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Long-Term Outcome After Acute Pancreatitis

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Introduction

Most patients with acute pancreatitis recover completely without any further symptoms or morphological alterations within days or weeks after discharge. This observation was described in the original definition of acute pancreatitis by the Consensus Symposium 1963 in Marseille [1]. However, recent reports on long-term outcome after acute pancreatitis show growing evidence that there is a certain risk for late pancreatitis-associated complications even after mild clinical courses [2–5].

Functional impairments can occur immediately or even years after sustaining acute pancreatitis [2,3,5–8], specifically loss of endocrine function resulting in diabetes mellitus type 3 or exocrine insufficiency with the need for pancreatic enzymes substitution, have been described in numerous studies [2,9–11]. Etiology or severity of the index episode are not clearly associated with the overall risk for an impairment of pancreatic function. In addition, episodes of pain with a considerable impact on quality of life can occur at any point of time after the initial event of acute pancreatitis. These possibly recurrent pain sensations bear a high risk for chronification and may be associated with recurrent pancreatitis; there is also a certain overlap with clinical courses of chronic pancreatitis [2,5,12,13]. This latter correlation has been examined in several recent publications [2–5,14–20]. It is sometimes difficult to distinguish between the primary episode of acute pancreatitis as a symptom of a chronic disease and chronic pancreatitis developing as a long-term consequence of pancreatitis. Morphological characteristics (i.e., those found in cross-sectional imaging at the initial episode of pancreatitis) can be useful for this differentiation as preexisting signs of subclinical chronic pancreatitis may be found in terms of fibrosis or calcifications and can be clearly distinguished from typical signs of new-onset acute pancreatitis.

In contrast to chronic pancreatitis, little is known about histomorphologic pathways and alterations of recurrent acute pancreatitis. One hypothesis is the so-called necrosis–fibrosis sequence [21], which suggests that acute inflammatory changes after an initial and acute damage of the pancreas result in mesenchymal cell activation with various patterns of subsequent fibrosis development and obstruction of pancreatic ducts. Another model is based on a "sentinel acute pancreatitis event (SAPE)," postulating a long-lasting intrapancreatic activation of immunomodulatory and stellate cells during the index episode. These alterations lead to hypersensitivity of the pancreas when responding to potential stimuli, resulting in recurrent attacks of acute and eventually chronic pancreatitis [22]. Despite these hypotheses, the possible pathophysiologic link between acute and chronic pancreatitis remains controversial and is not well understood [23].

Because there are no follow-up guidelines for clinical examinations and imaging after acute pancreatitis and histopathologic findings for such patients are rare due to the infrequent need for operations with respective tissue harvesting, the frequency of such alterations is unknown. In available cross-sectional imaging, alterations of the pancreatic duct, parenchyma, or surrounding areas (i.e., formation of pseudocysts or fluid collections) can be observed during both short- and long-term courses. These morphological findings may be correlated with the severity of the first attack and the type of treatment, in particular interventional or surgical necrosectomy.

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Their extent and the underlying initial etiology of the primary acute pancreatitis episode determine clinical outcome patterns. In alcohol-related acute pancreatitis a recurrent and eventually chronic course is observed more often than it is in a biliary genesis of the disease [13,15,19,20]. This fact underlines the importance of avoiding further exposure to risk factors such as alcohol and nicotine as a basic precaution following a first pancreatitis episode [14,24,25]. Furthermore, patient education can be regarded as a simple method to reduce the lifelong risk of recurrence and associated healthcare costs [20,24]. Follow-up examinations should therefore address the above-mentioned topics and should include clinical and laboratory as well as imaging examinations, when necessary. This chapter gives an overview of the long-term sequelae of acute pancreatitis with regard to risk factors, diagnosis, and management.

