., Manusama, E. R., Nieuwenhuijs, V. B., Schaapherder, A. F., … Gooszen, H. G. (2014). Early versus On-Demand Nasoenteric Tube Feeding in Acute Pancreatitis. *New England Journal of Medicine*, *371*(21), 1983–1993. https://doi.org/10.1056/NEJMoa1404393

Bakker, O. J., van Santvoort, H., Besselink, M. G. H., Boermeester, M. A., Eijck, C. van, Dejong, K., van Goor, H., Hofker, S., Ali, U. A., Gooszen, H. G., & Bollen, T. L. (2013). Extrapancreatic necrosis without pancreatic parenchymal necrosis: a separate entity in necrotising pancreatitis? *Gut*, *62*(10), 1475–1480. https://doi.org/10.1136/GUTJNL-2012-302870

Bakker, O. J., van Santvoort, H. C., van Brunschot, S., Geskus, R. B., Besselink, M. G., Bollen, T. L., van Eijck, C. H., Fockens, P., Hazebroek, E. J., Nijmeijer, R. M., Poley, J. W., van Ramshorst, B., Vleggaar, F. P., Boermeester, M. A., Gooszen, H. G., Weusten, B. L., & Timmer, R. (2012). Endoscopic Transgastric vs Surgical Necrosectomy for Infected Necrotizing Pancreatitis: A Randomized Trial. *JAMA*, *307*(10), 1053–1061. https://doi.org/10.1001/JAMA.2012.276

Balani, A. R., & Grendell, J. H. (2008). Drug-Induced Pancreatitis Incidence, Management and Prevention. *Drug Safety*, *31*(10), 823–837.

Baltatzis, M., Mason, J. M., Chandrabalan, V., Stathakis, P., McIntyre, B., Jegatheeswaran, S., Jamdar, S., O'Reilly, D. A., & Siriwardena, A. K. (2016).

Antibiotic use in acute pancreatitis: An audit of current practice in a tertiary centre. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *16*(6), 946–951. https://doi.org/10.1016/J.PAN.2016.08.012

Balthazar, E. J., & Fisher, L. A. (2001). Hemorrhagic complications of pancreatitis: radiologic evaluation with emphasis on CT imaging. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *1*(4), 306–313. https://doi.org/10.1159/000055829

Balthazar, E. J., Robinson, D. L., Megibow, A. J., & Ranson, J. H. C. (1990). Acute pancreatitis: value of CT in establishing prognosis. *Radiology*, *174*(2), 331–336. https://doi.org/10.1148/RADIOLOGY.174.2.2296641

Bang, J. Y., Arnoletti, J. P., Holt, B. A., Sutton, B., Hasan, M. K., Navaneethan, U., Feranec, N., Wilcox, C. M., Tharian, B., Hawes, R. H., & Varadarajulu, S. (2019). An Endoscopic Transluminal Approach, Compared With Minimally Invasive Surgery, Reduces Complications and Costs for Patients With Necrotizing Pancreatitis. *Gastroenterology*, *156*(4), 1027-1040.e3. https://doi.org/10.1053/J.GASTRO.2018.11.031

Banks, P. A., Bollen, T. L., Dervenis, C., Gooszen, H. G., Johnson, C. D., Sarr, M. G., Tsiotos, G. G., Vege, S. S., Windsor, J. A., Horvath, K. D., Mortele, K. J., Gardner, T. B., van Santvoort, H., Pelaez-Luna, M., Yadav, D., Stefanidis, G., Delakidis, S., Morgan, D. E., Thoeni, R. F. L., … Zyromski, N. J. (2013). Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*, *62*(1), 102–111. https://doi.org/10.1136/GUTJNL-2012-302779

Banks, P. A., Freeman, M. L., Fass, R., Baroni, D. S., Mutlu, E. A., Bernstein, D. E., Parkman, H. P., Bharucha, A. E., Prather, C., Brugge, W. R., Pratt, D. S., Chang, L., Roach, A. C., Chey, W., Sampliner, R. E., Cohen, M. E., Sridhar, S., Cunningham, J. T., Vakil, N., … Zfass, A. M. (2006). Practice guidelines in acute pancreatitis. *The American Journal of Gastroenterology*, *101*(10), 2379–2400. https://doi.org/10.1111/J.1572-0241.2006.00856.X

Baron, T. H., DiMaio, C. J., Wang, A. Y., & Morgan, K. A. (2020). American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis. *Gastroenterology*, *158*(1), 67-75.e1. https://doi.org/10.1053/j.gastro.2019.07.064

Baron, T. H., Thaggard, W. G., Morgan, D. E., & Stanley, R. J. (1996). Endoscopic therapy for organized pancreatic necrosis. *Gastroenterology*, *111*(3), 755–764. https://doi.org/10.1053/GAST.1996.V111.PM8780582

Barrie, J., Jamdar, S., Smith, N., McPherson, S. J., Siriwardena, A. K., & O'Reilly, D. A. (2018). Mis-use of antibiotics in acute pancreatitis: Insights from the United Kingdom's National Confidential Enquiry into patient outcome and death (NCEPOD) survey of acute pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *18*(7), 721–726. https://doi.org/10.1016/J.PAN.2018.05.485

Bausch, D., Wellner, U., Kahl, S., Kuesters, S., Richter-Schrag, H. J., Utzolino, S., Hopt, U. T., Keck, T., & Fischer, A. (2012). Minimally invasive operations for

acute necrotizing pancreatitis: Comparison of minimally invasive retroperitoneal necrosectomy with endoscopic transgastric necrosectomy. *Surgery*, *152*(3), S128–S134. https://doi.org/10.1016/J.SURG.2012.05.021

Beger, H. G., & Rau, B. M. (2007). Severe acute pancreatitis: Clinical course and management. *World Journal of Gastroenterology : WJG*, *13*(38), 5043. https://doi.org/10.3748/WJG.V13.I38.5043

Beger, H. G., Rau, B., Mayer, J., & Pralle, U. (1997). Natural course of acute pancreatitis. *World Journal of Surgery 1997 21:2*, *21*(2), 130–135. https://doi.org/10.1007/S002689900204

Bellani, G., Laffey, J. G., Pham, T., Fan, E., Brochard, L., Esteban, A., Gattinoni, L., van Haren, F., Larsson, A., McAuley, D. F., Ranieri, M., Rubenfeld, G., Thompson, B. T., Wrigge, H., Slutsky, A. S., Pesenti, A., LUNG SAFE Investigators, & ESICM Trials Group. (2016). Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*, *315*(8), 788–800. https://doi.org/10.1001/jama.2016.0291

Berger, Z., Mancilla, C., Tobar, E., Morales, M. P., Baró, M., Carrasco, M., Cordero, J., Cruz, R., Cruz, R., Lara, C., Ledesma, S., Ramírez, G., Sierralta, A., Godoy, L., & Valdés, E. (2020). Acute pancreatitis in Chile: A multicenter study on epidemiology, etiology and clinical outcome. Retrospective analysis of clinical files. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *20*(4), 637–643. https://doi.org/10.1016/j.pan.2020.04.016

Bergert, H., Hinterseher, I., Kersting, S., Leonhardt, J., Bloomenthal, A., & Saeger, H. D. (2005). Management and outcome of hemorrhage due to arterial pseudoaneurysms in pancreatitis. *Surgery*, *137*(3), 323–328. https://doi.org/10.1016/j.surg.2004.10.009

Bertelli, E., Gregorio, F. di, Bertelli, L., & Mosca, S. (1995). The arterial blood supply of the pancreas: a review - I. The superior pancreaticoduodenal and the anterior superior pancreaticoduodenal arteries. An anatomical and radiological study. In *Surgical and Radiologic Anatomy* (Vol. 17, Issue 2, pp. 97–106). Springer-Verlag. https://doi.org/10.1007/BF01627566

Bertilsson, S., Håkansson, A., & Kalaitzakis, E. (2017). Acute pancreatitis: Impact of alcohol consumption and seasonal factors. *Alcohol and Alcoholism*, *52*(3), 383–389. https://doi.org/10.1093/alcalc/agx005

Besselink, M. G. H. (2011). Splanchnic vein thrombosis complicating severe acute pancreatitis. *HPB : The Official Journal of the International Hepato Pancreato Biliary Association*, *13*(12), 831–832. https://doi.org/10.1111/j.1477-2574.2011.00411.x

Besselink, M. G., van Santvoort, H. C., Boermeester, M. A., Nieuweohuijs, V. B., van Goor, H., Dejong, C. H. C., Schaapherder, A. F., & Gooszen, H. G. (2009). Timing and impact of infections in acute pancreatitis. *British Journal of Surgery*, *96*(3), 267–273. https://doi.org/10.1002/BJS.6447

Besselink, M. G., van Santvoort, H. C., Renooij, W., de Smet, M. B., Boermeester, M. A., Fischer, K., Timmerman, H. M., Ahmed Ali, U., Cirkel, G. A., Bollen, T. L.,

van Ramshorst, B., Schaapherder, A. F., Witteman, B. J., Ploeg, R. J., van Goor, H., van Laarhoven, C. J., Tan, A. C., Brink, M. A., van der Harst, E., … Gooszen, H. G. (2009). Intestinal barrier dysfunction in a randomized trial of a specific probiotic composition in acute pancreatitis. *Annals of Surgery*, *250*(5), 712–719. https://doi.org/10.1097/SLA.0B013E3181BCE5BD

Besselink, M. G., Venneman, N. G., Go, P. M., Broeders, I. A., Siersema, P. D., Gooszen, H. G., & van Erpecum, K. J. (2009). Is complicated gallstone disease preceded by biliary colic? *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *13*(2), 312–317. https://doi.org/10.1007/S11605-008-0729-Y

Besselink, M., van Santvoort, H., Freeman, M., Gardner, T., Mayerle, J., Vege, S. S., Werner, J., Banks, P., McKay, C., Fernandez-del Castillo, C., French, J., Gooszen, H., Johnson, C., Sarr, M., Takada, T., Windsor, J., Saluja, A., Liddle, R., Papachristou, G., … Acute, W. G. I. A. P. A. P. A. (2013). IAP/APA evidence-based guidelines for the management of acute pancreatitis. *PANCREATOLOGY*, *13*(4, 2), E1–E15. https://doi.org/10.1016/j.pan.2013.07.063

Bhandari, V., Jaipuria, J., Singh, M., & Chawla, A. S. (2013). Intra-abdominal pressure in the early phase of severe acute pancreatitis: canary in a coal mine? Results from a rigorous validation protocol. *Gut and Liver*, *7*(6), 731–738. https://doi.org/10.5009/GNL.2013.7.6.731

Bhatia, M., Fei, L. W., Cao, Y., Hon, Y. L., Huang, J., Puneet, P., & Chevali, L. (2005). Pathophysiology of acute pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *5*(2–3), 132–144. https://doi.org/10.1159/000085265

Blom, R. L. G. M., van Heijl, M., Busch, O. R. C., & van Berge Henegouwen, M. I. (1993). Acute Pancreatitis in the Postoperative Course after Esophagectomy: A Major Complication Described in 4 Patients. *Case Rep Gastroenterol*, *3*, 382–388. https://doi.org/10.1159/000258092

Boland, B., Colquhoun, S., Menon, V., Kim, A., Lo, S., & Nissen, N. N. (2010). Current surgical management of infected pancreatic necrosis. *The American Surgeon*, *76*(10), 1096–1099.

Bollen, T. L., Singh, V. K., Maurer, R., Repas, K., van Es, H. W., Banks, P. A., & Mortele, K. J. (2012). A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. *American Journal of Gastroenterology*, *107*(4), 612–619. https://doi.org/10.1038/AJG.2011.438

Boone, B., Zureikat, A., Hughes, S. J., Moser, A. J., Yadav, D., Zeh, H. J., & Lee, K. K. W. (2013). Abdominal Compartment Syndrome Is an Early, Lethal Complication of Acute Pancreatitis. *The American Surgeon*, *6*, 601–607.

Bosmann, M., Schreiner, O., & Galle, P. R. (2009). Coexistence of Cullen's and Grey Turner's signs in acute pancreatitis. *The American Journal of Medicine*, *122*(4), 333–334. https://doi.org/10.1016/J.AMJMED.2008.08.032

Boxhoorn, L., van Dijk, S. M., van Grinsven, J., Verdonk, R. C., Boermeester, M. A., Bollen, T. L., Bouwense, S. A. W., Bruno, M. J., Cappendijk, V. C., Dejong, C. H. C., van Duijvendijk, P., van Eijck, C. H. J., Fockens, P., Francken, M. F. G.,

van Goor, H., Hadithi, M., Hallensleben, N. D. L., Haveman, J. W., Jacobs, M. A. J. M., … Besselink, M. G. (2021). Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. *New England Journal of Medicine*, *385*(15), 1372–1381. https://doi.org/10.1056/NEJMOA2100826/SUPPL_FILE/NEJMOA2100826_DATA-SHARING.PDF

Boxhoorn, L., Voermans, R. P., Bouwense, S. A., Bruno, M. J., Verdonk, R. C., Boermeester, M. A., van Santvoort, H. C., & Besselink, M. G. (2020). Acute pancreatitis. *The Lancet*, *396*(10252), 726–734. https://doi.org/10.1016/S0140-6736(20)31310-6

Bradley, E. L., & Allen, K. (1991). A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. *American Journal of Surgery*, *161*(1), 19–25. https://doi.org/10.1016/0002-9610(91)90355-H

Brown, A., Baillargeon, J. D., Hughes, M. D., & Banks, P. A. (2002). Can fluid resuscitation prevent pancreatic necrosis in severe acute pancreatitis? *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *2*(2), 104–107. https://doi.org/10.1159/000055899

Brown, A., Orav, J., & Banks, P. A. (2000). Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas*, *20*(4), 367–372. https://doi.org/10.1097/00006676-200005000-00005

Brown, L. A., Hore, T. A., Phillips, A. R. J., Windsor, J. A., & Petrov, M. S. (2014). A systematic review of the extra-pancreatic infectious complications in acute pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *14*(6), 436–443. https://doi.org/10.1016/J.PAN.2014.09.010

Büchler, M., Malfertheiner, P., Frieß, H., Isenmann, R., Vanek, E., Grimm, H., Schlegel, P., Friess, T., & Beger, H. G. (1992). Human pancreatic tissue concentration of bactericidal antibiotics. *Gastroenterology*, *103*(6), 1902–1908. https://doi.org/10.1016/0016-5085(92)91450-I

Büchler, M. W., Gloor, B., Müller, C. A., Friess, H., Seiler, C. A., & Uhl, W. (2000). Acute necrotizing pancreatitis: treatment strategy according to the status of infection. *Annals of Surgery*, *232*(5), 619–622. https://doi.org/10.1097/00000658-200011000-00001

Burkey, S. H., Valentine, R. J., Jackson, M. R., Modrall, J. G., & Clagett, G. P. (2000). Acute pancreatitis after abdominal vascular surgery. *Journal of the American College of Surgeons*, *191*(4), 373–380. https://doi.org/10.1016/S1072-7515(00)00701-8

Buter, A., Imrie, C. W., Carter, C. R., Evans, S., & McKay, C. J. (2002). Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. *The British Journal of Surgery*, *89*(3), 298–302. https://doi.org/10.1046/J.0007-1323.2001.02025.X

Butler, J. R., Eckert, G. J., Zyromski, N. J., Leonardi, M. J., Lillemoe, K. D., & Howard, T. J. (2011). Natural history of pancreatitis-induced splenic vein

thrombosis: a systematic review and meta-analysis of its incidence and rate of gastrointestinal bleeding. *HPB : The Official Journal of the International Hepato Pancreato Biliary Association*, *13*(12), 839–845. https://doi.org/10.1111/J.1477-2574.2011.00375.X

Çakar, İ., Keven, A., Eseroğlu, E., & Çubuk, S. M. (2020). Role of extrapancreatic necrosis volume in determining early prognosis in patients with acute pancreatitis. *Abdominal Radiology*, *45*(5), 1507–1516. https://doi.org/10.1007/s00261-019-02188-9

Castillo, C. F. del, Rattner, D. W., Makary, M. A., Mostafavi, A., McGrath, D., & Warshaw, A. L. (1998). Débridement and closed packing for the treatment of necrotizing pancreatitis. *Annals of Surgery*, *228*(5), 676–684. https://doi.org/10.1097/00000658-199811000-00007

Cecconi, M., de Backer, D., Antonelli, M., Beale, R., Bakker, J., Hofer, C., Jaeschke, R., Mebazaa, A., Pinsky, M. R., Teboul, J. L., Vincent, J. L., & Rhodes, A. (2014). Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Medicine*, *40*(12), 1795–1815. https://doi.org/10.1007/s00134-014-3525-z

Chaudhary, A., Sachdev, A., & Negi, S. (2001). Biliary complications of pancreatic necrosis. *International Journal of Pancreatology : Official Journal of the International Association of Pancreatology*, *29*(3), 129–131. https://doi.org/10.1385/IJGC:29:3:129

Chen, H., Li, F., Sun, J. B., & Jia, J. G. (2008). Abdominal compartment syndrome in patients with severe acute pancreatitis in early stage. *World Journal of Gastroenterology*, *14*(22), 3541–3548. https://doi.org/10.3748/WJG.14.3541

