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Natural History of Recurrent Acute and Chronic Pancreatitis

Rohit Das[1], *Jorge D. Machicado*[2], *and Dhiraj Yadav*[1]

[1] *Division of Gastroenterology & Hepatology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA*
[2] *Division of Gastroenterology & Hepatology, Department of Medicine, University of Michigan, Ann Arbor, MI, USA*

Introduction

Pancreatitis, especially chronic, is a low prevalence disease. Consequently, the focus of epidemiologic studies of pancreatitis has primarily been to define the disease at the level of individual patients. In the past two decades, the importance of understanding the distribution of risk factors and disease at the population level has been recognized. This has enabled determination of disease estimates and understand the relationship between acute pancreatitis (AP) and chronic pancreatitis (CP) at the population level. Demonstration that subsets of patients with AP develop recurrent acute pancreatitis (RAP) and/or progress to CP provides empiric evidence that these conditions represent stages of a disease continuum. Knowledge of the risks and factors associated with disease progression will help in risk stratification, prediction, and developing strategies for altering the natural history of disease.

This chapter will focus on the burden of disease, natural course and survival of AP, RAP, and CP. For AP, the emphasis will not be on the severity and outcome of the initial attack, but rather the risk of readmissions, recurrences, and progression to CP. In CP, the prevalence and natural history of clinical features, i.e., pain, endocrine and exocrine insufficiency, bone health, and the risk of pancreatic cancer will be discussed. Finally, we will summarize available data on the quality of life.

Natural History After First Attack of AP

Disease Burden, Etiology, and Severity

AP is one of the leading gastrointestinal causes of hospitalization in the United States [1]. The estimated incidence of AP in recent studies is 30–50 per 100,000 population. AP affects all age groups, but is most frequent in middle-aged and older individuals [2]. Gallstones and excessive alcohol consumption account for about 60–70% of all cases, the latter being more common in men when compared to women. Other etiologies include metabolic factors (hypertriglyceridemia, hypercalcemia), endoscopic retrograde cholangiopancreatography (ERCP), medications, genetic mutations (*PRSS1*, *SPINK1*, *CFTR*, *CTRC*), obstructive causes (such as pancreatic duct stricture, etc.), and trauma. In 10–25% patients no identifiable etiology is found on evaluation [2]. The two main determinants of mortality in AP are the presence of infected necrosis and organ failure, especially when persistent (>48 h) or involving more than one organ [3]. The risk of death increases with age and comorbidities [4]. Increased morbidity is seen in patients with local complications who do not have organ failure [5].

Readmissions

After the first attack of AP, about 20–30% patients are readmitted to hospital (Table 40.1). The reason for readmission differs based on time since discharge from the hospital. Vipperla et al. [6] differentiated between early (<30 days after index AP) and late (>30 days) readmissions and found that early readmissions were more likely due to smoldering symptoms from AP and/or local complications, whereas late admissions were more likely to be due from recurrent AP episodes. Younger age, alcohol use and/or alcohol-related etiology, non-private medical insurance, increased length of stay during index admission, and discharge to long-term care facilities have been identified as predictors of readmissions [6–8].

The Pancreatitis Activity Scoring System (PASS) was developed in 2017 as a tool to measure disease activity

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Table 40.1 Summary of recent studies examining rates and risk factors for readmission after a first attack of acute pancreatitis.

Author, year, design	Cohort size	Follow-up time (months)	Readmission rate (%)				Time to readmission (months)	Risk factors for readmission
			Overall	Alcoholic	Biliary	Idiopathic		
Yadav et al., 2014 [7] Retrospective	5239	39.0	22	40	15	32	Unclear	Younger age Alcoholic etiology Subsequent diagnosis of CP
Vipperla et al., 2014 [6] Retrospective	127	36.0	34	60	29	59	1.3	Younger age Male gender Alcoholic or idiopathic etiology Severe disease at index attack
Garg et al., 2018 [8] Retrospective	243816	Unclear	16	Not stated			Unclear	Younger age Non-private medical insurance Discharge to long-term care facilities Increased length of stay

CP: chronic pancreatitis.

and better predict the prognosis of AP. PASS incorporates organ failure, systemic inflammatory response syndrome (SIRS), abdominal pain, opiate requirement and diet tolerance, with each component having a different weight according to their prognostic importance [9]. In a prospective study examining the predictive utility of PASS, a score of >60 was highly associated with readmission within 30 days of AP discharge [10].