Risk Factors

Risk factors for long-term complications of acute pancreatitis have been examined in several cohort studies in recent years [4,5,7,14]. With regard to recurrent episodes of acute pancreatitis, a recent meta-analysis including nearly 8500 patients showed an overall risk of 22% with a nearly twofold increase in alcoholic etiology (38%) and a lower risk for biliary etiology (17%) [4]. With regard to biliary etiology, early removal of the gallbladder after the index episode of pancreatitis reduces the risk of recurrence [5,14]. In nonbiliary etiology, persistence of smoking and alcohol consumption are well-documented risk factors for both recurrent acute episodes as well as progression of primary acute to chronic pancreatitis in the long term [5,7,14]. Nevertheless, some authors report experience with patients who show a progression to chronic pancreatitis despite stopping consumption of alcohol and nicotine [14,15]. In addition, male patients seem to have a higher risk of progression to chronic pancreatitis, even when lifestyle-associated risk factors are excluded [4]. Risk factors for functional failure after acute pancreatitis include preceding necrosectomy, which leads to both exocrine and endocrine insufficiency due to the procedure-associated loss of tissue itself and the disease-specific damage to the remaining tissue [5,26,27]. Again, the risk for developing progressive pancreatic dysfunction and diabetes mellitus or exocrine dysfunction is increased in men [4,6]. Moreover, a subset of patients may also have unrecognized genetic risk alterations leading to increased risk of progressive pancreatic failure and chronic pancreatitis through an effect on trypsinogen activation [28]. Tables 37.1 and 37.2 summarize studies on patterns and risk factors for long-term sequelae after acute pancreatitis.

Endocrine Pancreatic Dysfunction

Hyperglycemia, impaired glucose tolerance, and diabetes mellitus occur frequently as a consequence of acute pancreatitis and have therefore been investigated as primary or secondary endpoints of several large studies on the loss of pancreatic function on long-term follow-up. A recent review analysed 34 studies focusing on diabetes mellitus after acute pancreatitis [3]. The authors concluded that especially pancreatic diabetes mellitus (type III) and impaired glucose metabolism after acute pancreatitis are increasingly recognized clinical findings requiring more detailed research on it as the published data are inconsistent. Of interest, one of two included meta-analyses had examined 24 prospective studies published between 1968 and 2009, and revealed that nearly 40% of patients showed a prediabetic metabolic situation or a full clinical manifestation of diabetes mellitus [2]. Within 12 months after the index episode of acute pancreatitis the prevalences of hyperglycemia and diabetes mellitus were 19% and 15%, respectively. After a 5-year observation period, the risk for diabetes mellitus showed a twofold increase compared with the prevalence after 12 months. A Dutch cohort study on 669 patients described a new onset of diabetes mellitus in 20% of the patients during a median follow-up time of 57 months [7]. These data are consistent with findings of a Taiwanese study, which showed a comparable twofold increase of diabetes risk after 10 years in nearly 3000 acute pancreatitis patients, regardless of the severity of the initial course of the disease [6].

In severe courses characterized by extensive parenchyma necrosis and the need for necrosectomy, the correlation between loss of tissue and function seems to provide an explanation for these observations, especially when the body and tail of the pancreas are affected. Decay of a considerable amount of islets predisposes for functional deterioration and 15–30% of patients undergoing extensive necrosectomy show insulin-dependency soon after recovery [5]. This is comparable to outcomes following distal pancreatectomy for other indications, with a rate of postoperative diabetes mellitus of approximately 10% [30–32], and underlines the relevance of the pancreatic body and tail for the endocrine function of the gland due to the pronounced location of islet cells in these segments of the pancreas. In contrast, the pathophysiologic explanation for mild episodes of acute pancreatitis resulting in endocrine insufficiency and an increased risk of diabetes mellitus remains unclear.

Exocrine Dysfunction

In the early phase after acute pancreatitis, exocrine function is often compromised and is easily diagnosed

Table 37.1 Patterns of long-term sequelae after acute pancreatitis.