Chen, H., Wang, W., Ying, X., Deng, X., Peng, C., Cheng, D., & Shen, B. (2020). Predictive factors for postoperative pancreatitis after pancreaticoduodenectomy: A single-center retrospective analysis of 1465 patients: Predictors of postoperative pancreatitis. *Pancreatology*, *20*(2), 211–216. https://doi.org/10.1016/J.PAN.2019.11.014

Chen, H. Z., Ji, L., Li, L., Wang, G., Bai, X. W., Cheng, C. D., & Sun, B. (2017). Early prediction of infected pancreatic necrosis secondary to necrotizing pancreatitis. *Medicine (United States)*, *96*(30). https://doi.org/10.1097/MD.0000000000007487

Cho, J. H., Kim, T. N., Chung, H. H., & Kim, K. H. (2015). Comparison of scoring systems in predicting the severity of acute pancreatitis. *World Journal of Gastroenterology*, *21*(8), 2387–2394. https://doi.org/10.3748/WJG.V21.I8.2387

Choi, J. H., Kim, M. H., Oh, D., Paik, W. H., Park, D. H., Lee, S. S., Seo, D. W., & Lee, S. K. (2014). Clinical relevance of the revised Atlanta classification focusing on severity stratification system. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *14*(5), 324–329. https://doi.org/10.1016/J.PAN.2014.08.001

Chong, E., Ratnayake, C. B., Saikia, S., Nayar, M., Oppong, K., French, J. J., Windsor, J. A., & Pandanaboyana, S. (2021). Endoscopic transmural drainage is associated with improved outcomes in disconnected pancreatic duct syndrome: a systematic

review and meta-analysis. *BMC Gastroenterology*, *21*(1), 87. https://doi.org/10.1186/s12876-021-01663-2

Cirocchi, R., Birindelli, A., Biffl, W. L., Mutafchiyski, V., Popivanov, G., Chiara, O., Tugnoli, G., & di Saverio, S. (2016). What is the effectiveness of the negative pressure wound therapy (NPWT) in patients treated with open abdomen technique? A systematic review and meta-analysis. *The Journal of Trauma and Acute Care Surgery*, *81*(3), 575–584. https://doi.org/10.1097/TA.0000000000001126

Clavien, P. A., Burgan, S., & Moossa, A. R. (1989). Serum enzymes and other laboratory tests in acute pancreatitis. *The British Journal of Surgery*, *76*(12), 1234–1243. https://doi.org/10.1002/bjs.1800761205

Clemens, D. L., Schneider, K. J., Arkfeld, C. K., Grode, J. R., Wells, M. A., & Singh, S. (2016). Alcoholic pancreatitis: New insights into the pathogenesis and treatment. *World Journal of Gastrointestinal Pathophysiology*, *7*(1), 48. https://doi.org/10.4291/WJGP.V7.I1.48

Coccolini, F., Roberts, D., Ansaloni, L., Ivatury, R., Gamberini, E., Kluger, Y., Moore, E. E., Coimbra, R., Kirkpatrick, A. W., Pereira, B. M., Montori, G., Ceresoli, M., Abu-Zidan, F. M., Sartelli, M., Velmahos, G., Fraga, G. P., Leppaniemi, A., Tolonen, M., Galante, J., … Catena, F. (2018). The open abdomen in trauma and non-trauma patients: WSES guidelines. *World Journal of Emergency Surgery 2018 13:1*, *13*(1), 1–16. https://doi.org/10.1186/S13017-018-0167-4

Connor, S. (2016). Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. *HPB : The Official Journal of the International Hepato Pancreato Biliary Association*, *18*(8), 642–651. https://doi.org/10.1016/J.HPB.2016.05.006

Connor, S., Alexakis, N., Raraty, M. G. T., Ghaneh, P., Evans, J., Hughes, M., Garvey, C. J., Sutton, R., & Neoptolemos, J. P. (2005). Early and late complications after pancreatic necrosectomy. *Surgery*, *137*(5), 499–505. https://doi.org/10.1016/J.SURG.2005.01.003

Criddle, D. N., McLaughlin, E., Murphy, J. A., Petersen, O. H., & Sutton, R. (2007). The Pancreas Misled: Signals to Pancreatitis. *Pancreatology*, *7*(5–6), 436–446. https://doi.org/10.1159/000108960

da Costa, D. W., Bouwense, S. A., Schepers, N. J., Besselink, M. G., van Santvoort, H. C., van Brunschot, S., Bakker, O. J., Bollen, T. L., Dejong, C. H., van Goor, H., Boermeester, M. A., Bruno, M. J., van Eijck, C. H., Timmer, R., Weusten, B. L., Consten, E. C., Brink, M. A., Spanier, B. W. M., Bilgen, E. J. S., … Boerma, D. (2015). Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet (London, England)*, *386*(10000), 1261–1268. https://doi.org/10.1016/S0140-6736(15)00274-3

Dambrauskas, Z., Gulbinas, A., Pundzius, J., & Barauskas, G. (2007). Meta-analysis of prophylactic parenteral antibiotic use in acute necrotizing pancreatitis. *Medicina (Kaunas, Lithuania)*, *43*(4), 291–300.

Dambrauskas, Z., Parseliunas, A., Gulbinas, A., Pundzius, J., & Barauskas, G. (2009). Early recognition of abdominal compartment syndrome in patients with acute

pancreatitis. *World Journal of Gastroenterology*, *15*(6), 717–721. https://doi.org/10.3748/wjg.15.717

Darrivere, L., Lapidus, N., Colignon, N., Chafai, N., Chaput, U., Verdonk, F., Paye, F., & Lescot, T. (2018). Minimally invasive drainage in critically ill patients with severe necrotizing pancreatitis is associated with better outcomes: an observational study. *Critical Care (London, England)*, *22*(1). https://doi.org/10.1186/S13054-018-2256-X

Davis, P. J. B., Eltawil, K. M., Abu-Wasel, B., Walsh, M. J., Topp, T., & Molinari, M. (2013). Effect of obesity and decompressive laparotomy on mortality in acute pancreatitis requiring intensive care unit admission. *World Journal of Surgery*, *37*(2), 318–332. https://doi.org/10.1007/S00268-012-1821-8/FIGURES/2

de Beaux, A. C., Palmer, K. R., & Carter, D. C. (1995). Factors influencing morbidity and mortality in acute pancreatitis; an analysis of 279 cases. *Gut*, *37*(1), 121–126. https://doi.org/10.1136/gut.37.1.121

de Campos, T., Cerqueira, C., Kuryura, L., Parreira, J. G., Soldá, S., Perlingeiro, J. A. G., Assef, J. C., & Rasslan, S. (2008). Morbimortality indicators in severe acute pancreatitis. *JOP : Journal of the Pancreas*, *9*(6), 690–697.

de Keulenaer, B., Regli, A., de Laet, I., Roberts, D. J., & Malbrain, M. L. N. G. (2015). What's new in medical management strategies for raised intra-abdominal pressure: evacuating intra-abdominal contents, improving abdominal wall compliance, pharmacotherapy, and continuous negative extra-abdominal pressure. *Anaesthesiology Intensive Therapy*, *47*(1), 54–62. https://doi.org/10.5603/AIT.A2014.0065

de Waele, J. J., Hoste, E., Blot, S. I., Decruyenaere, J., & Colardyn, F. (2005). Intra-abdominal hypertension in patients with severe acute pancreatitis. *Critical Care (London, England)*, *9*(4), 1–6. https://doi.org/10.1186/CC3754/FIGURES/3

de Waele, J. J., Hoste, E., Blot, S. I., Hesse, U., Pattyn, P., de Hemptinne, B., Decruyenaere, J., Vogelaers, D., & Colardyn, F. (2004). Perioperative factors determine outcome after surgery for severe acute pancreatitis. *Critical Care (London, England)*, *8*(6), R504-11. https://doi.org/10.1186/cc2991

de Waele, J. J., Rello, J., Anzueto, A., Moreno, R., Lipman, J., Sakr, Y., Pickkers, P., Leone, M., Ferguson, A., Oud, L., & Vincent, J. L. (2014). Infections and use of antibiotics in patients admitted for severe acute pancreatitis: data from the EPIC II study. *Surgical Infections*, *15*(4), 394–398. https://doi.org/10.1089/SUR.2012.228

D'Egidio, A., & Schein, M. (1991). Pancreatic pseudocysts: a proposed classification and its management implications. *The British Journal of Surgery*, *78*(8), 981–984. https://doi.org/10.1002/BJS.1800780829

Dellinger, E. P., Tellado, J. M., Soto, N. E., Ashley, S. W., Barie, P. S., Dugernier, T., Imrie, C. W., Johnson, C. D., Knaebel, H. P., Laterre, P. F., Maravi-Poma, E., Kissler, J. J. O., Sanchez-Garcia, M., & Utzolino, S. (2007). Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Annals of Surgery*, *245*(5), 674–683. https://doi.org/10.1097/01.SLA.0000250414.09255.84

de-Madaria, E., Soler-Sala, G., Sánchez-Payá, J., Lopez-Font, I., Martínez, J., Gómez-Escolar, L., Sempere, L., Sánchez-Fortún, C., & Pérez-Mateo, M. (2011). Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. *The American Journal of Gastroenterology*, *106*(10), 1843–1850. https://doi.org/10.1038/ajg.2011.236

Dholakia, K., Pitchumoni, C. S., & Agarwal, N. (2004). How often are liver function tests normal in acute biliary pancreatitis? *Journal of Clinical Gastroenterology*, *38*(1), 81–83. https://doi.org/10.1097/00004836-200401000-00017

Dickson, A., & Imrie, C. (1984). The incidence and prognosis of body wall ecchymosis in acute pancreatitis. *SURGERY GYNECOLOGY & OBSTETRICS*, *159*(4), 343–347.

DiMagno, M. (2011). *Oktoberfest Binge Drinking and Acute Pancreatitis: Is There Really No Relationship?* https://doi.org/10.1016/j.cgh.2011.07.022

Ding, L., Yu, C., Deng, F., He, W.-H., Xia, L., Zhou, M., Lan, G.-L., Huang, X., Lei, Y.-P., Zhou, X.-J., Zhu, Y., & Lu, N.-H. (2019). New Risk Factors for Infected Pancreatic Necrosis Secondary to Severe Acute Pancreatitis: The Role of Initial Contrast-Enhanced Computed Tomography. *Digestive Diseases and Sciences*, *64*(2), 553–560. https://doi.org/10.1007/s10620-018-5359-y

Ding, N., Sun, Y. H., Wen, L. M., Wang, J. H., Yang, J. H., Cheng, K., Lin, H., & Chen, Q. L. (2020). Assessment of prophylactic antibiotics administration for acute pancreatitis: a meta-analysis of randomized controlled trials. *Chinese Medical Journal*, *133*(2), 212. https://doi.org/10.1097/CM9.0000000000000603

Doepel, M., Eriksson, J., Halme, L., Kumpulainen, T., & Höckerstedt, K. (1993). Good long-term results in patients surviving severe acute pancreatitis. *The British Journal of Surgery*, *80*(12), 1583–1586. https://doi.org/10.1002/bjs.1800801229

Donhauser, J. L., & Bigelow, N. H. (1958). Atypical symptom-sign complex of acute pancreatitis. *The American Journal of Surgery*, *96*(1), 61–65. https://doi.org/10.1016/0002-9610(58)90873-0

Driedger, M., Zyromski, N. J., Visser, B. C., Jester, A., Sutherland, F. R., Nakeeb, A., Dixon, E., Dua, M. M., House, M. G., Worhunsky, D. J., Munene, G., & Ball, C. G. (2020). Surgical Transgastric Necrosectomy for Necrotizing Pancreatitis: A Single-stage Procedure for Walled-off Pancreatic Necrosis. *Annals of Surgery*, *271*(1), 163–168. https://doi.org/10.1097/SLA.0000000000003048

Dufour, M. C., & Adamson, M. D. (2003). The Epidemiology of Alcohol-Induced Pancreatitis. *Pancreas*, *27*(4), 286–290. https://doi.org/10.1097/00006676-200311000-00002

Dumonceau, J.-M., Delhaye, M., Tringali, A., Arvanitakis, M., Sanchez-Yague, A., Vaysse, T., Aithal, G. P., Anderloni, A., Bruno, M., Cantú, P., Devière, J., Enrique Domínguez-Muñoz, J., Lekkerkerker, S., Poley, J.-W., Ramchandani, M., Reddy, N., & van Hooft, J. E. (2019). Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline-Updated August 2018. *Endoscopy*, *51*, 179–193. https://doi.org/10.1055/a-0822-0832

Easler, J., Muddana, V., Furlan, A., Dasyam, A., Vipperla, K., Slivka, A., Whitcomb, D. C., Papachristou, G. I., & Yadav, D. (2014). Portosplenomesenteric venous

thrombosis in patients with acute pancreatitis is associated with pancreatic necrosis and usually has a benign course. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *12*(5), 854–862. https://doi.org/10.1016/J.CGH.2013.09.068

Eckerwall, G. E., Tingstedt, B. B. Å., Bergenzaun, P. E., & Andersson, R. G. (2007). Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery—A randomized clinical study. *Clinical Nutrition*, *26*(6), 758–763. https://doi.org/https://doi.org/10.1016/j.clnu.2007.04.007

Ellis, M. P., French, J. J., & Charnley, R. M. (2009). Acute pancreatitis and the influence of socioeconomic deprivation. *The British Journal of Surgery*, *96*(1), 74–80. https://doi.org/10.1002/BJS.6414

Evans, L., Rhodes, A., Alhazzani, W., Antonelli, M., Coopersmith, C. M., French, C., Machado, F. R., Mcintyre, L., Ostermann, M., Prescott, H. C., Schorr, C., Simpson, S., Wiersinga, W. J., Alshamsi, F., Angus, D. C., Arabi, Y., Azevedo, L., Beale, R., Beilman, G., … Levy, M. (2021). Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Medicine 2021 47:11*, *47*(11), 1181–1247. https://doi.org/10.1007/S00134-021-06506-Y

Evans, R. P., Mourad, M. M., Pall, G., Fisher, S. G., & Bramhall, S. R. (2017). Pancreatitis: Preventing catastrophic haemorrhage. *World Journal of Gastroenterology*, *23*(30), 5460. https://doi.org/10.3748/wjg.v23.i30.5460

Feng, F., Tan, H., Li, X., Qiao, Y., Chen, C., Lin, Y., Li, Z., & Shen, J. (2018). Incidence and Risk Factors of Acute Pancreatitis After Scoliosis Surgery: A Prospective Study. *Spine*, *43*(9), 630–636. https://doi.org/10.1097/BRS.0000000000002389

Feng, L., Guo, J., Wang, S., Liu, X., Ge, N., Wang, G., & Sun, S. (2021). Endoscopic Transmural Drainage and Necrosectomy in Acute Necrotizing Pancreatitis: A Review. *Journal of Translational Internal Medicine*, *9*(3), 168–176. https://doi.org/10.2478/jtim-2021-0031

Fischer, A., Schrag, H. J., Keck, T., Hopt, U. T., & Utzolino, S. (2008). Debridement and drainage of walled-off pancreatic necrosis by a novel laparoendoscopic rendezvous maneuver: experience with 6 cases. *Gastrointestinal Endoscopy*, *67*(6), 871–878. https://doi.org/10.1016/J.GIE.2007.10.059

Fitz, R. H. (1889). Acute pancreatitis: A consideration of pancreatic hemorrhage, hemorrhagic, suppurative, and gangrenous pancreatitis, and of disseminated fat necrosis. *Boston Med Surg J*, *120*, 181–187.

Flati, G., Andrén-Sandberg, A., la Pinta, M., Porowska, B., & Carboni, M. (2003). Potentially fatal bleeding in acute pancreatitis: pathophysiology, prevention, and treatment. *Pancreas*, *26*(1), 8–14. https://doi.org/10.1097/00006676-200301000-00002

Fleischman, G. (1815). *Leichenöffnungen*. Johann Jakob Palm.

Frank, C. D., & Adler, D. G. (2006). Post-ERCP pancreatitis and its prevention. *Nature Clinical Practice. Gastroenterology & Hepatology*, *3*(12), 680–688. https://doi.org/10.1038/NCPGASTHEP0654

Freeny, P. C., Hauptmann, E., Althaus, S. J., Traverso, L. W., & Sinanan, M. (1998). Percutaneous CT-guided catheter drainage of infected acute necrotizing pancreatitis: techniques and results. *AJR. American Journal of Roentgenology*, *170*(4), 969–975. https://doi.org/10.2214/AJR.170.4.9530046

Frey, C. F., Zhou, H., Harvey, D. J., & White, R. H. (2006). The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. *Pancreas*, *33*(4), 336–344. https://doi.org/10.1097/01.MPA.0000236727.16370.99

Frey, C., Zhou, H., Harvey, D., & White, R. H. (2007). Co-morbidity is a strong predictor of early death and multi-organ system failure among patients with acute pancreatitis. *Journal of Gastrointestinal Surgery*, *11*(6), 733–742. https://doi.org/10.1007/S11605-007-0164-5/TABLES/4

Friedreich N. (1878). Diseases of the pancreas. In *Cyclopedia of the Practice of Medicine* (Ziemssen H, Vol. 3, pp. 549–630). William Wood.