These data suggest that focused discharge planning may reduce the risk of early readmissions—i.e., ensuring that the patients' symptoms are well controlled and they have received counseling for behavior modification. In patients with severe AP, close follow-up with relevant specialists (e.g., nutrition, gastroenterologist, surgeon) is helpful to determine the need and timing of cross-sectional imaging, duration of enteral feeds, and "step-up" therapy. Many patients with severe AP need short-term stay at a transitional care facility or rehabilitation unit prior to safe discharge home.

First Recurrence

The risk of recurrent AP (RAP) after the first attack has been evaluated in several, mostly retrospective, population and nonpopulation based studies (Table 40.2). The overall risk of a subsequent attack of AP is ~20% during a median follow-up period ranging from 4 to 8 years. Similar to the first attack, among patients with a second attack of AP, alcohol, gallstones, and idiopathic are the most common etiologies [11–13]. When compared with the first attack of AP, subsequent recurrence is generally milder with an overall lower mortality [14].

The risk of recurrent attack is highest among patients with alcohol etiology (35–40%) followed by idiopathic and biliary AP (both 10–20%) [11–13]. Takeyama et al. noted that the risk of subsequent recurrence was directly related to continued alcohol consumption—the risk was highest in patients who continued drinking at the same level, and lowest among patients who stopped drinking completely [15]. Contrary to what many physicians may believe, counseling against alcohol consumption has a significant impact on patient behavior. This was tested empirically in a randomized controlled trial (RCT), where repeated counseling of patients led to a significant decrease in the risk of abdominal pain attacks, AP episodes and hospitalizations [16].

After an attack of biliary pancreatitis, the risk of recurrence can be dramatically reduced by early cholecystectomy. This has been demonstrated in RCTs, as well as in meta-analyses of published data [17]. In patients with mild biliary pancreatitis, cholecystectomy should be considered as close to the attack of AP as possible, preferably during the same admission. In patients with severe AP, cholecystectomy should be delayed until resolution of inflammatory changes in the pancreas/pancreatic area. In patients with pancreatic/peripancreatic collections that need drainage, a surgical approach (preferably laparoscopic or minimally invasive) to address this along with a cholecystectomy should be considered [18]. In patients with another known etiology, i.e., medications, hypertriglyceridemia, hypercalcemia, etc., addressing the inciting cause will decrease the risk of recurrence [19].

Tobacco abuse has been a consistent association with the risk of recurrent AP (odds ratio 1.5–2) [11,13,20]. Therefore, after an attack of AP, patients should be informed about this risk and counseled for tobacco cessation. This will be especially relevant in patients in whom the cause was alcohol, hypertriglyceridemia, genetic or idiopathic, or if the AP attack was moderate to severe. Individual studies have also shown that age and severity of initial attack may also play a role in recurrent attacks [11,13,20].

The burden of recurrent AP at a population level is not well defined. Using information on the total number of admissions for AP in the USA and applying the incident AP rates from California, approximate number of recurrent attacks can be estimated [1,21]. Among the 275,000 annual admissions for AP in the USA, approximately 150,000–160,000 would be incident attacks, while the remaining 115,000–125,000 would represent RAP (first or subsequent recurrences), readmissions for ongoing symptoms or complications of AP, or acute CP.

Subsequent Recurrences

Alcohol is the most common etiology of subsequent recurrences, followed by idiopathic pancreatitis, genetic causes, hypertriglyceridemia, and underlying CP as other important causes. The role of pancreas divisum and sphincter of Oddi dysfunction in causing initial or recurrent AP attacks is controversial [22].

