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# Acute Relapsing Pancreatitis

## What can be Done to Prevent Relapses?

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## Introduction

Results of epidemiological and experimental studies suggest that acute pancreatitis (AP), recurrent acute pancreatitis (RAP), and chronic pancreatitis (CP) represent a disease continuum [1]. About one-fifth of patients with a single episode of AP develop RAP, and one-third of those with RAP subsequently progress to CP [2]. The risk of progression of AP and RAP to CP is determined by several patient- and disease-related factors, a subset of which are modifiable. This provides an opportunity for clinicians to employ primary and secondary preventive strategies to alter the natural course and reduce the burden of disease. In this chapter, we review the definition, epidemiology, etiological framework, and diagnostic work-up for RAP, risk stratification for disease progression, and approaches to prevent recurrences and progression.

## Definition

The term RAP was first used over 70 years ago, and broadly refers to at least two separate documented episodes of AP with a period of resolution between attacks [3]. Recently, an international group of experts [4] proposed a mechanistic definition of RAP as:

> A syndrome of multiple distinct acute inflammatory responses originating within the pancreas in individuals with genetic, environmental, traumatic, morphologic, metabolic, biologic, and/or other risk factors, who experienced 2 or more episodes of documented AP, separated by at least 3 months.

Not emphasized in these definitions is that a subset of patients with RAP may have morphological and/or histological features of CP. When morphological abnormalities such as calcifications and/or ductal abnormalities are present in the setting of RAP, a diagnosis of CP is clear [1]. These patients often have one or more features of CP, such as abdominal pain, organ dysfunction (diabetes, exocrine insufficiency), and impaired quality of life. A subset of patients who do not have obvious morphological changes may still have histological changes of CP (i.e. fibrosis, atrophy). These patients have early CP, but establishing this diagnosis is often difficult with currently available diagnostic modalities [5]. The term "chronic relapsing pancreatitis" (CRP) has been used to describe the subset of patients with RAP with histological changes of CP, who will eventually declare themselves as CP [6]. In these patients recurrent attacks of AP represent a manifestation of CP before definitive hallmarks are documented. In contrast, the term "acute relapsing pancreatitis" (ARP) is used to describe RAP due to identifiable causes of pancreatitis, such as gallstones or medications, that do not progress to CP [7]. A major problem with the use of these definitions is reliance on pancreatic histology, which is rarely ever obtained in the diagnostic work-up of RAP. Moreover, it is now well established that not all patients with AP and RAP typically associated with CP (e.g. alcohol, idiopathic) show morphological progression. Because of these uncertainties, terms like CRP and ARP are no longer used in clinical practice, but their concepts are helpful in retrospect to describe the natural course of RAP. Throughout this chapter, we therefore use the term RAP preferentially, without differentiating ARP and CRP.

## Burden

The prevalence of CP in the United States was recently published in a population-based study to be about 235 000 [8].

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Assuming about 50% of all CP patients to have RAP during their clinical course [9], this would equal 117 000 cases. In a meta-analysis, it was estimated that 36% of patients with RAP progress to CP [2]. This translates to at least 450 000–500 000 prevalent cases of RAP in the United States. Since there are no studies that directly report on the prevalence of RAP and the burden of CP is available in only a few populations, a similar approach could be applied to other populations to generate estimates for the prevalence of RAP.

## Demographics

The age and sex distribution of patients with RAP mirrors that in patients with AP and CP. Patients with alcoholic pancreatitis are more likely to be male, while those with gallstone pancreatitis are more likely to be female [10]. The median age of patients with RAP is typically intermediate between that of patients with AP and CP [10,11]. Patients with other etiologies are usually distributed equally between the two sexes. Patients with idiopathic pancreatitis have a bimodal distribution, while those with genetic etiologies are typically younger at the time of clinical presentation [10,12,13].

**Table 20.1** Causes of recurrent acute pancreatitis.[a]

| Cause | Approximate frequency (%) |
|---|---|
| Alcohol | 25–50 |
| Gallstones | 10–30 |
| Idiopathic | 10–30 |
| Genetic (*CFTR*, *SPINK1*, *PRSS1*, *CTRC*, *CPA*) | 5–10 |
| Hypertriglyceridemia | 3–5 |
| Autoimmune pancreatitis | 2 |
| Celiac disease | 1 |
| Other autoimmune diseases | 1 |
| Obstructive causes (e.g. stricture, tumor, ampullary adenoma, IPMN) | <5 |
| Pancreas divisum | Controversial |
| Sphincter of Oddi dysfunction | Controversial |
| Hyperparathyroidism and hypercalcemia | Rare |
| Drugs | Rare |
| Post-necrotic | Unknown |
| Post-ERCP pancreatitis | Unknown |

[a] This is not an exhaustive list.
ERCP, endoscopic retrograde cholangiopancreatography; IPMN, intraductal papillary mucinous neoplasm.

## Etiology

Table 20.1 shows a circumscribed list of causes of RAP. Heavy alcohol consumption and gallstones are the cause in 60–70% of RAP cases [14,15]. The risk of RAP after a single episode of gallstone-related AP is directly related to whether cholecystectomy is performed and how long after an attack such a procedure is undertaken. Cholecystectomy during index AP admission or within 30 days virtually eliminates the risk of subsequent attacks [16]. Exceptions to this would be when a stone has been inadvertently left or develops over time in the bile duct, or when a pancreatic duct stricture or disconnected duct develops as a consequence of necrotizing pancreatitis.