Fritz, S., Hackert, T., Hartwig, W., Rossmanith, F., Strobel, O., Schneider, L., Will-Schweiger, K., Kommerell, M., Büchler, M. W., & Werner, J. (2010). Bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis derives from small bowel rather than from colon. *American Journal of Surgery*, *200*(1), 111–117. https://doi.org/10.1016/J.AMJSURG.2009.08.019

Gao, L., Zhang, J. zhu, Gao, K., Zhou, J., Li, G., Li, B. qiang, Ye, B., Ke, L., Tong, Z. hui, & Li, W. qin. (2020). Management of colonic fistulas in patients with infected pancreatic necrosis being treated with a step-up approach. *HPB*, *22*(12), 1738–1744. https://doi.org/10.1016/J.HPB.2020.03.021/ATTACHMENT/8C0BB515-893C-4409-B754-F71D96D6E59C/MMC1.DOCX

García-Barrasa, A., Borobia, F. G., Pallares, R., Jorba, R., Poves, I., Busquets, J., & Fabregat, J. (2009). A Double-blind, Placebo-controlled Trial of Ciprofloxacin Prophylaxis in Patients with Acute Necrotizing Pancreatitis. *Journal of Gastrointestinal Surgery*, *13*(4), 768–774. https://doi.org/10.1007/s11605-008-0773-7

Gardner, T. B., Vege, S. S., Chari, S. T., Pearson, R. K., Clain, J. E., Topazian, M. D., Levy, M. J., & Petersen, B. T. (2008). The effect of age on hospital outcomes in severe acute pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *8*(3), 265–270. https://doi.org/10.1159/000134274

Garg, P. K., & Singh, V. P. (2019). Organ Failure Due to Systemic Injury in Acute Pancreatitis. *Gastroenterology*, *156*(7), 2008–2023. https://doi.org/10.1053/J.GASTRO.2018.12.041

Garret, C., Canet, E., Corvec, S., Boutoille, D., Péron, M., Archambeaud, I., le Thuaut, A., Lascarrou, J. B., Douane, F., Lerhun, M., Regenet, N., Coron, E., & Reignier, J. (2020). Impact of prior antibiotics on infected pancreatic necrosis microbiology in ICU patients: a retrospective cohort study. *Annals of Intensive Care*, *10*(1), 82. https://doi.org/10.1186/S13613-020-00698-0

Gloor, B., Müller, C. A., Worni, M., Stahel, P. F., Redaelli, C., Uhl, W., & Büchler, M. W. (2001). Pancreatic Infection in Severe Pancreatitis: The Role of Fungus

and Multiresistant Organisms. *Archives of Surgery*, *136*(5), 592–596. https://doi.org/10.1001/ARCHSURG.136.5.592

Gluck, M., Ross, A., Irani, S., Lin, O., Hauptmann, E., Siegal, J., Fotoohi, M., Crane, R., Robinson, D., & Kozarek, R. A. (2010). Endoscopic and percutaneous drainage of symptomatic walled-off pancreatic necrosis reduces hospital stay and radiographic resources. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *8*(12), 1083–1088. https://doi.org/10.1016/J.CGH.2010.09.010

Gomatos, I. P., Halloran, C. M., Ghaneh, P., Raraty, M. G. T., Polydoros, F., Evans, J. C., Smart, H. L., Yagati-Satchidanand, R., Garry, J. M., Whelan, P. A., Hughes, F. E., Sutton, R., & Neoptolemos, J. P. (2016). Outcomes From Minimal Access Retroperitoneal and Open Pancreatic Necrosectomy in 394 Patients With Necrotizing Pancreatitis. *Annals of Surgery*, *263*(5), 992–1001. https://doi.org/10.1097/SLA.0000000000001407

Gonzelez, H. J., Sahay, S. J., Samadi, B., Davidson, B. R., & Rahman, S. H. (2011). Splanchnic vein thrombosis in severe acute pancreatitis: a 2-year, single-institution experience. *HPB : The Official Journal of the International Hepato Pancreato Biliary Association*, *13*(12), 860. https://doi.org/10.1111/J.1477-2574.2011.00392.X

Grady, T., Saluja, A., Kaiser, A., & Steer, M. (1996). Edema and intrapancreatic trypsinogen activation precede glutathione depletion during caerulein pancreatitis. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *271*(1), G20–G26. https://doi.org/10.1152/ajpgi.1996.271.1.G20

Gramlich, L., Kichian, K., Pinilla, J., Rodych, N. J., Dhaliwal, R., & Heyland, D. K. (2004). Does enteral nutrition compared parenteral nutrition result in better outcome in critically ill adult patients? A systematic review of the literature. *NUTRITION*, *20*(10), 843–848. https://doi.org/10.1016/j.nut.2004.06.003

Griswold, M. G., Fullman, N., Hawley, C., Arian, N., Zimsen, S. R. M., Tymeson, H. D., Venkateswaran, V., Tapp, A. D., Forouzanfar, M. H., Salama, J. S., Abate, K. H., Abate, D., Abay, S. M., Abbafati, C., Abdulkader, R. S., Abebe, Z., Aboyans, V., Abrar, M. M., Acharya, P., … Gakidou, E. (2018). Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *392*(10152), 1015–1035. https://doi.org/10.1016/S0140-6736(18)31310-2

Gurusamy, K. S., Pallari, E., Hawkins, N., Pereira, S. P., & Davidson, B. R. (2016). Management strategies for pancreatic pseudocysts. *The Cochrane Database of Systematic Reviews*, *2016*(4). https://doi.org/10.1002/14651858.CD011392.PUB2

Habashi, S., & Draganov, P. v. (2009). Pancreatic pseudocyst. *World Journal of Gastroenterology : WJG*, *15*(1), 38. https://doi.org/10.3748/WJG.15.38

Hallensleben, N. D., Timmerhuis, H. C., Hollemans, R. A., Pocornie, S., van Grinsven, J., van Brunschot, S., Bakker, O. J., van der Sluijs, R., Schwartz, M. P., van Duijvendijk, P., Römkens, T., Stommel, M. W. J., Verdonk, R. C., Besselink, M. G., Bouwense, S. A. W., Bollen, T. L., van Santvoort, H. C., &

Bruno, M. J. (2021). Optimal timing of cholecystectomy after necrotising biliary pancreatitis. *Gut*, *0*, 1–9. https://doi.org/10.1136/GUTJNL-2021-324239

Halonen, K. I., Pettilä, V., Leppäniemi, A. K., Kemppainen, E. A., Puolakkainen, P. A., & Haapiainen, R. K. (2002). Multiple organ dysfunction associated with severe acute pancreatitis. *Critical Care Medicine*, *30*(6), 1274–1279. https://doi.org/10.1097/00003246-200206000-00019

Halonen, K. I., Pettilä, V., Leppäniemi, A. K., Kemppainen, E. A., Puolakkainen, P. A., & Haapiainen, R. K. (2003). Long-term health-related quality of life in survivors of severe acute pancreatitis. *Intensive Care Medicine*, *29*(5), 782–786. https://doi.org/10.1007/s00134-003-1700-8

Hamada, S., Masamune, A., Kikuta, K., Hirota, M., Tsuji, I., & Shimosegawa, T. (2014). Nationwide epidemiological survey of acute pancreatitis in Japan. *Pancreas*, *43*(8), 1244–1248. https://doi.org/10.1097/MPA.0000000000000200

Haney, C. M., Kowalewski, K. F., Schmidt, M. W., Koschny, R., Felinska, E. A., Kalkum, E., Probst, P., Diener, M. K., Müller-Stich, B. P., Hackert, T., & Nickel, F. (2020). Endoscopic versus surgical treatment for infected necrotizing pancreatitis: a systematic review and meta-analysis of randomized controlled trials. *Surgical Endoscopy*, *34*(6), 2429–2444. https://doi.org/10.1007/S00464-020-07469-9/TABLES/4

Harrison, D. A., D'Amico, G., & Singer, M. (2007). Case mix, outcome, and activity for admissions to UK critical care units with severe acute pancreatitis: A secondary analysis of the ICNARC Case Mix Programme Database. *Critical Care*, *11*(SUPPL. 1), 1–8. https://doi.org/10.1186/CC5682/FIGURES/4

Hartwig, W., Werner, J., Müller, C. A., Uhl, W., & Büchler, M. W. (2002). Surgical management of severe pancreatitis including sterile necrosis. *Journal of Hepato-Biliary-Pancreatic Surgery*, *9*(4), 429–435. https://doi.org/10.1007/s005340200053

He, W., Chen, P., Lei, Y., Xia, L., Liu, P., Zhu, Y., Zeng, H., Wu, Y., Ke, H., Huang, X., Cai, W., Sun, X., Huang, W., Sutton, R., Zhu, Y., & Lu, N. (2022). Randomized controlled trial: neostigmine for intra-abdominal hypertension in acute pancreatitis. *Critical Care*, *26*(1), 52. https://doi.org/10.1186/s13054-022-03922-4

Henderson, J. R., Daniel, P. M., & Fraser, P. A. (1981). The pancreas as a single organ: the influence of the endocrine upon the exocrine part of the gland. *Gut*, *22*(2), 158–167. https://doi.org/10.1136/GUT.22.2.158

Hendrickson, M., & Naparst, T. R. (2003). Abdominal surgical emergencies in the elderly. *Emergency Medicine Clinics of North America*, *21*(4), 937–969. https://doi.org/10.1016/S0733-8627(03)00072-5

Hines, O. J., & Pandol, S. J. (2019). Management of severe acute pancreatitis. *BMJ*, *367*. https://doi.org/10.1136/BMJ.L6227

Hirota, M., Inoue, K., Kimura, Y., Mizumoto, T., Kuwata, K., Ohmuraya, M., Ishiko, T., Beppu, T., & Ogawa, M. (2003). Non-occlusive mesenteric ischemia and its associated intestinal gangrene in acute pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *3*(4), 316–322. https://doi.org/10.1159/000071770

Hochreiter, M., Köhler, T., Schweiger, A. M., Keck, F. S., Bein, B., von Spiegel, T., & Schroeder, S. (2009). *Open Access Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial*. https://doi.org/10.1186/cc7903

Hofbauer, B., Saluja, A. K., Lerch, M. M., Bhagat, L., Bhatia, M., Lee, H. S., Frossard, J. L., Adler, G., & Steer, M. L. (1998). Intra-acinar cell activation of trypsinogen during caerulein-induced pancreatitis in rats. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *275*(2 38-2). https://doi.org/10.1152/AJPGI.1998.275.2.G352/ASSET/IMAGES/LARGE/AGIJG0088808Z.JPEG

Hollemans, R. A., Bollen, T. L., van Brunschot, S., Bakker, O. J., Ali, U. A., van Goor, H., Boermeester, M. A., Gooszen, H. G., Besselink, M. G., & van Santvoort, H. C. (2016). Predicting Success of Catheter Drainage in Infected Necrotizing Pancreatitis. *Annals of Surgery*, *263*(4), 787–792. https://doi.org/10.1097/SLA.0000000000001203

Hollemans, R. A., Hallensleben, N. D. L., Mager, D. J., Kelder, J. C., Besselink, M. G., Bruno, M. J., Verdonk, R. C., & van Santvoort, H. C. (2018). Pancreatic exocrine insufficiency following acute pancreatitis: Systematic review and study level meta-analysis. *Pancreatology*, *18*(3), 253–262. https://doi.org/10.1016/j.pan.2018.02.009

Horvath, K. D., Kao, L. S., Wherry, K. L., Pellegrini, C. A., & Sinanan, M. N. (2001). *A technique for laparoscopic-assisted percutaneous drainage of infected pancreatic necrosis and pancreatic abscess*. *15*, 1221–1225. https://doi.org/10.1007/s004640080166

Howard, T. J. (2007). As good as it gets: The study of prophylactic antibiotics in severe acute pancreatitis. In *Annals of Surgery* (Vol. 245, Issue 5, pp. 684–685). https://doi.org/10.1097/01.sla.0000261458.39058.fc

Howard, T. J., Rhodes, G. J., Selzer, D. J., Sherman, S., Fogel, E., & Lehman, G. A. (2001). Roux-en-Y internal drainage is the best surgical option to treat patients with disconnected duct syndrome after severe acute pancreatitis. *Surgery*, *130*(4), 714–721. https://doi.org/10.1067/msy.2001.116675

Huang, W., de la Iglesia-García, D., Baston-Rey, I., Calviño-Suarez, C., Lariño-Noia, J., Iglesias-Garcia, J., Shi, N., Zhang, X., Cai, W., Deng, L., Moore, D., Singh, V. K., Xia, Q., Windsor, J. A., Domínguez-Muñoz, J. E., & Sutton, R. (2019). Exocrine Pancreatic Insufficiency Following Acute Pancreatitis: Systematic Review and Meta-Analysis. *Digestive Diseases and Sciences*, *64*(7), 1985–2005. https://doi.org/10.1007/s10620-019-05568-9

Huh, J. H., Jeon, H., Park, S. M., Choi, E., Lee, G. S., Kim, J. W., & Lee, K. J. (2018). Diabetes Mellitus is Associated With Mortality in Acute Pancreatitis. *Journal of Clinical Gastroenterology*, *52*(2), 178–183. https://doi.org/10.1097/MCG.0000000000000783

Hwang, S. O., Lee, T. H., Park, J. W., Park, S. H., & Kim, S. J. (2010). Endoscopic management of multiple colonic fistulae secondary to acute pancreatitis (with video). *Gastrointestinal Endoscopy*, *71*(2), 395–397.

https://doi.org/10.1016/J.GIE.2009.10.045/ATTACHMENT/EEF2A2A2-EEC2-4B6C-AB35-76F6F6AA647A/MMC1.MPG

Iannuzzi, J. P., King, J. A., Leong, J. H., Quan, J., Windsor, J. W., Tanyingoh, D., Coward, S., Forbes, N., Heitman, S. J., Shaheen, A. A., Swain, M., Buie, M., Underwood, F. E., & Kaplan, G. G. (2022). Global Incidence of Acute Pancreatitis Is Increasing Over Time: A Systematic Review and Meta-Analysis. *Gastroenterology*, *162*(1), 122–134. https://doi.org/10.1053/J.GASTRO.2021.09.043/ATTACHMENT/BCF8D5C9-C3B3-468E-B0B2-31916FC3BAFC/MMC1.PDF

II, D. M. G., & Mullady, D. K. (2012). Attempted Endoscopic Closure of a Pancreaticocolonic Fistula with an Over-The-Scope Clip. *JOP. Journal of the Pancreas*, *13*(6), 712–714. https://pancreas.imedpub.com/attempted-endoscopic-closure-of-a-pancreaticocolonic-fistula-with-an-overthescope-clip.php?aid=1008

Imam, Z., Simons-Linares, C. R., & Chahal, P. (2020). Infectious causes of acute pancreatitis: A systematic review. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *20*(7), 1312–1322. https://doi.org/10.1016/J.PAN.2020.08.018

Inoue, S., Epstein, M. D., Alexander, J. W., Trocki, O., Jacobs, P., & Gura, P. (1989). Prevention of yeast translocation across the gut by a single enteral feeding after burn injury. *JPEN. Journal of Parenteral and Enteral Nutrition*, *13*(6), 565–571. https://doi.org/10.1177/0148607189013006565

Iqbal, U., Anwar, H., & Scribani, M. (2018). Ringer's lactate versus normal saline in acute pancreatitis: A systematic review and meta-analysis. *Journal of Digestive Diseases*, *19*(6), 335–341. https://doi.org/10.1111/1751-2980.12606

Isaji, S., Takada, T., Mayumi, T., Yoshida, M., Wada, K., Yokoe, M., Itoi, T., & Gabata, T. (2015). Revised Japanese guidelines for the management of acute pancreatitis 2015: Revised concepts and updated points. *Journal of Hepato-Biliary-Pancreatic Sciences*, *22*(6), 433–445. https://doi.org/10.1002/JHBP.260

Isenmann, R., Rau, B., & Beger, H. G. (2001). Early Severe Acute Pancreatitis: Characteristics of a New Subgroup. *Pancreas*, *22*(3). https://journals.lww.com/pancreasjournal/Fulltext/2001/04000/Early_Severe_Acute_Pancreatitis__Characteristics.8.aspx

Isenmann, R., Rünzi, M., Kron, M., Kahl, S., Kraus, D., Jung, N., Maier, L., Malfertheiner, P., Goebell, H., & Beger, H. G. (2004). Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology*, *126*(4), 997–1004. https://doi.org/10.1053/J.GASTRO.2003.12.050

Ito, K., Igarashi, Y., Mimura, T., Kishimoto, Y., Kamata, I., Kobayashi, S., Yoshimoto, K., & Okano, N. (2013). Severe Acute Pancreatitis with Complicating Colonic Fistula Successfully Closed Using the Over-the-Scope Clip System. *Case Reports in Gastroenterology*, *7*(2), 314. https://doi.org/10.1159/000354276

Jaakkola, M., & Nordback, I. (1993). Pancreatitis in Finland between 1970 and 1989. *Gut*, *34*(9), 1255–1260. https://doi.org/10.1136/GUT.34.9.1255

Jaber, S., Chanques, G., Sebbane, M., Salhi, F., Delay, J.-M., Perrigault, P.-F., & Eledjam, J.-J. (2006). Noninvasive positive pressure ventilation in patients with respiratory failure due to severe acute pancreatitis. *Respiration; International Review of Thoracic Diseases*, *73*(2), 166–172. https://doi.org/10.1159/000088897