Approximately one-third of patients who have a recurrence after the first attack of AP will have one or more subsequent recurrences. Burden of recurrent AP was further quantified in in two previous studies. Among 562 patients with a first attack of alcoholic AP who survived the index admission, Sand et al. reported at least one recurrence in 260 (46%) patients. Among these patients, 133 (51%) had only one recurrence, 49 (19%) had two recurrences, 39 (15%) had three recurrences, and 39 (15%) had four or more recurrences [23]. Among patients who underwent a cholecystectomy for presumed biliary pancreatitis, Trna et al. noted the risk of subsequent attacks to be related to the presence of abnormal liver function tests and documentation of gallbladder stones or sludge. Among patients who did not have either, 26% had a second attack, and 9% had a third attack of AP [24]. Although few empiric data is available, the risk of

Table 40.2 Summary of recent studies examining the rate and risk factors for development of recurrent acute pancreatitis (RAP) after a first attack of acute pancreatitis.

Author, year	Cohort size	Follow-up time (years)	RAP rate (%)				Time to recurrence (months)	Risk factors for RAP
			Overall	Alcoholic	Biliary	Idiopathic		
Lankisch et al., 2009 [12] Prospective	532	8.0	17	33	12	14	Unclear	Younger age Alcoholic etiology Male gender
Yadav et al., 2012 [13] Retrospective	7456	3.3	29	52	18	26	7.2	Younger age Alcoholic etiology Tobacco use
Bertilsson et al., 2015 [11] Retrospective	1457	4.2	23	37	17	24	5.1	Alcoholic etiology Severe disease at index attack Tobacco use
Ahmed Ali et al., 2016 [20] Prospective	669	4.8	17	Not stated			5.0	Younger age Idiopathic etiology Tobacco abuse Severe disease at index attack

multiple attacks of AP seems high in patients with genetic mutations (e.g., *PRSS1*, *CFTR*) [25]. The risk of recurrences would also be higher in patients with uncommon causes of AP, such as hypertriglyceridemia, hypercalcemia, etc., especially if the underlying cause is not corrected, but definitive data on the burden of attacks in these patients is limited.

Diabetes and Exocrine Insufficiency After AP

Recent data have documented that AP increases the risk of diabetes mellitus (DM) and exocrine pancreatic insufficiency (EPI) irrespective of severity. In two population-based studies patients with mild AP were about two times more likely to develop DM than age- and sex-matched controls [26,27]. In a systematic review of 24 prospective studies, the pooled prevalence of newly diagnosed DM after the first episode of AP was reported to be 23% (95% CI 16–31%), and increased with the duration of follow-up [28]. The risk of DM after AP is greater in patients with severe AP, necrotizing pancreatitis and in those with alcohol etiology. The mechanisms leading to DM are not well defined.

With regards to EPI, a meta-analysis of 39 studies reported that the pooled prevalence of EPI after an index episode of AP was 35% and the prevalence was greater during the time of AP hospitalization [29]. The risk of EPI increased with disease severity, presence of necrosis, and alcohol etiology.

Quality of Life After AP

Several studies have demonstrated that AP deleteriously impacts quality of life. In a single-center prospective study of 91 patients, patients who experienced AP had a significantly lower physical healthcare-related quality of life (HRQOL) as compared to controls even after 14 months of AP [30]. Factors associated with lower physical HRQOL included the presence of ongoing abdominal pain and use of analgesics, disability, and smoking. Multiorgan failure was the only disease-related factor associated with a lower physical HRQOL.

Progression to CP

Many studies evaluating the natural history after a first attack of AP have determined the risk of progression to CP (Table 40.3) [11–13,20]. In a meta-analysis of 14 studies consisting of 8492 patients, Sankaran et al. reported that following a sentinel attack of AP the pooled prevalence of RAP was 22% (38% for alcohol etiology, 17% for biliary etiology) and of CP was 10% [31]. The three factors consistently shown to have an independent effect on disease progression have been alcohol etiology, tobacco abuse, and RAP. The association with severity of AP is less consistent and has been noted in some studies.