Author, year, country, observation period	Patients (*n*) etiology	Diabetes mellitus *n* (%)	Exocrine dysfunction *n* (%)	Recurrent pancreatitis *n* (%)	Chronic pancreatitis *n* (%)	Median follow-up
Pelli [15], 2000, Finland, 1972–1991	562 alcoholic	nm	nm	260 (46%)	nm	38 months
Lund [19], 2006, Sweden, 1995–1998	138 alcoholic: 61 biliary: 48	nm	nm	41% nonbiliary vs. 10% biliary	nm	6 years
Yasuda [29], 2008, Japan, 1990–2006	45 alcoholic: 23 biliary: 10	16 (36%)	18 (40%)	8 (18%)	8 (18%)	56 months
Nøjgaard [18], 2011, Denmark, 1977–1982	352 alcoholic: 129 biliary: 44	nm	nm	Nm	85 (24%) alcoholic: 41 (48%)	nm
Castoldi [16], 2013, Italy, 2001–2003	631 alcoholic: 36 biliary: 439	22 (3.5%)	16 (2.5%)	80 (13%)	nm	52 months
Yadav [20], 2014, USA, 1996–2005	6010 alcoholic: 1223 biliary: 1647	nm	nm	1950 (32%) with at least 1 readmission due to pancreatitis		39 months
Ahmed Ali [7], 2016, Netherlands, 12/2003–03/2007	669 alcoholic: 153 biliary: 384	136 (20%)	34 (5%)	117 (17%)	51 (8%)	57 months
Tu [17], 2017, China, 1995–2016	113 alcoholic: 3 biliary: 65	34 (30%) +impaired glucose tolerance 33 (29%)	40 (35%)	nm	nm	30 months
Karjula [25], 2019, Finland, 1995–2012	1644 alcoholic:1173 biliary: 217	nm	nm	510/1173 alcoholic (44%) 104/471 nonalcoholic (22%)	nm	114 months
Maatman [27], 2020, USA, 2005–2017	647 necrotizing alcoholic: 133 biliary: 317	195/549 (35%)	108/571 (19%)	nm	93/571 (16%)	46 months

nm, not mentioned.

by clinical symptoms of diarrhea, steatorrhea, and maldigestion. In the long term, the reported prevalence rates of exocrine dysfunction differ considerably in the available studies [5,7,26,33]. A study by Sand and Nordback reports 25% of patients having exocrine failure after necrosectomy in a follow-up period of 2–5 years [5], whereas other studies with comparable observation times reported much higher rates of 55% after mild and up to 83% after severe courses, independent of the etiology of acute pancreatitis [33–35].

Symptoms of exocrine failure can be controlled very well in most patients by oral enzyme replacement to prevent maldigestion, malabsorption, and consecutive malnutrition. Supplementation of the diet with fat-soluble vitamins in the follow-up period should also be considered [36]. A discontinuation of enzyme supplementation may be possible as several studies have reported a potential for long-term recovery of exocrine function within 12–24 months after acute pancreatitis [5,34], which is comparable to the functional recovery often observed after pancreatic resections for other indications.

Table 37.2 Risk factors for long-term complications of acute pancreatitis.

Author, publication year, country, number of patients Long-term complications	Lankisch [14], 2009, Germany, 532	Ahmed Ali [7], 2016, Netherlands, 669	Yasuda [29], 2008, Japan, 45	Nøjgaard [18], 2011, Denmark, 352	Sankaran [4], 2015, meta-analysis, 8492	Shen [6], 2015, Taiwan, 2966	Karjula [25], 2019, Finland, 1644	Tu [17], 2017, China, 113	Nikkola, [8], 2017, Finland, 77
Recurrent acute pancreatitis	Age >40 years, male, biliary etiology without subsequent cholecystectomy	Younger age, nonbiliary etiology, smoking, pancreatic necrosis	Severity of initial attack	Smoking	nm	nm	alcohol	nm	nm
Progression to chronic pancreatitis	Alcohol consumption, heavy smoking, recurrent acute pancreatitis	Nonbiliary etiology, smoking, pancreatic necrosis	Severity of initial attack	nm	Alcohol, smoking, men > women	nm	nm	nm	nm
Death related to acute pancreatitis	nm	nm	nm	nm	nm	nm	alcohol	nm	Recurrent acute pancreatitis
Diabetes mellitus	nm	nm	nm	nm	nm	Men > women (HR 3.21 vs. 1.58)	nm	Pancreatic necrosis >50%	Recurrent acute pancreatitis

OR: odds ratio; HR: hazard ratio; nm: not mentioned.