Jacobs, M. L., Daggett, W. M., Civette, J. M., Vasu, M. A., Lawson, D. W., Warshaw, A. L., Nardi, G. L., & Bartlett, M. K. (1977). Acute pancreatitis: analysis of factors influencing survival. *Annals of Surgery*, *185*(1), 43–51. https://doi.org/10.1097/00000658-197701000-00007

Jain, S., Padhan, R., Bopanna, S., Jain, S. K., Dhingra, R., Dash, N. R., Madhusudan, K. S., Gamanagatti, S. R., Sahni, P., & Garg, P. K. (2020). Percutaneous Endoscopic Step-Up Therapy Is an Effective Minimally Invasive Approach for Infected Necrotizing Pancreatitis. *Digestive Diseases and Sciences*, *65*(2), 615–622. https://doi.org/10.1007/S10620-019-05696-2/TABLES/4

Jiang, W., Tong, Z., Yang, D., Ke, L., Shen, X., Zhou, J., Li, G., Li, W., & Li, J. (2016). Gastrointestinal Fistulas in Acute Pancreatitis With Infected Pancreatic or Peripancreatic Necrosis: A 4-Year Single-Center Experience. *Medicine*, *95*(14). https://doi.org/10.1097/MD.0000000000003318

Jin, T., Jiang, K., Deng, L., Guo, J., Wu, Y., Wang, Z., Shi, N., Zhang, X., Lin, Z., Asrani, V., Jones, P., Mittal, A., Phillips, A., Sutton, R., Huang, W., Yang, X., Xia, Q., & Windsor, J. A. (2018). Response and outcome from fluid resuscitation in acute pancreatitis: a prospective cohort study. *HPB*, *20*(11), 1082–1091. https://doi.org/10.1016/j.hpb.2018.05.018

Johnson, C. D., & Abu-Hilal, M. (2004). Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut*, *53*(9), 1340–1344. https://doi.org/10.1136/GUT.2004.039883

Johnson, C. D., Kingsnorth, A. N., Imrie, C. W., McMahon, M. J., Neoptolemos, J. P., McKay, C., Toh, S. K. C., Skaife, P., Leeder, P. C., Wilson, P., Larvin, M., & Curtis, L. D. (2001). 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*(1), 62–69. https://doi.org/10.1136/GUT.48.1.62

Juliusson, S. J., Nielsen, J. K., Runarsdottir, V., Hansdottir, I., Sigurdardottir, R., & Björnsson, E. S. (2018). Lifetime alcohol intake and pattern of alcohol consumption in patients with alcohol-induced pancreatitis in comparison with patients with alcohol use disorder. *Https://Doi.Org/10.1080/00365521.2018.1455893*, *53*(6), 748–754. https://doi.org/10.1080/00365521.2018.1455893

Junare, P. R., Udgirkar, S., Nair, S., Debnath, P., Jain, S., Modi, A., Rathi, P., Rane, S., & Contractor, Q. (2020). Splanchnic Venous Thrombosis in Acute Pancreatitis: Does Anticoagulation Affect Outcome? *Gastroenterology Research*, *13*(1), 25. https://doi.org/10.14740/GR1223

Kalfarentzos, F., Kehagias, J., Mead, N., Kokkinis, K., & Gogos, C. A. (1997). Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: Results of

a randomized prospective trial. *British Journal of Surgery*, *84*(12), 1665–1669. https://doi.org/10.1046/j.1365-2168.1997.02851.x

Kamal, A., Sinha, A., Hutfless, S. M., Afghani, E., Faghih, M., Khashab, M. A., Lennon, A. M., Yadav, D., Makary, M. A., Andersen, D. K., Kalloo, A. N., & Singh, V. K. (2017). Hospital admission volume does not impact the in-hospital mortality of acute pancreatitis. *HPB : The Official Journal of the International Hepato Pancreato Biliary Association*, *19*(1), 21–28. https://doi.org/10.1016/J.HPB.2016.10.013

Kanth, V. R., & Reddy, D. N. (2014). Genetics of acute and chronic pancreatitis: An update. *World Journal of Gastrointestinal Pathophysiology*, *5*(4), 427. https://doi.org/10.4291/WJGP.V5.I4.427

Karjula, H., Saarela, A., Ohtonen, P., Ala-Kokko, T., Mäkelä, J., & Liisanantti, J. H. (2019). Long-term Outcome and Causes of Death for Working-age Patients Hospitalized Due to Acute Pancreatitis With a Median Follow-up of 10 Years. *Annals of Surgery*, *269*(5), 932–936. https://doi.org/10.1097/SLA.0000000000002612

Kaya, E., Dervisoglu, A., & Polat, C. (2007). Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis. *World Journal of Gastroenterology*, *13*(22), 3090–3094. https://doi.org/10.3748/wjg.v13.i22.3090

Ke, L., Ni, H. bin, Sun, J. K., Tong, Z. H., Li, W. Q., Li, N., & Li, J. S. (2012). Risk factors and outcome of intra-abdominal hypertension in patients with severe acute pancreatitis. *World Journal of Surgery*, *36*(1), 171–178. https://doi.org/10.1007/S00268-011-1295-0/TABLES/4

Ke, L., Ni, H. bin, Tong, Z. H., Li, W. Q., Li, N., & Li, J. S. (2011). Intra-abdominal Pressure and Abdominal Perfusion Pressure: Which is a Better Marker of Severity in Patients with Severe Acute Pancreatitis. *Journal of Gastrointestinal Surgery*, *15*(8), 1426–1432. https://doi.org/10.1007/S11605-011-1553-3/TABLES/5

Ke, L., Ni, H. bin, Tong, Z. H., Li, W. Q., Li, N., & Li, J. S. (2013). The importance of timing of decompression in severe acute pancreatitis combined with abdominal compartment syndrome. *Journal of Trauma and Acute Care Surgery*, *74*(4), 1060–1066. https://doi.org/10.1097/TA.0B013E318283D927

Kelly, T. R. (1984). Gallstone pancreatitis. Local predisposing factors. *Annals of Surgery*, *200*(4), 479–485. https://doi.org/10.1097/00000658-198410000-00009

Kemppainen, E. A., Hedström, J. I., Puolakkainen, P. A., Sainio, V. S., Haapiainen, R. K., Perhoniemi, V., Osman, S., Kivilaakso, E. O., & Stenman, U. H. (1997). Rapid measurement of urinary trypsinogen-2 as a screening test for acute pancreatitis. *The New England Journal of Medicine*, *336*(25), 1788–1793. https://doi.org/10.1056/NEJM199706193362504

Keskinen, P., Leppaniemi, A., Pettila, V., Piilonen, A., Kemppainen, E., & Hynninen, M. (2007). Intra-abdominal pressure in severe acute pancreatitis. *World Journal of Emergency Surgery : WJES*, *2*(1). https://doi.org/10.1186/1749-7922-2-2

Khan, J., Nordback, I., & Sand, J. (2013). Serum Lipid Levels Are Associated with the Severity of Acute Pancreatitis. *Digestion*, *87*(4), 223–228. https://doi.org/10.1159/000348438

Khanna, A. K., Meher, S., Prakash, S., Tiwary, S. K., Singh, U., Srivastava, A., & Dixit, V. K. (2013). Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and Procalcitonin in Predicting Severity, Organ Failure, Pancreatic Necrosis, and Mortality in Acute Pancreatitis. *HPB Surgery*, *2013*. https://doi.org/10.1155/2013/367581

Kim, K. O., & Kim, T. N. (2012). Acute pancreatic pseudocyst: Incidence, risk factors, and clinical outcomes. *Pancreas*, *41*(4), 577–581. https://doi.org/10.1097/MPA.0B013E3182374DEF

Kirkpatrick, A. W., Roberts, D. J., de Waele, J., Jaeschke, R., Malbrain, M. L. N. G., de Keulenaer, B., Duchesne, J., Bjorck, M., Leppaniemi, A., Ejike, J. C., Sugrue, M., Cheatham, M., Ivatury, R., Ball, C. G., Reintam Blaser, A., Regli, A., Balogh, Z. J., D'Amours, S., Debergh, D., … Olvera, C. (2013). Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Medicine*, *39*(7), 1190–1206. https://doi.org/10.1007/S00134-013-2906-Z

Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). APACHE II: a severity of disease classification system. *Critical Care Medicine*, *13*(10), 818–829.

Kochar, B., Akshintala, V. S., Afghani, E., Elmunzer, B. J., Kim, K. J., Lennon, A. M., Khashab, M. A., Kalloo, A. N., & Singh, V. K. (2015). Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. *Gastrointestinal Endoscopy*, *81*(1), 143-149.e9. https://doi.org/https://doi.org/10.1016/j.gie.2014.06.045

Kristiansen, L., Grønbæk, M., Becker, U., & Tolstrup, J. S. (2008). Risk of pancreatitis according to alcohol drinking habits: a population-based cohort study. *American Journal of Epidemiology*, *168*(8), 932–937. https://doi.org/10.1093/AJE/KWN222

Kudsk, K. A., Croce, M. A., Fabian, T. C., Minard, G., Tolley, E. A., Poret, H. A., Kuhl, M. R., & Brown, R. E. X. O. (1992). Enteral Versus Parenteral Feeding Effects on Septic Morbidity After Blunt and Penetrating Abdominal Trauma. *Annals of Surgery*, *215*(5). https://journals.lww.com/annalsofsurgery/Fulltext/1992/05000/Enteral_Versus_Parenteral_Feeding_Effects_on.13.aspx

Kühlbrey, C. M., Samiei, N., Sick, O., Makowiec, F., Hopt, U. T., & Wittel, U. A. (2017). Pancreatitis After Pancreatoduodenectomy Predicts Clinically Relevant Postoperative Pancreatic Fistula. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *21*(2), 330–338. https://doi.org/10.1007/S11605-016-3305-X

Kulkarni, S., Bogart, A., Buxbaum, J., Matsuoka, L., Selby, R., & Parekh, D. (2015). Surgical transgastric debridement of walled off pancreatic necrosis: an option for patients with necrotizing pancreatitis. *Surgical Endoscopy*, *29*(3), 575–582. https://doi.org/10.1007/S00464-014-3700-X

Kumar, A., Gupta, M., Kochhar, S., Singh, R., & Lehl, S. S. (2021). Short-term outcome of local pancreatic complications in a public hospital from North India.

Postgraduate Medical Journal, *97*(1153), 723–729. https://doi.org/10.1136/POSTGRADMEDJ-2019-137444

Kumar, A., Singh, N., Prakash, S., Saraya, A., & Joshi, Y. K. (2006). Early Enteral Nutrition in Severe Acute Pancreatitis: A Prospective Randomized Controlled Trial Comparing Nasojejunal and Nasogastric Routes. *Journal of Clinical Gastroenterology*, *40*(5). https://journals.lww.com/jcge/Fulltext/2006/05000/Early_Enteral_Nutrition_in_Severe_Acute.13.aspx

Kumaravel, A., Zelisko, A., Schauer, P., Lopez, R., Kroh, M., & Stevens, T. (2014). Acute pancreatitis in patients after bariatric surgery: incidence, outcomes, and risk factors. *Obesity Surgery*, *24*(12), 2025–2030. https://doi.org/10.1007/S11695-014-1337-4

Kurdia, K. C., Irrinki, S., Chala, A. v., Bhalla, A., Kochhar, R., & Yadav, T. D. (2020). Early intra-abdominal hypertension: A reliable bedside prognostic marker for severe acute pancreatitis. *JGH Open*, *4*(6), 1091–1095. https://doi.org/10.1002/JGH3.12393

Kwak, S. W., Kim, S., Lee, J. W., Lee, N. K., Kim, C. W., Yi, M. S., Kim, G. H., & Kang, D. H. (2009). Evaluation of unusual causes of pancreatitis: Role of cross-sectional imaging. *European Journal of Radiology*, *71*(2), 296–312. https://doi.org/10.1016/J.EJRAD.2008.04.006

Kwong, W. T. Y., Ondrejková, A., & Vege, S. S. (2016). Predictors and outcomes of moderately severe acute pancreatitis - Evidence to reclassify. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *16*(6), 940–945. https://doi.org/10.1016/J.PAN.2016.08.001

Lankisch, P. G., Apte, M., & Banks, P. A. (2015). Acute pancreatitis. *The Lancet*, *386*(9988), 85–96. https://doi.org/10.1016/S0140-6736(14)60649-8/ATTACHMENT/E9F07E5D-08FF-4A79-AFF2-A5C7F4F2BA7F/MMC1.PDF

Lankisch, P. G., Assmus, C., Lehnick, D., Maisonneuve, P., & Lowenfels, A. B. (2001). Acute pancreatitis: does gender matter? *Digestive Diseases and Sciences*, *46*(11), 2470–2474. https://doi.org/10.1023/A:1012332121574

Lankisch, P. G., Dröge, M., & Gottesleben, F. (1995). Drug induced acute pancreatitis: incidence and severity. *Gut*, *37*(4), 565–567. https://doi.org/10.1136/GUT.37.4.565

Lankisch, P. G., Lowenfels, A. B., Maisonneuve, P., & Oría, A. (2002). What is the risk of alcoholic pancreatitis in heavy drinkers? *Pancreas*, *25*(4), 411–412. https://doi.org/10.1097/00006676-200211000-00015

Lankisch, P. G., Mahlke, R., Graf, D., Becher, R., & Riesner, K. (1995). Painless Acute Pancreatitis Mimicking Pancreatic Carcinoma. *Pancreas*, *10*(4). https://journals.lww.com/pancreasjournal/Fulltext/1995/05000/Painless_Acute_Pancreatitis_Mimicking_Pancreatic.15.aspx

Lankisch, P. G., Weber-Dany, B., Hebel, K., Maisonneuve, P., & Lowenfels, A. B. (2009). The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease. *Clinical Gastroenterology and Hepatology :*

The Official Clinical Practice Journal of the American Gastroenterological Association, *7*(6), 702–705. https://doi.org/10.1016/J.CGH.2009.02.020

Lankisch, P. G., Weber-Dany, B., Maisonneuve, P., & Lowenfels, A. B. (2009). Skin signs in acute pancreatitis: frequency and implications for prognosis. *Journal of Internal Medicine*, *265*(2), 299–301. https://doi.org/10.1111/J.1365-2796.2008.02004.X

Lankisch, P. G., Weber-Dany, B., Maisonneuve, P., & Lowenfels, A. B. (2012). Pancreatic pseudocysts: Prognostic factors for their development and their spontaneous resolution in the setting of acute pancreatitis. *Pancreatology*, *12*(2), 85–90. https://doi.org/10.1016/J.PAN.2012.02.007

Lankisch, P., Schirren, C., & Kunze, E. (1991). Undetected fatal acute pancreatitis: why is the disease so frequently overlooked? *Am J Gastroenterol*, *86*(3), 322–326. https://www.webofscience.com/wos/woscc/full-record/WOS:A1991FB76300015

Lariño-Noia, J., de la Iglesia-García, D., González-Lopez, J., Díaz-Lopez, J., Macías-García, F., Mejuto, R., Quiroga, A., Mauriz, V., Jardí, A., Iglesias-García, J., & Domínguez-Muñoz, J. E. (2021). Endoscopic drainage with local infusion of antibiotics to avoid necrosectomy of infected walled-off necrosis. *Surgical Endoscopy*, *35*(2), 644–651. https://doi.org/10.1007/S00464-020-07428-4/TABLES/3

Lawrence, C., Howell, D. A., Stefan, A. M., Conklin, D. E., Lukens, F. J., Martin, R. F., Landes, A., & Benz, B. (2008). Disconnected pancreatic tail syndrome: potential for endoscopic therapy and results of long-term follow-up. *Gastrointestinal Endoscopy*, *67*(4), 673–679. https://doi.org/10.1016/j.gie.2007.07.017

le Mée, J., Paye, F., Sauvanet, A., O'Toole, D., Hammel, P., Marty, J., Ruszniewski, P., & Belghiti, J. (2001). Incidence and reversibility of organ failure in the course of sterile or infected necrotizing pancreatitis. *Archives of Surgery (Chicago, Ill. : 1960)*, *136*(12), 1386–1390. https://doi.org/10.1001/ARCHSURG.136.12.1386

Leach, S. D., Gorelick, F. S., & Modlin, I. M. (1990). Acute pancreatitis at its centenary. The contribution of Reginald Fitz. *Annals of Surgery*, *212*(1), 109–113. https://doi.org/10.1097/00000658-199007000-00014

Lee, J. K., Kwak, K. K., Park, J. K., Yoon, W. J., Lee, S. H., Ryu, J. K., Kim, Y. T., & Yoon, Y. B. (2007). The efficacy of nonsurgical treatment of infected pancreatic necrosis. *Pancreas*, *34*(4), 399–404. https://doi.org/10.1097/MPA.0B013E318043C0B1

Lee, P. J., & Papachristou, G. I. (2019). New insights into acute pancreatitis. *Nature Reviews Gastroenterology & Hepatology 2019 16:8*, *16*(8), 479–496. https://doi.org/10.1038/s41575-019-0158-2

