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SLOVENSKO ZDRUŽENJE  
ZA GASTROENTEROLOGIJO  
IN HEPATOLOGIJO





## Dear Colleagues!

Department of Abdominal Surgery of the University Medical Centre Ljubljana in collaboration with Slovenian Association of Hepatology and Gastroenterology which was founded in 1967 is organizing a scientific meeting about acute pancreatitis.

The primary purpose of 1<sup>st</sup> HPB Symposium Ljubljana is to bring physicians and investigators together to advance understanding of the origin and progression of acute pancreatitis and to provide optimal treatments to our patients as soon as possible. This meeting is led by academic physicians who are committed to collaboration in supporting patients who desperately need answers. The internationally renowned speakers from more than 10 EU member countries and other European countries testify to the high scientific level of the symposium. It is designed for gastroenterologists, intensivists, surgeons and radiologists and all physicians interested in pancreatic diseases.

It is, in fact, the first HPB meeting in Slovenia, but it emerged by well-known annual meetings 'Hepatobiliary School' held almost two decades ago by professors Markovič and Gadžijev. According with tradition the aims of this symposium are: (1) to discuss recent medical, scientific and technical advances in various disciplines relevant to acute pancreatitis, (2) to prioritize efforts for overcoming theoretical, technical, biological, medical, endoscopic, surgical, logistical, financial and regulatory barriers to improve detection, diagnosis, prevention and treatments and (3) to organize multidisciplinary working groups to address the needs and methods for acute pancreatitis care based on new knowledge and opportunities. In the future, it is our wish that this biannual meeting will provide platform to conduct well-designed multicentre studies in a large region of west-east Balkans.

Acute pancreatitis is increasing in incidence worldwide. The majority of patients who develop acute pancreatitis recover, and overall only about 2% die.

However, in up to 20% of individuals the disease is severe and may be complicated by organ failure, infections, a prolonged stay in the intensive care unit, or the need for surgical intervention; and mortality in this group may reach 20–30%. Over the last years, some developments in the management of pancreatitis have evolved, and these developments are having an impact in the treatment of patients, lowering the morbidity and mortality.

Prevalent dogma that infected necrosis complicating necrotizing pancreatitis mandates immediate or eventual necrosectomy for a successful outcome has been challenged. Recent approach of a primary, non-operative treatment involving directed antibiotics with percutaneous drainage (when indicated) have led to better outcomes when compared with primary operative necrosectomy. The treatment of infected (and sterile) necrotizing pancreatitis has evolved tremendously since 2000. The realization that severe acute pancreatitis associated with infected pancreatic parenchyma and peripancreatic necrosis is not an abscess that can be evacuated solely by drainage ushered in the new paradigm of treatment. Since then, the management of sterile and infected necrosis has evolved further with several major conceptual advances: (1) the move from a primary operative necrosectomy to one of a primary nonoperative, supportive management of patients with sterile necrosis; (2) the shift in treatment paradigm that infected necrosis requires immediate operative necrosectomy to that of an attempt to suppress the systemic effects of infected necrosis by the use of focused, intravenous antibiotics to postpone the timing of the inevitable eventual necrosectomy; (3) the move from an open operative necrosectomy via laparotomy with various forms of peripancreatic drainage to one of a minimal access necrosectomy (not just drainage) by other percutaneous, endoscopic, laparoscopic, minimal open access or a combined approach to accomplish a focused necrosectomy without the peripancreatic sequelae related to a full, open laparotomy; (4) some

patients with infected necrosis actually may be treated successfully without any formal attempt at either drainage or necrosectomy. This latter concept has not yet been embraced fully by clinicians.

During the meeting we will address the real questions of WHO, HOW LONG, WHEN, and WHAT is the role of conservative treatment and percutaneous drainage, and WHAT CRITERIA should be used to abandon this approach to adopt a more aggressive endoscopic, laparoscopic, or open approach involving some form of necrosectomy.

HPB surgery has dramatically changed over the past decades. Parallel to the latter, interdisciplinary management of HPB diseases is becoming increasingly significant, and the topic of this first congress reflects these dramatic changes. Interdisciplinary approach in treatment of acute pancreatitis, new diagnostic and interventional techniques and improved knowledge on supportive care during treatment, are only few interesting topics of this symposium.

This event will offer opportunities to share knowledge, listen to distinguished lecturers, meet new and reconnect with old friends. There is little doubt that our HPB community is a growing one, as not only surgeons but also other specialists are joining us in pursuit of better care for our patients. I am sure that 1<sup>st</sup> HPB Symposium Ljubljana will be not only a high-level scientific meeting, but also a place where old friends can come together and a place where many new friendships will be made.

Finally, I would like to thank all the lecturers, guests, colleagues and sponsors that contributed to the organization of the 1<sup>st</sup> HPB Symposium Ljubljana.

Assist. Prof. Blaž Trotovšek, MD, PhD



Ljubljana March 1<sup>st</sup> 2018

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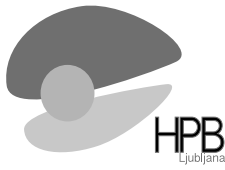
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# 1<sup>st</sup> HPB Symposium Ljubljana

## Program

### Friday, March 16<sup>th</sup> 2018

<b>09.00–11.00</b>	Registration
<b>11.00–11.10</b>	Opening Ceremony ( <b>Trotovšek</b> )
<b>11.10–11.40</b>	<b>State of the Art Lecture</b> Classification and Guidelines for Treatment of Acute Pancreatitis ( <b>Dervenis</b> )

11.40–12.00	Aetiology and Incidence of Acute Pancreatitis ( <b>Strniša</b> )
12.00–12.20	Prognostic Factors, Assessment of Severity and Mortality ( <b>Milan</b> )
12.20–12.40	Diagnostic Approach - Radiological Pathway ( <b>Garbajs</b> )
12.40–13.00	Antibiotic Treatment in Acute Pancreatitis ( <b>Beović</b> )
13.00–13.20	Moderate Rate Acute Pancreatitis ( <b>Conlon</b> )
13.20–13.40	Role of a Surgeon in Early Phase Acute Pancreatitis ( <b>Radenković</b> )
14.40–15.00	ERCP in Acute Biliary Pancreatitis ( <b>Rustemović</b> )
15.00–15.20	Complications of ERCP-View of a Gastroenterologist ( <b>Šmid</b> )
15.20–15.40	Complications of ERCP-View of a Surgeon ( <b>Tomazič</b> )
15.40–16.00	Preoperative Treatment in the Intensive Care Unit ( <b>Knafelj</b> )
16.00–16.20	Step-up Approach in Acute Pancreatitis ( <b>Škegro</b> )
16.20–16.40	Nutritional Support in Acute Pancreatitis ( <b>Rotovnik Kozjek</b> )
17.20–17.40	Indications for Intervention - View of a Gastroenterologist ( <b>Mervie</b> )
17.40–18.00	Indications for Intervention - View of a Radiologist ( <b>Popovič</b> )

18.00–18.20	Indications for Intervention - View of a Surgeon ( <b>Ivanecz</b> )
18.20–18.40	Postoperative Treatment in the Intensive Care Unit ( <b>Mirković</b> )
18.40–19.00	Rationale for Programmed Abdominal Lavage in Acute Pancreatitis ( <b>Patrlj</b> )
19.00–19.15	Closing remarks ( <b>Stanisavljević</b> )

### Saturday, March 17<sup>th</sup> 2018

<b>09.00–09.30</b>	<b>Meet the Professor:</b> Prof. Eldar Gadžijev
09.30–10.00	Necrosectomy - Who is Better: A Gastroenterologist or a Surgeon? ( <b>Plut, Trotovšek</b> )
10.00–10.20	Complications after Pancreatic Surgery ( <b>Potrč</b> )
10.20–10.40	Complications after Pancreas Transplantation ( <b>Kocman</b> )
10.40–10.55	Videoscopic Assisted Retroperitoneal Debridement and MARNP ( <b>Đokić</b> )
10.55–11.10	Negative Pressure Therapy in Acute Pancreatitis - Indications ( <b>Petrič</b> )
11.10–11.25	Negative Pressure Therapy in AP-Single Institution Experience ( <b>Zelić</b> )
12.00–12.20	Planning and Timing of Cholecystectomy ( <b>Grosek</b> )
12.20–12.40	Pancreatitis after Pancreatic Trauma ( <b>Karamarković</b> )
12.40–13.00	Pancreatic Pseudocyst ( <b>Matić</b> )
<b>13.05–13.25</b>	<b>Eldar Gadžijev lecture:</b> First live donor combined liver and bowel transplantation in UK ( <b>Vilca-Melendez</b> )
13.30–15.00	Free Topics
<b>15.00</b>	Closing Ceremony ( <b>Tomazič</b> )



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# Acute Pancreatitis: Epidemiology and Etiology

Luka Strniša\*

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**Key words:** acute pancreatitis, epidemiology, etiology

## ABSTRACT

Acute pancreatitis is an acute inflammatory process of the pancreas. The inflammation can remain localized to the gland or can involve other regional tissues or distant organ systems. The diagnosis of acute pancreatitis requires two of the following three features: abdominal pain characteristic of acute pancreatitis; serum amylase and lipase levels three or more times the upper limit of normal; and characteristic findings of acute pancreatitis on cross-sectional imaging. Three degrees of severity were defined in the 2012 revision of the Atlanta Criteria: mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis. The rate of mortality in severe acute pancreatitis is about 20–50% versus none in the mild acute pancreatitis group. The incidence of acute pancreatitis varies in Europe from 4.6 to 100/100 000. In most patients (75–85%) with acute pancreatitis, the etiology of their disease can be determined. In industrialized countries, gallstones and alcohol abuse are the most frequent reasons for acute pancreatitis. The peak incidence for alcoholic pancreatitis is around 35–44 years whereas the incidence of gallstone pancreatitis is commonest in the elderly.

## WHAT IS ACUTE PANCREATITIS

Acute pancreatitis is an acute inflammatory process of the pancreas and has various causes. The inflammation can remain localized to the gland or can involve other regional tissues or distant organ systems. The initial step in the pathogenesis of acute pancreatitis is conversion of trypsinogen to trypsin within acinar cells in sufficient quantities to overwhelm normal mechanisms to remove active trypsin. The pathophysiology of acute pancreatitis starts with acinar injury that, if unchecked, leads to local inflammatory complications and systemic inflammatory response. Pathophysiologic mechanisms include microcirculatory injury, leukocyte chemoattraction, release of pro- and anti-inflammatory cytokines, oxidative stress, leakage of pancreatic fluid into the region of the pancreas, and bacterial translocation to the pancreas and systemic circulation. Pancreatic infection (infected necrosis and infected pseudocyst) can occur from the haematogenous route or translocation of bacteria from the colon into the lymphatic system. Under normal circumstances, bacterial translocation does not occur because there are complex immunologic and morphologic barriers to it. How-

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ver, during acute pancreatitis, these barriers break down, which can result in local and systemic infection.

Acute pancreatitis is divided into two pathological types: interstitial oedematous pancreatitis and necrotizing pancreatitis. In interstitial oedematous pancreatitis, the gland is diffusely enlarged due to inflammatory edema. On macroscopic analysis scattered foci of fat necrosis are found. Haemorrhage and necrosis are absent, and changes resolve partially or completely over the course of one week. The key gross features of necrotizing pancreatitis are necrosis and haemorrhage. The lesion is often patchy in distribution, with confluent areas of varying extent and foci of relatively spared pancreatic tissue forming zones of necrosis and haemorrhage. This inflammatory process involves both peripancreatic tissue and peripheral pancreatic parenchyma, while a core of viable pancreas tissue remains in the center of the gland. Likewise, fat necrosis is not only present in and around the pancreas but also develops at distant sites. Necrosis is usually associated with haemorrhage and may extend into the surrounding tissues, for example, the mesentery and perarenal space, and from there to the subcutaneous tissues leading to discoloration of the flank (Grey Turner's sign) or periumbilical area (Cullen's sign). This destructive inflammation produces a large collection of peripancreatic fluid, which is mostly loculent in appearance and fetid in odor. Because many of the constituent cells (acinar, ductal, and islet cells) and tissues (stroma, fat) of the pancreas are affected, severe inflammation leads to significant organ loss with a reduction in both exocrine and endocrine function. Neutrophils dominate the inflammatory cell infiltrate and increase over time. Blood vessels can be involved in the necrotic process or can develop thrombosis within severely affected areas of the pancreas (1).

## EPIDEMIOLOGY

The incidence of acute pancreatitis in Europe varies from 4.6 to 100/100 000. One local Slovenian study estimated the incidence at 69/100.000 (2). The most common causes were alcohol abuse (39%) and

gallstones (39%). Idiopathic or unexplained pancreatitis represented 11%, hyperlipaemic pancreatitis 3%, neoplasia 2% and after endoscopic retrograde cholangiopancreatography (ERCP) 3% of all cases. A review of etiologies of pancreatitis in Europe concluded that the highest ratios of gallstone to alcohol etiologies were identified in Southern Europe (Greece, Turkey, Italy and Croatia) with lowest ratios mainly in Eastern Europe (Latvia, Finland, Romania, Hungary, Russia and Lithuania) (3).

As the population is becoming increasingly overweight, the incidence of gallstones, the most common cause of acute pancreatitis, is rising. An increase in the annual incidence of acute pancreatitis has been observed in most recent studies. The overall mortality rate from acute pancreatitis appears to be decreasing gradually to less than 5%. The rate of mortality in severe acute pancreatitis is about 20–50% versus none in the mild acute pancreatitis group. In alcoholic acute pancreatitis the incidence peaks in the 35–44-year age group, and the highest incidence of acute biliary pancreatitis is among the eldest age groups (65+ years).

Approximately 75–80% of patients with acute pancreatitis, have a quick resolution of the disease process (interstitial pancreatitis) without long-term sequelae. However, in close to 20% of patients, a more protracted course develops, often related to the necrotizing process (necrotizing pancreatitis) lasting weeks to months. Mortality is related to a combination of factors, including organ failure secondary to sterile necrosis, infected necrosis, or complications from surgical intervention. There are two peaks for mortality in acute pancreatitis. Most studies in the United States and Europe reveal that about half the deaths occur within the first week or two, usually from multiple organ failure. Death can be very rapid. About one-quarter of all deaths in Scotland occurred within 24 hours of admission, and one third within 48 hours. After the second week of illness, patients succumb to pancreatic infection associated with multiple organ failure. Some studies in Europe report a very high late mortality rate from infection. It is unclear if high rate of late mortality from infection is related to endoge-

nous infection of the pancreatic necrosis or surgical interventions for infectious complications.

## CLINICAL PICTURE

Most patients with acute pancreatitis experience abdominal pain, usually in the epigastrium, with radiation to the back in approximately half of cases. The onset may be swift, with pain reaching maximum intensity within 30 minutes, frequently unbearable, and characteristically persists without relief for more than 24 hours. The pain is often associated with nausea, vomiting, fever, tachycardia, leucocytosis, and elevated pancreatic enzyme levels in the blood and urine. Physical examination usually reveals moderate to severe upper abdominal tenderness often associated with guarding. These clinical findings parallel pathological changes with microscopic interstitial edema and fat necrosis of the pancreas. These alterations can extend to large areas of pancreatic and peripancreatic necrosis and haemorrhage.

The 2013 Atlanta Criteria define three grades of pancreatitis: mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis (4). This classification includes criteria of transient organ failure, persistent organ failure, and local or systemic complications. Mild acute pancreatitis is characterized by the absence of organ failure and the absence of local or systemic complications. Patients with mild acute pancreatitis respond to appropriate fluid administration with prompt normalization of physical signs and laboratory values. These patients can usually be discharged during the early phase. Moderately severe acute pancreatitis presents with transient organ failure or local or systemic complications in the absence of persistent organ failure. Peripancreatic fluid collection defines a local complication, resulting in prolonged abdominal pain, leucocytosis and fever, and potentially preventing the implementation of enteral nutrition. This form of acute pancreatitis may resolve without intervention or may require a prolonged care. Mortality of moderately severe acute pancreatitis is far less than that of severe acute pancreatitis. Severe acute pancreatitis is defined by persistent organ failure and

local complications, such as necrosis, abscess, or pseudocyst. The mortality rate in severe acute pancreatitis is about 20–50% versus none in the mild acute pancreatitis group.

## DIAGNOSIS

The diagnosis of acute pancreatitis requires two of the following three features: abdominal pain characteristic of acute pancreatitis; serum amylase and/or lipase three or more times the upper limit of normal; and characteristic findings of acute pancreatitis on transabdominal US, contrast-enhanced CT scan or MRI. This definition allows for the possibility that an amylase and lipase might be less than three times the upper limit of normal in acute pancreatitis. In a patient with abdominal pain characteristic of acute pancreatitis and serum enzyme levels that are lower than three times the upper limit of normal, a CT scan must be performed to confirm a diagnosis of acute pancreatitis (1).

## ETIOLOGY

### Obstruction

The most common obstructive process leading to pancreatitis are gallstones, which cause approximately 40% of cases of acute pancreatitis. However, only 3–7% of patients with gallstones develop pancreatitis. Gallstone pancreatitis is more common in women than men because gallstones are more frequent in women. Acute pancreatitis occurs more frequently when stones are less than 5 mm in diameter because small stones are more likely than large stones to pass through the cystic duct and cause ampullary obstruction. Cholecystectomy and clearing the bile duct of stones prevents recurrence, confirming the cause-and-effect relationship. Biliary sludge is a viscous suspension in gallbladder bile that may contain small (< 3 mm) stones (i.e. microlithiasis). Because small stones can hide in biliary sludge, the two are commonly referred to together as biliary sludge and microlithiasis. Biliary sludge is asymptomatic in most patients. It is usually composed of cholesterol mono-

hydrate crystals or calcium bilirubinate granules. On US, sludge produces a mobile, low-amplitude echo that does not produce an acoustic shadow and that layers in the most dependent part of the gallbladder. Sludge may result from functional bile stasis, such as that associated with prolonged fasting or total parenteral nutrition, or from mechanical stasis such as occurs in distal bile duct obstruction. Commonly, biliary sludge is found in patients with idiopathic acute pancreatitis. Multiple studies have found that cholecystectomy reduces the recurrence of idiopathic pancreatitis by approximately half (5, 6).

The pathogenesis of gallstone-related pancreatitis is unknown. Factors that may initiate gallstone pancreatitis include reflux of the bile into the pancreatic duct or obstruction of the pancreatic duct at the ampulla from stone(s) or oedema resulting from the passage of a stone. Reflux of the bile into the pancreatic duct could occur when the distal bile and pancreatic ducts form a common channel, and a gallstone becomes impacted in the duodenal papilla. Alternatively, bile could reflux into the pancreatic duct from the duodenum through an incompetent sphincter of Oddi injured by recent passage of a gallstone.

Experimentally, reflux of the bile into the pancreatic duct, particularly if the bile is infected or mixed with pancreatic enzymes, causes pancreatic injury. The mixture of bile and pancreatic enzymes increase the permeability of the main pancreatic duct, which is associated with local parenchymal inflammation. The common channel theory is somewhat problematic because pancreatic duct pressure is invariably higher than bile duct pressure, making bile reflux into the pancreatic duct unlikely. Reflux of the bile from the duodenum is also unlikely because pancreatitis does not occur in conditions with easily demonstrable reflux, such as after surgical sphincteroplasty or endoscopic sphincterotomy (7).

A popular theory for the mechanism of gallstone pancreatitis is that an impacted gallstone in the distal bile duct obstructs the pancreatic duct, increasing pancreatic pressure, thereby damaging ductal and acinar

cells. Experiments in the opossum supporting this theory are the observations that ligation of the pancreatic duct causes severe necrotizing pancreatitis and that decompression of the ductal system within three days prevents progression to acinar cell necrosis and severe inflammation.

Even small tumours in the pancreas can obstruct the duct and induce repetitive episodes of acute pancreatitis. Patients with pancreatic adenocarcinoma rarely develop acute pancreatitis even when the tumor obstructs the duct completely. Also, intraductal papillary mucinous neoplasm and adenomas of the major papilla can cause acute pancreatitis.

## Alcohol

Alcohol causes at least 30% of cases of acute pancreatitis, and alcohol is the most common etiology of chronic pancreatitis in developed countries. Interestingly, only 10% of chronic alcoholic patients develop chronic pancreatitis. The classic teaching is that alcohol causes chronic pancreatitis and that alcoholic patients who present with clinically acute pancreatitis have underlying chronic disease. However, a small percentage of patients with alcohol-induced acute pancreatitis by clinical criteria do not have, or progress to, chronic pancreatitis, even with continued alcohol abuse. By contrast, a small percentage of chronic alcoholic patients develop attacks of acute pancreatitis that are indistinguishable from other forms of acute pancreatitis but eventually develop chronic pancreatitis after 10–20 years of alcohol abuse. Early in the course of the disease, when attacks occur, the diagnosis of underlying chronic pancreatitis is difficult without tissue specimens, because the diagnosis of chronic pancreatitis is usually made after definite signs of chronic pancreatitis appear (e.g. pancreatic calcification, exocrine and endocrine insufficiency, or typical duct changes by CT or ERCP). Most of the models described suggest possible mechanisms of alcohol-related injury, including perturbations in exocrine function, changes in cellular lipid metabolism, induction of oxidative stress, and activation of stellate cells. However, the exact mechanism of pancreatic damage

by ethyl alcohol remains unclear and may be related to other factors. Alcohol could be directly toxic to the acinar cell because it causes lipid accumulation, leading to cellular necrosis and eventual fibrosis. However, in contrast to what is seen in liver disease, a steatopancreatitis precursor to fibrosis has not been demonstrated. It is interesting that years of alcohol exposure are required for precipitation of alcoholic pancreatitis. Alcohol increases the mitogenicity of pancreatic fluid, leading to formation of protein plugs and stones. Ductal obstruction by stones can lead to stasis of pancreatic fluid and further stone formation, eventually leading to atrophy and fibrosis of the gland.

In contrast to the stone theory, which is based on the development of fibrosis without acute pancreatitis, the necrosis-fibrosis hypothesis entails the development of fibrosis from recurrent, perhaps subclinical, attacks of acute pancreatitis. Inflammation and necrosis from the initial episodes of acute pancreatitis produce scarring in the periductular areas, and scarring obstructs the ductules, leading to stasis within the duct and subsequent stone formation. Support for this theory comes from histopathologic studies that revealed mild perilobular fibrosis in resolving acute pancreatitis, with marked fibrosis with ductal distortion occurring later. It is thought that a stepwise progression occurs to fibrosis from recurrent episodes of acute pancreatitis. The correlation between the frequency and severity of acute attacks to the rate of progression to chronic pancreatitis supports this theory.

## Drugs

Medications are an infrequent but important cause of acute pancreatitis. Although there are reports that drug-induced acute pancreatitis accounts for 1–4% of all cases, drug-induced acute pancreatitis probably accounts for less than 1% of cases. More than 120 drugs have been implicated, mostly from anecdotal case reports, however, clinicians must be careful not to blame a drug when a patient with acute pancreatitis does not have an obvious underlying cause. Many of the published case reports suffer from a combination of inadequate criteria for the diagnosis of acute

pancreatitis, failure to rule out more common causes, or a lack of a rechallenge with the medication. Also, many case reports inappropriately implicate drugs when the latter have been administered for very long periods (> 6 months) before the onset of acute pancreatitis. Drug-induced pancreatitis tends to occur within 4–8 weeks of beginning a drug.

## Lipids

Hypertriglyceridemia is the third most common identifiable cause of pancreatitis after gallstones and alcoholism, accounting for 2–5% of cases. Serum triglyceride concentrations above 11 mmol/L may precipitate attacks of acute pancreatitis. The pathogenesis of hypertriglyceridaemic pancreatitis is unclear, but the release of free fatty acids by lipase may damage pancreatic acinar cells or endothelial cells. Most people who abuse alcohol have moderate but transient elevations of the serum triglyceride levels because alcohol itself not only damages the pancreas but also increases serum triglyceride concentrations in a dose-dependent manner. In contrast with acute pancreatitis from other causes, the serum amylase and lipase level may not be substantially elevated at presentation.

## Hyperkalaemia

Hyperkalaemia of any cause is rarely associated with acute pancreatitis. Proposed mechanisms include deposition of calcium salts in the pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma

## Trauma

Either penetrating trauma (gunshot or stab wounds) or blunt trauma can damage the pancreas. In most cases, there is also injury to adjacent viscera.

## Post-endoscopic retrograde cholangiopancreatography pancreatitis

Acute pancreatitis is the most common and feared complication of ERCP, associated with substantial morbidity and occasional mortality. Around 2000 ERCPs are performed annually in Slovenia. Asymptomatic hyperamylasemia occurs commonly after ERCP, probably because of absorption of pancreatic enzymes through the papillotomy cut. Clinical acute pancreatitis occurs in 5% of diagnostic ERCPs, 7% of therapeutic ERCPs, and up to 25% in those with suspected sphincter of Oddi dysfunction or in those with a history of post-ERCP pancreatitis.

The mechanisms that lead to post-ERCP pancreatitis are complex and not fully understood. Rather than a single pathogenesis, post-ERCP pancreatitis is believed to be multifactorial, involving a combination of chemical, hydrostatic, enzymatic, mechanical, and thermal factors. Some risk factors have been identified as predictors of post-ERCP:

- Patient-related: young age, female gender, suspected sphincter of Oddi dysfunction, recurrent pancreatitis, history of post-ERCP pancreatitis, normal serum bilirubin level;
- Procedure-related: pancreatic duct injection, difficult cannulation, pancreatic sphincterotomy, precut access, balloon dilation;
- Operator- or technique-related: trainee participation, non-use of a guidewire for cannulation, failure to use a pancreatic duct stent in a high-risk procedure.

Pancreatitis may develop in up to 24 hours after ERCP. Studies have found serum pancreatic enzymes after ERCP as useful predictors of pancreatitis development. Serum amylase values above four-times the upper limit of normal or lipase levels above eight-times the upper limit of normal four hours after completing the procedure have a high specificity (> 90%) for predicting post-ERCP pancreatitis (8). Conversely, if the serum amylase was less than 1.5-times the upper limit of normal or lipase less than two-times the upper limit of nor-

mal, pancreatitis was unlikely. In the presence of abdominal pain, a normal serum amylase and/or lipase rules out acute pancreatitis at that moment.

A recent multicentre, double-blinded, randomized controlled trial of 602 patients undergoing a high-risk ERCP demonstrated a significant reduction of post-ERCP pancreatitis when given post-procedure rectal indomethacin (9). Other than rectal nonsteroidal anti-inflammatory drugs have failed to show any consistent benefit in multiple randomized studies evaluating several drugs.

Pancreatic stent placement decreases the risk of post-ERCP pancreatitis in high-risk patients and has become a standard practice for patients who are thought to be at high risk for pancreatitis after the procedure. It is effective presumably by preventing cannulation-induced oedema that can cause pancreatic duct obstruction. In all reported studies, which cumulatively include 1500 high-risk patients undergoing ERCP, only one patient developed severe pancreatitis after a pancreatic duct stent had been placed (10).

Guidewire cannulation, whereby the biliary or pancreatic duct is initially cannulated by a guidewire inserted through the catheter or sphincterotome, has been shown to decrease the risk of pancreatitis. However, the decrease in post-ERCP pancreatitis could be related to a decreased need for precut sphincterotomy in patients undergoing guidewire cannulation.

## Pancreas divisum

Pancreas divisum is the most common congenital malformation of the pancreas, occurring in 5–10% of the general healthy population, the vast majority of who never develop pancreatitis. Controversy continues to surround the issue as to whether pancreas divisum with otherwise normal ductal anatomy is a cause of acute recurrent pancreatitis.

## Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction is also a controversial cause of acute pancreatitis. The main argument in favour of this entity as a cause of acute pancreatitis is the many observational series that report that endoscopic pancreatic sphincterotomy or surgical sphincteroplasty reduces recurrent attacks of pancreatitis. However, a recent prospective study found that despite endoscopic therapy, patients with pancreas divisum or Sphincter of Oddi dysfunction had recurrent attacks in 50% and 55%, respectively (11).

## Genetic Factors

Genetic mutations in the trypsinogen gene or trypsin inhibitors have been well documented as a cause of chronic pancreatitis. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene have also been implicated in acute and chronic pancreatitis. The CFTR anion channel allows for chloride and bicarbonate secretion into the pancreatic ducts and thus allows flushing of the liberated enzymes and proenzymes into the duodenum. There are more than 1200 mutations that have been described for the CFTR gene. Some of these are considered severe and some mild. Homozygous severe mutations produce a viscid, concentrated, acidic pancreatic juice leading to ductal obstruction and pancreatic insufficiency in infancy. Heterozygotes of minor or major mutations may lead to acute recurrent or chronic pancreatitis by altering acinar or ductal cell function (e.g. alteration of bicarbonate conductance) (7). CFTR mutations associated with pancreas divisum could have a synergistic effect in the pathogenesis of acute pancreatitis. Although most patients with pancreas divisum (7–10% of the general population) never develop pancreatic disease, it may be that those persons who also harbour dysfunction in the CFTR transporter are at risk of developing pancreatitis when both are present in the same host (1).

## Autoimmune pancreatitis

Autoimmune pancreatitis typically presents as a mass or fullness in the pancreas or with signs and symptoms of chronic pancreatitis. Acute pancreatitis resulting from autoimmune pancreatitis is rare.

## Rare causes

Rare causes of pancreatitis are systemic or local ischemia as a result of vasculitis, emboli or intraoperative hypotension. Infection with viruses or parasites can cause pancreatitis. *Ascaris lumbricoides* is a frequent cause of pancreatitis in some countries. Anatomic developmental disorders such as annular pancreas, choledochocoele or peripapillary diverticula can also be implicated as causes of acute pancreatitis.

## References

1. Podolsky DK, Camilleri M, Gregory Fitz J, eds. Yamada's Textbook of Gastroenterology. 6th ed. Hoboken: Wiley-Blackwell; 2015.
2. Vujasinovic M, Makuc J, Tepes B. Impact of a clinical pathway on treatment outcome in patients with acute pancreatitis. *World J Gastroenterol*. 2015; 21 (30): 9150-5.
3. Roberts SE, Morrison-Rees S, John A. The incidence and aetiology of acute pancreatitis across Europe. *Pancreatol*. 2017; 17 (2): 155-65.
4. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of classification and definitions by international consensus. *Gut*. 2013; 62 (1): 102-11.
5. Rätty S, Pulkkinen J, Nordback I, et al. Can laparoscopic cholecystectomy prevent recurrent idiopathic acute pancreatitis?: a prospective randomized multicenter trial. *Ann Surg*. 2015; 262 (5): 736-41.
6. Stevens CL, Abbas SM, Watters DA. How does cholecystectomy influence recurrence of idiopathic acute pancreatitis? *J Gastrointest Surg*. 2016; 20 (12): 1997-2001.
7. Feldman M, Friedman L, Brandt L, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th ed. Philadelphia: Saunders; 2015.
8. Lee YK, Yang MJ, Kim SS, et al. Prediction of post-endoscopic retrograde cholangiopancreatography pancreatitis using 4-hour post-endoscopic retrograde cholangiopancreatography serum amylase and lipase levels. *J Korean Med Sci*. 2017; 32 (11): 1814-9.
9. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med*. 2012; 366 (15): 1414-22.
10. Singh P, Das A, Isenberg G, et al. Does prophylactic pancreatic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials. *Gastrointest Endosc*. 2004; 60 (4): 544-50.
11. Wilcox CM, Seay T, Kim H, et al. Prospective endoscopic ultrasound-based approach to the evaluation of idiopathic pancreatitis: causes, response to therapy, and long-term outcome. *Am J Gastroenterol*. 2016; 111 (9): 1339-48.

# Acute Pancreatitis: Assessment of Severity, Prognostic Factors, and Mortality

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## ABSTRACT

Acute pancreatitis is a complex disease that results in significant morbidity and mortality. The majority of articles suggest that mortality related to acute pancreatitis has, on the whole, reduced over time. Early severity stratification remains a challenging issue to overcome to improve outcome. In this review article, we focused on recent publications related to assessment of severity of acute pancreatitis, i.e., scoring systems and individual biochemical markers and their role in predicting clinical outcomes. Based on data presented, what seems to be evident is that there is no single scoring system that can be regarded as the most useful in acute pancreatitis.

## INTRODUCTION

Acute pancreatitis (AP) is a complex disease that results in significant morbidity and mortality. The majority of articles suggest that AP-related mortality has, on the whole, reduced over time (1, 2). This can be attributed to a whole host of factors, including better recognition of the signs of severity (through the assistance of severity indices), and newer therapies for the complications associated with AP (1).

Early severity stratification remains a challenging issue to overcome to improve outcome (3). In this review article, we will focus on recent publications related to assessment of severity of AP, i.e., scoring systems and individual biochemical markers and their role in predicting clinical outcomes.

Before we start presenting results of recent publications, we want to look at survey data on AP severity assessment in daily clinical practice in Switzerland (4). It is interesting that not all, but 87% of participants (193/233 from 63 hospitals) use scoring systems (4). The most frequently used are Ranson (87%) and Acute Physiology and Chronic Health Evaluation (APACHE) II (23%) scores. A majority of participants were not satisfied with the currently available tool to assess severity (59%). Only 12% of all participants use the revised Atlanta classification. The authors concluded that further efforts must be made to expand physicians' awareness of scores' existence and significance (4).

The best known, revised Atlanta classification of AP was published in 2012 to provide simple functional clinical and morphological classification. The modification (5):

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- addresses the clinical course and severity of disease,
- divides AP into interstitial edematous AP and necrotizing AP
- distinguishes an early phase (first week) and late phase (after the first week) and
- emphasizes systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF).

The goal is for radiologists, gastroenterologists, surgeons, and pathologists to use the revised classification to standardize imaging terminology to facilitate treatment planning and enable precise comparison of results among different departments and institutions (5, 6). Based on a recent survey (4), we need to put more effort to implement revised Atlanta classification in everyday practice.

The Bedside Index for Severity in Acute Pancreatitis (BISAP) was developed for prediction of in-hospital mortality in AP. Classification and Regression Tree (CART) analysis was applied on data collected from 17,992 cases of AP from 212 hospitals in 2000–2001. The new scoring system was validated on data collected from 18,625 AP cases from 177 hospitals in 2004–2005 in the United States (7). Five variables were identified for prediction of in-hospital mortality. One point is assigned for the presence of each during the first 24 hours: blood urea nitrogen > 25 mg/dL, impaired mental status, SIRS, age > 60 years or the presence of pleural effusion. The BISAP area under the curve (AUC) during revalidation was 0.82 versus APACHE II score of 0.83 (7). Since first revalidation, 12 other studies used BISAP index to determine predictive performance, and systematic review has been performed to determine prognostic accuracy of the BISAP for severe AP (7). In meta-analysis, pooled AUC was higher than in original revalidation study. It was 0.85 for BISAP and 0.92 for revised Atlanta classification (8). With high heterogeneity, BISAP has very good performance for severe AP across different patient population and aetiologies, but the impact of incorporating the BISAP into clinical practice to improve outcome in AP is still unknown (8).

The most recent paper by Vasudevan et al. (9) looked at different scoring systems and biochemical markers, and how well they predicted outcome in AP. They include the APACHE II score  $\geq 7$ , BISAP  $\geq 2$ , SIRS score  $\geq 3$  and C-reactive protein  $\geq 82$ ng/mL predicted severity of AP. They also found that predictors of infected pancreatic necrosis were as follows: PANC 3 score  $\geq 1$ , BISAP score  $\geq 2$  and Marshall score  $\geq 2$  and C-reactive protein  $\geq 98$  (9). In the same study, predictors of mortality were BISAP  $\geq 2$ , APACHE II  $\geq 10$  and blood urea nitrogen  $\geq 17$  (9).

They also suggested that BISAP and APACHE II were comparable in predicting outcome, but unlike APACHE II, BISAP predicted all three outcomes with the same cut off and hence is robust scoring system (9). Despite this finding, APACHE II score remains gold standard in assessing severity of AP.

Early Warning Score (EWS) has been extensively used in the United Kingdom, as a score that facilitate early detection of unwell patients on medical wards with the aim to start treatment on time. Jones et al. (10) compared EWS score with different variables and APACHE II score by including 629 patients with AP. They found EWS was the best predictor of adverse outcomes (AUC values 0.81, 0.84 and 0.83 for days 1, 2 and 3, respectively) and was the most accurate predictor of mortality on both days 2 and 3 (AUC values 0.88 and 0.89, respectively). Multivariate analysis revealed that a EWS  $\geq$  two was independently associated with severity of pancreatitis, adverse outcome, and mortality (10).

Another general scoring system, Emergency General Surgery disease grading system to measure anatomical severity, although recently introduced in clinical practice (by American Association for the Surgery of Trauma), has shown initial validity for prediction of length of hospital stay and increased rates of readmission in AP patients (11).

Recent study conducted by Beduchi et al. and another study conducted by Paanda et al., both

aimed to assess the efficacy of PANC 3 score to predict AP severity (haematocrit, body mass index (BMI) and pleural effusion) by including 64 and 74 patients, respectively, in the studies (12, 13). They both found PANC 3 score easy and quick to use, with 50% sensitivity and 100% accuracy, with 91% positive and 100% negative predictive value (12). Beduchi's et al. study performed in Brazil agrees with Jekura's et al. study performed in Japan conducted on 116 patients with AP (14). Multiple logistic regression analysis revealed that BMI of 25 kg/m<sup>2</sup> was associated with significant mortality. They suggested to add BMI > 25 kg/m<sup>2</sup> as an additional parameter to a Japanese prognostic factor score to enhance predictive value of the prognostic factor score for AP-related mortality (14).

However, the role of BMI is not as clear-cut from the literature as it might seem – the findings of many papers would appear to suggest that higher BMI increases one's risk of AP (14), yet a recent analysis by Kim et al. found lower BMI to be closely associated with mortality in AP (15). While it seems plausible that the comorbidities associated with a higher BMI may put one at risk of a poorer prognosis from AP (such as fatty liver), the findings of Kim et al. arguably mean that the relationship between BMI and prognosis in AP would be worth elucidating further (15).

Promising multivariate prediction model for patients with AP in intensive care unit that has better AUC than APACHE II (0.91 versus 0.80), has been recently presented (16). Variable with statistical significance in multivariate analysis were age, no alcoholic and no biliary etiology, development of shock, development of respiratory failure, need of continuous renal replacement therapy and intra-abdominal pressure (16). The only issue with this scoring system is that patients were already admitted to the intensive care unit and they already developed SIRS and MOF. When AP patients already reach intensive care unit stage, it is very obvious that the outcome may be poor.

## **BIOCHEMICAL MARKERS AS PREDICTORS OF SEVERITY OF ACUTE PANCREATITIS**

Recent study conducted by Hong et al. showed that albumin levels within 24 hours of patient admission correlate with the development of persistent organ failure and mortality in AP (17). As levels of serum albumin decrease, the incidence of organ failure is 3.5%, 10.6%, and 41.6% in patients with normal albumin, mild and severe hypoalbuminemia, respectively. Decreased albumin levels were also proportionally associated with prolonged hospital stay ( $p < 0.001$ ) and the risk of death ( $p < 0.001$ ). Multivariate analysis suggested that biliary etiology, chronic concomitant diseases, hematocrit, blood urea nitrogen, and the serum albumin level were independently associated with persistent organ failure (17). All these factors have already been looked at as indicators of severity of AP (8, 9, 10) and they have been included in different scoring systems (8, 9, 10). In Hong's et al. study, blood urea nitrogen and the serum albumin level were also independently associated with mortality. Area under receiver operating characteristic curves of albumin for predicting organ failure and mortality were 0.78 and 0.87, respectively (17).

Another biochemical marker that has potential to predict organ failure or death in patients with AP is cortisol. Study performed to assess whether copeptin, pro-atrial natriuretic peptide, proadrenomedullin, and cortisol are associated with disease severity in patients with AP included 142 patients with AP (18). Disease severity was rated by the Atlanta 1992 and 2012 criteria and organ failure by the modified Marshall score. The aforementioned laboratory markers, C-reactive protein, and procalcitonin were measured. Patients with moderate to severe AP showed significantly higher plasma concentrations of all biomarkers than did those with mild AP. Mortality from severe AP was as high as 21%. All biomarkers except cortisol had only modest discriminatory ability, with areas under the receiver operating characteristic curve between 0.44 and 0.66. Cortisol showed an AUC of 0.78 compared with the APACHE

II score with an AUC of 0.75. Authors concluded that cortisol was the best predictor of organ failure or death (18). All biomarkers were associated with disease severity to a similar degree as C-reactive protein, the criterion-standard marker in AP.

Intestinal fatty acid binding protein (IFAB) is another promising prognostic marker in AP. Based on prospective study that compared 94 AP patients with 100 control patients, that has found significantly higher IFAB in AP group ( $p < 0.001$ ) and also higher IFAB level of IFAB in patients with severe AP versus mild AP ( $p = 0.03$ , the authors propped a model by which IFABP  $> 350$  pg/mL and citruline  $< 18$ mcg/L can predict poor prognosis in 34% of patients with AP (19).

Total serum calcium and albumin-corrected calcium measured within 24 hours of AP are also useful severity predictors in AP (20).

It is well known that coagulation disorders can develop with severe AP. Plasma thrombin-antithrombin III complex (TAT) levels are markers of coagulation disorder. When measuring TAT in 46 patients with AP and 30 healthy volunteers, Fidan et al. found plasma TAT level significantly higher in severe AP group compared with AP group and healthy control. Based on this study, coagulation disorder is more pronounced as severity of disease increased (21).

Based on data presented, what seems to be evident is that there is no single scoring system that can be regarded as the most useful in AP. A systematic review by Gravante et al. found that, except APACHE II, most do not have a high degree of sensitivity, specificity or predictive value (22). Moreover, one of the criticisms of the use of APACHE II in the management of AP is that it requires the collection of a large number of parameters, many of which are unlikely to be relevant in AP (7). It seems likely, therefore, that the use of scoring systems in AP will continue to be an extensively debated and studied area in the literature.

Arguably the commonest mode of death in AP is MOF, which can be defined as ‘the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention’ (23). The SIRS is commonly associated with MOF, and its persistence is known to be a risk factor for the development of MOF and death in AP (24). It is, however, important to note that organ dysfunction in AP is a process and that the stage at which a patient is in this process can determine their overall mortality – early organ dysfunction usually has no significant effect on mortality, but deteriorating organ dysfunction has high mortality (25). Early, prompt management can, therefore, have a tremendous impact on patient outcomes.

Arguably the most important risk factor in AP is infected pancreatic necrosis – it occurs in up to 70% of patients with AP during the natural disease course (26), and the mortality rate is more than 20% (27). However, the use of prophylactic antibiotics to prevent this complication occurring is highly controversial, with some articles suggesting that antibiotic prophylaxis reduces mortality in AP (28, 29), and others demonstrating no significant beneficial effect of antibiotic prophylaxis (30). Current management guidelines do not definitively commit one way or another on the issue of antibiotic prophylaxis in AP – indeed; guidelines from the United Kingdom Working Party on Acute Pancreatitis recommend that if antibiotics are used at all, they should be given for a maximum of 14 days (27). Interestingly, a recent study by Baxter et al. found that the routine use of nonsteroidal anti-inflammatory drugs in AP might help prevent some of the complications associated with AP, including pancreatic necrosis (although it was found to make no significant difference on mortality) (30). While the use of nonsteroidal anti-inflammatory drugs as a therapeutic measure in AP is something that needs to be explored. Further, this finding offers a potential breakthrough in the prevention of this highly fatal complication.

## References

1. Bank S, Singh P, Pooran N, et al. Evaluation of factors that have reduced mortality from acute pancreatitis over the past 20 years. *Journal of clinical gastroenterology*. 2002; 35 (1): 50-60.
2. Agarwal S, George J, Padhan RK, et al. Reduction in mortality in severe acute pancreatitis: a time trend analysis over 16 years. *Pancreatology*. 2016; 16 (2): 194-9.
3. Deng L, Hu C, Cai WH, et al. Plasma cytokines can help to identify the development of severe acute pancreatitis on admission. *Medicine*. 2017; 96: 1-9.
4. Staubli SM, Oertli D, Nebiker CA. Assessing the severity of acute pancreatitis (ASAP) in Switzerland: a nationwide survey on severity assessment in daily clinical practice. *Pancreatology*. 2017; 17 (3): 356-63.
5. Thoeni R. The revised Atlanta classification of acute pancreatitis: its importance for the radiologist and its effect on treatment. *Radiology*. 2012; 3: 751-64.
6. Ignatavicius P, Gulla A, Cernauskis K, et al. How severe is moderately severe acute pancreatitis? Clinical validation of 2012 revised Atlanta classification. *World J Gastroenterol*. 2017; 23 (43): 7785-90.
7. Wu BU, Johannes RS, Sun X, et al. The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut*. 2008; 57: 169801703.
8. Chandra S, Murali A, Bansal R, et al. The Bedside Index for Severity in Acute Pancreatitis: a systematic review of prospective studies to determine predictive performance. *J Community Hosp Intern Med Perspect*. 2017; 7 (4): 208-13.
9. Vasudevan S, Goswami P, Sonika U, et al. Comparison of various scoring systems and biochemical markers in predicting the outcome in acute pancreatitis. *Pancreas*. 2018; 47 (1): 65-71.
10. Jones MJ, Neal CP, Ngu WS, et al. Early warning score independently predicts adverse outcome and mortality in patients with acute pancreatitis. *Langenbecks Arch Surg*. 2017; 402 (5): 811-9.
11. Younis M, Hernandez M, Ray-Zack M, et al. Validation of AAST EGS grade for acute pancreatitis. *Gastrointest Surg*. 2018 Jan 16. doi:10.1007/s11605-017-3662-0 [Epub ahead of print]
12. Beduchi MG, Mello ALP, Von-Muhlen B, et al. The PANC 3 score predicting severity of acute pancreatitis. *Arq Bras Cir Dig*. 2016; 29 (1): 5-8.
13. Panda C, Nayak NK, Bechera MR, et al. PANC 3 score as a simple cost-effective scoring system in predicting severity of acute pancreatitis. *Int Surg J*. 2017; 4 (12): 4066-70.
14. Ikeura T, Kato K, Takaoka M, et al. A body mass index > 25kg/m<sup>2</sup> is associated with a poor prognosis in patients with acute pancreatitis: a study of Japanese patients. *Hepatobiliary Pancreas Dis Int*. 2017; 16 (6): 645-51.
15. Kim YJ, Kim DB, Chung WC, et al. Analysis of factors influencing survival in patients with severe acute pancreatitis. *Scandinavian journal of gastroenterology*. 2017; 52 (8): 904-8.
16. Zubia-Olaskoaga F, Maravi-Poma E, Urreta-Barallobre I, et al. Development and validation of a multivariate prediction model for patients with acute pancreatitis in intensive care medicine. *Pancreatology*. 2018; 18 (2): 161-7.
17. Hong W, Lin S, Zippi M, et al. Serum albumin is independently associated with persistent organ failure in acute pancreatitis. *Can J Gastroenterol Hepatol*. 2017; 2017: 5297143.
18. Nebiker CA, Staubli S, Schafer J, et al. Cortisol outperforms novel cardiovascular, inflammatory, and neurohumoral biomarkers in the prediction of outcome in acute pancreatitis. *Pancreas*. 2018; 47 (1): 55-64.
19. Goswami P, Sonika U, Moka P, et al. Intestinal fatty acid binding protein and citrulline as markers of gut injury and prognosis in patients with acute pancreatitis. *Pancreas*. 2017; 46 (10): 1275-80.
20. Pokharel A, Sigdel PR, Phuyal S, et al. Prediction of severity of acute pancreatitis using total serum calcium and albumin-corrected calcium: a prospective study in tertiary center hospital in Nepal. *Surg Res Pract*. 2017; 2017: 1869091.
21. Fidan S, Erkut M, Cosar AM, et al. Higher thrombin-antithrombin III complex levels may indicate severe acute pancreatitis. *Dig Dis*. 2018 Jan 12. doi: 10.1159/000485613. [Epub ahead of print]
22. Gravante G, Garcea G, Ong SL, et al. Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. *Pancreatology*. 2009; 9 (5): 601-14.
23. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992; 20 (6): 864-74.
24. Mofidi R, Duff MD, Wigmore SJ, et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Brit J Surg*. 2006; 93 (6): 738-44.
25. Sharma VK, Howden CW. Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: a meta-analysis. *Pancreas*. 2001; 22 (1): 28-31.
26. Isenmann R, Rünzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology*. 2004; 126 (4): 997-1004.
27. Baxter KA, Pucher PH, Berry DP, et al. The effect of non-steroidal anti-inflammatory drugs on severity of acute pancreatitis and pancreatic necrosis. *Ann R Coll Surg Engl*. 2018; 100 (3): 199-202.

# The Role of Imaging in Acute Pancreatitis

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**Key words:** acute pancreatitis, ultrasound, contrast-enhanced CT, magnetic resonance cholangiopancreatography, revised Atlanta classification, CT severity score

## ABSTRACT

Acute pancreatitis is an acute inflammatory disease of the pancreas that may also involve surrounding structures and remote organs. Imaging plays an important role as it confirms the diagnosis, identifies causative factors, helps to grade the extent and severity of disease, is crucial for the early detection of complications and helps to guide treatment. Ultrasound is the first-line imaging modality in our center for determining the cause of the disease (e.g., gallstones) and to rule out other causes of acute abdomen. Magnetic resonance cholangiopancreatography is reserved for detection of choledocholithiasis, not shown on other modalities, for further characterization of collections, to help diagnose disconnected pancreatic duct and for patients in whom contrast-enhanced CT is contraindicated. Contrast-enhanced CT is considered the gold standard in the evaluation of acute pancreatitis, as it evaluates the extent and evolution of the disease, stages its severity and detects complications. Imaging of acute pancreatitis requires familiarity with the appropriate radiologic nomenclature as defined by the revised Atlanta classification so that

imaging descriptions are standardized and communication with clinicians and surgeons is precise. The purpose of this review article is to present an overview of acute pancreatitis and the role of different imaging modalities, as well as to emphasize the importance of revised Atlanta classification and CT severity score.

## INTRODUCTION

Acute pancreatitis (AP) is an acute inflammation of the pancreas resulting from an autodigestion of the gland. In approximately 80% of patients, AP is a self-limiting disease which subsides spontaneously, while 15–20% of patients develop severe form of disease, characterized by the development of pancreatic or peripancreatic necrosis, resulting in general and local complications responsible for a mortality rate of 8–35% (1, 2). The incidence of AP in Slovenia in 2001 was 40/100.000 with younger patients (between 20 and 40 years) being affected more commonly recently. Gallstones and alcohol are the most common causes of AP, and additional variants occur when patients are stratified by sex (2, 3).

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## DIAGNOSIS AND THE ROLE OF IMAGING MODALITIES

According to revised Atlanta classification, two of the following three criteria must be met for the diagnosis of AP: 1) acute onset of persistent, severe epigastric pain, 2) lipase/amylase elevation > three times the upper limit of normal and 3) characteristic imaging features on imaging modalities (4). Imaging modalities available for the diagnosis of AP include US, contrast-enhanced CT (CE-CT), MRI and magnetic resonance cholangiopancreatography (MRCP). Although many patients will meet the criteria for AP by symptoms and laboratory results alone and may not require imaging initially, imaging may be performed early in the disease course when the cause of the disease is unclear, to look for causative factors such as cholelithiasis and pancreatic cancer. Imaging for the diagnosis of pancreatitis is also appropriate when abdominal pain suggests pancreatitis, but the amylase or lipase level is not elevated to the threshold value, which is often the case at delayed presentation. Also, imaging helps to grade the extent and severity of AP, is crucial for the early detection of complications and to help guide treatment (5, 6). The onset of pancreatitis is considered to coincide with the first day of pain, not the day on which the patient presents for care or the day of hospital admission (4).

Imaging of AP requires not only understanding of the disease subtypes and associated complications but also familiarity with the appropriate radiologic nomenclature as defined by the Atlanta symposium in 1992 and more recently, modified by the Acute Pancreatitis Classification Working Group in 2008 (7, 8). It is important for the radiologist to adopt

this new nomenclature so that imaging descriptions are standardized and communication with clinical and surgical colleagues is precise to properly manage the patient (8).

## ULTRASOUND

Ultrasound is usually the first-line imaging modality in our center in suspected biliary pancreatitis and to rule out alternative diagnosis, because it is quick, easy to perform, readily available, avoids radiation

and can be carried out at bedside. The advantage of US in the early AP is to evaluate the gallbladder and biliary tract to detect gallstones (Figure 1) and the dilatation of the bile ducts. Changes in pancreatic parenchyma due to AP may only be seen in 30% of cases. In such cases, enlarged gland with obscured margins and hypoechoic parenchyma due to interstitial edema may be seen. Focal ill-defined hypo- or hyperechoic areas of edema or hemorrhage in the parenchyma and peripancreatic fluid collections may be seen. Also, US is used to characterize the contents of the



*Figure 1. Ultrasound shows gallstones (arrow) in the lumen of the fully distended gallbladder with no signs of acute cholecystitis*

fluid collections. One of the major limitations of US is the inability to make differential diagnosis of the interstitial and necrotizing pancreatitis (9, 10).

## COMPUTED TOMOGRAPHY

CE-CT is considered the gold standard in the evaluation of AP. It plays a significant role in evaluating the extent of disease and evolution of the disease and its complications (11). In 2012, International Association of Pancreatology/American Pancreatic Association (IAP/APA) evidence-based guidelines provided recommendations concerning key aspects of medical and surgical management of AP. According to these guidelines, the indications for initial CT assessment

in patients with AP are 1) diagnostic uncertainty, 2) confirmation of severity based on clinical predictors of severe AP, or 3) failure to respond to conservative treatment or in the setting of clinical deterioration. Optimal timing for initial CT assessment is at least 72–96 hours after onset of symptoms (12). Routine early CT in AP is not recommended for the following reasons: 1) there is no evidence that early CT improves clinical outcome or that early detection of necrosis will influence treatment, 2) CT scoring systems are not superior to clinical scoring systems in predicting prognosis and severity of disease (13), 3) there is evidence to suggest that an early (inappropriate) CT may increase the duration of hospital stay (14), has low yield without direct management implications (15), does not improve clinical outcomes (16), and poses risks of contrast allergy and nephrotoxicity. Early CT (before 72 hours) may be useful to rule out bowel ischemia or intra-abdominal perforations in patients presenting with both AP and acute abdomen. Follow-up CT (or in some cases MRI) is indicated when there is a lack of clinical improvement, clinical deterioration, or especially when invasive intervention is considered (12).

It is recommended to perform multidetector CT with thin collimation and slice thickness (i.e., 5 mm or less), 100–150 mL of non-ionic intravenous contrast material at a rate of 3 mL/s, during the pancreatic and portal venous phase (i.e., 50–70 seconds delay). During follow-up, only a portal venous phase is sufficient (12). Adding the arterial phase to this protocol makes vascular complications, such as hemorrhage and pseudoaneurysms to be detected more clearly. Unenhanced CT helps in detecting calcified gallstones and pancreatic calcifications in chronic pancreatitis and adds to diagnosis of suspected intra-abdominal or pancreatic hemorrhage (17).

## MAGNETIC RESONANCE IMAGING

According to the revised Atlanta classification, MRI imaging is reserved for detection of choledocholithiasis (Figure 2a) not visualized on CE-CT images (18, 19) and to further characterize collections for the

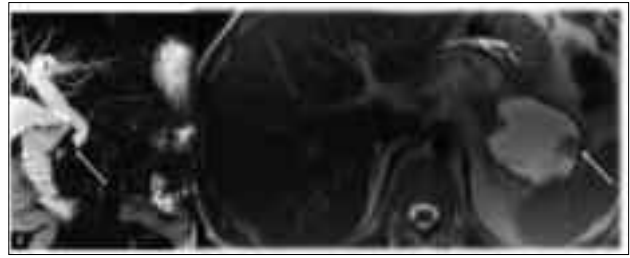


Figure 2. Magnetic resonance cholangiopancreatography. A – coronal plane showing gallstone (arrow) in the common billiary duct, just before papilla Vateri, B – T2 sequence in axial plane showing walled off necrosis with non-liquefied material (arrow) inside it

presence of non-liquefied material (debris and necrotic fatty tissue) (Figure 2b) (20). MRI has an important role in patients in whom CE-CT is contraindicated (e.g., due to allergy to iodinated intravenous contrast agents or pregnancy) (20, 21). It may also better show the disconnection of the pancreatic duct that creates persistent fistulation and inflammation with an increased incidence of infection (22).

## REVISED ATLANTA CLASSIFICATION

In the revised Atlanta classification system, new definitions were created to stratify AP into two subcategories based on imaging findings: interstitial oedematous pancreatitis (IEP) and necrotizing pancreatitis. The imaging-based revised classification involves careful assessment of CT images for collections of fluid and non-liquefied material in and around the pancreas (i.e., areas of pancreatic parenchymal and peripancreatic necrosis). The terminology for fluid collections is completely revised. It is important for the radiologist to adopt this new nomenclature so that imaging descriptions are standardized and communication with clinical and surgical colleagues is precise. The classification also points out other important findings to be evaluated with imaging such as causes of pancreatitis, including cholecystolithiasis and choledocholithiasis, or complications related to AP (extrahepatic biliary dilatation; splenic, portal, and mesenteric venous thrombosis; varices; arterial pseudoaneurysm; pleural effusion; and ascites). Also, inflammatory changes due to pancreatic secretions in other intra-abdominal organs need to be reported.

## Interstitial oedematous pancreatitis and necrotizing pancreatitis

IEP is more common and represents non-necrotizing inflammation of the pancreas. At CE-CT, the entire pancreas will enhance, with no unenhanced (necrotic) areas (Figure 3a). Necrotizing pancreatitis accounts for 5–10% of cases of AP (4). There are three subtypes of necrotizing pancreatitis; the subtypes are based on the anatomic area of necrotic involvement: 1) pancreatic only, 2) peripancreatic only, and 3) combined pancreatic and peripancreatic, which is the most common (75% of cases). The combined subtype

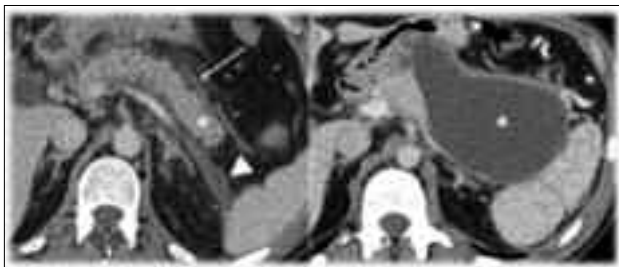


Figure 3. Interstitial oedematous pancreatitis. A – axial contrast-enhanced CT in venous phase, shows enlarged, heterogeneously enhanced gland (\*), with indistinct margins and some stranding and minimal fluid (arrow) in the peripancreatic fat; acute peripancreatic fluid collection in the anterior pararenal space (arrowhead) is also present. B – five weeks later, the collection becomes more organised with capsule and is termed pseudocyst



Figure 4. Acute necrotizing pancreatitis – combined pancreatic and peripancreatic necrosis. A – axial CT image in venous phase shows pancreas that is almost completely non-enhancing (\*), only a small part of processus uncinatus is enhancing; non-enhancing peripancreatic acute necrotic collections in the left and right pararenal spaces are also present (arrow). B – axial CT image obtained four weeks after onset, capsule is evident and some heterogeneity (\*) is seen within this collection, reflecting the presence of non-liquefied material in walled-off necrosis. C – walled-off necrosis in left anterior pararenal space (\*) and left paracolic space (arrow) are seen on axial CT images

demonstrates non-enhancing pancreatic parenchyma, as well as non-enhancing heterogeneous peripancreatic collections, and typically accumulating in the lesser sac and anterior pararenal space (Figure 4a) (23).

## Pancreatic and peripancreatic collections

The revised Atlanta classification makes an important distinction between collections that contain purely fluid (those encountered in IEP) and collections that contain necrotic debris in addition to fluid (those encountered in necrotizing pancreatitis) and includes

Table 1. Revised Atlanta classification of fluid collections in acute pancreatitis. IEP – interstitial edematous pancreatitis, APFC – acute peripancreatic fluid collection, ANC – acute necrotic collection, WON – walled-off necrosis

Type of acute pancreatitis	Fluid collections
< 4 weeks after onset	
IEP	APFC
Necrotizing pancreatitis	ANC <ul style="list-style-type: none"> <li>• parenchymal necrosis alone</li> <li>• peripancreatic necrosis alone</li> <li>• pancreatic and peripancreatic necrosis</li> </ul>
≥ 4 weeks after onset	
IEP	pancreatic pseudocyst
Necrotizing pancreatitis	WON

new definitions that more accurately describe the various types of collections encountered: acute peripancreatic fluid collection (APFC), pseudocyst, acute necrotic collection (ANC), and walled-off necrosis (WON). The important distinctions for classifying collections correctly are the time course (< 4 weeks or ≥ four weeks from onset of pain and the presence or absence of necrosis at imaging (Table 1).

APFC occur during the first four weeks and are present only in patients with IEP because the pathogenesis involves inflammation without necrosis. They are visualized as homogeneous fluid-attenuation collections that lack a wall (Figure 3a). They are always peripancreatic in location (4). Most APFCs resolve spontaneously, and drainage should not be performed because of the risk of infecting an otherwise sterile collection (24). If an APFC has not resolved after four weeks, it is referred to as a pseudocyst. It becomes more organized and develops a capsule that manifests as an enhancing wall at CE-CT (Figure 3b). Pseudocysts may have a connection to the pancreatic ductal system, which is best seen at MRCP.

ANC are present within the first four weeks of symptom onset and are poorly organized necrotic collections that occur only in necrotizing pancreatitis (Figure 4a). They are often multiple, with a loculated appearance, and may extend inferiorly as far as the pelvic sidewalls. They typically demonstrate a variable amount of fluid and can be distinguished from APFCs by the presence of non-liquefied debris, such as solid-appearing components or fat globules within the fluid. In the early phase of pancreatitis, differentiating between an APFC and an ANC can be difficult, and the diagnosis of necrosis may be uncertain. Imaging in the second week is usually helpful for distinguishing an APFC from an ANC. After four weeks

the collection is referred to as WON, has a thick enhancing wall, contains fluid and necrotic fat and pancreatic tissue, which are well demonstrated at both CE-CT and MRI as non-liquefied debris within the fluid (Figure 4b, Figure 4c, and Figure 2b). WON may be confined to the pancreatic parenchyma but more commonly occurs in the peripancreatic space and can often occur in both locations, with a coalescent collection extending from the lesser sac into a portion of parenchyma (4). There is evidence that MRI outperforms CT with better assessment of the ratio of fluid to necrotic debris in collections older than four weeks. Therefore, MRI is a valuable alternative to CE-CT for planning interventions because it allows determination of the amount of necrotic debris that must be removed using more aggressive interventions (25).