The risk due to alcohol consumption is directly linked to the amount, duration, and cumulative exposure to alcohol [17]. Several epidemiological studies have consistently reported that heavy alcohol consumption (more than four to five drinks daily) is associated with a 2.5–3 times greater risk of pancreatitis when compared with abstainers and light drinkers, after adjusting for potential confounders [18]. However, only about 5% of individuals who drink heavily develop any form of pancreatitis [19]. Individual susceptibility could in part be related to genetic (e.g. polymorphisms in *CLDN2*, alcohol or aldehyde dehydrogenase genes) [20,21] or nongenetic factors. One such nongenetic cofactor is smoking, which has a dose-dependent effect on the risk of pancreatitis [22].

Other well-recognized causes of RAP are less frequently found in clinical practice. Hypertriglyceridemia-induced pancreatitis typically affects patients with poorly controlled diabetes, alcoholics, those using certain medications (e.g. propofol, estrogens, protease inhibitors), and in the third trimester of pregnancy [23]. These individuals have an underlying lipid abnormality, which in the presence of these secondary factors increases the risk of hypertriglyceridemia. A large Danish prospective study demonstrated that the risk of pancreatitis was 2.3-fold greater in individuals with a serum triglyceride level of 177–265 mg/dl, and 8.7-fold greater with levels higher than 443 mg/dl when compared with normal triglyceride levels (<89 mg/dl) [24]. These data suggest that the cutoff for increasing risk of pancreatitis may be much lower than 1000 mg/dl, which has been the typical level associated with pancreatitis.

Over 100 drugs are associated with AP. Mechanisms by which medications cause pancreatitis vary and if not discontinued can lead to recurrences. In a recent Swedish population study, almost half of the patients with a first episode of AP were using one or more drugs associated with pancreatitis; however, drug-induced pancreatitis accounted for only 2% of the incident cases of AP [25]. Celiac disease doubles the risk of pancreatitis by sensitizing the pancreas to altered levels of autoregulatory enteric

hormones and papillary inflammation [26]. Patients with autoimmune pancreatitis (AIP), especially with idiopathic duct centric pancreatitis (type 2), can also develop RAP [27]. Pancreatic duct obstruction resulting from a miscellaneous group of disorders that includes annular pancreas, type 3 choledochal cyst, post-necrotic stricture, main or mixed duct intraductal papillary mucinous neoplasm (IPMN), ampullary tumors, and pancreatic tumors can be a cause of RAP [28].

Very early onset RAP can occur with hereditary pancreatitis, a rare autosomal dominant disorder caused by gain-of-function mutations in the cationic trypsinogen (*PRSS1*) gene [29]. Pathogenic variants in the serine peptidase inhibitor Kazal type 1 (*SPINK1*) and cystic fibrosis transmembrane conductance regulator (*CFTR*) genes are strongly associated with RAP when compared with controls or patients with a single episode of AP [30,31]. The risk of clinical pancreatitis in cystic fibrosis patients who are pancreas sufficient is related to the amount of residual *CFTR* function, and up to 13% may have RAP [32]. Mutations in other genes, such as chymotrypsin C (*CTRC*), calcium-sensing receptor (*CASR*), and carboxypeptidase (*CPA*), also increase the risk of pancreatitis [33].

The causal relationship of pancreas divisum and sphincter of Oddi dysfunction with RAP is controversial. Proponents of pancreas divisum as a causal agent of RAP hypothesize that impaired pancreatic ductal drainage through the small minor papilla causes outflow obstruction and RAP. This is supported by several retrospective studies showing a higher prevalence of pancreas divisum in RAP patients when compared with controls [34]. Arguments against include pancreas divisum being common in the general population (up to 5–10%) [35], so additional factors are likely needed to develop RAP. One such factor may be *CFTR* mutations, which are overrepresented in patients with RAP compared with controls and pancreatitis patients with other etiologies [36]. With regard to sphincter of Oddi dysfunction, elevated sphincter pressures are highly prevalent in patients with idiopathic RAP, raising the possibility that this could be the result of previous attacks rather than the cause [37].

Despite thorough etiological evaluation, approximately 10–30% of patients with RAP have no identifiable etiology [38]. The proportion of patients diagnosed with idiopathic RAP depends on thoroughness of the history and diagnostic work-up. Performance of endoscopic ultrasound and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP; preferably with secretin) and testing for metabolic causes (e.g. hypertriglyceridemia, hypercalcemia), autoimmune causes (e.g. celiac disease), and genetic mutations (in *PRSS1*, *CFTR*, *SPINK1*, *CTRC* genes) may uncover the etiologies previously described, thereby reducing the proportion of truly idiopathic cases. High-quality imaging studies may also uncover changes suggestive of CP that were initially not evident.

## Diagnostic Work-up

Figure 20.1 shows a diagnostic algorithm for patients with RAP. The first step is obtaining a good medical history and physical examination. A history of previous attacks of AP is relevant for accurately diagnosing RAP, including documentation of each attack, severity, and management, when possible. This requires extensive review of medical records to exclude other causes of abdominal pain, hyperamylasemia, hyperlipasemia, and smoldering pancreatitis, in order to avoid overdiagnosing RAP.