Lee, S. P., Nicholls, J. F., & Park, H. Z. (1992). Biliary sludge as a cause of acute pancreatitis. *The New England Journal of Medicine*, *326*(9), 589–593. https://doi.org/10.1056/NEJM199202273260902

Lefor, A. T., Vuocolo, P., Parker, F. B., & Sillin, L. F. (1992). Pancreatic Complications Following Cardiopulmonary Bypass: Factors Influencing

Mortality. *Archives of Surgery*, *127*(10), 1225–1231. https://doi.org/10.1001/ARCHSURG.1992.01420100087015

Lemma, A., Åberg, F., Mäkisalo, H., Vikatmaa, P., Mentula, P., Leppäniemi, A., & Sallinen, V. (2020). Predictors of insufficient recanalization and portal hypertensive complications after treatment of non-cirrhotic, non-malignant portal vein thrombosis - a population-based study. *Scandinavian Journal of Gastroenterology*, *55*(11), 1324–1332. https://doi.org/10.1080/00365521.2020.1823465

Lenhart, D. K., & Balthazar, E. J. (2008). MDCT of acute mild (nonnecrotizing) pancreatitis: abdominal complications and fate of fluid collections. *AJR. American Journal of Roentgenology*, *190*(3), 643–649. https://doi.org/10.2214/AJR.07.2761

Leppäniemi, A. K., Hienonen, P. A., Siren, J. E., Kuitunen, A. H., Lindström, O. K., & Kemppainen, E. A. J. (2006). Treatment of abdominal compartment syndrome with subcutaneous anterior abdominal fasciotomy in severe acute pancreatitis. *World Journal of Surgery*, *30*(10), 1922–1924. https://doi.org/10.1007/S00268-006-0024-6

Leppäniemi, A., Tolonen, M., Tarasconi, A., Segovia-Lohse, H., Gamberini, E., Kirkpatrick, A. W., Ball, C. G., Parry, N., Sartelli, M., Wolbrink, D., van Goor, H., Baiocchi, G., Ansaloni, L., Biffl, W., Coccolini, F., di Saverio, S., Kluger, Y., Moore, E., & Catena, F. (2019). 2019 WSES guidelines for the management of severe acute pancreatitis. *World Journal of Emergency Surgery 2019 14:1*, *14*(1), 1–20. https://doi.org/10.1186/S13017-019-0247-0

Lewellen, K. A., Maatman, T. K., Heimberger, M. A., Ceppa, E. P., House, M. G., Nakeeb, A., Schmidt, C. M., & Zyromski, N. J. (2020). Pancreatic Adenocarcinoma Causing Necrotizing Pancreatitis: Not as Rare as You Think? *Journal of Surgical Research*, *250*, 53–58. https://doi.org/https://doi.org/10.1016/j.jss.2019.12.036

Lindkvist, B., Appelros, S., Manjer, J., Berglund, G., & Borgström, A. (2008). A prospective cohort study of smoking in acute pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *8*(1), 63–70. https://doi.org/10.1159/000114868

Lipinski, M., Rydzewska-Rosolowska, A., Rydzewski, A., & Rydzewska, G. (2015). Fluid resuscitation in acute pancreatitis: Normal saline or lactated Ringer's solution? *World Journal of Gastroenterology*, *21*(31), 9367–9372. https://doi.org/10.3748/WJG.V21.I31.9367

Lu, J. di, Cao, F., Ding, Y. X., Wu, Y. D., Guo, Y. L., & Li, F. (2019). Timing, distribution, and microbiology of infectious complications after necrotizing pancreatitis. *World Journal of Gastroenterology*, *25*(34), 5162–5173. https://doi.org/10.3748/WJG.V25.I34.5162

Ma, X., Li, L., Jin, T., & Xia, Q. (2020). [Harmless acute pancreatitis score on admission can accurately predict mild acute pancreatitis]. *Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University*, *40*(2), 190–195. https://doi.org/10.12122/J.ISSN.1673-4254.2020.02.09

Maatman, T. K., Ceppa, E. P., Fogel, E. L., Easler, J. J., Gromski, M. A., House, M. G., Nakeeb, A., Schmidt, C. M., Sherman, S., & Zyromski, N. J. (2020). Biliary Stricture after Necrotizing Pancreatitis: An Underappreciated Challenge. *Annals of Surgery*, *Epub ahead of press*. https://journals.lww.com/annalsofsurgery/Fulltext/9000/Biliary_Stricture_after_Necrotizing_Pancreatitis_.94085.aspx

Maatman, T. K., Nicolas, M. E., Roch, A. M., Lewellen, K. A., Al-Azzawi, H. H., Ceppa, E. P., House, M. G., Nakeeb, A., Schmidt, C. M., & Zyromski, N. J. (2020). Colon Involvement in Necrotizing Pancreatitis: Incidence, Risk Factors, and Outcomes. *Annals of Surgery*. https://journals.lww.com/annalsofsurgery/Fulltext/9000/Colon_Involvement_in_Necrotizing_Pancreatitis_.94392.aspx

Maatman, T. K., Roch, A. M., Lewellen, K. A., Heimberger, M. A., Ceppa, E. P., House, M. G., Nakeeb, A., Schmidt, C. M., & Zyromski, N. J. (2020). Disconnected Pancreatic Duct Syndrome: Spectrum of Operative Management. *The Journal of Surgical Research*, *247*, 297–303. https://doi.org/10.1016/j.jss.2019.09.068

Madenci, A. L., Michailidou, M., Chiou, G., Thabet, A., Fernández-Del Castillo, C., & Fagenholz, P. J. (2014). A contemporary series of patients undergoing open debridement for necrotizing pancreatitis. *American Journal of Surgery*, *208*(3), 324–331. https://doi.org/10.1016/J.AMJSURG.2013.11.004

Maher, M. M., Lucey, B. C., Gervais, D. A., & Mueller, P. R. (2004). Acute Pancreatitis: The Role of Imaging and Interventional Radiology. *CardioVascular and Interventional Radiology*, *27*(3), 208–225. https://doi.org/10.1007/s00270-003-1907-7

Maisonneuve, P., Lowenfels, A. B., & Lankisch, P. G. (2021). The harmless acute pancreatitis score (HAPS) identifies non-severe patients: A systematic review and meta-analysis. *Pancreatology*, *21*(8), 1419–1427. https://doi.org/10.1016/J.PAN.2021.09.017

Manrai, M., Kochhar, R., Gupta, V., Yadav, T. D., Dhaka, N., Kalra, N., Sinha, S. K., & Khandelwal, N. (2018). Outcome of Acute Pancreatic and Peripancreatic Collections Occurring in Patients With Acute Pancreatitis. *Annals of Surgery*, *267*(2), 357–363. https://doi.org/10.1097/SLA.0000000000002065

Mao, E. Q., Tang, Y. Q., Fei, J., Qin, S., Wu, J., Li, L., Min, D., & Zhang, S. D. (2009). Fluid therapy for severe acute pancreatitis in acute response stage. *Chinese Medical Journal*, *122*(2), 169–173. https://doi.org/10.3760/CMA.J.ISSN.0366-6999.2009.02.011

Marik, P. E., & Zaloga, G. P. (2004). Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ*, *328*(7453), 1407. https://doi.org/10.1136/bmj.38118.593900.55

Maringhini, A., Uomo, G., Patti, R., Rabitti, P., Termini, A., Cavallera, A., Dardanoni, G., Ciambra, M., Laccetti, M., Biffarella, P., & Pagliaro, L. (1999). Pseudocysts in Acute Nonalcoholic Pancreatitis Incidence and Natural History. *Digestive Diseases and Sciences*, *44*(8).

Marshall, J. C., Cook, D. J., Christou, N. v., Bernard, G. R., Sprung, C. L., & Sibbald, W. J. (1995). Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Critical Care Medicine*, *23*(10), 1638–1652. https://doi.org/10.1097/00003246-199510000-00007

Marstrand-Joergensen, M. R., Bertilsson, S., & Kalaitzakis, E. (2020). Extrapancreatic infections are common in acute pancreatitis and they are related to organ failure: A population-based study. *European Journal of Gastroenterology and Hepatology*, 1293–1300. https://doi.org/10.1097/MEG.0000000000001847

Martin, N. D., Codner, P., Greene, W., Brasel, K., & Michetti, C. (2020). Contemporary hemodynamic monitoring, fluid responsiveness, volume optimization, and endpoints of resuscitation: an AAST critical care committee clinical consensus. *Trauma Surgery & Acute Care Open*, *5*(1), e000411. https://doi.org/10.1136/TSACO-2019-000411

Martínez, J., Johnson, C. D., Sánchez-Payá, J., de Madaria, E., Robles-Díaz, G., & Pérez-Mateo, M. (2006). Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *6*(3), 206–209. https://doi.org/10.1159/000092104

Matull, W. R., Pereira, S. P., & O'Donohue, J. W. (2006). Biochemical markers of acute pancreatitis. *Journal of Clinical Pathology*, *59*(4), 340–344. https://doi.org/10.1136/JCP.2002.002923

Mayer, J., Rau, B., Gansauge, F., & Beger, H. G. (2000). Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. *Gut*, *47*(4), 546–552. https://doi.org/10.1136/GUT.47.4.546

Mazaki, T., Ishii, Y., & Takayama, T. (2006). Meta-analysis of prophylactic antibiotic use in acute necrotizing pancreatitis. *British Journal of Surgery*, *93*(6), 674–684. https://doi.org/10.1002/BJS.5389

McClave, S. A., Greene, L. M., Snider, H. L., Makk, L. J. K., Cheadle, W. G., Owens, N. A., Dukes, L. G., & Goldsmith, L. J. (1997). Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. *JOURNAL OF PARENTERAL AND ENTERAL NUTRITION*, *21*(1), 14–20. https://doi.org/10.1177/014860719702100114

McKay, C. J., Evans, S., Sinclair, M., Carter, C. R., & Imrie, C. W. (1999). High early mortality rate from acute pancreatitis in Scotland, 1984-1995. *The British Journal of Surgery*, *86*(10), 1302–1305. https://doi.org/10.1046/j.1365-2168.1999.01246.x

Mentula, P., Hienonen, P., Kemppainen, E., Puolakkainen, P., & Leppäniemi, A. (2010). Surgical decompression for abdominal compartment syndrome in severe acute pancreatitis. *Archives of Surgery (Chicago, Ill. : 1960)*, *145*(8), 764–769. https://doi.org/10.1001/ARCHSURG.2010.132

Meyrignac, O., Lagarde, S., Bournet, B., Mokrane, F. Z., Buscail, L., Rousseau, H., & Otal, P. (2015). Acute Pancreatitis: Extrapancreatic Necrosis Volume as Early Predictor of Severity. *Radiology*, *276*(1), 119–128. https://doi.org/10.1148/radiol.15141494

Mier, J., Luque-De León, E., Castillo, A., Robledo, F., & Blanco, R. (1997). Early versus late necrosectomy in severe necrotizing pancreatitis. *The American Journal of Surgery*, *173*(2), 71–75. https://doi.org/10.1016/S0002-9610(96)00425-4

Miulescu, R., Balaban, D. V., Sandru, F., & Jinga, M. (2020). Cutaneous Manifestations in Pancreatic Diseases—A Review. *Journal of Clinical Medicine*, *9*(8), 1–11. https://doi.org/10.3390/JCM9082611

Mofidi, R., Duff, M. D., Wigmore, S. J., Madhavan, K. K., Garden, O. J., & Parks, R. W. (2006). Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *The British Journal of Surgery*, *93*(6), 738–744. https://doi.org/10.1002/BJS.5290

Mofidi, R., Lee, A. C., Madhavan, K. K., Garden, O. J., & Parks, R. W. (2007). Prognostic Factors in Patients Undergoing Surgery for Severe Necrotizing Pancreatitis. *World Journal of Surgery*, *31*(10), 2002–2007. https://doi.org/10.1007/s00268-007-9164-6

Mofidi, R., Suttie, S. A., Patil, P. v., Ogston, S., & Parks, R. W. (2009). The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: Systematic review. *Surgery*, *146*(1), 72–81. https://doi.org/10.1016/J.SURG.2009.02.013

Moggia, E., Koti, R., Belgaumkar, A. P., Fazio, F., Pereira, S. P., Davidson, B. R., & Gurusamy, K. S. (2017). Pharmacological interventions for acute pancreatitis. *The Cochrane Database of Systematic Reviews*, *4*(4). https://doi.org/10.1002/14651858.CD011384.PUB2

Mohamed, S. R., & Siriwardena, A. K. (2008). Understanding the colonic complications of pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *8*(2), 153–158. https://doi.org/10.1159/000123607

Montravers, P., Kantor, E., Constantin, J. M., Lefrant, J. Y., Lescot, T., Nesseler, N., Paugam, C., Jabaudon, M., & Dupont, H. (2019). Epidemiology and prognosis of anti-infective therapy in the ICU setting during acute pancreatitis: a cohort study. *Critical Care*, *23*(1), 1–15. https://doi.org/10.1186/S13054-019-2681-5/FIGURES/4

Moraes, J. M. M., Felga, G. E. G., Chebli, L. A., Franco, M. B., Gomes, C. A., Gaburri, P. D., Zanini, A., & Chebli, J. M. F. (2010). A Full Solid Diet as the Initial Meal in Mild Acute Pancreatitis is Safe and Result in a Shorter Length of Hospitalization: Results From a Prospective, Randomized, Controlled, Double-blind Clinical Trial. *Journal of Clinical Gastroenterology*, *44*(7). https://journals.lww.com/jcge/Fulltext/2010/08000/A_Full_Solid_Diet_as_the_Initial_Meal_in_Mild.17.aspx

Moran, R. A., Halloran, C., Guo, Q., Umapathy, C., Jalaly, N. Y., Jain, S., Cowzer, D., Cuadrado Robles, E. P., Quesada-Vázquez, N., Szentesi, A., Papp, M., Chua, T., Márta, K., Sampath, K., Jin, D. X., Sahebally, S. M., Kuschnereit, T. P., Khashab, M. A., Rock, C., … Singh, V. K. (2022). Early infection is an independent risk factor for increased mortality in patients with culture-confirmed

infected pancreatic necrosis. *Pancreatology*, *22*(1), 67–73. https://doi.org/10.1016/J.PAN.2021.11.003

Mouli, V. P., Sreenivas, V., & Garg, P. K. (2013). Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. *Gastroenterology*, *144*(2). https://doi.org/10.1053/J.GASTRO.2012.10.004

Mourad, N., Zhang, J., Rath, A. M., & Chevrel, J. P. (1994). The venous drainage of the pancreas. *Surgical and Radiologic Anatomy*, *16*, 37–45.

Müller, C. A., Uhl, W., Printzen, G., Gloor, B., Bischofberger, H., Tcholakov, O., & Büchler, M. W. (2000). Role of procalcitonin and granulocyte colony stimulating factor in the early prediction of infected necrosis in severe acute pancreatitis. *Gut*, *46*(2), 233–238. https://doi.org/10.1136/GUT.46.2.233

Nakajima, K. (2016). Low serum amylase and obesity, diabetes and metabolic syndrome: A novel interpretation. *World Journal of Diabetes*, *7*(6), 112–121. https://doi.org/10.4239/wjd.v7.i6.112

Nakanishi, N., Shimono, T., Yamamoto, A., & Miki, Y. (2016). CT evaluation and clinical factors predicting delayed colonic perforation following acute pancreatitis. *Japanese Journal of Radiology*, *34*(1), 10–15. https://doi.org/10.1007/S11604-015-0491-5

Nally, D. M., Kelly, E. G., Clarke, M., & Ridgway, P. (2014). Nasogastric nutrition is efficacious in severe acute pancreatitis: a systematic review and meta-analysis. *British Journal of Nutrition*, *112*(11), 1769–1778. https://doi.org/DOI: 10.1017/S0007114514002566

Nassar, T. I., & Qunibi, W. Y. (2019). AKI associated with acute pancreatitis. In *Clinical Journal of the American Society of Nephrology* (Vol. 14, Issue 7, pp. 1106–1115). American Society of Nephrology. https://doi.org/10.2215/CJN.13191118

Nikkola, A., Nikkola, J., Kari, E., Roponen, A., Tapaninaho, A., Sand, J., & Laukkarinen, J. (2020). The Incidence and etiology of Acute Pancreatitis in Finland have changed - a population-based study in 2014-2015. *Pancreatology*, *20*, S80. https://doi.org/10.1016/J.PAN.2020.07.122

Nikkola, J., Rinta-Kiikka, I., Räty, S., Laukkarinen, J., Lappalainen-Lehto, R., Järvinen, S., Seppänen, H., Nordback, I., & Sand, J. (2014). Pancreatic morphological changes in long-term follow-up after initial episode of acute alcoholic pancreatitis. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *18*(1), 164–170; discussion 170-1. https://doi.org/10.1007/s11605-013-2279-1

Nitsche, C., Maertin, S., Scheiber, J., Ritter, C. A., Lerch, M. M., & Mayerle, J. (2012). Drug-induced pancreatitis. *Current Gastroenterology Reports*, *14*(2), 131–138. https://doi.org/10.1007/S11894-012-0245-9/TABLES/2

Nordback, I., Pelli, H., Lappalainen-Lehto, R., Järvinen, S., Räty, S., & Sand, J. (2009). The Recurrence of Acute Alcohol-Associated Pancreatitis Can Be Reduced: A Randomized Controlled Trial. *Gastroenterology*, *136*(3), 848–855. https://doi.org/10.1053/J.GASTRO.2008.11.044