## Infection and local complications

Any collection can be sterile or infected, although infection occurs far more frequently in necrotic collections. The only imaging finding of an infected collection is the presence of gas within the collection (Figure 5) (4). Infected collections can also manifest with gas bubbles due to a pancreatic-enteric fistula, which can occasionally be seen when necrotic collections erode through the bowel wall, most commonly in the colon and duodenum (Figure 6) (26).



*Figure 5. Infected necrosis. Axial un-enhanced CT shows gas bubbles (arrow) in the acute necrotic collection in bursa omentalis, suggesting secondary infection of the collection*



*Figure 6. Pancreaticoenteric fistula. Axial contrast-enhanced CT shows fistula (arrow) between walled-off necrosis in the mesentery and small bowel loop. Gas bubbles (\*) due to secondary infection from fistula are seen in walled-off necrosis*

In addition to infection, vascular complications are common, occurring in a quarter of patients with AP, and can cause substantial morbidity and mortality. Inflammatory reactions can lead to splenic vein thrombosis, the most common vascular complication. Second, pancreatic enzymes can cause vessel erosion and lead to either spontaneous arterial hemorrhage or pseudoaneurysm of (in order of decreasing frequency) the splenic, gastroduodenal, and pancreaticoduodenal arteries (Figure 7) (27).

## COMPUTED TOMOGRAPHY SEVERITY INDEX

A significant progress has been achieved in the evaluation of patients with AP with computed tomography severity index (CTSI) classification developed by Balthazar et al. in 1990. The classification was found to have an excellent correlation between necrosis, the length of hospitalization, development of complications and death (in patients with CTSI  $\geq 7$ , the morbidity rate was 92% with the mortality rate 17%) (11). In 2004, Mortelet et al. applied 'The Modified CTSI' which simplifies the evaluation of fluid collections and necrosis rate and adds the ex-

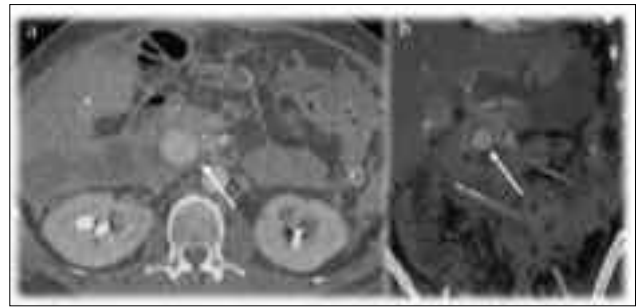


Figure 7. Pseudoaneurysm as a consequence of acute necrotizing pancreatitis. A – axial and B – coronal contrast-enhanced CT shows pseudoaneurysm that is feeding from gastroduodenal and superior mesenteric artery

trapancreatic complications (Table 2) (28). Compared to Acute Physiology and Chronic Health Evaluation (APACHE) II score, CTSI more accurately diagnoses clinically severe disease and better correlates with need for intervention and pancreatic infection (29).

## CONCLUSION

Alongside with clinical and laboratory findings, imaging plays an important role in the management of AP. Imaging confirms the diagnosis, identifies etiology, helps to grade the extent and severity of disease and

Table 2. Modified computed tomography severity index for severity of acute pancreatitis. 0–2 – mild acute pancreatitis, 4–6 – moderate acute pancreatitis, 7–10 – severe acute pancreatitis

Prognostic indicator	Points
Pancreatic inflammation	
Normal pancreas	0
Enlargement of the pancreas	1
Peripancreatic inflammation	2
One acute peripancreatic fluid collection	3
Two or more acute peripancreatic fluid collection	4
Pancreatic necrosis	
None	0
30%	2
30–50%	4
>50%	6
Maximum 10 points	

helps detecting complications and to guide treatment. Ultrasound is used to rule out biliary pancreatitis and to exclude other pathologic conditions. Computed tomography is the modality of choice to stage the severity of disease, to detect the presence and extent of fluid collections and necrosis, to identify complications and to guide treatment. MRCP is especially useful for imaging patients with iodine allergies. It may assist in diagnosis of choledocholithiasis, characterizing collections and evaluation of an abnormal or disconnected pancreatic duct. The choice of the proper imaging modality depends on the clinical condition of the patient and the onset of epigastric pain in AP.

## References

1. Fagniez PL, Rotman N. Acute pancreatitis. In: Holzheimer RG, Mannick JA, eds. Surgical treatment: evidence-based and problem-oriented. Munich: Zuckschwerdt; 2001.
2. Skok P, Čeranić D, Genslitskaya E. Akutni pankreatitis – rezultati prospektivne raziskave. Zdrav Vestn. 2008; 77: 573-8.
3. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013; 144 (6): 1252-61.
4. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013; 62 (1): 102-11.
5. O'Connor OJ, McWilliams S, Maher MM. Imaging of acute pancreatitis. Am J Roentgenol. 2011; 197 (2): W221-5.
6. Türkvatn A, Erden A, Türko lu MA, et al. Imaging of acute pancreatitis and its complications. Part 1: acute pancreatitis. Diagn Interv Imaging. 2015; 96 (2): 151-60.
7. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg. 1993; 128 (5): 586-90.
8. Thoeni RF. The revised Atlanta classification of acute pancreatitis: its importance for the radiologist and its effect on treatment. Radiology. 2012; 262 (3): 751-64.
9. Jeffrey RB. Sonography in acute pancreatitis. Radiol Clin North Am. 1989; 27 (1): 5-17.
10. Silverstein W, Isikoff M, Hill M, et al. Diagnostic imaging of acute pancreatitis: prospective study using CT and sonography. Am J Roentgenol. 1981; 137 (3): 497-502.
11. Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990; 174 (2): 331-6.
12. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatolgy. 2013; 13 (4 Suppl 2): e1-
13. Bollen TL, Singh VK, Maurer R, et al. A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. Am J Gastroenterol. 2012; 107 (4): 612-9.
14. Fleszler F, Friedenberg F, Krevsky B, et al. Abdominal computed tomography prolongs length of stay and is frequently unnecessary in the evaluation of acute pancreatitis. Am J Med Sci. 2003; 325 (5): 251-5.
15. Spanier BWM, Nio Y, van der Hulst RWM, et al. Practice and yield of early CT scan in acute pancreatitis: a dutch observational multicenter study. Pancreatolgy. 2010; 10 (2-3): 222-8.
16. Morteale KJ, Ip IK, Wu BU, et al. Acute pancreatitis: imaging utilization practices in an urban teaching hospital—analysis of trends with assessment of independent predictors in correlation with patient outcomes. Radiology. 2011; 258 (1): 174-81.
17. Saokar A, Rabinowitz CB, Sahani DV. Cross-sectional imaging in acute pancreatitis. Radiol Clin North Am. 2007; 45 (3): 447-60.
18. Chang JH, Lee IS, Lim YS, et al. Role of magnetic resonance cholangiopancreatography for choledocholithiasis: analysis of patients with negative MRCP. Scand J Gastroenterol. 2012; 47 (2): 217-24.
19. Hekimoglu K, Ustundag Y, Dusak A, et al. MRCP vs. ERCP in the evaluation of biliary pathologies: review of current literature. J Dig Dis. 2008; 9 (3): 162-9.
20. Manikkavasakar S, AIObaidy M, Busireddy KK, et al. Magnetic resonance imaging of pancreatitis: an update. World J Gastroenterol. 2014; 20 (40): 14760-77.
21. Oto A, Ernst R, Ghulmiyyah L, et al. The role of MR cholangiopancreatography in the evaluation of pregnant patients with acute pancreaticobiliary disease. Br J Radiol. 2009; 82 (976): 279-85.
22. Sandrasegaran K, Tann M, Jennings SG, et al. Disconnection of the pancreatic duct: an important but overlooked complication of severe acute pancreatitis. Radiographics. 2007; 27 (5): 1389-1400.
23. Baker ME, Nelson RC, Rosen MP, et al. ACR Appropriateness Criteria® acute pancreatitis. Ultrasound Q. 2014; 30 (4): 267-73.
24. Lenhart DK, Balthazar EJ. MDCT of acute mild (nonnecrotizing) pancreatitis: abdominal complications and fate of fluid collections. AJR Am J Roentgenol. 2008; 190 (3): 643-9.
25. Kamal A, Singh VK, Akshintala VS, et al. CT and MRI assessment of symptomatic organized pancreatic fluid collections and pancreatic duct disruption: an interreader variability study using the revised Atlanta classification 2012. Abdom Imaging. 2015; 40 (6): 1608-16.
26. Tüney D, Altun E, Barlas A, et al. Pancreatico-colonic fistula after acute necrotizing pancreatitis. Diagnosis with spiral CT using rectal water soluble contrast media. JOP. 2008; 9 (1): 26-9.
27. Shyu JY, Sainani NI, Sahni VA, et al. Necrotizing pancreatitis: diagnosis, imaging, and intervention. Radiographics. 2014; 34 (5): 1218-39.
28. Morteale KJ, Wiesner W, Intriene L, et al. A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. Am J Roentgenol. 2004; 183 (5): 1261-5.
29. Bollen TL, Singh VK, Maurer R, et al. Comparative evaluation of the modified CT severity index and CT severity index in assessing severity of acute pancreatitis. Am J Roentgenol. 2011; 197 (2): 386-92.

# Antibiotic Treatment in Acute Pancreatitis

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**Key words:** antibiotics, infection, pancreatitis

## ABSTRACT

Infection of pancreatic necrosis seriously aggravates the course of pancreatitis. Gram-negative bacilli and anaerobes from the intestinal flora were the most common pathogens involved in the infection of pancreatic necrosis in the past. Gram-positive flora became more important recently because of antibiotic prophylaxis and prolonged course of the disease. In most cases, infection of necrosis develops in the second phase of the disease. In addition to infection of pancreatic necrosis, extra-pancreatic infections may complicate the course of diseases in critically ill patients with severe pancreatitis. Infection of pancreatic necrosis can be definitively diagnosed with fine needle aspiration and culture of the aspirate. Contrast-enhanced CT showing extra-luminal air in the necrosis is helpful when fine needle aspiration is not indicated. Procalcitonin level may be used as another diagnostic tool. Routine antibiotic prophylaxis of infection of pancreatic necrosis is currently not recommended, but further studies are needed. The choice of antibiotics for the infection of pancreatic necrosis depends upon the antimicrobial spectrum, local antimicrobial susceptibility of the potential causative agents

and the penetration of antibiotics in the pancreatic tissue. The duration of antibiotic treatment in patients with infected pancreatic necrosis is not well defined and depends upon the feasibility of the source control.

## INTRODUCTION

The annual incidence of acute pancreatitis ranges from 13 to 45 per 100,000 people (1). The incidence is increasing probably as a consequence of obesity epidemics and related increase in gallstones. Most cases are mild and improve spontaneously. Severe necrotizing form develops in 15–20% of patients (2, 3). Overall mortality has decreased in recent years to 2%, but it remains above 30% in most severe forms of disease. Severe forms are defined primarily with systemic inflammatory response and organ failure. In most severe cases, the so-called critical pancreatitis, organ failure is combined with infection of pancreatic necrosis (2). Overall, a half of deaths in patients with pancreatitis are caused by infected necrosis (4). Necrosis affecting 30% of pancreatic tissue on contrast-enhanced CT increases the risk of infection (5).

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## MICROBIOLOGY AND PATHOGENESIS OF INFECTED PANCREATIC NECROSIS

Typical gastrointestinal flora with predominance of Gram-negative bacilli and anaerobes was reported as causative agent of infected pancreatic necrosis in the past. More recently, it was found that Gram-positive microorganisms prevail probably because of frequent preceding antibiotic treatment and prolonged survival. Enterococci and coagulase-negative staphylococci became common isolates from pancreatic necrosis. Multiple microorganisms are isolated in most cases (6). The isolated flora is often resistant to antibiotics which limits the choice of antibiotic treatment and further complicates the course of the disease (3). Fungal infections, another consequence of broad-spectrum antibiotics and intensive care (bacteriology), are also clearly linked to increased hospital stays cost, reoperations, as well as overall morbidity and mortality (3). The incidence of fungal infections of pancreatic necrosis varies from 5 to 8%, but it may increase to 15 or even 70% in patients who need surgical intervention and is higher in patients with prior antibiotic exposure (7). The pathogenesis of infection in pancreatic necrosis is not fully elucidated, but the flora and the benefit of enteral nutrition or selective digestive decontamination suggest translocation of bacteria because of its altered permeability caused by systemic inflammation and local situation in the abdominal cavity (5).

## CLINICAL COURSE OF INFECTION IN PATIENTS WITH SEVERE PANCREATITIS

The course of severe pancreatitis may be divided in two phases. The first phase is characterized by systemic inflammatory response related to pancreatic inflammation rather than infection. Extra-pancreatic foci of infection such as cholecystitis, cholangitis, bacteremia or pneumonia may be present in some cases (5). The second phase that develops 7–14 days later is dominated by infectious complications, most often infected pancreatic necrosis (4). The development of infected pancreatic necrosis has been shown to peak between weeks 2 and 4 (5). Other types of infection may develop in the second phase as well as complications of prolonged diseases and intensive care treatment (5). The types of infections and their usual timing are presented in Table 1.

## DIAGNOSIS OF INFECTION IN PANCREATIC NECROSIS

Definitive diagnosis of infection requires positive culture or Gram stain from CT- or US-guided fine needle aspiration (FNA) biopsy or open surgery. FNA is a safe method with minimal risk for false positivity; false negative results appear in 10%. If infection is highly suspected, the FNA may be repeated (5). Some authors do not recommend routine FNA because of insufficient proof that possible

Table 1. Infections in patients with severe pancreatitis (8)

Type of infection	Frequency (%)	Timing (days)
Infected necrosis	47	17.6
Pneumonia	28	10.7
Bacteraemia	11	13.7
Gastrointestinal infections	8	16.8
Urinary tract infections	6	20.5

shortening of the diagnostic procedure improves the outcome (9). Instead, FNA should be used selectively when there is no clinical response to adequate therapy, or when the clinical and imaging features of infection are uncertain (10). However, in the settings with high prevalence of antimicrobial resistance and especially in patients previously treated with broad-spectrum antibiotics, FNA may become a more important diagnostic tool. Contrast-enhanced CT may be highly suggestive for infection if there are extra-luminal air bubbles found in necrotic tissue (5), but some authors warn against solely relying on the presence of extra-luminal gas, which may lead to overtreatment in a patient who

is doing clinically well without antibiotics or any intervention (3). Procalcitonin (PCT) has been investigated as a tool for the diagnosis of infected pancreatic necrosis. In an older study, a cut-off value at 1.8 ng/mL was suggested with sensitivity and specificity above 90%. A larger more recent study found that at PCT concentration  $\geq 5.6$  ng/mL infected necrosis and multiple organ dysfunction can be diagnosed with 90% sensitivity and 89% specificity. The distinction between infected and non-infected necrosis can be made at PCT level  $\geq 4.0$  ng/mL with 65% sensitivity and 89% specificity (11, 12).

*Table 2. Recent meta-analyses on the efficacy of antibiotic prophylaxis in patients with acute pancreatitis. RTC – randomized controlled trial*

Author, year (ref.)	Time of publication of the studies included in the meta-analysis	Number of studies included in the meta-analysis	Type of studies included in the meta-analysis	Results
Jafri, 2009 (14)	until May 2008	8	RTC	Infected necrosis: no effect Surgery: no effect Mortality: no effect Significant reduction of extra-pancreatic infections
Villatoro, 2010 (15)	November 2008	7	RTC	Infected necrosis: no effect Surgery: no effect Mortality: no effect Extra-pancreatic infection: no effect Fungal infections: no effect Significant reduction in pancreatic infection and no effect on mortality with imipenem
Wittau, 2011 (16)	1980 to December 2009	14	RTC	Infected necrosis: no effect Surgery: no effect Mortality: no effect Extra-pancreatic infection: no effect
Jiang, 2012 (13)	Up to 2009	11	RTC	No effect on mortality.
Lim, 2015 (17)	Up to October 2013	11	Two cohort studies, 9 RTC	Infected necrosis: no effect Mortality: effect was shown in cohort studies and all studies, but not in RTC Surgery and fungal infections: no effect

## ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis in acute pancreatitis has been a matter of debate for decades. The first studies gave negative results probably because of the spectrum of antibiotics and inclusion of patients with milder forms of pancreatitis. After the introduction of new broad-spectrum antimicrobial agents, there were several studies that showed some benefit of prophylaxis. The studies were small and heterogeneous, and therefore unconvincing; however, their results were confirmed by the first meta-analysis (5). After the year 2000, two well-designed larger studies that followed turned the circle again: none of them was able to show any benefit of antibiotic prophylaxis (5, 13). Several studies and meta-analyses were published after that; their results do not support antibiotic prophylaxis in general. Recent meta-analyses are presented in Table 2.

Based on the existing body of evidence there is a large consensus that antibiotic prophylaxis in severe acute pancreatitis is not recommended (1–3, 5, 9, 10, 18). However, some authors warn against relying on the evidence that is still weak (19). The compliance of the wide-spread guidance is still very poor; a systematic review of studies and patient-based data published in 2016 showed that antibiotic prophylaxis is still given to 41–88% of patients with acute pancreatitis. Partially the poor adherence to guidance is caused by the level of evidence. Further larger well-designed studies are needed to improve the evidence. Currently, for practical purposes, some authors suggest individualized approach (10, 13) with antibiotic prophylaxis in very severely ill patients.

## ANTIBIOTIC THERAPY

Antibiotic therapy in acute pancreatitis may be empirical or targeted. The decision for empirical treatment that may also be called the treatment on demand is based on clinical deterioration of patients including signs and symptoms suggestive of infection. The above mentioned diagnostic tools such as CT scan and PCT may be used to guide the

decision. Appropriate samples for cultures should be done before the start of the treatment. As in other cases of severely ill patients, empirical antibiotics may be discontinued if relevant cultures (blood cultures, FNA) remain sterile. The choice of antibiotic in empirical treatment should target mixed flora including Gram-negative rods and anaerobes, but also Gram-positive cocci in patients who received antibiotic therapy for prophylaxis or an extra-pancreatic infections. Local susceptibility patterns should be taken into account. Another important factor is the penetration of the drug into the pancreatic tissue. The penetration of aminoglycosides is insufficient. Ureidopenicillins (piperacillin) and higher generation cephalosporins penetrate moderately well, but this may be compensated with their good bactericidal efficacy for the susceptible microorganisms. The best penetration was observed for fluoroquinolones and carbapenems. Fluoroquinolones should be combined with anti-anaerobic agents, usually metronidazole, and another drug with good pancreatic penetration (5). The choice of antibiotics may be complicated in infections with multi-resistant microorganisms. Prudent antibiotic prescribing and infection prevention measures should be undertaken to avoid the colonization and infection of patients with difficult-to-treat microorganisms.

The duration of antibiotic treatment of infected pancreatic necrosis is not well defined. A recent study reports on 14 days therapy with a wide range from 10 to 64 days (20). In the case of adequate source control, there is no need for prolonged treatment. Patients should be followed clinically, with repeated imaging studies and possible additional source control if needed and feasible. Antibiotics may be discontinued if the infection seems to be healed. In clinically stable patients with prolonged antibiotic treatment, the termination of the therapy may be attempted even if the symptoms of inflammation have not completely disappeared (21).

## References

1. Lankish PG, Apte M, Banks PA. Acute pancreatitis. *Lancet*. 2015; 386: 85-96.
2. Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. *N Engl J Med*. 2016; 375: 1972-81.
3. Ball CG, Hameed SM, Dixon E, et al. Severe acute pancreatitis for the acute care surgeon. *J Trauma Acute Care Surg*. 2016; 80: 1015-22.
4. Bakker OJ, van Santvoort HC, Besselink MGH, et al. Prevention, detection, and management of infected necrosis in severe acute pancreatitis. *Curr Gastroenterol Rep*. 2009; 11: 104-10.
5. Howard TJ. The role of antimicrobial therapy in severe acute pancreatitis. *Surg Clin North Am*. 2013; 93: 586-93.
6. Howard TJ, Temple MB. Prophylactic antibiotics alter the bacteriology of infected necrosis in severe acute pancreatitis. *Am Coll Surg*. 2002; 195: 759-67.
7. Eggimann P, Jamdar S, Siriwardena AK. Pro/con debate: Antifungal prophylaxis is important to prevent fungal infection in patients with acute necrotizing pancreatitis receiving broad-spectrum antibiotics. *Critical Care*. 2006; 10: 229.
8. Xue P, Deng LH, Zhang ZD, et al. Infectious complications in patients with severe acute pancreatitis. *Dig Dis Sci*. 2009; 54: 2748-53.
9. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology*. 2013; 13 (4 Suppl 2): e1-15.
10. The Italian Association for the Study of the Pancreas. Consensus guidelines on severe acute pancreatitis. *Dig Liver Dis*. 2015; 47: 532-43.
11. Rau B, Steinbach G, Gansauge F, et al. The potential role of procalcitonin and interleukin 8 in the prediction of infected necrosis in acute pancreatitis. *Gut*. 1997; 41: 832-40.
12. Rau BM, Kemppainen EA, Gumbs AA, et al. Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalcitonin (PCT). *Ann Surg*. 2007; 245: 745-54.
13. Jaing K, Huang W, Yang XN, et al. Present and future of prophylactic antibiotics for severe acute pancreatitis. *World J Gastroenterol*. 2012; 18: 279-84.
14. Jafri NS, Mahid SS, Idsteinc SR, et al. Antibiotic prophylaxis is not protective in severe acute pancreatitis: a systematic review and meta-analysis. *Am J Surg*. 2009; 197: 806-13.
15. Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev*. 2010; (5): CD002941.
16. Wittau M, Mayer B, Scheele J, et al. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scand J Gastroenterol*. 2011; 46: 261-70.
17. Lim CLL, Lee W, Liew YX, et al. Role of antibiotic prophylaxis in necrotizing pancreatitis: a meta-analysis. *J Gastrointest Surg*. 2015; 19: 480-91.
18. Phillip V, Steiner JM, Alguel H. Early phase of acute pancreatitis: assessment and management. *World J Gastrointest Pathophysiol*. 2014; 5: 158-68.
19. Imrey PB, Law R. Antibiotic prophylaxis for severe acute pancreatitis. *Am J Surgery*. 2012; 203: 556-7.
20. Zerem E, Imamović G, Susić A, et al. Step-up approach to infected necrotising pancreatitis: a 20-year experience of percutaneous drainage in a single centre. *Dig Liver Dis*. 2011; 43: 478-83.
21. Mazuski JE, Tessier JM, Kay AK, et al. The surgical infection society revised guidelines on the management of intra-abdominal infection. *Surg Infect*. 2017; 18: 1-75.

# Management of Moderately Severe Pancreatitis: Individualised Treatment for Each Patient

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**Key words:** pancreatitis, acute, management, diagnosis, moderately severe

## ABSTRACT

Acute pancreatitis is an inflammatory condition of the pancreas that is painful and at times deadly. Severe acute pancreatitis constitutes 20% of the patients presenting to hospital with acute pancreatitis. In acute pancreatitis early recognition, vigorous fluid resuscitation, careful pulmonary care and close supervision is required. In severe cases patients will also require intensive care unit admission. Although the incidence of acute pancreatitis is on the rise, due to more systematic approach and specialist care outcomes have improved over the last decade. But this improvement comes at a cost and acute pancreatitis is considered as a significant burden on health systems across the world. Before 2012, acute pancreatitis was categorised as mild or severe. In 2012 with revised classification of acute pancreatitis two phases early and late, while three categories of severity mild, moderate and severe were identified. Moderately severe pancreatitis is defined by the presence of transient organ failure, local complications (peripancreatic fluid collections, pancreatic and peripancreatic necrosis) or exacerbation of co-morbidities. In this review article we have outlined symptoms, causes, diagnosis and management of moderately severe pancreatitis and complications arising

because of the disease process. It also provides simple but clear guideline and suggestions to clinicians for management of this illness.

## INTRODUCTION

Acute pancreatitis is one of the most common gastrointestinal diseases diagnosed worldwide. The severity of inflammation can vary from very mild self-limiting inflammation to severe disease causing severe inflammation and necrosis of pancreas, which can result in multiple organ failure and is associated with mortality. Pancreatitis can be a very challenging and complex disease for clinicians.

The incidence of pancreatitis varies worldwide ranging from 5 to 80 per 100000. Approximately 20% of patients admitted with acute pancreatitis have severe form of the disease and need admission to intensive care unit. As the number of patients suffering from pancreatitis are increasing as shown by epidemiological study conducted by our unit (1), so is the number of patients with severe acute pancreatitis. This results in significant burden on intensive care services accounting for 8.7% intensive therapy unit bed occupancy in tertiary referral centres in

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Scotland (2). The financial cost of treating acute pancreatitis in UK had been estimated at £200 million per year in 2012 (3). While acute pancreatitis-related estimated cost was \$3.7 billion in US in 2004 (4).

The incidence is on the rise; the clinical outcome of pancreatitis has improved over the recent decades due to a systematic approach to diagnosis, better understanding of pathology, monitoring and management of the patients by specialists dedicated to managing pancreatitis and its complications. The focus of this review will be the management of complications of moderately severe acute pancreatitis.

## SYMPTOMS

The most common presentation of pancreatitis is severe, sharp epigastric pain which often radiates through to back. Onset of pain is usually sudden and reaches maximum intensity in matter of minutes to hours. Pain is classically described as boring knife like constant pain which is not relieved by simple analgesics. Nausea, vomiting and dry retching are common associated symptoms. Depending on severity of disease patients could appear from well to extremely ill with shock.

## AETIOLOGY

The two most common causes of pancreatitis are cholelithiasis and alcohol accounting for about 80% of the cases. There is regional and gender based variation as to the aetiology of the pancreatitis. Alcohol being more common cause among men while cholelithiasis remained most common cause of pancreatitis in females. There is also geographical variation found for example gallstones being the predominant cause in Greece while alcohol being most common cause in Hungary (5). There is a steady rise in alcohol related pancreatitis in many countries especially in young population (1). But it is not uncommon to diagnose pancreatitis in patients in absence of these two aetiologies. The other causes of pancreatitis are iatrogenic, hereditary, autoimmune (6), hyperlipidaemia, trauma,

neoplasms, drugs, toxins and idiopathic. List of possible aetiologies are given in Table 1.

Table 1. List of causes of pancreatitis

Aetiologies of acute pancreatitis
<p><b>Common causes:</b></p> <ul style="list-style-type: none"> <li>• Gallstones (including microlithiasis)</li> <li>• Alcohol</li> <li>• Idiopathic</li> <li>• Hyperlipidaemia</li> <li>• Hypercalcemia</li> <li>• Sphincter of Oddi dysfunction</li> <li>• Drugs and toxins</li> <li>• Post-endoscopic retrograde cholangiopancreatography</li> <li>• Traumatic</li> <li>• Postoperative</li> </ul> <p><b>Uncommon causes:</b></p> <ul style="list-style-type: none"> <li>• Pancreas divisum</li> <li>• Periapillary cancer</li> <li>• Cancer of the pancreas</li> <li>• Periapillary diverticulum</li> <li>• Vasculitis</li> </ul> <p><b>Rare causes:</b></p> <ol style="list-style-type: none"> <li>1. Infective: <ul style="list-style-type: none"> <li>• Coxsackie virus</li> <li>• Mumps</li> <li>• HIV</li> <li>• Parasitic</li> <li>• Ascariasis</li> </ul> </li> <li>2. Autoimmune: <ul style="list-style-type: none"> <li>• Systemic lupus erythematosus</li> <li>• Sjogren's syndrome a-1</li> <li>• Antitrypsin deficiency</li> </ul> </li> </ol>

## DIAGNOSIS

History and examination consistent with pancreatitis along with raised amylase or lipase (more than three times the normal limit) is considered diagnostic for acute pancreatitis. Serum amylase concentration increases almost immediately after the onset of an acute episode, but the magnitude of increase in serum amylase has no correlation with severity of the disease. Milder form of pancreatitis is often associated with higher level of amylase as compared to the critical disease. In addition author and co-workers demonstra-

ted that a rise of 90 mg/dL in C-reactive protein from admission to 48 hours can predict the severity of pancreatitis (7). Glasgow-Imrie Criteria (8) and APACHE-II are used to determine severity of the disease. It takes into account number of variables which are explained in detail in Table 2. Imrie score of three or more is considered as high risk for severe pancreatitis. The laboratory values are usually evaluated at 48 hours after admission, not upon admission. This scoring system was developed in the 1980s, prior to significant advances in the treatment and evaluation of pancreatitis, including advanced imaging.

Table 2. Glasgow criteria – a scoring index for severity of acute pancreatitis. PaO<sub>2</sub> – arterial partial pressure of oxygen, WBC – white blood count, LDH – lactate dehydrogenase

	Yes	No
PaO <sub>2</sub> < 59.3 mmHg (7.9 kPa)	+1	+0
Age > 55 years	+1	+0
WBC >15 x 10 <sup>9</sup> /μL (10 <sup>9</sup> /L)	+1	+0
Calcium < 8 mg/dL (2 mmol/L)	+1	+0
Urea > 44.8 mg/dL (16 mmol/L)	+1	+0
LDH > 600 IU/L	+1	+0
Albumin <3.2 g/dL (32 g/L)	+1	+0
Glucose >180 mg/dL (10 mmol/L)	+1	+0

Table 3. Original Atlanta classification and Revised Atlanta classification

Classification of Acute Pancreatitis	
Atlanta Classification 1992	Revised Atlanta Classification 2012
Mild acute pancreatitis (Acute interstitial/oedematous pancreatitis)	Mild acute pancreatitis <ul style="list-style-type: none"> <li>• No organ failure</li> <li>• No local or systemic complications</li> </ul>
Severe acute pancreatitis (acute haemorrhagic necrotising pancreatitis)	Moderately severe acute pancreatitis <ul style="list-style-type: none"> <li>• Organ failure that resolves within 48 hours</li> <li>• Local or systemic complications without persistent organ failure</li> </ul>
	Severe acute pancreatitis <ul style="list-style-type: none"> <li>• Persistent organ failure (&gt; 48 hours)</li> </ul> Single organ failure Multiple organ failure

Diagnosis of pancreatitis is confirmed by radiological investigation usually contrast-enhanced CT scan due to other conditions associated with hyperamylasaemia. Once diagnosis of pancreatitis is made, accurately predicting the severity of the disease helps in following appropriate management strategy for the patient. Many scoring systems have been devised to report severity of the disease, but none of them has proven perfect. Clinical judgment based upon clinical and laboratory data at admission might underestimate the severity of acute pancreatitis. These scoring systems are superior to clinical judgment for triaging patients to more intensive care and aggressive therapy.

## CLASSIFICATION

In 1992, the Atlanta classification for acute pancreatitis was introduced as a universally applicable classification system for the various manifestations of acute pancreatitis. This system was designed to facilitate understanding and correlation of findings seen by gastroenterologists, pathologists, radiologists, and surgeons. This approach was to be particularly useful for assessment and treatment of the various fluid collections identified during acute pancreatitis. This initial Atlanta classification system represented major progress, but advancing knowledge of the disease process, improved imaging, and ever-changing treatment options such as minimally invasive radiologic, endos-

copic, and laparoscopic procedures soon rendered some of the definitions inadequate or ambiguous, presenting a need to revise and update the Atlanta classification. In 2008, a global consensus statement was developed that included broad and international participation of many experts in the field of pancreatitis and was led by the Acute Pancreatitis Classification Working Group. This working group gathered input and revised the Atlanta classification system to improve clinical assessment and management of acute pancreatitis and to clarify appropriate terms for peripancreatic fluid collections, pancreatic and/or peripancreatic necrosis, and their changes over time. The Revised Atlanta Classification in 2012 (9) specifically introduced a new category of moderately severe pancreatitis Table 3.

Mild acute pancreatitis is characterised by the absence of organ failure and absence of local or systemic complications. Patients with mild acute pancreatitis respond well to conservative management and mortality is very rare (10).

Moderately severe acute pancreatitis is characterised by the presence of transient organ failure and local or systemic complications. Moderately severe acute pancreatitis may resolve without intervention but may require prolonged specialist care. Moderately severe pancreatitis is associated with less mortality than severe pancreatitis (11), but frequently requires interventional management of local complications and surveillance for long term complications and progression to chronic pancreatitis.

Severe acute pancreatitis is characterised by persistent organ failure (12, 13). Organ failure that develops during the early phase is set in motion by the activation of cytokine cascades resulting in systemic inflammatory response syndrome (SIRS) (12, 14, 15). When SIRS (Table 4) is present and persistent (12, 13, 16), there is an increased risk of progression to persistent organ failure. Persistent organ failure may be single or multiple organ failure. Patients who develop persistent organ failure within the first few days of the disease are at increased risk of death, with a mortality

as high as 50% (12–14). The development of infected necrosis among patients with persistent organ failure is associated with high mortality.

## MANAGEMENT

Management of acute pancreatitis is initially conservative and supportive involving analgesia, fluid resuscitation, oxygen therapy and monitoring of intake and output. Early and adequate fluid resuscitation (first 24–48 hours of admission) is associated with decreased rates of persistent SIRS and organ failure (17). After a brief period of fasting, oral diet should be introduced and there is no evidence to support prolong fasting in mild cases (18). The most important considerations in mild cases involve defining aetiology to reduce the risk of further attacks and performing early cholecystectomy in the setting of mild biliary pancreatitis (19, 20). In acute severe pancreatitis with persistent organ failure, management should be in an intensive care setting for multiple organ support and goal directed monitoring and therapy. Otherwise the management principles will be as outlined below for moderately severe pancreatitis.

## MANAGEMENT PRINCIPLES IN MODERATELY SEVERE ACUTE PANCREATITIS

In moderate cases, frequent non-invasive monitoring, observations and investigations are required to monitor progress of disease. Patients should receive high dose proton pump inhibitors due to the risk of stress ulceration and gastrointestinal bleeding. There should be early consideration for consultations with and transfer to specialist units with access to radiological, endoscopic and surgical expertise. Early systemic complications such as pleural effusions should be drained if causing respiratory compromise.

We advocate early initiation of enteral feeding which is associated with reduced infective complications and reduced hospital stay of patients (21). Nasojejunal feeding can be safely and effectively established at the bedside (22) (Figure 1). The benefit over parenteral nutrition may be partly due to preservation of the gut

membrane, reduced bacterial translocation and therefore less infective transformation of pancreatic necrosis and fluid collections (23). Nasogastric feeding has been demonstrated to be as effective as nasojejunal in small trials (17). A randomised trial has also



Figure 1. Plain film demonstrating good position of a nasojejunal feeding tube

shown that in severe cases, oral feeding can be initiated early if tolerated by the patient (24). However,

nasojejunal feeding has the advantage of maintaining the enteral route even in patients with persistent nausea, vomiting and delayed gastric emptying. Parenteral feeding should be second-line only, where enteral feeding is not tolerated or difficult to establish, or occasionally in the management of persistent pancreatic fistula.

A major focus of the management in moderately severe pancreatitis involves the timing and methods of intervention for the most common local complications; pancreatic necrosis and peripancreatic fluid collections. These can be classified practically as acute pancreatic necrosis and acute pancreatic fluid collections (PFCs). Invasive intervention should be delayed if possible for four weeks to allow maturation to walled-off necrosis (WON) and chronic fluid collections or pseudocysts. If patient is asymptomatic, stable and no signs of infection are present, collections can be managed conservatively. Reasons for intervention include suspected infected necrosis or mechanical complications of PFCs or pseudocysts such as gastric outlet or biliary obstruction (Figure 2). It is now well established that initial radiologically guided, percutaneous catheter drainage should be undertaken rather than open primary surgical necrosectomy. This can be

followed by minimally invasive, video-assisted, retroperitoneal debridement if necessary (25).

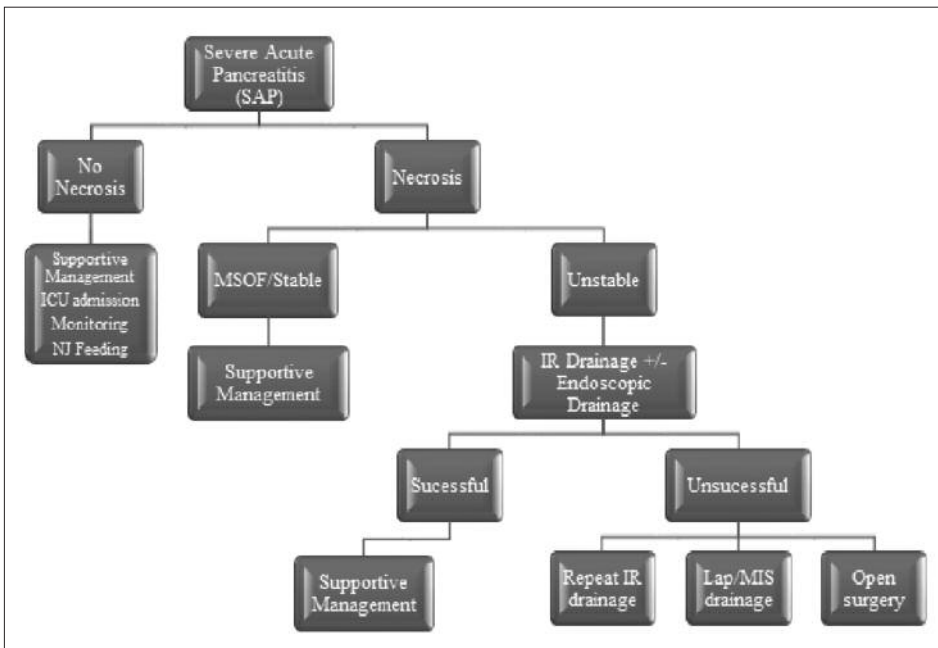


Figure 2. Algorithm explaining the pathway for the management of collections in pancreatitis

In many cases, percutaneous drainage alone will be sufficient for WON (Figure 3). More recently, a completely endoscopic approach has become an attractive alternative for both WON and acute PFCs. This consists of endoscopic ultrasound-guided transluminal drainage followed, if necessary, by endoscopic necrosectomy (26). In some cases, lapa-

roscopic (24) or open surgery is still required for persistent phlegmon or persistent fistula. The over-riding principle of all forms of interventional management should favour an organ-preserving approach, which involves debridement or necrosectomy combined with a drainage strategy that maximizes post procedural evacuation of retroperitoneal debris and exudate (27).



Figure 3. Computed tomography showing a large bore retroperitoneal percutaneous drainage catheter

Antibiotic prophylaxis remains controversial in moderately severe pancreatitis and should be carefully considered. Obtaining needle aspirations of WON or

PFCs for culture is not practical and no longer recommended (17). In the absence of persistent organ failure, justification for antibiotic usage would include suspicion of infected necrosis due to persistent fever, raised inflammatory markers or radiological findings such as gas within necrotic collections.

Endoscopic drainage is very effective for mature pseudocysts and preferable to surgical pseudocyst-enterostomy (21, 22) (Figure 4). Endoscopic stenting of the main pancreatic duct is also a useful adjunct to percutaneous drainage in cases of main duct disruption with persistent pancreatic fistula which can occur in the setting of significant necrosis.

In the setting of moderately severe pancreatitis due to gallstones, urgent endoscopic retrograde choangiopancreatography (ERCP) for choledocholithiasis is only recommended if the patient develops cholangitis, otherwise it should be delayed until the acute episode is resolving. Definitive cholecystectomy should be delayed until resolution of WON and PFCs (17). In cases where there is a predicted long delay, consideration should be given to performing ERCP and sphincterotomy to avoid recurrent acute pancreatitis. Biliary obstruction can complicate acute pancreatitis of other aetiology due to compression initially or inflammatory strictures in later stages. ERCP and biliary stenting is usually effective but per-

cutaneous transhepatic external biliary drainage may be required if there is concomitant duodenal compression or necrosis.

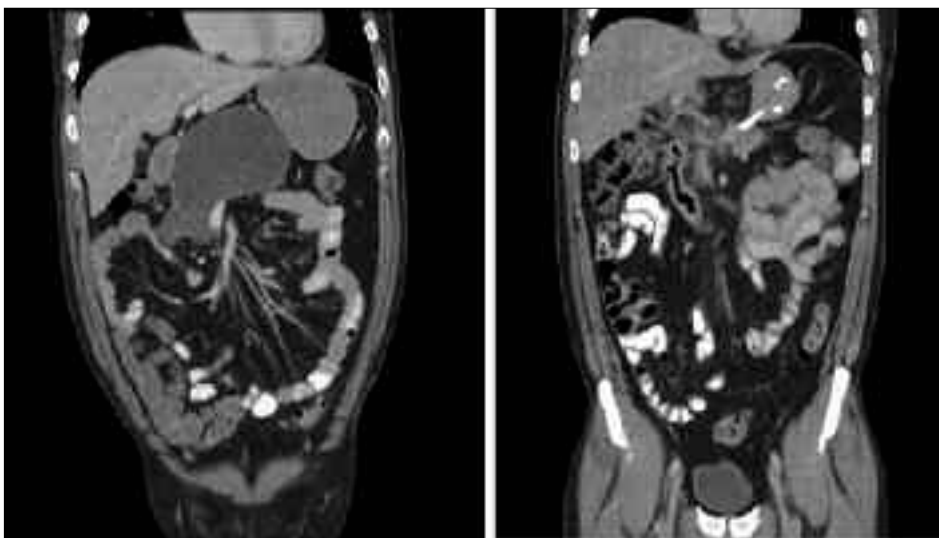


Figure 4. Computed tomography showing a pseudocyst (left) and endoscopically placed pseudocyst-gastrostomy stent with almost complete resolution (right)

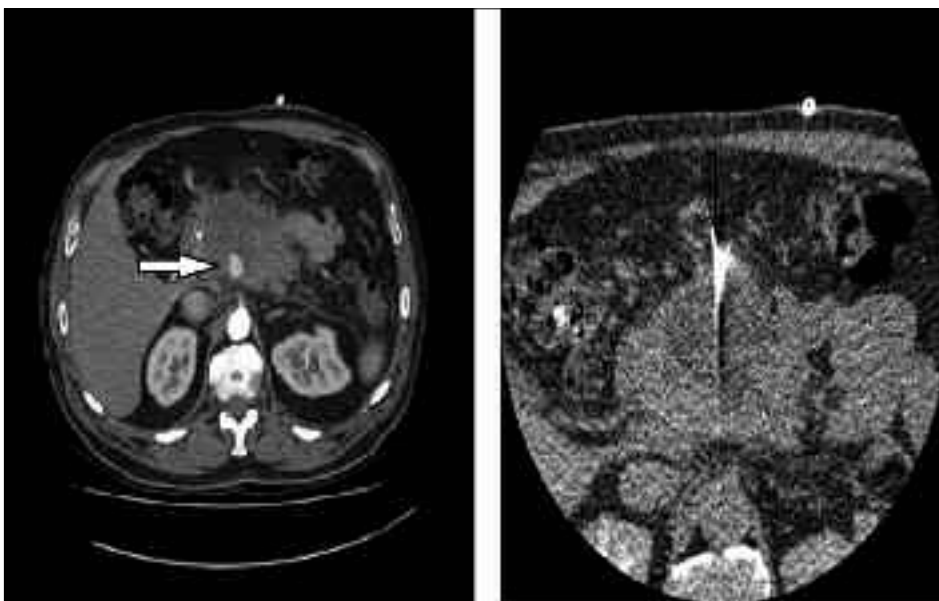
Pseudoaneurysm formation is a relatively uncommon complication if both necrotising pancreatitis and persistent pseudocysts. Affected vessels include the gastroduodenal and splenic artery. They may be detected incidentally during contrast CT

scanning but may cause life-threatening haemorrhage. They can present with intra-abdominal or gastrointestinal tract bleeding. Image-guided thrombin injections or angiography and embolization are the preferred treatment methods (28) (Figure 5). Venous thrombosis of the splenic or portal vein is commonly observed in necrotising pancreatitis due to inflammation and direct venous compression. We do not advocate routine anti-coagulation although this should be considered if there is significant extension of thrombosis into either the intra-hepatic portal vein or the superior mesenteric vein.

Due to advances in management and modern interventional techniques, mortality in moderately severe pancreatitis is low but it comes with high morbidity (11). It is therefore crucial that specialist centres and referring hospitals develop follow-up protocols to deal with the long-term complications. It is estimated that one third of patients will develop diabetes. This pancreaticogenic or type 3c diabetes can be poorly managed if not recognised early and may require specialist endocrine input (29). We estimate that at least 10% will progress to chronic pancreatitis. Exocrine deficiency is often underdiagnosed and can become established at a much shorter interval pre-

viously thought (30). The associated malabsorption and systemic inflammation means that patients are at higher risk of osteoporosis (19).

In conclusion, moderately severe pancreatitis is a complex process that requires specialist input from surgeons, gastroenterologists, radiologists, nurse-specialists and dieticians and a multi-disciplinary team approach long-term management.



*Figure 5. Computed tomography showing a gastroduodenal artery pseudoaneurysm in a patient with necrotising pancreatitis (white arrow: left) treated with image-guided thrombin injection (right)*

## References

1. O'Farrell A, Allwright S, Toomey D, et al. Hospital admission for acute pancreatitis in the Irish population, 1997–2004: could the increase be due to an increase in alcohol-related pancreatitis? *J Public Health*. 2007; 29 (4): 398-404.
2. Mole D, Garden OJ, Iredale J. Alcohol and global health: focus on acute pancreatitis needed. *The Lancet*. 2009; 374 (9694): 976-7.
3. Mole D, Haddow C, Cook B, et al. Critical care resource use and mortality from severe acute pancreatitis in Scotland: 2008 to 2010. *HPB (Oxford)*. 2012; 14: 633.
4. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. *Gastroenterology*. 2009; 136 (2): 376-86.
5. Gullo L, Migliori M, Oláh A, et al. Acute pancreatitis in five European countries: etiology and mortality. *Pancreas*. 2002; 24 (3): 223-7.
6. Toomey D, Swan N, Torreggiani W, et al. Autoimmune pancreatitis. *Br J Surg*. 2007; 94 (9): 1067-74.
7. Stirling AD, Moran NR, Kelly ME, et al. The predictive value of C-reactive protein (CRP) in acute pancreatitis—is interval change in CRP an additional indicator of severity? *PHB (Oxford)*. 2017; 19 (10): 874-80.
8. Blamey S, Imrie C, O'Neill J, et al. Prognostic factors in acute pancreatitis. *Gut*. 1984; 25 (12): 1340-6.
9. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013; 62 (1): 102-11.
10. Singh VK, Bollen TL, Wu BU, et al. An assessment of the severity of interstitial pancreatitis. *Clin Gastroenterol Hepatol*. 2011; 9 (12): 1098-103.
11. Vege SS, Gardner TB, Chari ST, et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include “moderately severe acute pancreatitis”. *Am J Gastroenterol*. 2009; 104 (3): 710-5.
12. Johnson C, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut*. 2004; 53 (9): 1340-4.
13. Mofidi R, Duff M, Wigmore S, et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *BJS*. 2006; 93 (6): 738-44.
14. Buter A, Imrie C, Carter C, et al. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. *BJS*. 2002; 89 (3): 298-302.
15. Muckart DJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. *Crit Care Med*. 1997; 25 (11): 1789-95.
16. Singh VK, Wu BU, Bollen TL, et al. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. *Clin Gastroenterol Hepatol*. 2009; 7 (11): 1247-51.
17. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013; 108 (9): 1400-15.
18. Duggan S, Smyth N, Sullivan M, et al. A transatlantic survey of nutrition practice in acute pancreatitis. *J Hum Nutr Diet*. 2012; 25 (4): 388-97.
19. O'Reilly D, McPherson S, Sinclair M, et al. Lessons from a national audit of acute pancreatitis: a summary of the NCE-POD report ‘Treat the Cause’. *Pancreatol*. 2017; 17 (3): 329-33.
20. Da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet*. 2015; 386 (10000): 1261-8.
21. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ*. 2004; 328 (7453): 1407.
22. Duggan S, Egan S, Smyth N, et al. Blind bedside insertion of small bowel feeding tubes. *Ir J Med Sci*. 2009; 178 (4): 485-9.
23. Kalfarentzos F, Kehagias J, Mead N, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *BJS*. 1997; 84 (12): 1665-9.
24. Bakker OJ, van Brunschot S, van Santvoort HC, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *New Engl J Med*. 2014; 371 (21): 1983-93.
25. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *New Engl J Med*. 2010; 362 (16): 1491-502.
26. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotizing pancreatitis: a multicentre randomised trial. *Lancet*. 2018; 391 (10115): 51-8.
27. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. *Pancreatol*. 2002; 2 (6): 565-73.
28. Evans RP, Mourad MM, Pall G, et al. Pancreatitis: preventing catastrophic haemorrhage. *World J Gastroenterol*. 2017; 23 (30): 5460-8.
29. Duggan S, Ewald N, Kelleher L, et al. The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. *Eur J Clin Nutr*. 2017; 71 (1): 3-8.
30. Duggan SN, Chonchubhair HMN, Lawal O, et al. Chronic pancreatitis: a diagnostic dilemma. *World J Gastroenterol*. 2016; 22 (7): 2304-13.

# Complications of Endoscopic Retrograde Cholangiopancreatography

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**Key words:** endoscopic retrograde cholangiopancreatography, endoscopic sphincterotomy, complications, risk factors

## ABSTRACT

Endoscopic retrograde cholangiopancreatography (ERCP) combines upper endoscopy with radiographic imaging of bile and pancreatic ducts, thus allowing a variety of therapeutic interventions. Its benefits in the minimally invasive management of biliary and pancreatic disorders are challenged by a higher potential for serious complications than any other standard endoscopic technique (estimated at 5%). The most frequent complications of ERCP and endoscopic biliary sphincterotomy are pancreatitis, cholangitis, haemorrhage and duodenal perforation. A number of less common adverse events have also been described including cardiopulmonary complications, aspiration, contrast allergy, impaction of a retrieval basket and numerous other events reported in only small numbers of patients or individual case reports.

## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) combines upper endoscopy with radiographic imaging of bile and pancreatic ducts (1), thus allowing a variety of therapeutic interventions (2, 3). The procedure is invasive and is associated with a relatively high risk of complications. However, its invasiveness, cost and complication rate still compare favourably to alternative surgical approach to pancreatobiliary pathology (4).

Standard protocols improve the safety of ERCP. These include pre-defined indications for the procedure, analgesia and sedation protocols, recommendations regarding appropriate therapeutic techniques and the education and experience level of endoscopists, performing the procedure (5).

Success and complication rates both correlate with the experience of the endoscopist performing the procedure. At least 180-200 procedures (including at least 80 deep cannulations of the desired duct) should be performed during the training period and adequate number of procedures should be performed annually to maintain the acquired competence (6–8).

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## INDICATIONS

The sensitivity and specificity for detection of common bile duct stones does not differ significantly between ERCP, magnetic resonance cholangiopancreatography and endoscopic ultrasound. However, the complication rate of the latter two is significantly lower than that of ERCP. ERCP should therefore be used only with therapeutic intent. ERCP (with endoscopic sphincterotomy) should be performed in patients with high probability of (or confirmed) choledocholithiasis, with or without associated acute biliary pancreatitis or cholangitis. It is also indicated as palliative procedure in patients with biliary obstruction due to pancreatic or biliary cancers and therapeutic procedure in selected patients with chronic pancreatitis. Diagnostic ERCP is not indicated in patients with sphincter of Oddi dysfunction type 2 and should not be performed in patients with low probability of common bile duct stones and in patients without defined pancreaticobiliary pathology (2, 3).

The most important step in the prevention of ERCP-associated complications is adherence to indications and avoidance of unnecessary procedures (9).

## PREPROCEDURAL PREPARATION

Patients should not ingest any solid food for 8–12 hours before the procedure and should undergo basic laboratory tests, including complete blood count and prothrombin time. Anticoagulants use should be held for appropriate period of time prior to the procedure (9). Patients should be made aware of the risks and benefits associated with the procedure during the procurement of the informed consent (11).

## COMPLICATIONS OF ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Endoscopic procedures can result in different negative outcomes. Complications are undesired events that require medical management resulting in hospital admission or prolongation of hospital stay. Incidents are undesired events, which do not classify as complications (and can be organisational in nature). Adverse effects are unwanted but inevitable consequences of the procedure, such as the loss of normal sphincter activity due to sphincterotomy (11, 12).

Complications, resulting from ERCP can be broadly divided into focal, resulting from direct endoscopic contact (e.g. perforation) or nonspecific, occurring outside upper gastrointestinal tract (e.g. cardiopulmonary complications). Complications may be early (within 30-day period after the procedure) or late. The severity of the complications can be assessed based on the length of the hospital stay, the need for blood transfusions, intensive care unit admission, and surgical intervention or on the resulting long-term disability or death (13, 14).

The overall incidence of the ERCP-related complications differs significantly among the studies. Specific complications (pancreatitis, perforation, bleeding, cholangitis) occur in 6.9% of the procedures, according to the pooled data of 21 studies involving 16,855 patients. Severe events were reported in 1.7% and 55 deaths were reported (0.33%) (15).

### Pancreatitis

Acute pancreatitis is the most common complication of ERCP and is defined as clinical syndrome of typical upper abdominal pain and rise in plasma lipase or amylase levels. Isolated elevation of serum amylase concentration in the absence of abdominal pain is common after ERCP, but has no clinical significance (16, 17).

The estimate of post-ERCP pancreatitis (PEP) incidence rates from 1.6 to 15% and is usually mild (resulting in up to three days of hospital stay prolongation). Severe acute pancreatitis (resulting in hospitalization of more than 10 days or local complications) is reported in 0.8% with a 0.2% mortality rate (18, 19).

Risk factors for the occurrence of PEP include endoscopist inexperience, difficult cannulation, pancreatic duct injection, pancreatic sphincterotomy, sphincter of Oddi dysfunction, younger patient age, female sex, normal serum bilirubin and a history of recurrent pancreatitis (20).

The most important aspect of PEP prevention is close attention to good ERCP technique, supplemented by the use of rectal nonsteroidal anti-inflammatory drugs. The number of cannulation attempts should be minimal and care has to be taken to avoid unnecessary pancreatic duct cannulation and contrast injection. Pancreatic stents should be prophylactically placed in all patients with high risk for developing PEP (21). Rectal use of indomethacin or diclofenac before or shortly after ERCP significantly reduces the incidence of PEP and is recommended in all patients undergoing the procedure (21–23).

## **Bleeding**

Post-ERCP bleeding is usually associated with sphincterotomy. Other causes (Mallory-Weiss tears or submucosal haemorrhages resulting from papilla manipulation, ampullary tumours, undetected bleeding diathesis) are highly infrequent (14, 18).

Bleeding severity can be graded as mild, with clinical evidence of bleeding, haemoglobin drop of less than 30 g/L and no need for blood transfusions. Moderate bleeding requires blood transfusions of four units or less, but no surgical or angiographic intervention. Severe bleeding requires surgical or angiographic treatment or blood transfusion of five units or more. The half of all bleeding complications occurs immediately after sphincterotomy. Bleeding can be delayed for up to several days post-procedure. Post-ERCP

bleeding frequency has significantly decreased in the recent decades and now occurs after 1.2% of procedures and is associated with a mortality of 0.05% (23).

Sphincterotomy is the most frequent reason for post-ERCP bleeding. Patient-related risk factors include coagulopathy, anticoagulation and antiplatelet drugs, cirrhosis, renal failure and hemodialysis. Technique-related factors that can lead to bleeding are rapid cutting, sphincterotomy length and needle-knife sphincterotomy (24).

The risk of bleeding can be reduced by identification of patients at risk, correcting coagulopathy, holding anticoagulant medications before the procedure and the use of adequate technique. Complete blood count and prothrombin time have to be obtained prior to the procedure in all patients (25).

Most episodes of post sphincterotomy bleeding stop spontaneously and the bleeding is rarely life threatening, except in patients with a bleeding diathesis. Haemostasis is usually achieved endoscopically, using diluted adrenaline injection, haemoclipping, balloon tamponade or temporally covered self-expanding metal stent insertion. Surgical or angiographic interventions are rarely indicated (25).

## **Septic complications**

Septic complications of ERCP include ascending cholangitis, acute cholecystitis, liver abscess, infected pancreatic pseudocyst and infection caused by iatrogenic perforation. These complications are infrequent, but associated with highest mortality of all ERCP-related complications (5, 6, 14, 26).

Pathogenic bacteria can enter the biliary tract by retrograde or haematogenous route. Immunocompromised patients and patients with obstruction of biliary pathways are most susceptible to septic complications (27). Gram-negative enteric bacteria are most frequent causative organisms. Multidrug-resistant pathogens have caused several outbreaks of nosoco-

mial infections due to technical problems with cleaning of duodenoscopes in the recent years (28).

Asymptomatic periprocedural bacteraemia often accompanies ERCP, however clinical consequences are rare and antibiotic prophylaxis is not indicated in most patients (28, 29).

Ascending cholangitis is the most frequent septic complication of ERCP and usually results from incomplete drainage of obstructed biliary system. Its incidence is estimated at 0.4–10% (28–32). Cholangitis usually occurs 24–72 hours after the procedure. Its course can be mild with fever lasting 24–48 hours, moderate, requiring endoscopic or percutaneous intervention, or severe with septic shock or requirement for surgical intervention (33, 34). Cholangitis can lead to liver abscess formation.

Acute cholecystitis occurs in 0.1–6% of procedures and is usually caused by influx of non-sterile contrast medium into the gallbladder or obstruction of cystic duct by covered metal stents. Clinical presentation and treatment do not differ from acute cholecystitis from other causes (30–32).

Infections of the pancreas are uncommon. Pseudocyst infection can occur due to pancreatic duct injection (30).

Prevention of septic complications of ERCP includes the use of prophylactic antibiotic therapy, when indicated (30). Endoscopes have to be properly reprocessed and radiographic contrast solution has to be sterile. Biliary obstruction should be endoscopically decompressed and patients with failed definitive decompression should be referred for percutaneous or surgical drainage (32).

## Perforation

Four types of perforation can result from ERCP (33). Free bowel wall perforations (type I) are rare and usually occur in patient with pre-existent strictures, diverticula or surgically altered anatomy.

Retroperitoneal perforations (type II) occur secondary to periampullary injury and are the most common, reported in 0.5–2.1% (34). Perforation of the pancreatic or biliary duct (type III) can occur due to guidewire or dilatation of biliary strictures. Type IV perforation (retroperitoneal air alone) can be asymptomatic, resulting from sealed microperforation, and requires careful observation, but no intervention in the absence of symptoms.

The risk of perforation of any type increases with the duration of the procedure, performance of sphincterotomy and biliary stricture dilatation (35, 36).

Free abdominal perforation (type I) is usually recognized early due to clear clinical and radiologic signs. Retroduodenal perforations (type II) can be recognized fluoroscopically during the procedure or later during evaluation of post-ERCP abdominal pain. CT should be performed in all patients suspected of having a perforation; plain radiographic films do not carry appropriate sensitivity (37).

Patients with type I perforations require surgical treatment. Retroduodenal perforations can be managed endoscopically with covered stents or over-the-scope clips, followed by fasting and intravenous hydration, nasogastric suction and parenteral antibiotic therapy. Surgical treatment is required in 20–50% of patients and necessity for surgical treatment is associated with 9.4% mortality (15, 17, 38). Prognosis of patients with perforation depends upon prompt diagnosis, the clinical setting and patient comorbidities.

## References

1. ASGE Standards of Practice Committee, Chandrasekhara V, Khashab MA, et al. Adverse events associated with ERCP. *Gastrointest Endosc.* 2017; 85 (1): 32-47.
2. Cohen S, Bacon BR, Berlin JA, et al. National Institutes of Health State-of-the-Science Conference Statement: ERCP for diagnosis and therapy January 14-16, 2002. *Gastrointest Endosc.* 2002; 56 (6): 803-9.
3. Adler DG, Baron TH, Davila RE, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas. *Gastrointest Endosc.* 2005; 62 (1): 1-8.
4. ASGE Standards of Practice Committee, Early DS, Ben-Menachem T, et al. Appropriate use of GI endoscopy. *Gastrointest Endosc.* 2012; 75 (6): 1127-31.