Recurrent Pancreatitis and Chronic Pancreatitis

Regarding the frequency and timeline of progressive pancreatic disease after acute pancreatitis, about 20% of all patients and 50% of patients with an alcoholic etiology show recurrent episodes within 10–20 years, but most recurrences occur during the first years after the initial attack [4,5,7]. Overall, 1 out of 10 patients will suffer from a progression to chronic pancreatitis [4], which may be associated with few symptoms for a long period but may finally result in end-stage findings of chronic pancreatitis despite a subclinical course (Fig. 37.1). In the case of recurrent acute episodes, the risk of progression to chronic pancreatitis shows a three- to fourfold increase, which is, again, pronounced in patients with an underlying alcoholic etiology [7].

Quality of Life and Pain

Several outcome studies report on the occurrence of pain and the quality of life after acute pancreatitis [5,7,12,13]. An observational study on 145 patients from Finland showed no impairment of quality of life, regardless of pancreatitis etiology, compared to the general population [12]. Similar results are shown in several smaller observational studies, even after necrosectomy [5]. In contrast, in a Polish study patients suffering from severe alcohol-induced acute pancreatitis showed a reduced quality of life in comparison to those with a biliary origin of the disease with regard to social and family life as well as emotional well-being [13]. How far persisting alcohol consumption after the index episode of pancreatitis contributes to these findings, however, remains unclear from the study data. With regard to chronic pain, a large Dutch cohort study including 669 patients found that 13% had recurrent episodes of pain related to acute pancreatitis [7]. A recent large US analysis observed 647 patients with necrotizing pancreatitis, who were treated and followed up in a single center [27]. The authors describe less commonly reported long-term complications such as chronic pain in 8%, strictures of the bile duct (16%), the pancreatic duct (5%), or the duodenum (5%) as well as splanchnic vein thrombosis (45%). Of interest, 340 (59%) patients developed complications that needed invasive intervention after completely recovering from necrotizing pancreatitis [27].

Incisional Hernia

With the implementation of minimally invasive management of infected pancreatic necrosis during the initial episode of acute pancreatitis, open surgical interventions have considerably decreased and are regarded as the last resort in modern treatment concepts [37,38]. Less than 5% of patients with acute pancreatitis need to