Nordback, I., Pelli, H., Lappalainen-Lehto, R., & Sand, J. (2009). Is it long-term continuous drinking or the post-drinking withdrawal period that triggers the first acute alcoholic pancreatitis? *Https://Doi.Org/10.1080/00365520510023413*, *40*(10), 1235–1239. https://doi.org/10.1080/00365520510023413

Nordback, I., Sand, J., Saaristo, R., & Paajanen, H. (2001). Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis--a single-center randomized study. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *5*(2), 113–119. https://doi.org/10.1016/S1091-255X(01)80021-4

Norman, J. G., Fink, G. W., Denham, W., Yang, J., Carter, G., Sexton, C., Falkner, J., Gower, W. R., & Franz, M. G. (1997). Tissue-specific cytokine production during experimental acute pancreatitis. A probable mechanism for distant organ dysfunction. *Digestive Diseases and Sciences*, *42*(8), 1783–1788. https://doi.org/10.1023/A:1018886120711

Nykänen, T., Udd, M., Peltola, E. K., Leppäniemi, A., & Kylänpää, L. (2017). Bleeding pancreatic pseudoaneurysms: management by angioembolization combined with therapeutic endoscopy. *Surgical Endoscopy*, *31*(2), 692–703. https://doi.org/10.1007/s00464-016-5023-6

O'Farrell, A., Allwright, S., Toomey, D., Bedford, D., & Conlon, K. (2007). Hospital admission for acute pancreatitis in the Irish population, 1997 2004: could the increase be due to an increase in alcohol-related pancreatitis? *Journal of Public Health (Oxford, England)*, *29*(4), 398–404. https://doi.org/10.1093/PUBMED/FDM069

Oría, A., Cimmino, D., Ocampo, C., Silva, W., Kohan, G., Zandalazini, H., Szelagowski, C., & Chiappetta, L. (2007). Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. *Annals of Surgery*, *245*(1), 10–17. https://doi.org/10.1097/01.sla.0000232539.88254.80

Pá Rniczky, A., Zs Kui, B., Szentesi, A., Balá Zs, A., & Kos Szűcs, A. ′. (2016). *Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis*. https://doi.org/10.1371/journal.pone.0165309

Padhan, R. K., Jain, S., Agarwal, S., Harikrishnan, S., Vadiraja, P., Behera, S., Jain, S. K., Dhingra, R., Dash, N. R., Sahni, P., & Garg, P. K. (2018). Primary and Secondary Organ Failures Cause Mortality Differentially in Acute Pancreatitis and Should be Distinguished. *Pancreas*, *47*(3), 302–307. https://doi.org/10.1097/MPA.0000000000000998

Pamies-Guilabert, J., del Val Antoñana, A., Collado, J. J., Rudenko, P., & Meseguer, A. (2020). Pancreatic necrosis volume – A new imaging biomarker of acute pancreatitis severity. *European Journal of Radiology*, *130*, 109193. https://doi.org/10.1016/j.ejrad.2020.109193

Paola, A., Rocha, C., Schawkat, · Khoschy, & Mortele, K. J. (2020). Imaging guidelines for acute pancreatitis: when and when not to image. *Abdominal Radiology*, *45*, 1338–1349. https://doi.org/10.1007/s00261-019-02319-2

Papachristou, G. I., Takahashi, N., Chahal, P., Sarr, M. G., & Baron, T. H. (2007). *Peroral Endoscopic Drainage/Debridement of Walled-off Pancreatic Necrosis*. https://doi.org/10.1097/01.sla.0000254366.19366.69

Parekh, D. (2006). Laparoscopic-assisted pancreatic necrosectomy: A new surgical option for treatment of severe necrotizing pancreatitis. *Archives of Surgery (Chicago, Ill. : 1960)*, *141*(9), 895–902. https://doi.org/10.1001/ARCHSURG.141.9.895

Parenti, D. M., Steinberg, W., & Kang, P. (1996). Infectious causes of acute pancreatitis. *Pancreas*, *13*(4), 356–371. https://doi.org/10.1097/00006676-199611000-00005

Párniczky, A., Kui, B., Szentesi, A., Balázs, A., Szűcs, Á., Mosztbacher, D., Czimmer, J., Sarlós, P., Bajor, J., Gódi, S., Vincze, Á., Illés, A., Szabó, I., Pár, G., Takács, T., Czakó, L., Szepes, Z., Rakonczay, Z., Izbéki, F., … Hegyi, P. (2016). Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis. *PLOS ONE*, *11*(10), e0165309. https://doi.org/10.1371/journal.pone.0165309

Partelli, S., Tamburrino, D., Andreasi, V., Mazzocato, S., Crippa, S., Perretti, E., Belfiori, G., Marmorale, C., Balzano, G., & Falconi, M. (2020). Implications of increased serum amylase after pancreaticoduodenectomy: toward a better definition of clinically relevant postoperative acute pancreatitis. *HPB : The Official Journal of the International Hepato Pancreato Biliary Association*, *22*(11), 1645–1653. https://doi.org/10.1016/J.HPB.2020.03.010

Pascual, I., Sabater, L., Añón, R., Calvete, J., Pacheco, G., Muñoz, E., Lizarraga, J., Sastre, J., Peña, A., Mora, F., Pérez-Griera, J., Ortega, J., & Benages, A. (2013). Surgical versus nonsurgical treatment of infected pancreatic necrosis: more arguments to change the paradigm. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *17*(9), 1627–1633. https://doi.org/10.1007/S11605-013-2266-6

Pederzoli, P., Bassi, C., Vesentini, S., & Campedelli, A. (1993). A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surgery, Gynecology & Obstetrics*, *176*(5), 480–483. https://europepmc.org/article/med/8480272

Peery, A. F., Crockett, S. D., Murphy, C. C., Lund, J. L., Dellon, E. S., Williams, J. L., Jensen, E. T., Shaheen, N. J., Barritt, A. S., Lieber, S. R., Kochar, B., Barnes, E. L., Fan, Y. C., Pate, V., Galanko, J., Baron, T. H., & Sandler, R. S. (2019). Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. *Gastroenterology*, *156*(1), 254-272.e11. https://doi.org/10.1053/J.GASTRO.2018.08.063

Pelli, H., Sand, J., Laippala, P., & Nordback, I. (2000). Long-term follow-up after the first episode of acute alcoholic pancreatitis: time course and risk factors for recurrence. *Scandinavian Journal of Gastroenterology*, *35*(5), 552–555. https://doi.org/10.1080/003655200750023840

Perez, A., Whang, E. E., Brooks, D. C., Moore, F. D., Hughes, M. D., Sica, G. T., Zinner, M. J., Ashley, S. W., & Banks, P. A. (2002). Is severity of necrotizing

pancreatitis increased in extended necrosis and infected necrosis? *Pancreas*, *25*(3), 229–233. https://doi.org/10.1097/00006676-200210000-00003

Petersson, U., Acosta, S., & Björck, M. (2007). Vacuum-assisted wound closure and mesh-mediated fascial traction - A novel technique for late closure of the open abdomen. *World Journal of Surgery*, *31*(11), 2133–2137. https://doi.org/10.1007/S00268-007-9222-0/TABLES/2

Petrov, M. S., Chong, V., & Windsor, J. A. (2011). Infected pancreatic necrosis: not necessarily a late event in acute pancreatitis. *World Journal of Gastroenterology*, *17*(27), 3173–3176. https://doi.org/10.3748/wjg.v17.i27.3173

Petrov, M. S., Shanbhag, S., Chakraborty, M., Phillips, A. R. J., & Windsor, J. A. (2010). Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology*, *139*(3), 813–820. https://doi.org/10.1053/J.GASTRO.2010.06.010

Petrov, M. S., van Santvoort, H. C., Besselink, M. G. H., van der Heijden, G. J. M. G., Windsor, J. A., & Gooszen, H. G. (2008). Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis: a meta-analysis of randomized trials. *Archives of Surgery (Chicago, Ill. : 1960)*, *143*(11), 1111–1117. https://doi.org/10.1001/ARCHSURG.143.11.1111

Phillip, V., Schuster, T., Hagemes, F., Lorenz, S., Matheis, U., Preinfalk, S., Lippl, F., Saugel, B., Schmid, R. M., & Huber, W. (2013). Time period from onset of pain to hospital admission and patients' awareness in acute pancreatitis. *Pancreas*, *42*(4), 647–654. https://doi.org/10.1097/MPA.0B013E3182714565

Qu, C., Yu, X., Duan, Z., Zhou, J., Mao, W., Wei, M., Cao, L., Zhang, J., Zhang, H., Ke, L., Tong, Z., & Li, W. (2021). Clinical characteristics and management of gastric outlet obstruction in acute pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *21*(1), 64–68. https://doi.org/10.1016/J.PAN.2020.11.010

Rainio, M., Lindström, O., Udd, M., Louhimo, J., & Kylänpää, L. (2017). Diclofenac Does Not Reduce the Risk of Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis in Low-Risk Units. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *21*(8), 1270–1277. https://doi.org/10.1007/S11605-017-3412-3

Rainio, M., Lindström, O., Udd, M., Puolakkainen, P., Stenman, U. H., & Kylänpää, L. (2021). Repeated Negative Urine Trypsinogen-2 Dipstick Test Rules out Diagnosis of Post-ERCP Pancreatitis. *Journal of Clinical Gastroenterology*, *55*(4), 361–366. https://doi.org/10.1097/MCG.0000000000001429

Ramsey, P. S., & Podratz, K. C. (1999). Acute pancreatitis after gynecologic and obstetric surgery. *American Journal of Obstetrics and Gynecology*, *181*(3), 542–546. https://doi.org/10.1016/S0002-9378(99)70490-4

Rana, S. S., Bhasin, D. K., Sharma, R. K., Kathiresan, J., & Gupta, R. (2014). Do the morphological features of walled off pancreatic necrosis on endoscopic ultrasound determine the outcome of endoscopic transmural drainage? *Endoscopic Ultrasound*, *3*(2), 118–122. https://doi.org/10.4103/2303-9027.131039

Rana, S. S., Sharma, V., Sharma, R. K., Chhabra, P., Gupta, R., & Bhasin, D. K. (2015). Clinical significance of presence and extent of extrapancreatic necrosis in acute pancreatitis. *Journal of Gastroenterology and Hepatology*, *30*(4), 794–798. https://doi.org/10.1111/JGH.12793

Ranson, J. H., Rifkind, K. M., Roses, D. F., Fink, S. D., Eng, K., & Spencer, F. C. (1974). Prognostic signs and the role of operative management in acute pancreatitis. *Surgery, Gynecology & Obstetrics*, *139*(1), 69–81.

Rao, K. N., Tuma, J., & Lombardi, B. (1976). Acute hemorrhagic pancreatic necrosis in mice. Intraparenchymal activation of zymogens, and other enzyme changes in pancreas and serum. *Gastroenterology*, *70*(5 PT.1), 720–726.

Raraty, M. G. T., Halloran, C. M., Dodd, S., Ghaneh, P., Connor, S., Evans, J., Sutton, R., & Neoptolemos, J. P. (2010). Minimal access retroperitoneal pancreatic necrosectomy: Improvement in morbidity and mortality with a less invasive approach. *Annals of Surgery*, *251*(5), 787–793. https://doi.org/10.1097/SLA.0B013E3181D96C53

Rasilainen, S. K., Mentula, P. J., & Leppäniemi, A. K. (2012). Vacuum and mesh-mediated fascial traction for primary closure of the open abdomen in critically ill surgical patients. *British Journal of Surgery*, *99*(12), 1725–1732. https://doi.org/10.1002/BJS.8914

Räty, S., Pulkkinen, J., Nordback, I., Sand, J., Victorzon, M., Grönroos, J., Helminen, H., Kuusanmäki, P., Nordström, P., & Paajanen, H. (2015). Can laparoscopic cholecystectomy prevent recurrent idiopathic acute pancreatitis? *Annals of Surgery*, *262*(5), 736–741. https://doi.org/10.1097/SLA.0000000000001469

Räty, S., Sand, J., Lantto, E., & Nordback, I. (2006). Postoperative acute pancreatitis as a major determinant of postoperative delayed gastric emptying after pancreaticoduodenectomy. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *10*(8), 1131–1139. https://doi.org/10.1016/J.GASSUR.2006.05.012

Räty, S., Sand, J., & Nordback, I. (2007). Detection of postoperative pancreatitis after pancreatic surgery by urine trypsinogen strip test. *The British Journal of Surgery*, *94*(1), 64–69. https://doi.org/10.1002/BJS.5572

Rau, B. M., Bothe, A., Kron, M., & Beger, H. G. (2006). Role of Early Multisystem Organ Failure as Major Risk Factor for Pancreatic Infections and Death in Severe Acute Pancreatitis. *Clinical Gastroenterology and Hepatology*, *4*(8), 1053–1061. https://doi.org/https://doi.org/10.1016/j.cgh.2006.05.030

Rau, B., Pralle, U., Mayer, J. M., & Beger, H. G. (2003). Role of ultrasonographically guided fine-needle aspiration cytology in the diagnosis of infected pancreatic necrosis. *British Journal of Surgery*, *85*(2), 179–184. https://doi.org/10.1046/J.1365-2168.1998.00707.X

Rawla, P., Bandaru, S. S., & Vellipuram, A. R. (2017). Review of Infectious Etiology of Acute Pancreatitis. *Gastroenterology Research*, *10*(3), 153. https://doi.org/10.14740/GR858W

Reichling, C., Nobile, L., Pezzullo, M., Navez, J., Bachir, N., D'Haene, N., Maris, C., Musala, C., Fernandez Y. Viesca, M., Grimaldi, D., & Delhaye, M. (2020). Non-occlusive Mesenteric Ischemia as a Fatal Complication in Acute Pancreatitis: A

Case Series. *Digestive Diseases and Sciences*, *65*(4), 1212–1222. https://doi.org/10.1007/S10620-019-05835-9

Reilly, L. M., Ramos, T. K., Murray, S. P., Cheng, S. W. K., & Stoney, R. J. (1994). Optimal exposure of the proximal abdominal aorta: A critical appraisal of transabdominal medial visceral rotation. *Journal of Vascular Surgery*, *19*(3), 375–390. https://doi.org/10.1016/S0741-5214(94)70065-6

Ren, Z., Yang, F., Wang, X., Wang, Y., Xu, M., Frank, J. A., Ke, Z. ji, Zhang, Z., Shi, X., & Luo, J. (2016). Chronic plus binge ethanol exposure causes more severe pancreatic injury and inflammation. *Toxicology and Applied Pharmacology*, *308*, 11–19. https://doi.org/10.1016/J.TAAP.2016.08.012

Robbins, A. J., Lusczek, E., Bellin, M. D., Benner, A., Alwan, F. S., & Beilman, G. J. (2021). Thromboembolic Complications in the First Year After Acute Pancreatitis Diagnosis. *Pancreas*, *50*(5), 751. https://doi.org/10.1097/MPA.0000000000001827

Roberts, S. E., Akbari, A., Thorne, K., Atkinson, M., & Evans, P. A. (2013). The incidence of acute pancreatitis: impact of social deprivation, alcohol consumption, seasonal and demographic factors. *Alimentary Pharmacology & Therapeutics*, *38*(5), 539. https://doi.org/10.1111/APT.12408

Roberts, S. E., Morrison-Rees, S., John, A., Williams, J. G., Brown, T. H., & Samuel, D. G. (2017). The incidence and aetiology of acute pancreatitis across Europe. *Pancreatology*, *17*(2), 155–165. https://doi.org/10.1016/J.PAN.2017.01.005

Roch, A. M., Maatman, T. K., Carr, R. A., Colgate, C. L., Ceppa, E. P., House, M. G., Lopes, J., Nakeeb, A., Schmidt, C. M., & Zyromski, N. J. (2019). Venous Thromboembolism in Necrotizing Pancreatitis: an Underappreciated Risk. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *23*(12), 2430–2438. https://doi.org/10.1007/S11605-019-04124-0

Rodriguez, J. R., Razo, A. O., Targarona, J., Thayer, S. P., Rattner, D. W., Warshaw, A. L., & Fernández-Del Castillo, C. (2008). Debridement and Closed Packing for Sterile or Infected Necrotizing Pancreatitis: Insights into Indications and Outcomes in 167 Patients. *Annals of Surgery*, *247*(2), 294. https://doi.org/10.1097/SLA.0B013E31815B6976

Røkke, O., Harbitz, T. B., Liljedal, J., Pettersen, T., Fetvedt, T., Heen, L. Ø., Skreden, K., & Viste, A. (2007). Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. *Scandinavian Journal of Gastroenterology*, *42*(6), 771–776. https://doi.org/10.1080/00365520601173855

Rompianesi, G., Hann, A., Komolafe, O., Pereira, S. P., Davidson, B. R., & Gurusamy, K. S. (2017). Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis. In *Cochrane Database of Systematic Reviews* (Vol. 2017, Issue 4). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD012010.pub2

Ros, E., Navarro, S., Bru, C., Garcia-Pugés, A., & Valderrama, R. (1991). Occult microlithiasis in "idiopathic" acute pancreatitis: prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. *Gastroenterology*, *101*(6), 1701–1709. https://doi.org/10.1016/0016-5085(91)90410-m

Runkel, N. S. F., Moody, F. G., Smith, G. S., Rodriguez, L. F., LaRocco, M. T., & Miller, T. A. (1991). The role of the gut in the development of sepsis in acute pancreatitis. *Journal of Surgical Research*, *51*(1), 18–23. https://doi.org/10.1016/0022-4804(91)90064-S

Runzi, M., Niebel, W., Goebell, H., Gerken, G., & Layer, P. (2005). Severe acute pancreatitis: nonsurgical treatment of infected necroses. *Pancreas*, *30*(3), 195–199. https://doi.org/10.1097/01.MPA.0000153613.17643.B3

Sadr Azodi, O., Orsini, N., Andrén-Sandberg, Å., & Wolk, A. (2011). Effect of type of alcoholic beverage in causing acute pancreatitis. *British Journal of Surgery*, *98*(11), 1609–1616. https://doi.org/10.1002/BJS.7632

Sainio, V., Kemppainen, E., Puolakkainen, P., Haapiainen, R., Schröder, T., Kivilaakso, E., Valtonen, V., Taavitsainen, M., & Kivisaarl, L. (1995). Early antibiotic treatment in acute necrotising pancreatitis. *The Lancet*, *346*(8976), 663–667. https://doi.org/10.1016/S0140-6736(95)92280-6

Sakorafas, G. H., Tsiotos, G. G., & Sarr, M. G. (1999a). Experience with Duodenal Necrosis A Rare Complication of Acute Necrotizing Pancreatitis. In *International Journal of Pancreatology* (Vol. 25, Issue 2).