5. Cotton PB. Analysis of 59 ERCP lawsuits; mainly about indications. *Gastrointest Endosc.* 2006; 63 (3): 378-82.
6. Petrini JL Jr. Fools rush in ... *Gastrointest Endosc.* 2006; 63 (3): 383-4.
7. Young HS, Keeffe EB. Complications of gastrointestinal endoscopy. In: Feldman M, Scharschmidt BF, Sleisenger MH. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*, 6th ed. Philadelphia: WB Saunders; 1998. p. 301.
8. Jowell PS, Baillie J, Branch MS, et al. Quantitative assessment of procedural competence. A prospective study of training in endoscopic retrograde cholangiopancreatography. *Ann Intern Med.* 1996; 125 (12): 983-9.
9. Huibregtse K. Complications of endoscopic sphincterotomy and their prevention. *N Engl J Med* 1996; 335 (13): 961-3.
10. Trap R, Adamsen S, Hart-Hansen O, et al. Severe and fatal complications after diagnostic and therapeutic ERCP: a prospective series of claims to insurance covering public hospitals. *Endoscopy.* 1999; 31 (2): 125-30.
11. Cotton PB. Outcomes of endoscopy procedures: struggling towards definitions. *Gastrointest Endosc.* 1994; 40 (4): 514-8.
12. Fleischer DE. Better definition of endoscopic complications and other negative outcomes. *Gastrointest Endosc.* 1994; 40 (4): 511-4.
13. Petersen BT. ERCP outcomes: defining the operators, experience, and environments. *Gastrointest Endosc.* 2002; 55 (7): 953-8.
14. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc.* 1991; 37 (3): 383-93.
15. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol.* 2007; 102 (8): 1781-8.
16. Pieper-Bigelow C, Stocchi A, Levitt MD. Where does serum amylase come from and where does it go? *Gastroenterol Clin North Am.* 1990; 19 (4): 793-810.
17. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med.* 1996; 335 (13): 909-18.
18. Rabenstein T, Schneider HT, Hahn EG, et al. 25 years of endoscopic sphincterotomy in Erlangen: assessment of the experience in 3498 patients. *Endoscopy.* 1998; 30 (9): A194-201.
19. Testoni PA, Bagnolo F, Caporuscio S, et al. Serum amylase measured four hours after endoscopic sphincterotomy is a reliable predictor of postprocedure pancreatitis. *Am J Gastroenterol* 1999; 94 (5): 1235-41.
20. Testoni PA, Bagnolo F. Pain at 24 hours associated with amylase levels greater than 5 times the upper normal limit as the most reliable indicator of post-ERCP pancreatitis. *Gastrointest Endosc* 2001; 53 (1): 33-9.
21. Elmunzer BJ, Waljee AK, Elta GH, et al. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. *Gut.* 2008; 57 (9): 1262-7.
22. Dai HF, Wang XW, Zhao K. Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis. *Hepatobiliary Pancreat Dis Int.* 2009; 8 (1): 11-6.
23. Masci E, Toti G, Mariani A, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol.* 2001; 96 (2): 417-23.
24. Vandervoort J, Soetikno RM, Tham TC, et al. Risk factors for complications after performance of ERCP. *Gastrointest Endosc.* 2002; 56 (5): 652-6.
25. Christensen M, Matzen P, Schulze S, et al. Complications of ERCP: a prospective study. *Gastrointest Endosc.* 2004; 60 (5): 721-31.
26. Williams EJ, Taylor S, Fairclough P, et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy.* 2007; 39 (9): 793-801.
27. Wang P, Li ZS, Liu F, et al. Risk factors for ERCP-related complications: a prospective multicenter study. *Am J Gastroenterol.* 2009; 104 (1): 31-40.
28. Subhani JM, Kibbler C, Dooley JS. Review article: antibiotic prophylaxis for endoscopic retrograde cholangiopancreatography (ERCP). *Aliment Pharmacol Ther.* 1999; 13 (2): 103-16.
29. Anderson DJ, Shimpi RA, McDonald JR, et al. Infectious complications following endoscopic retrograde cholangiopancreatography: an automated surveillance system for detecting postprocedure bacteremia. *Am J Infect Control.* 2008; 36 (8): 592-4.
30. Llach J, Bordas JM, Almela M, et al. Prospective assessment of the role of antibiotic prophylaxis in ERCP. *Hepatogastroenterology.* 2006; 53 (70): 540-2.
31. Devičre J, Motte S, Dumonceau JM, et al. Septicemia after endoscopic retrograde cholangiopancreatography. *Endoscopy.* 1990; 22 (2): 72-5.
32. Motte S, Deviere J, Dumonceau JM, et al. Risk factors for septicemia following endoscopic biliary stenting. *Gastroenterology.* 1991; 101 (5): 1374-81.
33. Howard TJ, Tan T, Lehman GA, et al. Classification and management of perforations complicating endoscopic sphincterotomy. *Surgery.* 1999; 126 (4): 658-63.
34. Stapfer M, Selby RR, Stain SC, et al. Management of duodenal perforation after endoscopic retrograde cholangiopancreatography and sphincterotomy. *Ann Surg.* 2000; 232 (2): 191-8.
35. Enns R, Eloubeidi MA, Mergener K, et al. ERCP-related perforations: risk factors and management. *Endoscopy.* 2002; 34 (4): 293-8.
36. Jayaprakash B, Wright R. Common bile duct perforation—an unusual *Gastrointest Endosc* 1986; 32 (3): 246-7.
37. Lambiase RE, Cronan JJ, Ridlen M. Perforation of the common bile duct during endoscopic sphincterotomy: recognition on computed tomography and successful percutaneous treatment. 1989; 14 (1): 133-6.
38. Martin DF, Tweedle DE. Retroperitoneal perforation during ERCP and endoscopic sphincterotomy: causes, clinical features and management. *Endoscopy.* 1990; 22 (4): 174-5.

# Management of Complications after Endoscopic Retrograde Cholangiopancreatography: Outcomes after Surgical Treatment

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## ABSTRACT

**Background.** Severe complications after endoscopic retrograde cholangiopancreatography (ERCP) are perforation, bleeding, and necrotizing pancreatitis. This study aimed to analyze the results of surgical treatment of severe complications after ERCP and to identify possible risk factors associated with complications after surgical repair.

**Methods.** Complications after ERCP requiring surgical intervention at the Department of Abdominal Surgery at University Medical Centre Ljubljana between January 2003 and December 2013 were evaluated. Data about incidence, management, and outcome were retrospectively collected from medical records.

**Results.** Surgical intervention of complications following ERCP was required in 29 patients. The indication for ERCP was therapeutic in 21 (72.4%) patients and diagnostic in eight (27.6%) patients. Sphincterotomy was done in 26 (89.7%) patients with an addition of pre-cutting technique in six (20.7%) patients. Duodenal diverticula were observed in five (17.2%) patients. Endoscopists

noted difficulties during the procedure in 12 (41.4%) patients. There were 23 perforations; three retained Dormia baskets, two unstoppable bleedings and one patient with severe necrotizing pancreatitis. A tailored approach was used for selection of patients requiring operative treatment. Postoperative morbidity was 44.8% and mortality 10.3%. Indication for ERCP ( $p=0.015$ ), sphincterotomy ( $p=0.025$ ) and presence of diverticula ( $p=0.027$ ) influenced the type of perforation. In older patients ( $p=0.128$ ), patients with American Society of Anaesthesiologists (ASA) score 3/4 ( $p=0.085$ ) or heart rate before surgery  $> 100$  beats/minute ( $p=0.045$ ) postoperative complications occurred more frequently. ASA score and heart rate were statistically significant predictive factors for mortality ( $p=0.046$  and  $0.003$ ).

**Conclusions.** ERCP is a procedure with considerable risk for complications and tailored approach is advocated in the management of them. Patient age and comorbidities considerably influence morbidity and mortality after operation.

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## INTRODUCTION

Since its introduction in 1968, endoscopic retrograde cholangiopancreatography (ERCP) has become commonly performed endoscopic procedure (1). The diagnostic and therapeutic utility of ERCP has been well demonstrated for a variety of biliary and pancreatic diseases, including management of choledocholithiasis, diagnosis and management of biliary and pancreatic neoplasms, and postoperative management of biliary complications (2). Although ERCP, with or without sphincterotomy, is considered as a safe procedure, it is associated with small number of serious complications, such as pancreatitis, perforation, bleeding, and cholangitis (3). Reported complication rates vary widely in the published literature. However, experienced and referral centers report complication rate of less than 1% (4). With increased availability of less invasive tools such as magnetic resonance cholangiopancreatography and endoscopic US, ERCP is nowadays less commonly used for diagnostic purposes. Instead, we can observe greater diversity and complexity of procedures performed with ERCP in increasingly ill patients (elderly, with significant comorbidity, often in need of palliative treatment for known malignant disease). Therefore, severity of complications after ERCP is expected to follow accordingly.

Perforations related to ERCP occur in 0.3–1.3% of patients (5, 6), with mortality rate of 15–18% (7). Retroperitoneal perforations represent the majority of cases and are usually due to sphincterotomy. Less commonly, intraperitoneal perforations are observed which are caused by endoscope itself (6). Since these injuries are rare, there are no consensus guidelines about their management. Howard and Stapfer independently proposed a similar classification scheme for duodenal perforations and selective management based on the type of injury (7, 8).

- Stapfer et al. classified ERCP-related duodenal perforation into four types as follows (Figure 1) (7):
- Stapfer type I: duodenal perforation caused by the endoscope (often lateral duodenal wall),

- Stapfer type II: periampullary perforation of the medial wall of the duodenum associated with sphincterotomy or precut papillotomy,
- Stapfer type III: perforation of the bile or pancreatic duct due to instrumentation (guidewires, baskets, stenting),
- Stapfer type IV: retroperitoneal air alone, usually related to insufflation to maintain patency of a lumen and as such, it is not considered a true perforation.

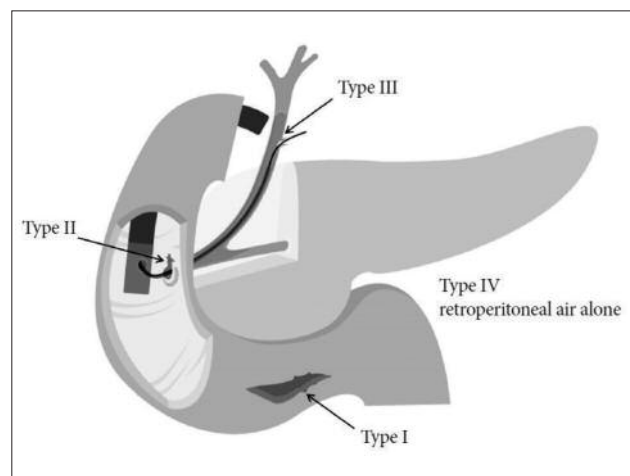


Figure 1. Classification of endoscopic retrograde cholangiopancreatography-related duodenal perforations according to Stapfer et al. (9). Type I – lateral duodenal wall perforation, Type II – periampullary perforation, Type III – ductal perforation, Type IV – retroperitoneal air alone

Traditionally, perforations after ERCP have been managed surgically (6, 10). However, in recent studies, several cases of successful conservative management for selected patients have been reported (7), and tailored approach was proposed (11). A tailored approach aims at recognition of patients with perforations that require operative treatment based on the type of injury and clinical findings (11). Immediate surgical treatment is required in Stapfer type I perforations as well as certain Stapfer type II perforations (either being large or associated with initial non-operative treatment failure) (7, 8, 11). Patients are also treated surgically in case of retained Dormia basket, severe pancreatitis or bleeding after sphincterotomy that could not be stopped with endoscopic techniques.

Our study aimed to analyze the results of surgical treatment of severe complications after ERCP in a single surgical referral center and to report useful treatment modalities. The secondary aim was to detect risk factors associated with outcome.

## PATIENTS AND METHODS

A retrospective review of ERCP-related complications that were surgically managed at the Department of Abdominal Surgery at University Medical Centre Ljubljana between January 2003 and December 2013 was conducted. We attempted to identify clinical outcomes and evaluate factors associated with postoperative morbidity and mortality. Charts were reviewed for the following data: demographics, American Society of Anaesthesiologists (ASA) score, heart rate before operation, indication for ERCP (diagnostic, therapeutic), technical characteristics of ERCP (sphincterotomy, pre-cutting technique, diverticula), time between ERCP and operation, type of complication (perforation type according to Stapfer, retained Dormia basket, bleeding, necrotising pancreatitis), type of operative management, postoperative hospital stay, postoperative complications and mortality.

Categorical data are presented as absolute numbers or percentages and were analyzed with Pearson's chi-square or Fisher's exact test where appropriate. Continuous variables were categorized and also tested with Pearson's chi-square test. A double-

sided p-value of <0.05 was considered statistically significant. All statistical analyses were carried out using the IBM Statistical Package for Social Sciences for Windows, version 22.0 (Armonk, NY: IBM Corporation).

## RESULTS

During a 10-year period, 29 patients required surgical treatment of ERCP-related complications. The majority of patients (23/29) underwent ERCP at University Medical Centre Ljubljana. In the same period, 10.280 ERCP procedures were performed. Therefore, overall rate of complications requiring surgical management was 0.2%. The other six patients were referred to our department from other hospitals.

### Patient demographics

There were 17 (58.6%) men and 12 (41.4%) women, with median age of 66 years (range 23–88 years). Nine (31.0%) patients had ASA score of 2, 13 (44.8%) patients had ASA score of 3, six (20.7%) patients had ASA score of 4 and one (3.4%) patient had ASA score of 5.

### Technical details

The indication for ERCP was therapeutic in 20 (69.0%) patients and was performed for removal of

Table 1. Complications after ERCP that required surgical management. N – number of patients with complication

Complication	N
Periampullary perforation (Stapfer type II)	11
Lateral duodenal wall perforation (Stapfer type I)	7
Ductal perforation (Stapfer type III)	4
Retained Dormia basket	3
Bleeding	2
Periampullary perforation and bleeding	1
Pancreatitis	1

bile duct stones (N=15), treatment of leak after laparoscopic cholecystectomy (N=2), stent placement in periampullary tumor (N=2) and stent placement in primary sclerosing cholangitis (N=1). Diagnostic ERCP was performed in the remaining nine (31.0%) patients as workup of elevated liver function tests. Endoscopists reported difficulties during the procedure in 12 (41.4%) patients, whereas the rest of ERCP procedures were uneventful. Sphincterotomy was done in 27 (93.1%) patients with an addition of pre-cutting technique in six (20.7%). Diverticula were present in five (17.2%) patients.

## Complications

The most frequent complication was Stapfer type II perforation (N=11), followed by Stapfer type I perforation (N=7). All the complications with their incidence are listed in Table 1. A complication was recognized during ERCP in 12 (41.4%) patients. We noted six perforations; three retained Dormia basket and three patients with bleeding. Radiological confirmation of complication was achieved with abdominal US (N=1), abdominal CT (N=11) or a combination of US and CT (N=5).

## Surgical management

All patients with confirmed perforation were surgically managed as soon as possible. The same was true for patients with retained Dormia basket. Bleedings were surgically treated only if endoscopic and supportive medical management failed. Patients with pancreatitis were also managed non-surgically and surgery was performed only if necessary.

The time between ERCP and operation was < 24 hours in 17 (58.6%) patients, 24–72 hours in nine (31.0%) patients and > 1 week in three patients. The reason for such delay in surgical treatment was unknown in one patient, who was transferred to our department from another hospital. The other two patients had minor bile duct perforation, which became clinically obvious so late. Heart rates of patients before operation were < 80 beats/minute

in 18 patients, 80–100 beats/minute in 7 patients and > 100 beats/minute in three patients.

In all three cases of bleeding from sphincterotomy site, hemostatic sutures were applied. Additionally, cholecystectomy was performed, and T-tube was inserted. In one of these three cases, a duodenal diverticulum and large perforation were found. Here, duodenojejunostomy was performed at the end of the procedure. Retained Dormia baskets were removed after choledochotomy or pancreatotomy. In both cases with Dormia basket retained in common bile duct, T-tube was inserted. In one case where Dormia basket was retained in the pancreatic duct, pancreaticojejunostomy was performed. In duodenal perforations, primary suture of perforation was performed, and T-tube was inserted for temporary removal of bile flow. In cases of large perforation or inflammation in the retroperitoneal space, pyloric exclusion or antrectomy was done. In one case of retroperitoneal perforation after sphincterotomy, Whipple procedure was performed due to periampullary adenocarcinoma. All operative procedures are listed in Table 2.

Postoperative course was complicated in 13 (44.8%) patients. Most frequently, abscess fluid collections were observed (seven patients). Other complications were colocutaneous fistula, pancreatitis, bleeding, bile duct stenosis, fluidothorax, and inflammation of operative wound. Reoperation was needed in five (17.2%) patients due to abscess fluid collection. Operative drainage was performed in three patients. In fourth patient, T-tube was removed, and choledochojejunostomy was created. In fifth patient that previously underwent antrectomy with Billroth II reconstruction, the latter was converted into Roux-en-Y anastomosis. Additionally, right hemicolectomy with Brooke ileostomy was required due to gangrenous right colon. Unfortunately, three (10.3%) patients died after operation due to bleeding, pancreatitis and septic complications after reoperation for retroperitoneal abscess fluid collection. Postoperative hospital stay ranged from 8–132 days, with an average of 27 days.

Table 2. Details on operative treatment of complications after endoscopic retrograde cholangiopancreatography. N – number of patients. D1 – proximal horizontal part of the duodenum

Complication	Procedure	N
Stapfer type I perforation	Cholecystectomy, T-tube, primary repair	4
	T-tube, primary repair	2
	Antrectomy (together with perforation in D1), Billroth II reconstruction	1
Stapfer type II perforation	T-tube, primary repair	4
	Cholecystectomy, T-tube, primary repair	2
	T-tube	1
	Primary repair	1
	Choledohoscopy, biopsy, T-tube	1
	T-tube, necrosectomy, primary repair, pyloric exclusion	1
	Whipple procedure	1
Stapfer type II perforation with bleeding	Cholecystectomy, T-tube, hemostatic sutures, duodenojejunostomy	1
Stapfer type III perforation	Cholecystectomy, T-tube	1
	T-tube, evacuation of fluid collection	1
	Duodenotomy, extraction of stone and stent, T-tube, evacuation of fluid collection	1
	Cholecystectomy, Roux-en-Y choledochojejunostomy	1
Retained Dormia basket	Cholecystectomy, duodenotomy, extraction of Dormia basket and stone, T-tube	2
	Pancreatectomy, extraction of Dormia basket, pancreaticojejunostomy	1
Bleeding	Cholecystectomy, T-tube, duodenotomy, hemostatic sutures	2
Pancreatitis	Cholecystectomy, T-tube	1

In statistical analysis, a correlation between different variables and type of complication after ERCP was tested (Table 3). With increasing ASA score, there were more lateral wall perforations (Stapfer type I) (22.2% in ASA2, 23.1% in ASA3, 33.3% in ASA4;  $p=0.021$ ). All complications that occurred after diagnostic ERCP procedures were retroperitoneal (Stapfer type II) (100%), whereas perforations after therapeutic ERCP were retroperitoneal only in 55.0% and lateral wall perforations occurred in 35.0% ( $p=0.053$ ). In the presence of diverticulum, we observed lateral wall perforations in 60.0%. If

the diverticulum was not present, complication mainly occurred as retroperitoneal perforation (75.0%) ( $p=0.112$ ). All perforations that occurred after pre-cutting technique were retroperitoneal (100%). On the other hand, 25.0% of perforations that occurred after normal sphincterotomies were located in the lateral wall. However, this difference was not statistically significant ( $p=0.196$ ). The type of complication after ERCP was associated with heart rate before operation – all patients with bleeding presented with tachycardia ( $> 100$  beats/minute) ( $p=0.054$ ). The results are listed in Table 3.

Table 3. Correlation between different variables and the type of complication after endoscopic retrograde cholangiopancreatography (Stapfer type I perforation, Stapfer type II perforation, bleeding). ASA – American Society of Anaesthesiologists score, ERCP – endoscopic retrograde cholangiopancreatography

	Post-ERCP complication type	
	$\chi^2$	p-value
Age	6.705	0.349
ASA	14.882	0.021*
Indication for ERCP	5.872	0.053
Evidence of diverticulum	4.371	0.112
Sphincterotomy with or without pre-cutting technique	6.038	0.196
Heart rate	5.830	0.054
Time between ERCP and operation	2.145	0.342

\*statistical significance

Since morbidity after operative procedure is a major concern, statistical analysis was performed to test the correlation between different variables and postoperative morbidity (Table 4). Postoperative morbidity was reported in 55.0% and 22.2% of patients that underwent therapeutic and diagnostic ERCP, respectively (p=0.101). Similarly, higher postoperative morbidity rates were observed in patients with heart rate before surgery of >100 beats/minute

when compared to ones with heart rate of < 100 beats/minute (75.0% vs. 33.3%, respectively). (p=0.044). Higher ASA scores were associated with greater postoperative complication rate (0.0% in ASA2, 61.5% in ASA3, 66.7% in ASA4 and 100.0% in ASA5; p=0.011). The same variables were evaluated regarding postoperative mortality. All three patients who died were found to have tachycardia (heart rate > 100/minute) before surgery (p=0.003).

Table 4. Correlation between different variables and postoperative morbidity and mortality

	Morbidity		Mortality	
	$\chi^2$	p-value	$\chi^2$	p-value
Sex	0.083	0.537	2.362	0.124
Age	4.997	0.172	0.740	0.864
ASA	11.168	0.011*	10.062	0.018*
Indication for ERCP	2.696	0.101	1.506	0.220
Evidence of diverticulum	1.506	0.220	0.679	0.404
Sphincterotomy with or without pre-cutting technique	0.679	0.706	1.506	0.471
Heart rate	4.067	0.044*	8.784	0.003*
Time between ERCP and operation	0.083	0.774	2.362	0.124

\*statistical significance

Interestingly, all three patients were male ( $p=0.124$ ) and were operated  $> 24$  hours after ERCP ( $p=0.124$ ). Again, there was good correlation between ASA score and mortality rate (0.0% in ASA2, 7.7% in ASA3, 16.7% in ASA4 and 100.0% in ASA5;  $p=0.018$ ). In Table 4, results of correlation between different variables and postoperative morbidity and mortality are listed.

## DISCUSSION

Although it is regarded as a safe procedure, ERCP is technically complex and carries a potential for serious complications. Overall complication rate after ERCP of up to 10% is reported in the literature (4, 7, 12). However, several factors, including indication for the procedure and endoscopic expertise, were found to influence the ERCP outcome (4, 12, 13). In our review of 10,280 ERCP procedures performed at University Medical Centre Ljubljana during the 10-year period, we identified 23 complications that required surgical treatment (six other patients were referred from other hospitals). This results in the complication rate of 0.2% which is in line with serious complication rate that was previously reported in other high-volume centers, being  $< 1\%$  (4).

Perforation related to ERCP is rare but serious complication with great mortality if overlooked and left untreated. There is still no consensus on the appropriate treatment. Management algorithms have been proposed but are based on low level of evidence due to relative infrequency and heterogeneity of endoscopic injuries. Traditionally, immediate surgical management for ERCP-related perforations was advocated. However, successful conservative management for selected patients have been reported (7, 11). Howard and Stapfer independently proposed a similar classification scheme for duodenal perforations (7, 8). In this paper, the ERCP-related perforations were categorized according to Stapfer since this is currently the most widely used classification system.

In a systematic review by Cirocchi et al. (13), immediate surgical treatment was found to give the best results regarding postoperative reintervention and mortality rate in patients with Stapfer type I perforations. The converse was true in patients with Stapfer type III and IV perforations as they are usually small can close spontaneously and can, therefore, be managed non-operatively. However, the approach to patients with Stapfer type II perforation remains controversial and should be individualized based on the perforation severity, patient's condition and reserve (11, 13). When periampullary laceration is not considered large, patients can initially undergo conservative treatment given their clinical condition is stable with no signs of sepsis. Delayed operative exploration is required in minority of patients and depends on clinical findings (septic deterioration despite conservative treatment) and CT imaging (fluid collections suggesting continuous leak from the perforation site) (7, 11).

A tailored approach was proposed to determine the need for immediate operative treatment based on the type of injury and clinical findings (11). Importantly, failed non-surgical management was associated with higher mortality, morbidity and reoperation rates as well as prolonged hospital stay (7). Similar was observed when the delay in surgical treatment was due to undiagnosed perforation (8).

Postoperative mortality of 16.6–37.5% was reported in patients with ERCP-related perforations that underwent surgical treatment (either immediate or after non-operative treatment failure) (7, 11, 14, 15). In our series, none of the patients that was referred to our department for surgical treatment of perforation died. Nevertheless, we observed overall postoperative mortality rate of 10.3%. Three patients died who were operated due to post-ERCP bleeding ( $N=2$ ) and post-ERCP pancreatitis ( $N=1$ ). Overall postoperative morbidity rate was 44.8%. Five patients required reoperation, among whom three were reoperated more than one time. Although not statistically significant, we observed higher rates of postoperative morbidity in patients undergoing

therapeutic ERCP compared to diagnostic one. Besides, postoperative morbidity and mortality rates were higher in patients with higher ASA score. The majority (69.0%) of patients had ASA score of 3 or more and approximately half (55.2%) of the patients were older than 65 years, reflecting the complexity of our patient population.

When comparing the treatment strategies from previous reports and reviewing the outcomes of our patient series, we acknowledged that our approach to patients with ERCP-related complications is rather aggressive. Early surgical treatment was offered to all patients with severe complication, especially when perforation was suspected. All patients with confirmed perforation were surgically managed as soon as possible. Since we reviewed data over a 10-year period during 2003–2013, this may be because patients included in the review were operated on by different surgical teams in different eras with varying surgical techniques and trends. Nevertheless, a rather aggressive approach proved to be beneficial in our case series regarding postoperative morbidity and mortality rates. We believe that rapid identification of post-ERCP complication and early recognition of patients that need to be managed operatively is essential for better outcome. Prompt intervention may minimize the morbidity and mortality associated with that complication. Besides, elderly and frail patients may be offered a surgical management earlier since they have no reserves to withstand the physiological stress in case of failure of non-operative management.

In conclusion, no guidelines on appropriate management of ERCP-related severe complications exist due to their rarity and insufficient evaluation. Although surgical management was advocated in the past, management has shifted toward a more selective approach in the last decades. Early diagnosis is required for timely and safe surgical intervention. A rather aggressive surgical approach, offering early surgical management in selected cases provided best outcome in our setting.

## References

1. McCune WS, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of Vater: a preliminary report. *Ann Surg.* 1968; 167: 752-6.
2. Maple JT, Ben-Menachem T, Anderson MA, et al. The role of endoscopy in the evaluation of suspected choledocholithiasis. *Gastrointest Endosc.* 2010; 71 (1): 1-9.
3. Trap R, Adamsen S, Hart-Hansen O, et al. Severe and fatal complications after diagnostic and therapeutic ERCP: a prospective series of claims to insurance covering public hospitals. *Endoscopy.* 1999; 31 (2): 125-30.
4. Salminen P, Laine S, Gullichsen R. Severe and fatal complications after ERCP: analysis of 2555 procedures in a single experienced center. *Surg Endosc.* 2008; 22: 1965-70.
5. Enns R, Elobbeidi MA, Mergener K, et al. ERCP-related perforations: risk factors and management. *Endoscopy.* 2002; 34: 293-8.
6. Martin DF, Tweedle DE. Retroperitoneal perforation during ERCP and endoscopic sphincterotomy: causes, clinical features, and management. *Endoscopy.* 1990; 22: 174-5.
7. Stapfer M, Selby RR, Stain SC, et al. Management of duodenal perforation after endoscopic retrograde cholangiopancreatography and sphincterotomy. *Ann Surg.* 2000; 232: 191-8.
8. Howard TJ, Lehman GA, Sherman S et al. Classification and management of perforations complicating endoscopic sphincterotomy. *Surgery.* 1999; 126: 658-65.
9. Park SM. Recent advanced endoscopic management of endoscopic retrograde cholangiopancreatography related duodenal perforations. *Clin Endosc.* 2016; 49 (4): 376-82.
10. Sarr MG, Fishman EK, Milligan FD et al. Pancreatitis or duodenal perforation after peri-Vaterian therapeutic endoscopic procedures: diagnosis, differentiation, and management. *Surgery.* 1987; 100: 461-6.
11. Polydorou A, Vezakis A, Fragulidis G, et al. A tailored approach to the management of perforations following endoscopic retrograde cholangiopancreatography and sphincterotomy. *J Gastroint Surg.* 2011; 15: 2211-7.
12. Glomsaker T, Hoff G, Kvaloy JT, et al. Patterns and predictive factors of complications after endoscopic retrograde cholangiography. *Br J Surg.* 2013; 100 (3): 373-80.
13. Cirocchi R, Kelly MD, Griffiths EA, et al. A systematic review of the management and outcome of ERCP related duodenal perforations using a standardized classification system. *Surgeon.* 2017; 15 (6): 379-87.
14. Ercan M, Bostanci EB, Dalgic T, et al. Surgical outcome in patients with perforation after endoscopic retrograde cholangiopancreatography. *J Laparoendoscop Adv Surg Tech A.* 2012; 22 (4): 371-7.
15. Aygerinos DV, Llaguna OH, Lo AY, et al. Management of endoscopic retrograde cholangiopancreatography-related duodenal perforations. *Surg Endosc.* 2009; 23 (4): 833-8.

# A Step-up Approach in Acute Pancreatitis – a Review

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**Key words:** *step-up approach, severe acute pancreatitis, necrosectomy*

## ABSTRACT

Acute pancreatitis remains one of the leading causes for hospitalization in the United States. Although most cases are mild and require no surgical treatment, severe acute pancreatitis is still a life-threatening condition requiring active approach in treatment. Until the 80s, the treatment of necrotizing pancreatitis was limited and consisted of ostomies and sump drains and subtotal pancreatectomies. Since then, a variety of methods have been introduced, and today minimally invasive techniques are used. With the introduction of a step-up approach, further improvements in treatment of severe acute pancreatitis have been done with a reduction in mortality rate.

## INTRODUCTION

Acute pancreatitis is one of the leading causes for hospitalization due to gastrointestinal disorders (1). The incidence of acute pancreatitis continues to rise in the Western countries and reaches 14/100 000 people per year (2–4). Although most cases are mild and self-limiting, mortality rate of severe acute pancreatitis remains high with more than 3,000 deaths per year in the United States (5).

Before the early 70s of the last century, there were no adequate studies to stratify the severity of acute pancreatitis. In 1974, Ranson et al. published criteria in assessing prognosis in early acute pancreatitis (6). The first widely accepted scoring system was Balthazar-Ranson CT scoring system, published in 1985. Balthazar et al. widened the scoring system by including proofs of necrosis due to application of intravenous contrast in 1990. Still today it is the most commonly used radiological scoring system (6).

The Atlanta classification of severity, published in 1992, made it possible to stratify hospitalized patients into two groups: mild acute pancreatitis and severe acute pancreatitis (6, 7). The Atlanta classification of severity was revised in 2012 and severity of pancreatitis was divided into mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis. It is important to point out that radiological definitions of local complications associated with interstitial and necrotizing pancreatitis were included in the classification (6, 8). In the case of interstitial pancreatitis, peripancreatic fluid collections and pseudocysts can be found on radiological examination, while necrotizing pancreatitis can be radiologically defined as acute necrotic collection and walled-off necrosis (6, 8).

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Nowadays there are two opposite approaches to treating necrotizing pancreatitis. The first one prefers 'step-down' approach in which open necrosectomy is the first choice, followed by less invasive methods used for residual collections. The second one prefers 'step-up' approach, which relies initially on less invasive techniques (9).

## TREATMENT OF NECROTIZING PANCREATITIS

Currently, the main indication for surgical treatment in severe acute pancreatitis is the infection of pancreatic or peripancreatic necrosis, especially when it is associated with organ failure (10). Conventional open necrosectomy has a high rate of postoperative complications and a high rate of postoperative diabetes. The earlier the surgery is performed during the development of acute pancreatitis, the poorer the results of surgical treatment (11–16).

In the 70s, surgical treatment of necrotizing pancreatitis consisted of ostomies and sump drains and subtotal pancreatectomies with drainage. However, in the 80s, debridement of necrosis with variety of techniques was widely performed (6). Later, in the first years of 21<sup>st</sup> century, a minimally invasive retroperitoneal necrosectomy came in use (6, 17).

Radiological drainage of infected pseudocyst and necrosis has undergone improvement so that, in a certain percentage, the collections can be adequately percutaneously drained without the need for surgical intervention (6).

Endoscopic drainage of walled-off necrosis (so-called since 2012) was reported in 1996, suggesting that endoscopic therapy may be a viable management option. Eleven patients were included in the study; nine of them did not need a surgical intervention afterward (18).

In 2006 the Dutch research group presented the randomized controlled multicentre trial where minimally invasive step-up approach was compared to maximal necrosectomy in patients with acute necrotizing pan-

creatitis (PANTER trial) (19). The results were published in 2010 in the *New England Journal of Medicine* (20).

The key in step-up approach is not the removal of all necrotic tissue but rather the control of septic focus (20).

## THE PANTER TRIAL

In an article published in the *New England Journal of Medicine*, two approaches in dealing with necrotizing pancreatitis were compared – the step-up approach and, the traditional, open necrosectomy. In the study, 88 patients with necrotizing pancreatitis were randomly assigned to receive either an open necrosectomy or the minimally invasive step-up approach. The step-up approach consisted of percutaneous drainage, followed by a minimally invasive retroperitoneal necrosectomy (video-assisted retroperitoneal debridement) if necessary. Major complications (such as new onset multiple organ failure or multiple systemic complications, perforation of a visceral organ, enterocutaneous fistula, bleeding) or death were observed as primary endpoint. In the group of patients that received open necrosectomy, major morbidity or death was observed in 69% (31/45) of patients as opposed to the group receiving a step-up approach where major morbidity or death was seen in 40% (17/43) of cases. In the latter group, 35% of patients were treated with percutaneous drainage only. The step-up approach group also had less incisional hernias and new-onset diabetes. The study concluded that the new step-up approach had better outcome than open necrosectomy in patients with necrotizing pancreatitis (20).

## HOSPITAL DEL MAR GROUP

In an article by Hospital Del Mar group published in *International Journal of Surgery*, two management options for patients with severe acute pancreatitis were compared. In a cohort retrospective study, two groups of patients were observed. Group A consisted of patients treated up to June 2010. Patients were managed primarily with surgery. Group B consisted of patients treated since July 2010. These patients were

primarily managed with minimally invasive methods. In the group A, 19 out of 83 patients had at least one laparotomy, and five were managed with minimally invasive methods. In the group B, 17 out of 81 patients were treated with minimally invasive methods, and three patients had a laparotomy. While there were no differences between the two groups in the time spent in intensive care unit and hospital time in general, there was a significant difference in overall mortality and postoperative mortality (18.1% and 50% in group A versus 6.2% and 0% in group B, respectively). The group concluded that the step-up approach in combination with minimally invasive surgery is a feasible way of dealing with severe acute pancreatitis leading to a significant drop in mortality rate (21).

## OUR EXPERIENCE

In our hospital, patients with acute pancreatitis are hospitalized at the Department of Internal Medicine, where further treatment is conducted according to the guidelines. Severe acute pancreatitis cases are hospitalized in the intensive care unit of this department. There, further intensive treatment is done using a step-up approach according to the guidelines if possible or not otherwise indicated.

## CONCLUSION

Patients with severe acute pancreatitis should be treated in specialty centers by a multidisciplinary team providing minimally invasive techniques as part of the step-up approach. The benefits of the step-up approach regarding reduction of acute complications, but also late-onset complications such as diabetes, were proven in multiple studies. Accordingly, reduction of complication leads to cost reduction. Taking all of these facts into account, a minimally invasive step-up approach presents a preferred treatment strategy.

## References

1. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases. *Am J Gastroenterol.* 2006; 101 (9): 2128-38.
2. Fagenholz PJ, Castillo CF, Harris NS, et al. Increasing United States hospital admissions for acute pancreatitis, 1988-2003. *Ann Epidemiol.* 2007; 17 (7): 491-7.

3. Yousaf M, McCallion K, Diamond T. Management of severe acute pancreatitis. *Br J Surg.* 2003; 90 (4): 407-20.
4. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology.* 2013; 144 (6): 1252-61.
5. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology.* 2012; 143 (5): 1179-87.
6. Banks PA. Acute pancreatitis: landmark studies, management decisions, and the future. *Pancreas.* 2016; 45 (5): 633-40.
7. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg.* 1993; 128 (5): 586-90.
8. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013; 62 (1): 102-11.
9. Windsor JA. Minimally invasive pancreatic necrosectomy. *Br J Surg.* 2007; 94 (2): 132-3.
10. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. *Pancreatology.* 2002; 2 (6): 565-73.
11. Poves I, Fabregat J, Biondo S, et al. Results of treatment in severe acute pancreatitis. *Rev Esp Enferm Dig.* 2000; 92 (9): 586-94.
12. Bausch D, Wellner U, Kahl S, et al. Minimally invasive operations for acute necrotizing pancreatitis: comparison of minimally invasive retroperitoneal necrosectomy with endoscopic transgastric necrosectomy. *Surgery.* 2012; 152 (3 Suppl 1): S128-34.
13. Mier J, León EL, Castillo A, et al. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg.* 1997; 173 (2): 71-5.
14. Besselink MG, de Bruijn MT, Rutten JP, et al. Surgical intervention in patients with necrotizing pancreatitis. *Br J Surg.* 2006; 93 (5): 593-9.
15. Poves Prim I, Fabregat Pous J, Garcia Borobia FJ, et al. Early onset of organ failure is the best predictor of mortality in acute pancreatitis. *Rev Esp Enferm Dig.* 2004; 96 (10): 705-13.
16. Tsiotos GG, Luque-de León, Sarr MG. Long-term outcome of necrotizing pancreatitis treated by necrosectomy. *Br J Surg.* 1998; 85 (12): 1650-3.
17. Carter CR, McKay CJ, Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: an initial experience. *Ann Surg.* 2000; 232 (2): 175-80.
18. Baron TH, Thaggard WG, Morgan DE, et al. Endoscopic therapy for organized pancreatic necrosis. *Gastroenterology.* 1996; 111 (3): 755-64.
19. Besselink MG, van Santvoort HC, Nieuwenhuijs VB, et al. Minimally invasive 'step-up approach' versus maximal necrosectomy in patients with acute necrotising pancreatitis (PANTER trial): design and rationale of a randomised controlled multicenter trial [ISRCTN13975868]. *BMC Surg.* 2006; 6: 6.
20. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med.* 2010; 362 (16): 1491-502.
21. Morató O, Poves I, Ilzarbe L, et al. Minimally invasive surgery in the era of step-up approach for treatment of severe acute pancreatitis. *Int J Surg.* 2018 Jan 30. doi: 10.1016/j.ijssu.2018.01.017. [Epub ahead of print]

# Nutritional Support in Acute Pancreatitis

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**Key words:** acute pancreatitis, inflammation, nutritional support, pharmaconutrition

## ABSTRACT

Acute pancreatitis is an acute inflammatory pancreatic disease with a complex pathophysiological background. It can vary from mild to severe form, with multiple organ failure and severe tissue catabolism. In recent years, the incidence is increasing in younger population; it can be associated with earlier alcohol intake. Severe forms are more frequent in chronic patient, who already have an inflammation-related cachectic metabolic predisposition. On the physiological level, nutritional support translates into a metabolic support and modulation of catabolism. As such, it represents the important part of multimodal approach to the patient with acute pancreatitis. The main aim of nutritional strategy is prevention or treatment of malnutrition, immune system modulation, and gut barrier protection. Therefore, after evaluating the nutritional and metabolic status of a patient, an early treatment with medical, nutritional therapy is recommended. In severe cases, such therapy can be more significant as a measure to prevent infection rather than just achieving optimal nutrition. There is some evidence supporting the use of pharmaconutrition, including probiotics, glutamine, omega-3 fatty acids, and vitamins.

## INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory pancreatic disease (1). The so-called ‘Sentinel Acute Pancreatitis Event’ (SAPE) hypothesis explains the pathogenesis of AP as ‘sentinel event’ or vicious circle of inflammation which is caused by different etiological causes. The acute insult is mediated via migration of early pro-inflammatory cells into and around pancreatic acinus, followed by stimulation of premature activation of proteolytic enzymes, auto-digestion and lastly pro-fibrotic response in pancreatic tissue. Another mechanism which can occur simultaneously is the inhibition of pancreatic products retained in the pancreatic tissue. The extent and severity of disease are related to pathophysiological metabolic consequences of pancreatic inflammation and patient’s previous nutritional and metabolic condition.

Approximately 80% of patients have a mild form of disease. There is evidence that the incidence of mild AP is increasing in younger population, mainly males. This trend may be associated with earlier alcohol intake. As expected, more severe forms occur more frequently in older patients with comorbidities

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who can be already pre-cachectic or even cachectic. In such cases, AP represents a complex metabolic syndrome associated with inflammation related to the chronic disease development. This makes an adequate nutritional support especially crucial in patients with severe and complicated pancreatitis. In severe AP, undernutrition has a negative impact on the nutritional status and the disease progression. Additionally, the pathophysiology-based scientific evidence highlighted the proper use of nutritional strategy as a key therapeutic mode to limit inflammation and to prevent or treat AP-related complications (2). The current review describes nutritional requirements and the role of nutritional management in multimodal management of AP.

## **METABOLIC CHANGES AND NUTRITIONAL REQUIREMENTS DURING ACUTE PANCREATITIS**

In AP, basal metabolism is increased, mainly under the influence of systemic inflammatory response cytokine mediators. In severe cases of AP, the use of indirect calorimetry is recommended to avoid over- or underfeeding. The resting energy expenditure varies according to the disease severity and duration. A range between 77–158% of the predicted energy expenditure has been reported (3). The non-protein energy intake of 25–35 kcal/kg body weight/day is recommended (Table 1). Overfeeding and hyperglycemia should be avoided. In cases of septic complications, the rate of protein catabolism is elevated in 80% of cases, and nutrient requirements are increased. A prolonged negative nitrogen balance may contribute to the loss of functional body mass and adverse clinical outcome (4).

### **Carbohydrate metabolism**

Systemic inflammatory response syndrome (SIRS) and oxidative stress result in insulin resistance and changes in glucose metabolism. Gluconeogenesis from protein degradation is increased, and glucose intake is an important source of energy and helps, to certain degree, offset the protein catabolism (5). However, the administration of glucose in excess

can overload the metabolic needs and may be even harmful due to hyperglycemia development and lipids synthesis. Evidence of glucose intolerance occurs in the majority of cases (incidence 85%) (6). Poor control of hyperglycemia is one of the major risk factors for infections and further metabolic complications. Strict monitoring and the adaptation of glucose intake to metabolic needs is one of the key elements of nutritional supports. Blood glucose concentration should not exceed ten mmol/L (180 mg/L). In case of hyperglycemia, insulin treatment is recommended; the dosage should not be higher than 4–6 units/hour. The impaired glucose oxidation rate cannot be normalized by insulin administration. Daily intake of 3–6 g/kg body weight of carbohydrates is recommended (Table 1).

### **Protein metabolism**

Protein degradation is increasing with severity and complications of AP. In patients with septic complications, the nitrogen losses are as much as 20–40 g/day. An increase in protein turnover must be compensated with nutritional support. The optimal goal of daily protein supply is 1.2–1.5 g/kg body weight (Table 1). Lower protein intakes must be individually adapted in patients with renal or severe hepatic failure.

### **Lipids metabolism**

Alterations in lipids metabolism are increasing with the severity of AP. An elevated serum level of triglycerides is a common finding in AP. The influence of SIRS on lipid metabolism is probably the main contributing factor, but not all mechanisms of altered lipid metabolism are entirely clear. The evidence for fat intake intolerance can be found in only 12–15% of cases (6). Severe hyperlipidemia may also contribute to the development of AP (7). Lipids can be given up to 1 g/kg body weight/day, but blood triglyceride levels must be monitored carefully (Table 1). The ideal concentration of plasma triglycerides should be < 4 mmol/L (363 mg/L); however, blood levels of triglycerides up to 12 mmol/L (1090 mg/L) are tolerated.

Table 1. Daily energy and macronutrients intake in acute pancreatitis (2). BW – body weight

Energy	25–35 kcal/kg BW
Protein	1.2–1.5 g/kg BW
Carbohydrates	3–6 g/kg BW, depends on blood glucose concentration (aim for < 10 mmol/L)
Lipids	Up to 1 g/kg BW, depends on blood triglyceride concentration (aim for < 4 mmol/L)

## EXOCRINE PANCREATIC STIMULATION BY MACRONUTRIENTS

Oral and enteral forms of enteral nutrition (EN) may stimulate the exocrine pancreatic secretion. The potential stimulation of exocrine pancreatic enzyme secretion was considered as a possibly harmful consequence of enteral or oral feeding. However, it seems that in severe AP the secretory response to EN is suppressed enough to allow the inflammation to resolve, even with continued delivery of EN (8, 9). Recently, the research evidence that showed a minimal stimulation of exocrine pancreas secretion has changed the nutritional concept in AP profoundly. Current guidelines recommend that enteral feeding into the jejunum 20–120 cm beyond the ligament of Treitz can be safe and without any major stimulation of autodigestive processes in the pancreas while maintaining the gut integrity by modulating the gastrointestinal tract systemic immunity (7, 10, 11, 12). Since similar findings were presented for gastric and

oral feedings, it seems that the same nutritional approach can be seen as a therapeutic possibility in current management of AP (13, 14, 15). Moreover, as oral and gastric enteral feeding approaches are more simple for the patient, it is now the right time to state that current evidence does not support an early start of nasoenteric tube feeding in all patients with severe AP in order to reduce the risks of infection, complications, and death (Table 2) (16). Based on guidelines from gastroenterology and pancreatic societies, tube feeding is indicated when patients are predicted not to be able to tolerate an oral diet for up to seven days, regardless of disease severity (17).

The intravenous infusion of macronutrients is safe regarding exocrine pancreatic stimulation (18). The administration of glucose intravenously does not stimulate exocrine pancreatic secretion. The main risk of intravenous glucose in AP is hyperglycemia. Intravenous lipids do not stimulate pancreatic exocrine secretion.

Table 2. The benefits of enteral nutrition

Enteral nutrition	Maintain gut integrity (reduce bacterial challenge)
	Set tone for systemic immunity (down-regulate immune response)
	Attenuate oxidative stress
	Lessen disease severity
	Promote faster resolution of the disease process
	Reduce complications (less infection and need for surgical intervention, shorter hospital length of stay, and possibly less multiple organ failure)

## NUTRITIONAL MANAGEMENT OF ACUTE PANCREATITIS

The first step in nutritional care process in AP is to diagnose the severity AP (Table 3). It includes clinical, laboratory and radiological criteria. In patients with chronic illnesses, diagnostic criteria for cachexia may be considered (Table 3) (20). They include markers of nutritional and metabolic status and markers of inflammation. In the International Classification of Disease 10 system (ICD-10, Diagnosis code R-64), cachexia is defined as a wasting condition associated with major chronic illnesses (cancer, chronic obstructive pulmonary disease, chronic heart failure, chronic kidney failure, chronic infection, sepsis, etc.) (Figure 1). Fluid therapy is an essential part of nutritional support therapy.

In the past, the bowel rest was a part of clinical routine of AP management. It was thought that this approach would limit the inflammation associated with AP. Current guidelines, however, which are based on recent scientific research, recommend early oral/enteral feeding (Table 4).

### Nutritional support in mild to moderate pancreatitis

Oral feeding in AP is associated with shorter length of stay, decreases of pain, less opioid therapy and less food intolerance (22, 10). There is no evidence that low-fat diet would be better than a regular diet and there is no need for a liquid diet (23, 24). Early EN support can be of importance in patients with pre-existing severe malnutrition or situations when early refeeding (in 5–7 days) was not possible (24). Parenteral nutrition (PN) is not recommended unless the patient is malnourished (11, 24).

### Nutritional support in severe acute pancreatitis

In patients with severe AP and patients with comorbidities, an early nutritional support is necessary. An early EN can reduce the incidence of complications and have an important contribution to increased survival rate. It is important to start feeding as soon as possible since the major benefits of early feeding are effective only if it begins in 48 hours (ESPEN

Table 3. Key diagnostic terms based on the Atlanta 2012 Classification (20)

Diagnosis of acute pancreatitis (two of the following):	Abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back)
	Serum lipase activity (or amylase) at least three times greater than the upper limit of normal
	Characteristic findings of acute pancreatitis on computed tomography or magnetic resonance imaging
<p><b>Mild acute pancreatitis:</b> No organ failure, local or systemic complications</p> <p><b>Moderately severe acute pancreatitis:</b> Organ failure that resolves within 48 hours and/or local or systemic complications without persistent organ failure</p> <p><b>Severe acute pancreatitis:</b> Persistent organ failure &gt; 48 hours</p> <p><b>Interstitial edematous acute pancreatitis:</b> Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis</p> <p><b>Necrotizing acute pancreatitis:</b> Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis</p>	
Complications	Local complications of acute pancreatitis: acute peripancreatic fluid collections, pancreatic pseudocysts, acute necrotic collections, walled-off pancreatic necrosis
	Organ failure and systemic complications of acute pancreatitis: respiratory - $\text{PaO}_2/\text{FiO}_2 \leq 300$ ; cardiovascular - systolic blood pressure < 90 mm Hg (off inotropic support), not fluid responsive, or $\text{pH} < 7.3$ ; renal - serum creatinine $\geq 170 \mu\text{mol/L}$

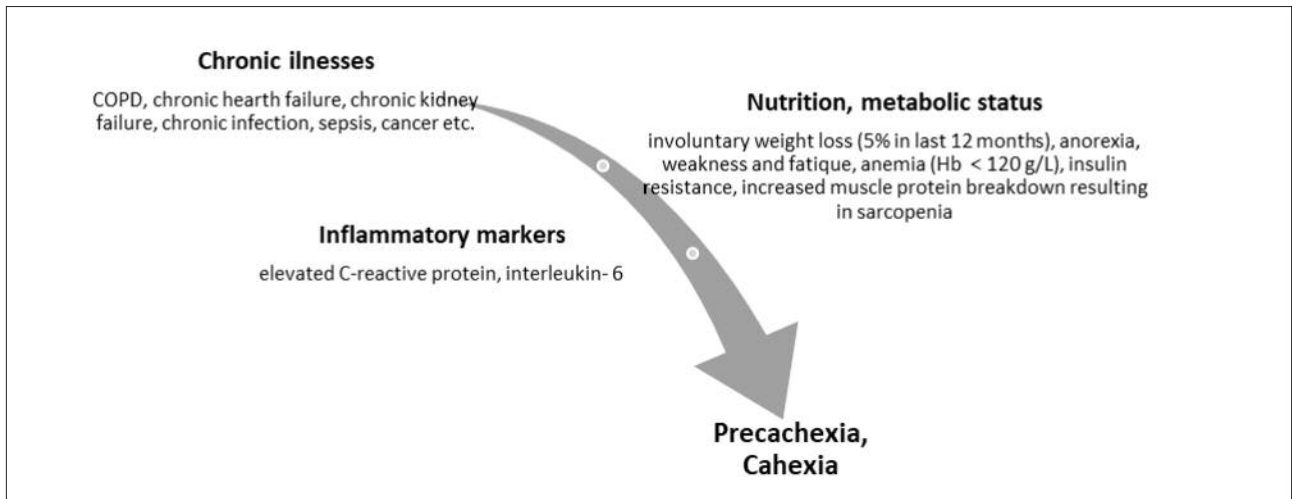
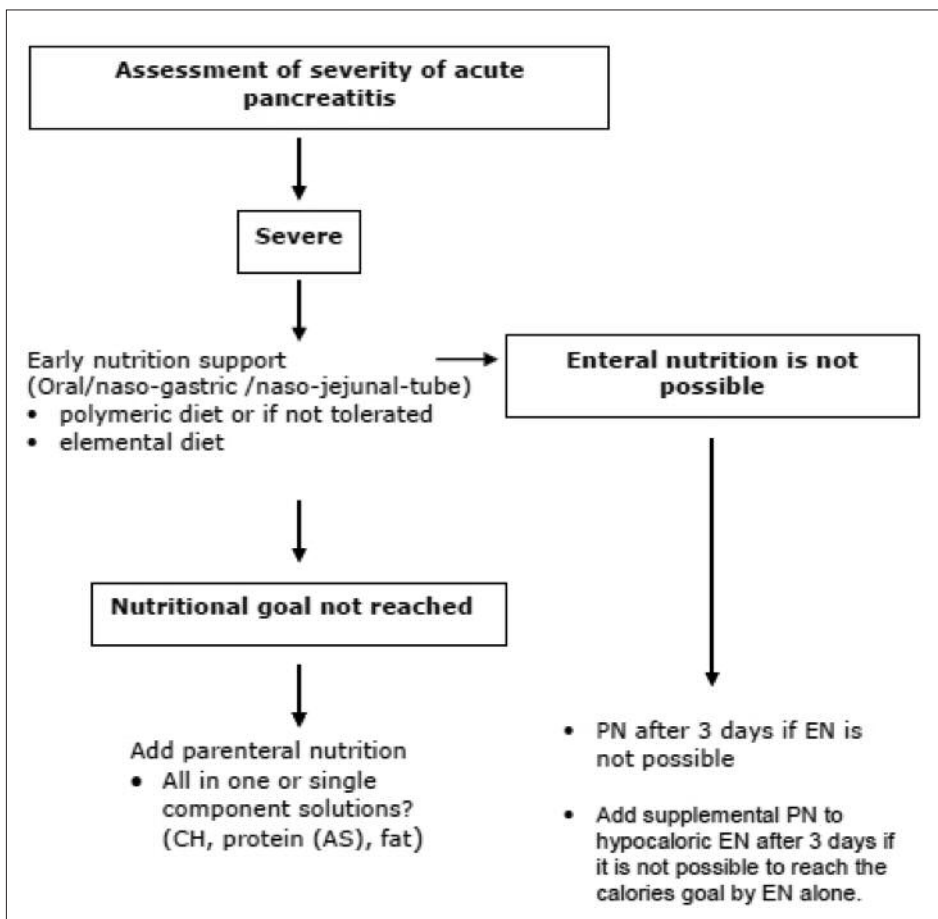


Figure 1. Pre-cachexia diagnosis (21)

Guidelines: Grade A (24)). In the last decade, the nutritional strategy in AP has changed. The nutritional management has shifted from PN to EN. Enteral feeding in AP has been shown to reduce

catabolism and loss of lean body mass as well as to modulate the acute phase response and potentially down-regulate the splanchnic cytokine response (Table 2). EN is safe and well-tolerated form of nutritional support in AP

Table 4. A clinical approach for nutrition in severe acute pancreatitis (7).  
CH – carbohydrates, PN – parenteral nutrition, EN – enteral nutrition



continuous infusion of EN is currently preferred to cyclic or bolus enteral feeding. In patients with severe AP, the adequate EN is not always possible. In such case, EN can be combined with PN to reach nutritional goals (Table 4) (24, 26).

In last years, the nature of EN in severe AP has been newly defined. Jejunal feeding is not always necessary, and gastric or even oral feeding is sometimes possible (3). However, a clear outline of recommendations cannot be given. A potential useful approach in

patients who have or will develop a severe form of pancreatitis is illustrated in Table 5.

Table 5. Practical approach to feeding in acute pancreatitis.

Try to start early (48–72 hours) with an oral nutrition regimen
<i>If not tolerated</i>
Place a multilumen gastro/jejunal tube and start with gastric feeding
<i>If not tolerated</i>
Start jejunal feeding

In clinical practice, more trials using such concepts are warranted. The major advantage of gastric feeding is to reduce the time to the feeding onset, facilitate delivery of EN, and minimize chances for ileus and intolerance. Despite the slightly increased risk of aspiration with gastric feeding, an evaluation for ‘residual’ gastric volume does not seem to be helpful in resolving this issue. The limitation of jejunal feeding is the need for expertise in tube placement below the ligament of Treitz.

Still, a matter of debate is also the use of recommended elemental enteral formulas (7). Today, it is common to start with a standard polymeric formula, and if this is not tolerated, a peptide-based formula is used. This approach is supported by the meta-analysis from Petrov et al. (27). They concluded that the polymeric formula compared to the (semi)elemental formula showed no significantly higher risk of feeding intolerance, infectious complication or mortality in AP patients. Also, the cost of polymeric formulas is known to be lower. These findings are in line with new guidelines from the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) (23).

## Pharmaconutrition

At present, formulas with pharmaconutrients cannot generally be recommended because the current evidence still needs confirmation from larger stud-

ies. Potential pharmaconutrients are glutamine, arginine, n-3 polyunsaturated fatty acids, antioxidants and pre- and probiotics.

There is a possible benefit of glutamine supplementation in patients with AP (28). With glutamine supplementation, many beneficial effects were found, such as a faster recovery of immunological parameters, shorter recovery period and less disease complications.

The concept of using pre- and probiotics to prevent intestinal bacterial translocation is very attractive and had been studied in many trials with inconclusive outcomes. The guidelines from SCCM and ASPEN concluded that the use of probiotics could be considered in patients with severe AP who are receiving early EN (23). The remaining problems are the lack of standardized commercial products and that different probiotics in different dosages have been used in the studies.

## Fluids

Fluid requirements should be assessed within six hours after the admission and re-assessed at frequent intervals for the next 24–48 hours (10). A hydration therapy is critical to prevent further organ failure and reduce mortality. An early aggressive hydration has the highest beneficial impact in the first 6–12 hours (28). However, if more than 4 L of fluids are given in first 24 hours, this approach can worsen the prognosis. Evidence indicates enhanced SIRS and higher CRP values in patients who received saline in comparison to Lactated Ringer’s (LR). That can be explained by saline infusion causing higher acid load on acinar and inflammatory cells whereas LR solution contains sodium lactate which reduces immune activation in models of AP. According to this explanation, LR solution may be the preferred isotonic crystalloid replacement fluid (28).

## SUMMARY

Among all patients with AP, 75–80% have a form of mild to moderate disease and need individually adapted nutritional support if they are at nutritional risk. Patients with a severe disease, complications or the need for surgery, require an early nutritional support. In the severe cases, an early nutritional support can be more significant as a measure to prevent infection rather than as a mean of providing nutritional support.

## References

1. Whitcomb DC. Hereditary pancreatitis: a model for inflammatory disease of the pancreas. *Best Pract Res Clin Gastro.* 2002; 16: 347-63.
2. Meier R, McLave SA. ESPEN LLL Programme: Nutrition in acute pancreatitis [internet]. c1998-2018. Dosegljivo na: <http://www.espen.org/education/lll-programme>
3. Dickerson RN, Vehe KL, Mullen JL, et al. Resting energy expenditure in patients with pancreatitis. *Crit Care Med.* 1991; 19: 484-90.
4. Sitzmann JV, Steinborn PA, Zinner MJ, et al. Total parenteral nutrition and alternate energy substrates in treatment of severe acute pancreatitis. *Surg Gynecol Obstet.* 1989; 168: 311-7.
5. Alpers DH. Digestion and absorption of carbohydrates and protein. In: Johnson LR, et al., eds. *Physiology of the Gastrointestinal Tract* (2nd edition). New York: Raven Press; 1987. p. 1469-87.
6. Havala T, Schronts E, Cerra F. Nutritional support in acute pancreatitis. *Gastro Clin N Amer.* 1989; 18: 525-42.
7. Greenberger NJ. Pancreatitis and hyperlipidemia. *N Engl J Med.* 1973; 289: 586-7.
8. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol.* 2013; 108: 1400-15.
9. Al-Omran M, Albalawi ZH, Tashkandi MF, et al. Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane Database Syst Rev.* 2010; (1): CD002837.
10. Greenberg JA, Hsu J, Bawazeer M, et al. Clinical practice guideline: management of acute pancreatitis. *Can J Surg.* 2016; 59: 128-40.
11. Jokoe M, Takada T, Mayumi T, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. *J Hepatobiliary Pancreat Sci.* 2015; 22 (6): 405-32.
12. Mirtallo JM, Forbes A, McClave SA, et al. International consensus guidelines for nutrition therapy in pancreatitis. *JPEN J Parenter Enteral Nutr.* 2012; 36 (3): 284-91.
13. Bakker OJ, van Brunschot S, van Santvoort HC, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med.* 2014; 371 (21): 1983-93.
14. Bruno MJ. Improving the outcome of acute pancreatitis. *Dig Dis.* 2016; 34: 540-5.
15. Boumitri C, Brown E, Kahaleh M. Necrotizing pancreatitis: current management and therapies. *Clin Endosc.* 2017; 50: 357-65.
16. van Baal MC, Bollen TL, Bakker OJ, et al. The role of routine fine-needle aspiration in the diagnosis of infected necrotizing pancreatitis. *Surgery.* 2014; 155 (3): 442-8.
17. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology.* 2013; 13 (4 Suppl 2): e1-15.
18. Niederau C, Niederau M, Luthen R, et al. Pancreatic exocrine secretion in acute experimental pancreatitis. *Gastroenterology.* 1990; 99 (4): 1120-7.
19. Niederau C, Sonnenberg A, Erckenbrecht J. Effects of intravenous infusion of amino acids, fat, or glucose on unstimulated pancreatic secretion in healthy humans. *Dig Dis Sci.* 1985; 30: 445-55.
20. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013; 62: 102-11.
21. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* 2011; 12: 489-95.
22. Eckerwall GE, Tingstedt BB, Bergenzaun PE, et al. Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery—a randomized clinical study. *Clin Nutr.* 2007; 26: 758-63.
23. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition therapy in adult critically ill patient: SCCM and ASPEN. *JPEN J Parenter Nutr.* 2016; 40 (2): 159-211.
24. Meier R, Ockenga J, Pertkiewicz M, et al. ESPEN Guidelines on Enteral Nutrition: pancreas. *Clin Nutr.* 2006; 25: 275-84.
25. Gianotti L, Meier R, Lobo DN, et al. ESPEN Guidelines on Parenteral Nutrition: pancreas. *Clin Nutr.* 2009; 28 (4): 428-35.
26. Petrov MS, Loveday BP, Pylypchuk RD, et al. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. *Br J Surg.* 2009; 96 (11): 1243-52.
27. Jeurnink SM, Nijs MM, Prins HAB, et al. Antioxidants as a treatment for acute pancreatitis: a meta-analysis. *Pancreatology.* 2015; 3 (15): 203-8.
28. Afghani E, Pandol SJ, Shimosegawa T, et al. Acute pancreatitis—progress and challenges: a report on an international symposium. *Pancreas* 2015; 44(8):1195-1210.

# Indications for Intervention in Acute Pancreatitis—View of a Gastroenterologist

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**Key words:** endoscopic ultrasonography, lumen-apposing metal stents, necrosectomy, pancreatic fluid collections, pseudocyst, pancreatic necrosis

## INTRODUCTION

Gastroenterologists are often confronted with the delayed complications of necrotizing pancreatitis. One such complication is walled-off necrosis (WON), which represents the local encapsulation of necrotic debris that typically takes more than a month to demarcate from the remnants of acute necrosis. Knowing this natural history is important when considering the timing of invasive interventions for managing both infected and sterile WON. Optimal intervention strategies for this condition have evolved over the past several decades. In the distant past, WON was managed almost exclusively with open surgical debridement. Unfortunately, this method was associated with excessive morbidity and mortality. Therefore, the intervention shifted to percutaneous catheter drainage, which was limited in efficacy by an inability to adequately debride large amounts of necrosis.

A major current focus is on the technique and devices used for endoscopic transmural management. There has been a debate about whether plastic stents, which have been the standard for years but are limited by their narrow luminal caliber, are

well suited for draining necrotic collections, and thus newer types of stents with larger calibres have been investigated. Self-expanding metal stents (SEMS) have appeared to be effective, but some limitations have been encountered, including migration, ingrowth, bleeding, and stent occlusion.

