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Dig Dis Sci. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Dig Dis Sci. 2017 July ; 62(7): 1683–1691. doi:10.1007/s10620-017-4510-5.

Epidemiology of recurrent acute and chronic pancreatitis: Similarities and differences

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Abstract

Emerging data in the past few years suggest that acute (AP), recurrent acute (RAP) and chronic pancreatitis (CP) represent a disease continuum. This review discusses the similarities and differences in the epidemiology of RAP and CP. RAP is a high-risk group, comprised of individuals at varying risk of progression. The premise is that RAP is an intermediary stage in the pathogenesis of CP, and a subset of RAP patients during their natural course transition to CP. Although many clinical factors have been identified, accurately predicting the probability of disease course in individual patients remains difficult. Future studies should focus on providing more precise estimates of the risk of disease transition in a cohort of patients, quantification of clinical events during the natural course of disease, and discovery of biomarkers of the different stages of the disease continuum. Availability of clinically-relevant endpoints and linked biomarkers will allow more accurate prediction of the natural course of disease over an intermediate or long term based characteristics of an individual patient. These endpoints will also provide objective measures for use in clinical trials of interventions that aim to alter the natural course of disease.

Keywords

chronic pancreatitis; recurrent acute pancreatitis; epidemiology

Introduction

Acute (AP) and chronic pancreatitis (CP) were believed to be distinct entities as late as the Marseilles conference in 1984.[1] In this revised classification, it was commented that progression from AP to CP is extremely uncommon. The Revised Marseilles[1] and Cambridge[2] classifications acknowledged that alcoholic CP may present as a clinical episode of AP, and the latter classification further acknowledged that development of CP is not inevitable in all patients with alcoholic AP. It was also commented that at least 30% of all CP might be of idiopathic etiology.[1] These expert recommendations were drawn from observations that the etiology of CP in the large majority of patients was alcohol, and

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Potential competing interests: No relevant conflicts of interest.

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supported by autopsy studies documenting frequent occurrence of pancreatic fibrosis in heavy alcoholics without clinical history of pancreatitis.[3]

The concept that recurrent attacks of AP lead to CP by healing of the areas of necrosis with fibrotic tissue was proposed initially by Comfort et al in 1946.[4] Later, Kloppel and Maillet described the necrosis-fibrosis sequence hypothesis, which was confirmed by clinicopathological studies in well-characterized patients with CP.[5–8] The SAPE (Sentinel Acute Pancreatitis Event) hypothesis built upon the necrosis-fibrosis theory, and suggested AP as a sentinel event in the pathogenesis of CP, which, in the presence of continuing exposure to risk factors and aberrations in the repair process leads to CP.[9] Over the past 2 decades, clinical data accumulated from human studies confirms that AP, recurrent acute pancreatitis (RAP) and CP represent a disease continuum.[10, 11]

This review discusses the similarities and differences in the epidemiology of RAP and CP. The premise is that RAP is an intermediary stage in the pathogenesis of CP, and a subset of RAP patients during their natural course transition to CP. Recognition of this continuum has clinical relevance to develop preventive strategies before the irreversible features of end-stage CP are established.

Definitions of RAP and CP

The term RAP was first used ~70 years ago.[12] This broad term refers to the presence of at least two separate documented episodes of pancreatitis with a period of resolution in between, and the absence of definitive changes of CP. The differentiation between RAP and CP is based on morphology and/or histology of the pancreas. A subset of RAP patient may show histological evidence of CP, however, due to the lack of histology in most patients during clinical care, and for the purpose of this review, differentiation between the two is based primarily on evidence of definitive changes of CP on cross-sectional studies.

RAP was defined by two distinct terms in the first Marseilles symposium in 1963[13] - relapsing acute pancreatitis or acute recurrent pancreatitis (ARP) to describe relapsing acute events due to a removable cause of pancreatitis, which does not progress to CP (such as gallstones, medications); and chronic relapsing pancreatitis (CRP) to describe relapsing attacks of AP associated with anatomic and functional derangement where the probability of transition to CP is high. In patients with CRP, recurrent attacks of AP could therefore be considered to be the manifestation of CP before definitive hallmarks are documented. Conceptually, these definitions are helpful in retrospect to describe the natural course of RAP. However, due to the difficulty to clinically distinguish between these groups, these terms were deleted from the Revised Marseilles and Cambridge classifications, and are not used in clinical practice.[1, 2] Our description of RAP in this review does not differentiate between ARP and CRP. We make specific comments on the relevance of etiology(ies) and situations to the probability of disease progression.