Sakorafas, G. H., Tsiotos, G. G., & Sarr, M. G. (1999b). Extrapancreatic necrotizing pancreatitis with viable pancreas: a previously under-appreciated entity. *Journal of the American College of Surgeons*, *188*(6), 643–648. https://doi.org/10.1016/S1072-7515(99)00045-9

Sakorafas, G. H., & Tsiotou, A. G. (2000). Etiology and pathogenesis of acute pancreatitis: Current concepts. *Journal of Clinical Gastroenterology*, *30*(4), 343–356. https://doi.org/10.1097/00004836-200006000-00002

Saluja, A. K., Bhagat, L., Lee, H. S., Bhatia, M., Frossard, J. L., & Steer, M. L. (1999). Secretagogue-induced digestive enzyme activation and cell injury in rat pancreatic acini. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *276*(4 39-4). https://doi.org/10.1152/AJPGI.1999.276.4.G835/ASSET/IMAGES/LARGE/AGIJ30328007X.JPEG

Sand, J., Välikoski, A., & Nordback, I. (2009). Epidemiology: Alcohol consumption in the country and hospitalizations for acute alcohol pancreatitis and liver cirrhosis during a 20-year period. *Alcohol and Alcoholism*, *44*(3), 321–325. https://doi.org/10.1093/alcalc/agn121

Sandrasegaran, K., Tann, M., Jennings, S. G., Maglinte, D. D., Peter, S. D., Sherman, S., & Howard, T. J. (2007). Disconnection of the Pancreatic Duct: An Important But Overlooked Complication of Severe Acute Pancreatitis. *RadioGraphics*, *27*(5), 1389–1400. https://doi.org/10.1148/rg.275065163

Sarathi Patra, P., Das, K., Bhattacharyya, A., Ray, S., Hembram, J., Sanyal, S., & Dhali, G. K. (2014). Natural resolution or intervention for fluid collections in acute severe pancreatitis. *The British Journal of Surgery*, *101*(13), 1721–1728. https://doi.org/10.1002/BJS.9666

Sarles, H. (2010). The Exocrine Pancreas. *International Review of Physiology*, *12*, 173–221. https://doi.org/10.4199/C00026ED1V01Y201102ISP014

Sarri, G., Guo, Y., Iheanacho, I., & Puelles, J. (2019). Moderately severe and severe acute pancreatitis : a systematic review of the outcomes in the USA and European Union-5. *BMJ Open Gastroenterology*, *6*(1). https://doi.org/10.1136/BMJGAST-2018-000248

Schepers, N. J., Bakker, O. J., Besselink, M. G., Ahmed Ali, U., Bollen, T. L., Gooszen, H. G., van Santvoort, H. C., & Bruno, M. J. (2019). Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. *Gut*, *68*(6), 1044–1051. https://doi.org/10.1136/GUTJNL-2017-314657

Schepers, N. J., Hallensleben, N. D. L., Besselink, M. G., Anten, M. P. G. F., Bollen, T. L., da Costa, D. W., van Delft, F., van Dijk, S. M., van Dullemen, H. M., Dijkgraaf, M. G. W., van Eijck, C. H. J., Erkelens, G. W., Erler, N. S., Fockens, P., van Geenen, E. J. M., van Grinsven, J., Hollemans, R. A., van Hooft, J. E., van der Hulst, R. W. M., … Bruno, M. J. (2020). Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. *Lancet (London, England)*, *396*(10245), 167–176. https://doi.org/10.1016/S0140-6736(20)30539-0

Schiffl, H. (2006). Renal recovery from acute tubular necrosis requiring renal replacement therapy: a prospective study in critically ill patients. *Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *21*(5), 1248–1252. https://doi.org/10.1093/ndt/gfk069

Schmid, S. W., Uhl, W., Friess, H., Malfertheiner, P., & Büchler, M. W. (1999). The role of infection in acute pancreatitis. *Gut*, *45*(2), 311–316. https://doi.org/10.1136/GUT.45.2.311

Schwarz, M., Isenmann, R., Meyer, H., & Beger, H. G. (1997). [Antibiotic use in necrotizing pancreatitis. Results of a controlled study]. *Deutsche Medizinische Wochenschrift (1946)*, *122*(12), 356–361. https://doi.org/10.1055/S-2008-1047621

Seifert, H., Biermer, M., Schmitt, W., Jurgensen, C., Will, U., Gerlach, R., Kreitmair, C., Meining, A., Wehrmann, T., & Rosch, T. (2009). Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD Study). *Gut*, *58*(9), 1260–1266. https://doi.org/10.1136/gut.2008.163733

Seifert, H., Wehrmann, T., Schmitt, T., Zeuzem, S., & Caspary, W. F. (2000). Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. *The Lancet*, *356*(9230), 653–655. https://doi.org/10.1016/S0140-6736(00)02611-8

Senapati, D., Debata, P. K., Jenasamant, S. S., Nayak, A. K., Gowda S., M., & Swain, N. N. (2014). A prospective study of the Bedside Index for Severity in Acute Pancreatitis (BISAP) score in acute pancreatitis: An Indian perspective. *Pancreatology*, *14*(5), 335–339. https://doi.org/10.1016/J.PAN.2014.07.007

Sharbidre, K. G., Galgano, S. J., & Morgan, D. E. (2020). Traumatic pancreatitis. *Abdominal Radiology*, *45*(5), 1265–1276. https://doi.org/10.1007/S00261-019-02241-7/FIGURES/15

Sharma, P. K., Madan, K., & Garg, P. K. (2008). Hemorrhage in acute pancreatitis: should gastrointestinal bleeding be considered an organ failure? *Pancreas*, *36*(2), 141–145. https://doi.org/10.1097/MPA.0b013e318158466e

Shen, H. N., Lu, C. L., & Li, C. Y. (2012). Epidemiology of first-attack acute pancreatitis in Taiwan from 2000 through 2009: a nationwide population-based study. *Pancreas*, *41*(5), 696–702. https://doi.org/10.1097/MPA.0B013E31823DB941

Shen, Q. X., Xu, G. X., & Shen, M. H. (2017). Effect of early enteral nutrition (EN) on endotoxin in serum and intestinal permeability in patients with severe acute pancreatitis. *EUROPEAN REVIEW FOR MEDICAL AND PHARMACOLOGICAL SCIENCES*, *21*(11), 2764–2768.

Shi, N., Liu, T., de la Iglesia-Garcia, D., Deng, L., Jin, T., Lan, L., Zhu, P., Hu, W., Zhou, Z., Singh, V., Dominguez-Munoz, J. E., Windsor, J., Huang, W., Xia, Q., & Sutton, R. (2020). Duration of organ failure impacts mortality in acute pancreatitis. *Gut*, *69*(3), 604–605. https://doi.org/10.1136/gutjnl-2019-318241

Shimosegawa, T., Ueda, T., Kuroda, Y., Takeyama, Y., Yasuda, T., Matsumura, N., Sawa, H., Nakajima, T., Sakagami, J., Kataoka, K., Kashima, K., & Otsuki, M. (2006). LONG-TERM OUTCOME OF ACUTE PANCREATITIS. *Pancreas*, *33*(1). https://journals.lww.com/pancreasjournal/Fulltext/2006/07000/LONG_TERM_OUTCOME_OF_ACUTE_PANCREATITIS.19.aspx

Simo, K. A., Niemeyer, D. J., Swan, R. Z., Sindram, D., Martinie, J. B., & Iannitti, D. A. (2014). Laparoscopic transgastric endolumenal cystogastrostomy and pancreatic debridement. *Surgical Endoscopy*, *28*(5), 1465–1472. https://doi.org/10.1007/s00464-013-3317-5

Singh, N., Sharma, B., Sharma, M., Sachdev, V., Bhardwaj, P., Mani, K., Joshi, Y. K., & Saraya, A. (2012). Evaluation of Early Enteral Feeding Through Nasogastric and Nasojejunal Tube in Severe Acute Pancreatitis: A Noninferiority Randomized Controlled Trial. *Pancreas*, *41*(1). https://journals.lww.com/pancreasjournal/Fulltext/2012/01000/Evaluation_of_Early_Enteral_Feeding_Through.21.aspx

Singh, V. K., Bollen, T. L., Wu, B. U., Repas, K., Maurer, R., Yu, S., Mortele, K. J., Conwell, D. L., & Banks, P. A. (2011). An assessment of the severity of interstitial pancreatitis. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *9*(12), 1098–1103. https://doi.org/10.1016/J.CGH.2011.08.026

Singh, V. K., Wu, B. U., Bollen, T. L., Repas, K., Maurer, R., Johannes, R. S., Mortele, K. J., Conwell, D. L., & Banks, P. A. (2009). A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. *The American Journal of Gastroenterology*, *104*(4), 966–971. https://doi.org/10.1038/ajg.2009.28

Singh, V. K., Wu, B. U., Bollen, T. L., Repas, K., Maurer, R., Mortele, K. J., & Banks, P. A. (2009). Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. *Clinical Gastroenterology and Hepatology : The*

Official Clinical Practice Journal of the American Gastroenterological Association, *7*(11), 1247–1251. https://doi.org/10.1016/J.CGH.2009.08.012

Skouras, C., Hayes, A. J., Williams, L., Garden, O. J., Parks, R. W., & Mole, D. J. (2014). Early organ dysfunction affects long-term survival in acute pancreatitis patients. *HPB : The Official Journal of the International Hepato Pancreato Biliary Association*, *16*(9), 789. https://doi.org/10.1111/HPB.12259

Slack, J. M. W. (1995). Developmental biology of the pancreas. *Development*, *121*(6), 1569–1580. https://doi.org/10.1242/DEV.121.6.1569

Smit, M., Buddingh, K. T., Bosma, B., Nieuwenhuijs, V. B., Hofker, H. S., & Zijlstra, J. G. (2016). Abdominal Compartment Syndrome and Intra-abdominal Ischemia in Patients with Severe Acute Pancreatitis. *World Journal of Surgery*, *40*(6), 1454–1461. https://doi.org/10.1007/S00268-015-3388-7/TABLES/4

Somani, P., Sunkara, T., & Sharma, M. (2017). Role of endoscopic ultrasound in idiopathic pancreatitis. *World Journal of Gastroenterology*, *23*(38), 6952. https://doi.org/10.3748/WJG.V23.I38.6952

Soran, A., Chelluri, L., Lee, K. K., & Tisherman, S. A. (2000). Outcome and quality of life of patients with acute pancreatitis requiring intensive care. *The Journal of Surgical Research*, *91*(1), 89–94. https://doi.org/10.1006/jsre.2000.5925

Sternby, H., Bolado, F., Canaval-Zuleta, H. J., Marra-López, C., Hernando-Alonso, A. I., Del-Val-Antoñana, A., García-Rayado, G., Rivera-Irigoin, R., Grau-García, F. J., Oms, L., Millastre-Bocos, J., Pascual-Moreno, I., Martínez-Ares, D., Rodríguez-Oballe, J. A., López-Serrano, A., Ruiz-Rebollo, M. L., Viejo-Almanzor, A., González-De-La-Higuera, B., Orive-Calzada, A., … De-Madaria, E. (2019). Determinants of Severity in Acute Pancreatitis: A Nation-wide Multicenter Prospective Cohort Study. *Annals of Surgery*, *270*(2), 348–355. https://doi.org/10.1097/SLA.0000000000002766

Sternby, H., Hartman, H., Johansen, D., Thorlacius, H., & Regnér, S. (2017). IL-6 and CRP are superior in early differentiation between mild and non-mild acute pancreatitis. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *17*(4), 550–554. https://doi.org/10.1016/J.PAN.2017.05.392

Stigliano, S., Sternby, H., de Madaria, E., Capurso, G., & Petrov, M. S. (2017). Early management of acute pancreatitis: A review of the best evidence. *Digestive and Liver Disease*, *49*(6), 585–594. https://doi.org/10.1016/J.DLD.2017.01.168

Strömberg, C., Johansson, G., & Adolfsson, A. (2007). Acute abdominal pain: diagnostic impact of immediate CT scanning. *World Journal of Surgery*, *31*(12), 2347–2354. https://doi.org/10.1007/S00268-007-9233-X

Sugimoto, M., Sonntag, D. P., Flint, G. S., Boyce, C. J., Kirkham, J. C., Harris, T. J., Carr, S. M., Nelson, B. D., Bell, D. A., Barton, J. G., & Traverso, L. W. (2018). Biliary Stenosis and Gastric Outlet Obstruction: Late Complications After Acute Pancreatitis With Pancreatic Duct Disruption. *Pancreas*, *47*(6), 772–777. https://doi.org/10.1097/MPA.0000000000001064

Talukdar, R., Ingale, P., Choudhury, H. P., Dhingra, R., Shetty, S., Joshi, H., Pradeep, K. R., Mahapatra, L., Mazumder, S., Pradeep, J. K., Thakker, B., Chaudhary, A., Kumar, A., Reddy, D. N., Rao, G. v., Ramesh, H., Bhat, N., Garg, P., & Kochhar,

R. (2014). Antibiotic use in acute pancreatitis: An Indian multicenter observational study. *Indian Journal of Gastroenterology*, *33*(5), 458–465. https://doi.org/10.1007/S12664-014-0494-7/TABLES/5

Tao, H. Q., Zhang, J. X., & Zou, S. C. (2004). Clinical characteristics and management of patients with early acute severe pancreatitis: experience from a medical center in China. *World Journal of Gastroenterology*, *10*(6), 919–921. https://doi.org/10.3748/WJG.V10.I6.919

Teng, T. Z. J., Tan, J. K. T., Baey, S., Gunasekaran, S. K., Junnarkar, S. P., Low, J. K., Huey, C. W. T., & Shelat, V. G. (2021). Sequential organ failure assessment score is superior to other prognostic indices in acute pancreatitis. *World Journal of Critical Care Medicine*, *10*(6), 355–368. https://doi.org/10.5492/wjccm.v10.i6.355

Tenner, S., Baillie, J., Dewitt, J., & Vege, S. S. (2013). American College of Gastroenterology guideline: management of acute pancreatitis. *The American Journal of Gastroenterology*, *108*(9), 1400–1415. https://doi.org/10.1038/AJG.2013.218

Tenner, S., Dubner, H., & Steinberg, W. (1994). Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. *The American Journal of Gastroenterology*.