Lankisch et al. noted that progression to CP occurred almost exclusively in patients with alcohol etiology [12]. However, in other studies progression was also noted with nonalcoholic or idiopathic CP, albeit at a lower rate. The role of tobacco, especially in combination with alcohol in disease progression is important. Ali et al. reported that while the cumulative risk of progression to CP overall was 7.6%, it was 18% among current smokers, and increased to 30% in current smokers who also had alcohol etiology [20]. Therefore, including the counseling of tobacco cessation along with alcohol abstinence should be emphasized. Genetic factors also seem to play a role in the development of CP, but outside of hereditary pancreatitis, little empiric data is available [25].

Perhaps the strongest risk factor for disease progression is RAP, and the risk of progression in these patients is ~30–40%. Bertilsson et al. noted that among patients who transitioned to CP, 74% had at least two AP attacks, and 54% had more than two attacks. When compared with alcohol or tobacco (hazard ratio between 2 and 3), the risk of progression to CP in RAP is much higher (hazard ratio ~6) [11].

Natural History of Chronic Pancreatitis

Disease Burden, Demographics, and Etiology

Recent population studies estimate that the incidence of CP ranges from 4 to 14 per 100,000 per year, and the prevalence ranges from 42 to 73 per 100,000 population [19,32]. The prevalence of CP peaks at the age of 45–55 years and has a male predominance [32]. Alcohol is the most common cause of CP worldwide (frequency ~40–70%), followed by idiopathic etiology (frequency ~20–30%) [19]. Smoking is a well-recognized factor for CP and works in a dose-dependent manner—the risk of CP is fivefold greater in those smoking over 35 pack-years compared to never smokers [33]. The role of genetic factors is increasingly recognized and mutations in some susceptibility genes (*PRSS1*, *SPINK1*, *CFTR*, *CTRC*, *CPA*, *CASR*) are found in 10–15% of CP patients. Alcoholic CP is seen more commonly in men, while the other etiologies are more evenly distributed in both sexes [33]. The diagnosis of CP is preceded by AP in at least 50% of patients [34]. This has been well demonstrated in patients with hereditary and alcoholic CP, in whom AP precedes the progression of CP by 10 years [19].

Table 40.3 Summary of recent studies examining the incidence and risk factors for development of chronic pancreatitis after acute pancreatitis.

			CP rate (%)					
Author, year	**Cohort size**	**Follow-up time (years)**	**Overall**	**Alcoholic**	**Idiopathic**	**RAP**	**Time to CP (months)**	**Risk factors for RAP**
Lankisch et al., 2009 [12] Prospective	532	8.0	4	13	0	22	Unclear	Alcoholic etiology Recurrent acute pancreatitis Tobacco use
Yadav et al., 2012 [13] Retrospective	7456	3.3	13	28	10	32	10.4	Alcoholic etiology Recurrent acute pancreatitis Tobacco use
Bertilsson et al., 2015 [11] Retrospective	1457	4.2	5	17	6	Not stated	5.1	Alcoholic etiology Recurrent acute pancreatitis Severe disease at index attack Tobacco use
Ahmed Ali et al., 2016 [20] Prospective	669	4.8	8	Not stated			21.0	Younger age Idiopathic etiology Tobacco abuse Severe disease at index attack

AP: acute pancreatitis; CP: chronic pancreatitis; RAP: recurrent acute pancreatitis.

Natural History of Pain

Abdominal pain is the hallmark of CP, and often prompts patients to seek medical attention. A recent systematic review of 42 studies demonstrated that 88% of CP patients experience abdominal pain at some point during the disease course [35]. Emerging data has demonstrated that the temporal nature of pain is a more important determinant of patient outcomes than the intensity of pain [36,37]. On cross-sectional assessments of abdominal pain in CP patients, approximately 60–70% have constant pain and 30–40% have intermittent pain; however, 60% alternate between pain patterns during the disease course [36,37]. Constant pain is associated with lower quality of life, higher rates of disability, and greater need for resource utilization (e.g., hospitalizations, pain medications) as compared to intermittent pain [36–38]. This effect is independent of the intensity of abdominal pain.