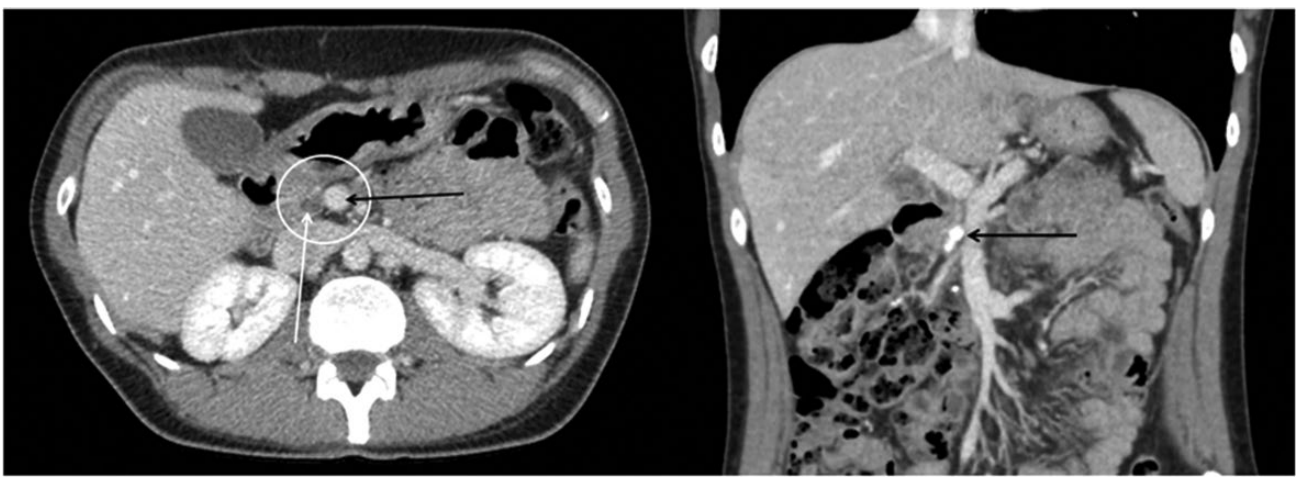

Figure 37.1 A 39-year-old female patient 9 years after a solitary episode of severe acute pancreatitis following hemorrhagic shock and acute respiratory distress syndrome (ARDS) due to atonic bleeding after cesarean section. This was followed by complete recovery and primary discharge from hospital after 5 weeks and complete remission of residual pseudocysts over a 6-month period. Afterwards, the patient had no clinical symptoms for 8 years before recurrent abdominal pain attacks irradiating to the back occurred. CT scan revealed nearly complete atrophy of the pancreatic parenchyma (left side, white circle; black arrow: portal vein, white arrow: bile duct) and a calcification in the pancreatic head (right side, black arrow). As no signs of inflammation, tumor suspicion, or endocrine insufficiency were present, symptomatic treatment was successful (oral enzyme replacement and analgesia).

be treated by open surgery (e.g., in case of unsuccessful minimally invasive necrosectomy, for bleeding control, or due to organ perforation). These patients show a high rate of surgical site infections (80%) [34] and a correlating high risk of developing an incisional hernia (21–40%) [27, 40]; surgical reintervention is often required for symptomatic, functional, and cosmetic aspects of these, often large, hernias.

Pancreatic Cancer and Pancreas-Related Death

In general, death related to acute pancreatitis, besides short-term mortality during a severe necrotizing course, seems to be rare and not related to progression to chronic pancreatitis and finally pancreatic cancer. A German study reported on four deaths of pancreatic cancer in 532 patients (0.8%) observed after acute pancreatitis during an average follow-up of 7.8 years, which occurred 9–56 months after acute pancreatitis, none of them with a diagnosis of chronic pancreatitis [14]. In an Italian study, 3 of 631 patients (0.5%) died of pancreatic cancer 5, 6, and 19.9 months after acute pancreatitis with unknown etiology in the first case and biliary etiology in the others [16]. These data support the conclusion that the initial pancreatitis event may be a symptom of an already existing tumor rather than pancreatic cancer and the related mortality is a long-term consequence of acute pancreatitis. A recent study on 1644 patients from Finland showed, that after an acute episode of alcohol-induced pancreatitis with the need for hospitalization, long-term mortality was four times higher than that in an age- and sex-matched control population [25]. The most common cause of death was pancreatic cancer in patients with nonalcoholic acute pancreatitis, while patients with alcoholic pancreatitis died mostly by alcohol-related diseases.

Imaging Findings

Most episodes of mild acute pancreatitis do not result in any morphologic changes and, after restitution, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) scans show a normal pancreas without any damage to the gland or the duct system. Even when functional impairment occurs, this is not necessarily associated with any pathological imaging findings. This is also observed in most cases of diabetes mellitus of other genesis and in many patients with endocrine dysfunction without underlying chronic pancreatitis. In contrast, severe episodes of acute pancreatitis with or without the need for interventional or surgical treatment often result in morphologic pancreatic alterations of varying extent.

Common reversible or irreversible findings on CT or MRI imaging include:

- inhomogeneity of the parenchyma;
- atrophy of the parenchyma;
- duct alteration (strictures/dilation);
- residual peripancreatic fluid collections;
- pseudocysts.

Diagnosis of the abovementioned alterations alone does not require any measures, unless accompanying symptoms are present. Further follow-up examinations should be performed to evaluate a potential dynamic of these changes and recognize potential need for any interventional or surgical therapy early to prevent ongoing destruction of the pancreatic parenchyma in the case of recurrent pancreatitis episodes or development of chronic pancreatitis or chronic pain. The management of pseudocysts and persisting postpancreatitis fistulas is described in Chapters 34 and 35.

Another important aspect is the recognition of cystic lesions as the cause of acute pancreatitis and their differentiation from residual pseudocysts. It has been reported that 13–67% of all patients with intraductal papillary mucinous neoplasia (IPMN) show an episode of acute pancreatitis as their initial symptom [41–43]. However, this is frequently misdiagnosed and studies in the past report on a delay in diagnosis of a cystic neoplasm as the trigger of acute pancreatitis of several years or even more than two decades [41–43]. With growing awareness of cystic neoplasms in recent years this may be avoided in the future as distinguishing postinflammatory duct dilatation and pseudocysts from IPMN is of high importance because of the malignant potential of IPMN.