After a diagnosis of RAP has been established, the next step is to investigate the etiology. Careful assessment of amount, duration, and cumulative exposure to alcohol and tobacco is mandatory. Presence of jaundice or abnormal liver tests during attacks can point to alcoholic pancreatitis, gallstone pancreatitis, AIP, or pancreatitis from an obstructive pancreatobiliary pathology. RAP with new-onset diabetes or significant weight loss may occur in the setting of pancreatic cancer or CP. Eliciting a personal history of male infertility, hyperlipidemia, inflammatory bowel disease, celiac disease, or abdominal trauma can provide clues to etiology. All prescribed and over-the-counter medications need to be reviewed, including anesthetics and antibiotics administered during procedures. Family history of pancreatic disease, cystic fibrosis, celiac disease, hyperlipidemia, and premature atherosclerotic diseases should be obtained. Procedural history needs to include prior endoscopic, radiological, and surgical pancreatobiliary interventions.

Transabdominal ultrasound is widely available, and should be the first step for patients with an intact gallbladder to assess for the presence of gallbladder stones or sludge. The absence of abnormal liver tests and gallbladder sludge decreases the probability of biliary etiology, and therefore cholecystectomy has a limited role in reducing future attacks in these patients [39]. After ruling out alcohol and gallstone etiologies, one needs to consider evaluating other potential etiologies such as hypercalcemia, hypertriglyceridemia, celiac disease, and AIP. Contrast-enhanced pancreas protocol computed tomography (CT) is usually the next cross-sectional study. If this is normal, contrast-enhanced MRI with secretin-stimulated MRCP is helpful in further assessment of the pancreatic parenchyma, ductal system, and

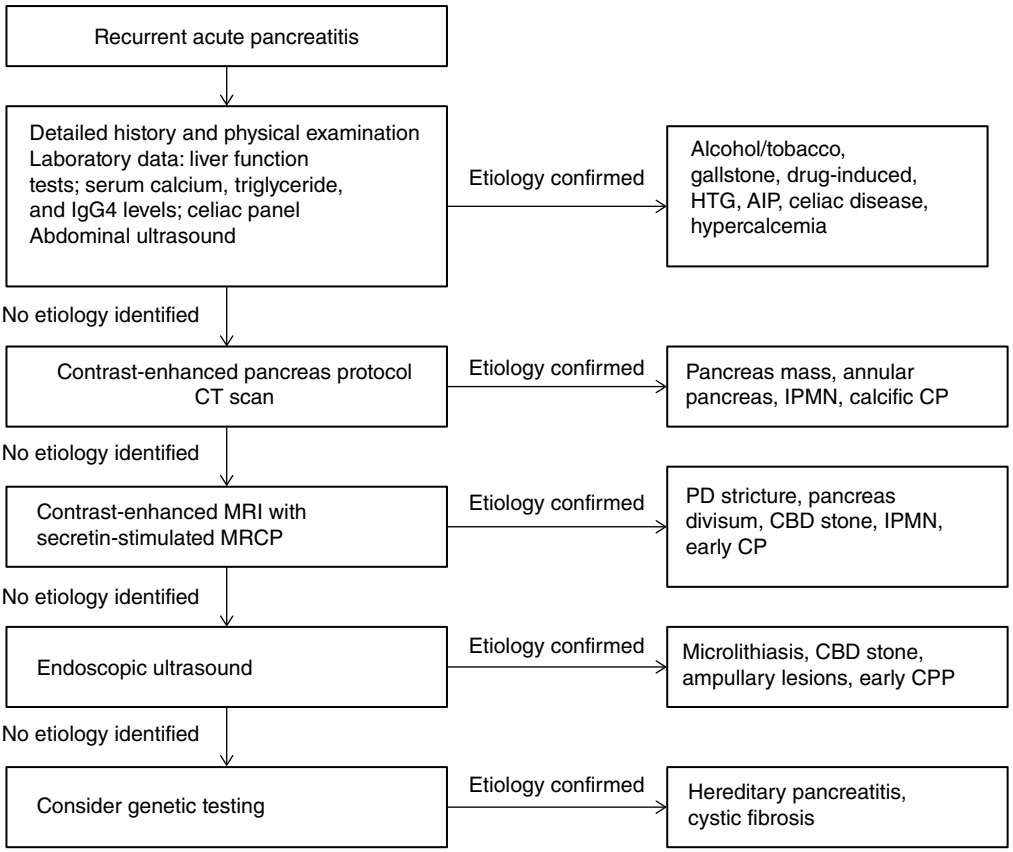


**Figure 20.1** Approach to etiological evaluation of recurrent acute pancreatitis. AIP, autoimmune pancreatitis; CBD, common bile duct; CP, chronic pancreatitis; HTG, hypertriglyceridemia; IPMN, intraductal papillary mucinous neoplasm; PD, pancreatic duct.

presence and type of local complications. Evaluating genetic abnormalities (polymorphisms in *CFTR*, *PRSS1*, *SPINK1*, and *CTRC* genes) is helpful especially in young patients.