Recently, a novel dumbbell-shaped, lumen-apposing metal stent (LAMS) was designed with the idea that the opposing flanges would help anchor the stent, and the wide-bore saddle region would permit easy re-entrance into the cavity for debridement. In general, multiple endoscopic sessions are typically required, especially because LAMS must be removed. However, the actual number of endoscopic sessions needed tends to vary, largely because there is significant patient-to-patient heterogeneity in the size, location, and composition of WON collections. Also, the technique and endoscopist comfort level with more aggressive necrosectomy have evolved over the past decade, and these could factor into the number of procedures required for resolution. LAMS have been shown to have high clinical (77–92%) and technical success (97.5–100%) rates for drainage of peripancreatic fluid collections (PFCs), including both pancreatic pseudocysts (PP) and WON, along with low adverse

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event rates (5–11%). Due to their increased luminal diameter, LAMS are preferable in patients where endoscopic necrosectomy is required.

We found that LAMS had excellent clinical efficacy for management of PFCs with a technical success of 98% with low heterogeneity and clinical success rate of 93% with moderate heterogeneity. To further refine our results, we conducted a subgroup analysis to evaluate the clinical success in both PP and WON. We did not find any significant difference in clinical success for management of PP and WON. This is contrary to the previous studies on endoscopic drainage with plastic stents and fully covered SEMs which reported around 90% clinical success for PP while only 50–65% for WON. We believe that this is due to multitude of reasons. First of all, larger diameter allows both PP and WON to empty promptly in the gastric or duodenal lumen, thereby increasing success rate. Furthermore, larger luminal diameter allows direct endoscopic necrosectomy and irrigation via nasocystic catheter which probably explain the same clinical success in WON when compared to PP. On the other hand, the benefit of performing endoscopic retrograde cholangiopancreatography and transpapillary pancreatic ductal drainage in addition to endoscopic US-guided transmural drainage was assessed. Among 174 patients with pseudocysts, 95 received transmural drainage, and 79 received combined drainage. Transpapillary drainage was unsuccessful in more than half of the patients with attempted transpapillary stenting. No difference in long-term resolution rates was observed. Also, transpapillary drainage was negatively associated with pseudocyst resolution, indicating that the presence of a pancreatic stent may hinder the patency and maturation of the cystoenterostomy fistula.

During endoscopic US-guided drainage, the pseudocyst is first visualized using a linear echo-endoscope to determine the best puncture site. In general, transgastric puncture is more preferable than transduodenal puncture owing to more stable position of the endoscope and better luminal visibility in the stomach. Colour Doppler mode would be utilized to

ensure the absence of aberrant vessels or varies along the intended puncture track. After puncture of the pseudocyst by a 19-gauge needle, the track is dilated with either electrocautery or balloon dilator. One or two double pigtail plastic stents would be placed in the pseudocyst using the double wire technique.

## References

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013; 62 (1): 102-11.
2. Varadarajulu S, Bang JY, Sutton BS, et al. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology*. 2013; 145 (3): 583-90.
3. Bang JY, Varadarajulu S. Transmural drainage versus transpapillary stenting and transmural drainage: not an open and shut case...yet. *Gastrointest Endosc*. 2016; 83 (5): 1046.
4. Sharaiha RZ, Tyberg A, Khashab MA. Endoscopic therapy with lumen-apposing metal stents is safe and effective for patients with pancreatic walled-off necrosis. *Clin Gastroenterol Hepatol*. 2016; 14 (12): 1797-1803.
5. Bang JY, Hasan MK, Navaneethan U, et al. Lumen-apposing metal stents for drainage of pancreatic fluid collections: when and for whom? *Dig Endosc*. 2017; 29 (1): 83-90.
6. Adler JM, Gardner TB. Lumen-apposing metal stents for walled-off necrosis: how effective are they? *Clin Gastroenterol Hepatol*. 2016; 14 (12): 1804-5.
7. Siddiqui AA, Kowalski TE, Loren DE, et al. Fully covered self-expanding metal stents versus lumen-apposing fully covered self-expanding metal stent versus plastic stents for endoscopic drainage of pancreatic walled-off necrosis: clinical outcomes and success. *Gastrointest Endosc*. 2017; 85 (4): 758-65.

# Indications for Intervention in Acute Pancreatitis – View of a Radiologist

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**Key words:** acute pancreatitis, complications, embolization, pancreatic fluid collections, percutaneous drainage, pseudoaneurysm, treatment

## ABSTRACT

Pancreatic fluid collections and vascular complications are frequent complications of pancreatitis. The revised Atlanta Classification classified pancreatic fluid collections as acute or chronic, with chronic fluid collections subdivided into pseudocysts and walled-off pancreatic necrosis. Management of pancreatic fluid collections has evolved over the past two decades from surgical necrosectomy to more conservative, less invasive procedures, such as percutaneous drainage, percutaneous pseudocyst-gastrostomy, endoscopic transgastric necrosectomy, and video-assisted retroperitoneal debridement. Major vascular complications related to pancreatitis can cause life-threatening hemorrhage and have to be dealt with as an emergency. Embolization is the most frequent treatment of choice in patients with acute hemorrhage. This article aims to present the role of minimally-invasive interventional therapies, such as percutaneous drainage, percutaneous pseudocyst-gastrostomy and endovascular embolization in patients with complications of pancreatitis.

## INTRODUCTION

Management of necrotizing fluid pancreatitis has evolved over the past two decades from more aggressive and traditional surgical necrosectomy to more conservative management relying on minimally invasive percutaneous and endoscopic necrosectomy (1, 2). Percutaneous drainage is performed using the same techniques as are used for conventional intraabdominal collection drainage. According to the revised Atlanta Classification, in many cases of acute pancreatitis, there are three well-defined fluid collections: acute peripancreatic fluid collections (APFCs) and the so-called walled-off pancreatic necrosis (WON) or pseudocysts which both develop in the late phase of the disease (Figure 1b, 2b). In many cases, these anatomic entities can be successfully treated with radiological interventional methods (3).

Venous thrombosis, involving the splenic, mesenteric, or portal veins, is the most frequent vascular complication. Pseudoaneurysm formation is the second most frequent vascular complication of pancreatitis, resulting from vessel erosion, usually caused by a pseudocyst and WON (4). The most commonly involved vessels are the splenic, gastroduodenal, and pancreaticodu-

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denal arteries (Figure 3a). Pseudoaneurysms are not an early complication because they take time to develop. However, they are associated with high mortality rates due to the risk of rupture, ranging from around 12% if treated to > 90% if untreated. The risk factors for major vascular complications include necrotizing pancreatitis, multiple organ failure, sepsis, and pancreatic fluid collections such as abscesses, pseudocysts or WON. Previous pancreatic necrosectomy, long-term anticoagulation therapy, and underlying vasculitis also elevate the probability of developing this complication (5).

Hemorrhage is as a life-threatening complication of pancreatitis, which may occur with or without the prior formation of a pseudoaneurysm after surgical intervention, or as a consequence of the formation of varices, and may occur in the peritoneal cavity, retroperitoneum, gastrointestinal tract, or directly in the Wirsung duct.

Interventional radiologists play a crucial role in the treatment of vascular complications of pancreatitis. Surgery is indicated in the presence of hemodynamic instability. Embolization is the most frequent treatment of choice in patients with acute hemorrhage or peripancreatic pseudoaneurysms using a variety of embolic agents, such as coils and glue (6).

This article aims to present the role of minimally-invasive interventional therapies such as percutaneous drainage, percutaneous pseudocyst-gastrostomy and endovascular embolization in patients with complications of pancreatitis.

## PERCUTANEOUS DRAINAGE

### Procedure

Percutaneous drainage of APFCs is a well-established and common procedure, and a simple drainage will often suffice for these collections (1, 7, 8). The drainage catheter is predominantly placed under US guidance. Strict sterility is maintained, and local anesthesia is applied. For therapeutic drainage, if possible,

a retroperitoneal approach is preferred over an anterior transperitoneal approach (Figure 2). In most cases, Seldinger image-guided technique is used for drainage catheter insertion. The Seldinger technique, named after the Swedish radiologist Sven-Ivar Seldinger, consists of advancing an 18-gauge needle into the target collection under US, CT or cone beam CT guidance. After the access is obtained, contrast injection under fluoroscopy can be performed to evaluate the extent of the collection and to elucidate any fistulous connections to the main pancreatic duct or adjacent bowel. A 0.035-inch guidewire is advanced through the needle, and the needle is exchanged for the catheter over the wire and secured into the drained collection. Depending on the quality of the fluid, different sizes of drains should be used. If there is an abscess, the thicker (14–30 French), otherwise the thinner (8–10 French) pig-tail catheter is to be used (Figure 2d). The drained fluid should be sent for bacteriological analysis in each case. Multiple drains can be inserted at a time if necessary. Each catheter should be irrigated with 5–10 mL of sterile saline solution at least three times per day. Drainage catheters typically remain in place until the drained fluid is clear and <10–30 mL per day (7, 8). Follow-up imaging to confirm drainage catheter position and document collection resolution is often necessary. Ultrasound examination is the most suitable for the observation of size and change of the fluid collection. It is inexpensive and can also be performed at the bedside.

### Complications

Complications, related to percutaneous drainage, such as injury of the surrounding organs and bleeding, are rare (2%) (1, 8). More commonly, the drain can become clogged or dislodged, requiring replacement. A late complication of percutaneous drainage is the development of pancreatic fistulae to the skin or gastrointestinal tract; however, most of fistulas close spontaneously (8).

## **PERCUTANEOUS PSEUDOCYST-GASTROSTOMY**

In 1985, professor S. Hancke of Denmark developed an original method using US-guided percutaneous intervention to ensure prolonged internal cystogastric drainage until the pseudocyst collapses and seals off (9, 10). It can be done under local anesthesia without laparotomy. The endoscopist introduces gastroscope into the stomach. A 20-cm 18-gauge needle is inserted under US guidance. The route of a needle insertion into the pseudocyst through both, the anterior and posterior gastric wall, is ascertained by the endoscopist. If the route cannot be confirmed, the puncture needs to be repeated. After a guidewire and a dilator have been introduced according to Seldinger's method, a double pigtail catheter is inserted so that its distal curve reaches into the pseudocyst and its proximal curve into the stomach lumen (Figure 1e). A 15-cm pigtail catheter is attached to the front part of a 30-cm 18-gauge needle with mandrin. Behind the pigtail, there is a 15-cm hard catheter (the so-called 'pusher') attached to the needle as well; using this, the front part of the pigtail is pushed with a wire into the pseudocyst while the distal part remains in the stomach. The depth of catheter insertion can be regulated with the help of a thread, which is also attached to the needle. Finally, the wire, thread, and the pusher are removed. The difference in pressures forces the pseudocyst contents into the stomach. The position of the distal curve is monitored by US, as it can be seen in the remaining peripancreatic liquid. The position of the proximal curve in the stomach lumen is assessed by the endoscopist. The endoscope is also used for minor adjustments of the proximal curve position and the cutting of a thread when it cannot be removed spontaneously.

## **PERCUTANEOUS DRAINAGE OF ACUTE PERIPANCREATIC FLUID COLLECTIONS AND PSEUDOCYST**

APFC develop in the early phase of interstitial edematous pancreatitis (IEP) (Figure 1a). They develop within the peritoneal and retroperitoneal spaces and less frequently in the mediastinum. Early in the course

of the disease (<4 weeks), the APFCs do not have definite epithelial walls and their boundaries are limited by the natural fascial barriers of retroperitoneum and peritoneum (11). In most cases, spontaneous resolution occurs without intervention. If APFCs do not resolve spontaneously and persist beyond four weeks, an identifiable wall is developed, and APFCs become pseudocysts (Figure 1b, 1c). Approximately 25% of pseudocyst can cause a spectrum of symptoms, mostly related to mass effects (11, 12). Pseudocysts can also become infected, necessitating treatment. When they are associated with some local complications, such as infection, hemorrhage, rupture and symptoms, such as abdominal distension, nausea, vomiting and upper GI bleeding, intervention is needed.

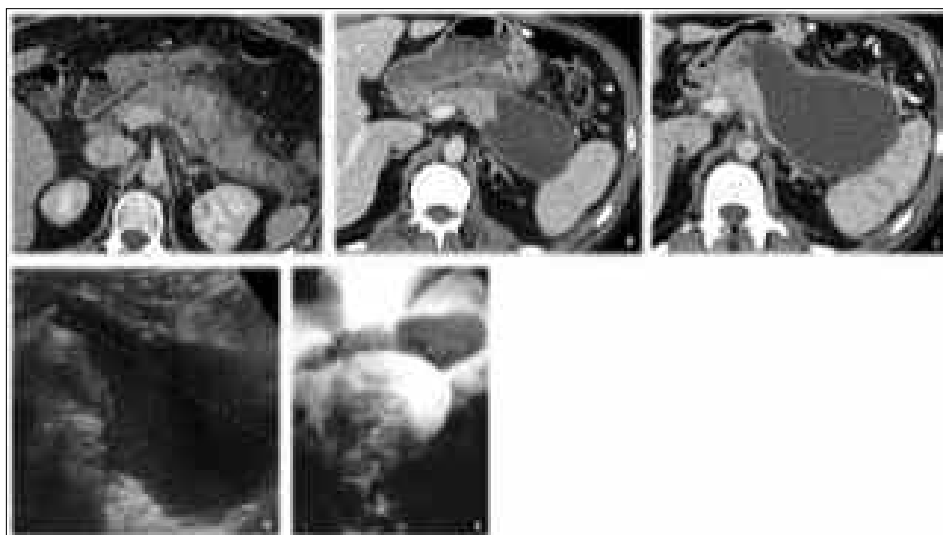
Percutaneous drainage involves a placement of an external drainage catheter into the pseudocyst. Once the presence of non-liquefied material and infection has been excluded, simple percutaneous drainage is usually sufficient for large and symptomatic pseudocysts. Most infected pseudocysts are drained percutaneously rather than surgically (1, 2, 12). Initial studies comparing surgical drainage to percutaneous drainage found both procedures to be efficacious (13). However, more recent comparative studies have generally favored percutaneous drainage over surgical drainage, with some studies even demonstrating a mortality benefit (1, 11, 13). Percutaneous drainage has been recently compared also to endoscopic drainage. A recent study directly comparing percutaneous vs. endoscopic management retrospectively reviewed 81 patients (14). This study found equal technical success rates and adverse events rates between the techniques, but a decreased reintervention rate, a shorter hospital stay, and a decreased number of follow-up abdominal imaging studies among patients treated with endoscopic drainage. Internal drainage is a percutaneous US-guided internal cystogastric drainage of pancreatic pseudocysts using a double pigtail catheter. The method is minimally invasive and also feasible in high-risk surgical patients. It requires a team, consisting of an interventional radiologist, an ultrasonographer, and an endoscopist. In properly selected patients, the results are excellent. Pseudocyst should be mature and

preferably connected to the posterior wall of the stomach. Optimally, pseudocyst should measure  $> 5$  cm, although a slightly smaller pseudocysts ( $4.5 \times 4$  cm) were successfully treated as well (10).

## PERCUTANEOUS DRAINAGE OF ACUTE NECROTIC COLLECTIONS AND WALLED-OFF PANCREATIC NECROSIS

Percutaneous image-guided drainage for acute necrotic collection (ANC) or WON involves placement of a catheter into collection under US guidance with fluoroscopy, CT or cone beam CT guidance (Figure 2). Ideally, a retroperitoneal approach is taken. Non-infected ANCs do not require intervention at an early phase (2, 7, 11). If they cause symptoms, such as abdominal pain and mechanical obstruction, clinical deterioration, or signs of sepsis, intervention is needed (2, 11). In WON patients, if they are asymptomatic and WON is not infected, it is not necessary to perform intervention, regardless of the size and distension. If those patients experience symptoms, such as severe pain, obstruction or in a case of infected WON, they

should be treated (1, 2, 11, 12). Percutaneous drainage procedure has proved to be effective alternative to surgery, particularly early in the course of complications from severe acute pancreatitis with necrosis. If CT demonstrates residual collections, and little or no drainage from the percutaneous catheter is observed, several drainage catheters may have to be placed and irrigated to achieve percutaneous necrosectomy and to reduce toxicity (2). Traditionally, the success rate of percutaneous drainage alone (defined as survival without the need for additional surgical necrosectomy) ranged from 35–84%, with mortality rates ranging from 5.6–34% and morbidity ranges of 11–42%, most commonly due to pancreatic cutaneous fistulas and pancreaticoenteric fistulas, which occur in as many as 20% of cases (1, 11). Consequently, percutaneous drainage is more often used as an adjunct therapy, often serving as the first step of a step-up approach to endoscopic or surgical drainage. The Dutch PANTER trial illustrated this concept by comparing open necrosectomy with a less-invasive step-up approach in 88 patients (15). In the step-up approach, patients first underwent percutaneous drainage of the collec-



*Figure 1. Percutaneous US-guided internal cystogastric drainage of pancreatic pseudocysts using a double pigtail catheter. Evolution of interstitial edematous pancreatitis and pancreatic pseudocyst during 10 months in a 49-year-old male patient. A – axial CT image of interstitial edematous pancreatitis; B – during the course of the disease the patient developed a pancreatic pseudocyst as shown on the CT image; C – axial CT eight months after the onset of interstitial edematous pancreatitis; D – US image obtained right before the percutaneous pigtail catheter placement; E – fluoroscopic image, obtained during procedure (pigtail catheter)*

tion, followed by a minimally invasive retroperitoneal necrosectomy, if clinical improvement was not achieved. Results showed that the minimally invasive approach was associated with an overall decreased mortality rate, fewer major and long-term complications, and reduced overall healthcare costs. Of note, percutaneous drainage alone without subsequent necrosectomy was achieved in 35% of patients.

Two different strategies are applied for percutaneous treatment. The first comprises the insertion of US-

guided percutaneous drainage to evacuate the infected PFCs and then, along with the administration of antibiotics, waiting for clinical improvement and a complete resolution of the disease. Multiple drainage catheters may be inserted, and irrigations can be made through them. Drainage catheters can be replaced as often as necessary. The aim of this strategy, known as the ‘step-up approach,’ is to improve the patient’s condition and to delay surgery until the infectious pancreatic necrosis is better delimited. Several studies have shown that with the placement of percutaneous drains alone, 23–47% of patients can achieve complete resolution of the acute disease and do not require any additional procedures (1, 15). The second strategy consists of placement of a percutaneous drainage as a guide to locate the anatomic space where the necrosis should be drained. After placing the drains, the patient is immediately transferred to the operating theater. At that time, using either general anesthesia or local anesthesia with sedation, the tract is progres-

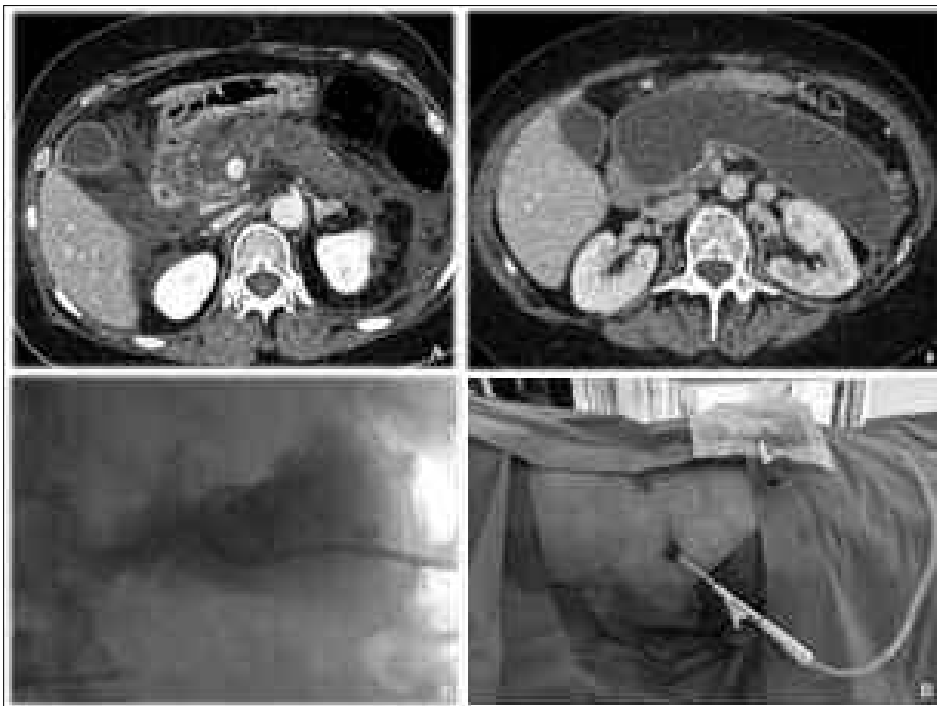
sively dilated until obtaining a diameter (30 French) large enough for the insertion of a rigid nephroscope (video-assisted retroperitoneal debridement), through which the necrosis can be washed and fragments removed under direct vision. Large caliber drains are then inserted through the tract to allow continuous washing. This maneuver can be repeated as often as necessary to achieve complete removal of necrosis fragments (1, 2, 8, 16).

## ENDOVASCULAR APPROACH

### Procedure

Procedures are usually performed in the endovascular suite under local anesthesia. Femoral artery is the preferential access site. A 5-French sheath is placed into accessed artery. The celiac (CA) and superior mesenteric arteriograms (SMA) are performed by injecting 30–50 mL of iodinated contrast material at

the rate of 5–6 mL/second. A 4-French or 5-French catheter is telescoped through the sheath, through which a microcatheter is used for embolization. Exclusion of the pseudoaneurysm from systemic circulation can be achieved by slowing the flow within the pseudoaneurysm (using coils, stent grafts), inducing thrombosis (coils and liquid embolic agents) and stimulating inflammation (coils and liquid agents). Coils or micro coils are the preferred and most widely used agents for embolization of pseudoaneurysms (4, 5). Another option for successful embolization of a pseudoaneurysm while pre-



*Figure 2. A 64-year-old man with gallstone-induced severe necrotizing pancreatitis. A – axial contrast-enhanced CT image obtained six days after the admission shows extensive pancreatic necrosis and peripancreatic fluid accumulation; B – axial contrast enhanced CT image shows walled-off necrosis obtained right before percutaneous drainage catheter placement 51 days after onset of symptoms; C – a retroperitoneal percutaneous drain insertion under US and fluoroscopic control; D – image shows percutaneous placement of 12-French catheters*

servicing distal organ perfusion is stent-assisted coiling of a pseudoaneurysm. An uncovered metallic stent is selectively placed across the neck of the pseudoaneurysm to preserve the flow within a visceral vessel. The aneurysm is then cannulated through the interstices of the stent and embolized with micro coils. Alternatively, endovascular treatment with placement of a covered stent across the pseudoaneurysm isolates the aneurysm from the circulation while preserving flow to the organ (Figure 3). It should be emphasized that, when treating aneurysms in the pancreaticoduodenal distribution, a careful search for an occlusion of collateral supply to these aneurysms is essential before ending the procedure. When pseudoaneurysms are associated with pseudocyst formation, cyst decompression should be undertaken. Postembolization angiography of both the SMA and CA is performed to ensure successful exclusion of the aneurysmal segment.

## Indications

All patients, presenting with hemorrhage, unstable hemodynamic status and mass effect symptoms due to a pseudoaneurysm, need embolization. However, due to high mortality of rupture, all pseudoaneurysms require treatment as soon as detected (4, 7, 17). Since pseudoaneurysms have thin walls, their size does not correlate with the risk of rupture. Small pseudoa-

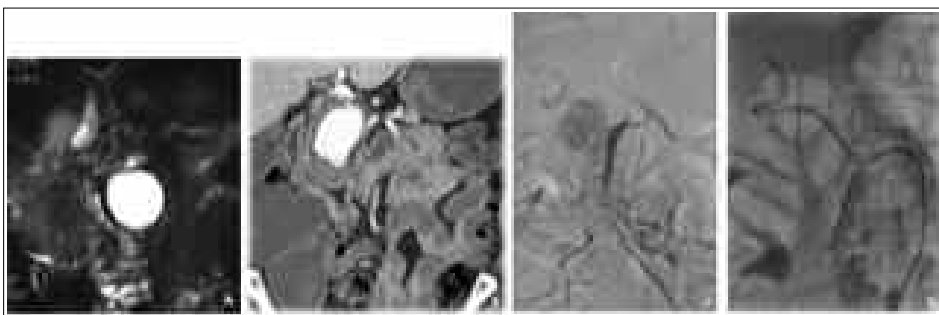
neurysms may cause life-threatening hemorrhage, while a large pseudoaneurysm may be detected incidentally. However, this is not the case with true aneurysms that need treatment when sized > 2 cm or with mass effect. Embolization for incidentally detected pseudoaneurysms in asymptomatic patients is still controversial. Due to high risk and mortality of rupture, we embolize all pseudoaneurysms irrespective of whether the patient is symptomatic or not.

## Complications

Complications can be divided into puncture site, intervention site, and postembolization complications. Puncture site complications include bleeding, hematoma, pseudoaneurysm formation, arterial thrombosis, arteriovenous fistula and nerve damage. Most of these complications are rare if proper puncture and postprocedural compression is done. Closure devices may also be used for hemostasis with good results. Intervention site complications include rupture of the pseudoaneurysm, arterial dissection, non-target embolization, distal migration of coils, and straight deployment of a coil. Recurrence of the pseudoaneurysm may occur secondary to its incomplete exclusion or collateral supply, and rarely due to migration of coils, and needs repeated embolization (6, 7).

## Follow-up

Follow-up is an important and integral part of the management of pseudoaneurysms. For pseudoaneurysms, visible on ultrasonography, follow-up with the same modality 24–48 hours after the procedure and possibly one month later is adequate (17). Computed tomography angiography is usually not required in asymptomatic patients,



*Figure 3. Patient with severe blood loss after surgical treatment of pancreatic pseudocyst. A – MRI of pancreatic pseudocyst prior to surgery; B – axial CT image demonstrates large (symptomatic) pseudoaneurysm; C – angiography demonstrates pseudoaneurysm of the right hepatic artery arising from the superior mesenteric artery (replaced right hepatic artery to the superior mesenteric artery), coil embolization of the artery is contraindicated due to possibility of an end-organ ischemia; D – thus, covered stent-graft was deployed across the site of arterial injury with complete exclusion of pseudoaneurysm*

but becomes necessary when there is a strong clinical suspicion of recurrence and when pseudoaneurysm is inaccessible to US imaging. Endovascular approach is the treatment of choice for recurrent pseudoaneurysms and in failed cases. Thus, follow-up evaluation varies from case to case and initially includes clinical assessment, followed, if necessary, by US or CTA.

## CONCLUSION

The role of interventional radiology in the management of acute pancreatitis complications falls into two main categories: percutaneous drainage of PFCs and endovascular management of pancreatitis-related pseudoaneurysms. Percutaneous drainage for both PFCs, pseudocysts, and WON is indicated for infected collections or when they cause severe symptoms. The majority of the pseudoaneurysms can be successfully treated with endovascular repair.

## References

1. Tyberg A, Karia K, Gabr M, et al. Management of pancreatic fluid collections: a comprehensive review of the literature. *World J Gastroenterol.* 2016; 22 (7): 2256-70.
2. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol.* 2013; 108 (9): 1400-15.
3. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013; 62 (1): 102-11.
4. Košutić I, Garbajs M, Popović P. The importance of radiological examinations in most frequent diseases of the pancreas. *Gastroenterolog.* 2016; 21: 78-87.
5. Belli AM, Markose G, Morgan R. The role of interventional radiology in the management of abdominal visceral artery aneurysms. *Cardiovasc Intervent Radiol.* 2012; 35: 234-43.
6. Popović P, Garbajs M. Diagnostika in znotrajžilno zdravljenje arterijskih pseudoanevrizem. *Anevrizmatska bolezen arterij;* 2013 Apr 12–13; Otočec: Združenje za žilne bolezni, Slovensko zdravniško društvo; p. 251-262.
7. Dupuis CS, Baptista V, Whalen G, et al. Diagnosis and management of acute pancreatitis and its complications. *Gastrointest Interv.* 2013; 2: 36-46.
8. Poves I, Burdío F, Dorcaratto D, et al. Minimally invasive technique in the treatment of severe acute pancreatitis. *Centr Eur J Med.* 2014; 9 (4): 580-7.
9. Hancke S, Flugel H, Domsche W. Catheter drainage of pancreatic pseudocyst into the stomach. *Endoscopy.* 1985; 20: 75-7.
10. Sever M, Vidmar D, Šurlan M, et al. Percutaneous drainage of pancreatic pseudocyst into the stomach. *Surg Endos.* 1998; 12: 1249-53.
11. Freeman ML, Werner J, van Santvoort HC, et al. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. *Pancreas.* 2012; 41: 1176-94.
12. Karakayali FY. Surgical and interventional management of complications caused by acute pancreatitis. *World J Gastroenterol.* 2014; 20: 13412-23.
13. Johnson MD, Walsh RM, Henderson JM, et al. Surgical versus nonsurgical management of pancreatic pseudocysts. *J Clin Gastroenterol.* 2009; 43: 586-90.
14. Akshintala VS, Saxena P, Zaheer A, et al. A comparative evaluation of outcomes of endoscopic versus percutaneous drainage for symptomatic pancreatic pseudocysts. *Gastrointest Endosc.* 2014; 79: 921-8.
15. van Santvoort HC, Beddelink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med.* 2010; 362 (16): 1491-502.
16. Raraty MG, Halloran CM, Dodd S, et al. Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. *Ann Surg.* 2010; 251: 787-93.
17. Madhusudhan KS, Venkatesh HA, Gamanagatti S, et al. Interventional radiology in the management of visceral artery pseudoaneurysm: a review of techniques and embolic materials. *Korean J Radiol.* 2016; 17(3): 351-62.

# Acute Pancreatitis and Indications for Intervention: a Surgeon's View

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**Key words:** acute pancreatitis, intervention, minimally invasive techniques, surgery, video-assisted retroperitoneal drainage

## ABSTRACT

Acute pancreatitis is one of the most common gastrointestinal disorders requiring urgent hospitalization worldwide. It is a highly unpredictable disease with a wide range of clinical courses. Most attacks of acute pancreatitis are mild to moderate and resolve spontaneously, but about 10% of patients will develop severe acute pancreatitis. Uncomplicated acute pancreatitis is a one-week disease. Failure to recover or the persistence of local and systemic signs of pancreatic inflammation beyond the first week are signs that a complication may be brewing. Recognizing the natural course of severe acute pancreatitis is necessary in multidisciplinary approach. Only a small subset of necrotizing pancreatitis patients will require emergent surgery in less than four weeks from the onset of acute pancreatitis for organ failure and acute decompensation due to an intra-abdominal catastrophe. The strategy of postponing surgical intervention beyond four weeks from the onset of acute pancreatitis was implemented in the treatment algorithm several years ago. Surgical removal of pancreatic necrosis can be achieved by open or minimally invasive approach. Necrosectomy can be performed at once or in a staged manner (open-staged or closed-contin-

ous lavage). These methods do not compare with, but rather complement other techniques. In general, surgical intervention should be done – if at all – at a late stage after the onset of pancreatitis.

## INTRODUCTION

The incidence of acute pancreatitis (AP) varies considerably throughout the world, with a reported annual incidence of 13–45 cases per 100.000 persons (1). Gallstones and alcohol misuse are long-established risk factors, but several new causes have emerged. Ninety percent of patients will have a mild form of interstitial edematous pancreatitis, and most of them will resolve spontaneously. However, about 10% of patients will develop severe AP. In the United States alone, AP leads to 270.000 hospital admissions annually, and inpatient costs exceed 2.5 billion dollars (2). The mortality reaches up to 30% in patients that develop pancreatic necrosis and suffer a severe course (3).

The natural course of the disease has two stages: the early toxic/hypovolemic phase, and the late septic phase. Hypovolemia and organ failure caused by excessive fluid sequestration and the release of biologically active compounds dominate the early phase in the first

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two weeks. During the late course, local and systemic septic complications are the main findings (4).

Recognizing the natural course of severe AP in a multidisciplinary approach has become the standard of care and decreased the mortality to about 20% during the past 20 years. Beside improved intensive care management and progress in interventional drainage, postponing surgical interventions from early necrosectomy to delayed operation had a beneficial effect on the outcome of these patients (5). Consequently, recent guidelines recommended that invasive intervention (i.e., percutaneous catheter drainage, endoscopic transluminal drainage or necrosectomy) should be delayed where possible until at least four weeks after initial presentation to allow the collection to become ‘walled-off.’ But regardless of the time from the onset of AP and the presence of necrosis, patients with intra-abdominal catastrophes (hemorrhage, visceral ischemia, perforation, abdominal compartment syndrome) require immediate intervention (6).

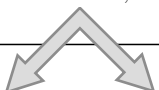



## NATURAL COURSE OF THE DISEASE

Ninety percent of patients will have a mild form of interstitial edematous pancreatitis, but about 10% will develop severe AP. According to the Revised Atlanta Classification, AP can be subdivided into two types: interstitial edematous pancreatitis and necrotizing pancreatitis. In the Revised Atlanta Classification, clear definitions of pancreatic and peripancreatic collections are made (7, 8).

Interstitial edematous pancreatitis usually resolves within the first week. Some patients will develop acute peripancreatic fluid collections (APFC) that will resolve with medical support alone or will go on to develop a pancreatic pseudocyst. Pancreatic pseudocyst presents as a delayed (usually four weeks) complication of interstitial edematous pancreatitis with a well-defined wall and devoid of solid material.

The subject of this article concerns those patients who develop necrotizing pancreatitis. These patients

Figure 1. Natural course of acute pancreatitis

ACUTE PANCREATITIS			
<b>Interstitial Edematous Pancreatitis (IEP)</b> Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis		<b>Necrotizing Pancreatitis</b> Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis	
			
<b>Recovery without consequences</b>	<b>Acute Peripancreatic Fluid Collection (APFC)</b> Peripancreatic collection of fluid associated with IEP with no peripancreatic or pancreatic necrosis	<b>Acute Post-Necrotic Collection (APNC)</b> A collection containing both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic gland and/or the peripancreatic tissues	<b>EARLY</b> First weeks after onset of pancreatitis
			
<b>Pancreatic Pseudocyst</b> A collection of fluid outside the pancreas with a defined inflammatory wall and with minimal or no necrosis		<b>Walled-Off Necrosis (WON)</b> A collection of pancreatic and/or peripancreatic necrosis with a defined inflammatory wall persisting for >4 weeks after onset of necrotizing pancreatitis	<b>LATE</b> ≥4 weeks after onset of pancreatitis
		<b>Post-Necrosectomy Pseudocyst</b> A special type of pseudocyst that may develop in a patient with necrotizing pancreatitis after treatment by necrosectomy usually related to an orphaned tail or disconnected duct syndrome	

develop APNC involving necrosis of the pancreatic parenchyma and the peripancreatic tissue, the pancreatic parenchyma alone, or the peripancreatic tissue alone. When APNC persists beyond four weeks from the onset of pancreatitis, the term walled-off necrosis (WON) can be applied. These terms represent morphologic abnormalities noted on contrast-enhanced CT scan that are used for classification purposes and to guide treatment (Figure 1).

When treating patients with necrotizing pancreatitis, it is important to be cognizant of the time from onset of symptoms since recent data demonstrates that delayed intervention leads to lower morbidity and mortality rates. Over a four-week period, APCs evolve: the peripancreatic tissue inflammation subsides, the tissue within the collection demarcates into viable and non-viable components, and the perimeter of the collection matures into the defined wall of WON. A distinction should also be made between sterile and infected necrosis since the presence of infection means a different prognosis, natural history, and approach to treatment. Patients with sterile WON will usually resolve over time without any intervention. In fact, a percutaneous drain should not be placed into sterile collections unless there is a very good indication since it will iatrogenically infect the collection after a short time and complicate the patient's management. A small subset of patients with sterile WON will require pancreatic necrosectomy either because of persistent symptoms such as anorexia, early satiety, vomiting, pain, fever, or failure to thrive. All patients with WON who become infected require treatment with parenteral antibiotics in combination with effective drainage/necrosectomy (9, 10).

## INFECTION

Infection develops in 30–70% of patients with necrotizing pancreatitis and accounts for more than 80% of deaths from AP. The risk of infection increases with the amount of pancreatic glandular necrosis and the time from the onset of AP, peaking at three weeks. Infection is presumed when there is gas present in the WON on CT scan. It is also diagnosed definitively

with an image-guided fine needle aspiration (FNA) showing positive Gram stain and culture. Since patients carry a significant risk of converting from sterile to infected tissue over time, patients should be followed closely, and an FNA performed if clinically indicated with a change in abdominal pain, fever, or leukocytosis. Since FNA has a false negative rate of about 10%, a negative FNA may be repeated after appropriate intervals, such as 5–7 days, if a clinical suspicion of infection persists. FNA has a low iatrogenic infection rate along with a high sensitivity and specificity (10).

However, according to evidence-based guidelines, routine percutaneous FNA of peripancreatic collections to detect bacteria is not indicated, because clinical signs (i.e., persistent fever, increasing inflammatory markers) and imaging signs (i.e., gas in peripancreatic collections) are accurate predictors of infected necrosis in the majority of patients. Although the diagnosis of infection can be confirmed by FNA, there is a risk of false-negative results (6). According to an international expert survey, none of the experts use FNA routinely, 85% selectively and 15% never (11).

## INDICATIONS AND TIMING FOR INTERVENTION

Once the patient is determined to be infected, they require complete external drainage or face a near 100% mortality. While deciding amongst percutaneous, endoscopic, video-assisted, laparoscopic or open surgical options, a percutaneous drain should be placed within 24 hours of a diagnosis of infection to initiate external drainage (12). Once a percutaneous drain has been placed, the catheters should be upsized every 3–4 days to an 18–20-French goal. A CT is repeated about two weeks after the first drain was placed. If the patient has a remaining large collection and at least four weeks have elapsed since onset of disease, plans are made for surgery. In general, surgery for APNC should be delayed until the WON phase due to lower morbidity and mortality. While waiting for this safer time, sepsis control can be temporized with percutaneous drains and when necessary, the addition of parenteral antibiotics. Careful attention must be paid to

the protein and calorie requirements in these patients which are very high. Most patients are unable to consume their total caloric needs, and almost all will require supplemental enteral or parenteral nutrition and close monitoring of their nutritional status with serum markers. Enteral nutrition (nasogastric or nasojejunal) is the preferred route when tolerated since it has been shown to be associated with significant decreases in the risk of pancreatitis associated morbidity and mortality (13).

But regardless of the presence of necrosis, a small subset of severe pancreatitis patients will require emergency surgery for organ failure and acute decompensation due to an intra-abdominal catastrophe such as haemorrhage, visceral ischemia, perforation, and abdominal compartment syndrome. Acute decompensation is most often due to a reactivation of the systemic inflammatory response or a non-surgical source of infection. Because of this, intensive support should be given for 24–48 hours along with a search for the cause, but if an intra-abdominal catastrophe is suspected the patient will need an emergency laparotomy (14).

## INDICATIONS FOR SURGERY

- Severe AP with APFC or APNC, less than four weeks from the onset of pancreatitis, with organ failure and suspected intra-abdominal catastrophe unresponsive to 24–48 hours of intensive support.
- WON, by definition greater than four weeks from the onset of necrotizing pancreatitis, that is:
  - infected; with infection documented by gas seen in the collection on contrast-enhanced CT scan or with a positive FNA or
  - sterile but symptomatic.

## PREOPERATIVE PLANNING AND SURGICAL APPROACHES TO NECROSECTOMY

There are many excellent surgical options for pancreatic debridement (15). Transgastric endoscopic meth-

ods and percutaneous drains can also be used as primary or adjunctive methods.

Percutaneous drainage (PD) of pancreatic necrosis involves placement of single or multiple catheters that are used for irrigation and drainage of retroperitoneum. Surgical intervention can be postponed, and even the need for surgical necrosectomy can be eliminated in many patients. Over the past two decades, PD has been increasingly utilized to stabilize critical patients both as ‘a bridge to surgery’ and sometimes as definitive therapy. The preferred route for PD is retroperitoneal approach through the flank because it avoids enteric leaks and dissemination of infected material into the peritoneal cavity. Also, a retroperitoneal approach for PD allows the tract to be used as guidance for retroperitoneal surgical video-assisted retroperitoneal necrosectomy (VARD). PD is beneficial especially as a prelude to definitive necrosectomy or when combined with another modality of treatment. However, PD is technically not adequate or feasible when retroperitoneal hemorrhage, bowel necrosis, duodenal/biliary obstruction further complicates ANP. One of the drawbacks, when PD is used alone, is also limited ability to remove necrotic debris (16).

Advances in technology and instrumentation allow the use of minimally invasive techniques which lessen the surgical stress in an already compromised patient. Minimally invasive methods are increasingly being used for operative necrosectomy in patients with infected WON with open necrosectomy reserved for patients who fail minimal access techniques or require an emergent exploration.

Several minimally invasive techniques have been developed. Despite small variations in the different techniques applied, they have in common that infected necrosis of the retroperitoneum is accessed under endoscopic visualization with subsequent necrosectomy and lavage. The techniques involve either intraoperative dilatation of a percutaneous drain tract, which was created by US- or CT-guidance preoperatively, or a direct approach of the infection with a retroperitoneoscope. Depending on the location of the infectious tissue,

access can be gained from the left or the right flank and over one or more routes (17).

In general, access to debridement involves retroperitoneal or transperitoneal approach by open or minimally invasive surgery.

The most popular surgical minimally invasive retroperitoneal debridement methods are:

- step-up approach consisting of PD followed by VARD,
- percutaneous necrosectomy and sinus tract endoscopy, and
- minimal access retroperitoneal pancreatic necrosectomy (MARPN).

The minimally invasive transperitoneal debridement method is laparoscopic debridement.

Methods for open transperitoneal or retroperitoneal debridement are:

- necrosectomy followed by continuous postoperative lavage,
- conventional drainage with placement of standard surgical drains and reoperation as needed,
- open management technique with necrosectomy followed by scheduled re-laparotomies through an open abdomen (laparostomy and system of a continuous negative pressure), and
- open retroperitoneal approach through the base of the 12<sup>th</sup> rib.

The techniques described here will be the minimally invasive methods. Open retroperitoneal approach through the base of the 12<sup>th</sup> rib followed by continuous postoperative lavage is the open method upon which a majority of these minimally invasive surgical techniques are based.

The step-up approach and VARD technique was described by Horvath et al. which now has phase I feasibility, phase II safety and efficacy, and phase III randomized controlled data supporting its use (18–20). The phase III results from the Dutch PANTER trial have provided strong data in support of the step-up

approach. In this randomized controlled trial, patients with infected pancreatic or peripancreatic tissue were randomized to either open necrosectomy or minimally invasive step-up approach. Patients randomized to the step-up arm had a lower rate of incidence of postoperative organ failure, a lower rate of major complications, and a lower risk of death. Postoperatively, the step-up arm had fewer incisional hernias, less diabetes, less exocrine insufficiency with the need for pancreatic enzyme supplementation, and lower healthcare utilization and medical costs. Also, surgical intervention (other than drain placement) was avoided in one-third of patients in the step-up arm (20).

Once the patient with WON is determined to be infected, a percutaneous drain is placed. If this drain is not effective, a VARD will be needed. The patient will need a minimum of one percutaneous drain placed into the collection from the flank, to be used as an intraoperative guide. When doing the VARD procedure, the surgeon follows the path of this drain through the retroperitoneum and into the collection. Even if another drain is already in place, it is important for the interventional radiologist to place a drain as close as possible to the left mid-axillary line just under the costal margin for operative guidance. The position of this drain inside the collection and its location to nearby anatomical structures will be used by the surgeon to guide operative debridement. A VARD technique involves a small subcostal incision followed by placement of a port. Through port, a video scope is inserted. Necrosectomy is achieved with irrigation, hydrodissection and different instruments which are inserted directly through the wound (10).

### **Percutaneous necrosectomy and sinus tract endoscopy**

The method was first described by Carter et al. (21). Sinus tract endoscopy involves intraoperative dilatation of the percutaneous drain tract followed by irrigation, lavage, and suction using a flexible or rigid endoscope (22).

## **Percutaneous necrosectomy**

Percutaneous necrosectomy starts with insertion of an 8-French pigtail catheter into the cavity of retroperitoneal necrotic collection, the surgeon having carefully selected a path that will allow subsequent dilatation. A path of choice is to enter the area of infected necrosis between the lower pole of the spleen and the splenic flexure. In predominately right-sided pancreatic head necrosis, they used a path through the gastrocolic omentum, anterior to the duodenum. However, this results in a more technically difficult necrosectomy and prevents dependent postoperative drainage. The catheter is secured, and the patient is transferred to the operating room. With the patient under general anesthesia, access to the infected cavity is maintained using a guidewire, over which the catheter tract is then dilated to 30-French using graduated dilators and radiologic guidance. This allows a 30-French special guidewire to be inserted. An operating nephroscope that allows intermittent irrigation and suction with a 4 mm working channel is then passed along the special guidewire into the infected cavity. Piecemeal removal of solid material (necrosectomy) is then performed using soft grasping forceps through the working channel by repeatedly passing the instrument into the cavity until all loose necrotic tissue is removed. Finally, a drain is passed into the cavity to allow high volume continuous postoperative lavage (500 mL/hour).

## **Sinus tract endoscopy**

This method is used in patients with a previous primary debridement, either at open laparotomy or after the above technique, in whom residual sepsis is suspected. In the operating room and under general anesthesia, the previously sited drain or drains are removed. Either flexible or a rigid endoscopic system is used, depending on the suspected amount of residual necrosis. Sinus tract endoscopy using a flexible endoscope is tedious, and only small fragments of necrotic tissue can be removed with each pass of the endoscope. However, the advantage is access to pockets of necrosis which can be limited when using rigid endoscopic systems. For flexible

endoscopy, each tract is dilated to 45-French using a balloon dilator. A flexible endoscope is then passed through the skin opening. Irrigation and suction allows fluid collection to be cleared, and residual solid necrotic tissue or adherent slough can be teased away using a variety of endoscopic instruments. At the end of the procedure, a tube drain is placed in the cavity, after which lavage begins again.

## **Minimal access retroperitoneal pancreatic necrosectomy**

This method was described by Rarity et al. Under CT-guidance a 12-French pigtail catheter was inserted into the infected cavity. After moving the patient to the operating room, the catheter was exchanged over a guide wire with serial dilators to 30-French size. A nephroscope was then used for access, and metal forceps used for piecemeal removal. Two drains were placed for irrigations (23). The same group has shown significant benefits for a minimal access approach including fewer complications and deaths compared with open necrosectomy (24).

## **Laparoscopic debridement**

Laparoscopic debridement is performed with laparoscopic visualization followed by necrosectomy through separate ports. Laparoscopic debridement through transperitoneal route has gained little acceptance because of the risk of disseminating retroperitoneal infection into the peritoneal cavity. There have been only a few case series related to the laparoscopic approach. Parekh described using three ports for access: a hand access device and two standard laparoscopic ports. Access to the retroperitoneum was obtained either through an infracolic approach or the greater omentum between the stomach and colon. Gentle finger dissection was used for debridement, and several drains were left for postoperative drainage (25). Zhu et al. described using at least four standard ports, and going through the gastrocolic ligament to approach the pancreas. A special retractor was used to elevate the stomach for exposure. Many drainage tubes were used for postoperative lavage (26).

The laparoscopic approach may be theoretically suitable late in the course of the disease for patients with WON who has to undergo simultaneous cholecystectomy. However, it should be undertaken only by highly experienced minimally invasive surgeons.

## CHOLECYSTECTOMY

All patients with pancreatitis should have a US of the gallbladder performed. If gallstones or sludge are present, a cholecystectomy should be planned. Patients undergoing VARD should have a laparoscopic cholecystectomy within six months following complete resolution of the peripancreatic collections and inflammatory process. Patients undergoing a transperitoneal open or laparoscopic necrosectomy may have a cholecystectomy attempted at the time of their surgery; however, it may not be possible to perform a safe cholecystectomy when there is a large amount of necrosis because of significant inflammation in the portal vein.

## POSTOPERATIVE LAVAGE

With both the minimally invasive and open necrosectomy procedures, postoperative lavage can be performed. Saline or Ringer's lactate is continuously infused in through a percutaneous drain at about 100-200 mL/hour and passively drains out through other drains. Postoperative lavage is continued for up to five days or until the effluent is clear. Following the lavage period, all drains are opened to gravity drainage. A CT scan is first obtained two weeks postoperatively to evaluate the collections. Criteria for drain removal include all the following:

- complete resolution of retroperitoneal collections on contrast-enhanced CT scan,
- drain outputs of 10mL/day or less, and
- absence of elevated amylase levels in the drain effluent.

## COMPLICATIONS

The main complications of pancreatic necrosectomy include:

- perioperative hemorrhage,
- enteric fistulas (including gastric, small bowel, and large bowel),
- pancreatic fistulas, most often from a disconnected duct ('orphaned tail'),
- incisional hernias, and
- pancreatic endocrine and exocrine insufficiency.

Bleeding occurs if vessels traversing the cavity are debrided or disrupted or by using the suction device too aggressively. Structures traversing the cavity that do not easily fracture with gentle blunt pressure are blood vessels unless proven otherwise and should be left undisturbed. If significant hemorrhage is detected, the first step is to tightly pack the retroperitoneal wound and wait. This is often sufficient to stop most bleeding and to gain hemodynamic stability. Adjunctive use of angiographic embolization should also be strongly considered. Dissection of the indurated and inflamed tissues of the retroperitoneum is discouraged as this will frequently result in further hemorrhage. The distorted anatomy also makes routine exposure techniques extremely difficult. If packing does not quickly control bleeding in VARD, there should be a low threshold for performing an open laparotomy with retroperitoneal packing followed by angiographic embolization.

Visceral injury to the left colon during VARD is best avoided by accessing the retroperitoneum under direct vision and utilizing preoperatively placed drainage catheters as a digital manual road-map into the cavity. Blunt finger dissection also facilitates safe entry into the cavity, minimizing the risk of visceral injury. Despite careful technique, patients will still develop enteric fistulas. Fistulas may require prolonged PD, but almost all fistulas will close without surgery. Patience is required since most enteric fistulas will not close until all collections are drained, and the patient is anabolic and has a normal serum albumin which may take months. Most pancreatic fistulae can also be

treated with patience and PD. Persistent pancreatic fistulas are treated with a distal pancreatectomy of the orphaned tail (10, 27).

## IS NECROSECTOMY OBSOLETE FOR INFECTED NECROTIZING PANCREATITIS?

Necrosectomy has been a mainstay of surgical procedures for infected necrotizing pancreatitis. Currently, the management of necrotizing pancreatitis has undergone a paradigm shift toward minimally invasive techniques for necrosectomy, obviating the need for open necrosectomy in most cases (28). There is increasing evidence that minimally invasive approaches are associated with improved outcomes over traditional open necrosectomy (18–28). A recent international multidisciplinary consensus conference emphasized the superiority of minimally invasive approaches over standard open surgical approaches (9).

Recently, however, increasing evidence on the efficacy of endoscopic technique shows good outcomes when treating walled-off necrotizing pancreatitis without a necrosectomy (29). Moreover, a simple PD can eliminate the need for necrosectomy in many patients. The success of these drainage-only procedures raises the question of whether necrosectomy is obsolete. With further refinement of the drainage procedures, a paradigm shift from necrosectomy to drainage might be inevitable (30).

## CONCLUSIONS

The treatment of necrotizing pancreatitis has undergone significant advances. Many lessons have been learned from the stalwart work done by surgeons in the past century. Changes over that time include improved intensive care, a move toward delayed surgery to after four weeks from the onset of symptoms, and the use of percutaneous drains and other minimal access techniques. With these advances, patients are experiencing a much lower morbidity and mortality than in the past. The less invasive approach can potentially keep an infection compartmentalized, specifically

avoiding contamination of virgin spaces, such as the peritoneal cavity. It may reduce systemic inflammatory and septic response as a consequence of a major open operation and release of infected necrosis.

## References

1. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013; 144: 1252-61.
2. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012; 143: 1179-87.
3. McKay CJ, Imrie CW. The continuing challenge of early mortality in acute pancreatitis. *Br J Surg*. 2004; 91: 1243-4.
4. Beger HG, Rau B, Isenmann R. Natural history of necrotizing pancreatitis. *Pancreatology*. 2003; 3: 93-101.
5. Stirling AD, Moran NR, Kelly ME, et al. The predictive value of C-reactive protein (CRP) in acute pancreatitis – is interval change in CRP an additional indicator of severity? *HPB (Oxford)*. 2017; 19: 874-80.
6. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology*. 2013; 13 (4 Suppl 2): e1-15.
7. Banks PA, Bollen TL, Dervenis C, et al. Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013; 62: 102-11.
8. Kadiyala, Suleiman SL, McNabb-Baltar J, et al. The Atlanta classification, revised Atlanta classification, and determinant-based classification of acute pancreatitis: which is best at stratifying outcomes? *Pancreas*. 2016; 45: 510-5.
9. Freeman ML, Werner J, van Santvoort HC, et al. International Multidisciplinary Panel of Speakers and Moderators. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. *Pancreas*. 2012; 41: 1176–94.
10. Horvath KD. Debridement for pancreatic necrosis. In: Lillemoe K, Jarnagin W, eds. *Hepatobiliary and pancreatic surgery*. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. p. 101-15.
11. van Grinsven J, van Brunshot S, Bakker OJ, et al. Diagnostic strategy and timing of intervention in infected necrotizing pancreatitis: an international expert survey and case vignette study. *HPB (Oxford)*. 2016; 18: 49-56.
12. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. *Lancet*. 2015; 386: 85-96.
13. Mofidi R, Lee AC, Madhavan KK, et al. Prognostic factors in patients undergoing surgery for severe necrotizing pancreatitis. *World J Surg*. 2007; 31: 2002-7.
14. Wittau M, Scheele J, Gözl I, et al. Changing role of surgery in necrotizing pancreatitis: a single-center experience. *Hepatogastroenterology*. 2010; 57: 1300-4.
15. Navaneethan U, Vege SS, Chari ST, et al. Minimally invasive techniques in pancreatic necrosis. *Pancreas*. 2009; 38: 867-75.

16. van Baal MC, van Santvoort HC, Bollen TL, et al. Dutch Pancreatitis Study Group. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. *Br J Surg.* 2011; 98: 18-27.
17. Bello B, Matthews JB. Minimally invasive treatment of pancreatic necrosis. *World J Gastroenterol.* 2012; 18: 6829-35.
18. Horvath KD, Kao LS, Wherry KL, et al. A technique for laparoscopic-assisted percutaneous drainage of infected pancreatic necrosis and pancreatic abscess. *Surg Endosc.* 2001; 15: 1221-5.
19. Horvath KD, Freeny P, Escallon J, et al. Safety and efficacy of videoscopic assisted retroperitoneal debridement (VARD) for infected pancreatic collections: a multicenter, prospective, single-arm phase II study. *Arch Surg.* 2010; 145: 817-25.
20. van Santvoort HC, Besselink MG, Bakker OJ, et al. Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med.* 2010; 362: 1491-502.
21. Carter CR, McKay CJ, Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: an initial experience. *Ann Surg.* 2000; 232: 175-80.
22. Goenka MK, Goenka U, Mujoo MY, et al. Pancreatic necrosectomy through sinus tract endoscopy. *Clin Endosc.* 2018 Jan 4. doi: 10.5946/ce.2017.066. [Epub ahead of print].
23. Raraty MG, Halloran CM, Dodd S, et al. Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. *Ann Surg.* 2010; 251: 787-93.
24. Gomatos IP, Halloran CM, Ghaneh P, et al. Outcomes from minimal access retroperitoneal and open pancreatic necrosectomy in 394 patients with necrotizing pancreatitis. *Ann Surg.* 2016; 263: 992-1001.
25. Parekh D. Laparoscopic-assisted pancreatic necrosectomy: a new surgical option for treatment of severe necrotizing pancreatitis. *Arch Surg.* 2006; 141: 895-903.
26. Zhu JF, Fan XH, Zhang XH. Laparoscopic treatment of severe acute pancreatitis. *Surg Endosc.* 2001; 15: 146-8.
27. Karakayali FY. Surgical and interventional management of complications caused by acute pancreatitis. *World J Gastroenterol.* 2014; 20: 13412-23.
28. Seifert H, Biermer M, Schmitt W, et al. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD Study). *Gut.* 2009; 58: 1260-66.
29. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. *Lancet.* 2018; 391: 51-8.
30. Chang YC. Is necrosectomy obsolete for infected necrotizing pancreatitis? Is a paradigm shift needed? *World J Gastroenterol.* 2014; 20: 16925-34.

# Postoperative Treatment of Severe Acute Pancreatitis in the Intensive Care Unit

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## ABSTRACT

Severe acute pancreatitis is a clinical disorder associated with significant morbidity and mortality. The main characteristic of the disease is severe systemic inflammation which can be complicated by multiple organ failure and infection of pancreatic necrosis. Repeated assessment of acute pancreatitis severity based on clinical signs, intensive care monitoring, blood tests and imaging tools should be performed to determine the optimal way of treatment for each patient. Infectious complications in severe acute pancreatitis are important problem and have an impact on outcome in patients who survived the first inflammatory hit of the disease. Diagnosis of infected pancreatic necrosis is often challenging, but should not delay adequate treatment, which consists of source control and antimicrobial agents. At this moment, the only rational indication for antibiotic treatment is documented infection. Surgical treatment of severe acute pancreatitis is nowadays delayed and includes minimally invasive techniques. Postoperative care of patients with severe acute pancreatitis is oriented towards supportive treatment and prevention of complications.

## INTRODUCTION

Severe acute pancreatitis (SAP) is severe inflammatory disorder associated with significant morbidity and mortality. According to different studies, mortality from SAP ranges from less than 10% to more than 80% (1). Early phase of SAP is characterized by severe systemic inflammatory response and subsequent multiple organ failure. In later stages, SAP can be complicated by infection of pancreatic and peripancreatic necroses and sepsis which further deteriorate multiple organ dysfunction. Surgical management of SAP was the gold standard of therapy in previous decades. Lately, this approach has changed due to many reports of better survival in patients in whom surgical treatment was delayed or was minimally invasive. Nevertheless, surgery should be performed in some patients. The main goals of postoperative management are to provide adequate supportive treatment and to prevent or timely recognize complications. Approach to postoperative intensive care management of patients with SAP is reviewed in this article.

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## IDENTIFICATION AND TREATMENT OF ORGAN DYSFUNCTION

### Circulation

Extensive hemodynamic monitoring of patients with SAP is important not only in postoperative period but in general. Systemic inflammatory response syndrome (SIRS) is present from the beginning of SAP (1, 2). Postoperatively, hemodynamic instability results not only from severe inflammation but can be a consequence of severe postoperative bleeding or sepsis. PiCCO™ and Lidco™ technology and rarely Swan-Ganz catheter (in the case of heart failure and acute respiratory distress syndrome (ARDS)) are used for continuous hemodynamic monitoring. Echocardiography is also used for non-invasive evaluation of circulatory status of such unstable patient. In the early stage of SAP, it is important to stabilize the patient with adequate fluid resuscitation. Inadequate fluid resuscitation and consequent prolongation of shock aggravate organ failure, which is strongly related to early mortality (3, 4). Postoperatively, the main concern should be not to overload the patient with intravenous fluids. Vigorous fluid resuscitation that was used in the past is nowadays not acceptable anymore because of many negative side effects which can deteriorate patient's status (aggravation of intra-abdominal hypertension (IAH) with deterioration of abdominal organ blood flow and their function). Endpoints of randomized controlled trials (RCT) are that conservative fluid resuscitation in comparison to liberal is associated with lower incidence of organ dysfunction (odds ratio 0.69) and lower mortality (odds ratio 0.40) (5). Most of such patients are mechanically ventilated, and fluid resuscitation should be applied to maintain stroke volume variability (SVV) or pulse pressure variability (PPV) around 10% which indicate euvolemic status. SVV and PPV are both dynamic variables of preload and are superior in mechanically ventilated patients in comparison to static variables (for example central venous pressure, intra-thoracic blood volume index, global end-diastolic volume index) (6, 7). After optimization of patient's fluid status, mean blood pressure of 65 mmHg should be main-

tained by the use of vasoactive drugs. Urine output should be kept at least 0.5 mL/kg/hour while monitoring pulse, blood pressure, oxygen saturation, and blood tests. Balanced electrolyte infusions (Ringer lactate) are recommended by IAP/APA (International Association of Pancreatology/American Pancreatic Association), while some studies indicate increased mortality in SAP if colloid infusions are used (8, 9, 10). In some cases, specific electrolyte solutions are used to correct electrolyte disturbance.