Natural history studies have quantified the risk of progression after a single attack of AP or RAP.[10] Although this risk is consistently greater in patients with alcohol and genetic etiologies, transition to CP is not absolute even in these groups. Moreover, a small but

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significant fraction of patients with other etiologies may also transition to CP. As our focus moves from symptomatic management of CP to considerations for primary and secondary prevention, and with new treatments potentially available for testing in the near future, identifying subsets of patients who are at high-risk of progression, irrespective of etiology, to definite CP would be important, as they may be candidates for treatments that may alter the natural course of disease. RAP is an example of one such high-risk group, within which there will be subgroups with varying risk of progression based on etiology, genetic mutations, environmental factors, and clinical features. It is also important to recognize that while the majority of CP patients are preceded by at least one attack of AP, up to a third of patients may have subclinical AP episodes or no history of AP at all.[14]

There is no current consensus definition of CP. Among the many proposed over the years, a consistent requirement has been the documentation of irreversible changes either histologically (i.e. fibrosis, atrophy) or morphologically (i.e. calcifications, ductal abnormalities) with or without other accompanying features (e.g. pain, AP or RAP), organ dysfunction (diabetes, exocrine insufficiency) and impaired quality of life.[1, 2, 13, 15–20] The limitation of these definitions is their reliance on the end-stage features. While a definition of probable CP has been suggested in the presence of subtle histologic or morphologic findings, diagnosing CP at an earlier stage can be challenging.[16, 21] Development of obvious morphological changes, which are surrogate for fibrosis on histology, may take months to years to develop. Moreover, clinical features (e.g. pain, diabetes and exocrine insufficiency) do not always correlate with morphological features of CP.[22] Thus, waiting for development of advanced features of CP may limit ones' ability to intervene at an earlier stage.

Recognizing these limitations, a new consensus definition was recently proposed by a group of experts from the United States, Germany, India, Italy, and Japan.[23] They defined CP as *a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.* The key features of this definition are the recognition that end-stage disease is a result of progression through earlier stages, which although not required, are often observed clinically during the evolution of CP. The stages of the disease begin with no pancreatic disease, and transition through AP, RAP, early CP, established CP and end-stage CP. The last two stages are similar to the definitions mentioned earlier and characterized by irreversible features such as pancreatic atrophy, fibrosis, duct distortion and stricture, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction, and dysplasia with or without a pain syndrome.

Incidence and prevalence

The incidence of first-attack of AP in population studies over the past 2 decades from different countries ranges from 15 to 45 per 100,000 per year.[24–29] In a systematic review of published studies, the risk of recurrence after the first-attack of AP was noted to be ~20%, and the risk of progression in patients with at least one recurrence (i.e. RAP) to CP to be ~35%.[10] Data are also available on the incidence of CP, and in a few studies, on the prevalence of CP during the same time period. The incidence of CP ranges from 4 to 14 per 100,000 per year, and prevalence from 13 to 52 per 100,000 population.[30–35]

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The exact incidence and prevalence of RAP are unknown. One can use information on the incidence of first-episode AP and the risk of recurrences to generate estimates for the burden of RAP in the general population. The approximate estimates of incidence rates for AP and CP in the US are 40–50 and 4–5 per 100,000 population per year respectively, and the prevalence of CP is 40–50 per 100,000 population (total cases ~150,000–200,000, adjusted for underestimation and racial differences). Using this information, the rates of recurrence after first-attack of AP, and possibility of additional attacks of AP in patients with RAP, the approximate incidence of RAP is likely ~8–10 per 100,000 per year, and its prevalence ~110–140 per 100,000 population (~350,000–500,000 cases).

Demographics

First-attack of AP typically affects individuals in their sixth decade of life, with either a slight male preponderance or a similar gender distribution.[24] Patients with RAP are younger, typically in their fourth or fifth decade of life, and more likely to be men.[36–39] In a large retrospective study describing all AP admissions during a 20-year period in a single Swedish hospital, patients with RAP were 5 years younger and of male predominance when compared with the entire study population.[39] CP patients are also predominantly male, and usually diagnosed in the fifth or sixth decades of life.[14, 30, 32, 40, 41]

Differences in the age and sex distribution of RAP patients when compared with those with first-attack AP is likely related to a narrower spectrum of etiologies (less gallstones, more alcohol) and a higher risk of recurrence in younger patients (<40 years).[11, 38, 42] An earlier age at onset of RAP when compared with CP suggests the possibility of continuum of the disease process. This has been elegantly demonstrated in studies of patients with hereditary and alcoholic etiologies.

Hereditary pancreatitis typically presents in childhood, with variable frequency of RAP attacks until CP progression by the second or third decade of life.[43, 44] The peak incidence for alcoholic CP in women is between 35–44 years and in men between 45–54, whereas peak incidence of alcoholic AP is 10 years earlier.[32, 45] Incidence of idiopathic AP increases with age and plateaus after 65 years of age, while idiopathic CP has a bimodal age distribution with first peak during the third decade of life (early onset) and a second peak during the sixth to seventh decades of life (late onset).[32, 45, 46]

Racial differences have been described for AP and CP. When compared with whites, black patients with AP are more likely to be diagnosed with alcoholic etiology, and they have a higher rate for re-hospitalization.[42, 47] In the NAPS2 studies, black CP patients were noted to have 4.3 times greater odds for physician-reported alcohol etiology when compared with white CP patients.[14] It is likely that these differences will also be reflected for RAP.