In patients with negative diagnostic work-up, endoscopic ultrasound (EUS) can be used to evaluate for microlithiasis, choledocholithiasis, ampullary lesions, CP, and other parenchymal or ductal pancreatic abnormalities, which might not have been identified by cross-sectional imaging [40]. In a meta-analysis of 34 studies, the diagnostic yield of EUS was better than that of MRCP (64% vs. 31%) when other tests were unrevealing [41]. MRCP is superior for identifying pancreatic ductal strictures and pancreas divisum, while EUS performs better in the detection of biliary stones, microlithiasis, and sludge [41,42]. A normal or minimally abnormal EUS does not exclude or diagnose CP, and the confounding effect of several factors (e.g. age, alcohol, tobacco, and diabetes) on parenchymal and ductal changes needs to be considered [43,44]. Use of diagnostic endoscopic retrograde cholangiopancreatography (ERCP) or microscopic bile crystal analysis are no longer recommended in the work-up of RAP [4,45].

## Natural History and Risk of Progression

The natural history of RAP can follow one of three clinical courses:

1) Patients may experience further attacks of AP or none at all;
2) Develop varying combinations of abdominal pain symptoms and functional derangement but do not progress to the obvious morphological changes of CP with or without attacks of AP;
3) Progress to CP.

In a meta-analysis of 14 cohort studies, the risk of progression from single AP attack to RAP was 22%, and from RAP to CP was 36% (Figure 20.2) [2]. Risk factors associated with disease progression included etiology, ongoing alcohol and tobacco use, and number and severity of AP attacks [46–49]. Modification of these risk factors offers a window of opportunity for preventing RAP and progression to CP. Patients with AP or RAP can be stratified based

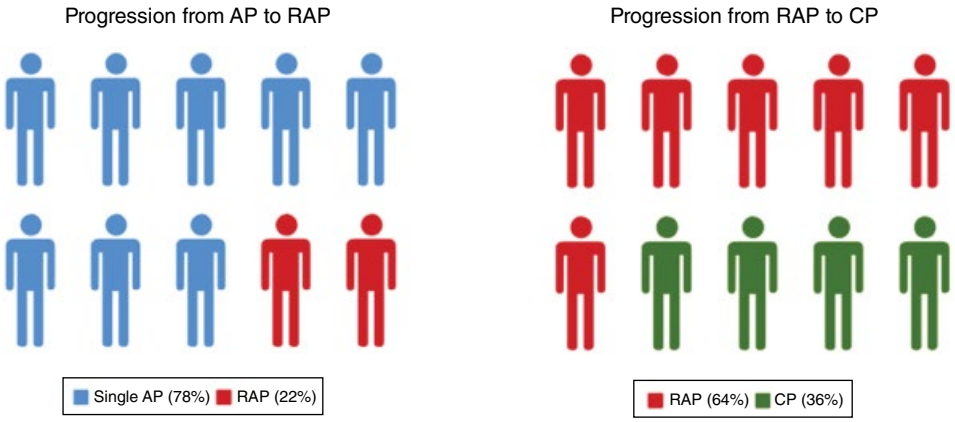


**Figure 20.2** Risk of progression from acute pancreatitis (AP) to recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP). *Source:* adapted from Sankaran et al. [2].

on risk factors into low-, intermediate-, or high-risk categories for disease progression (Table 20.2).

Patients in the high-risk category for progression include those with hereditary pancreatitis (and other genetic abnormalities), alcoholic pancreatitis, and necrotizing pancreatitis. Hereditary pancreatitis related to *PRSS1* mutation has the greatest risk of transition from AP to RAP and CP. Overall, about 80% of subjects carrying the mutation have one or more episodes of AP, and about 50% progress to CP [50,51]. Following a first episode of alcoholic pancreatitis, 25–50% progress to RAP, and of those with alcoholic RAP 40–80% progress to CP [17]. The risk of progression is modified by an individual's drinking and smoking habits. Patients who continue drinking at the same level have a threefold to fourfold greater risk for subsequent recurrences and progression to CP when compared with those who stop drinking completely [52]. Furthermore, current smoking doubles the risk of recurrences as compared to nonsmokers [49]. With regard to pancreatic necrosis, in a multicenter Danish cohort of 669 patients who survived a first episode of AP, it was demonstrated that necrotizing pancreatitis was independently associated with higher risk of recurrences [odds ratio (OR) 2.5, 95% confidence interval (CI) 1.5–4.3] and higher risk of progression to CP (OR 8.8, 95% CI 4.1–18.9) [49].

**Table 20.2** Stratification of recurrent acute pancreatitis based on risk of progression to chronic pancreatitis.

| |
|---|
| **High risk (>40%)** |
| Alcohol related[a] |
| Necrotizing acute pancreatitis[b] |
| Hereditary (*PRSS1*)[c] |
| **Intermediate risk (10–40%)** |
| Hypertriglyceridemia[a] |
| Idiopathic[b] |
| **Low risk (<10%)** |
| Gallstone[a] |
| Drug induced[a] |
| Post-ERCP[a] |
| **Additional factors** |
| Smoking[a] |
| Number of attacks[b] |
| Severity of acute pancreatitis[b] |
| Genetic variants[c] |

[a] Modifiable.
[b] Potentially modifiable.
[c] Not modifiable.

Idiopathic and hypertriglyceridemia etiologies fall in the intermediate-risk category for progression. After a first episode of idiopathic pancreatitis, 18–26% subsequently develop RAP, and 20–50% of patients with idiopathic RAP progress to CP [17]. In the Danish cohort study, an idiopathic etiology of the index attack was independently associated with a 2.5-fold greater odds of RAP, and with fourfold greater odds of progressing to CP [49]. Risk of progression in idiopathic RAP may depend on additional modifiable and genetic factors. Disease progression in hypertriglyceridemia-induced pancreatitis was recently evaluated in a single-center retrospective study, which demonstrated that the risk of recurrent attacks was 32%, with 17% eventually progressing to CP [53]. The risk of recurrences was directly linked to serum triglyceride control, poorly controlled diabetes, and alcohol intake.