Thandassery, R. B., Yadav, T. D., Dutta, U., Appasani, S., Singh, K., & Kochhar, R. (2013). Dynamic nature of organ failure in severe acute pancreatitis: the impact of persistent and deteriorating organ failure. *HPB*, *15*(7), 523–528. https://doi.org/10.1111/J.1477-2574.2012.00613.X

Tran, A., Fernando, S. M., Rochwerg, B., Inaba, K., Bertens, K. A., Engels, P. T., Balaa, F. K., Kubelik, D., Matar, M., Lenet, T. I., & Martel, G. (2022). Prognostic factors associated with development of infected necrosis in patients with acute necrotizing or severe pancreatitis - A systematic review and meta-analysis. *Journal of Trauma and Acute Care Surgery*, *92*(5), 940–948. https://doi.org/10.1097/TA.0000000000003502

Trompeter, M., Brazda, T., Remy, C. T., Vestring, T., & Reimer, P. (2001). Non-occlusive mesenteric ischemia: etiology, diagnosis, and interventional therapy. *European Radiology 2001 12:5*, *12*(5), 1179–1187. https://doi.org/10.1007/S00330-001-1220-2

Tsai, K., Wang, S. S., Chen, T. S., Kong, C. W., Chang, F. Y., Lee, S. D., & Lu, F. J. (1998). Oxidative stress: an important phenomenon with pathogenetic significance in the progression of acute pancreatitis. *Gut*, *42*(6), 850–855. https://doi.org/10.1136/GUT.42.6.850

Tse, F., & Yuan, Y. (2012). Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database of Systematic Reviews*, *5*. https://doi.org/10.1002/14651858.CD009779.PUB2/INFORMATION/EN

Tu, Y., Jiao, H., Tan, X., Sun, L., & Zhang, W. (2013). Laparotomy versus retroperitoneal laparoscopy in debridement and drainage of retroperitoneal

infected necrosis in severe acute pancreatitis. *Surgical Endoscopy*, *27*(11), 4217–4223. https://doi.org/10.1007/S00464-013-3026-0

Uchino, S., Kellum, J. A., Bellomo, R., Doig, G. S., Morimatsu, H., Morgera, S., Schetz, M., Tan, I., Bouman, C., Macedo, E., Gibney, N., Tolwani, A., Ronco, C., & Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. (2005). Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*, *294*(7), 813–818. https://doi.org/10.1001/jama.294.7.813

Udd, M., Leppäniemi, A. K., Bidel, S., Keto, P., Roth, W.-D., & Haapiainen, R. K. (2007). Treatment of bleeding pseudoaneurysms in patients with chronic pancreatitis. *World Journal of Surgery*, *31*(3), 504–510. https://doi.org/10.1007/s00268-006-0209-z

Valeriani, E., Riva, N., di Nisio, M., & Ageno, W. (2019). Splanchnic Vein Thrombosis: Current Perspectives. *Vascular Health and Risk Management*, *15*, 449. https://doi.org/10.2147/VHRM.S197732

van Baal, M. C., Bollen, T. L., Bakker, O. J., van Goor, H., Boermeester, M. A., Dejong, C. H., Gooszen, H. G., van der Harst, E., van Eijck, C. H., van Santvoort, H. C., & Besselink, M. G. (2014). The role of routine fine-needle aspiration in the diagnosis of infected necrotizing pancreatitis. *Surgery*, *155*(3), 442–448. https://doi.org/10.1016/J.SURG.2013.10.001

van Baal, M. C., van Santvoort, H. C., Bollen, T. L., Bakker, O. J., Besselink, M. G., & Gooszen, H. G. (2011). Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. *The British Journal of Surgery*, *98*(1), 18–27. https://doi.org/10.1002/BJS.7304

van Brunschot, S., Besselink, M. G., Bakker, O. J., Boermeester, M. A., Gooszen, H. G., Horvath, K. D., & van Santvoort, H. C. (2013). Video-Assisted Retroperitoneal Debridement (VARD) of Infected Necrotizing Pancreatitis: An Update. *Current Surgery Reports*, *1*(2), 121–130. https://doi.org/10.1007/s40137-013-0015-0

van Brunschot, S., Fockens, P., Bakker, O. J., Besselink, M. G., Voermans, R. P., Poley, J.-W., Gooszen, H. G., Bruno, M., & van Santvoort, H. C. (2014). Endoscopic transluminal necrosectomy in necrotising pancreatitis: a systematic review. *Surgical Endoscopy*, *28*(5), 1425–1438. https://doi.org/10.1007/s00464-013-3382-9

van Brunschot, S., Hollemans, R. A., Bakker, O. J., Besselink, M. G., Baron, T. H., Beger, H. G., Boermeester, M. A., Bollen, T. L., Bruno, M. J., Carter, R., French, J. J., Coelho, D., Dahl, B., Dijkgraaf, M. G., Doctor, N., Fagenholz, P. J., Farkas, G., Castillo, C. F. del, Fockens, P., … van Santvoort, H. C. (2018). Minimally invasive and endoscopic versus open necrosectomy for necrotising pancreatitis: a pooled analysis of individual data for 1980 patients. *Gut*, *67*(4), 697–706. https://doi.org/10.1136/gutjnl-2016-313341

van Brunschot, S., Schut, A. J., Bouwense, S. A., Besselink, M. G., Bakker, O. J., van Goor, H., Hofker, S., Gooszen, H. G., Boermeester, M. A., & van Santvoort, H. C. (2014). Abdominal compartment syndrome in acute pancreatitis: a systematic

review. *Pancreas*, *43*(5), 665–674. https://doi.org/10.1097/MPA.0000000000000108

van Brunschot, S., van Grinsven, J., van Santvoort, H. C., Bakker, O. J., Besselink, M. G., Boermeester, M. A., Bollen, T. L., Bosscha, K., Bouwense, S. A., Bruno, M. J., Cappendijk, V. C., Consten, E. C., Dejong, C. H., van Eijck, C. H., Erkelens, W. G., van Goor, H., van Grevenstein, W. M. U., Haveman, J. W., Hofker, S. H., … Schoon, E. J. (2018). Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. *The Lancet*, *391*(10115), 51–58. https://doi.org/10.1016/S0140-6736(17)32404-2

van Damme, L., & de Waele, J. J. (2018). Effect of decompressive laparotomy on organ function in patients with abdominal compartment syndrome: A systematic review and meta-analysis. *Critical Care*, *22*(1), 1–11. https://doi.org/10.1186/S13054-018-2103-0/TABLES/5

van Grinsven, J., van Brunschot, S., van Baal, M. C., Besselink, M. G., Fockens, P., van Goor, H., van Santvoort, H. C., & Bollen, T. L. (2018). Natural History of Gas Configurations and Encapsulation in Necrotic Collections During Necrotizing Pancreatitis. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *22*(9), 1557–1564. https://doi.org/10.1007/S11605-018-3792-Z

van Minnen, L. P., Besselink, M. G. H., Bosscha, K., van Leeuwen, M. S., Schipper, M. E. I., & Gooszen, H. G. (2004). Colonic Involvement in Acute Pancreatitis A Retrospective Study of 16 Patients. *Dig Surg*, *21*, 33–40. https://doi.org/10.1159/000075824

van Santvoort, H. C., Bakker, O. J., Bollen, T. L., Besselink, M. G., Ahmed Ali, U., Schrijver, A. M., Boermeester, M. A., van Goor, H., Dejong, C. H., van Eijck, C. H., van Ramshorst, B., Schaapherder, A. F., van der Harst, E., Hofker, S., Nieuwenhuijs, V. B., Brink, M. A., Kruyt, P. M., Manusama, E. R., van der Schelling, G. P., … Gooszen, H. G. (2011). A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*, *141*(4), 1254–1263. https://doi.org/10.1053/J.GASTRO.2011.06.073

van Santvoort, H. C., Besselink, M. G., Bakker, O. J., Hofker, H. S., Boermeester, M. A., Dejong, C. H., van Goor, H., Schaapherder, A. F., van Eijck, C. H., Bollen, T. L., van Ramshorst, B., Nieuwenhuijs, V. B., Timmer, R., Laméris, J. S., Kruyt, P. M., Manusama, E. R., van der Harst, E., van der Schelling, G. P., Karsten, T., … Gooszen, H. G. (2010). A step-up approach or open necrosectomy for necrotizing pancreatitis. *The New England Journal of Medicine*, *362*(16), 1491–1502. https://doi.org/10.1056/NEJMOA0908821

van Santvoort, H. C., Besselink, M. G. H., Horvath, K. D., Sinanan, M. N., Bollen, T. L., van Ramshorst, B., & Gooszen, H. G. (2007). Videoscopic assisted retroperitoneal debridement in infected necrotizing pancreatitis. *HPB*, *9*(2), 156–159. https://doi.org/10.1080/13651820701225688

Vila, J. J. (2010). Endoscopic ultrasonography and idiopathic acute pancreatitis. *World Journal of Gastrointestinal Endoscopy*, *2*(4), 107–111. https://doi.org/10.4253/wjge.v2.i4.107

Villatoro, E., Mulla, M., & Larvin, M. (2010). Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *The Cochrane Database of Systematic Reviews*, *2010*(5). https://doi.org/10.1002/14651858.CD002941.PUB3

Vincent, J. L., Moreno, R., Takala, J., Willatts, S., de Mendonça, A., Bruining, H., Reinhart, C. K., Suter, P. M., & Thijs, L. G. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine 1996 22:7*, *22*(7), 707–710. https://doi.org/10.1007/BF01709751

Vissers, R. J., Abu-Laban, R. B., & McHugh, D. F. (1999). Amylase and lipase in the emergency department evaluation of acute pancreatitis 1. *Journal of Emergency Medicine*, *17*(6), 1027–1037. https://doi.org/10.1016/S0736-4679(99)00136-5

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., & STROBE Initiative. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology (Cambridge, Mass.)*, *18*(6), 800–804. https://doi.org/10.1097/EDE.0b013e3181577654

Wang, G. J., Gao, C. F., Wei, D., Wang, C., & Ding, S. Q. (2009). Acute pancreatitis: Etiology and common pathogenesis. *World Journal of Gastroenterology : WJG*, *15*(12), 1427. https://doi.org/10.3748/WJG.15.1427

Wei, A. L., Guo, Q., Wang, M. J., Hu, W. M., & Zhang, Z. da. (2016). Early complications after interventions in patients with acute pancreatitis. *World Journal of Gastroenterology*, *22*(9), 2828–2836. https://doi.org/10.3748/WJG.V22.I9.2828

Werner, J., Hartwig, W., Hackert, T., & Büchler, M. W. (2005). Surgery in the treatment of acute pancreatitis--open pancreatic necrosectomy. *Scandinavian Journal of Surgery : SJS : Official Organ for the Finnish Surgical Society and the Scandinavian Surgical Society*, *94*(2), 130–134. https://doi.org/10.1177/145749690509400209

Werner, J., Saghir, M., Fernandez-Del Castillo, C., Warshaw, A. L., & Laposata, M. (2001). Linkage of oxidative and nonoxidative ethanol metabolism in the pancreas and toxicity of nonoxidative ethanol metabolites for pancreatic acinar cells. *Surgery*, *129*(6), 736–744. https://doi.org/10.1067/MSY.2001.113891

Wilson, J. S., Bernstein, L., McDonald, C., Tait, A., McNeil, D., & Pirola, R. C. (1985). Diet and drinking habits in relation to the development of alcoholic pancreatitis. *Gut*, *26*(9), 882–887. https://doi.org/10.1136/GUT.26.9.882

Windsor, A. C. J., Kanwar, S., Li, A. G. K., Barnes, E., Guthrie, J. A., Spark, J. I., Welsh, F., Guillou, P. J., & Reynolds, J. v. (1998). Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut*, *42*(3), 431–435. https://doi.org/10.1136/GUT.42.3.431

Wittau, M., Mayer, B., Scheele, J., Henne-Bruns, D., Dellinger, E. P., & Isenmann, R. (2011). Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scandinavian Journal of Gastroenterology*, *46*(3), 261–270. https://doi.org/10.3109/00365521.2010.531486/SUPPL_FILE/IGAS_A_531486_SM0001.DOC

Wolbrink, D. R. J., Kolwijck, E., ten Oever, J., Horvath, K. D., Bouwense, S. A. W., & Schouten, J. A. (2020). Management of infected pancreatic necrosis in the intensive care unit: a narrative review. *Clinical Microbiology and Infection*, *26*(1), 18–25. https://doi.org/10.1016/J.CMI.2019.06.017/ATTACHMENT/37D61F03-8B31-4313-95A5-675743C5463D/MMC1.DOCX

Wu, B. U., Hwang, J. Q., Gardner, T. H., Repas, K., Delee, R., Yu, S., Smith, B., Banks, P. A., & Conwell, D. L. (2011). Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *9*(8). https://doi.org/10.1016/J.CGH.2011.04.026

Wu, B. U., Johannes, R. S., Sun, X., Tabak, Y., Conwell, D. L., & Banks, P. A. (2008). The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut*, *57*(12), 1698–1703. https://doi.org/10.1136/GUT.2008.152702

Wu, L. M., Sankaran, S. J., Plank, L. D., Windsor, J. A., & Petrov, M. S. (2014). Meta-analysis of gut barrier dysfunction in patients with acute pancreatitis. *The British Journal of Surgery*, *101*(13), 1644–1656. https://doi.org/10.1002/BJS.9665

Xiao, A. Y., Tan, M. L. Y., Wu, L. M., Asrani, V. M., Windsor, J. A., Yadav, D., & Petrov, M. S. (2016). Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. *The Lancet Gastroenterology & Hepatology*, *1*(1), 45–55. https://doi.org/10.1016/S2468-1253(16)30004-8

Xue, P., Deng, L. H., Zhang, Z. da, Yang, X. N., Wan, M. H., Song, B., & Xia, Q. (2009). Infectious complications in patients with severe acute pancreatitis. *Digestive Diseases and Sciences*, *54*(12), 2748–2753. https://doi.org/10.1007/S10620-008-0668-1

Yadav, D., Agarwal, N., & Pitchumoni, C. S. (2002). A critical evaluation of laboratory tests in acute pancreatitis. *The American Journal of Gastroenterology*, *97*(6), 1309–1318. https://doi.org/10.1111/j.1572-0241.2002.05766.x

Yadav, D., Hawes, R. H., Brand, R. E., Anderson, M. A., Money, M. E., Banks, P. A., Bishop, M. D., Baillie, J., Sherman, S., DiSario, J., Burton, F. R., Gardner, T. B., Amann, S. T., Gelrud, A., Lawrence, C., Elinoff, B., Greer, J. B., O'Connell, M., Barmada, M. M., … Whitcomb, D. C. (2009). Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Archives of Internal Medicine*, *169*(11), 1035–1045. https://doi.org/10.1001/ARCHINTERNMED.2009.125

Yadav, D., & Lowenfels, A. B. (2006). Trends in the epidemiology of the first attack of acute pancreatitis: A systematic review. *Pancreas*, *33*(4), 323–330. https://doi.org/10.1097/01.mpa.0000236733.31617.52

Yadav, D., & Lowenfels, A. B. (2013). The Epidemiology of Pancreatitis and Pancreatic Cancer. *Gastroenterology*, *144*(6), 1252–1261. https://doi.org/10.1053/J.GASTRO.2013.01.068

Yang, A. L., & McNabb-Baltar, J. (2020). Hypertriglyceridemia and acute pancreatitis. *Pancreatology : Official Journal of the International Association of*

Pancreatology (IAP) ... [et Al.], *20*(5), 795–800. https://doi.org/10.1016/J.PAN.2020.06.005

Yang, A. L., Vadhavkar, S., Singh, G., & Omary, M. B. (2008). Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Archives of Internal Medicine*, *168*(6), 649–656. https://doi.org/10.1001/ARCHINTE.168.6.649

Yao, L., Huang, X., Li, Y., Shi, R., & Zhang, G. (2010). Prophylactic Antibiotics Reduce Pancreatic Necrosis in Acute Necrotizing Pancreatitis: A Meta-Analysis of Randomized Trials. *Digestive Surgery*, *27*(6), 442–449. https://doi.org/10.1159/000318780

Yoo, D., Park, S. Y., Hwang, D. W., Lee, J. H., Song, K. B., Lee, W., Park, Y., Jun, E., & Kim, S. C. (2021). Lack of Association between Postoperative Pancreatitis and Other Postoperative Complications Following Pancreaticoduodenectomy. *Journal of Clinical Medicine*, *10*(6), 1–13. https://doi.org/10.3390/JCM10061179

Zerem, E., Imamović, G., Sušić, A., & Haračić, B. (2011). Step-up approach to infected necrotising pancreatitis: a 20-year experience of percutaneous drainage in a single centre. *Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*, *43*(6), 478–483. https://doi.org/10.1016/J.DLD.2011.02.020

Zhang, Y., Zhang, S.-Y., Gao, S.-L., Liang, Z.-Y., Yu, W.-Q., & Liang, T.-B. (2015). Successful Resolution of Gastric Outlet Obstruction Caused by Pancreatic Pseudocyst or Walled-Off Necrosis After Acute Pancreatitis: The Role of Percutaneous Catheter Drainage. *Pancreas*, *44*(8). https://journals.lww.com/pancreasjournal/Fulltext/2015/11000/Successful_Resolution_of_Gastric_Outlet.17.aspx

Zilio, M. B., Eyff, T. F., Azeredo-Da-Silva, A. L. F., Bersch, V. P., & Osvaldt, A. B. (2019). A systematic review and meta-analysis of the aetiology of acute pancreatitis. *HPB*, *21*(3), 259–267. https://doi.org/10.1016/J.HPB.2018.08.003

Zubia-Olaskoaga, F., Maraví-Poma, E., Urreta-Barallobre, I., Ramírez-Puerta, M. R., Mourelo-Fariña, M., & Marcos-Neira, M. P. (2016). Comparison Between Revised Atlanta Classification and Determinant-Based Classification for Acute Pancreatitis in Intensive Care Medicine. Why Do Not Use a Modified Determinant-Based Classification? *Critical Care Medicine*, *44*(5), 910–917. https://doi.org/10.1097/CCM.0000000000001565

Zyromski, N. J. (2013). Laparoscopic Transgastric Pancreatic Débridement. *Current Surgery Reports 2013 1:2*, *1*(2), 114–120. https://doi.org/10.1007/S40137-013-0020-3

Zyromski, N. J., Vieira, C., Stecker, M., Nakeeb, A., Pitt, H. A., Lillemoe, K. D., & Howard, T. J. (2007). Improved outcomes in postoperative and pancreatitis-related visceral pseudoaneurysms. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*, *11*(1), 50–55. https://doi.org/10.1007/s11605-006-0038-2