Postpancreatitis Care and Follow-Up Visits

Six to eight weeks after hospital discharge due to an episode of acute pancreatitis, a clinical control examination can be recommended to document the status, including symptoms and nutritional status with regard to pancreatic function, blood tests, and imaging in cases of severe acute pancreatitis. In case of biliary acute pancreatitis, cholecystectomy (preferably by a laparoscopic approach) must be scheduled if it has not been performed during the initial hospital stay. There is good evidence concerning the indication and timing of cholecystectomy which shows that a delay of this operation results in an increased

risk of recurrent biliary pancreatitis [4,5,44]. For mild biliary pancreatitis cholecystectomy should be performed during index admission. In contrast, in patients with severe pancreatitis, cholecystectomy can safely be performed after resolution of symptoms (4–6 weeks). A similar time frame should be chosen for patients who undergo sphincterotomy during biliary pancreatitis [44]. Besides biliary pancreatitis, a Finnish study suggested that recurrence of idiopathic acute pancreatitis can also be prevented effectively by laparoscopic cholecystectomy, which should be evaluated for the respective patients [45].

No general guideline or consensus recommendations for long-term follow-up visits after acute pancreatitis exist to date. From the clinical point of view, follow-up at 6-monthly intervals during the first 2 years seems to be reasonable, followed by yearly examinations thereafter [46]. A possible scheme for follow-up could include:

- documentation of abdominal and unspecific symptoms;
- clinical examination;
- blood samples for the determination of routine parameters (including HbA_{1c}, electrolytes, creatinine, urea, liver enzymes, amylase, lipase, white and red blood cell counts, and C-reactive protein) as well as the serum tumor markers CEA and CA19–9;
- analyses of genetic factors (*PRSS1*, *SPINK1*, *CFTR*) in the case of unclear etiology of the underlying acute pancreatitis [4,28];
- cross-sectional imaging with abdominal CT or MRI scan.

Conclusions

Overall, the majority of patients show a good long-term outcome after acute pancreatitis. However, one out of four patients will develop some kind of problem in the long run, including endocrine or exocrine dysfunction, recurrent acute pancreatitis, or transition to chronic pancreatitis even many years after the initial event. Risk factors for clinical deterioration are incompletely examined and understood at present. Lifestyle habits, such as ongoing consumption of alcohol and nicotine, have been shown to increase this risk, especially for patients with alcohol-induced first attack of acute pancreatitis. Following biliary pancreatitis, removal of the gallbladder is an essential measure for prevention of future relapses and should preferably be performed during the initial hospital stay in mild pancreatitis and 6–8 weeks after recovery from a severe episode. To detect long-term loss of function before progression to an irreversible stage, regular follow-up is recommended, including clinical examination and blood tests at 6- to 12-month intervals to check for new onset of diabetes mellitus as well as maldigestion due to pancreatic exocrine dysfunction even when patients are asymptomatic. In the case of abdominal complaints, cross-sectional imaging should be considered. Pathologic findings alone (i.e., atrophy of the pancreatic parenchyma) do not require immediate intervention but should be further monitored during regular follow-up. In the case of transition to chronic pancreatitis with fibrosis and calcifications of the pancreas or dilatation of the pancreatic duct in combination with episodes of pain, a tailored approach including timely surgery should be considered to prevent ongoing deterioration of function and symptoms.

Recommendations for follow-up schemes after acute pancreatitis have not yet been standardized by international guidelines. The number of recent studies shows that heterogeneous protocols are being used in clinical practice and underlines the need for better and evidence-based recommendations to examine the long-term outcome of patients after acute pancreatitis as it is one of the most frequent gastrointestinal indications for inpatient treatment. The rising interest in this area and the results themselves underline the need for implementation of regular follow-up. This would allow a systematic evaluation of the risk of diabetes mellitus, pancreatitis relapse, and development of chronic pancreatitis, all of which exert an immense impact on healthcare costs. The possibility of earlier recognition and prevention of these complications on a risk-stratified basis could offer significant benefits.

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