The risk for disease progression for gallstone, drug-induced, or post-ERCP pancreatitis is generally low. Risk of recurrent AP attacks after a first episode of gallstone pancreatitis can be up to 20–30% if cholecystectomy or endoscopic sphincterotomy are not performed; however, the risk of recurrence is minimal following these interventions [54,55]. Development of CP following gallstone

pancreatitis is rare, and only 2–6% of patients progress to CP, likely related to postnecrotic mechanisms or other factors [49,52]. Future studies are needed to assess the risk of progression for other etiologies of RAP.

Predicting the course of RAP in an individual patient is difficult. Attack frequency can be highly variable, ranging from less than one every five years to more than one every month [56]. In-hospital survival in RAP patients is better in comparison with the sentinel attack [57]. Every additional episode of RAP is independently associated with a threefold greater risk of progression to CP [49]. The prevalence and pattern of pain and pancreatic functional derangement in RAP patients who do not develop the morphological changes of CP is not well known. Quality of life in patients with RAP is significantly lower than in healthy controls, as recently demonstrated in a study of 508 patients with RAP from a large multicenter US cohort [11]. There are no data on long-term survival in patients with RAP.

## Preventing Recurrences and Disease Progression

Following recovery from AP, it is of paramount importance to prevent RAP and further progression to CP. A holistic prevention model was recently proposed using the classic framework of primary, secondary, and tertiary prevention [58]. In primary prevention, interventions are applied to individuals in the general population or in patients with a single episode of AP to decrease the incidence of RAP. Secondary prevention involves early identification of individuals with RAP to apply interventions that can reduce morbidity and disease progression. Finally, tertiary prevention aims at minimizing

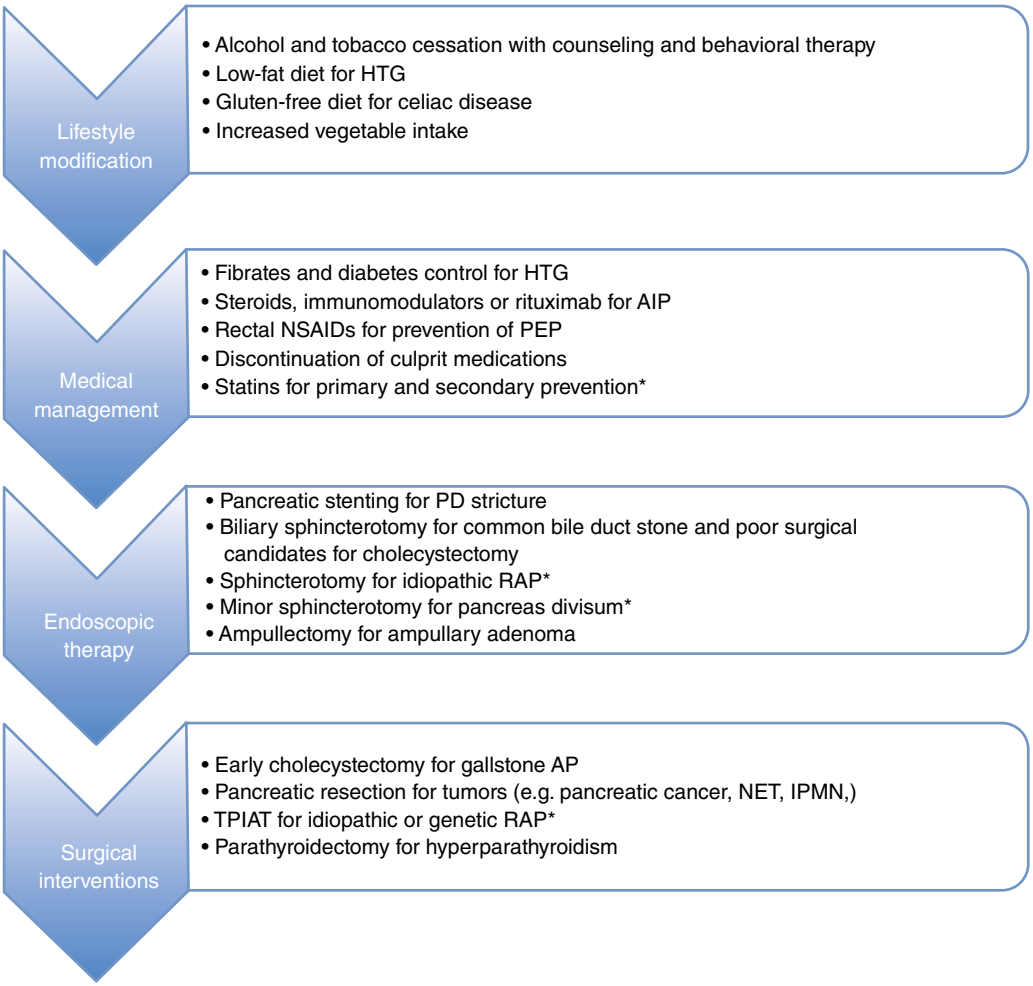


**Figure 20.3** Interventions to prevent recurrent acute pancreatitis (RAP) and chronic pancreatitis progression. AIP, autoimmune pancreatitis; AP, acute pancreatitis; HTG, hypertriglyceridemia; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; NSAID, nonsteroidal anti-inflammatory drug; PD, pancreatic duct; PEP, post-ERCP pancreatitis; TPIAT, total pancreatectomy with islet autotransplantation. *, Beneficial in observational studies but needs further investigation.

the resulting sequelae of RAP. Figure 20.3 shows lifestyle, medical, endoscopic, and surgical interventions.