### Ventilation

Acute respiratory failure (ARF) in SAP is usually a combination of hypoxemic and hypercapnic ARF. Hypoxemia is a result of capillary endothelial and alveolar epithelial damage, which promote development of ARDS. These changes are surrogate for ventilation-perfusion mismatch, for decrease of diffusion capacitance for oxygen and formation of right-left intrapulmonary shunt. On the other hand, ileus, ascites and meteorism of gut increase intra-abdominal pressure (IAP) which together with pleural effusions decreases compliance of respiratory system. This increases work of breathing which causes exhaustion of respiratory muscles, leading to hypercapnic respiratory failure. Patients with SAP suffer from severe pain, and concomitant use of strong opioid analgesics can depress respiratory drive and aggravate hypercapnic ARF. In mild forms of acute pancreatitis, non-invasive ventilation can be performed but only in hypoxemic type of ARF, while in SAP the ventilatory support is mostly invasive and is completely based on algorithms for protective lung ventilation. All approaches that are usually used in ARDS patients for setup ventilation parameters (see below) can also be used in patients with ARDS caused by SAP. Prone positioning is relatively contraindicated in case IAP is high or if intra-abdominal operation with negative pressure wound therapy insertion was performed. The primary targets for ARDS treatment are to ensure adequate gas exchange while minimizing the risk of ventilator-induced lung injury. Both pharmacologic (muscle relaxation by using neuromuscular blocking agents, inhaled vasodilators, corticosteroids) and non-pharmacologic strategies (lung

recruitment, positive end-expiratory pressure (PEEP) selection, tidal volume setting,  $O_2$  and  $CO_2$  target matching protective ventilatory strategies, prone positioning and extracorporeal assistance) are used to reach this objective (11, 12). The gravity is the main reason for collapsing dorsal part of lung parenchyma in ARDS patient. This phenomenon is even more pronounced in extra-pulmonary ARDS as is the case in SAP where elevated diaphragm, because of IAH, compresses lung tissue even more. IAH has serious impact on function of respiratory as well as peripheral organs. In the presence of alveolar capillary damage, which occurs in ARDS, IAH promotes lung injury as well as oedema, impedes the pulmonary lymphatic drainage, and increases intra-thoracic pressure, leading to atelectasis, airway closure and deterioration of respiratory mechanics and gas exchange. In these regions, during each breath cycle, the lung tissue opens during inhalation and collapses during exhalation, causing the formation of atelectrauma. Talmore et al. described a protocol of PEEP adjustment by using transpulmonary pressure ( $P_{TP}$ ) (difference between airways ( $P_{AW}$ ) and oesophageal ( $P_{ESO}$ ) pressure) which must be positive at the end of expiration to prevent atelectrauma to occur (13).  $P_{ESO}$  is usually measured at the level of the heart. It very closely reflects the pressure in surrounding collapsed lung tissue.  $P_{ESO}$  is not the same as pleural pressure, but it is very closely related to changes in pleural pressure. In this study, PEEP setting guided by  $P_{ESO}$  improved oxygenation, respiratory system compliance and cumulative survival in comparison to conventional protocol guided by ARDSnet  $PaO_2/FiO_2$  tables. At the moment, there is lack of data from RCT on how to manage ARDS patients with IAH although some suggestions have been made. According to these, optimal ventilator management of patients with ARDS and IAH would include the following: a) measurement of intra-abdominal and  $P_{ESO}$  and hemodynamic monitoring; b) ventilation setting with protective tidal volume, recruitment manoeuvre, and level of PEEP set according to the 'best' compliance of the respiratory system or the lung; c) deep sedation with or without neuromuscular paralysis in severe ARDS; and d) open abdomen in selected patients with severe abdominal compartment syndrome (14, 15).

## Intra-abdominal hypertension

Incidence of IAH in SAP is between 60–85% (16). This high incidence is the reason that IAP should be measured in each SAP patient admitted to intensive care unit. Main reasons for IAH in SAP are inflammatory process in retroperitoneal space, formation of ascites and ileus. Four levels of IAH are described by World Society for Abdominal Compartment Syndrome (WSACS): grade I IAP 12–15 mmHg; grade II: IAP 16–20 mmHg; grade III: IAP 21–25 mmHg; grade IV: IAP > 25 mmHg. For normal function of abdominal organs the abdominal perfusion pressure (APP), defined by the difference between mean arterial pressure (MAP) and intra-abdominal pressure ( $APP = MAP - IAP$ ), should be  $\geq 60$  mmHg. ACS is present when IAP above 20 mmHg and  $APP \leq 60$  mmHg is accompanied by failure of at least one organ (most frequently associated with decrease in diuresis pointed out as acute renal failure) (17). The other important moment is the speed of IAH development. In acute development (in a few hours), ACS can occur at lower or higher levels of IAP and APP. When IAH develops within several weeks or months (like in pregnancy or obesity), ACS does not occur.

In patients with SAP, IAP should be measured each 4–6 hours. In daily practice, IAP is measured by using additional pressure setup placed on urinary catheter which is inserted into urinary bladder. Alternative approach is to insert additional balloon catheter into the stomach or to insert commercially available NutriVent™ probe which allows to measure  $P_{ESO}$ , needed for  $P_{TP}$  calculation, and gastric pressure ( $P_{GA}$ ) which represents intra-abdominal one (18).

With non-surgical approaches, the IAP should be kept  $\leq 15$  mmHg and  $APP \geq 60$  mmHg with no signs of intra-abdominal organ failure. Non-surgical procedures for lowering IAP are:

1. Improving compliance of abdominal wall:
  - adequate analgesia and sedation,
  - inclination of upper body  $< 20^\circ$ ,
  - use Trendelenburg position if possible, and
  - the use of neuromuscular blocking agents.

2. Removal of content from intra-abdominal cavity:
  - gastric and gut decompression by insertion of nasogastric or rectal tube,
  - the use of prokinetic drugs (neostigmine),
  - the use of enema,
  - reduction or abolishment of enteral feeding,
  - colonoscopic decompression, and
  - insertion of urinary catheter.
3. Optimization of fluid resuscitation:
  - avoid excessive fluid infusion,
  - the use of hypertonic or colloid solutions,
  - the use of diuretics in hemodynamically stable patients, and
  - in the case of oliguric or anuric acute renal failure replacement renal therapy should be used.
4. Optimization of systemic and regional organ blood flow:
  - continuous hemodynamic monitoring for optimization of preload and the use of inotropic/vasoactive drugs for optimal oxygen delivery, and
  - optimal ventilation (see above).

In case of secondary ACS where IAP, despite non-surgical interventions, is above 20 mmHg and organ failure occurs, surgical methods for abdominal decompression have to be employed. Surgical laparostomy should be performed either by median laparotomy or even more frequently by bilateral transversal laparotomy (19, 20). Three different methods for temporary laparostomy formation are currently used: a) technique for skin closure; b) technique for fascia closure; c) closure technique by continuous negative pressure in use (VAC technique).

## Infection control

More than 80% of patients with SAP die due to secondary infections of pancreatic and peripancreatic necrosis (21). Main source of infection is intestinal microbiota, which is translocated to pancreatic tissue from hyperpermeable gut during systemic inflammation. The most common pathogens are *Escherichia coli* (26%), *Pseudomonas* spp. (16%), *Staphylococcus*

spp. (15%), *Klebsiella* spp. (10%), *Proteus* spp. (10%), *Streptococcus* spp. (4%), *Enterobacter* spp. (3%), *Enterococcus* spp. And anaerobic bacteria (16%). By rule, fungal superinfection occurs late in the disease course, usually several weeks to months after the beginning of inflammation (8).

At the moment there is lack of data on effectiveness of prophylactic antibiotic treatment (22). In the review article by Villatoro et al. which included seven RCTs with 404 patients, there was no significant difference in mortality between patients who received prophylactic antibiotic treatment versus patients who received placebo (8.4% versus 14.4%, non-significant). At the same time, there were no differences in the amount of infected necrosis between the groups (19.7% versus 24.4%, non-significant). There was only significant reduction in overall infection rate in the group that received treatment (37.5% vs. 51.9%). When fluoroquinolones in combination with metronidazole were used, there were no differences in mortality rate, incidence of secondary pancreatic necrosis infections and incidence of overall infections rate, respectively. On the other hand, when imipenem was used instead, there was significant reduction in incidence of secondary pancreatic necrosis infections, but again without any impact on survival. Conclusion of the study was that there were not enough data to support prophylactic use of antibiotics in SAP (23). In 2012 another meta-analysis in SAP was published and failed to confirm positive effect of prophylactic antibiotic treatment on survival rate. They calculated that 1429 patients have to be treated by antibiotics to prevent one death (24). Similar data were published by Wittau et al. in another meta-analysis of 14 RCTs and no differences were observed in mortality rate, the incidence of infected pancreatic necrosis and non-pancreatic infection, as well as the rate of surgical interventions between treatment and control group (25). In a prospective randomized study by Maravi-Poma et al., incidence of local and systemic mycoses was tripled in SAP patients who received prolonged antibiotic treatment (26). Improper use of antibiotics increases the incidence of antibiotic-associated diarrhea and diarrhea caused by *Clostridium difficile*. As side effects of prophylactic antibiotic treat-

ment seem to outweigh its benefits, routine use of antibiotics in SAP cannot be recommended (27).

The only rationale for antibiotic use in SAP is proven infection of pancreatic necrosis (8). Clinically, it is very difficult to distinguish between sterile and infected necrosis. Infected pancreatic necrosis should be suspected when prominent SIRS persists for more than 7–10 days and if clinical condition worsens. In this case, CT-guided fine needle aspiration of suspected infected pancreatic or peripancreatic tissue should be performed. Pancreatic necrosis is present when bacteria are isolated from this material or when air inclusions are seen on CT scan. If percutaneous drainage of such areas is planned, CT-guided fine needle aspiration is not necessary.

At the moment, there is lack of data for empirical antibiotic treatment recommendation. Some studies favor imipenem and ertapenem, which penetrate pancreatic tissue very well and reach the tissue concentration above minimal inhibitory concentration for bacteria, most frequently found in pancreatic necrosis (28, 29). Similar data are available for moxifloxacin (30). In vitro efficacy of all three antibiotics against bacteria most often isolated from pancreatic necrosis (*E. coli*, *Enterobacter cloacae*, *Enterococcus faecalis* and *Bacteroides fragilis*) were very similar to each other, with only moxifloxacin being more efficient against *E. cloacae*, *E. faecalis* and anaerobic bacteria in mixed cultures (31). Precise data about length of the treatment are not available. Most authors suggest that treatment should be continued at least fourteen days after removal of infection source (8, 27, 32).

Mortality of SAP patient with infected pancreatic necrosis is up to 30% and is in 80% related to septic complications. In patients with infected pancreatic necrosis and multiple organ failure without surgical treatment, mortality is close to 100% (33). Mortality decreases if surgical procedures are employed. Dutch researchers published data about decreased mortality in patients where step surgical approach was used (percutaneous drainage or endoscopic transluminal drainage followed by minimally invasive retroperi-

toneal necrosectomy). If possible, surgical procedures should be delayed by the fourth week. In that time, pancreatic necrosis is expected to be surrounded by granulation tissue (34). Pancreatic abscess can occur late in the course SAP. Antibiotic treatment in combination with percutaneous drainage is usually sufficient treatment option. In case abscess persists, surgical drainage should be performed. For SAP in association with cholangitis, urgent endoscopic retrograde cholangiopancreatography (ERCP) is indicated in the first 24 hours while for the rest of the biliary pancreatitis there is lack of data for identification of proper period when ERCP should be performed (8).

Most common infection complications after pancreatic necrosectomy are infection of the remaining pancreatic tissue and common hospital infections such as ventilation-associated pneumonia, catheter-related infections, etc. Behrman et al. reported 17.8% occurrence of postoperative pancreatic infections in patients after elective pancreatic necrosis resection. Polymicrobial infections were seen in 55% of patients. Prolonged use of vancomycin was associated with occurrence of vancomycin-resistant enterococci (35).

## Nutrition

Optimal nutritional support in SAP has been under debate for decades. Bowl at rest (nothing by mouth) strategy has been implemented conventionally to treat SAP (36, 37, 38). However, dietary restrictions exacerbate patient's malnutrition due to imbalance between reduced food intake and higher nutritional requirements, leading to further catabolism, bacterial translocation (39), and ultimate mortality (40). Evidence of clinical trials has demonstrated parenteral nutrition (PN) in preventing pancreatic stimulation and many benefits of enteral nutrition (EN). However, in daily practice, it remains challenging to predict whether EN will be tolerated in patients with acute pancreatitis (41). Strategic approaches to include nutritional supplements have also been attempted to provide additional immune regulatory and antioxidative effects. Probiotics and prebiotics have been shown to stabilize disturbed intestinal barrier.

However, currently, there is no firm evidence that probiotic use improves mortality in critically ill patients (42, 43). Due to immunosuppressive and inflammatory nature of the disease, immunonutrients like glutamine and omega-3 fatty acids have been added to parenteral or enteral formulas to modulate immune functions, suppress the hyperinflammatory responses, and re-establish tissue and organ homeostasis in clinical practice (44, 45). Supplements with antioxidative properties like glutamine and vitamin C have also been suggested to provide additional beneficial effects (46). In a meta-analysis by Yao H et al. where PN was compared with EN in SAP, EN was associated with a significant reduction in overall mortality (risk ratio 0.36, 95% CI 0.20–0.65,  $p=0.001$ ) and the rate of multiple organ failure (risk ratio 0.39, 95% CI 0.21–0.73,  $p=0.003$ ). Author concluded that EN should be recommended as the preferred route of nutrition for critically ill patients with SAP (47). In case oral feeding is not tolerated, enteral feeding through a nasogastric or nasojejunal feeding tube should be attempted within the first 72 hours of administration. PN should be minimized for its risks of infection and other complications. Only if enteral route is not available or tolerated, PN may be considered. Overall, nutritional support plays a critical role in clinical management of SAP, although the optimal timing remains unclear. Predicting the nutritional tolerance of patients with acute pancreatitis remains challenging as the current evaluation system needs to be improved. Various nutritional supplement(s) together with PN or EN with currently mixed clinical outcomes is a subject of interest for future evaluation and may lead to promising outcomes (48). Another meta-analysis compare early enteral nutrition (EEN) with delayed ones (DEN) and conclude that EEN within 48 hours is superior to DEN beyond 48 hours for patients with SAP; however, more studies are required to verify this conclusion (49). Otherwise, nutrient requirements for patients with SAP can be found in ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines: a) energy 25–35 kcal/kg body weight/day; b) protein 1.2–1.5 g/kg body weight/day; c) carbohydrates 3–6 g/kg body weight/day corresponding to blood glucose concentration between

6 and 10 mmol/L); d) lipids up to 2 g/kg body weight/day corresponding to blood triglyceride concentration below 12 mmol/L (50).

## **Pain control**

Pain is the main feature of acute pancreatitis and is the main reason for admission of majority of patients (51–53). There are no extensive studies on the pharmacological control of pain in acute pancreatitis which is quite surprising given the importance of this symptom during the disease. There is also lack of evidence regarding degree of efficacy of the various pharmacological substances used to treat different forms of acute pancreatitis. On the other hand, there are several reports concerning the possibility that non-steroidal anti-inflammatory drugs (NSAIDs) may actually induce acute pancreatitis (54–57). On the other hand, NSAIDs have also been used to prevent ERCP-induced acute pancreatitis (58). In meta-analysis by Pezzilli et al., authors attempted to answer the questions whether NSAIDs may induce acute pancreatitis, whether their prophylactic use can prevent post-ERCP pancreatitis, and whether they are capable of controlling pain in acute pancreatitis. They concluded that: 1) there is a risk for acute pancreatitis associated with the use of NSAIDs and, in clinical practice, it seems that naproxen should be the preferred analgesic in limiting the risk of development of acute pancreatitis; 2) both diclofenac and indomethacin may significantly reduce the risk of acute pancreatitis after ERCP resulting in major clinical and economic benefits and, finally, 3) NSAIDs are able to control the pain in patients with acute pancreatitis. However, further clinical studies on the best NSAID to be used in clinical practice are needed. An example comes from the use of diclofenac; this is a drug largely used to treat pain in acute pancreatitis. It is useful in preventing post-ERCP pancreatitis, but it is considered as major NSAID responsible for inducing acute pancreatitis in general population (59).

Acute pancreatitis is always very painful. There is some drug options for treating pain, and stronger analgesics (opioids) are often needed. Analgesics are

usually given as infusion therapy or through epidural catheter. Sometimes it is possible to adjust the dose of the analgesics by patient himself (so-called patient-controlled analgesia) where overdosing is less possible.

Opioids may be an appropriate choice for treatment of acute pancreatitis pain. Compared with other analgesic options, opioids may decrease requirement for supplementary analgesia. There is currently no difference regarding risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesia options. Recently published meta-analysis on acute pancreatitis pain included five RCTs with a total of 227 participants (age range 23–76 years; 65% men) (60). Opioids assessed were intravenous and intramuscular buprenorphine, intramuscular pethidine, intravenous pentazocine, transdermal fentanyl and subcutaneous morphine. Buprenorphine is non-narcotic analgesic with effect superior to procaine which, unlike procaine, does not exacerbate acute pancreatitis by inducing contraction of the sphincter of Oddi (61). Buprenorphine has an analgesic effect similar to that of pethidine. One RCT, comparing subcutaneous morphine with intravenous metamizole reported non-significant reduction in improvement of pain intensity (primary outcome) (risk ratio 0.50, 95% CI 0.19–1.33). Three studies compared analgesia using opioids with non-opioid treatments. After excluding one study in which opioids were used through continuous intravenous infusion, there was a decrease in the number of patients requiring supplementary analgesia (risk ratio 0.53, 95% CI 0.30–0.93). In a single study, there were no differences regarding the need of supplementary analgesia between patients who received buprenorphine or pethidine (risk ratio 0.82, 95% CI 0.61–1.10). There were no differences in pancreatitis complications between the drugs tested. No clinically serious or life-threatening adverse events occurred related to treatment. No differences for this outcome were found between opioid and non-opioid treatments, or for type of adverse event (nausea-vomiting and somnolence-sedation). One death in the procaine group was reported across all trials. One RCT comparing pethidine with intramuscular buprenorphine reported non-significant differences of supplementary analgesic,

adverse events, and survival. One RCT comparing fentanyl with placebo found no difference in adverse events. Findings of this review are limited by the lack of information to allow full appraisal of the risk of bias, measurement of relevant outcomes and small numbers of participants and events covered by the trials.

Epidural anesthesia (EA) is widely used to induce analgesia in the perioperative period and has been used to decrease pain in patients with SAP (62). Also, experimental studies have shown a specific beneficial effect of EA in SAP attributed to a sympathetic nerve blockade that redistributes splanchnic blood flow to non-perfused pancreatic regions (63, 64). First RCT on the use of EA for treatment of acute pancreatitis showed that there were no complications of epidural procedure, no catheter-related infections, and no hemodynamic complications during median time of EA of 5.7 days (65). Authors were able to show a significant improvement in arterial perfusion of the pancreas which was observed in 13/30 (43%) measurements in the EA group, and in 2/27 (7%) measurements in the control group. In the EA group, none of the patients developed clinical sepsis and only one needed intubation, whereas, in control group, six patients needed intubation for acute respiratory distress (7.7% versus 27.3% were intubated, respectively,  $p=0.22$ ). Furthermore, the use of antibiotics was not different between two groups (61.5% of patients of EA group and 68.2% of control group,  $p=0.689$ ), nor was the duration of therapy. During hospitalization, EA group developed nine cases of loco-regional complications and 10 cases of systemic complications compared to controls with 12 cases of loco-regional complications and 13 systemic complications. Visual Analogue Scale evaluation showed improvement in subjective pain during the first 12 days in the EA group compared to the control group, with a significant difference on day of EA implementation and at ten days. The results for the mean pain score on a scale 1–10 were before randomization 6.55 versus 7.31,  $p=0.57$ ; after EA implementation 1.6 versus 3.5,  $p=0.02$ ; at day one 0.57 versus 2,  $p=0.06$ ; at day five 1.86 versus 1.38,  $p=0.69$ ; at day ten 0.2 versus 2.33,  $p=0.034$ ; at day twelve 0 versus 2.8,  $p=0.071$ . Conclusion of the study was that EA is a safe

procedure which significantly increased blood flow to the pancreatic gland with consequent lower development of necrosis and suggest a trend towards improvement of clinical outcome for patients with SAP.

## CONCLUSION

In intensive care medicine, SAP remains to be a challenging clinical disorder with multiple complications and high mortality. Main pathophysiological mechanisms with impact on outcome are uncontrolled systemic inflammatory response from the beginning and infection of pancreatic necrosis in late phase of the disease. Pre- and postoperative management of SAP patients must offer intensive care monitoring and supportive therapy. Timely recognition of potential complications, especially infections, improves outcome of SAP.

## References

- De Waele JJ. Acute pancreatitis. *Curr Opin Crit Care*. 2014; 20: 1-7.
- McMahon MJ. Acute pancreatitis. In: Misiewicz JJ, Pounder RE, Venables CW, eds. *Diseases of the gut and pancreas*. Oxford: Blackwell; 1994. p. 427-40.
- Blum T, Maisonneuve P, Lowenfels AB, et al. Fatal outcome in acute pancreatitis: its occurrence and early prediction. *Pancreatol*. 2001; 1: 23-41.
- Mutinga M, Rosenbluth A, Tenner SM, et al. Does mortality occur early or late in acute pancreatitis? *Int J Pancreatol*. 2000; 28: 91-5.
- Wu BU. Editorial: fluid resuscitation in acute pancreatitis: striking the right balance. *AM J Gastroenterol*. 2011; 106: 1851-2.
- Cherpanath TGV, Geerts BF, Groeneveld ABJ, et al. Basic concepts of fluid responsiveness. *Neth Heart J*. 2013; 21 (12): 530-6.
- Grassi P, Lo Nigro L, Berlot G, et al. Pulse pressure variation as a predictor of fluid responsiveness in mechanically ventilated patients with spontaneous breathing activity: a pragmatic observational study. *HCR Proc Intensive Care Cardiovasc Anesth*. 2013; 5 (2): 98-109.
- Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for management of acute pancreatitis. *Pancreatol*. 2013; 13 (4 Suppl 2): e1-15.
- Wu BU, Hwang JQ, Gardner TH, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clin Gastroenterol Hepatol*. 2011; 9: 710-7.
- Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2013; (2): CD000567.
- Pelosi P, Gama de Abreu M, Rocco PRM. New and conventional strategies for lung recruitment in acute respiratory distress syndrome. *Critical Care*. 2010; 14: 210-6.
- Umbrello M, Formenti P, Bolgiagli L, et al. Current concepts of ARDS: a narrative review. *Int J Mol Sci*. 2017; 18 (64): 1-20.
- Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med*. 2008; 359 (20): 2095-104.
- Pelosi P, Vargas M. Mechanical ventilation and intra-abdominal hypertension: 'Beyond good and evil'. *Critical Care*. 2012; 16: 18-8.
- Ferron FR, Pedregosa TA, Garcia MR, et al. Intraabdominal and thoracic pressure in critically ill patients with suspected intraabdominal hypertension. *Med Intensiva*. 2011; 35 (5): 274-9.
- Mirković T. Akutni pankreatitis. In: Pavel-Eržen V, ed. 22. tečaj CEEA. Ljubljana: Slovensko združenje za anesteziologijo in intenzivno medicine, Slovensko zdravniško društvo; 2014. p. 73-90.
- Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*. 2013; 39: 1190-206.
- Chiumello D, Gallazzi E, Mario A, et al. A validation study of a new nasogastric polyfunctional catheter. *Intensive Care Med*. 2011; 37 (5): 791-5.
- De Waele JJ, Hoste EA, Malbrain ML. Decompressive laparotomy for abdominal compartment syndrome – a critical analysis. *Crit Care*. 2006; 10: 51-8.
- Leppäniemi A, Mentula P, Hienonen P, et al. Transverse laparotomy is feasible and effective in the treatment of abdominal compartment syndrome in severe acute pancreatitis. *World J Emerg Surg*. 2008; 3: 3-6.
- Maher MM, Lucey BC, Gervais DA, et al. Acute pancreatitis: the role of imaging and interventional radiology. *Cardiovasc Intervent Radiol*. 2004; 27: 208-25.
- Wittau M, Mayer B, Scheele J, et al. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scand J Gastroenterol*. 2011; 46: 261-70.
- Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev*. 2010; 12: CD002941.
- Jiang K, Huang W, Yang XN, et al. Present and future of prophylactic antibiotics for severe acute pancreatitis. *World J Gastroenterol*. 2012; 18: 279-84.
- Wittau M, Mayer B, Scheele J, et al. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scand J Gastroenterol*. 2011; 46: 261-70.
- Maraví-Poma E, Gener J, Alvarez-Lerma F, et al. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. *Intensive Care Med*. 2003; 29: 1974-80.
- Greenberg JA, Hsu J, Bawazeer M, et al. Clinical practice guideline: management of acute pancreatitis. *Can J Surg*. 2016; 59: 128-40.
- Brattström C, Malmberg AS, Tyden G. Penetration of imipenem into human pancreatic juice following single intravenous dose administration. *Chemotherapy*. 1989; 35: 83-7.
- Wittau M, Wagner E, Kaefer V, et al. Intraabdominal tissue concentration of ertapenem. *J Antimicrob Chemother*. 2006; 57: 312-6.

30. Wacke R, Förster S, Adam U, et al. Penetration of moxifloxacin into the human pancreas following a single intravenous or oral dose. *J Antimicrob Chemother.* 2006; 58: 994-9.
31. Schubert S, Dalhoff A. Activity of moxifloxacin, imipenem, and ertapenem against *Escherichia coli*, *Enterobacter cloacae*, *Enterococcus faecalis*, and *Bacteroides fragilis* in monocultures and mixed cultures in an in vitro pharmacokinetic/pharmacodynamic model simulating concentrations in the human pancreas. *Antimicrob Agents Chemother.* 2012; 56: 6434-6.
32. Whitcomb DC. Clinical practice. Acute pancreatitis. *N Engl J Med.* 2006; 354: 2142-50.
33. Gloor B, Müller CA, Worni M, et al. Late mortality in patients with severe acute pancreatitis. *Br J Surg.* 2001; 88: 975-9.
34. van Santvoort HC, Besselink MG, Bakker OJ, et al. Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med.* 2010; 362: 1491-502.
35. Behraman SW, Bahr MH, Dickson PV, et al. The microbiology of secondary postoperative pancreatic infections: Implications for antimicrobial management. *Arch Surg.* 2011; 146: 613-9.
36. Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. *J Parenter Enteral Nutr.* 1997; 21: 133-56.
37. Singh VK, Moran RA, Afghani E, et al. Treating acute pancreatitis: what's new? *Expert Rev Gastroenterol Hepatol.* 2015; 9: 901-11.
38. Janisch NH, Gardner TB. Advances in management of acute pancreatitis. *Gastroenterol Clin North Am.* 2016; 45: 1-8.
39. Fritz S, Hackert T, Hartwig W, et al. Bacterial translocation and infected pancreatic necrosis in acute necrotizing pancreatitis derives from small bowel rather than from colon. *Am J Surg.* 2010; 200: 111-7.
40. Petrov MS, van Santvoort HC, Besselink MG, et al. Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis: a meta-analysis of randomized trials. *Arch Surg.* 2008; 143: 1111-7.
41. Lodewijckx PJ, Besselink MG, Witteman BJ, et al. Nutrition in acute pancreatitis: a critical review. *Expert Rev Gastroenterol Hepatol.* 2016; 10 (5): 571-80.
42. Muftuoglu MA, Isikgor S, Tosun S, et al. Effects of probiotics on the severity of experimental acute pancreatitis. *Eur J Clin Nutr.* 2006; 60: 464-8.
43. Barraud D, Bollaert PE, Gibot S. Impact of the administration of probiotics on mortality in critically ill adult patients: a meta-analysis of randomized controlled trials. *Chest.* 2013; 143: 646-55.
44. Lei QC, Wang XY, Xia XF, et al. The role of omega-3 fatty acids in acute pancreatitis: a meta-analysis of randomized controlled trials. *Nutrients.* 2015; 7: 2261-73.
45. Jafari T, Feizi A, Askari G, et al. Parenteral immunonutrition in patients with acute pancreatitis: a systematic review and meta-analysis. *Clin Nutr.* 2015; 34: 35-43.
46. Perez S, Pereda J, Sabater L, et al. Redox signaling in acute pancreatitis. *Redox Biol.* 2015; 5: 1-14.
47. Yao H, He C, Deng L, et al. Enteral versus parenteral nutrition in critically ill patients with severe pancreatitis: a meta-analysis. *Eur J Clin Nutr.* 2018; 72 (1): 66-8.
48. Pan LL, Li J, Shamoan M, et al. Recent advances on nutrition in treatment of acute pancreatitis. *Front Immunol.* 2017; 8: 762.
49. Feng P, He C, Liao G, et al. Early enteral nutrition versus delayed enteral nutrition in acute pancreatitis: A PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore).* 2017; 96 (46): e8648.
50. Meier R, Beglinger C, Layer P, et al. ESPEN Consensus Group. ESPEN guidelines on nutrition in acute pancreatitis. European Society of Parenteral and Enteral Nutrition. *Clin Nutr.* 2002; 21 (2): 173-83.
51. Jakobs R, Adamek MU, von Bubnoff AC, et al. Buprenorphine or procaine for pain relief in acute pancreatitis. A prospective randomized study. *Scand J Gastroenterol.* 2000; 35: 1319-23.
52. Stevens M, Elser R, Asher G. Transdermal fentanyl for the management of acute pancreatitis pain. *Appl Nurs Res.* 2002; 15: 102-10.
53. Kahl S, Zimmermann S, Pross M, et al. Procaine hydrochloride fails to relieve pain in patients with acute pancreatitis. *Digestion.* 2004; 69: 5-9.
54. Mennecier D, Ceppa F, Sinayoka L, et al. Acute pancreatitis after treatment by celcoxib. *Gastroenterol Clin Biol.* 2007; 31: 668-9.
55. Heluwaert F, Pofelski J, Germain E, et al. Piroxicam and acute pancreatitis. *Gastroenterol Clin Biol.* 2006; 30: 635-6.
56. Mete D, Milon A, Belon G, et al. Acute pancreatitis and ketoprofen. *Gastroenterol Clin Biol.* 2001; 25: 721-2.
57. Aygencel G, Akbuga B, Keles A. Acute pancreatitis following naproxen intake. *Eur J Emerg Med.* 2006; 13: 372.
58. Murray B, Carter R, Imrie C, et al. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology.* 2003; 124 (7): 1786-91.
59. Pezzilli R, Morselli-Labate AM, Corinaldesi R. NSAIDs and acute pancreatitis: a systematic review. *Pharmaceuticals.* 2010; 3: 558-71.
60. Basurto Ona X, Rigau Comas D, Urrútia G. Opioids for acute pancreatitis pain. *Cochrane Database Syst Rev.* 2013; 26 (7): CD009179.
61. Takeda K, Takada T, Kawarada Y, et al. JPN Guidelines for the management of acute pancreatitis: medical management of acute pancreatitis. *J Hepatobiliary Pancreat Surg.* 2006; 13 (1): 42-7.
62. Bernhardt A, Kortgen A, Niesel HCh, et al. Using epidural anesthesia in patients with acute pancreatitis—prospective study of 121 patients. *Anaesthesiol Reanim.* 2002; 27: 16-22.
63. Sielenkämper AW, Eicker K, van Aken H. Thoracic epidural anaesthesia increases mucosal perfusion in ileum of rats. *Anesthesiology.* 2000; 93: 844-51.
64. Freise H, Anthonen S, Fischer LG, et al. Continuous thoracic epidural anaesthesia induces segmental sympathetic block in the awake rat. *Anesth Analg.* 2005; 100: 255-62.
65. Sadowski SM, Andrea A, Morel P, et al. Epidural anesthesia improves pancreatic perfusion and decreases the severity of acute pancreatitis. *World J Gastroenterol.* 2015; 21 (43): 12448-56.

# Necrosectomy in Acute Pancreatitis – Who is Better: the Surgeon’s View

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## ABSTRACT

In recent years we witnessed dramatic changes in the management of patients with acute necrotizing pancreatitis. We moved from open surgery which was often performed too early in the course of disease to less aggressive procedures, trying to delay surgical treatment as long as possible. Surgery might be considered as an option in the early phase of the disease only when abdominal compartment syndrome evolves as a consequence of underlying disease and resuscitation. Additionally, surgical treatment is required in late phase for patients with proven infected pancreatic necrosis and organ failure where other measures and techniques have failed to improve patient’s condition. For these patients, surgical debridement is still considered the treatment of choice. The strategy of a ‘step-up’ approach, performing first percutaneous or even endoscopic drainage of infected collections, and continuing with surgical procedures through new access routes (preferably retroperitoneal) or endoscopic necrosectomy in case of absence of improvement, has been now widely adopted. These concepts require a multi-disciplinary approach to acute necrotizing pancreatitis regarding open necrosectomy in the management of

severe acute necrotizing pancreatitis. The ‘step-up’ approach significantly reduced morbidity and mortality in acute necrotizing pancreatitis when compared to primary surgical intervention. Patients have to be referred to reference centers where all the needed resources, knowledge and logistics is available.

## INTRODUCTION

Acute pancreatitis (AP) is associated with an overall mortality of about 5% and due to an incidence between 30 and 45/100.000 people per year; it is a frequent and potentially fatal disease (1, 2). In most cases, AP represents a mild, self-limited disease but in 15–25% severe acute pancreatitis (SAP) develops, manifested with pancreatic parenchymal and peripancreatic tissue necrosis (3). The mortality, however, depends on disease severity and may be as high as 20% in patients with severe and complicated pancreatitis (1, 3). Pancreatic necrosis (PN) accounts for substantial additional morbidity, with mortality rates remaining as high as 10–20% despite the advances in critical care (3). Characteristics of moderate and severe pancreatitis are local or systemic complications. Local complications include acute peripancre-

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atic fluid collections, pancreatic pseudocysts, acute necrotic collections and walled-off necrosis (WON). Acute necrotizing pancreatitis (ANP) evolves in about 10–30% of the patients with AP and is associated with a particularly poor outcome (1, 3). The clinical course of SAP is divided in two phases. An early inflammatory phase that lasts first two weeks, and a late phase after the first two weeks marked by infectious complications. Mortality rates in the event of infected ANP increase up to 30% with surgical intervention and nearly 100% in the absence of any intervention (4).

Historically, early open surgical intervention with laparotomy for extensive PN had been broadly adopted. Nearly all patients with ANP have been treated with open necrosectomy (ON). ON used to be performed early in the course of the inflammation, even in patients with sterile necrosis (5). However, due to a high morbidity and the need of repetitive laparotomy, outcomes were unsatisfactory (6). During the last decade, several studies showed better outcome for less invasive treatment approaches including transgastric and percutaneous drainage or endoscopic necrosectomy (ENS). Nowadays, it is accepted that intervention is only indicated if infected necrosis is suspected and that intervention should be delayed for at least 3–4 weeks after onset of pancreatitis if possible. The so-called step-up approach consisting of conservative treatment followed by drainage and minimally invasive interventions results in a decrease in overall morbidity and defines the recommended standard care of therapy nowadays (7).

The most common indication for surgery of PN is infection which can be accompanied by single or multiple organ failure. It is a rare event during the first week of clinical course. Secondary infection of PN develops later in 40–70% of patients with a mortality rate greater than 20%. Infected PN is found in 80% of patients dying from AP. In contrast, mortality for sterile PN is low and can be successfully treated by a conservative approach, although surgery might be required for late complications or persistent ANP (8).

The diagnosis of infected PN is based on the presence of sepsis with CT findings of extraluminal gas in necrotic areas of pancreas and surrounding tissue. Diagnosis is confirmed by positive cultures of percutaneous fine-needle aspirates of necrosis and fluid. A persistent single or multiple organ failure refractory to supportive treatment may also constitute an indication for surgery. Several studies have shown that, oppositely to what happens when infection constitutes the indication for surgery, necrosectomy does not provide a significant benefit regarding mortality, and thus, it must be considered as the last resource in a patient in whom medical treatment does not result in improvement (9). Indication for surgery in ANP must derive from the need to control complications and not to influence the inflammatory process itself. The intention of every procedure must be removal of all necrotic and infected tissue. Number and localization of fluid collections and viscosity of the content are determining factors for the selection of the best therapeutic approach. Morbidity associated to open pancreatic debridement includes pancreatic fistula (50%), endo- and exocrine pancreatic failure (20%), intestinal fistula (10%) and the common prolonged hospitalization and delay in the incorporation to daily life activities (10).

In surgical approach, debridement is preferred over resection because it preserves the most of functional pancreatic tissue. Resection is often technically impossible and is associated with unacceptable morbidity and mortality in patients with ANP (10). The best results are obtained when the indication for surgery may be delayed up to one month after the onset of the clinical symptoms. Unless evident infection of necrosis exists, survival improves as the surgical procedure is postponed. A better demarcation of necrosis and its conversion to WON involves less bleeding and less removal of viable tissues during surgical procedure (9).

Two different treatment strategies define the timing of the surgical approach for a patient with ANP. ‘Step-down’ consists of immediate surgical approach when there is an established indication, and later a more conservative treatment for the residual disease. Currently, there is increasing evidence in the literature,

that a 'step-up' concept, where more conservative procedures (percutaneous, laparoscopic or endoscopic) constitute the initial treatment of patients with ANP and a final surgical ON is performed later in the course of disease, and only when necessary, is superior to the 'step-down' concept regarding the survival and morbidity.

## **RATIONALE AND TIMING OF NECROSECTOMY**

Intention of necrosectomy performed with preservation of remaining vital pancreatic tissue is to accomplish locally focused control of necrosis and ascites from the lesser sac and the peritoneal cavity. Continuous lavage of the lesser sac and peritoneal cavity influences the systemic inflammatory response and has been shown to be a useful adjunct of necrosectomy (11). This diminishes or interrupts the devastating progress of inflammation and absorption or systemic release of various inflammatory mediators that account for remote organ failure (12).

Also, necrosectomy should be restricted to patients with PN in whom conservative, endoscopic or interventional treatment has failed. Development of multiple organ dysfunction syndrome (MODS) or even failure (MOF) frequently complicates the early phase of the disease, but half of these patients respond well to conservative management (13). Therefore, prolonged intensive conservative treatment is essential for the selection of patients who do not require surgery. The effectiveness of necrosectomy in patients with PN is also directly related to the grade of demarcation of necrosis. Demarcation develops at the end of the 2<sup>nd</sup> week after symptom onset (14). The presence of infected PN is nowadays a uniformly accepted indication for drainage, interventional or surgical. However, this indication for surgery has also been challenged, and even some patients with infected PN can be treated conservatively, and extended conservative treatment protocols may result in a favorable outcome (15). In critically ill patient with infected PN, it remains to be proven how much conservative treatment someone can bear before interventional or sur-

gical techniques becomes necessary to prevent further deterioration of patient's condition. Deterioration with MODS and MOF can occur in SAP within a few hours or days after the onset of symptoms. In the past, early surgical intervention was favored. However, outcomes were rather disappointing and associated with mortality rates of up to 65%. When comparing early (within 72 hours of symptoms) with late (at least 12 days after onset) pancreatic debridement in patients with ANP, mortality rates were 56% and 27%, respectively (16). Every effort should be made to avoid surgical intervention in the first two weeks even in the presence of MOF and withholding of necrosectomy until four weeks (17). Nowadays, there is general agreement that surgery in ANP should be performed as late as possible (8). The late phase, two weeks after the onset of the disease, is agreed to provide optimal operative conditions with well demarcated necrotic tissue. Procedures should be limited to pure debridement and only one single intervention. This approach decreases the risk of bleeding, perforation of intestine and occurrence of intestinal fistula, minimizes the loss of vital pancreatic tissue, and thus reduces the rate of endocrine and exocrine pancreatic insufficiency. Only in the case of proven infected necrosis, uncontrollable intraabdominal hypertension with compartment syndrome or in the presence of rare complications, such as massive bleeding or bowel perforation, early surgery is justified in patients with SAP.

## **OPEN PANCREATIC NECROSECTOMY**

During the last decades, numerous surgical procedures in SAP has been proposed for the surgical management of SAP, from minimally invasive to extensive resections. Neither of them accomplished a significant reduction in the overall mortality of SAP (16). The reason for such disappointing results is linked to the fact that none of these treatment protocols sufficiently addressed the underlining pathophysiological mechanisms of the disease.

It is obvious that appropriate operative technique for the treatment of ANP is not resection but should consist of careful removal of PN and preservation of vital

pancreatic tissue and organs in vicinity. This concept resulted in decreased mortality rates that were originally greater than 50%, to about 20% (18). However, despite these improvements, recurrent sepsis after necrosectomy because of inadequate drainage or incomplete necrosectomy, continues to pose a major drawback. Currently, necrosectomy aims to remove the focus of necrotic and infected tissue so that further complications are avoided by limiting the inflammatory process. This can be achieved with minimal injury to vital pancreatic tissue and organs in vicinity and maximization of postoperative removal of pus, necrotic remnants, and fluid with pancreatic exocrine secretions and other inflammatory mediators (19).

ON was considered as the standard gold treatment for decades, and it was usually associated to a therapeutic 'step-down' approach. Traditional ON through a mid-line or subcostal bilateral incision consists of assessment of the entire abdominal cavity, debridement of the necrotic pancreatic tissue and the access to lesser sac and pancreatic area through the hepatogastric and gastrocolic ligament or by a transmesenteric access through the transverse mesocolon, depending on necrosis extension and localization. Once the necrosis is exposed and samples for bacterial and fungal cultures taken, debridement is carried out bluntly. After all loose debris has been removed, the retroperitoneal cavity is irrigated. Whenever it is possible adequate debridement should be achieved within a single procedure. Once the necrosectomy has been performed, the options that were described are:

- Closure of the abdominal wall over drains and 'relaparotomy on demand' depending on clinical course (20);
- Scheduled laparotomies with repeated lavage, usually every second day, until debridement has been completed. Open abdomen and temporary abdominal closure techniques are recommended when this approach is selected, but scheduled laparotomies closing the abdomen after each revision have also been reported (21);
- Necrosectomy combined with open packing (22);
- Necrosectomy combined with closed packing (23);

- Closed technique with abdominal wall closure over lavage system with large-bore drains in the pancreatic area (24);
- Focused open necrosectomy (FON) with US guidance (25);
- Necrosectomy with scheduled re-explorations combined with open abdomen treatment and temporary abdominal closure with negative pressure wound therapy with instillation (NPWTi) in retroperitoneum.

Currently closed technique of ON with abdominal wall closure over lavage system in the pancreatic area is the most recommended option based on mortality below 10%. This is significantly inferior to those associated to the rest of the techniques except to the NPWTi technique. Comparing different methods of ON is difficult because of the heterogeneity of patients and surgeons (9, 10, 26). Although necrosectomy is performed in a more or less identical fashion, the techniques differ in the way they provide exit channels pus and infected debris. In some techniques drainage of the retroperitoneum is active, combined with either continuous lavage or intermittent soaking. Series of patients treated with ON at experienced care centers showed mortality rates below 15% for all techniques. Results of different techniques of ON are presented in Table 1.

### **On-demand relaparotomy**

When adequate debridement is achieved during ON within a single procedure, drains are placed in retroperitoneum, or abdominal cavity and abdominal wall is closed. If adequate source control is achieved no further relaparotomies are needed. Relaparotomy is only performed in patients with clinical deterioration or lack of clinical improvement with a likely intra-abdominal cause. Other infections must be ruled out using laboratory tests, imaging modalities, or both. Deterioration after the previous procedure is considered in case of ACS, intra-abdominal bleeding with hemodynamic instability, burst abdomen, perforation of visceral organ, anastomotic leakage, ischemia or necrosis of a visceral organ and finally intra-abdominal abscess that cannot be drained percutaneously.

Table 1. Mortality of open necrosectomy procedures

Technique	Patients (n)	Infected necrosis, n (%)	Mortality, n (%)	Relaparotomy, n (%)
<b>Open packing</b>				
Bradley 1993	71	71 (100)	15	1–5/patient
Branum 1998	50	42 (84)	6 (12)	2–13/patient
Bosscha 1998	28	28 (100)	11 (39)	17/patient
Nieuwenhuijs 2003	38	18 (47)		
<b>Planned relaparotomies</b>				
Sarr 1991	23	18 (75)	4 (17)	2–>5/patient
Tsiotos 1998	72	57 (79)	18 (25)	1–7/patient
<b>Closed packing</b>				
Fernandez 1998	64	36 (56)	4 (6)	11 (17)
Rodriguez 2008	167	120 (72)	19 (11.4)	21 (12.6)
<b>Closed continuous lavage</b>				
Beger 1988	95	37 (39)	8 (8)	26 (27)
Farkas 1996	123	123 (100)	9 (7)	
Buchler 2000	29	27 (93)	7 (24)	6 (22)
Nieuwenhuijs 2003	21		7 (33)	
<b>Negative pressure wound therapy-instillation</b>				
Trotovšek 2017	10	10 (100)	1 (10%)	3/patient

### Scheduled laparotomies with repeated lavage

The necrotic space is unroofed in a controlled fashion, with care to protect neighbouring vital anatomical structures. Necrosectomy is carried out by a non-aggressive, blunt dissection without inducing hemorrhage. All necrotic tissues amenable to debridement are removed at the initial procedure. After necrosectomy and irrigation of the debrided areas, abdominal wall closure is performed. Fascia can be sewn, and abdominal wall closed. Contemporary approach is to leave abdomen open and to temporarily close the abdominal wall with one of the temporary abdominal wall closure techniques. Negative pressure wound closure techniques, especially V.A.C.<sup>®</sup> with ABThera<sup>™</sup> dressing (KCI, San Antonio) are most often used with

currently the best results regarding the survival rate and frequency of delayed primary fascial closure (27). Reoperation is performed 48 hours after the initial procedure, and additional necrosectomy and debridement are performed as needed. Procedures are repeated at 48 hours intervals until source control has been achieved. When all necrotic debris has been removed, the abdomen is closed over drains.

### Necrosectomy combined with open packing

The open packing technique is based on the continuous re-exploration principle, with open lavage of the necrotic areas. After debridement, the lesser sac is lined with non-adherent sheet, to protect adjacent intestinal surfaces and to prevent injuries, and packed.

The abdomen is left open, and re-exploration and debridement performed every 24 to 48 hours until necrosectomy is complete and there is evidence of granulations. The wound then heals entirely by secondary intention, or it is closed over drains, with or without lavage of the cavity (22). This approach has been mostly abandoned.

### **Necrosectomy combined with closed packing**

The goal of this technique is to perform a single operation with thorough debridement and removal of necrotic and infected tissue while minimizing the need for reoperation or subsequent pancreatic drainage. Access to the pancreas is gained via the left mesocolon. Entry into the necrotic cavity is made bluntly, and the cavity with its recesses is explored and necrotic tissue and fluid evacuated. When necrosis is present also on the right side, an additional incision in the right mesocolon is made, or even paracolic gutters are opened to remove all necrotic tissue. After irrigation of pancreatic bed, Penrose drains stuffed with gauze (23) are used for packing the large, stiff cavity that results after debridement. Drains fill the cavity and provide compression and not only drain the area. The number of drains depends on the size of the cavity, and they are gradually removed during the first week after procedure.

Also, soft, silicone, closed suction drains are introduced in cavity too and are removed when they have no more output. The abdomen is closed, primarily as usual (23).

### **Closed technique with lavage system**

ON with continuous lavage of the lesser sac and retroperitoneum is performed over two to four flushing drains. The

abdomen is closed and lavage with 10–15 L/24 hours is performed for few days to allow sufficient drainage of debris and exudates. This procedure seems to have the lowest mortality and is advocated by the authors (26).

### **Focused open necrosectomy with ultrasound guidance**

Laparotomy and FON is performed with the assistance of perioperative ultrasound. FON can be an alternative method to conventional ON in patients with infected necrosis and unresolved sepsis. After routine implementation of intraoperative navigation with ultrasound, FON was implemented using small lumbar and subcostal approaches in the surgical treatment of patients with infected necrosis. ON and drainage were performed through small, focused lumbar or subcostal incisions accessing infected necrotic tissue and fluid collections. Percutaneous catheter drainage inserted before surgery for temporary sepsis control is used as a guide and helps to perform less traumatic intervention. In patients with several distant infected necrosis or fluid collections, repeated interventions to achieve drainage and removal of sequestrations is used, providing necrosectomy and drainage in several steps, when necessary. Mortality can be as low as 6% in selected patients.



*Figure 1. The V.A.C. VERAFLO CLEANSE™ dressing (KCI, San Antonio) is inserted in retroperitoneal space through opened gastrocolic ligament*

## Negative pressure wound therapy with instillation

After entering the peritoneal cavity through bilateral upper transversal incision, gastrocolic ligament is divided. Exploration of the entire pancreas, as well as determination of the extent of necrosis, is performed. The necrotic space is unroofed in a controlled fashion, with care to protect neighbouring vital anatomical structures. Necrosectomy is carried out, and all devitalized tissues amenable to debridement are removed avoiding hemorrhage at the initial necrosectomy. After necrosectomy, an extensive irrigation of the debrided areas is performed. The V.A.C. VERAFLU CLEANSE™ dressing (KCI, San Antonio) is inserted in retroperitoneal space. The tubular shape of it allows flexibility in addressing wounds with complex geometries. Special structure and material of the foam provides non-aggressive way of tamponade, suction, and instillation of fluid in retroperitoneal space where ON was performed (Figure 1). Temporary abdominal wall clo-

sure with ABThera™ dressing (KCI, San Antonio) is achieved and tubular foam is pulled through the ABThera™ dressing (Figure 2) and positioned under the double channel T.R.A.C. pad® intended for use with V.A.C. ULTA™ Negative Pressure Wound Therapy System with instillation capability. Reoperation is performed 48 hours after the initial procedure, and not more than three changes of dressings are performed to avoid damage to surrounding organs and vessels and to prevent lateralization of the abdominal wall. Instillation is performed for 30 minutes with 500 mL of saline in cycles of 4–6 hours of continuous negative pressure (125 mmHg). Additional necrosectomy and blunt debridement are performed as needed. In 6–8 days after initial procedure, when pancreatic bed is clean of necrotic debris, the abdomen is closed over drains. Drains are routed through retroperitoneum to the flanks, posterior to the hepatic and splenic flexure of colon. Abdominal wall is closed with continuous slowly absorbable suture. Mortality in feasibility study was 10%.



Figure 2. The V.A.C. VERAFLU CLEANSE™ dressing (KCI, San Antonio) (thick arrow) is inserted in retroperitoneal space. Temporary abdominal wall closure with ABThera™ dressing (KCI, San Antonio) (long arrow) is achieved and tubular foam is pulled through the ABThera™ dressing

## CONCLUSION

The operative management of AP is focused on managing the acute complications and the long-term sequelae. Using the least amount of intervention to achieve the stated goals has always been the case. However, the evolution of interventional, endoscopic and minimally invasive surgical techniques has greatly expanded the tools available. With new approaches and with introduction of less invasive treatment modalities than ON, patients are experiencing a much lower morbidity and mor-

tality than in the past. ON has been a golden standard of surgical procedures for infected necrotizing pancreatitis. Currently, the management is moving toward minimally invasive techniques for necrosectomy, obviating the need for ON in most cases. Percutaneous drainage by itself can eliminate the need for necrosectomy in many patients. But in selected cases where other methods have failed, surgery and ON remains the last option in managing of these critically ill patients.

## References

1. Roberts SE, Akbari A, Thorne K, et al. The incidence of acute pancreatitis: impact of social deprivation, alcohol consumption, seasonal and demographic factors. *Aliment Pharmac Ther.* 2013; 38: 539-48.
2. Phillip V, Huber W, Hagemes F, et al. Incidence of acute pancreatitis does not increase during Oktoberfest but is higher than previously described in Germany. *Clin Gastroenterol Hepatol.* 2011; 9: 995-1000.
3. Freeman ML, Werner J, van Santvoort HC, et al. Interventions for necrotizing ancreatitis: summary of a multidisciplinary consensus conference. *Pancreas.* 2012; 41: 1176-94.
4. Petrov MS, Shanbhag S, Chakraborty M, et al. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology.* 2010; 139: 813-20.
5. Branum G, Galloway J, Hirchowit W, et al. Pancreatic necrosis: results of necrosectomy, packing, and ultimate closure over drains. *Ann Surg.* 1998; 227: 870-7.
6. Hartwig W, Werner J, Muller CA, et al. Surgical management of severe pancreatitis including sterile necrosis. *J Hepatobiliary Pancreat Surg.* 2002; 9: 429-35.
7. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology.* 2011; 141: 1254-63.
8. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. *Pancreatology.* 2002; 2: 565-73.
9. Martin RF, Hein AR. Operative management of acute pancreatitis. *Surg Clin North Am.* 2013; 93: 595-610.
10. Da Costa DW, Boerma D, van Santvoort HC, et al. Staged multidisciplinary step-up management for necrotizing pancreatitis. *Br J Surg.* 2014; 101: 65-79.
11. Mayer J, Rau B, Gansauge F, et al. Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. *Gut.* 2000; 47 (4): 546-52.
12. Nieuwenhuijs VB, Besselink MGH, van Minnen LP, et al. Surgical management of acute necrotizing pancreatitis: a 13-year experience and a systematic review. *Scand J Gastroenterol Suppl.* 2003; 38: 111-6.
13. Flint R, Windsor JA. Early physiological response to intensive care as a clinically relevant approach to predicting the surgery outcome in severe acute pancreatitis. *Arch Surg.* 2004; 139: 438-43.
14. Tsiotos GG, Luque-de León E, Sarr MG. Long-term outcome of necrotizing pancreatitis treated by necrosectomy. *Br J Surg.* 1998; 85: 1650-3.
15. Runzi M, Niebel W, Goebell H, et al. Severe acute pancreatitis: nonsurgical treatment of infected necroses. *Pancreas.* 2005; 30: 195-9.
16. Beger HC, Rau B, Isenmann R. Natural history of necrotizing pancreatitis. *Pancreatology.* 2003; 3: 93-101.
17. Besselink MGH, Verwer TJ, Schoenmaeckers EJP, et al. Timing of surgical intervention in necrotizing pancreatitis. *Arch Surg.* 2007; 142: 1194-201.
18. Oleynikov D, Cook C, Sellers B, et al. Decreased mortality from necrotizing pancreatitis. *Am J Surg.* 1998; 176 (6): 648-53.
19. Werner J, Feuerbach S, Uhl W, et al. Management of acute pancreatitis: from surgery to interventional intensive care. *Gut.* 2005; 54 (3): 426-36.
20. Van Ruler O, Mahler CV, Boer KR, et al. Comparison of on-demand vs. planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. *JAMA.* 2007; 298 (8): 865-72.
21. Sarr MG, Nagorney DM, Mucha P, et al. Acute necrotizing pancreatitis: management by planned, staged pancreatic necrosectomy/debridement and delayed primary wound closure over drains. *Br J Surg.* 1991; 78: 576-81.
22. Bradley EL. Management of infected pancreatic necrosis by open drainage. *Ann Surg.* 1987; 206 (4): 542-50.
23. Rodriguez JR, Razo AO, Targarona J, et al. Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. *Ann Surg.* 2008; 247 (2): 294-9.
24. Beger HC, Buchler MW, Bittner R, et al. Necrosectomy and postoperative local lavage in necrotizing pancreatitis. *Br J Surg.* 1988; 75: 207-12.
25. Pupelis G, Fokin V, Zeiza K, et al. Focused open necrosectomy in necrotizing pancreatitis. *HPB (Oxford).* 2013; 15 (7): 535-40.
26. Schneider L, Büchler MW, Werner J. Acute pancreatitis with an emphasis on infection. *Infect Dis Clin North Am.* 2010; 24: 921-41.
27. Cheatham ML, Demetriades D, Fabian TC, et al. Prospective study examining clinical outcomes associated with a negative pressure wound therapy system and Barker's vacuum packing technique. *World J Surg.* 2013; 37 (9): 2018-30.

# Impact Factors for Perioperative Morbidity and Mortality and Repercussion of Perioperative Morbidity and Long-Term Survival in Pancreatic Head Resection

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**Key words:** pancreatic resections, complications, impact factors

## ABSTRACT

**Background:** The present study analyses complications after pancreatic resections, however, the focus was to reveal any impact factors for perioperative morbidity and mortality as well as repercussion of perioperative morbidity on long-term survival in pancreatic head resection.

**Methods:** In a retrospective study, altogether 300 patients after pancreatic resections were analyzed for morbidity and mortality. Of these, 240 were pancreatic head resections or total pancreatectomies (PD/TP), 57 left pancreatectomies and three Frey procedures. According to Clavien-Dindo classification, all complications with grade II and more were defined as overall complications (OAC). Clinical-pathologic factors of 240 patients after PD/TP were further analyzed for correlations with morbidity, 30- and 90-day mortality, and long-term survival. Overall complications, all surgical (ASC), all general (AGC), and some specific types of complications like leaks from the pancreatoenteric anastomosis (PL) or pancreatic fistula (PF; type A, B, and C),

leaks from other anastomoses (OL), bleeding (BC), and abscesses (AA) were studied for correlation with clinical-pathologic factors.

**Results:** For all pancreatic resections, the incidence of OAC was 34%, ASC 27%, and AGC 14%. Overall 30- and 90-day mortality were 4.7% and 7.3%, respectively, and decreased to 2.8% and 4.5% in the second period ( $p=0.025$ ). In left pancreatectomies, the incidence of OAC was 22.8%, ASC 19.3%, and AGC 14%. The 30- and 90-day mortality rates were 3.5% and 5.3%, respectively (in the first and second period), and dropped to 0% in the second period. In PD/TP, the incidence of OAC was 37.1%, ASC 29.2%, and AGC 15.8%. All surgical complications presented themselves as PL, OL, BC and AA in 19% (of 208 PD), 5.8%, 5.8% and 2.5%, respectively. Age, ASA score, amylase on drains, and PF B and C correlated significantly with different types of complications in PD/TP. The 30- and 90-day mortality for PD/TP was 5% and 7.9%, respectively (in the first and second period), and decreased to 3.5% and 5.6% in the second period. In three patients with Frey procedure, there were no complications and no fatalities.

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**Conclusions:** Morbidity after pancreatic resections remains stable. However, 30- and 90-day mortality decreased. High amylase on drains and higher mean age were independent indicators of morbidity, whereas PL and BC revealed as independent predictor for 30-day mortality, and physical status, OAC and PFC for 90-day mortality.

## INTRODUCTION

Pancreatic resection, especially pancreatic head resection or total pancreatectomy (PD/TP), remains a significant challenge for many pancreaticobiliary surgeons. The complications associated with pancreatic procedures are well described (1, 2). They are usually of higher grade than in comparable abdominal surgical procedures. Many attempts have been made to lower these complications (1, 3–7). Some authors have claimed that modifications of the surgical techniques, especially the formation of the pancreaticojejunostomy, could have a positive impact on the postoperative course. Others have claimed that a better selection of patients would decrease the morbidity and mortality (8–13). Since perioperative morbidity and mortality are important predictors for long-term survival of patients after PD (14, 15), we performed a retrospective study to determine factors associated with perioperative and specific surgical complications, general complications, and perioperative mortality. The identification of such negative prognostic factors could help to prevent complications or even mortality and could, therefore, have an impact on long-term survival after pancreatic surgery. Factors like postoperative pancreatic fistula, age, and poor general condition have all been determined to have a negative impact on the postoperative course (1, 4, 13, 16, 17). The drawbacks of some of these studies, however, are the small number of included patients, the inclusion of low-volume centers, and the short-term postoperative follow-up of the patients. In our study, we, therefore, evaluated which clinical-pathologic factors significantly influence morbidity, mortality, and long-term results in our reference institution for pancreatic diseases, where meanwhile 40–50 pancreatic procedures are

performed annually. Preoperative workup, surgical procedures, and postoperative care became highly standardized. All these factors enabled us to perform a detailed study of factors influencing the perioperative course after pancreatic surgery.

## PATIENTS AND METHODS

For the present retrospective study, the data of 300 patients after pancreatic resections performed from January 1, 2008, to March 31, 2017, at the Department of Abdominal Surgery at University Medical Centre Maribor were analyzed. Clinical and pathological data were prospectively stored in a computerized database. Data for the follow-up were obtained by our outpatient follow-up and by the National cancer register of Slovenia. Complete follow-up was obtained up to June 1, 2017. We obtained informed consent from all patients and performed all procedures, according to the guidelines of the Helsinki Declaration. The analysis includes patients having had PD and TP. There are no urgent resections included. The indications for the resection were malignant and premalignant lesions of the region sited in the head of pancreas, and chronic pancreatitis in few cases (Table 1).

## PREOPERATIVE WORKUP

Patients' preoperative physical status was expressed by the American Society of Anaesthesiology (ASA) score (18). Before the surgery, all patients were submitted to CT. Additional abdominal MRI or endoultrasonography (EUS) with or without biopsy was done only in selected patients. Beside usual standard laboratory blood tests, tumor markers CEA and CA 19-9 were also evaluated. Preoperative endoscopic biliary drainage (EBD) was done in patients with bilirubin value > 200 mmol/l or in subicteric patients when further preoperative workup was necessary.

## Preoperative preparation

Intravenous antibiotic (1.5 g cefuroxime and 0.5 g metronidazole or 0.35 g gentamycin and 0.6 g clindamycin) and subcutaneous antithrombotic (4000 IE

Table 1. Indications for pancreatic resection in 300 patients. PD/TP – pancreatic head resection/total pancreatectomy, MD-IPMN – main duct-intraductal papillary mucinous neoplasm

Indication for pancreatic resection	All	PD/TP
Pancreatic adenocarcinoma	164	135
	54.7%	56.7%
Neuroendocrine tumor of the pancreas	21	9
	7%	3.8%
<b>MD-IPMN</b>	6	3
	2%	0.8%
Franz's tumor	3	1
	1.0%	0.4%
Non-Hodgkin lymphoma	2	2
	0.7%	0.8%
Distal bile duct carcinoma	43	43
	14.3%	17.9%
Adenocarcinoma of the papilla Vateri	30	30
	10%	12.5%
Duodenal adenocarcinoma	8	8
	2.7%	3.3%
Gastric cancer	2	2
	0.7%	0.8%
Chronic pancreatitis	16	7
	5.3%	2.9%
Pancreatic cystadenoma	4	0
	1.3%	0%
Metastasis of renal cell carcinoma	1	0
	0.3%	0%
<b>Total</b>	<b>300</b>	<b>240</b>

enoxaparin or 3800 nadroparin or 5000 IE dalteparin) prophylaxis were successively used in all patients one hour and 12 hours before operation. Urine catheter and nasogastric tube were usually inserted after induction of anesthesia.

### Surgical technique

The usual operative approach was median or bilateral subcostal laparotomy. After confirming respectability (no distant dissemination, no tumor infiltration of the coeliac trunk, hepatic artery or superior mesenteric

artery), the strategy was to perform a curable resection (R0) in malignant and premalignant lesions and to relieve symptoms as in chronic pancreatitis. Usually, pylorus-preserving PD, Whipple resection or TP (in patients with very soft texture of the pancreas unsuitable for anastomosis) were performed. In malignant disease, lymphadenectomy was done in hepatoduodenal ligament, around common hepatic artery, superior mesenteric artery (usually 180–270°), and occasionally between vena cava and aorta. Resection borders on the bile duct and pancreas were checked for neoplastic infiltration by frozen section examination. If infiltra-

tion of the superior mesenteric (VMS) or portal vein (VP) was suspected, en bloc resection of the infiltrated vein was done to assure the curability of resection.