The mechanisms of pain in CP are complex, multifactorial, and poorly understood. Pain can be due to structural complications in the pancreas (pancreatic duct obstruction from stricture or stone, pancreatic inflammation, pseudocyst) or peripancreatic organs (bile duct stricture, duodenal obstruction). Resolution of these complications does not always result in pain control, and many patients with painful CP do not have these structural complications, suggesting sensitization of peripheral and/or central nociceptive pathways [33]. However, differentiating visceral pancreatic pain from central nervous system alterations is challenging in clinical practice, and novel pain assessment tools (e.g., comprehensive pain assessment score, pancreatic quantitative sensory testing) are being investigated to better classify pain profiles and to more effectively guide treatment choices.

Although medical management with nonopioid analgesics is the first step in the management of painful CP, this is often insufficient. In a recent US population study, 25% of CP patients are prescribed opiates and CP had the highest prescription rates among all GI disorders [39]. This is concerning, given the adverse events associated with opioid use. Endoscopic and surgical interventions are needed in a subset of patients with pain refractory to noninvasive interventions. In a US population-based study, 22% of CP patients required endoscopic procedures and 11% underwent surgical interventions over 10-year follow-up; however, a higher proportion of patients receive endoscopic and/or surgical interventions at referral centers [40].

One aspect that has recently been investigated is the interaction of psychiatric comorbidities with pain in CP. In a recent retrospective US cohort, patients with CP had sevenfold greater risk of anxiety (37%) and fivefold greater risk of depression (47%) compared with the general population [41]. The presence of psychiatric comorbidities in CP patients has been associated with higher pain prevalence, pain severity, and pain interference scores [42]. These data indicate that psychiatric comorbidities should be evaluated in CP patients, and their management is likely to improve pain management.

The concept of pain *burn-out* in CP was proposed by Ammann et al. decades ago, based on the observation that over 80% of patients with alcoholic CP became pain-free at a median of 5 years from disease onset. In recent years, an accumulating body of evidence has emerged that refutes this theory. In a large single-center retrospective cohort of 279 CP patients, 47% still complained of abdominal pain at a median period of 12 years from disease onset [43]. In multivariate analysis, this and other studies have shown that disease duration is not associated with pain relief [37,43].

Approximately 1 in 10 patients experience a painless disease course, with the majority of these (57%) having idiopathic/genetic etiology [35]. Patients with painless CP are diagnosed when undergoing abdominal imaging for other reasons and are found with calcifications and/or significant ductal changes. In general, these patients do not benefit from endoscopic or surgical interventions.

Diabetes Mellitus

Diabetes mellitus (DM) is a well-known complication of CP. In a recent systematic review of 15 studies, the incidence of new-onset DM was 15% within 3 years and 33% after 5 years of CP diagnosis [44]. In prospective studies with longer follow-up, the cumulative incidence of DM is 40–50% at 10 years and >80% at 25 years [40,45]. The pathogenesis of DM in CP has been thought to be a result of progressive parenchymal fibrosis with impaired insulin secretion. Several epidemiologic studies have supported this theory, by demonstrating that the risk of DM increases with certain CP specific characteristics (disease duration, calcifications, exocrine insufficiency, pancreatic surgery) [46,47]. This pathophysiologic paradigm has been challenged by recent large cross-sectional multicenter studies that reported an increased risk of DM in CP with traditional type 2 DM risk factors (age, overweight/obesity, family history of DM, dyslipidemia) [46,47]. This has suggested that DM in CP, at least in a subset of patients, may be a subtype of type 2 DM, and future studies are needed to better define the mechanisms of DM in CP.

Diabetes in CP is difficult to treat and about half become insulin dependent [44]. The risk of all-cause mortality and hospitalizations in CP patients with diabetes is greater than in patients with type 2 DM [48].