Primary prevention for RAP can target the general population and those with prior AP. The approach would be to reduce exposure to environmental factors, recommend a healthy diet, and address the modifiable etiologies for AP, such as gallstones, medications, and hypertriglyceridemia [58,59]. Judicious selection of patients for ERCP can reduce the risk of post-ERCP pancreatitis. For patients undergoing ERCP, the risk of post-ERCP pancreatitis can be reduced by 40–60% using rectal nonsteroidal anti-inflammatory drugs (e.g. indometacin) [60,61]. There are promising data on the beneficial effects of statins on the incidence of AP, disease course, and decreased mortality after AP [62].

For alcohol- and/or tobacco-related pancreatitis, counseling, behavioral therapy, and pharmacological interventions are helpful. If available, structured programs for alcohol rehabilitation and smoking cessation should be offered to patients. A randomized controlled trial of 129 patients with a first episode of alcoholic AP demonstrated reduction in the incidence of RAP and the total number of recurrences with frequent counseling every 6 months compared with single counseling at the time of AP [63]. The risk of recurrences of gallstone pancreatitis can be reduced by timely cholecystectomy. Based on the results of the PONCHO trial, same-admission cholecystectomy should be preferred in surgically fit patients with mild pancreatitis [64]. Cholecystectomy should be delayed in patients with moderate and severe AP to allow for improvement of local inflammatory processes [65]. For patients who are not suitable for cholecystectomy, ERCP with biliary sphincterotomy can reduce the risk of recurrent pancreatitis [54]. In hypertriglyceridemia-induced pancreatitis, the risk of recurrences is directly linked to tight serum triglyceride control [66]. Therefore, counseling for diet and lifestyle modification, diabetes control, and medical therapy can prevent disease progression [67].

There are no proven interventions to reduce the risk of recurrences and disease progression in patients with idiopathic pancreatitis. In patients with low burden of attacks, one can recommend healthy lifestyle modification. The efficacy of biliary or pancreatic sphincterotomy in patients with idiopathic RAP is unproven, and there is no evidence that sphincter of Oddi manometry predicts response to any type of sphincterotomy [68,69]. At present, ERCP with biliary sphincterotomy for idiopathic RAP should only be offered at expert centers, especially in patients without genetic abnormalities and with high burden of RAP attacks (more than three attacks yearly) [4]. The role of endoscopic therapy in RAP associated with pancreas divisum is also unclear, and data are limited to uncontrolled studies and one small pilot randomized controlled trial [70]. A multicenter sham-controlled randomized trial is currently enrolling patients to assess the role of minor papilla sphincterotomy in patients with idiopathic RAP and pancreas divisum [71]. A highly selected group of patients with idiopathic RAP who have intractable symptoms despite different interventions may benefit from total pancreatectomy with islet autotransplantation, with subsequent improvement in pain and quality of life [72].

## Conclusion

Patients with RAP are at increased risk for progression to CP, high healthcare utilization, and impaired quality of life. The risk of disease progression can be stratified as low, moderate, and high, based on disease etiology, ongoing alcohol and tobacco use, number and severity of AP attacks, and genetic factors. The basis for preventing recurrences and disease progression rests on an organized and rational diagnostic work-up. Targeted lifestyle, medical, endoscopic and surgical interventions can reduce the burden of RAP at different levels of prevention.

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## References

1 Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology* 2016;16(2):218–224.

2 Sankaran SJ, Xiao AY, Wu LM, et al. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. *Gastroenterology* 2015;149(6):1490–1500.e1.

3 Doubilet H, Mulholland JH. Recurrent acute pancreatitis: observations on etiology and surgical treatment. *Ann Surg* 1948;128(4):609–638.