Vascular reconstruction was done by direct continuous 6.0 monofilament non-absorbable suture; however, if more extended distance had to be bridged, vascular prosthesis was used. Anastomosis to pancreatic stump was exclusively performed by duct to mucosa end-to-side pancreaticoenteric anastomosis (PEA) using 5.0 monofilament non-absorbable sutures in two layers followed by single-layer bilioenteric anastomosis (BEA) with interrupted 5.0 absorbable poly filament sutures. In selected patients (mostly with thin duct and soft texture of the pancreas), trans-anastomotic lost stent was used. The continuity of the gastrointestinal tract was further established by omega gastroenteric anastomosis (GEA) done with 3.0 absorbable monofilament sutures. In all patients, single-layer continuous enteroenteric anastomosis (EEA) between afferent and efferent loop was done with 4.0 polyfilament absorbable suture. Two drains were placed in the right subhepatic region (one in space of resected head of the pancreas and one above BEA anastomosis) and one in the Douglas region.

## Postoperative care

Almost all patients were admitted in the high dependency unit except if admission to the intensive care unit was indicated. Patients started to receive fluid food on the first day. Gastric tube was removed after appearance of bowel movements or the first stools. Amylase was checked in the drained fluid on day 3 and after that when any clinical suspicion for anastomotic leaks was present. In selected patients (soft pancreas remnant) however, parenteral somatostatin (6 mg/24 h) was administrated for 6–10 days.

## Definitions and statistical analyses

All complications (OAC) according to Clavien–Dindo classification grade II or more were considered as postoperative morbidity (19). All surgical (ASC), all general (AGC), and all surgical and general complica-

tions (SGC) were analyzed. Also, special group of complications like leak from PEA (PL), leaks not from PEA (OL), abdominal abscess (AA) and abdominal or intestinal bleeding (BC) were identified. Any postoperative mortality within 30 and 90 days was considered a probable consequence of surgery and was declared as postoperative mortality (30- and 90-day mortality). Receiver operating curve (ROC) analysis for morbidity and mortality determined the threshold values of amylase secretion on abdominal drains. An area under curve (AUC) of > 0.75 was used to determine the value of significance. The ROC analysis was used to determine sensitivity and specificity of the determined amylase cut-off value, which revealed to be more than seven ukat/L.

Sensitivity and specificity for prediction of pancreatic fistula (PF) type B or C at cut-off seven ng/mL were 100% and 85.4%, respectively. Consequently, any secretion of amylase-rich fluid on drains more than seven ukat/L was defined as elevated. Patients with high amylase on drains from PEA were declared to have PF and were retrospectively classified in three types of PF (A, B, C), respecting clinical picture, therapeutic consequences, and ISGPF (International Study Group of Pancreatic Fistula) recommendations (20).

Two chronologically successive groups of patients (period 1 (P1): from January 1, 2008, to December 31, 2012 (124 patients); and period 2 (P2): from January 1, 2013, to March 31, 2017 (176 patients) were compared for perioperative morbidity, and 30- and 90-day mortality.

Continuous data are expressed as mean  $\pm$  standard deviation, and categorical variables are given as percentages. Continuous variables were compared with Student's t-tests for parametric data and Mann-Whitney U tests for nonparametric data. Chi-square tests were used for comparisons of discrete variables.

All of the predictors that were significant on univariate analysis ( $p > 0.05$ ) were included in the multivariate analysis. In the multivariate analysis, a binary logistic model was used. Survival analysis was performed with

the Kaplan-Meier method. The differences between groups were compared with the log-rank test. P-values < 0.05 were defined as the limit of significance. For statistical analysis, SPSS version 22.0 for Windows 7 (IBM Analytics, Armonk, NY) was used.

Our study aimed to evaluate the incidence of morbidity and mortality and to reveal any correlations with clinical-pathologic factors. In addition to morbidity and mortality, the impact of morbidity and mortality on survival was studied. The second aim was to reveal any differences between two chronologically successive groups (P1 and P2).

## RESULTS

Altogether 300 patients had pancreatic resection (male 160, female 140, mean age 66.4 years). The indications for resections and characteristics of the analyzed patients after all pancreatic resections, left pancreatectomy and PD/PT are presented in Table 1 and Table 2a–d. For all pancreatic resections, the incidence of OAC was 34%, ASC 27%, and AGC 14%. Overall 30- and 90-day mortality were 4.7 and 7.3%, respectively, and decreased to 2.8 and 4.5% (p=0.025) in P2. In left pancreatectomies, the incidence of OAC was 22.8%, ASC 19.3%, and AGC 14%. The 30- and 90-day mortality rates were 3.5 and 5.3%, respectively (P1 and P2), and dropped to 0% in P2. In three patients with Frey procedure, there was no complications and no fatalities.

Table 2a. Clinical-pathologic features in 300 patients after pancreatectomy. P1 – first study period (2008–2012), P2 – second study period (2013–2017), ASA – American Society of Anaesthesiologists score

		P1	P2	All	p-value
Gender	male	62	98	160	0.4
		50%	55.7%	53.3%	
	female	62	78	140	
		50%	44.3%	45.7%	
Age	mean (years)	66.1 ± 9.9	65.98 ± 10.1	66.4	0.9
ASA	1	25	57	82	0.06
		20.2%	32.4%	27.3%	
	2	70	83	153	
		56.5%	47.2%	51%	
	3	29	36	65	
		23.4%	20.5%	21.7%	
Hospital stay (n = 278)	mean (days)	20.2 ± 13.6	18.7 ± 12.4	19.3	0.3
Overall complications (OAC)		42	60	102	0.5
		33.9%	34.1%	34%	
Surgical complications (ASC)		30	51	81	0.2
		24.2%	29%	27%	
General complications (AGC)		22	20	42	0.08
		17.2%	11.4%	14%	
30-day mortality		9	5	14	0.06
		7.3%	2.8%	4.7%	
90-day mortality		14	8	22	0.025
		11.3%	4.5%	7.3%	

Table 2b. Clinical-pathologic features in 57 patients after left pancreatectomy. P1 – first study period (2008–2012), P2 – second study period (2013–2017), ASA – American Society of Anaesthesiologists score

		P1	P2	All	p-value
Gender	male	11	16	27	0.17
		50%	55.2%	53.3%	
	female	17	13	30	
		50%	43.3%	45.7%	
Age	mean (years)	59.4 ± 13.4	58.5 ± 12.2	58.9	0.8
ASA	1	8	12	20	0.58
		28.6%	41.4%	35.1%	
	2	17	14	31	
		60.7%	48.3%	54.4%	
	3	3	3	6	
		10.7%	10.3%	10.5%	
Hospital stay (n=278)	mean (days)	16.8 ± 9.4	18.4 ± 16.3	17.7	0.68
Overall complications (OAC)		8	5	13	0.24
		28.6%	17.2%	22.8%	
Surgical complications (ASC)		6	5	11	0.47
		21.4%	17.2%	19.3%	
General complications (AGC)		5	3	8	0.33
		17.9%	10.3%	14%	
30-day mortality		2	0	2	0.23
		7.1%	0%	3.5%	
90-day mortality		3	0	22	0.035
		10.7%	0%	7.3%	

The incidence of OAC in PD/TP was 37.1%, ASC occurred in 29.2% whereas AGC in 14.2%. All surgical complications presented themselves as PL, OL, BC and AA in 19% (of 208 PD), 5.8%, 5.8% and 2.5%, respectively. In case of OL, five were from GEA and ten from BEA. Bleeding occurred in altogether 14/240 patients. Two patients had early intestinal bleeding, and 12 occurred after 24 hours. Other rare surgical complications occurred in altogether 4.5% (Table 3). All general complications in PD/TP are described in Table 4.

Drained fluid was checked for amylase in 189/207 patients after PD. Elevated amylase more than seven ukat/L on drains was found in 73 patients (38.6%). In

63 patients (33.3%), the high amylase on drains originated from PEA whereas in 10 patients amylase-rich secretion evidently did not originate from PEA (six bile leaks, two leaks from GEA, one ileus, and one strangulation of the mobile cecum). The rate of PF A was 14.4%, PF B 9.6%, and PF C 9.6%. Determination of PF in groups A, B and C did not correlate with means of amylase value in discharged secretion on drains in ordinal fashion; it was rather the consequence of clinical factors and therapeutic measures.

One of the common consequences of complications was significantly prolonged hospital stay (OAC: 30.9 ± 16 vs. 14.2 ± 4.5 days;  $p < 0.0001$ ). Overall 30- and 90-day mortality was 5% and 7.9%.

Table 2c. Observed clinical-pathologic features in patients after pancreatic head resection and total pancreatectomy. P1 – first study period (2008–2012), P2 – second study period (2013–2017), ASA – American Society of Anesthesiologist score

		P1	P2	All	p-value
Gender (n=240)	male	51	80	131	0.4
		53.1%	55.6%	54.6%	
	female	45	64	109	
		46.9%	44.4%	45.4%	
Age (n=240)	mean (years)	66.1 ± 9.9	65.98 ± 10.1	66.4	0.91
ASA (n=240)	1	17	43	17	0.103
		17.7%	29.9%	17.7%	
	2	53	68	53	
		55.2%	47.2%	55.2%	
	3	26	33	26	
		27.1%	22.9%	27.1%	
Preoperative histology (n=240)		4	32	36	0.0001
		4.2%	22.2%	15.0%	
Hospital stay (n=222)	mean (days)	21.2 ± 14.5	19 ± 11.6	19.8	0.138
Preoperative total bilirubin (n=240)	mean (mmol/L)	67.6 ± 71.5	79.0 ± 85.5	74.7	0.028
Preoperative endoscopic biliary drainage (n=240)		34	51	85	0.554
		35.4%	35.4%	35.4%	

### Correlation of clinical-pathologic factors and perioperative morbidity in pancreatic head resection and total pancreatectomy

#### Age and physical status

Patients with OAC and AGC were older, and their physical status according to ASA was worse. Physical status was worse also in a group of patients with PL (29.5% vs. 16.1%;  $p=0.042$ ). Regarding this, no correlations were found in other subsets of complications (AA, BC, and OL) (Table 5).

#### Preoperative bilirubin value and endoscopic biliary drainage

At our disposal were only bilirubin values from the period within a week before the PD, and the majority of patients was transferred to our institution with already placed EBD more than one week before the operation. This prevented us to make any conclu-

sive analysis on this issue. Patients with preoperatively placed EBD had lower mean preoperative bilirubin values than those without EBD ( $57.4 \pm 66$  vs.  $83.8 \pm 86$  mmol/L;  $p=0.005$ ). Increased mean bilirubin level was noted in BC ( $134.7 \pm 104$  vs.  $70.7 \pm 71.6$  mmol/L;  $p=0.005$ ). Endoscopic biliary drainage was in 37.6% of our patients associated with the occurrence of ASC and in 30% with PL (ASC: 37.6% vs. 24.5%,  $p=0.024$ , PL: 30% vs. 12.5%,  $p=0.004$ ), but there have been no correlations of EBD with other settings of complications (Table 5).

#### Type of resection and vascular resections

All clinical-pathologic factors were comparable in patients that underwent PD or TP, except AA which was more likely after TP (1% vs. 12.1%;  $p=0.004$ ). Resections of VMS/VP correlated only with AGC revealing even less complications if vascular resection has been done (2.5% vs. 16.5%;  $p=0.011$ ). This correlation was difficult to explain since patients with vascular

resection were comparable regarding the age and physical status (mean age: 65.2 vs. 66.1 years;  $p=0.556$ ; ASA3 vs. ASA1/2: 22.2% vs. 25%;  $p=0.456$ ) (Table 5).

#### Type and size of the tumor

Data of tumor dimensions were available for 201 patients. There was a high correlation between tumor size and tumor type revealing non-pancreatic carcinomas (NPCs) to be smaller and pancreatic adenocarcinomas (PACs) to be larger. In groups of OAC, ASC, and PL, smaller size of tumor significantly predicted the onset of complications. Calculation revealed that patients with NPC were more prone for onset of OAC than those with PAC (Table 5).

#### Amylase on drains

Complications after PD were associated with amylase rates more than seven ukat/L. The mean amylase value was increased only in OAC and ASC (OAC:

$150.6 \pm 252$  vs.  $21 \pm 62$ ;  $p < 0.0001$ , ASC:  $179.9 \pm 270$  vs.  $24 \pm 73$ ;  $p < 0.0001$ ). Since PF A has never been noticed, it did not have any negative impact on any complications. There is an inverse correlation of mean amylase level and AA ( $1.1 \pm$  vs.  $72.5 \pm 177$  ukat/L;  $p < 0.0001$ ) proving that abscesses did not originate from pancreatic leak. Smaller size of the tumor proved to be a predictor for the occurrence of PL ( $30.3 \pm 18$  vs.  $22.5 \pm 9$ ;  $p=0.001$ ). Amylase rates more than 7 ukat/L and PF B were more often noted in NPCs (amylase  $< 7$  ukat/L: 48.4% vs. 25.3%;  $p=0.002$ , PF B: 17.2% vs. 6.3%;  $p=0.029$ ), but there was no correlation at the whole between PF C and type of tumour (Table 5).

#### Correlation of clinical-pathologic factors and perioperative mortality in pancreatic head resection and total pancreatectomy

Patients who suffered complications in terms of OAC, ASC, AGC, BC, PL and PF C were at a significant

Table 2d. Observed clinical-pathologic features in patients after pancreatic head resection and total pancreatectomy. P1 – first study period (2008–2012), P2 – second study period (2013–2017), PD – pancreatic head resection, TP – total pancreatectomy, VMS – superior mesenteric vein, VP – portal vein

		P1	P2	All	p-value
Type of pancreatic head resection (n=240)	PD	92	115	207	0.0001
		95.8%	79.9%	86.3%	
	TP	4	29	33	
		4.2%	20.8%	14.2%	
Resection of VMS/VP (n=240)		12	28	40	0.17
		12.5%	19.4%	16.7%	
Type of vascular reconstruction (n=240)	Direct suture	10	14	24	0.043
		10.4%	9.7%	10.0%	
	Vascular graft	2	14	16	
		2.1%	9.7%	6.7%	
Overall complications (OAC) (n=240)		34	55	89	0.383
		35.4%	38.2%	37.1%	
30-day mortality (n=240)		7	5	12	0.152
		7.3%	3.5%	5.0%	
90-day mortality (n=240)		11	8	19	0.080
		11.5%	5.6%	7.9%	

Table 3. Surgical complications in patients after pancreatic head resection and total pancreatectomy. PF – pancreatic fistula. GEA – gastroenteroanastomosis

Type of all surgical complications (n=240)	n	%	% 90-day mortality
No surgical complications	169	70.4	3
PF B or C	28	11.7	25
PF B or C and bleeding	8	3.3	62.5
Bleeding in the intestines	2	0.8	0
Intraabdominal bleeding – no PF	4	1.7	25
Bile leak	10	4.2	0
Leak from GEA	5	2.1	20
Dehiscence of laparotomy	3	1.3	0
Intraabdominal abscess	6	2.5	0
Ileus	1	0.4	0
Thrombosis of vascular graft	2	0.8	0
Volvulus coeci	1	0.4	0
Stenosis of coeliac trunk	1	0.4	0
<b>Total</b>	<b>240</b>	<b>100.0</b>	<b>7.9</b>

Table 4. General complications in patients after pancreatic head resection and total pancreatectomy

Type of all general complications (n = 240)	n	%	% 90-day mortality
No general complications	202	84.2	5.0
Pneumonia	8	3.3	25
Cardiorespiratory decompensation	3	1.3	100
Heart failure	9	3.8	11.1
Pulmonary embolism	4	1.7	25
Different infections	10	4.2	10
Renal failure	1	0.4	100
Brain stroke	1	0.4	0
Miscellaneous	2	0.8	0
<b>Total</b>	<b>240</b>	<b>100.0</b>	<b>7.9</b>

higher risk for postoperative mortality (OAC 30-day: 13.5% vs. 0%;  $p < 0.0001$ , OAC 90-day: 20% vs. 0.7%;  $p < 0.0001$ , ASC 30-day: 14.3% vs. 1.2%;  $p < 0.0001$ , ASC 90-day: 20% vs. 2.9%;  $p < 0.0001$ , AGC 30-day: 14.1% vs. 4.3%;  $p < 0.0001$ , AGC 90-day: 20% vs. 2.9%;  $p < 0.0001$ , BC 30-day: 35.7% vs. 3.1%;  $p < 0.0001$ , BC 90-day: 34.3% vs. 7.2%;  $p < 0.0001$ , PL 30-day: 22.2% vs. 2%;  $p < 0.0001$ , PL 90-day: 33.3% vs. 3.2%;  $p < 0.0001$ , PF C 30-day: 33.3% vs.

2.9%;  $p < 0.0001$ , PF C 90-day: 50% vs. 4.7%;  $p < 0.0001$ ). On the other hand, OL and AA did not impact the 30- and 90-day mortality.

Age did not correlate to 30- or 90-day mortality; however, ASA physical status did (30-day: 11.9% vs. 2.8%;  $p=0.011$ , 90-day: 18.6% vs. 4.4%;  $p=0.001$ ).

Table 5. Correlation of clinicopathological factors and perioperative morbidity and mortality in 240 patients after pancreatic head resection and total pancreatectomy. OAC – overall complications, ASC – all surgical complications, BC – bleeding complications, OL – other anastomotic leak, AA – intraabdominal abscess, PL – pancreatic leak anastomosis, AGC – all general complications, NC – no complications, WC – with complications, ASA – American Society of Anaesthesiologists score, EBD – external biliary drainage, PD/TP – pancreatic head resection/total pancreatectomy, PAC – pancreatic adenocarcinoma, NPC – non-pancreatic carcinoma, PF C/B/A – pancreatic fistula type C/B/A. P1 – first study period (2008–2012), P2 – second study period (2013–2017)

	n		OAC	p-value	ASC	p-value	BC	p-value	OL	p-value	AA	p-value	PL	p-value	AGC	p-value
Age (years)	240	NC WC	64.6 ± 10 68.4 ± 9.1	0.005	65.3 ± 10.3 67.9 ± 9.1	0.051	66.2 ± 10 63.5 ± 12	0.452	66 ± 10 67.1 ± 8	0.665	65 73	0.056	65.7 ± 10 67.3 ± 8	0.256	65.4 ± 10 70.1 ± 9	0.007
Age (<70 and >69)	240	<70 >69	28.6% 43.7F%	0.011	23.8% 33.3%	0.071	8.6% 3.7%	0.094	4.8% 6.7%	0.369	0% 100%	0.030	16.3% 21.4%	0.234	8.6% 18.5%	0.021
ASA 1+2 vs. 3	240	ASA 1+2 ASA 3	32% 52.5%	0.004	23.8% 33.3%	0.042	5.5% 6.8%	0.465	5.5% 6.8%	0.465		0.457	16.1% 29.5%	0.042	10.5% 25.4%	0.006
Total bilirubin (mmol/l)	240	NC WC	70.1 ± 74 82.9 ± 89	0.271	68.3 ± 73.6 89.5 ± 93.1	0.062	71 ± 77 134 ± 104	0.005	74.4 ± 78 75.5 ± 108	0.969		0.231	68.1 ± 70 91.4 ± 99	0.195	79 ± 82 47.4 ± 61	0.033
EBD (no/yes)	240	No Yes	33.5% 43.5%	0.082	24.5% 37.6%	0.024	5.8% 5.9%	0.594	7.1% 3.5%	0.203		0.640	12.8% 30%	0.004	11.6% 18.8%	0.092
PD/TP	240	PD TP	37.2% 36.4%	0.545	29.5% 27.3%	0.488	6.3% 3%	0.400	5.8% 6.1%	0.600	1% 12.1%	0.004	-	-	13% 21.2%	0.126
Vascular resection (yes/no)	240	No Yes	39.5% 27.5%	0.115	30.0% 25.0%	0.334	4.5% 12.5%	0.063	6% 5%	0.578		0.738	21.1% 7.7%	0.083	16.5% 2.5%	0.011
Size of tumor (mm)	201	NC WC	32.3 ± 19 24.6 ± 12	0.001	31.7 ± 18.8 23.7 ± 10.1	0.002	29.5 ± 17 25 ± 10	0.187	29.4 ± 17 25.1 ± 13	0.320		0.069	30.3 ± 18 22.5 ± 9	0.001	29.7 ± 17 25.7 ± 15	0.211
Type of tumor PAC/NPC	216	PAC NPC	34.1% 46.9%	0.042	26.7% 37.0%	0.074	6.7% 4.9%	0.421	5.9% 7.4%	0.435		0.403	16.2% 25.7%	0.092	69.8 ± 183 83.5 ± 127	0.094
Amylase level (ukat/L)	187	NC WC	21.3 ± 62.1 150.6 ± 252	0.0001	24.0 ± 73 179.9 ± 270	0.0001	68.6 ± 175 128.1 ± 199	0.333	72.3 ± 180 62.5 ± 100	- 0.773	72.5 ± 177 1.1 ± 1	0.0001	22.2 ± 70 260 ± 310	0.0001	69.8 ± 183 83.5 ± 127	0.640
Amylase (>7 ukat/L)	187	< 7 > 7	20.2% 69.8%	0.0001	11.4% 61.6%	0.0001	3.5% 12.7%	0.022	1.7% 60.3%	0.0001		0.529	19.1% 100%	0.0001	35.6% 57.7%	0.033
PF C (yes/no)	187	No Yes	33.1% 100%	0.0001	23.7% 100%	0.0001	3% 38.9%	0.0001		0.318		0.818	10.7% 100%	0.0001	-	0.464

	n	OAC	p-value	ASC	p-value	BC	p-value	OL	p-value	AA	p-value	PL	p-value	AGC	p-value
PF B (yes/no)	187	33.1% 100%	0.0001	23.7% 100%	0.0001	6.5% 5.6%	0.676		0.318		0.818	10.7% 100%	0.0001	-	0.221
PF A (yes/no)	187	42.5% 22.2%	0.035	36.3% 0	0.0001		0.148		0.171		0.734	24% 100%	0.0001	-	0.141
PF B+C	187	25.2% 100%	0.0001	14.6% 100%	0.0001	2.6% 22.2	0.088		0.655						
Period of the study	240	35.4% 38.2%	0.383	25.0% 31.9%	0.036	2.1% 8.3%	0.485	5.2% 6.3%	0.230		0.230	16.9% 21.2%	0.292	17.7 11.8	0.137
Hospital stay (days)	240	14.2 ± 4 31.4 ± 16	0.0001	15.2 ± 6 32.9 ± 17	0.003	19.3 ± 13 31.9 ± 8	0.0001	18.1 ± 9 44.9 ± 29	0.0001	19.6 ± 13 29 ± 10	0.075	17.8 ± 12 30.7 ± 9	0.0001	18.4 ± 12 30.9 ± 10	0.0001

Patients with amylase-rich secretion more than 7 ukat/L were also at a higher risk to die within 30 or 90 days after operation (amylase > 7ukat/l 30-day: 14.3% vs. 1.7%; p=0.002, amylase > 7ukat/L 90-day: 20.6% vs. 3.4%; p < 0.0001). However, mean value of amylase on drains was significantly higher in patients that died within 90 days compared to those who died in 30 days (90-day: 172 ± 231 vs. 59.1 ± 170ukat/L; p = 0.013). Tumor type or size of the tumor, mean preoperative total bilirubin, EBD, and PF A and B did not correlate with 30- and 90-day mortality.

### Multivariate analysis in pancreatic head resection and total pancreatectomy

Predictors found to be significant for morbidity and 30- and 90-day mortality in the univariate analysis were included in the multivariate logistic regression analysis.

For OAC, higher mean age and drained amylase more than 7 ukat/L (age: CI 95%: 1.019–1.103; p=0.004, amylase > 7ukat/L: 95% CI: 0.045–0.204; p < 0.0001) were predictive. For ASC, higher mean amylases and drained amylase more than 7 ukat/L (mean amylase: 95% CI: 1.000–1.007; p=0.047, 95%, amylase > 7 ukat/L: 95% CI: 0.070–0.427; p < 0.0001) were specific. Moreover, for AGC, physical status, mean age and mean level of total bilirubin preoperatively (ASA: 95% CI: 1.007–1.121; p=0.028, mean age: 95% CI: 1.042–6.715; p < 0.041, mean total bilirubin: 95% CI: 0.981–0.999; p < 0.027) revealed as independent predictors.

For 30-day mortality, PL and BC revealed as independent predictors (PL: 95% CI: 0.026–0.522; p=0.005, BC: 95% CI: 0.024–0.537; p=0.006). In case of 90-day mortality, physical status, OAC and PF C (ASA: 95% CI: 1.404–16.514; p=0.012, OAC: 95% CI: 1.622–117.599; p=0.016, PF C: 95% CI: 2.030–28.244, p=0.003) were noticed as predictive factors.

## Survival analyses in pancreatic head resection and total pancreatectomy

Patients who had OAC, ASC, AA, OL or AGC have had comparable expectation for long-term survival to those without complications (OAC:  $866 \pm 139$  vs.  $760 \pm 174$  days, Log Rank:  $p=0.242$ ; ASC:  $866 \pm 134$  vs.  $901 \pm 216$  days, Log Rank:  $p=0.234$ ; AA: Log-rank:  $p=0.048$ , OL:  $836 \pm 123$  vs.  $1159 \pm 673$  days; Log-rank:  $p=0.760$ , AGC:  $866 \pm 135$  vs.  $760 \pm 197$  days, Log Rank:  $p=0.431$ ). Complications like PL in PD and BC in all resected patients seriously compromised the expected long-term survival (PL:  $938 \pm 67$  vs.  $499 \pm 146$  days; Log Rank:  $p=0.010$ , BC:  $901 \pm 128$  vs.  $409 \pm 457$  days; Log Rank:  $p=0.046$ ). On the other hand, in patients who survived complications, the long-term survival was not impacted by any complications.

## Differences between two chronologically successive groups in pancreatic head resection and total pancreatectomy

Two chronologically successive groups of patients were comparable on most clinical-pathologic factors except for preoperative gained histology, preoperative total bilirubin, and type of resection (Table 2). The indications for TP were: postoperative bleeding from the pseudoaneurysm of the proximal part of the common hepatic artery combined with leak of the PEA (one patient); PAC and main duct IPMN (nine patients); diffuse main duct IPMN (one patient); very soft pancreas (10 patients); positive resection margins (five patients); tumour extending to the body of the pancreas (five patients); and formerly removed left pancreas (two patients) (Table 1). Five out of 10 patients with extremely soft pancreas also had vascular reconstructions with prosthetic interposition, and three already had insulin-dependent diabetes. The overall (P1 and P2) 30- and 90-day mortality in our cohort were 5 and 7.9%, respectively. In P2, the rates for 30- and 90-day mortality became lower, 3.5% and 5%, respectively, but the statistical difference between P1 and P2 reveals only borderline statistical value ( $p=0.08$ ) (Table 2).

## DISCUSSION

Pancreatic resections present the only curative option for patients with malignant and premalignant diseases and relief of symptoms in selected group of patients with chronic pancreatitis. However, due to high morbidity and mortality, the treatment should not be worse than the disease (21).

Despite marked progress on the field of pancreatic resections, morbidity remains quite high for decades whereas mortality rates gradually improved (22–27).

There was no exception in our study with morbidity, irrelevant of type of resection, remained stable within the two observed periods. On the other hand the 30- and 90-day mortality for all resections together decreased in the second period (30-day: 2.8%,  $p=0.06$ ; 90-day: 4.5%,  $p=0.025$ ). Almost the same, decrease can be observed in PD/TP in P2, but the difference in 90-day mortality tightly misses the statistical significance (30-day: 3.5%, 90-day: 5.6%,  $p=0.06$ ). This result is well comparable to the reports of other authors. In many studies, postoperative mortality was defined traditionally as mortality within 30-days or during the initial hospitalization. This might had led to an underestimated postoperative morbidity and mortality rates. As shown by some meta-analyses, even in centers of excellence, the 90-day mortality rate is double of the 30-day mortality rate and significantly differs regarding the hospital volume. One of the consequences of postoperative morbidity for patients who survive the complication was significantly prolonged hospitalization (5, 15, 26, 18). In our study, it was ranging between 30 and 44 days.

It has often been documented that higher age and low physical status can significantly affect the occurrence of postoperative complications (12, 13). In our study, higher mean age and higher ASA score impacted the incidence of OAC and AGC. American Society of Anaesthesiologists score alone impacted ASC and PL. Regarding our results, higher mean age was an independent predictor for OAC and AGC whereas ASA score was for AGC. On the other hand, specific compli-

cations like BC, AA, and OL did not correlate with age or physical status. Age did not prove as an independent prognostic factor for any complications; however, ASA score did for 90-day mortality. Therefore, our results support the conclusion not to restrain patients from PD or TP only because of their age; however, caution is needed while selecting the patients for PD or TP.

There is an on-going debate on whether jaundiced patients with obstructive lesion and higher bilirubin in the head of the pancreas should be drained or not (29–34). Since only relevant laboratory data from the immediate preoperative period were at our disposal for the study, we can hardly profoundly discuss this issue. Based on our data, however, we observed higher mean total bilirubin values in patients with BC and lower for the group with AGC. The results regarding EBD match with the results from others revealing higher incidence of ASC and PL in patients with EBD (31, 35–38). There was no correlation of mean total bilirubin or EBD with 30- and 90-day mortality (32, 39, 40).

Our study confirms comparable results regarding the perioperative morbidity and mortality between PDs and TPs except for abdominal abscesses, which occurred more often in TP. This fact could speak for TP in selected cases of patients with pancreas remnant, untenable for PEA, especially in elderly in less good general condition who do not tolerate this kind of complications at all (41–43). In patients with pre-existing insulin-dependent diabetes, this decision could be even easier. Relevant criteria for decision-making in this regard are still missing. Further analyses are needed for long-term quality of life, especially concerning insulin-dependent diabetes (44–46).

Resection of VMS or VP for infiltration was formerly regarded as a relative contraindication for the PD. However, nowadays it presents a standard treatment and was performed in 16.7% of our patients. In our study, neither type of pancreatic resection nor the incidence of VMS/VP resection influenced the occurrence of postoperative morbidity and mortality (47–52).

The proportion of chronic pancreatitis in PACs and NPCs included in the reports can differ significantly, and if cases with predominantly hard pancreas remnant predominate, as in patients with chronic pancreatitis, the overall risk for postoperative morbidity and mortality rates could reveal at a lower rates. In our collective of patients, chronic pancreatitis and PAC contributed to 2.9% and 56.7% of patients, respectively, remaining more than 40% of patients with diseases where the pancreas remnant could be softer (Table 1) (9, 53–55).

To our results, concerning only PACs and NPCs, OACs were more likely to occur in NPCs and tumours of smaller size. Moreover, the majority of NPCs were also smaller than PACs. The size of tumor affects the onset of OAC, ASC, and PL; however, neither 30- nor 90-day mortality were statistically impacted by type or size of the tumor (56–58).

Patients with amylase more than seven ukat/L on drains and pancreatic fistula were retrospectively classified in three types of PF (A, B, C) respecting clinical picture, therapeutic consequences, and ISGPF PF recommendations (20). Mean values of amylase in discharged secretion did not differ between PF A, B, and C. There is consensus among all reports that PF negatively affected the postoperative course in patients after PD (59, 60).

Our experience with PF was similar. In PD, the high mean amylase on drains or amylase more than seven ukat/L predicted the onset of complications, especially if surgical complications were involved (OAC, ASC, and PL). However, exception was AA where the mean amylases on drains were low proving that abscesses did not originate from pancreatic leak. Pancreatic fistula type A was not associated with any serious morbidity in postoperative course of our patients. Patients with OAC, ASC, AGC, BC, PL, PF C and high mean amylase or amylase more than seven ukat/L are at a higher risk to die within 30 or 90 days. Although most studies agree about the impact of PF on morbidity and mortality, there are fewer consensuses on how to prevent the occurrence

of PF. Most effort is focused on how to perform a safe anastomosis in case of soft, friable pancreas texture with a thin pancreatic duct (5–7, 10, 61, 62).

Both periods (P1 and P2) were comparable regarding almost all clinical-pathologic factors except for type of pancreatic resection and vascular reconstructions, and the count of performed TPs. There were more TPs in P2 as in P1 (20.8% vs. 4.2%). Both types of pancreatectomies were comparable regarding age, physical status, tumor markers, mean bilirubin value, morbidity, and mortality. Logically, there were no PF in TP. In addition to other indications, TP was performed in 11 patients with pancreas remnant unsuitable for anastomosis. Our results regarding perioperative mortality is good (30- and 90-day mortality was 0%); however, the indications for TP must be posed very responsibly, and the informed consent must be done preoperatively in this issue (24, 41, 43).

Most subtypes of complications did not compromise the long-term survival in our cohort of patients. The exceptions were PLs in PDs and BCs in PDs and TPs where the 5-year survival was significantly compromised. On the other hand, in patients who survived any of these complications, the long-term survival was not impacted by any complications (59, 60, 63, 64).

In conclusion, the present study indicates that amylase-rich secret on drains and higher mean age are independent indicators for OAC whereas, PL and BC proved as an independent predictor for 30-day mortality, and physical status, OAC and PF C for 90-day mortality. Endoscopic biliary drainage, smaller size of tumor and NPC can provoke complications, however; there was no repercussion on postoperative mortality. Even though the decrease in 30- and 90-day mortality (3.5% and 5.6%) tightly missed the significance, the trend of better surgery in pancreatic resections in our institution seemed to be encouraging and can also be based on significant decrease in perioperative morbidity in all pancreatic resections together. Most subtypes of complications did not compromise the long-term survival in our cohort of patients. The exceptions were specific complications like PLs and BCs where

the 5-year survival was significantly compromised. On the other hand, in patients who survived these complications, the long-term survival was not impaired by any complication. The worse scenario in pancreatic resection is an older patient in bad physical condition having small tumor or NPC, amylase reach output on drains after resection, and eventually BC.

## References

1. Ho CK, Kleeff J, Friess H, et al. Complications of pancreatic surgery. *HPB (Oxford)*. 2005; 7: 99-108.
2. Kapoor VK. Complications of pancreatoduodenectomy. *Rozhl Chir*. 2016; 95: 53-9.
3. Penumadu P, Barreto SG, Goel M, et al. Pancreatoduodenectomy - preventing Complications. *Indian J Surg Oncol*. 2015; 6: 6-15.
4. Ren S, Liu P, Zhou N, Dong J, Liu R, Ji W. Complications after pancreaticoduodenectomy for pancreatic cancer: a retrospective study. *Int Surg* 2011; 96: 220-7.
5. Assumpcao L, Cameron JL, Wolfgang CL, et al. Incidence and management of chyle leaks following pancreatic resection: a high volume single-center institutional experience. *J Gastrointest Surg*. 2008; 12: 1915–23.
6. van Berge Henegouwen MI, de Wit LT, van Gulik TM, et al. Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy: drainage versus resection of the pancreatic remnant. *J Am Coll Surg*. 1997; 185: 18-24.
7. Vin Y, Sima CS, Getrajdman GI, et al. Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005. *J Am Coll Surg*. 2008; 207: 490-8.
8. Sperti C, Pasquali C, Ferronato A, et al. Median pancreatectomy for tumors of the neck and body of the pancreas. *J Am Coll Surg*. 2000; 190: 711-6.
9. Bourgouin S, Ewald J, Mancini J, et al. Predictive factors of severe complications for ampullary, bile duct and duodenal cancers following pancreaticoduodenectomy: multivariate analysis of a 10-year multicentre retrospective series. *Surgeon*. 2017; 15: 251-8.
10. Machado NO. Pancreatic fistula after pancreatectomy: definitions, risk factors, preventive measures, and management-review. *Int J Surg Oncol*. 2012; 2012: 602478.
11. Hashimoto Y, Traverso LW. Pancreatic anastomotic failure rate after pancreaticoduodenectomy decreases with microsurgery. *J Am Coll Surg*. 2010; 211: 510-21.
12. Riall TS, Sheffield KM, Kuo YF, et al. Resection benefits older adults with locoregional pancreatic cancer despite greater short-term morbidity and mortality. *J Am Geriatr Soc*. 2011; 59: 647–54.
13. Riall TS. What is the effect of age on pancreatic resection? *Adv Surg*. 2009; 43: 233-49.
14. Vollmer CM, Sanchez N, Gondek S, et al. A root-cause analysis of mortality following major pancreatectomy. *J Gastrointest Surg*. 2012; 16: 89-103.
15. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg*. 1997; 226: 248-60.

16. Partelli S, Pecorelli N, Muffatti F, et al. Early postoperative prediction of clinically relevant pancreatic fistula after pancreaticoduodenectomy: usefulness of C-reactive protein. *HPB (Oxford)*. 2017; 19 (7): 580-6.
17. Sperti C, Moletta L, Pozza G. Pancreatic resection in very elderly patients: a critical analysis of existing evidence. *World J Gastrointest Oncol*. 2017; 9: 30-6.
18. Crea N, Di Fabio F, Pata G, et al. APACHE II, POSSUM, and ASA scores and the risk of perioperative complications in patients with colorectal disease. *Ann Ital Chir*. 2009; 80: 177-81.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004; 240: 205-13.
20. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. 2005; 138: 8-13.
21. Rosenberg L. Treatment of pancreatic cancer. Promises and problems of tamoxifen, somatostatin analogs, and gemcitabine. *Int J Pancreatol*. 1997; 22: 81-93.
22. Neoptolemos JP, Russell RC, Bramhall S, Theis B. Low mortality following resection for pancreatic and periampullary tumours in 1026 patients: UK survey of specialist pancreatic units. UK Pancreatic Cancer Group. *Br J Surg*. 1997; 84: 1370-6.
23. Dominguez-Comesaña E, Gonzalez-Rodriguez FJ, Ulla-Rocha JL, et al. Morbidity and mortality in pancreatic resection. *Cirugia Espanola*. 2013; 91: 651-8
24. Stauffer JA, Nguyen JH, Heckman MG, et al. Patient outcomes after total pancreatectomy: a single centre contemporary experience. *HPB*. 2009; 11: 483-92.
25. Riediger H, Adam U, Utzolino S, et al. Perioperative outcome after pancreatic head resection: a 10-year series of a specialized surgeon in a university hospital and a community hospital. *J Gastrointest Surg*. 2014; 18: 1434-40.
26. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg*. 2015; 220: 530-6.
27. Cameron JL, Pitt HA, Yeo CJ, et al. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. *Ann Surg*. 1993; 217: 430-8.
28. Romano G, Agrusa A, Galia M, et al. Whipple's pancreaticoduodenectomy: surgical technique and perioperative clinical outcomes in a single center. *Int J Surg*. 2015; 21 Suppl 1: S68-71.
29. Álamo JM, Marín LM, Suarez G, et al. Improving outcomes in pancreatic cancer: key points in perioperative management. *World J Gastroenterol*. 2014; 20: 14237-45.
30. Jinkins LJ, Parmar AD, Han Y, et al. Current trends in preoperative biliary stenting in patients with pancreatic cancer. *Surgery*. 2013; 154: 179-89.
31. Singal AK, Ross WA, Guturu P, et al. Self-expanding metal stents for biliary drainage in patients with resectable pancreatic cancer: single-center experience with 79 cases. *Dig Dis Sci*. 2011; 56: 3678-84.
32. Sahora K, Morales-Oyarvide V, Ferrone C, et al. Preoperative biliary drainage does not increase major complications in pancreaticoduodenectomy: a large single center experience from the Massachusetts General Hospital. *J Hepatobiliary Pancreat Sci* 2016; 23: 181-7.
33. Pisters PW, Hudec WA, Hess KR, et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg*. 2001; 234: 47-55.
34. Scheufele F, Schorn S, Demir IE, et al. Preoperative biliary stenting versus operation first in jaundiced patients due to malignant lesions in the pancreatic head: a meta-analysis of current literature. *Surgery*. 2017; 161: 939-50.
35. Cavell LK, Allen PJ, Vinoya C, et al. Biliary self-expandable metal stents do not adversely affect pancreaticoduodenectomy. *Am J Gastroenterol*. 2013; 108: 1168-73.
36. Tsuboi T, Sasaki T, Serikawa M, et al. Preoperative biliary drainage in cases of borderline resectable pancreatic cancer treated with neoadjuvant chemotherapy and surgery. *Gastroenterol Res Pract*. 2016; 2016: 7968201.
37. Xiong JJ, Nunes QM, Huang W, et al. Preoperative biliary drainage in patients with hilar cholangiocarcinoma undergoing major hepatectomy. *World J Gastroenterol*. 2013; 19: 8731-9.
38. Kishi Y, Shimada K, Nara S, et al. The type of preoperative biliary drainage predicts short-term outcome after major hepatectomy. *Langenbecks Arch Surg*. 2016; 401: 503-11.
39. Coates JM, Beal SH, Russo JE, et al. Negligible effect of selective preoperative biliary drainage on perioperative resuscitation, morbidity, and mortality in patients undergoing pancreaticoduodenectomy. *Arch Surg*. 2009; 144: 841-7.
40. Ferrero A, Lo Tesoriere R, Viganò L, et al. Preoperative biliary drainage increases infectious complications after hepatectomy for proximal bile duct tumor obstruction. *World J Surg*. 2009; 33: 318-25.
41. Del Chiaro M, Rangelova E, Segersvärd R, et al. Are there still indications for total pancreatectomy? *Updat Surg*. 2016; 68: 257-63.
42. Müller MW, Friess H, Kleeff J, et al. Is there still a role for total pancreatectomy? *Ann Surg*. 2007; 246: 966-75.
43. Billings BJ, Christein JD, Harmsen WS, et al. Quality-of-life after total pancreatectomy: is it really that bad on long-term follow-up? *J Gastrointest Surg*. 2005; 9: 1059-67.
44. White MA, Agle SC, Fuhr HM, et al. Impact of pancreatic cancer and subsequent resection on glycemic control in diabetic and nondiabetic patients. *Am Surg*. 2011; 77: 1032-7.
45. Chu CK, Mazo AE, Sarmiento JM, et al. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. *J Am Coll Surg*. 2010; 210: 463-73.
46. Malleo G, Mazzeola F, Malpaga A, et al. Diabetes mellitus does not impact on clinically relevant pancreatic fistula after partial pancreatic resection for ductal adenocarcinoma. *Surgery*. 2013; 153: 641-50.
47. Marsoner K, Langeder R, Csengeri D, et al. Portal vein resection in advanced pancreatic adenocarcinoma: is it worth the risk? *Wien Klin Wochenschr*. 2016; 128: 566-72.
48. Hoshimoto S, Hishinuma S, Shirakawa H, et al. Reassessment of the clinical significance of portal-superior mesenteric vein invasion in borderline resectable pancreatic cancer. *Eur J Surg Oncol*. 2017; 43: 1068-75.
49. Riediger H, Makowiec F, Fischer E, et al. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. *J Gastrointest Surg*. 2006; 10: 1106-15.

50. Kulemann B, Hoepfner J, Wittel U, et al. Perioperative and long-term outcome after standard pancreaticoduodenectomy, additional portal vein and multivisceral resection for pancreatic head cancer. *J Gastrointest Surg.* 2015; 19: 438-44.
51. Cheung TT, Poon RTP, Chok KSH, et al. Pancreaticoduodenectomy with vascular reconstruction for adenocarcinoma of the pancreas with borderline resectability. *World J Gastroenterol.* 2014; 20: 17448-55.
52. Flis V, Potre S, Kobilica N, et al. Pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head with venous resection. *Radiol Oncol.* 2016; 50: 321-8.
53. Park JR, Li F, Oza VM, et al. High-grade pancreatic intraepithelial lesions: prevalence and implications in pancreatic neoplasia. *Hepatobiliary Pancreat Dis Int.* 2017; 16: 202-8.
54. Hwang IK, Kim H, Lee YS, et al. Presence of pancreatic intraepithelial neoplasia-3 in a background of chronic pancreatitis in pancreatic cancer patients. *Cancer Sci.* 2015; 106: 1408-13.
55. Thorat A, Huang WH, Yeh TS, et al. Pancreatic ductal adenocarcinoma presenting with acute and chronic pancreatitis as initial presentation: is prognosis better? A comparison study. *Hepatogastroenterology.* 2014; 61: 2110-6.
56. Ahmad Z, Din NU, Minhas K, et al. Epidemiologic data, tumor size, histologic tumor type and grade, pathologic staging and follow up in cancers of the ampullary region and head of pancreas in 311 Whipple resection specimens of Pakistani patients. *Asian Pac J Cancer Prev.* 2015; 16: 7541-6.
57. Perysinakis I, Avlonitis S, Georgiadou D, et al. Five-year actual survival after pancreatoduodenectomy for pancreatic head cancer. *ANZ J Surg.* 2015; 85: 183-6.
58. Petermann D, Demartines N, Schäfer M. Is tumour size an underestimated feature in the current TNM system for malignancies of the pancreatic head? *HPB.* 2013; 15: 872-81.
59. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: incidence, significance, and management. *Am J Surg.* 1994; 168: 295-8.
60. Seetharam P, Rodrigues GS. Postoperative pancreatic fistula: a surgeon's nightmare! An insight with a detailed literature review. *JOP.* 2015; 16: 115-24.
61. Suzuki Y, Fujino Y, Tanioka Y, et al. Factors influencing hepaticojejunostomy leak following pancreaticoduodenal resection; importance of anastomotic leak test. *Hepatogastroenterology.* 2003; 50: 254-7.
62. Conzo G, Gambardella C, Tartaglia E, et al. Pancreatic fistula following pancreatoduodenectomy. Evaluation of different surgical approaches in the management of pancreatic stump. Literature review. *Int J Surg.* 2015; 21 Suppl 1: S4-9.
63. Balachandran P, Sikora SS, Raghavendra Rao RV, et al. Haemorrhagic complications of pancreaticoduodenectomy. *ANZ J Surg.* 2004; 74: 945-50.
64. Rumstadt B, Schwab M, Korth P, et al. Hemorrhage after pancreatoduodenectomy. *Ann Surg.* 1998; 227: 236-4.

# Video-assisted Retroperitoneal Debridement and Minimal Access Retroperitoneal Pancreatic Necrosectomy

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## ABSTRACT

Pancreatic necrosis is an acute necrotic collection in which there is a variable amount of fluid and necrosis, and it is the most severe stage of inflammation associated with pancreatitis, being a potentially life-threatening disease. While sterile pancreatic necrosis without organ failure is treated conservatively, surgical debridement is the keystone in the management of infected pancreatic necrosis. Surgical intervention consists of laparotomy and necrosectomy. This is an invasive procedure that is associated with high morbidity and mortality rates. Being so, the interventions for necrotizing pancreatitis have undergone a paradigm shift away from open surgical necrosectomy towards minimally invasive techniques. Surgical necrosectomy through laparotomy is still the gold standard treatment of symptomatic pancreatic necrosis, despite its postoperative mortality rate of 20–40% and morbidity reaching as much as 78%. It is a successful procedure, but it is associated with significant morbidity due to risks of incisional hernia (25–50%), hemorrhage (10%), enteric fistula (17–20%), and mortality (6–34%). Therefore, some less invasive techniques have been developed, including radiological drainage and a minimal access

retroperitoneal approach. There are two basic types of this technique. One type, called video-assisted retroperitoneal debridement, is a hybrid technique combining open lumbotomy with a laparoscopic technique, introduced by Gambiez et al., who originally removed the necrotic debris visualized using a mediastinoscope through a small lumbotomy. The other is minimal access retroperitoneal pancreatic necrosectomy, introduced by Carter et al. In this technique, a nephroscope was originally used through a tract formed along a drain that was inserted during previous open necrosectomy. The visualization of the necrosis was aided by instillation of saline, and the necrotic debris was removed through the working channel of the nephroscope.

## INTRODUCTION

Pancreatic necrosis is an acute necrotic collection in which there is a variable amount of fluid and necrosis (1), and it is the most severe stage of inflammation associated with pancreatitis, being a potentially life-threatening disease. Infected pancreatic necrosis is a late infective complication of acute necrotizing pancreatitis in which infection tends to spread from the pan-

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creas to the peripancreatic tissues, retroperitoneum, and, more rarely, the peritoneal cavity. Bacterial translocation mainly from the gut is the most widely accepted mechanism in the pathogenesis of infected pancreatic necrosis (2). This condition is the most important risk factor contributing to death in severe acute pancreatitis, and it is accepted that infected pancreatic necrosis should be managed surgically to prevent sepsis. Surgical intervention consists of laparotomy and necrosectomy (3). This is an invasive procedure that is associated with high morbidity and mortality rates. Being so, the interventions for necrotizing pancreatitis have undergone a paradigm shift away from open surgical necrosectomy toward minimally invasive techniques. The surgical strategy for proven infected necrosis has evolved; nowadays open necrosectomy is more or less abandoned. Instead, a step-up approach is adopted, consisting of percutaneous drains, video-assisted retroperitoneal debridement (VARD) and minimal access retroperitoneal pancreatic necrosectomy (MARPN).

## **BACKGROUND**

Gallstones and alcohol are still the most frequent causes of acute pancreatitis, a disease with an increasing incidence during the past 20 years. This disease has a variety of clinical presentations from a mild, transitory illness to a severe, rapidly fatal disease. In about 80–90% of pancreatitis cases patients develop a mild and self-limited course with low morbidity and mortality (5). However, 10–20% of patients have a rapidly progressive inflammatory response associated with prolonged length of hospital stay and significant morbidity and mortality by developing severe forms of acute pancreatitis (6).

Severe acute pancreatitis has a two-phase clinical course. The early phase (1–2 weeks after the onset of symptoms) manifests the features of the systemic inflammatory response syndrome (SIRS) which implicates a complex inflammatory cascade and is often associated with multiple organ failure. The late phase is characterized by infectious complications, which are the major causes of mortality (2, 7, 8). Infection of

necrotic pancreatic parenchyma occurs in around 30% of patients with necrotizing pancreatitis (7) and is observed after the second week of the acute attack, usually as a consequence of bacterial translocation. Microorganisms responsive for the transformation of sterile into infected pancreatic necrosis enter pancreatic tissue through multiple pathways, including biliary and duodenal-pancreatic reflux, hematogenous and lymphatic dissemination, and local bacterial translocation from the gut being the most important route of infection (9).

Necrotizing forms may present as acute necrotic collections (intra- or extrapancreatic solid-liquid heterogeneous collection with no defined wall, diagnosed during the first four weeks of the clinical course) or walled-off necrosis (with similar characteristics but with well-defined wall and with a later diagnosis above four weeks) (9). Both events present themselves as critical factors determining the clinical course of acute pancreatitis. Without radiologic, endoscopic or surgical intervention, infected necrosis eventually leads to death in almost every patient.

## **A SURGICAL APPROACH – FROM NECROSECTOMY AND LAPAROTOMY TO MINIMALLY INVASIVE PROCEDURES**

While sterile pancreatic necrosis without organ failure is treated conservatively, surgical debridement is the keystone in the management of infected pancreatic necrosis (10). During the initial phase of acute necrotizing pancreatitis, the most important parts of medical treatment are fluid resuscitation, early enteral nutrition, endoscopic retrograde cholangiopancreatography if cholangitis is present and intensive care unit (ICU) support (9). On the contrary of sterile pancreatic necrosis, for infected necrotizing pancreatitis, the surgical approach is mandatory. Intervention is indicated when infection of (peri-)pancreatic necrosis is proven by fine needle aspiration, (peri-)pancreatic gas collections in the necrotic cavity are shown on CT scans or when sepsis persists after maximal support on the ICU (11).

Strategies for the management of patients with necrotizing pancreatitis remain controversial. Surgical necrosectomy through laparotomy is still the gold standard treatment of symptomatic pancreatic necrosis, despite its postoperative mortality rate of 20–40% and morbidity reaching as much as 78% (12). It is a successful procedure, but it is associated with significant morbidity due to risks of incisional hernia (25–50%), haemorrhage (10%), enteric fistula (17–20%), and mortality (6–34%) (13). Therefore, some less invasive techniques have been developed, including radiological drainage and a minimal access retroperitoneal approach (14).

Recent developments in minimally invasive procedures (laparoscopic, endoscopic, interventional radiologic) have been suggested as an alternative to open surgery and refueled the enthusiasm about the use of these techniques in the management of infected pancreatic necrosis. In this context, there has been changes in optimal time for surgery and the type of access for necrosectomy: from a classical open approach (with closure over large-bore drains for continued postoperative lavage or semi-open techniques with scheduled re-laparotomies), trends have changed to a ‘step-up’ philosophy with initial percutaneous drainage and posterior minimally invasive or endoscopic access to the retroperitoneal cavity for necrosectomy if no improvement has been previously achieved.

Percutaneous drainage is one of the first minimally invasive techniques employed for the treatment of infected pancreatic necrosis. The improvement of percutaneous necrosectomy is minimally invasive retroperitoneal necrosectomy performed under the visual control offered by optical devices.

Retroperitoneal approach constitutes the maximum example of minimally invasive necrosectomy (9). It is performed through small incisions with endoscopic material, guided by a percutaneous drainage. This drainage is placed once infection of pancreatic or peripancreatic necrosis is suspected. It is positioned in the (peri-)pancreatic collection through the left retroperitoneum in a lateral position to avoid access

to the abdominal cavity and to provide all the advantages of the minimally invasive approach (7).

There are two basic types of this technique. One type is VARD which is a hybrid technique combining open lumbotomy with a laparoscopic technique, introduced by Gambiez et al. (15) who originally removed the necrotic debris visualized using a mediastinoscope through a small lumbotomy. Another minimally invasive necrosectomy is MARPN, which was introduced by Carter et al. (15). In this technique, a nephroscope was originally used through a track formed along a drain that was inserted during previous open necrosectomy. The visualization of the necrosis was aided by instillation of saline, and the necrotic debris was removed through the working channel of the nephroscope (11, 15, 16).

All these minimally invasive endoscopic and laparoscopic techniques combine the benefits of open necrosectomy and percutaneous drainage while avoiding the problems associated with each of them (13). They have many advantages in comparison with open surgery such as reduced inflammatory response to intervention, substantially reduced extent of bacteremia, reduced risk of development of multiple organ failure, reduced rate of postoperative respiratory and wound complications, shorter stay in the ICU, and faster convalescence (12). Therefore, a staged, multidisciplinary, step-up approach with minimally invasive or endoscopic access for necrosectomy is widely accepted nowadays for management of pancreatic necrosis.

Although these approaches are increasingly gaining popularity since the morbidity and mortality rates have been decreased significantly, the main setback is the range of minimally invasive methods in treatment of acute necrotizing pancreatitis. That is the reason why there is a lack of studies comparing minimally invasive versus open surgery, and there is no unanimity on the optimal surgical strategy (12).

## **VIDEO-ASSISTED RETROPERITONEAL DEBRIDEMENT**

VARD is a technique that can be considered as a hybrid between endoscopic and open retroperitoneal necrosectomy (7). It is a procedure that aims at minimizing complications and mortality by reducing surgical stress in the already critically ill patients. This reduction is achieved by minimizing the surgical incision and staying exclusively in the retroperitoneum, without contaminating the intraperitoneal space.

The VARD procedure was first described by Horvath et al. in 2001 (17). This first report described the results of six patients who underwent percutaneous drainage followed by VARD from 1995 to 1999. Four of them were successfully treated, and laparotomy with its related complications was avoided. Following these results, there was a case-study in The Netherlands comparing 15 patients undergoing VARD with other 15 patients undergoing open necrosectomy in necrotizing pancreatitis (18). In the group that underwent VARD, there were less postoperative complications and a trend towards lower mortality supporting a potential benefit of the retroperitoneal approach over laparotomy (13, 18).

The VARD procedure is part of a step-up approach consisting of percutaneous retroperitoneal catheter drainage followed by VARD, if necessary. Once the necrosis infection is diagnosed, drainage is placed in the infected collection through the left retroperitoneum. If this does not lead to clinical improvement, surgery is needed. The surgery is preferably postponed until after four weeks since the beginning of the disease. This is considered as a key point in the procedure since it allows the peripancreatic or pancreatic collections to sufficiently demarcate and the wall to mature, thus optimizing the conditions for debridement.

To do the VARD, the patient is positioned in a supine position with the left side 30–40° elevated. Then a 4–5 cm left subcostal incision is made, in the left flank at the mid-axillary line, close to the exit point of the percutaneous drain. With the help of CT images and by

using the in situ percutaneous drain as a guide into the (peri-)pancreatic collection, the fascia is dissected and by that, the retroperitoneum is entered. The cavity is cleared of purulent material using a standard suction device. Following the percutaneous drain deeper into the cavity, loose necrotic material is removed while periodic irrigation and consequent suction are performed to enhance vision. When debridement can no longer be performed under direct vision, a single extra-long laparoscopic port is placed into the incision and video scope is introduced. At this stage CO<sub>2</sub> gas (10 L/min) can be infused through the percutaneous drain, still in position, to inflate the cavity, thereby facilitating inspection. Under videoscopic assistance, further debridement of retained necrotic tissue is performed with laparoscopic forceps.

The goal of VARD is not to remove all necrotic tissue. It allows for large pieces of necrosis to be removed, but only loose necrosis is removed to reduce the risk of bleeding from viable pancreatic tissue and nearby blood vessels. However, leaving large undrained pockets of necrosis should be avoided because this may cause on-going sepsis. In VARD, the small incision enables the surgeon to remove larger pieces of necrosis with a shorter operating time and less need for repetitive procedures. When the bulk of necrosis is removed, the cavity is irrigated with saline until the fluid comes clear and then the percutaneous drain is removed. After closing, continuous postoperative lavage is performed. One week after the procedure repeated CT is performed to evaluate the resolution of the collection and to assess whether necrosis is still present.

## **MINIMAL ACCESS RETROPERITONEAL PANCREATIC NECROSECTOMY**

MARPN is a minimally invasive procedure that has been showing benefits regarding morbidity and mortality when compared to traditional open approaches. When planning this minimal access approach, some technical considerations also need to be assessed in deciding appropriateness for a MARPN. Both a high-quality CT and an interventional radiologist are required to do this (14).

Having decided to perform a MARPN, the patient is transferred to the radiology department, and under CT guidance the access to the necrotic cavity is obtained via the left flank, and a 12-French pigtail catheter is inserted under CT-guidance (14, 19). Most commonly, this is through a window between the upper pole of the left kidney and lower pole of the spleen. Afterward, the patient is transferred to the operating theatre, placed in a supine position on the operating table and a sandbag can be used under the site of catheter entry to improve access to the track with the operating nephroscope. Under x-ray screening and general anaesthesia, the catheter is exchanged over a guide wire for serial renal dilators and the track is dilated to 30-French (19). Then the necrosis is removed with forceps and samples are sent for microbiological examination. After initial debridement, an irrigating drain, consisting of a 28-French chest drain and 10-French nasogastric tube sutured together, is inserted into the cavity and 0.9% saline solution is used to irrigate the cavity uninterruptedly at a rate of 125 mL/h. The patients are carefully monitored postoperatively, using serial CT scans and CRP measurements to follow disease progress. Repeated debridements are performed at 7- to 10-day intervals until the necrosis cavity is seen to be clear and lined by healthy granulation tissue.

It is standard that the initial procedure involving dilatation of the track is performed under general anesthetic with following procedures performed using local anesthetic with or without light sedation, according to patient preferences. In patients with severe comorbidities, such as aortic stenosis, local anesthetic can be used from the outset.

In some patients, more than one access path is created to gain access to all the necrotic areas—access from the right side or anteriorly is technically more challenging but feasible as long as the distance between the abdominal wall and necrosis is not too great. When the necrosis has been cleared, the irrigation is stopped, and the patient is discharged home with a simple tube drain left in situ. This is later removed during regular outpatient follow-up.

The indications for MARPN are the same as those for open intervention. Any apprehension over the possibility of co-existing intraperitoneal pathology, particularly ischemic colon disease, is a contraindication to a minimal access approach. Any suspicion of this should mandate a colonoscopy to assess the viability of the colon further.

## CONCLUSION

Minimally invasive techniques have been introduced for the management of infected pancreatic necrosis to minimize the perioperative trauma and to limit its negative influence on organ function. Nowadays, endoscopic, radiological, laparoscopic, and hybrid techniques combining different minimally invasive modalities are used for the treatment of acute pancreatitis, depending on the experience of the institution. There are no clinical or radiological criteria allowing the prediction of which minimally invasive techniques might prove successful in patients with infected necrosis (11). Therefore, the choice of a minimally invasive procedure depends mainly on the expertise of the treating team and the preferred technique used in the institution.

There are many minimally invasive techniques available for the treatment of complicated acute pancreatitis. In some patients, it is useful to combine various techniques or to use them at different stages of the disease. On the other hand, open necrosectomy does not exclude the possibility of subsequent usage of minimally invasive procedures. As compared with open necrosectomy, the step-up approach aims at control of the source of infection, rather than complete removal of the infected necrotic tissue, and that is the principal problem common to all the minimally invasive techniques, the difficulty in removal of the necrotic debris and the establishment of adequate drainage of the necrotic and purulent fluid (11, 15, 16, 20). Because of this, it is often necessary to repeat sessions of necrosectomy, which can be a disadvantage for these minimal procedures.

A multicentre study was enrolled by Medical centers in the Netherlands and published in the *New England*

Journal of Medicine in 2010. It randomly assigned 88 patients with necrotizing pancreatitis and suspected or confirmed infected necrotic tissue to undergo primary open necrosectomy or a step-up approach to treatment. The step-up approach consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. The conclusions of this study are presented in Table 1. This study revealed that the minimally invasive step-up approach, when compared with primary open necrosectomy, reduced the rate of major complications or death, as well as long-term complications, healthcare resource utilization, and total costs, among patients who had necrotizing pancreatitis and confirmed or suspected

secondary infection. With the step-up approach, more than one-third of patients were successfully treated with percutaneous drainage and did not require major abdominal surgery.