Exocrine Pancreatic Insufficiency

Initially CP patients lose pancreatic enzyme output, measured by direct or indirect pancreatic function tests, but maintain adequate digestive capacity, quantified by

normal coefficient of fat absorption (CFA ≥ 93%). The term exocrine dysfunction (stage I and II) has been coined for these patients, who do not have symptoms or vitamin deficiencies, and would not benefit from treatment [49]. As pancreatic function loss reaches near total (>90%), patients develop abrupt and marked impairment in digestive capacity (CFA < 85%), with clinical manifestations, and micronutrient deficiencies [50]. This state of insufficient digestive capacity due to severe loss of pancreatic function represents exocrine pancreatic insufficiency (EPI, stage III and IV) [49] The burden of EPI in CP is difficult to estimate, given the absence of simple and accurate tests to diagnose EPI in clinical practice. A recent US population study showed a cumulative incidence of 30% at 10 years of follow-up [40]. In other series, the prevalence of EPI ranges from 35% to 75%, with higher risk in alcoholic CP and with longer disease duration [51]

EPI from CP is frequently experienced as diarrhea, foul-smelling stools, flatulence, meteorism, abdominal discomfort/pain, and weight loss. Persistent malabsorption can cause deficits of fat-soluble vitamins A, D, E, and K, calcium, magnesium, zinc, thiamine and folic acid. Fortunately, EPI can be treated with the initiation of pancreatic enzyme replacement therapy (PERT), which has been shown to improve symptoms, nutritional status and quality of life. A minimal dose of at least 40,000 USP units of lipase with each meal is recommended. Despite its importance, a recent US study of administrative claims demonstrated that only 6.5% of CP patients receive any testing for EPI, and that among those treated with PERT, only 32% are prescribed appropriate dosing [51]. In this study, seeing a GI physician and formal testing for EPI were strong predictors for prescribing PERT and using an appropriate dose.

Metabolic Bone Disease

Long-term malnutrition from EPI and CP can lead to metabolic bone disease. In a systematic review of 10 studies reporting osteopathy in CP, the prevalence of osteopenia was 40% and of osteoporosis was 23% [52]. Similar estimates were reported in a recent multicenter US study of 282 patients with definitive CP, in which 39% had osteopenia and 17% had osteoporosis at the time of baseline DXA scan [53]. Risk factors independently associated with osteopathy included underweight body mass index, older age, female sex, and white race [53]. In a large VA cohort, CP was independently associated with greater risk of total fractures (5%), vertebral fractures (1%), and hip fractures (2%), compared to non-CP controls [54]. Therefore, assessments of bone mineral density are recommended for CP patients. However, this is often underperformed, and a recent single center study showed that a dual-energy X-ray absorptiometry test (DXA) was performed in only 21% of CP patients [55].

Pancreatic Cancer

Within the first 2 years of CP diagnosis, there is an excess of pancreatic cancer diagnosis, that may represent early cancers misdiagnosed as CP [56]. When excluding patients diagnosed with pancreatic cancer within 2 years of CP diagnosis, a meta-analysis of 13 observational studies showed that the risk of pancreatic cancer in CP is 16-fold greater than in the general population [57]. Even when excluding pancreatic cancer patients diagnosed within 5 years of CP, patients with CP still have eightfold greater risk of pancreatic cancer [57]. In a recent US population based study, the cumulative incidence of pancreatic cancer from initial CP diagnosis was 2% at 2 years and 3% at 5 years [58]. Age, obesity, and pancreatic ductal dilation are risk factors associated with higher incidence of pancreatic cancer [58].

Quality of Life

CP is a debilitating disease that negatively impacts quality of life. Factors that significantly decrease quality of life include constant pain, disability/unemployment, current smoking, and other comorbidities [38]. In a multicenter prospective study, anxiety and depression were also noticed to negatively impact quality of life in CP [42].

Survival

The overall survival and the standardized mortality ratio in CP patients is two- to fourfold higher when compared with the general population [59]. Most patients die from nonpancreatic causes such as cancers and cardiovascular diseases.

Conclusion

Studies in the past two decades have provided an insight into the population distributions and natural history of different stages of pancreatitis. Readmission to hospital is frequent after AP. After the first attack of AP, about 1 in 5 patients develop a recurrence and 1 in 10 progresses to CP. Alcohol and tobacco abuse are the main predictors of recurrence, and these along with RAP are the main predictors of progression to CP. Abdominal pain is the main symptom of CP, and a significant fraction of these patients develop exocrine and/or endocrine insufficiency during the disease course. CP is an established risk factor for pancreatic cancer, although, the absolute risk of this is low.

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