4 Guda NM, Muddana V, Whitcomb DC, et al. Recurrent acute pancreatitis: international state-of-the-science conference with recommendations. *Pancreas* 2018;47(6):653–666.
5 Whitcomb DC, Shimosegawa T, Chari ST, et al. International consensus statements on early chronic Pancreatitis. *Pancreatology* 2018;18(5):516–527.
6 Sarles H. Proposal adopted unanimously by the participants of the Symposium, Marseilles 1963. *Bibl Gastroenterol* 1965;7:7–8.
7 DiMagno EP, DiMagno MJ. Chronic pancreatitis: landmark papers, management decisions, and future. *Pancreas* 2016;45(5):641–650.
8 Machicado JD, Dudekula A, Tang G, et al. Period prevalence of chronic pancreatitis diagnosis from 2001–2013 in the commercially insured population of the United States. *Pancreatology* 2019;19(6):813–818.
9 Hori Y, Vege SS, Chari ST, et al. Classic chronic pancreatitis is associated with prior acute pancreatitis in only 50% of patients in a large single-institution study. *Pancreatology* 2019;19(2):224–229.
10 Lankisch PG, Assmus C, Maisonneuve P, et al. Epidemiology of pancreatic diseases in Luneburg County. A study in a defined German population. *Pancreatology* 2002;2(5):469–477.
11 Cote GA, Yadav D, Abberbock JA, et al. Recurrent acute pancreatitis significantly reduces quality of life even in the absence of overt chronic pancreatitis. *Am J Gastroenterol* 2018;113(6):906–912.
12 Layer P, Yamamoto H, Kalthoff L, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994;107(5):1481–1487.
13 Joergensen MT, Brusgaard K, Cruger DG, et al. Genetic, epidemiological, and clinical aspects of hereditary pancreatitis: a population-based cohort study in Denmark. *Am J Gastroenterol* 2010;105(8):1876–1883.
14 Gullo L, Migliori M, Pezzilli R, et al. An update on recurrent acute pancreatitis: data from five European countries. *Am J Gastroenterol* 2002;97(8):1959–1962.
15 Gao YJ, Li YQ, Wang Q, et al. Analysis of the clinical features of recurrent acute pancreatitis in China. *J Gastroenterol* 2006;41(7):681–685.
16 Kamal A, Akhuemonkhan E, Akshintala VS, et al. Effectiveness of guideline-recommended cholecystectomy to prevent recurrent pancreatitis. *Am J Gastroenterol* 2017;112(3):503–510.
17 Machicado JD, Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. *Dig Dis Sci* 2017;62(7):1683–1691.
18 Samokhvalov AV, Rehm J, Roerecke M. Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic review and a series of meta-analyses. *EBioMedicine* 2015;2(12):1996–2002.
19 Singhvi A, Yadav D. Myths and realities about alcohol and smoking in chronic pancreatitis. *Curr Opin Gastroenterol* 2018;34(5):355–361.
20 Whitcomb DC, LaRusch J, Krasinskas AM, et al. Common genetic variants in the CLDN2 and PRSS1–PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. *Nat Genet* 2012;44(12):1349–1354.
21 Zhong Y, Cao J, Zou R, et al. Genetic polymorphisms in alcohol dehydrogenase, aldehyde dehydrogenase and alcoholic chronic pancreatitis susceptibility: a meta-analysis. *Gastroenterol Hepatol* 2015;38(7):417–425.
22 Andriulli A, Botteri E, Almasio PL, et al. Smoking as a cofactor for causation of chronic pancreatitis: a meta-analysis. *Pancreas* 2010;39(8):1205–1210.
23 Scherer J, Singh VP, Pitchumoni CS, et al. Issues in hypertriglyceridemic pancreatitis: an update. *J Clin Gastroenterol* 2014;48(3):195–203.
24 Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern Med* 2016;176(12):1834–1842.
25 Bertilsson S, Kalaitzakis E. Acute pancreatitis and use of pancreatitis-associated drugs: a 10-year population-based cohort study. *Pancreas* 2015;44(7):1096–1104.
26 Sadr-Azodi O, Sanders DS, Murray JA, et al. Patients with celiac disease have an increased risk for pancreatitis. *Clin Gastroenterol Hepatol* 2012;10(10):1136–1142.e3.
27 Sah RP, Pannala R, Chari ST, et al. Prevalence, diagnosis, and profile of autoimmune pancreatitis presenting with features of acute or chronic pancreatitis. *Clin Gastroenterol Hepatol* 2010;8(1):91–96.
28 Guda NM, Romagnuolo J, Freeman ML. Recurrent and relapsing pancreatitis. *Curr Gastroenterol Rep* 2011;13(2):140–149.
29 Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996;14(2):141–145.
30 Aoun E, Muddana V, Papachristou GI, et al. SPINK1 N34S is strongly associated with recurrent acute pancreatitis but is not a risk factor for the first or sentinel acute pancreatitis event. *Am J Gastroenterol* 2010;105(2):446–451.
31 LaRusch J, Jung J, General IJ, et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. *PLoS Genet* 2014;10(7):e1004376.
32 Ooi CY, Dorfman R, Cipolli M, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. *Gastroenterology* 2011;140(1):153–161.
33 Whitcomb DC. Genetic risk factors for pancreatic disorders. *Gastroenterology* 2013;144(6):1292–1302.
34 Fogel EL, Toth TG, Lehman GA, et al. Does endoscopic therapy favorably affect the outcome of patients who have recurrent acute pancreatitis and pancreas divisum? *Pancreas* 2007;34(1):21–45.

**35** Bulow R, Simon P, Thiel R, et al. Anatomic variants of the pancreatic duct and their clinical relevance: an MR-guided study in the general population. *Eur Radiol* 2014;24(12):3142–3149.

**36** Bertin C, Pelletier AL, Vullierme MP, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. *Am J Gastroenterol* 2012;107(2):311–317.

**37** Elta GH. Sphincter of Oddi dysfunction and bile duct microlithiasis in acute idiopathic pancreatitis. *World J Gastroenterol* 2008;14(7):1023–1026.

**38** Guda NM, Trikudanathan G, Freeman ML. Idiopathic recurrent acute pancreatitis. *Lancet Gastroenterol Hepatol* 2018;3(10):720–728.

**39** Trna J, Vege SS, Pribramska V, et al. Lack of significant liver enzyme elevation and gallstones and/or sludge on ultrasound on day 1 of acute pancreatitis is associated with recurrence after cholecystectomy: a population-based study. *Surgery* 2012;151(2):199–205.