In conclusion, the role of minimally invasive techniques remains unclear, however, these techniques seem to be promising methods for the treatment of complicated acute pancreatitis, and they are gaining popularity among the surgical community. The selection of a minimally invasive procedure depends on the extent of necrosis, timing of intervention, patient's condition, and the experience and preference of the institution. Shortly, further develop-

Table 1. Summarized data from van Santvoort et al. study (20). ICU – intensive care unit

		Minimally invasive step-up approach (N=43)	Primary open necrosectomy (N=45)	Risk ratio (95% CI)	P-value
<b>Major complication or death</b>		17 (40%)	31 (69%)	0,57 (0,38–0,87)	0,006
<b>Major complications</b>	New-onset multiple organ failure or systemic complications	5 (12%)	19 (42%)	0,28 (0,11–0,67)	0,001
	Multiple organ failure	5 (12%)	18 (40%)		
	Multiple systemic complications	0	1 (2%)		
	Intraabdominal bleeding requiring intervention	7 (16%)	10 (22%)	0,73 (0,31–1,75)	0,48
	Enterocutaneous fistula or perforation of visceral organ requiring intervention	6 (14%)	10 (22%)	0,63 (0,25–1,58)	0,32
<b>Death</b>		<b>8 (19%)</b>	<b>7 (16%)</b>	<b>1,20 (0,48–3,01)</b>	<b>0,70</b>
<b>Other outcome</b>	Pancreatic fistula	12 (28%)	17 (38%)	0,74 (0,40–1,36)	0,33
	Incisional hernia	3 (7%)	11 (24%)	0,29 (0,09–0,95)	0,03
	New-onset diabetes	7 (16%)	17 (38%)	0,43 (0,20–0,94)	0,02
	Use of pancreatic enzymes	3 (7%)	15 (33%)	0,21 (0,07–0,67)	0,002
<b>Health care resources utilization</b>	Total number of operations per patient	0–6	1–7		
	Total number of drainage procedures per patient	1–7	0–6		
	Days in ICU – median (range)	9 (0–281)	11 (0–111)		
	Days in hospital – median (range)	50 (1–287)	60 (1–247)		

ments in minimally invasive techniques and increasing popularity of hybrid methods for the treatment of infected pancreatic necrosis might be expected.

## References

1. Dionigi R, Rovera F, Dionigi G, et al. Infected pancreatic necrosis. *Surg Infect (Larchmt)*. 2006; 7 Suppl 2: S49-52.
2. Sakorafas GH, Lappas C, Mastoraki A, et al. Current trends in the management of infected necrotizing pancreatitis. *Infect Disord Drug Targets*. 2010; 10 (1): 9-14.
3. van Santvoort HC, Besselink MGH, Horvath KD, et al. Videoscopic assisted retroperitoneal debridement in infected necrotizing pancreatitis. *HPB (Oxford)*. 2007; 9 (2): 156-9.
4. Lim E, Sundaramoorthy RS, Tan D, et al. Step-up approach and video-assisted retroperitoneal debridement in infected necrotizing pancreatitis: a case complicated by retroperitoneal bleeding and colonic fistula. *Ann Med Surg*. 2015; 4 (3): 225-9.
5. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*. 2011; 141 (4): 1254-63.
6. Jensen EH, Borja-Cacho D, Al-Refaie WB, et al. Exocrine Pancreas. In: Townsend CM, Sabiston DC, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*, 16th ed. Philadelphia, PA: Elsevier Saunders; 2012. p. 1515-47.
7. Brunschot S, Besselink MG, Bakker OJ, et al. Video-assisted retroperitoneal debridement (VARD) of infected necrotizing pancreatitis: an update. *Curr Surg Reports*. 2013; 1 (2): 121-30.
8. Nathens AB, Curtis JR, Beale RJ, et al. Management of the critically ill patient with severe acute pancreatitis. *Crit Care Med*. 2004; 32 (12): 2524-36.
9. Aranda-Narváez JM, González-Sánchez AJ, Montiel-Casado MC, et al. Acute necrotizing pancreatitis: surgical indications and technical procedures. *World J Clin Cases*. 2014; 2 (12): 840-5.
10. Beger HG, Rau BM. Severe acute pancreatitis: clinical course and management. *World J Gastroenterol*. 2007; 13 (38): 5043-51.
11. Besselink MG, van Santvoort HC, Nieuwenhuijs VB, et al. Minimally invasive 'step-up approach' versus maximal necrosectomy in patients with acute necrotising pancreatitis (PANTER trial): design and rationale of a randomised controlled multicenter trial [ISRCTN13975868]. *BMC Surg*. 2006; 6 (1): 6.
12. Wroński M, Cebulski W, Slodkowski M, et al. Minimally invasive treatment of infected pancreatic necrosis. *Gastroenterol Rev*. 2014; 6 (6): 317-24.
13. Horvath K. Safety and efficacy of video-assisted retroperitoneal debridement for infected pancreatic collections. *Arch Surg*. 2010; 145 (9): 817.
14. Werner J, Hartwig W, Hackert T, et al. Surgery in the treatment of acute pancreatitis—open pancreatic necrosectomy. *Scand J Surg*. 2005; 94 (2): 130-4.
15. Gambiez LP, Denimal FA, Porte HL, et al. Retroperitoneal approach and endoscopic management of peripancreatic necrosis collections. *Arch Surg*. 1998; 133: 66-72.
16. Carter CR, McKay CJ, Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: an initial experience. *Ann Surg*. 2000; 232 (2): 175-80.
17. Horvath KD, Kao LS, Wherry KL, et al. A technique for laparoscopic-assisted percutaneous drainage of infected pancreatic necrosis and pancreatic abscess. *Surg Endosc*. 2001; 15 (10): 1221-5.
18. van Santvoort HC, Besselink MG, Bollen TL, et al. Case-matched comparison of the retroperitoneal approach with laparotomy for necrotizing pancreatitis. *World J Surg*. 2007; 31 (8): 1635-42.
19. Raraty MGT, Halloran CM, Dodd S, et al. Minimal access retroperitoneal pancreatic necrosectomy. *Ann Surg*. 2010; 251 (5): 787-93.
20. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010; 362 (16): 1491-1502.

# Negative Pressure Therapy in Acute Pancreatitis – Indications

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## ABSTRACT

In last decades, development of minimally invasive approach is showing better clinical results compared to open surgical procedures in patients with acute necrotizing pancreatitis. However, there is still considerable proportion of patients with necrotizing pancreatitis who are not candidates for minimally invasive approach or in whom minimal invasive approach has failed. Negative pressure therapy shows some beneficial effect in patients complicated by intra-abdominal hypertension or abdominal compartment syndrome. Current literature lacks evidence-based definite guidelines regarding the use of negative pressure therapy. This paper reviews currently published indication for the use of negative pressure therapy in patients with severe acute necrotizing pancreatitis.

## INTRODUCTION

Treatment of a patient with severe acute necrotizing pancreatitis is challenging and associated with high rate of morbidity and mortality. Recent trends show advantages of the step-up approach compared to open surgical necrosectomy. However, there is still consid-

erable proportion of patients who are not candidates for minimally invasive or step-up approach. The use of negative pressure therapy (NPT) has introduced a new treatment modality in management of the open abdomen (OA).

## INTRA-ABDOMINAL HYPERTENSION AND ABDOMINAL COMPARTMENT SYNDROME

Severe acute necrotizing pancreatitis is associated with development of systemic inflammatory response syndrome (SIRS). Pathophysiological consequences of inflammatory response and local cytokine release are increased capillary leakage and development of a tissue edema (1–3). Gut edema results in a reduction or even obstruction of a venous outflow thus leading to elevated venous pressures (4–6). Elevated venous pressure leads to transvascular movement of fluid that exceeds draining capacity of the abdominal and the thoracic lymphatic system. As a consequence accumulation of peritoneal fluid is observed. This leads to development of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) with multiple organ failure (MOF) (4–6).

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## PANCREATIC NECROSIS

Pancreatitis starts in acinar cells with premature intracinar activation of digestive enzymes. As a consequence, activated pancreatic enzymes cause autodigestion and may cause cell death. Injury to the pancreatic duct or its branches results in a leakage of pancreatic enzymes into the lesser sac and the retroperitoneum with development of a pseudocyst. In severe form of acute pancreatitis cell death and autodigestion due to leakage of active form of pancreatic enzymes leads to devitalized tissue. The amount of necrotic tissue is one of the strongest predicting factor of mortality in necrotic pancreatitis. Pancreatic necrosis can follow three different outcomes: spontaneous resolution, persistent fluid collection with development of a pseudocyst or in a case of infection, formation of abscess or infected necrosis.

## OPEN SURGICAL TREATMENT IN ACUTE NECROTISING PANCREATITIS WITH INFECTED PANCREATIC NECROSIS

Surgery remains a cornerstone in treatment of abdominal sepsis. Elimination of necrotic tissue, lavage, and drainage of purulent material in combination with antibiotic therapy and intensive care treatment is considered gold standard in treating of abdominal sepsis. However, due to the natural course of severe necrotizing pancreatitis, surgical necrosectomy with a single operation is not achieved in majority of a patients (7–9). Consequently, numerous surgical interventions are needed. This invasive approach is associated with high rates of complications (34–95%) and death (11–39%) and with a risk of a long-term pancreatic endocrine and exocrine insufficiency (7–9).

## ABDOMINAL NEGATIVE PRESSURE THERAPY IN MANAGEMENT OF THE OPEN ABDOMEN

During the latest decades trends are shifting from traditional open surgical necrosectomy to minimally invasive necrosectomy with the use of a ‘step up’ approach.

A minimally invasive step-up approach, as compared with open surgical necrosectomy, reduced the rate of major complications and is thus associated with lower morbidity and mortality in patients with necrotizing pancreatitis and infected pancreatic necrosis (10). However, there is still considerable proportion of patients who are not candidates for minimally invasive treatment or in which minimally invasive treatment is not successful. This population of patients usually has more than one surgical procedure which leads to development of OA. The management of OA is associated with severe acute and late complications (11–13):

- high rate of enteroatmospheric fistula,
- persistent sepsis,
- MOF,
- development of ‘frozen abdomen’ and
- lateralization or destruction of abdominal wall muscles.

In recent years, the need for programmed surgical lavage led to the development of numerous techniques such as Bogota bag, towel clamp, and zipper technique. However, none of those above techniques proved to have satisfactory clinical results. Implementation of NPT in treating patients with an OA bears a promise for better clinical results.

Current indications for NPT treatment in patients with severe acute necrotizing pancreatitis are (14):

- ACS unresponsive to conservative or radiological percutaneous interventions,
- severe abdominal infection in cases when the source of sepsis cannot be fully controlled and
- acute mesenteric ischemia considered for a second look.

NPT offers a temporary abdominal closure in a patient with ACS. It also actively removes the exudate from all the abdominal compartments thus contributing to lowering systemic and locoregional inflammatory response. It also allows easy access to abdominal cavity in case of planned surgical necrosectomy or other surgical procedure. The best results have been demonstrated with a continuous pressure of 125 mmHg and a 24–72 hours interval between dressing changes (12).

The use of NPT prolonged historical interval for delayed primary fascial closure from four to five days to as long as one month after initial procedure (15). However, recent report from Kaplan et al. (13) showed that if the abdominal wall is not closed within 7–10 days, formation of adhesions and fascia retraction render this impossible. There is still no evidence-based conclusion which type of NPT regime offers best results, and further studies are needed. Inappropriate use of NPT can also lead to increased rate of enteroatmospheric fistula, bleeding, bowel obstruction, fascial retraction and development of frozen abdomen. Mortality rates vary between 7–38% (16, 17) and can even reach 50% in patients with peritonitis, severe sepsis or septic shock (16, 17).

## CONCLUSION

NPT offers new treatment possibilities and enhance patient recovery by removing cytokine-rich peritoneal fluid, alleviating IAH or ACS and allowing easy approach for planned lavage and necrosectomy. It is efficient and feasible in patients with severe acute necrotizing pancreatitis. Definitive protocol of NPT is still not agreed, and further prospective studies are needed.

## References

1. Rezende-Neto JB, Moore EE, Masuno T, et al. The abdominal compartment syndrome as a second insult during systemic neutrophil priming provokes multiple organ injury. *Shock*. 2003; 20: 303-8.
2. Moore-Olufemi SD, Xue H, Allen SJ, et al. Effects of primary and secondary intra-abdominal hypertension on mesenteric lymph flow: implications for the abdominal compartment syndrome. *Shock*. 2005; 23: 571-5.
3. Kowal-Vern A, Ortegell J, Bourdon P, et al. Elevated cytokine levels in peritoneal fluid from burned patients with intra-abdominal hypertension and abdominal compartment syndrome. *Burns*. 2006; 32: 563-9.
4. Richard SH, Irene EK. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003; 348: 138-50.
5. Radhakrishnan RS, Xue H, Weisbrodt N, et al. Resuscitation-induced intestinal edema decreases the stiffness and residual stress of the intestine. *Shock*. 2005; 24: 165-70.
6. Shah SK, Jimenez F, Walker PA, et al. Peritoneal fluid: a potential mechanism of systemic neutrophil priming in experimental intra-abdominal sepsis. *Am J Surg*. 2012; 203: 211-6.
7. Rau B, Bothe A, Beger HG. Surgical treatment of necrotizing pancreatitis by necrosectomy and closed lavage: changing patient characteristics and outcome in a 19-year, single-center series. *Surgery*. 2005; 138: 28-39.
8. Büchler MW, Gloor B, Müller CA, et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. *Ann Surg*. 2000; 232: 619-26.
9. Connor S, Alexakis N, Raraty MG, et al. Early and late complications after pancreatic necrosectomy. *Surgery*. 2005; 137: 499-505.
10. Hjalmar C, van Santvoort MD, Besselink MG, et al. Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010; 362: 1491-502.
11. Haldipur N, Cooper B, Sanyal S. Managing the open abdomen. *J R Army Med Corps*. 2006; 152: 143-7.
12. Björck M, Bruhin A, Cheatham M, et al. Classification, an important step to improve the management of patients with an open abdomen. *World J Surg*. 2009; 33: 1154-7.
13. Kaplan M, Banwell P, Orgill DP, et al. Guidelines for the management of the open abdomen. *Wounds*. 2005; 17: 1-24.
14. Plaudis H, Rudzats A, Melberga L, et al. Abdominal negative-pressure therapy: a new method in countering abdominal compartment and peritonitis – prospective study and critical review of literature. *Ann Intensive Care*. 2012; 2 Suppl 1: S23.
15. Petersson U, Acosta S, Björck M. Vacuum-assisted wound closure and mesh-mediated fascial traction—a novel technique for late closure of the open abdomen. *World J Surg*. 2007; 31: 2133-7.
16. Batacchi S, Matano S, Nella A, et al. Vacuum-assisted closure device enhances recovery of critically ill patients following emergency surgical procedures. *Crit Care*. 2009; 13: 194-202.
17. Sartelli M. A focus on intra-abdominal infections. *World J Emerg Surg*. 2010; 5 Suppl 9: 1-20.

# Planning and Timing of Cholecystectomy

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**Key words:** acute cholecystitis, delayed cholecystectomy, early cholecystectomy, laparoscopic cholecystectomy, biliary duct injury, acute pancreatitis, ERCP

## ABSTRACT

Acute cholecystitis is one of the most common causes of hospitalization for gastrointestinal disease. Subsequent surgical treatment is very often required. Although cholecystectomy is the definitive management, the timing of surgery about the first episode of acute cholecystitis remains an area of debate and considerable practice variation. Early cholecystectomy confers several benefits compared with delayed cholecystectomy not only for patients with acute cholecystitis but also for patients after endoscopic retrograde cholangiopancreatography as well as for patients with mild pancreatitis.

## INTRODUCTION

Gallstones are present in about 10–15% of the adult population of the Western world. Up to 5% of these adults become symptomatic; mostly they have biliary colic, many develop acute cholecystitis (AC).

AC is one of the most common causes of hospitalization for gastrointestinal disease. Subsequent surgical treatment is very often required. The disease can be mild, self-limiting or on the other hand, can even

present itself as a potentially life-threatening illness. This lethal potential of AC is strongly determined by the general condition of the patient. Initially, AC was considered a contraindication for laparoscopic cholecystectomy (LC). For quite a long time, surgeons performed LC only after they were sure the inflammation settled down completely because they feared of higher complication rates, including injury to the bile duct. Another reason for preferring to delay the operation was (is?) a strong belief that early operation increases the risk of an open operation. Hence, a waiting time of at least six weeks was employed. Even in the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines back in 1993, AC was considered a relative contraindication for LC (1). With growing surgical experience and published evidence, a laparoscopic approach for AC was established (2).

Endoscopic retrograde cholangiopancreatography (ERCP) is considered standard treatment for patients with common bile duct stones and is successful in more than 90% of patients. Nevertheless, ERCP can induce complications including pancreatitis and cholecystitis. These complications may affect a subsequent laparoscopic cholecystectomy, leading to conversion

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to open procedure, perioperative complications and longer operative time (3–6).

The incidence of acute biliary pancreatitis is increasing across the globe, probably due to increased risk of gallstone disease because of increase in obesity (7). In 80% of patients, the pancreatitis remains mild. However, 20% of patients develop severe pancreatitis, which is associated with high morbidity and mortality (8).

General recommendations for patients are to undergo cholecystectomy only after the signs of inflammation have resolved (i.e., interval cholecystectomy (IC)) (9). Published international guidelines recommend early LC for patients with mild pancreatitis. However, the definitions of early differ greatly between the guidelines. The International Association of Pancreatology (IAP) recommends that all patients with gallstone pancreatitis should undergo cholecystectomy as soon as the patient has recovered from the attack. American Gastroenterological Association and the British Society of Gastroenterology, on the other hand, recommend cholecystectomy within a 2- to 4-week interval after discharge. The rationale of early cholecystectomy is to reduce the risk of recurrent biliary adverse events. Among these, a recurrent attack of biliary pancreatitis could be severe and even fatal (10–13).

Nowadays the main controversies about treating this conditions are around the timing of surgery but also the need for surgery as compared to conservative management, particularly in high-risk surgical patients.

## REVIEW OF THE LITERATURE

Bile duct injury (BDI) is the most feared complication of cholecystectomy, laparoscopic as well as open. It has a substantial morbidity and even mortality with huge impact on quality of life and life expectancy. Observational studies have suggested a higher number of BDI in patients, operated early from the symptoms onset. However, several randomized controlled trials and meta-analyses subsequently published by Gurusamy, Kolla, Wu, Chong, and others did not

confirm these findings. These studies proved LC is safe with no significant differences in adverse events (including BDI) as well as no higher proportion of conversion to open cholecystectomy when compared to delayed LC. However, the early LC should be performed up to seven days from onset of symptoms (preferably within 72 hours) in a unit with appropriate surgical expertise (14–16).

Cochrane review agrees with these findings. In their meta-analysis, published in 2013, they analyzed six trials, where 488 participants with AC and fit to undergo LC were randomized to early LC (244 patients) and delayed LC (244 patients). Early LC was defined as LC performed within seven days of clinical presentation. Delayed LC was defined as routine LC, intended to be performed six weeks after the index admission. The researchers found no significant differences between early and late LC in mortality, BDI, and other serious adverse events or the incidence of conversion to open surgery. Moreover, approximately one-sixth of patients in the delayed group had either non-resolution of symptoms or recurrence of symptoms before their planned operation and had to undergo emergency LC. The authors concluded that early LC seems safe and may shorten the total hospital stay (17).

Tokyo guidelines propose that the treatment strategy should be considered and chosen after the assessment of the disease severity, the patient's general status, and underlying disease. Consequently, for mild AC (Grade I), the LC should be done as soon as possible after onset if the patient can withstand the surgery (as suggested by the Charlson Comorbidity Index (CCI) and American Society of Anaesthesiologists (ASA) score). If not, conservative treatment is indicated and delayed surgery considered once treatment is seen to take effect. Recommendation is the same for moderate AC (Grade II) provided the patient is in an advanced surgical center (ASC). However, if it is decided that the patient is not fit for surgery, conservative treatment with biliary drainage should be considered. For severe AC (Grade III), a normalization of function through organ support and antibiotics is the priority. After that, early LC can be considered in an ASC by a dedicated

hepato-pancreatic-biliary surgeon with extensive experience in the setting that allows for intensive care management. In patients, deemed not fit for surgery, conservative treatment is commenced with early biliary drainage considered if gallbladder inflammation cannot be controlled otherwise (18). Gallbladder drainage, also known as percutaneous cholecystostomy (PC) is indeed a potential alternative to cholecystectomy in high-risk patients, who are not suitable candidates for surgery due to co-morbidities. Its role is still not determined as there is a lack of good quality evidence to support its use.

According to recently published consensus guidelines of the World Society of Emergency Surgery (WSES) on AC, the LC should be offered to all patients with exception of those with high-risk morbidity or mortality as soon as the diagnosis of AC is made and the risk of choledocholithiasis evaluated. In agreement with Tokyo guidelines and other reports they also recommend early LC in favor to delayed LC as long as it is completed within ten days of onset of symptoms. Beyond ten days, the LC should not be offered to patients unless symptoms suggestive of worsening peritonitis or sepsis warrant an emergency surgical intervention. The WSES consensus, like Tokyo guidelines, also addresses the alternative treatments for high-risk patients. In a contrast to Tokyo guidelines in which PC is an integral part in both moderate as well a severe AC, WSES consensus considers PC as a possible alternative after the failure of conservative treatment only in a small subset of patients unfit for emergency surgery due to their severe co-morbidities (19). Currently, the CHOCOLATE trial is ongoing: it is a randomized controlled trial comparing PC with early LC in critically ill patients (APACHE score 7–14) with AC. Results of this trial may clarify the real role of PC (20).

Regarding the optimal timing of LC after ERCP, the evidence is scarce. In a systematic review published recently, Friis et al. included 14 studies (randomized controlled studies but also cohort studies) with a total of 1930 patients included. Their pooled estimate revealed an increase from a 4.2% conversion rate

when LC was performed within 24 hours from ERCP to 7.6% for 24–72-hour delay to 12.3% when performed within two weeks, to 12.3% for 2–6 weeks, and to a 14% conversion rate when operation was delayed more than six weeks. Accordingly, the authors concluded that it is preferable to perform LC within 24 hours from ERCP or within the first few days, at the latest, to reduce conversion rate. Moreover, early LC does not increase mortality, perioperative complications or length of stay. On the contrary, it reduces the risk of recurrence and progression of disease in the delay between ERCP and LC (21).

Traditionally, early LC for patients with mild pancreatitis was preferred, but only after an interval of varying length. However, the Dutch group published a very comprehensive review challenging such approach. In their review, they analyzed eight cohort studies and one randomized trial, all together including 998 patients. Cholecystectomy was performed during index admission in 483 patients (48%) without any reported readmissions. Interval cholecystectomy was performed in 515 patients (52%) after 40 days. Before IC, 95 patients (18%) had to be readmitted for recurrent biliary events, including recurrent biliary pancreatitis (43.8%). There were no differences in operative complications, conversion rate (7%) and mortality (0%) between index and IC. Authors concluded that cholecystectomy during index admission for mild biliary pancreatitis appears safe. Nevertheless they could not exclude selection bias as baseline characteristics were only reported in 26% of patients. Therefore the question is whether the two groups are truly comparable (22).

The review done by Gurusamy et al. is in agreement with these findings. Authors analysed one randomized controlled trial in which 50 participants with mild acute gallstone pancreatitis were randomized either to early LC (within 48 hours of admission irrespective of whether the abdominal symptoms were resolved or the laboratory values had returned to normal) or to delayed LC (surgery after resolution of abdominal pain and after the laboratory values had returned to normal). Authors concluded that

there is no increased risk of complications after early LC for mild acute biliary pancreatitis (23).

## CONCLUSION

Treating patients, fit for surgery, with LC as soon as possible after the onset of symptoms seems to be the best therapeutic strategy. However, while some authors believe that LC for patients with AC should be delayed if not performed up to 7–10 days, there are some who favor early LC regardless of the time from symptom onset, provided a sufficient laparoscopic experience exists. Despite the available evidence and expert consensus supporting early LC, rate of early surgery remains variable. Early LC seems to be the best approach for patients after ERCP or mild pancreatitis, as well. Gallbladder drainage, also known as percutaneous cholecystostomy, is a possible alternative to surgical treatment in a very select subgroup of critically ill patients, unfit for surgery. However, good evidence, clearly supporting its role, is lacking, at least for the time being.

## References

1. Society of American Gastrointestinal Endoscopic Surgeons (SAGES). The role of laparoscopic cholecystectomy. Guidelines for clinical application. *Surg Endosc.* 1993; 7: 369-70.
2. Johansson M, Thune A, Nelvin L, et al. Randomized clinical trial of open versus laparoscopic cholecystectomy in the treatment of acute cholecystitis. *Br J Surg.* 2005; 92: 44-9.
3. Boerma D, Raues EA, Keulemans YC, et al. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: a randomised trial. *Lancet.* 2002; 360: 761-5.
4. Ahn KS, Kim YH, Kang KJ, et al. Impact of preoperative ERCP on laparoscopic cholecystectomy: a case-controlled study with propensity score matching. *World J Surg.* 2015; 39: 2235-42.
5. Bostanci EB, Ercan M, Ozer I, et al. Timing of elective laparoscopic cholecystectomy after endoscopic retrograde cholangiopancreatography with sphincterotomy: a prospective observational study of 308 patients. *Langenbecks Arch Surg.* 2010; 395: 661-6.
6. Reinders JS, Goud A, Timmer R, et al. Early laparoscopic cholecystectomy improves outcomes after endoscopic sphincterotomy for choledocholithiasis. *Gastroenterology.* 2010; 138: 2315-20.
7. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas.* 2006; 33: 323-30.
8. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol.* 2006; 101: 2379-2400.
9. Nealon WH, Bawduinak J, Walser EM. Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone-associated acute pancreatitis with peripancreatic fluid collections. *Ann Surg.* 2004; 239: 741-9.
10. Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, Association of Upper GI Surgeons of Great Britain and Ireland. UK Guidelines for the management of acute pancreatitis. *Gut.* 2005; (54 Suppl 3): iii1-9.
11. Forsmark CE, Bailie J. AGA Institute technical review on acute pancreatitis. *Gastroenterology.* 2007; 132: 2022-44.
12. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. *Pancreatol.* 2002; 2: 565-73.
13. Hernandez V, Pascual I, Almela P, et al. Recurrence of acute gallstone pancreatitis and relationship with cholecystectomy after admission for acute biliary pancreatitis. *Pancreas.* 2010; 39: e42-7.
14. Asai K, Watanabe M, Kusachi S, et al. Evaluating the timing of laparoscopic cholecystectomy for acute cholecystitis in an experienced center based on propensity score matching. *Asian J Endosc Surg.* 2017; 10: 166-72.
15. Kolla SB, Aggarwal S, Kumar A, et al. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a prospective randomized trial. *Surg Endosc.* 2004; 18: 1323-7.
16. Gurusamy K, Samraj K, Gluud C, et al. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg.* 2010; 97: 141-50.
17. Gurusamy KS, Davidson C, Gluud C, et al. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. *Cochrane Database Syst Rev.* 2013; (6): CD005440.
18. Okamoto K, Suzuki K, Takada T, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. *J Hepatobiliary Pancreat Sci.* 2018; 25 (1): 55-72.
19. Ansaloni L, Pisano M, Coccolini F, et al. 2016 WSES guidelines on acute calculous cholecystitis. *World J Emerg Surg.* 2016; 11: 25.
20. Kortram K, van Ramshorst B, Bollen TL, et al. Acute cholecystitis in high risk surgical patients: percutaneous cholecystostomy versus laparoscopic cholecystectomy (CHOCOLATE trial): study protocol for a randomized controlled trial. *Trials.* 2012; 13: 7.
21. Friis C, Rothman JP, Burcharth J, et al. Optimal timing for laparoscopic cholecystectomy after endoscopic retrograde cholangiopancreatography: a systematic review. *Scand J Surg.* 2017 Dec 1; doi: 10.1177/1457496917748224. [Epub ahead of print]
22. van Baal MC, Besselink MG, Bakker OJ, et al. Timing of cholecystectomy after mild biliary pancreatitis. A systematic review. *Ann Surg.* 2012; 255: 860-6.
23. Gurusamy KS, Nagendran M, Davidson BR. Early versus delayed laparoscopic cholecystectomy for acute gallstone pancreatitis. *Cochrane Database Syst Rev.* 2013; 9: CD010326.

# Trauma to the Pancreas: What We Need to Know

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## ABSTRACT

Blunt pancreatic trauma is an uncommon injury but has high morbidity and mortality. In modern era of trauma care, pancreatic trauma remains a persistent challenge to radiologists and surgeons alike. Early detection of pancreatic trauma is essential to prevent subsequent complications. However, early pancreatic injury is often subtle on CT and can be missed unless specifically looked for. Signs of pancreatic injury on CT include laceration, transection, bulky pancreas, heterogeneous enhancement, peripancreatic fluid and signs of pancreatitis. Pancreatic ductal injury is a vital decision-making parameter as ductal injury is an indication for laparotomy. While lacerations involving more than half of pancreatic parenchyma are suggestive of ductal injury on CT, ductal injuries can be directly assessed on MRI or endoscopic retrograde cholangiopancreatography. Pancreatic trauma also shows temporal evolution with increase in extent of injury with time. They are associated with considerably high morbidity and mortality in cases of delayed diagnosis, incorrect classification of the injury, or delays in treatment.

## INTRODUCTION

The pancreas is a relatively uncommon organ to be injured in trauma (7–9%), occurring in less than 2% of blunt trauma cases. This injury is associated with considerably high morbidity and mortality in cases of delayed diagnosis, incorrect classification of the injury, or delays in treatment (1, 2). Mortality for pancreatic injuries ranges from 9% to 34%; however, only 5% of the pancreatic injuries are directly related to the fatal outcome. Physical examination is usually not reliable in the setting of acute pancreatic trauma (3). Early and accurate diagnosis can decrease morbidity and mortality, and various imaging modalities play a key role in recognition of pancreatic injuries (4, 5). Knowledge about the mechanisms of pancreatic injury, the presence of coexisting injuries, the time to diagnosis, the presence or absence of major ductal injury, and the roles of various imaging modalities are essential for prompt, early and accurate diagnosis. Early detection of disruption of the main pancreatic duct (MPD) is of paramount importance because such disruption is the main cause of delayed complications like pseudopancreatic cysts (6). The most common site of traumatic

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pancreatic injury is at the junction of the body and tail. Significant pancreatic injury may occur in the absence of abnormality on various imaging modalities (7). Conservative management is mainly advocated for pancreatic trauma without ductal injuries. CT is routinely used as the first-line imaging modality in acute abdominal trauma cases and is helpful in recognizing injuries to the pancreas and other organs and their associated complications (8). US is useful in cases of pancreatic ascites and pseudocyst formation, which are more likely to occur in cases with traumatic pancreatitis (3, 9). Magnetic resonance cholangiopancreatography (MRCP) allows direct imaging of the pancreatic duct and its disruption (10). Recently, with emphasis on early detection of ductal injury and an increasing trend towards non-operative management of low-grade pancreatic injuries, MRI, endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic stenting have also been incorporated into pancreatic trauma management protocols (2, 4–8).

## ANATOMIC CONSIDERATIONS

The pancreas is a long J-shaped, soft, lobulated retroperitoneal organ. It is situated transversely across the posterior abdominal wall, at the back of the epigastric and left hypochondriac regions at level of lumbar spine (L1–2) (11). The MPD of Wirsung traverses the entire length of the gland. The superior pancreaticoduodenal artery from the gastroduodenal artery and the inferior pancreaticoduodenal artery from the superior mesenteric artery run in the concave contour of the second part of the duodenum to supply the head of the pancreas. The pancreatic branches of the splenic artery supply the neck, body, and tail of the pancreas. The body and neck of the pancreas drain into the splenic vein, whereas the head drains into the superior mesenteric and portal veins. The proximity of many larger vessels such as the inferior vena cava, portal vein, and abdominal aorta makes injuries to the pancreas difficult to manage because of the risk of exsanguinating hemorrhage, which is a frequent cause of death in patients with a pancreatic injury. The splenic artery and splenic vein run superior and posterior to the body and tail of the pancreas and are

relatively easier to expose and control compared to the inferior vena cava and portal vein. The vascular anatomy causes problems in repairing the injuries to the head of the pancreas whereas injuries to the body and tail are easier to manage (11, 12) (Figure 1).

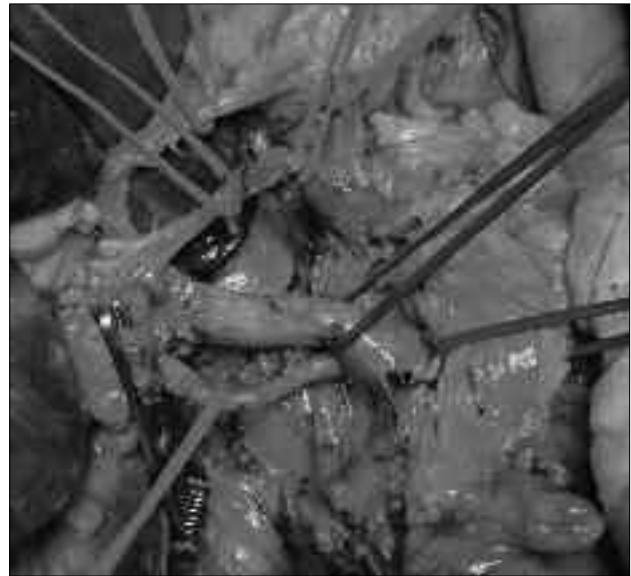


Figure 1. Vasculature of the pancreas

## CLASSIFICATION AND GRADING OF PANCREATIC INJURIES

Pancreatic injuries are classified and graded according to the damage to the pancreatic parenchyma and the ductal system. Grading of pancreatic injuries enables an exact description of injuries, can influence management and allows a comparison of outcomes and effective quality control of treatment (13). There are several classification systems of traumatic pancreatic injuries (14, 15) but the pancreatic organ injury scale (OIS) proposed by the American Association for the Surgery of Trauma (AAST) fulfils most of these criteria and at present is the universally accepted classification scheme (16). This OIS involves five grades, which concedes the significance of more complex injuries to the pancreas, particularly to the pancreatic duct and the pancreatic head (Table 1). This classification scheme can also be correlated with other organ injury scales, as well as integrated into more complex scoring systems, such as Injury Severity Score or Trauma Score-Injury Severity Score from

Table 1. Pancreatic organ injury scale according to American Association for the Surgery of Trauma.

Grade	Injury Description
I	Minor contusion or superficial laceration without duct injury
II	Major contusion or laceration without duct injury or tissue loss
III	Distal transection or parenchymal injury with duct injury
IV	Proximal transection or parenchymal injury involving ampulla
V	Massive disruption of pancreas head

which probability of survival of an individual case is determined.

## CLINICAL AND LABORATORY DIAGNOSIS

Pancreatic injury should be suspected in all polytrauma patients or patients with history of any high-risk mechanism of injury. Due to the deep retroperitoneal location of pancreas, early diagnosis of pancreatic injury may be missed. Isolated pancreatic trauma may be clinically occult initially and can present later with complications while in polytrauma patients, pancreatic trauma may be masked by signs of more severe other organ injuries (17). Clinically, patients may present with diffuse abdominal or epigastric pain, epigastric ecchymosis, abdominal guarding, tenderness and absent bowel sounds, along with metabolic acidosis and leucocytosis secondary to the inflammatory response induced by leakage of pancreatic enzymes (18, 19). Both serum amylase and lipase are unreliable markers for pancreatic trauma. While serum amylase is usually elevated after pancreatic trauma, it can also be normal in up to 40% of patients (20). Thus initial serum amylase levels are neither sensitive nor specific for diagnosis of pancreatic trauma and can also be elevated in non-pancreatic abdominal and bowel injuries (21, 22). Hence serum amylase determinations may support clinical suspicion in the diagnosis of pancreatic

trauma but are not reliable or cost-effective as screening tools. While absolute values of serum amylase do not correspond to the grade and severity of injury, hyperamylasemia in general is an indicator of development of complications, pancreatic fistula and pseudocyst formation (23). Also while initial amylase may be normal, repeat amylase measurements at later intervals, persistent or significant hyperamylasemia (more than three times baseline) are suggestive. Thus, the trend of serum amylase/lipase levels (increase/decrease) rather than any absolute value are helpful indicators of pancreatic involvement and development of subsequent complications (24, 25).

## IMAGING IN PANCREATIC TRAUMA

The objectives of imaging are: 1) to detect pancreatic trauma as early as possible to mitigate the consequences of delayed diagnosis; 2) to identify ductal injury; i.e. to identify grade 3 and above injuries as ductal involvement has higher morbidity and mortality; 3) to evaluate evolution of pancreatic trauma; and 4) to diagnose complications and facilitate image-guided interventions. With these objectives in mind, CT is the workhorse of imaging in pancreatic trauma. MRI with MRCP and ERCP are useful in definitive diagnosis of ductal injury both early and late cases while a newer modality like contrast-enhanced US (CEUS) has also been evaluated in pancreatic trauma.

## Ultrasound

A US examination will usually be performed to enable the diagnosis of free abdominal fluid or gross damage to the liver or spleen. The pancreas is not easily identified and examined to its full extent; therefore, pancreatic injuries, parenchymal or ductal, will frequently be missed. However, routine abdominal US examination in the emergency room will establish the diagnosis of an intra-abdominal injury and therefore establish the need for an urgent explorative laparotomy. To disclose MPD injury in blunt and penetration pancreatic trauma, intraoperative US has proven to be helpful.

## Computed tomography

When initially evaluating for injury, CT scanning is a simple, non-invasive means of evaluating the pancreas. New-generation helical CT scanners quickly enable an overview of abdominal injuries in severely traumatic patients. CT was reported to have 90% sensitivity in detecting pancreatic disruption by The et al. (30). Furthermore, CT allows additional assessment of the severity and extent of pancreatic tissue damage and concomitant injuries. Another factor affecting diagnostic performance in pancreatic trauma is the evolution of pancreatic injury. Findings can be subtle in early cases leading to a low CT sensitivity. In the study by Arkovitz et al. (26), CT had 85% sensitivity within the initial 24 hours after pancreatic injury while overall sensitivity was 90%. The pancreas can appear normal in 20–40% of patients with acute blunt pancreatic injuries, especially when imaging is done within the first 12 hours after injury. This is due to the obscuration of the fracture plane, hemorrhage, and close apposition of the pancreatic fragments. On repeat scanning at 12–24 hours, an abnormality which was initially ambiguous or subtle becomes more evident. Findings become more radiologically apparent over time with the development of post-traumatic pancreatitis, edema, leakage of pancreatic enzymes, and subsequent autodigestion of the surrounding parenchyma (27, 28). The delay in CT findings of pancreatic injury is especially pronounced in pediatric or thin patients who often

lack the contrast provided by surrounding adipose tissue to appreciate pancreatic injuries (29, 30). CT can either miss or underestimate depth of laceration too in very early stage because accumulation of fluid within the gap and separation of fragments is a time-dependent phenomenon (31). Thus, the inability to detect early pancreatic trauma even with advanced multidetector CT technology is not a reflection of failure of technology but due to the natural history and evolution of trauma (32).

## Magnetic resonance cholangiopancreatography

MRCP is another non-invasive diagnostic tool that allows the evaluation of pancreatic injuries with high sensitivity and specificity. Particularly in stable patients with suspected pancreatic injury, MRCP enables the non-invasive detection or exclusion of pancreatic duct trauma and pancreatic specific complications. It may, therefore, provide information that can be used to guide management decisions in the further course of pancreatic trauma patients; however, its purely diagnostic nature and its inability to provide real-time visualization of ductal findings and extravasation are two of its disadvantages. Recently, secretin-stimulated MRCP was also reported to be a safe, non-invasive test that can provide additional useful information about duct integrity and facilitate management (47).

## Endoscopic retrograde cholangiopancreatography

ERCP was documented to be a useful diagnostic tool, displaying sensitivity and specificity of 100% for pancreatic duct injury. ERCP was also reported to be the definitive test for pancreatic duct injury, particularly, to demonstrate the site of duct disruption and the grade of duct injury, whether the branch or main duct and partial or complete disruption of the MPD (53). Recently, ERCP has been shown not only to provide sufficient information for conclusive diagnosis but also to be an effective and safe non-operative treatment tool. In certain cases of leakages of the pancreatic duct, transpapillary stent insertion might seal the

injury and stabilize it in a way that eventually leads to resolution of the leakage.

## MANAGEMENT OF PANCREATIC INJURIES

Management of pancreatic trauma depends on 1) grade/severity of injury; 2) location of injury; 3) other associated abdominal injuries, and 4) time elapsed after injury (2, 9, 14). If CT shows ductal involvement (more than 50% depth of laceration), the operative management is preferred. If CT is equivocal, MRI (or ERCP) should be done to look for ductal involvement followed by laparotomy in presence of ductal involvement.

Many patients with pancreatic injuries have multiple associated injuries including vascular and other intra-abdominal organs injury; priority must be given to stabilizing the patient before any definitive management of the pancreatic injury. The initial priorities include control of hemorrhage and spillage of intestinal contents. The decision regarding therapeutic approach of the traumatic pancreatic injury, either with a conservative approach or a surgical approach, depends upon the integrity of the MPD, extent of pancreatic parenchymal damage, anatomical location of the injury, stability of the patient and degree of associated organ damage (33, 34). In patients with an isolated pancreatic contusion or superficial lacerations without ductal disruption, conservative management may be warranted. Treatment of traumatic pancreatitis consists of bowel rest, nasogastric suction, and nutritional support (35). ERCP-guided stent placement to the MPD injury has been indicated in select cases (36). Endoscopic transpapillary drainage has been successfully used to heal duct disruptions in the early phase of pancreatic trauma and in the delayed phase to treat the complications of pancreatic duct injuries. However, in patients with major ductal injury after blunt pancreatic trauma, morbidity and mortality greatly increase unless surgery is undertaken within the first 24 hours. By using the pancreatic OIS grading system of the AAST to help to guide the appropriate surgical management, the morbidity and

mortality in blunt pancreatic injury are decreased (37). Grades 1 and 2 are treated with non-operative management techniques or simple drainage, whereas injuries grade 3 or higher often require resection with possible reconstruction and drainage procedures (38). There are some alternative procedures that can be used for the management of high-grade blunt pancreatic injury, such as duodenal diversion, pyloric exclusion, the Whipple procedure or simple drainage, with the choice dependent on the patient's hemodynamic status and the presence or absence of associated duodenal injury (39, 40). Sometimes, the decision to perform a pancreaticoduodenectomy is unavoidable in select cases. If the patient is hemodynamically unstable, pancreaticoduodenectomy should be performed as a two-step procedure. After the initial damage control surgery, anastomoses are completed at a second surgery when the patient is stable (41). The standard of care in penetrating injuries is a surgical approach depending upon the location of the injury and associated abdominal injuries. Damage control surgery in hemodynamically unstable patients with massive injury to the pancreas and associated intra-abdominal organs reduces morbidity and mortality.

### Non-operative management

Literature on non-operative management of the injuries (NOMI) mostly pertains to pediatric patients with reported outcomes similar to operative management (42, 43). However, this approach can also be extended to adults (8). Proper patient selection (patients with low-grade injuries, isolated pancreatic injuries, and absence of ductal involvement on MRI or ERCP), continuous patient monitoring, radiological follow-up and availability of radiological or endoscopic interventions for management of local/pancreatic complications are keystones to successful NOMI (44, 45). In case of clinical and radiological progression of injury, subsequent surgical management is preferred over endoscopy as the laparotomy has better outcomes with lesser complications (2, 3).

## COMPLICATIONS, MORBIDITY, AND MORTALITY

Despite the relatively low incidence of pancreatic trauma, morbidity and mortality are high. While isolated pancreatic trauma has an incidence of less than 3% (46), the overall morbidity is 30–50% and mortality is 10–30%. There is a proportionately direct increase in adverse outcome with 1) increasing grade of injury; 2) associated organ injuries, and 3) delay in diagnosis with failure to identify ductal injuries (3, 9, 13, 24, 29, 47, 48). Approximately, one-third of the patients that survive the first 48 hours develop complications due to pancreatic injury. Complications include traumatic pancreatitis, pancreatitis-induced vascular complications such as pseudoaneurysms, pseudocysts, pancreatic fistulas, intra-abdominal abscesses, pancreatic strictures and chronic obstructive pancreatitis, wound complications, septicemia and multiple organ failure (14, 49, 50). Post-traumatic pancreatitis occurs due to missed or delayed diagnosis of ductal injury. The incidence of pancreatitis is 17% after pancreatic injury (51). Patients present with abdominal pain and hyperamylasemia. CT demonstrates typical imaging features of pancreatitis with bulky, heterogeneously enhancing pancreas, intrapancreatic and peripancreatic collections and can lead to sepsis and multiple organ failure. Treatment is usually conservative while pancreatectomy, debridement, and drainage may be done for failure of conservative treatment. Patients may also present with recurrent episodes of pancreatitis months after trauma due to persistent duct leak. This may require surgical intervention or endoscopic stenting (52–54). Pancreatic fistula is one of the commonest complications after pancreatic trauma. Its incidence varies from 20% in isolated pancreatic trauma to 35% in combined pancreaticoduodenal injuries (55–57). Fistula output more than 200 mL/day is a low-output fistula while output more than 500 mL/day is a high-output fistula. Conservative management with CT-guided drainage of fistula over weeks is the treatment of choice (58). In case of persistently high-output drainage or internal communication with a hollow viscus or pleural cavity, ERCP may be done to delineate the fistulous anatomy followed by surgery or endoscopic

stenting (5). Proximal fistulas are better treated by stenting or Roux-en-Y procedures while distal fistulas are treated by pancreatectomy (3, 14). Pancreatic pseudocysts more commonly occur after missed injuries to distal pancreas or as a sequelae of NOMI (14, 58). These are commonly located anterior to body and tail of pancreas. MRCP or ERCP should be done to look for communication with pancreatic duct. If communication is present, endoscopic stenting along with CT-guided percutaneous drainage is done (59, 60). If there is no communication with pancreatic duct, drainage alone is sufficient. If closely apposing stomach or bowel walls, surgical or endoscopic cystogastrostomy or cystoenterostomy are other therapeutic options (61). Peripancreatic abscess/infected walled-off collections usually occur secondary to contamination from hollow viscus or skin flora through the external drain. These increase morbidity and mortality due to ensuing sepsis (47, 61, 62–68). On imaging, air foci within peripancreatic collections are suggestive of infection. However, if external drainage is maintained, presence of air foci may be normal. In such cases, MRI can show debris within the collections while positive culture of fluid in the presence of fever, leucocytosis, and acidosis are diagnostic. Vascular complications such as pseudoaneurysms either occur due to complications of surgery or secondary to erosion of vessel wall by pancreatic enzymes (69, 70). Post-pancreatitis and post-traumatic pancreatic pseudoaneurysms commonly involve splenic, gastroduodenal and common hepatic arteries. Pseudoaneurysms are potentially life-threatening events and can rupture if untreated, leading to haemorrhagic death. Imminent rupture or bleeding pseudoaneurysms manifest as upper gastrointestinal bleed (haematemesis/melena) or haemobilia. If patient is hemodynamically stable, CT angiography is the modality of choice to diagnose site and size of pseudoaneurysms followed by angioembolization with coils, glue or thrombin. If hemodynamically unstable, patients can directly be taken for embolization (71–74). In cases of failure of embolization or in cases non-amenable to embolization, surgical management is done. Pancreatic duct strictures and chronic obstructive pancreatitis can occur as sequelae of NOMI wherein fibrosis at injury site can lead to pancreatic

duct strictures. Chronic obstruction and raised intraductal pressure leads to chronic obstructive pancreatitis, presenting months to years after trauma (75). MRI is useful in diagnosis while ERCP and endoscopic stenting are therapeutic. Other options include surgical pancreaticojejunostomy and distal pancreatectomy for distal strictures (76).

## SUMMARY

Pancreatic trauma remains a difficult diagnosis with high morbidity and mortality. While multiple detector CT is the mainstay for diagnosing pancreatic injury, early scans may miss pancreatic trauma, especially if not carefully looked for. Thus radiologists should have a very high index of suspicion for pancreatic injury and should carefully evaluate all CT scans for signs of pancreatic involvement.

Early diagnosis of ductal injury is essential to improve outcomes. If ductal involvement is equivocal on CT, MRI should be done to comment on ductal injury versus integrity and guide management. ERCP has a selective role in management of complications of pancreatic trauma. Since pancreatic injury is an evolving process, serial imaging with CT or MRI should be done to look for temporal evolution and follow-up in non-operative management of pancreatic trauma. Radiology also plays a crucial role in follow-up and management of complications in pancreatic trauma. In select situations, including minor injuries, a conservative approach may be successful. With modern imaging modalities and expertise in ERCP, isolated pancreatic duct injury can be successfully managed. A surgical approach is appropriate with major pancreatic injury that necessitates urgent surgical intervention.

## References

1. Stawicki SP, Schwab CW. Pancreatic trauma: demographics, diagnosis, and management. *Am Surg.* 2008; 74: 1133-45.
2. Biffi WL, Moore EE, Croce M, et al. Western Trauma Association critical decisions in trauma: management of pancreatic injuries. *J Trauma Acute Care Surg.* 2013; 75: 941-6.
3. Lin BC, Chen RJ, Fang JF, et al. Management of blunt major pancreatic injury. *J Trauma.* 2004; 56: 774-8.
4. Fisher M, Brasel K. Evolving management of pancreatic injury. *Curr Opin Crit Care.* 2011; 17: 613-7.
5. Bhasin DK, Rana SS, Rawal P. Endoscopic retrograde pancreatography in pancreatic trauma: need to break the mental barrier. *J Gastroenterol Hepatol.* 2009; 24: 720-8.
6. Nirula R, Velmahos GC, Demetriades D. Magnetic resonance cholangiopancreatography in pancreatic trauma: a new diagnostic modality? *J Trauma.* 1999; 47: 585-7.
7. Kong Y, Zhang H, He X, et al. Endoscopic management for pancreatic injuries due to blunt abdominal trauma decreases failure of nonoperative management and incidence of pancreatic-related complications. *Injury.* 2014; 45: 134-40.
8. Duchesne JC, Schmieg R, Islam S, et al. Selective nonoperative management of low-grade blunt pancreatic injury: are we there yet? *J Trauma.* 2008; 65: 49-53.
9. Cirillo RL, Koniaris LG. Detecting blunt pancreatic injuries. *J Gastrointest Surg.* 2002; 6: 587-98.
10. Daly KP, Ho CP, Persson DL, et al. Traumatic retroperitoneal injuries: review of multidetector CT findings. *Radiographics.* 2008; 28: 1571-90.
11. Moore EE, Moore FA. American Association for the Surgery of Trauma Organ Injury Scaling: 50th anniversary review article of the *Journal of Trauma.* *J Trauma.* 2010; 69: 1600-1.
12. Linsenmaier U, Wirth S, Reiser M, et al. Diagnosis and classification of pancreatic and duodenal injuries in emergency radiology. *Radiographics.* 2008; 28: 1591-1602.
13. Bradley EL, Young PR, Chang MC, et al. Diagnosis and initial management of blunt pancreatic trauma: guidelines from a multiinstitutional review. *Ann Surg.* 1998; 227: 861-9.
14. Chrysos E, Athanasakis E, Xynos E. Pancreatic trauma in the adult: current knowledge in diagnosis and management. *Pancreatol.* 2002; 2: 365-78.
15. Moretz JA, Campbell DP, Parker DE, et al. Significance of serum amylase level in evaluating pancreatic trauma. *Am J Surg.* 1975; 130: 739-41.
16. Adamson WT, Hebra A, Thomas PB, et al. Serum amylase and lipase alone are not cost-effective screening methods for pediatric pancreatic trauma. *J Pediatr Surg.* 2003; 38: 354-7.
17. Olsen WR. The serum amylase in blunt abdominal trauma. *J Trauma.* 1973; 13: 200-4.
18. Matsuno WC, Huang CJ, Garcia NM, et al. Amylase and lipase measurements in paediatric patients with traumatic pancreatic injuries. *Injury.* 2009; 40: 66-71.
19. Takishima T, Sugimoto K, Hirata M, et al. Serum amylase level on admission in the diagnosis of blunt injury to the pancreas: its significance and limitations. *Ann Surg.* 1997; 226: 70-6.

20. Bouwman DL, Weaver DW, Walt AJ. Serum amylase and its isoenzymes: a clarification of their implications in trauma. *J Trauma*. 1984; 24: 573-8.
21. Herman R, Guire KE, Burd RS, et al. Utility of amylase and lipase as predictors of grade of injury or outcomes in pediatric patients with pancreatic trauma. *J Pediatr Surg*. 2011; 46: 923-6.
22. Wong YC, Wang LJ, Lin BC, et al. CT grading of blunt pancreatic injuries: prediction of ductal disruption and surgical correlation. *J Comput Assist Tomogr*. 1997; 21: 246-50.
23. Lucas CE. Diagnosis and treatment of pancreatic and duodenal injury. *Surg Clin North Am*. 1977; 57: 49-65.
24. Smego DR, Richardson JD, Flint LM. Determinants of outcome in pancreatic trauma. *J Trauma*. 1985; 25: 771-6.
25. Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling, II: Pancreas, duodenum, small bowel, colon, and rectum. *J Trauma*. 1990; 30: 1427-9.
26. Arkovitz MS, Johnson N, Garcia VF. Pancreatic trauma in children: mechanisms of injury. *J Trauma*. 1997; 42: 49-53.
27. Gupta A, Stuhlfaut JW, Fleming KW, et al. Blunt trauma of the pancreas and biliary tract: a multimodality imaging approach to diagnosis. *Radiographics*. 2004; 24: 1381-95.
28. Stuhlfaut JW, Anderson SW, Soto JA. Blunt abdominal trauma: current imaging techniques and CT findings in patients with solid organ, bowel, and mesenteric injury. *Semin Ultrasound CT MR*. 2007; 28: 115-29.
29. Akhrass R, Kim K, Brandt C. Computed tomography: an unreliable indicator of pancreatic trauma. *Am Surg*. 1996; 62: 647-51.
30. Teh SH, Sheppard BC, Mullins RJ, et al. Diagnosis and management of blunt pancreatic ductal injury in the era of high-resolution computed axial tomography. *Am J Surg*. 2007; 193: 641-3.
31. Wong YC, Wang LJ, Fang JF, et al. Multidetector-row computed tomography (CT) of blunt pancreatic injuries: can contrast-enhanced multiphase CT detect pancreatic duct injuries? *J Trauma*. 2008; 64: 666-72.
32. Phelan HA, Velmahos GC, Jurkovich GJ, et al. An evaluation of multidetector computed tomography in detecting pancreatic injury: results of a multicenter AAST study. *J Trauma*. 2009; 66: 641-7.
33. Panda A, Kumar A, Gamanagatti S, et al. Evaluation of diagnostic utility of multidetector computed tomography and magnetic resonance imaging in blunt pancreatic trauma: a prospective study. *Acta Radiol*. 2015; 56: 387-96.
34. Wu B, Song B. Curved planar reformations in multi-slice spiral CT in pancreatic adenocarcinoma: prediction of invasion of pancreatic and peripancreatic ductal structures. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. 2006; 28: 71-5.
35. Paspulati RM. Multidetector CT of the pancreas. *Radiol Clin North Am*. 2005; 43: 999-1020.
36. Shanmuganathan K. Multi-detector row CT imaging of blunt abdominal trauma. *Semin Ultrasound CT MR*. 2004; 25: 180-204.
37. Venkatesh SK, Wan JM. CT of blunt pancreatic trauma: a pictorial essay. *Eur J Radiol*. 2008; 67: 311-20.
38. Rekhi S, Anderson SW, Rhea JT, et al. Imaging of blunt pancreatic trauma. *Emerg Radiol*. 2010; 17: 13-9.
39. Lane MJ, Mindelzun RE, Sandhu JS, et al. CT diagnosis of blunt pancreatic trauma: importance of detecting fluid between the pancreas and the splenic vein. *AJR Am J Roentgenol*. 1994; 163: 833-5.
40. Sivit CJ, Eichelberger MR, Taylor GA, et al. Blunt pancreatic trauma in children: CT diagnosis. *AJR Am J Roentgenol*. 1992; 158: 1097-1100.
41. Holalkere NS, Soto J. Imaging of miscellaneous pancreatic pathology (trauma, transplant, infections, and deposition). *Radiol Clin North Am*. 2012; 50: 515-28.
42. Sivit CJ, Eichelberger MR. CT diagnosis of pancreatic injury in children: significance of fluid separating the splenic vein and the pancreas. *AJR Am J Roentgenol*. 1995; 165: 921-4.
43. Yang L, Zhang XM, Xu XX, et al. MR imaging for blunt pancreatic injury. *Eur J Radiol*. 2010; 75: e97-101.
44. Soto JA, Alvarez O, Múnera F, et al. Traumatic disruption of the pancreatic duct: diagnosis with MR pancreatography. *AJR Am J Roentgenol*. 2001; 176: 175-8.
45. Fulcher AS, Turner MA, Yelon JA, et al. Magnetic resonance cholangiopancreatography (MRCP) in the assessment of pancreatic duct trauma and its sequelae: preliminary findings. *J Trauma*. 2000; 48: 1001-7.
46. Ragozzino A, Manfredi R, Scaglione M, et al. The use of MRCP in the detection of pancreatic injuries after blunt trauma. *Emerg Radiol*. 2003; 10: 14-8.
47. Gillams AR, Kurzawinski T, Lees WR. Diagnosis of duct disruption and assessment of pancreatic leak with dynamic secretin-stimulated MR cholangiopancreatography. *AJR Am J Roentgenol*. 2006; 186: 499-506.
48. Valentini M, Ansaloni L, Catena F, et al. Contrast-enhanced ultrasonography in blunt abdominal trauma: considerations after 5 years of experience. *Radiol Med*. 2009; 114: 1080-93.
49. Lv F, Tang J, Luo Y, et al. Emergency contrast-enhanced ultrasonography for pancreatic injuries in blunt abdominal trauma. *Radiol Med*. 2014; 119: 920-7.
50. Pannu HK, Fishman EK. Complications of endoscopic retrograde cholangiopancreatography: spectrum of abnormalities demonstrated with CT. *Radiographics*. 2001; 21: 1441-53.
51. Stone A, Sugawa C, Lucas C, et al. The role of endoscopic retrograde pancreatography (ERP) in blunt abdominal trauma. *Am Surg*. 1990; 56: 715-20.
52. Rogers SJ, Cello JP, Schecter WP. Endoscopic retrograde cholangiopancreatography in patients with pancreatic trauma. *J Trauma*. 2010; 68: 538-44.
53. Kim HS, Lee DK, Kim IW, et al. The role of endoscopic retrograde pancreatography in the treatment of traumatic pancreatic duct injury. *Gastrointest Endosc*. 2001; 54: 49-55.
54. Kozarek RA. Endoscopic therapy of complete and partial pancreatic duct disruptions. *Gastrointest Endosc Clin N Am*. 1998; 8: 39-53.
55. Bosboom D, Braam AW, Blickman JG, et al. The role of imaging studies in pancreatic injury due to blunt abdominal trauma in children. *Eur J Radiol*. 2006; 59: 3-7.
56. Leppäniemi AK, Haapiainen RK. Risk factors of delayed diagnosis of pancreatic trauma. *Eur J Surg*. 1999; 165: 1134-7.
57. Brestas PS, Karakyklas D, Gardelis J, et al. Sequential CT evaluation of isolated non-penetrating pancreatic trauma. *JOP*. 2006; 7: 51-5.

58. Horst HM, Bivins BA. Pancreatic transection. A concept of evolving injury. *Arch Surg.* 1989; 124: 1093-5.
59. Subramanian A, Dente CJ, Feliciano DV. The management of pancreatic trauma in the modern era. *Surg Clin North Am.* 2007; 87: 1515-32.
60. Patton JH, Lyden SP, Croce MA, et al. Pancreatic trauma: a simplified management guideline. *J Trauma.* 1997; 43: 234-9.
61. Sharpe JP, Magnotti LJ, Weinberg JA, et al. Impact of a defined management algorithm on outcome after traumatic pancreatic injury. *J Trauma Acute Care Surg.* 2012; 72: 100-5.
62. Asensio JA, Petrone P, Roldán G, et al. Pancreaticoduodenectomy: a rare procedure for the management of complex pancreaticoduodenal injuries. *J Am Coll Surg* 2003; 197: 937-42.
63. Seamon MJ, Kim PK, Stawicki SP, et al. Pancreatic injury in damage control laparotomies: is pancreatic resection safe during the initial laparotomy? *Injury.* 2009; 40: 61-5.
64. Wang GF, Li YS, Li JS. Damage control surgery for severe pancreatic trauma. *Hepatobiliary Pancreat Dis Int.* 2007; 6: 569-71.
65. Paul MD, Mooney DP. The management of pancreatic injuries in children: operate or observe. *J Pediatr Surg.* 2011; 46: 1140-3.
66. Wood JH, Partrick DA, Bruny JL, et al. Operative vs. nonoperative management of blunt pancreatic trauma in children. *J Pediatr Surg.* 2010; 45: 401-6.
67. Velmahos GC, Tabbara M, Gross R, et al. Blunt pancreatoduodenal injury: a multicenter study of the Research Consortium of New England Centers for Trauma (ReCONNECT). *Arch Surg.* 2009; 144: 413-20.
68. Wilson RH, Moorehead RJ. Current management of trauma to the pancreas. *Br J Surg.* 1991; 78: 1196-1202.
69. Silveira HJ, Mantovani M, Fraga GP. Trauma of pancreas: predictor's factors of morbidity and mortality related to trauma index. *Arq Gastroenterol.* 2009; 46: 270-8.
70. Recinos G, DuBose JJ, Teixeira PG, et al. Local complications following pancreatic trauma. *Injury.* 2009; 40: 516-20.
71. Bradley EL. Chronic obstructive pancreatitis as a delayed complication of pancreatic trauma. *HPB Surg.* 1991; 5: 49-60.
72. Akhrass R, Yaffe MB, Brandt CP, et al. Pancreatic trauma: a ten-year multi-institutional experience. *Am Surg.* 1997; 63: 598-604.
73. Fleming WR, Collier NA, Banting SW. Pancreatic trauma: Universities of Melbourne HPB Group. *Aust N Z J Surg.* 1999; 69: 357-62.
74. Lin BC, Fang JF, Wong YC, et al. Blunt pancreatic trauma and pseudocyst: management of major pancreatic duct injury. *Injury.* 2007; 38: 588-93.
75. Pang TC, Maher R, Gananadha S, et al. Peripancreatic pseudoaneurysms: a management-based classification system. *Surg Endosc.* 2014; 28: 2027-38.
76. Ahmed N, Vernick JJ. Pancreatic injury. *South Med J.* 2009; 102: 1253-6.

# Managing the Patient with Acute Pancreatitis in Medical Intensive Care Unit

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## INTRODUCTION

Majority of patients hospitalized with acute pancreatitis (AP) will develop mild AP caused by bile duct obstruction or excessive alcohol consumption. Less common causes include hyperlipemic AP or hypercalcemia. Idiopathic and iatrogenic AP (after endoscopic retrograde cholangiopancreatography (ERCP)) represent minority of AP. In cases of abdominal or thoracic trauma, clinical and laboratory signs of AP should be actively searched for.