**40** 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):1339–1348.

**41** Wan J, Ouyang Y, Yu C, et al. Comparison of EUS with MRCP in idiopathic acute pancreatitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2018;87(5):1180–1188.e9.

**42** Smith I, Ramesh J, Kyanam Kabir Baig KR, et al. Emerging role of endoscopic ultrasound in the diagnostic evaluation of idiopathic pancreatitis. *Am J Med Sci* 2015;350(3):229–234.

**43** Petrone MC, Arcidiacono PG, Perri F, et al. Chronic pancreatitis-like changes detected by endoscopic ultrasound in subjects without signs of pancreatic disease: do these indicate age-related changes, effects of xenobiotics, or early chronic pancreatitis? *Pancreatology* 2010;10(5):597–602.

**44** Mohapatra S, Majumder S, Smyrk TC, et al. Diabetes mellitus is associated with an exocrine pancreatopathy: conclusions from a review of literature. *Pancreas* 2016;45(8):1104–1110.

**45** Garg PK, Tandon RK, Madan K. Is biliary microlithiasis a significant cause of idiopathic recurrent acute pancreatitis? A long-term follow-up study. *Clin Gastroenterol Hepatol* 2007;5(1):75–79.

**46** Ammann RW, Muellhaupt B, Meyenberger C, et al. Alcoholic nonprogressive chronic pancreatitis: prospective long-term study of a large cohort with alcoholic acute pancreatitis (1976–1992). *Pancreas* 1994;9(3):365–373.

**47** Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. *Am J Gastroenterol* 2012;107(7):1096–1103.

**48** Bertilsson S, Sward P, Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. *Clin Gastroenterol Hepatol* 2015;13(9):1662–1669.e3.

**49** Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol* 2016;14(5):738–746.

**50** Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol* 2004;2(3):252–261.

51 Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. *Gut* 2009;58(1):97–103.

**52** Takeyama Y. Long-term prognosis of acute pancreatitis in Japan. *Clin Gastroenterol Hepatol* 2009;7(11 Suppl):S15–S17.

**53** Vipperla K, Somerville C, Furlan A, et al. Clinical profile and natural course in a large cohort of patients with hypertriglyceridemia and pancreatitis. *J Clin Gastroenterol* 2017;51(1):77–85.

**54** Hwang SS, Li BH, Haigh PI. Gallstone pancreatitis without cholecystectomy. *JAMA Surg* 2013;148(9):867–872.

**55** van Baal MC, Besselink MG, Bakker OJ, et al. Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. *Ann Surg* 2012;255(5):860–866.

**56** Romagnuolo J, Guda N, Freeman M, et al. Preferred designs, outcomes, and analysis strategies for treatment trials in idiopathic recurrent acute pancreatitis. *Gastrointest Endosc* 2008;68(5):966–974.

**57** Lee PJ, Bhatt A, Holmes J, et al. Decreased severity in recurrent versus initial episodes of acute pancreatitis. *Pancreas* 2015;44(6):896–900.

58 Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol* 2019;16(3):175–184.

**59** Alsamarrai A, Das SL, Windsor JA, et al. Factors that affect risk for pancreatic disease in the general population: a systematic review and meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol* 2014;12(10):1635–1644.e5.

**60** 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):1414–1422.

**61** Lyu Y, Cheng Y, Wang B, et al. What is impact of nonsteroidal anti-inflammatory drugs in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials. *BMC Gastroenterol* 2018;18(1):106.

**62** de-Madaria E. Statins for the prevention of acute pancreatitis. *Am J Gastroenterol* 2017;112(12):1765–1767.

**63** Nordback I, Pelli H, Lappalainen-Lehto R, et al. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. *Gastroenterology* 2009;136(3):848–855.

**64** 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):1261–1268.

**65** Kwong WT, Vege SS. Unrecognized necrosis at same admission cholecystectomy for pancreatitis increases organ failure and infected necrosis. *Pancreatology* 2017;17(1):41–44.

**66** Christian JB, Arondekar B, Buysman EK, et al. Determining triglyceride reductions needed for clinical impact in severe hypertriglyceridemia. *Am J Med* 2014;127(1):36–44.e1.

**67** Wu BU, Batech M, Dong EY, et al. Influence of ambulatory triglyceride levels on risk of recurrence in patients with hypertriglyceridemic pancreatitis. *Dig Dis Sci* 2019;64(3):890–897.

**68** Cote GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. *Gastroenterology* 2012;143(6):1502–1509.e1.

**69** Das R, Clarke B, Tang G, et al. Endoscopic sphincterotomy (ES) may not alter the natural history of idiopathic recurrent acute pancreatitis (IRAP). *Pancreatology* 2016;16(5):770–777.

**70** Michailidis L, Aslam B, Grigorian A, et al. The efficacy of endoscopic therapy for pancreas divisum: a meta-analysis. *Ann Gastroenterol* 2017;30(5):550–558.

**71** Cote GA, Durkalski-Mauldin VL, Serrano J, et al. SpHincterotomy for Acute Recurrent Pancreatitis randomized trial: rationale, methodology, and potential implications. *Pancreas* 2019;48(8):1061–1067.

**72** Bellin MD, Kerdsirichairat T, Beilman GJ, et al. Total pancreatectomy with islet autotransplantation improves quality of life in patients with refractory recurrent acute pancreatitis. *Clin Gastroenterol Hepatol* 2016;14(9):1317–1323.