Severe AP will develop in less than 20% and is characterized by concomitant organ failure (e.g., respiratory, circulatory, liver, renal, coagulopathy). Rather than concentrating on different scoring systems, clinicians should focus on risk factors associated with the development of AP (age, co-morbidities, presence of systemic inflammatory response syndrome (SIRS), sepsis, presence of pleural effusions, elevated hematocrit, increased body mass index (BMI), altered mental status). Vast majority of patients with AP will present to the emergency department with no organ failure or pancreatic necrosis. Those that initially present with symptoms lasting > 48 hours and have C-reactive protein > 150 are classified as having severe pancreatitis. It is of

utmost importance to initially recognize patients with severe AP and admit them to intensive care units (ICU) or high dependency units for close observation. The use of Ranson's criteria has limited value, and its use is discouraged. Acute Physiology and Chronic Health Evaluation (APACHE) II was developed for ICU use and is not discriminatory enough to use in early phase of AP. Its use in emergency department is not validated.

It is not possible to predict which patient will develop severe AP so closed monitoring with daily inflammatory, renal, pancreatic markers and arterial blood gasses (ABG) with arterial lactate is imperative.

Patient with AP developing or already with septic shock, acute respiratory insufficiency (ARI), multiple organ failure (MOF) should be admitted to ICU for close monitoring. Arterial line, central venous line, Foley catheter, nasogastric tube (or orogastric in intubated patients) should be placed. Arterial blood pressure should be monitored invasively; arterial catheter allows blood to be drawn for ABG analysis and lactate determination. Urine output should be assessed hourly.

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The course of severe AP typically shows two mortality peaks, first within the first week due to SIRS and MOF and second after 14 days due to (septic) complications. If not already performed within 24 hours of admission, ERCP with papillotomy and stent placement should be performed in patients with AP and concurrent cholangitis.

## DIAGNOSTIC PROCEDURES

Abdominal ultrasound to evaluate for cholelithiasis, dilated bile and pancreatic duct should be performed on all patients with AP regardless of their initial blood chemistry. Abdominal US can show potential pleural effusion, peripancreatic fluid, peripancreatic tissue involvement and additional abdominal pathology. It is readily available, non-invasive and cheap.

Contrast-enhanced CT is not an imaging method of choice in early course of AP as it does not add any diagnostic value to abdominal US, laboratory and clinical findings. It should be performed however after 72 hours if abdominal symptoms continue and patient deteriorates. CT is invaluable in later course of the disease (not discussed here).

## FLUID BALANCE

In acute phase fluid resuscitation is often required with volumes up to 6 L during initial 24 hours. After each fluid bolus (30 mL/kg ideal body weight) fluid responsiveness should be reassessed using invasive methods (stroke volume variation, global end-diastolic blood volume index (GEDV), velocity time index (VTI)) or non-invasively (vena cava diameter). Measuring central venous pressure to determine the volume status is obsolete method and should be abandoned. Haemoconcentration (assessed by hematocrit) must be avoided. Balanced crystalloids share numerous advantages over non-balanced ones. Use of colloids in AP setting, especially starches (HES), regardless whether balanced or not, is contraindicated (FDA, EMA) and should be avoided. Of note, early aggressive fluid administration is most beneficial within the first 12–24 hours, and may have little benefit beyond.

## ANALGESIA

Adequate analgesia blunts pro-inflammatory response during AP, suppresses sympathetic drive, has favorable effect on respiratory and physical therapy. Multimodal analgesia is recommended with opioid (tramadol, piritramide, fentanyl, sufentanil), paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) if not contraindicated in combination. Special attention must be paid for patients with renal failure in which opioids accumulate, and long-acting compounds such as piritramide are not optimal choice. In the same setting, NSAIDs are contraindicated as well. Rectal application of NSAIDs has shown to have favorable effect after ERCP.

Smaller studies consistently showed that thoracic epidural analgesia (TEA) with epidural catheter placed between 6<sup>th</sup> and 9<sup>th</sup> thoracic vertebra, enables opioid-sparing analgesia, secures adequate analgesia with improvement of gut motility, pancreatic and splanchnic arterial perfusion and seem to decrease mortality in patients with AP. We are still waiting for definite results from multicentre trial (EPIAN study). Hypotension should not be retained as a contraindication for TEA during AP since it is manageable by fluid administration or pharmacological interventions. Standard contraindications for epidural catheter apply, with notion that increased C-reactive protein does not automatically mean sepsis and should be interpreted in accordance to other variables.

## NUTRITIONAL SUPPORT

Early enteral nutrition via (oro)gastric route is not feasible in all patients with AP but should be heavily encouraged though. Early trial with minimal nutrients delivery (20 mL/hour) with standard high protein enteral formula should be used initially. Immunomodulatory formulas containing arginine, glutamine, and omega-3 fatty acids should be avoided. Gastric residues should not be monitored at regular predetermined intervals (e.g., every six hours). There is still no consensus among clinicians what is still acceptable residue or whether to return or discharge aspirated residue. In case of gastric passage blockage or lack of peri-

stalsis, positioning of enteral tube is recommended. Commercially available tubes include weighted tubes and Tiger tube specially designed to anchor into distal duodenum pass the Treitz ligament enabling direct enteral feeding. Some tubes have additional lumen enabling feeding into gut while venting through the gastric opening.

Routine use of prokinetic agents demonstrated no benefit; however, clinicians report regular use of metoclopramide (10 mg every 8 hours), neostigmine (0.5 mg every 8 hours) together with colonic enemas. To reverse opioid-induced constipation due to opioid analgesia use of methylnaltrexone (Relistor) is indicated. Parenteral nutrition should be avoided during first week and administration tailored individually (partial parenteral nutrition in combination with enteral or complete). Use of prokinetics is indicated in elevated intra-abdominal pressure (IAP). Enteral or parenteral erythromycin (500 mg every 8 hours) is indicated when metoclopramide and neostigmine are ineffective.

Extensive research has been done on enteral supplementation of prebiotics and probiotics in patients with AP. Results were mostly inconclusive (strain of bacteria from the same species, different species, number of colony-forming units, etc.) while some studies demonstrated increased mortality due to septic complication including endocarditis and bowel perforation. As for now, the use of pre- and probiotics in patients with AP is contraindicated.

## ANTIBIOTIC COVERAGE

Routine use of prophylactic antibiotics in patients with severe AP and sterile necrosis is not recommended. Up to 25% of pancreatic necroses will however eventually get infected, causative agents being enteric Gram negative bacteria (*E. coli*, *P. aeruginosa*) and anaerobes (*Bacteroides* spp.) and *Candida* spp. In one third the infection is polymicrobial. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis with anaerobic coverage (e.g., meropenem) may be useful in delaying percutaneous or surgical intervention, thus decreasing morbidity and mortality. Other classes include fluoroquinolones with metronidazole or high dose cephalosporins. Material for microbiological must be

obtained, and antibiotic therapy should be adequately tailored (targeted). Prophylactic use of anti-fungal agents is contraindicated. Material for microbiology cultivation should be obtained as soon as possible using US- or CT-guided fine needle biopsy. In case of open surgery, material should be obtained and sent for microbiology as well.

## PROTON PUMP INHIBITORS

Ulcer prophylaxis with proton pump inhibitors does not have direct favorable effect on the course of AP. Its use should be individually tailored.

## DEEP VENOUS THROMBOSIS PROPHYLAXIS

Prophylaxis for deep venous thrombosis in AP is recommended in all patients with severe AP. Surge in procoagulant inflammatory mediators, stasis, vessel spasm, and mass effects from the surrounding inflamed pancreas all contribute to splenic or portal vein thrombosis which occurs in up to 20%. Once the diagnosis is confirmed, therapeutic heparin treatment should begin. Standard unfractionated heparin has certain advantages over low molecular weight heparin, being cheaper, dosing easily adjustable, with predictable kinetics and available antidote.

## RESPIRATORY SUPPORT

SIRS, pleural effusions, decreased compliance of abdominal and thoracic wall because of volume loading and capillary leak all increase the work of breathing, inevitably leading to ARI. AP is one of the most common causes of acute respiratory distress syndrome. Non-invasive ventilation via face mask or helmet should be the initial approach. High-flow oxygen therapy is easy to use and can be applied in step down units as well in ICU. In comparison to non-invasive ventilation, high-flow oxygen therapy enables moisturizing and heating the delivered gasses. If non-invasive ventilation fails, invasive mechanical ventilation with strict adherence to protective ventilation principles should be applied.

## INTRA-ABDOMINAL HYPERTENSION

IAP monitoring via dedicated gastric tube (Nutrient) or measuring probe attached to Foley catheter is simple, non-invasive method that should be part of basic monitoring in every patient with AP that requires urinary catheterization or gastric tube placement. More than 60% of patients with AP will develop intra-abdominal hypertension (IAH) during the course of disease. Failure to recognize increase in IAP (> 12 mmHg) leads to end-organ failure. Factors that contribute to IAH are among others decrease in abdominal wall compliance, increase in intra-luminal contents, capillary leakage or fluid resuscitation. Pressures greater than 12 mmHg are consistent with IAH, and pressures > 20 mmHg together with new onset organ dysfunction is consistent with abdominal compartment syndrome (ACS).

Some authors recommend maintaining abdominal perfusion pressure (APP) greater than 60 mmHg; however, WSACS 2013 consensus management statement could make no recommendations for the use of APP in the resuscitation or management of patients. The majority of authors urge clinicians to implement techniques towards normalizing IAP and not on maintaining APP over predetermined value.

### Physiological derangements due to intra-abdominal hypertension

Increase in IAP leads to increased jugular venous pressure which in return impairs cerebral venous drainage and contributes to increased intra-cerebral pressure (ICP). Compression to inferior vena cava decreases right heart venous return and decreases cardiac output. Peripheral venous stasis, especially in lower extremities can compromise arterial flow. Combination of fluid resuscitation and increased IAP lead to increased central venous pressure (CVP) which in turn decreases visceral perfusion pressure leading to gut ischemia, bacterial translocation, and end-organ failure. Increased CVP impairs renal perfusion pressure leading to activation of renin-angiotensin-aldosterone system which additionally impairs mesenteric perfusion. IAH impairs lung functional residual capacity, increases ventilation/perfusion mismatch. Multiple organ

failure development often leads to acute respiratory distress syndrome.

Non-surgical interventions to reduce IAP include insertion of decompression gastric and rectal tube, initiating prokinetic agents, administering enemas, performing colonoscopic decompression when indicated and discontinuing enteral nutrition. Repositioning the patient in supine position (no head elevation) can be tried as an IAP lowering technique. The use of diuretics and renal replacement therapy with fluid removal can have favorable effect but is time-consuming. Especially in patients that already have intravascular volume depletion, diuretic use leads to acute kidney injury. The use of deep sedation and analgesia, or even neuromuscular blockade, may transiently improve abdominal wall compliance and reduce IAP while more durable treatments are being pursued. Applying high positive end-expiratory pressure (PEEP) seems to have little or no impact on IAP measurement. PEEP should be set to counterbalance IAP.

### Surgical decompression

Once a diagnosis of ACS is suspected or definitively made and conservative approach to reduce IAP failed, there should be rapid progression to surgical decompression. Although modern management of uncomplicated pancreatitis emphasizes avoidance of surgical intervention, surgical decompression may improve renal or respiratory function. Early surgical decompression is associated with reduced mortality in patients with severe acute pancreatitis, early multiple organ dysfunction syndrome, and abdominal compartment syndrome.

### References

1. Rogers WK, Garcia L. Intra-abdominal hypertension, abdominal compartment syndrome, and the open abdomen. *Chest*. 2018; 153 (1): 238-50.
2. Papavramidis TS, Marinis AD, Pliakos I, et al. Abdominal compartment syndrome – intra-abdominal hypertension: defining, diagnosing, and managing. *J Emerg Trauma Shock*. 2011; 4 (2): 279-91.
3. Sadowski SM, Andres A, Morel P, et al. Epidural anaesthesia improves pancreatic perfusion and decreases the severity of acute pancreatitis. *World J Gastroenterol*. 2015; 21 (43): 12448-56.
4. Mentula P, Hienonen P, Kempainen E, et al. Surgical decompression for abdominal compartment syndrome in severe acute pancreatitis. *Arch Surg*. 2010; 145 (8): 764-9.

# The Role of Conventional and Contrast-Enhanced Ultrasound in Acute Pancreatitis

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**Key words:** acute pancreatitis, ultrasound, contrast-enhanced ultrasound

## ABSTRACT

The diagnosis of acute pancreatitis is based on clinical and laboratory data. Transabdominal US as the first imaging modality used in the evaluation of patients with acute pancreatitis is usually able to determine its biliary cause. Sometimes it can show complications, and the extensiveness of the pathologic changes and enables graduation of severity of the disease. Contrast-enhanced US (CEUS) can demonstrate perfusion of the pancreas and can visualize a non-liquefied necrosis which was a main limitation of conventional US. CEUS offers several potential advantages compared with other imaging techniques, including lower costs, non-invasiveness, lack of radiation exposure, shorter scan times, and most importantly, the absence of nephrotoxicity. An imaging procedure with fewer side effects deserves consideration as a safer alternative. Besides many advantages, due to severe pain and bowel gas in pancreatitis both conventional US and CEUS have its limitations. In the review lecture, indications of other diagnostic imaging techniques and interventional procedures (Doppler, CEUS, CT, MRI, drainage, angiography with embolization, etc.) will be shown, and the role of conventional US and CEUS in the follow-up of the disease will be discussed.

## References

1. Rickes S, Neye H. Pancreatitis and pseudocysts. In: D'Onofrio M, ed. *Ultrasound of the pancreas*. Milan: Springer-Verlag Italia; 2012. p. 83-92.
2. Rickes S, Mönkemüller K, Malfertheiner P. Acute severe pancreatitis: contrast-enhanced sonography. *Abdom Imaging*. 2007; 32 (3): 362-4.
3. Rickes S, Uhle C, Kahl S, et al. Echo-enhanced ultrasound: a new valid initial imaging approach for severe acute pancreatitis. *Gut*. 2006; 55 (1): 74-8.
4. Fei Y, Li WQ. Effectiveness of contrast-enhanced ultrasound for the diagnosis of acute pancreatitis: a systematic review and meta-analysis. *Dig Liver Dis*. 2017; 49 (6): 623-9.

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# Early Cholecystectomy in Acute Calculous Cholecystitis Still Burdened by Serious Surgical Complications

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**Key words:** acute cholecystitis, early cholecystectomy, laparoscopic cholecystectomy, postoperative complications

## ABSTRACT

Early cholecystectomy in acute setting should be carried out in patients with less than 72 hours duration of symptoms. Most agree that surgical treatment can be safely done even in longer duration of symptoms. Despite attractiveness of quickly rendering patients pain-free, avoidance of prolonged antibiotic treatment and recurrent hospitalizations for interval cholecystectomy, not all patients are eligible for immediate surgical treatment. In multiple morbid, old and frail patients, persistence in conservative treatment, possibly bridged with percutaneous gallbladder drainage, might reduce mortality and morbidity rates in this population. Nevertheless, early surgical treatment will continue to play a major role in acute presentation of gallbladder inflammation. Surgeons should be aware of potential problems in identification of biliary anatomy, being ready to convert to open surgery thus avoiding disastrous bile duct injuries. Low threshold for conversion or bailing out with subtotal cholecystectomy remain a legitimate and valid option. In our department review, retrograde analysis of patients operated for acute cholecystitis in the last four years was undertaken. The

results are presented with emphasis on surgical complications management and mortality.

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# Characteristics and Flow of Patients with Acute Pancreatitis at Ljubljana Emergency Department

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**Key words:** acute pancreatitis, emergency department, wait time

## ABSTRACT

**Background.** Emergency Medical Unit at University Medical Centre Ljubljana is almost exclusive hospital entrance for patients with acute pancreatitis (AP) in Central Slovenian region (population 550.000). Data about emergency department flow for this group of patients are scarce in medical publications, and AP incidence report for our region is old. We assessed epidemiological characteristics of patients with AP and their flow at emergency department.

**Methods.** We reviewed emergency department medical records of patients with confirmed diagnosis of AP (ICD-10 diagnosis K85) in the year 2017. The Manchester triage system (MTS) was used to assign clinical priority to all patients (5 categories).

**Results.** Among 24,406 patients, 243 (0.1%) were diagnosed with AP (male 63%, female 37%) with an average age of  $60.2 \pm 18.2$  years (male  $59 \pm 17.1$ , female  $62 \pm 19.9$ ). Their assigned MTS category was yellow (urgent) in 88%, orange (very urgent) in 11%, and green or blue (non-urgent) in 1%. Ultrasound was performed in 148 patients (61%). At the emergency department, etiology of AP was determined in 30%

(68% biliary, 11% alcohol-induced, 11% idiopathic and 10% other). Wait time to emergency department physician examination was  $124 \pm 131$  minutes and overall time spent at emergency department was  $493 \pm 370$  minutes. 75% of patients were admitted to Department of Gastroenterology. MTS emerged as the only independent predictor of door to physician time ( $p=0.022$ ) and time spent in the emergency department ( $p=0.030$ ) after adjustment for etiology, age, gender and month of the year.

**Conclusions.** Regional incidence for AP in 2017 was 4.4/10.000. Patients were predominantly affected in their 6<sup>th</sup> decade, and at emergency department, AP etiology was determined in 30%. Average waiting time for a physician was approximately 2 hours, while overall time at the emergency department was 8.2 hours. The flow of patients with higher MTS was faster.

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# Early Prognostic Tool in Acute Pancreatitis at Ljubljana Emergency Department

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**Key words:** pancreatitis, emergency departments, Manchester triage system, BISAP score, disease course

## ABSTRACT

**Background.** Most episodes of acute pancreatitis (AP) are mild, needing only brief hospitalization. Severe AP occurs in 15–20% of patients. Severity scoring systems usually require 48 hours to become accurate. An earlier prognostic tool would be helpful. We aimed to assess the prognostic potential of Manchester triage system (MTS) score and Bedside Index for Severity in Acute Pancreatitis (BISAP) score (1).

**Methods.** A retrograde review of emergency department and hospital medical records of patients with confirmed diagnosis of AP at Emergency Medical Unit of University Medical Centre Ljubljana in 2017 was performed. BISAP score was calculated for each patient. Furthermore, the course of the disease was stratified into three groups: normal, severe and fatal.

**Results.** In 2017, 243 patients (0.1%) were diagnosed with AP (male 63%, female 37%) with an average age of  $60.2 \pm 18.2$  years (male  $59 \pm 17.1$ , female  $62 \pm 19.9$ ). Their consecutively assigned MTS category was predominantly yellow (urgent) in 88%, followed by orange (very urgent) in 11%, and green or blue (non-urgent) in 1%. Retrograde BISAP score could be calculated

in 224 patients (0 points 38%, 1 point 35%, 2 points 21%, 3 points 5%, 4 and 5 points 0%). Disease course was mild in 70% of patients, severe in 28 % and fatal in 2% of patients (4 patients). On a multivariate model, only BISAP emerged as an independent predictor of severe disease (OR 1.84; 95% CI 1.18–2.85;  $p=0.007$ ) after adjusting for age, gender, etiology and MTS score.

**Conclusions.** MTS has a poor prognostic value in acute pancreatitis. On the other hand we have shown that BISAP score, an early prognostic tool based on clinical, laboratory and radiological data, is a good predictor of severe disease.

## References

1. Wu BU, Johannes RS, Sun X, et al. The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut*. 2008; 57 (12): 1698-703.

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# Pancreatitis – Treating Patients with Infectious Complications in Surgical Department

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**Key words:** pancreatitis, inflammation, antibiotics

## ABSTRACT

**Introduction.** Pancreatitis is an inflammatory response of pancreas with changing morphology due to different causes, which are excessive alcohol consumption (60%), idiopathic (20–30%), or rare diseases (10%). Due to common pathological mechanisms, Atlanta classification divides pancreatitis to 1) interstitial oedematous acute pancreatitis and 2) acute necrotizing pancreatitis, characterized by inflammation, associated with pancreatic parenchymal necrosis and peripancreatic necrosis. Late consequences are pseudocyst formation with duodenum and common bile duct obstruction, thrombosis of splenic vein (and consequently portal hypertension), development of splenic artery pseudoaneurysm, and long-term metabolic complications, being exocrine and endocrine pancreas insufficiency, i.e., diabetes mellitus. Infection is a complication of acute pancreatitis presented in 10% of cases with different infectious agents.

**Methods.** Retrospective analysis included 95 patients diagnosed with pancreatitis treated at the Department of Abdominal Surgery at the University Medical Centre Ljubljana, during the 2-year observational period from January 2016 to December 2017.

Inflammatory parameters (C-reactive protein, white blood count), haemoculture results, body temperature, infectious complications including abdominal sepsis, hospitalization time and more severe complications were included in the study protocol.

**Results.** In 13/95 patients (13.7%) antibiotic treatment was prescribed at different treatment time; in 9/13 patients (69.2%) diagnosed with infectious complication, average hospitalization time was 25.5 days (range 14–37 days), while four patients were hospitalized for less than 14 days. Antibiotic prescription was based on positive inflammatory parameters (elevated white blood count and C-reactive protein) and elevated body temperature. Antibiotics were mostly prescribed empirically and were continued if sensitivity to antibiotic was proved on antibiogram. If not and after consulting infectiologist, empiric antibiotic treatment was switched to target. In 8/13 patients (61.53%), microbiology tests were performed. The microbiology results confirmed one sepsis with *Enterococcus faecium*, hospitalized for 14 days; one *Candida albicans*-positive haemocultures, hospitalized for 37 days; one septic shock with polymicrobial sepsis being transferred to the intensive care unit of the Department of Infectious Diseases after six days of treatment; and one *Citrobacter*

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*koseri* and *Enterococcus faecalis*-positive drain swab and haemocultures, hospitalized for 20 days. In three cases, the antibiotic scheme had to be changed. In the remaining six patients, antibiotic prescription was not changed; three patients were treated empirically, for one patient infectiologist was consulted, and in two patients the therapy was suitable to microbiology test results. Patients were treated as follows: in four cases ertapenem was prescribed, in two cases piperacillin/tazobactam, in two cases ertapenem was switched to piperacillin/tazobactam and one case was treated with cefazolin and metronidazole which were later switched to piperacillin/tazobactam, after infectiologist consult.

**Conclusions.** Data analysis showed higher infectious complication rate (13%) than reported in the literature (10%). Average hospitalization time in complicated pancreatitis is significantly prolonged, especially in the cohort of patients with metabolic complications supported with parenteral nutrition and infectious complications with sepsis (average 25.5 days). Positive fungal abdominal swab was treated with prolonged antifungal parenteral (later switched to oral) agents and supported with wide analgesic schema. Treatment of metabolic complications was started, if necessary. Data analysis showed insufficient approach to microbiological evidence-based treatment, only present in 61.53% of infectious complication. This cohort of patients presented with significantly higher complication rate (transient steatorrhea 5%, exocrine insufficiency 12%) and prolonged hospitalization time (14–37 days). Compared to the literature, prescription of antibiotic scheme was based on local resistance to antibiotic and only three cases needed to be switched to another antibiotic scheme. Essentially, lower identification rate based on haemoculture and abdominal swab was observed which might explain prolonged hospitalization and complication rate. Late complications are excluded to discussion and also surgical treatment protocol, this might also explain the incidence of some other late complications.

## References

1. Smrkolj V, ed. Kirurgija. Celje: Grafika Gracer; 2014.
2. Forsmark CE, Baillie J, AGA Institute Clinical Practice and Economics Committee, AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. *Gastroenterology*. 2007; 132 (5): 2022-44.
3. Greenberg JA, Hsu J, Bawazeer M, et al. Clinical practice guideline: management of acute pancreatitis. *Can J Surg*. 2016; 59 (2): 128-40.
4. Nordqvist C. All about acute pancreatitis [internet]. Chicago: University of Illinois-Chicago, School of Medicine; c2004–2018. Retrieved from: <https://www.medicalnewstoday.com/articles/160427.php>
5. Zarem E. Treatment of severe acute pancreatitis and its complications. *World J Gastroenterol*. 2014; 20 (38): 12879-92.
6. Parvin R, Louie T, Pitchumoni CS. Infectious complications of acute pancreatitis. *Infect Dis Clin Pract*. 2013; 21 (2): 94-104.
7. Barkin JA, Barkin JS. Infectious complications of acute pancreatitis. In: Schlossberg D, ed. *Clinical Infectious Disease*, 2<sup>nd</sup> ed. Cambridge: Cambridge University Press; 2015. p. 317-23.

# Acute Pancreatitis in Children after Abdominal Trauma

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**Key words:** paediatric blunt abdominal trauma, pancreatitis, surgery

## ABSTRACT

**Introduction.** Pediatric acute pancreatitis (PAP) is an emerging situation and most frequently the result of blunt abdominal trauma (23%, United States 15–37%). The condition is characterized with epigastric pain and elevated serum digestive enzymes. Despite modern diagnostic methodology and advanced clinical practice, PAP represents specific and serious clinical situation associated with significant morbidity and long-term consequences. Grade I–II require mostly conservative treatment and grades III–V surgical management.

**Methods.** Two pediatric medical records were analyzed based on the same mechanism of injury (blunt abdominal trauma due to bicycle accident): two boys of 11 years suffered an impact of handlebar into the left abdominal side. In the same mechanism of trauma, two different clinical situations were observed: grade II and grade III pancreas trauma treated conservatively and surgically (explorative laparotomy, evacuation of hematoma, drainage), respectively. Average hospital stay in both cases was ten days; both cases were transiently treated with parenteral nutrition, non-morphine based pain medication (paracetamol), pancreatic rest, restoration to metabolic homeostasis management and short-term antibiotic prescription.

**Results.** Due to prompt recognition of PAP due to blunt abdominal trauma both, clinical and surgical treatment modalities, resulted in no medical short- or long-term complications. Average hospital stay in both cases was 26 days; both cases were transiently treated with parenteral nutrition, non-morphine based pain medication (paracetamol), pancreatic rest, restoration to metabolic homeostasis management and short-term antibiotic prescription.

**Conclusions.** Traumatic pancreatitis (PAP) is an increasingly recognized clinical entity that needs to implement modern diagnostic approach and modalities. The treatment approach adapted to pediatric population need to be implemented to improve outcomes and reduce short and long-term consequences. Well-designed prospective studies are highly recommended for pediatric guidelines of PAP formation.

## References

1. Englum BR, Gulack BC, Rice HE, et al. Management of blunt pancreatic trauma in children: Review of the National Trauma Data Bank. *J Pediatr Surg.* 2016; 51 (9): 1526-31.
2. Antonsen I, Berle V, Søreide K. Blunt pancreatic injury in children. *Tidsskr Nor Laegeforen.* 2017; 137 (17).
3. Ghasoup A, Sadieh O, Mansor A, et al. Management of pancreatic injuries with blunt abdominal trauma in children, case series. *J Trauma Treat.* 2013; 2: 160.
4. Stanic D, Rakic G, Draskovic B, et al. Traumatic pancreatitis in children. *Acad J Ped Neonatal.* 2016; 2 (3).

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# Acute Pancreatitis in Pregnancy

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**Key words:** acute pancreatitis, pregnancy, pancreatitis in pregnancy, acute abdomen, abdominal pain

## ABSTRACT

Any cause for acute abdomen can occur coincidentally with pregnancy. Acute pancreatitis during pregnancy is rare but severe disease, with high maternal and fetal mortality. It usually occurs during the third trimester or the early postpartum period. Maternal mortality (37%) and perinatal mortality (40%) has recently decreased thanks to earlier diagnosis and some maternal and neonatal intensive care improvement. Acute pancreatitis in pregnancy is most commonly caused by gallstones (65–100%), alcohol abuse and hypertriglyceridemia. Most of the patients (60%) are diagnosed with pancreatitis in the third trimester. Conservative treatment during the first and third trimester and laparoscopic cholecystectomy during the second trimester and early postpartum period are recommended. A multidisciplinary approach, including gastroenterologists, obstetricians, and surgeon seems to be the key in improving threats, such as preterm labor, prematurity and in utero fetal death. As in any other disease associated with pregnancy, acute pancreatitis is associated with greater concerns as it deals with two lives rather than just one as in the non-pregnant population.

## ETIOLOGY

Acute pancreatitis in pregnancy (APIP) is rare condition with incidence of 1/1000–12,000 pregnant women. The wide variation in the incidence is influenced by the prevalence of its most important etiological factor, i.e., gallstone disease (4, 5). Some factors have been recognized as pathogenic cause for APIP: gallstone increased maternal age, increased pregnancy number, high fat diet, and high body mass index.

Cholesterol secretion in the hepatic bile increases in the second and third trimester compared to bile acids and phospholipids, leading to supersaturated bile. Fasting and postprandial gallbladder volumes became greater, with reduced rate and volume of emptying. Combination of physiological changes leads to the retention of cholesterol crystals and eventual gallstones. The formation of biliary sludge and stones is strongly associated with frequency and number of pregnancies.

Serum lipoproteins and triglycerides are three times elevated in pregnant women. Cholesterol is elevated 25–50 %, because of high estrogen rate. The limit of triglycerides is 300 mg/dL, and values that are needed to cause pancreatitis are as high as 750–1000 mg/dL

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(1, 6). The most common misdiagnosis of pancreatitis in the first trimester is hyperemesis. In women presenting with severe nausea and vomiting in the first trimester, consider obtaining amylase, lipase levels, and liver function tests which, when elevated, are diagnostic for pancreatitis.

## ACUTE PANCREATITIS DEFINITION

APIP is divided into three severity categories. Mild acute pancreatitis referred to pancreatitis without organ dysfunction or generalized complications. Moderate to severe pancreatitis referred to pancreatitis with transient organ dysfunction or localized/generalized complication within 48 hours after treatment. Severe pancreatitis referred to pancreatitis with persistent organ dysfunction or localized complications, including acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrosis and encapsulated necrosis (12). The generalized complication referred to two of the following: body temperature  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ ; white blood cell count  $> 12,000/\text{mm}^3$  or  $< 4000/\text{mm}^3$ ; heart rate  $> 90$  beats/minute, respiratory rate  $> 20$ /minute or  $\text{pCO}_2 < 32$  mmHg more than 48 hours after treatment. Acute gallstone pancreatitis was diagnosed by an increased alanine aminotransferase level  $> 150$  U/L within 48 hours of onset, as well as radiological evidence of abdominal US and magnetic resonance cholangiopancreatography (MRCP) (7). Hypertriglyceridemic pancreatitis is diagnosed based on Chinese guidelines for the management of acute pancreatitis (6) with either a serum triglyceride  $\geq 11.3$  mmol/L or serum triglyceride 5.65–11.3 mmol/L with a lipid turbidity appearance after excluding gallstone, alcohol or medication factors. Idiopathic pancreatitis was diagnosed with radiological evidence of pancreatitis after excluding gallstone, alcohol, hypertriglyceridemia, medication, trauma, autoimmune and surgical factors (7).

## DIAGNOSIS

The approach to pregnant patients with severe abdominal pain is very similar to that for non-pregnant

patients with acute abdomen. However, the physiologic changes associated with pregnancy must be considered when interpreting findings from the history and physical examination. Nausea, vomiting, constipation, increased frequency of urination, and pelvic or abdominal discomfort are frequently experienced in normal pregnancy.

The diagnosis of acute pancreatitis is often complicated by other obstetrical emergencies. Common clinical findings are sudden in onset, severe, constant abdominal pain and may radiate to the back, nausea, severe vomiting and general physical impairment. During physical exam, we can find epigastric tenderness and calm peristaltic, although it is difficult to interpret abdominal tenderness, muscular guarding and distention. The underlying inflammation has no direct contact with the parietal peritoneum, and this prevents the muscular response or guarding that would otherwise be expected (8). To help distinguish extra-uterine tenderness from uterine tenderness, examining with the patient in the right or left decubitus position displacing the gravid uterus to one side is helpful.

Diagnosis of APIP, based on Atlanta classification, requires two of the following three features: abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back), serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal characteristic findings or acute pancreatitis on contrast-enhanced CT and less commonly MRI or transabdominal US. Abdominal pain without elevated serum amylase/lipase activity requires imaging, while abdominal pain and positive enzymes does not require imaging (9).

US is probably the most frequently used radiologic modality for evaluating a pregnant abdomen. Also, it is the initial imaging technique of choice to identify a biliary etiology. Gallstones as a potential cause of AP are identified by abdominal US in most cases. Radiography and CT evaluation of patients who are pregnant is often a source of anxiety for the practicing clinician, although radiation exposure from a single diagnostic

procedure does not result in harmful fetal effects (10). Diagnostic endoscopic retrograde cholangiopancreatography is to be avoided whenever possible owing to the associated risks, including bleeding, perforation, pancreatitis and fetal radiation.

## TREATMENT

Initial treatment is supportive and includes intravenous fluids for hypovolemia, correction of electrolyte imbalances, glucose levels, calcium disturbances, withholding oral intake, nasogastric suction and total parental nutrition (11).

In evaluating pregnant patients with AP, the four important questions to be answered are: does the patient have AP; if it is AP, what is the predicted severity; is there a biliary etiology and what trimester of pregnancy is. The answer to the last question determines the choice of imaging studies and mode of therapy (12).

Patients with mild AP do not need antibiotics. In a pregnant patient, there are concerns with antibiotics being transplacentally transferred to the fetus with a risk of teratogenicity. Regardless of initial drug regimen, therapy should be modified to reflect the organisms recovered in blood cultures and the clinical status of the patient (4).

AP patients with gallstones need to be evaluated for early cholecystectomy to prevent recurrence of AP later on in the pregnancy when it could be more serious and dangerous. The second trimester is the best period for surgery since during this period organogenesis is complete, and the uterus is not big enough to obliterate the surgical view for laparoscopic approach. It has also been recognized that cholecystectomy during the second trimester is safe for both the mother and the fetus (13, 14).

The indications for surgery in pregnancy are severity of symptoms, obstructive jaundice, acute cholecystitis intractable to medical treatment and peritonitis. Although laparoscopy is accepted as safe, reports of

fetal demise after the procedure continue to occur in the literature (15). Several studies have indicated, however, that laparoscopic surgery can be safely performed on pregnant patients during any trimester, without an appreciably increased risk to the mother or fetus (16).

Pregnancy termination is made by experienced obstetricians and gastroenterologists after 34<sup>th</sup> week of pregnancy. The indications were confirmed fetal death in utero, obligation to use fetal-toxic medication for pancreatitis or organ failure. Approaches for pregnancy termination included Caesarean section, natural birth including pre-term and termed birth and natural or drug-induced abortion. Mode of delivery should also be decided by obstetric indications. If continuation of the pregnancy is expected to lead to maternal morbidity or mortality, delivery is indicated. If improvement of the maternal condition cannot be expected with delivery, treat the patient with the fetus in utero (3).

## CONCLUSION

Acute pancreatitis is rare in pregnancy, occurring most commonly in the third trimester. Among the various etiological factors for AP in pregnancy, gallstone disease is the most common one. Abdominal ultrasound, CT scan, endoscopic US, and MRCP are the available imaging studies in diagnosing a biliary etiology for AP. The general management of AP in pregnancy is supportive. Laparoscopic cholecystectomy is ideally performed in the second trimester when the risk to injure fetus is the least. We are limited with diagnostic and surgical therapy. Early diagnosis and good supportive care by multidisciplinary team are crucial to ensure good maternal and fetal outcomes.

## References

1. Pandey M, Shukla VK. Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. *Eur J Cancer Prev.* 2003; 12: 269-72.
2. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol.* 13 (4 Suppl 2): e1-15.
3. Elko B, Flis V, Breznik R. Akutni abdomen v nosečnosti. In: Žakelj V, Gadžijev EM, Flis V, et al. *Akutni abdomen.* Maribor: Založba Pivec; 2009.
4. Sivanesaratnam V. The acute abdomen and the obstetrician. *Baillieres Best Pract Res Clin Obstet Gynaecol.* 2000; 14 (1): 89-102.
5. Date RS, Kaushal M, Ramesh A. A review of the management of gallstone disease and its complications in pregnancy. *Am J Surg.* 2008; 196: 599-608.
6. Pancreas Study Group CSoG. Chinese guidelines for the management of acute pancreatitis (Shanghai, 2013). *J Clin Hepatol.* 29 (9): 656-60.
7. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013; 62 (1): 102–11.
8. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Guidelines for diagnostic imaging during pregnancy and lactation. *Obstet Gynecol.* 2016; 127 (2): e75-80.
9. Juneja SK, Gupta S, Virk SS, et al. Acute pancreatitis in pregnancy: a treatment paradigm based on our hospital experience. *Int J Appl Basic Med Res.* 2013; 3(2): 122-5.
10. Bank S, Singh P, Pooran N, et al. Evaluation of factors that have reduced mortality from acute pancreatitis over the past 20 years. *J Clin Gastroenterol.* 2002; 35: 50-60.
11. Swisher SG, Hunt KK, Schmit PJ, et al. Management of pancreatitis complicating pregnancy. *Am Surg.* 1994; 60: 759-62.
12. Swisher SG, Hunt KK, Schmit PJ, et al. Management of pancreatitis complicating pregnancy. *Am Surg.* 1994; 60: 759-62.
13. Date RS, Kaushal M, Ramesh A. A review of the management of gallstone disease and its complications in pregnancy. *Am J Surg.* 2008; 196: 599-608.
14. Carver TW, Antevil J, Egan JC, et al. Appendectomy during early pregnancy: what is the preferred surgical approach? *Am Surg.* 2005; 71 (10): 809-12.
15. Guidelines Committee of the Society of American Gastrointestinal and Endoscopic Surgeons. Guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy: this statement was reviewed and approved by the Board of Governors of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). *Surg Endosc.* 2008; 22 (4): 849-61.

# Lumen-Apposing Self-Expandable Metal Stent for Drainage of Pancreatic Fluid Collections: a Clinical Case

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**Key words:** endoscopy, lumen-apposing self-expandable metal stents, pancreatic fluid collections

## ABSTRACT

Pancreatic fluid collections (PFC) can be managed by a variety of options, including endoscopic, surgical and percutaneous drainage. Around 80% of patients with PFC are successfully treated by endoscopic treatment alone. Currently, metallic stents are used for PFC drainage. Lumen-apposing self-expandable metallic stents (LASEMS) are specifically designed to improve PFC drainage and cavity access. Double-pigtail stents may be placed through these metal stents to reduce migration rate and to reduce the risk of clogging in patients with an excessive amount of solid debris. We present a 54-year-old patient admitted to the Department of Gastroenterology at the University Medical Centre Ljubljana after pancreatitis that developed walled-off necrosis with superinfection. Initial extensive antibiotic treatment did not yield any results. Using the echoendoscope, we found a large collection adherent to the gastric wall. Under endoscopic ultrasound-guidance, LASEMS was placed to drain the PFC. For stent fixation, we also placed double-pigtail stent. Ultrasound exam showed walled-off necrosis regression and the patient was discharged two weeks later. Three weeks after discharge, the

patient developed sepsis and CT showed new PFC, which was managed by inserting second LASEMS and double-pigtail stent. Both PFCs were being irrigated endoscopically several times, and nasocystic catheter was also inserted for cyst irrigation. After a month of treatment, we removed one of the LASEMS and control CT showed complete regression of one of the PFC and extensive regression of the second PFC. The patient improved significantly and was discharged after two months.

## References

1. Douglas GA, Linda JT, Raza H, et al. A retrospective study evaluating endoscopic ultrasound-guided drainage of pancreatic fluid collections using a novel lumen-apposing metal stent on an electrocautery enhanced delivery system. *Endosc Ultrasound*. 2017; 6 (6): 389-93.
2. Bang JY, Hawes R, Bartolucci A, et al. Efficacy of metal and plastic stents for transmural drainage of pancreatic fluid collections; a systematic review. *Dig Endosc*. 2015; 7 (4): 486-98.

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# Interleukins-6, -8 and -10 in Predicting the Severity of Acute Pancreatitis – a Prospective Study from a Tertiary Institution

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## ABSTRACT

**Background.** Acute pancreatitis (AP) is acute inflammation of the gland that can extend to peripancreatic tissue and distant organs. Approximately 80% of patients suffer from edematous pancreatitis, a mild form of the disease, while 15–20% of patients develop necrotizing pancreatitis with various complications. The aim of the study was to determine the etiology of the disease, to evaluate the role of interleukins and different scoring systems in the course and outcome of the disease.

**Methods.** Patients with fulfilled diagnostic criteria for the diagnosis of AP (abdominal pain and at least a three-fold increase in activity of amylase and lipase) who were treated in the period from May 1, 2012, to January 31, 2015, were included. On admission and 48 hours later we analyzed extended laboratory parameters, including inflammatory markers and interleukins. Different imaging methods were performed during hospitalization. We built a severity scoring system by applying Ranson and Bedside Index of Severity in Acute Pancreatitis (BISAP) scores. By assessing these results and local and systemic complication, we classified AP according to

Atlanta classification into mild and severe. We performed a Mann-Whitney U test for comparison of independent samples (mild and severe course). A binomial logistic regression was performed to ascertain the effects of Ranson score and interleukins-6, -8 and -10 measured at admission and 48 hours later. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia, No. 36/11/09.

**Results.** In three-year period, 96 patients were treated, 59 (61.5%) males and 37 (38.5%) females, average age  $61.5 \pm 15.9$  years (range 22–91 years). The leading causes of AP were gallstones and alcohol consumption. The best predictor for severity of AP was interleukin-6, measured 48 hours after admission (AUC=0.84). Useful predictors of AP severity were also lactate dehydrogenase ( $p < 0.001$ ), serum glucose ( $p < 0.006$ ), difference in thrombocytes between the first and the third day ( $p < 0.001$ ), haemoglobin ( $p < 0.027$ ) and erythrocytes ( $p < 0.029$ ). Three patients (3%) died due to multiple organ failure.

**Conclusions.** Gallstones and alcohol are the most common causes of AP in our patients. The values of interleukin-6 and Ranson score are important for prediction of the severity of AP.

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## References

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013; 62: 102-11.
2. Papachristou GI, Muddana V, Yadav D, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol*. 2010; 105: 435-41.
3. Gunjaca I, Zunic J, Gunjaca M, et al. Circulating cytokine levels in acute pancreatitis-model of SIRS/CARS can help in the clinical assessment of disease severity. *Inflammation*. 2012; 35: 758-63.
4. Fisić E, Poropat G, Bilic-Zulle L, et al. The role of IL-6, 8 and 10, sTNF $\alpha$ , CRP and pancreatic elastase in the prediction of systemic complications in patients with acute pancreatitis. *Gastroenterol Res Pract*. 2013; 2013: 282645.
5. Skok P, Čeranić D, Genslitskaya E. Acute pancreatitis – results of a prospective study. *Zdrav Vestn*. 2008; 77: 573-8.

# The Dynamics of Acute Necrotic Collections Quantified with Texture Analysis

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**Key words:** acute necrotic collections, texture analysis

## ABSTRACT

**Background.** Pancreatic fluid collections are seen in up to 50% of cases of acute pancreatitis. Acute necrotic collections consist of inhomogeneous mixture of liquefied, necrotic fatty tissue along with solid pancreatic and extra-pancreatic debris. They may gradually resolve or persist as walled-off necrosis – a homogeneous well-demarcated fluid collection. However, quantification of changes in these collections has never been performed. We propose a texture analysis of these collections as a quantitative description of changes in acute necrotic collections.

**Methods.** In our retrospective study, we included all patients with acute necrotizing pancreatitis that were hospitalized at the Department of Abdominal Surgery, University Medical Centre Ljubljana from January 2016 until October 2017. All patients with two or more successive CT examinations and acute necrotic collections present on CT examinations were included. The analysis of CT images was performed at the Institute of Radiology, University Medical Centre Ljubljana. Two blinded radiologists analyzed all the images and determined heterogeneity of peripancreatic collections with LIFEx software sys-

tem. Periodic change of heterogeneity of peripancreatic fluid was determined with paired samples t-test.

**Results.** There were 19 patients in our group, 13 men (68%) and six women (32%). Fifty CT examinations were performed (mean 2.6 per patient, range 2–4 per patient). The median difference between the first and the last examination was 22 days (range 3–190 days). A texture analysis of one collection per examination was performed; altogether 19 fluid collections were analyzed (one per patient). The mean change in entropy was 7% (3.90 versus 3.62,  $p < 0,001$ ). The intraobserver agreement was calculated and will be reported in the final version.

**Conclusions.** Texture analysis of acute pancreatic necrotic collections is a feasible method capable of quantitative description of an evolution of acute necrotic collections with a decrease in entropy and increase in homogeneity. This finding has a potential role to help clinicians decide about further treatment options and finding the right timing for interventional or surgical procedure. Further studies with bigger sample size are needed to confirm this data.

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# Septic Shock in Severe Acute Pancreatitis, Treated with Cytosorb-Case Series

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**Key words:** pancreatitis, septic shock, cytokines, CytoSorb

## ABSTRACT

Severe acute pancreatitis can lead to systemic inflammatory response and multiple organ failure, associated with high mortality. Serum interleukin-6 and interleukin-8 levels appear to be correlated with severity of pancreatic inflammation. CytoSorb, cytokine adsorber, is indicated in situations where cytokines are elevated. In one-year period, four patients with severe acute pancreatitis were admitted to surgical intensive care unit. On admittance, they met criteria for septic shock and APACHE II score  $\geq 30$ . Creatinine clearance was reduced; values of urea, creatinine, lactate, C-reactive protein and procalci-

tonin were elevated in all patients. We treated the patients according to Surviving Sepsis Guidelines (fluid resuscitation and administration of norepinephrine for mean arterial pressure  $> 70$  mmHg). After CT scan confirmed necrotizing pancreatitis, patients were operated within 24 hours. Postoperatively patients become anuric and inflammatory parameters further increased. Haemodialysis was performed, but only on the median of six days after septic shock confirmation, CytoSorb was installed to the device. Patients received 2–3 consecutive treatments, lasting for 10–12 hours. Despite CytoSorb use and initial decline in interleukin-6 values, the condition of all four patients worsened.

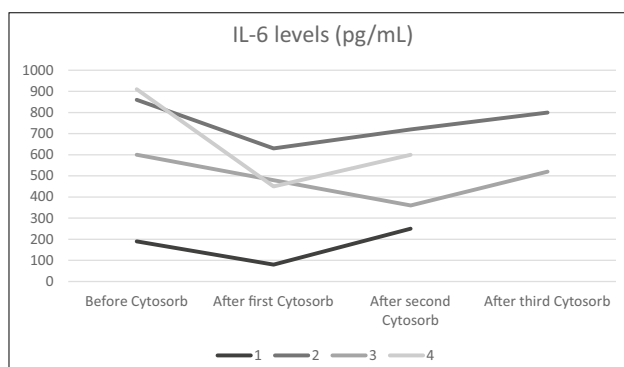


Figure 1. Plasma levels of interleukin-6 after CytoSorb treatment in patients 1 to 4. IL-6 – interleukin-6.

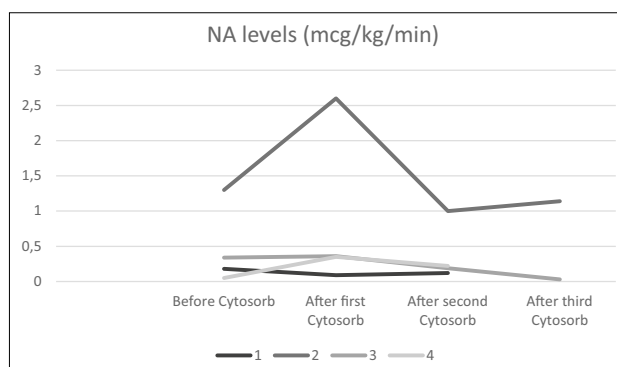


Figure 2. Noradrenaline demand after CytoSorb treatment in patients 1 to 4. NA – noradrenaline.

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Interleukin-6 values rose again, and all patients died. Researchers claim that earlier (within 24 hours) aggressive intervention during the onset of organ failure leads to more successful outcomes whereas the delay in the start of the therapy has poor response. The reason for ineffective treatment in our patients could be delayed CytoSorb use, patients' age and advanced pancreatic inflammation. We confirmed the opinion of other authors that Cytosorb treatment should be initiated immediately after the confirmation of a septic shock and multiple organ failure, before the irreversible organ and organ systems malfunction appear.

## References

1. Nieminen A, Maksimow M, Mentula P, et al. Circulating cytokines in predicting development of severe acute pancreatitis. *Critical Care*. 2014; 18 (3): R104.
2. Gomez-Cambronero LG, Sabater L, Pereda J, et al. Role of cytokines and oxidative stress in the pathophysiology of acute pancreatitis: therapeutic implications. *Curr Drug Targets Inflamm Allergy*. 2002; 1 (4): 393-403.
3. CytoSorbents™ [internet]. Berlin: CytoSorbents Europe GmbH; c2018 [accessed 2018 Feb 5]. Retrieved from: <http://cytosorbents.com/products/cyto-sorb/>
4. Kogelmann K, Jarczak D, Scheller M, et al. Hemoadsorption by CytoSorb in septic patients: a case series. *Critical Care*. 2017; 21 (1): 74.
5. Schadler D, Pausch C, Heise D, et al. The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. *PLoS One*. 2017; 12 (10): e0187015.

*Table 1. Patient characteristics, laboratory values and calculated parameters at admission to intensive care unit. APACHE II – Acute Physiology and Chronic Health Evaluation, CrCl – creatinine clearance, CRP – C-reactive protein, PCT – procalcitonin, PaO<sub>2</sub> – arterial oxygen partial pressure, FiO<sub>2</sub> – fractional inspired oxygen, SOFA – sequential organ failure assessment.*

Patient	Age	APACHE II		CrCl (mL/min)	Lactat	CRP	PCT	PaO <sub>2</sub> /FiO <sub>2</sub>	SOFA
1	71	30		20	1.85	72	1.64	10.2/30	19
2	75	41		15	1.35	103	0.77	13.8/40	12
3	74	38		34	11.6	194	25.83	12.5/60	18
4	72	36		31	22	322	9.28	14/40	14

*Table 2. Values before CytoSorb treatment. APACHE II – Acute Physiology and Chronic Health Evaluation, NA – noradrenaline, CrCl – creatinine clearance, CRP – C-reactive protein, PCT – procalcitonin, PaO<sub>2</sub> – arterial oxygen partial pressure, FiO<sub>2</sub> – fractional inspired oxygen, SOFA – sequential organ failure assessment, IL-6 – interleukin-6.*

Patient	APACHE II	NA (mcg/kg/min)	CrCl (mL/min)	Urea	Creatinine	Lactate	CRP	PCT	PaO <sub>2</sub> /FiO <sub>2</sub>	SOFA	IL6
1	30	0.18	22	11	139	3.2	116	2.91	11.7/30	18	190
2	48	1.3	13	47	364	13	104	7.24	12.5/70	20	860
3	36	0.34	21	13.5	255	2.3	264	36.76	9.5/60	20	600
4	30	0.05	20	28.5	170	5	58	2.83	9.9/50	20	910

# The Rationale for Programmed Abdominal Lavage in Acute Pancreatitis

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**Key words:** surgical debridement in acute pancreatitis, abdominal lavage

## ABSTRACT

Surgical lavage and necrosectomy used to be a standard treatment for both, sterile and infected necroses due to acute pancreatitis for decades. However, an early surgical lavage and necrosectomy in patients with sterile acute pancreatitis leads to the increased mortality and increased rate of perioperative complications. Since the surgical necrosectomy and lavage of the abdominal cavity in sterile necrosis following acute pancreatitis may lead to the infection, it is not advised as the treatment of choice. On the other hand, encouraging results were reported in patients with acute pancreatitis that were treated in conservative setting. There is also a promising attitude in the treatment of infected necrosis following acute pancreatitis using minimally invasive techniques such as endoscopic and percutaneous retroperitoneal drainage and lavage with satisfactory results. The rate in mortality and complications is lower than in patients treated with early surgical necrosectomy and lavage. However, surgical treatment is required in cases of infected necrosis where all other conservative and minimally invasive treatment patterns failed. It may be required even in cases of sterile necrosis

with the ongoing multiple organ failure. It is advised to postpone surgical intervention until the necrosis becomes walled-off if the patient's condition allows it. In cases of abdominal compartment syndrome, ongoing bleeding, bowel ischemia, and ongoing gastric outlet and bowel obstruction 4–8 weeks after acute pancreatitis onset, the surgical intervention is ultimate.

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# Pancreaticopleural Fistula – a Rare Complication of Pancreatitis

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**Key words:** pancreaticopleural fistula, pleural effusion, pancreatitis, complications

## ABSTRACT

Pancreaticopleural fistula is a rare complication of acute and chronic pancreatitis with an estimated incidence of 0.4% of patients with pancreatitis. It is caused by an inflammatory injury to the pancreatic duct which results in pancreatic duct disruption. This enables leakage of pancreatic secretions through the retroperitoneum into the pleural cavity, causing massive pleural effusion. Pancreaticopleural fistula poses a diagnostic problem since it typically presents with thoracic symptoms. Elevated amylase levels in pleural effusion is a characteristic finding. Besides, magnetic resonance cholangiopancreatography is an important diagnostic tool delineating pancreatic duct anatomy and guiding the management based on the extent of ductal changes (dilatation, disruption, obstruction). Due to its rarity, there is a lack of research opportunity to establish the optimal treatment. Initial conservative approach is currently employed with surgical treatment being the last resort in case of medical and endoscopic therapy failure. However, several studies support early surgical intervention since it reduces recovery time and has a higher success rate. We describe a case of a 64 year-old man who was transferred to our department from a peripheral hospital due to non-specific chest pain and undefined left-sided pleural effusion. CT examination revealed pancreatic pseudocyst with fistulous commu-

nication into the pleural cavity. Magnetic resonance cholangiopancreatography could not be performed due to pacemaker implantation. The patient was initially treated with repeated thoracocentesis and somatostatin-14 administration followed by several unsuccessful attempts of pancreatic duct stenting with endoscopic retrograde cholangiopancreatography. Since no clinical improvement was observed, the patient was finally treated surgically one month after the treatment was initiated. A cholecystectomy with necrosectomy and closure of the fistula was performed. After prolonged hospitalisation, the patient eventually recovered and remained clinically well during the outpatient follow-up four months postoperatively.

## References

1. Rockey DC, Cello JP. Pancreaticopleural fistula: report of 7 patients and review of the literature. *Medicine (Baltimore)*. 1990; 69 (6): 332-44.
2. Roberts KJ, Sheridan M, Morris-Stiff G, et al. Pancreaticopleural fistula: etiology, treatment and long-term follow-up. *Hepatobiliary Pancreat Dis Int*. 2012; 11 (2): 215-9.
3. Francisco E, Mendes M, Vale S, et al. Pancreaticopleural fistula: an unusual complications of pancreatitis. *BMJ Case Rep*. 2015; 2015: bcr2014208814.
4. Tay CM, Chang SKY. Diagnosis and management of pancreaticopleural fistula. *Singapore Med J*. 2013; 54 (4): 190-4.
5. King JC, Reber HA, Shiraga S, et al. Pancreatic-pleural fistula is best managed by early operative intervention. *Surgery*. 2010; 147 (1): 154-9.
6. Wronski M, Slodkowski M, Cebulski W, et al. Optimizing management of pancreaticopleural fistulas. *World J Gastroenterol*. 2011; 17 (42): 4696-703.

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# Ethical Dilemmas in the Treatment of Acute Pancreatitis

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## INTRODUCTION

Acute pancreatitis (AP) poses many professional as well as ethical dilemmas. Some of them are common, but each case has its problems that should be considered. Knowledge, technical ability, and ethical integrity are expected in surgeons, who should follow the four ethical principles (according Beauchamp and Childress):

- **Respect for autonomy:** respecting the decision-making capacities of autonomous persons, enabling individuals to make reasoned, informed choices.
- **Beneficence:** balancing the benefits of treatment against the risk and costs, acting in a way that benefits the patient.
- **Non-maleficence:** avoiding the causation of harm; all treatments involve some harm, but it should not be disproportionate to the benefits of treatment.
- **Justice:** distributing benefits, risks, and costs fairly; the patients in similar positions should be treated similarly.

## ABOUT ETHICS

Ethics is an essential discipline in the practice of surgery and represents the surgeon's best understanding of moral responsibility. Ethics requires an ability to distinguish degrees of value or lack thereof and evolves as reasoned reflection on clinical experience (Tamerla Chavis and Joann Starr).

Physician's responsibilities are:

- explanation of the patient's disease,
- explanation of untreated natural history,
- recommendation of most appropriate treatment,
- discussion of risks and benefits,
- discussion of anticipated outcome and
- discussion of treatment alternatives.

In AP, the patient's consciousness – his/her awareness of the severity of the disease – may sometimes represent a problem. Is the patient competent to decide clearly what does he/she want? If he/she is not competent, a surgeon should consider what course of action is in the patient's best interest.

## **SPECIFICS OF ACUTE PANCREATITIS**

AP is of benign nature, and therefore, there is a high probability of the patient recovering fully after the treatment. However, unpredictable (almost malignant) clinical course can occur with high mortality (3–17%) of treatment and with considerable costs. And because of its benign nature, AP poses several complex ethical issues. Patient autonomy and choice of treatment demands complex understanding and consciousness.

### **Diagnosing staging and severity**

Like with all other pathologies, a rational use of diagnostic investigations and tools is expected in AP. Therefore, decisions regarding certain investigations should be reached after consulting other involved specialists. It should be clear that what is professionally competent is also ethically justifiable. And it is always necessary to define and determine severity of the AP, using criteria like Acute Physiology and Chronic Health Evaluation (APACHE) II score. Following the staging criteria, the severity of disease should be defined and appropriate treatment planned!

### **Initial treatment and the relations between involved specialists**

Treatment of AP, always being conservative at the beginning, depends on the stage of the disease. In severe cases, the treatment should be in intensive care unit because the patient needs a complex support. Ethical issues sometimes emerge; they include who is responsible for the patient, or who should run the plan of treatment. Sometimes ethical problems may happen when there is a pressure from the intensivist doctor to operate the patient in the initial stage of disease because of some deterioration and supposed complication. In such cases, a sensible consultation and sober judgment are necessary. In an intensive care unit, both specialists are responsible for the surgical patient. Early surgical intervention is very rarely needed and has had poor results and high mortality. But we should keep in mind that complications such as bleeding ischemia, gangrene, and perforation are neverthe-

less possible. Decision-making may so be quite difficult. In such situations, the surgeon should also explain the situation to the patient and obtain consent after disclosure of all possible outcomes!

### **Feeding**

It was accepted that inside 48 hours after admission, a nasoenteral tube should be administered. Despite the evidence of its benefit, enteral feeding still creates some dilemmas because of possible bowel distension and paresis. Therefore, some doctors would feel uncomfortable introducing it. But since its benefit needs to be weighed against possible damage, it can represent not only a professional but also an ethical dilemma.

### **Complications and treatment decisions**

Within hours to days from the onset of AP, some complications may develop shock, pulmonary failure, renal failure, gastrointestinal bleeding, or multiple organ failure. A benign disease can become very serious, and appropriate decisions about how to manage the complications are crucial. Therefore, the treatment decisions should also consider the ethical view of the situation: how to inform the patient about becoming extremely handicapped, how to get his agreement with planned treatment, should his relatives be already involved, etc.

In biliary pancreatitis with cholangitis, endoscopic retrograde cholangiopancreatography should be performed within 24 hours, and patient's consent should be obtained before the procedure.

When timing the cholecystectomy, the necessity of the procedure should be explained to the patient and his/her consent obtained.

In necrotizing AP after infected necroses are confirmed, a step-up approach (percutaneous drainage followed by minimally invasive retroperitoneal necrosectomy) is recommended. Again, some ethical issues are disclosed. Some surgeons still prefer open necro-

sectomy, and as it is a benign disease, ethical concerns may arise because conflicting opinions may come from other colleagues.

Considerable ethical questions may arise in cases of pancreatic duct disruption with leakage. Decisions regarding treatment are often connected with ethical problems. Should the patient be treated endoscopically or surgically? When and what to do – distal pancreatectomy, pancreaticoduodenectomy (Whipple procedure)? How to manage the situation considering investigations and treatment possibilities in the institution, as well as the skill of the doctors involved in the treatment? Sometimes even transport to another institution should be considered and all these also raise ethical questions.

### **The timing of surgical interventions**

A surgical intervention with minimally invasive or conventional open techniques is indicated when an anatomic complication amenable to a mechanical solution is present. In acute necrotizing pancreatitis, the necrotic phlegmon is excised to limit a potential site of sepsis. In 'hemorrhagic' pancreatitis, surgical control of bleeding is necessary. Depending on the situation and local expertise, this situation may require an interventional radiologist, an interventional endoscopist, or a surgeon (individually or in combination). Professional competence should include essential ethical principles (the four principles).

### **CONCLUSION**

AP is a benign disease with an unpredictable (sometimes almost malignant) clinical course and therefore poses several complex ethical issues. When treating AP, surgeons should consider the four ethical principles: respect for autonomy, beneficence, non-maleficence, and justice. Rational use of diagnostic investigations and tools is not only a professional but also an ethical requirement. Relations with the intensivist doctor and other specialists sometimes generate ethical problems. A sensible consultation and sober judgment are necessary. Considerable ethical questions

may also arise when planning the treatment of complications.

### **UNEXPECTED COMPLICATIONS IN TREATING A JEHOVAH'S WITNESS PATIENT**

Informed consent is obtained for a premeditated surgical intervention to remove infected pancreatic necroses in a Jehovah's Witness patient. The patient refuses a blood transfusion during the informed consent process.

While performing debridement of pancreatic necroses, profuse excessive bleeding occurs, the patient deteriorates, and his blood pressure becomes difficult to maintain. Urgent blood replacement is needed. The patient is sedated and cannot participate in the discussion and amendment of the informed consent. The patient's wife is not a Jehovah's Witness and permits transfusion if necessary.

- a) Assume that the patient did not fully realize that he could die without a transfusion, and proceed to transfuse as clinically indicated.
- b) Since it is an open emergency procedure, transfuse.
- c) Transfuse on the wife's authority.
- d) Transfuse and do not tell the patient.
- e) Do not violate the patient's autonomy by transfusing even if that means the patient may die.