Etiology

Similar to the first-attack of AP, the two most common causes of RAP are heavy alcohol consumption and gallstones.[24, 36, 38] The relative contribution of heavy alcohol consumption is likely greater for RAP than gallstones, although this may vary based on the demographic distribution of the group at risk. Overall, the etiologic spectrum of RAP is narrower than AP,

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since many of the modifiable causes are often addressed or eliminated (e.g. gallstones, medications, etc.) after occurrence of the first-attack. Certain etiologies such as pancreas divisum, genetic causes, etc. are over-represented in RAP patients, in part due to performance of a more comprehensive work-up only after the occurrence of a second attack. The etiologic spectrum of CP overlaps with RAP, but is narrower, with alcohol by far being the most common etiology, followed by idiopathic and genetic etiologies.[14, 31, 34, 41] Table 1 shows a non-exhaustive list of causes of RAP and CP, of which select are discussed below.

The probability of recurrences after an episode of gallstone-related AP is directly related to whether and how long after an attack a cholecystectomy is performed. [48, 49] Cholecystectomy as soon as feasible after AP virtually eliminates the risk of subsequent attack(s), except for when a stone may have been inadvertently left or develops in the common bile duct. While 2 to 6% patients are reported to develop CP after a first episode of biliary pancreatitis[11, 42, 50], gallstones do not typically result in CP, except for obstructive mechanisms from a stricture in the pancreatic duct caused by necrotizing pancreatitis. It is likely that in many patients with presumed gallstone pancreatitis who transition to CP, AP was idiopathic or related to another unappreciated cause.

Alcohol is the most common cause of RAP and CP. Average amount, duration of drinking and cumulative exposure are the most important determinants of increased risk of pancreatitis related to alcohol. Estimates of risk (odds ratio or hazard ratio) related to *heavy* consumption (≥4–5 drinks/day) are consistent across studies.[51, 52] Cumulative exposure to alcohol was greater among patients with CP when compared with those who had AP in a study from Japan, and this difference was more apparent in women when compared with men.[53] Such a comparison has not been performed for RAP, but it is likely that cumulative alcohol exposure is lower in RAP patients when compared with CP. Alcohol increases the susceptibility to pancreatitis by affecting pancreatic physiology at multiple levels, of which the most important one is its ability to sensitizes the pancreas to other insults.[54, 55] One such co-factor is smoking, which can also increase the risk of pancreatitis independently.[56, 57] Genetic susceptibility can explain an increased risk of pancreatitis in some individuals who also drink. Examples of this include over representation of claudin-2 mutation in patients with RAP and CP with alcohol etiology, and of polymorphisms in alcohol metabolizing genes among patients with pancreatitis in Asian populations.[58–60]

Several genetic susceptibility factors can be identified in patients with RAP and CP, especially those with no other identifiable etiologies. Gain-of-function mutations in the cationic trypsinogen gene (*PRSS1*) cause hereditary pancreatitis, a rare autosomal dominant disorder with early onset of RAP and CP.[61] In contrast, a substitution of glycine by arginine at codon 191 of the anionic trypsinogen gene (*PRSS2*) is less frequent in CP patients when compared with controls, suggesting a protective effect.[62] Heterogeneous mutations of the serine peptidase inhibitor Kazal type 1 (*SPINK1*) gene are observed in 1–3% of the general population or in patients with a sentinel episode of AP, but in 11% of those with RAP, and in up to 42% of those with idiopathic CP in India.[63–65] Interestingly, a Chinese study showed that *SPINK1* variants are more common in early- than late onset-idiopathic CP (32 vs. 2%).[66] Mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene are common among patients with idiopathic CP – up to 25% are compound heterozygotes

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with a severe mutation on one and a mild-variable mutation on the second allele.[67] 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 and 5% may have RAP and CP.[68] More recently, minor *CFTR* gene mutations that primarily affect bicarbonate transport have also been associated with an increased risk of pancreatitis.[69] Mutations in other genes (e.g. chymotrypsin C [*CTRC*], calcium-sensing receptor [*CASR],* carboxypeptidase [*CPA*]) also increase susceptibility to pancreatitis, but precise estimates of risk for RAP and CP with these mutations is less clear.[70]

Hypertriglyceridemia (HTG) is a well-established cause of RAP, but not so for CP. HTG-related pancreatitis typically occurs in individuals with a common genetic abnormality of lipid metabolism and one or more secondary risk factors such as poorly controlled diabetes, heavy alcohol consumption, obesity, offending medication, and/or pregnancy.[71] Traditionally, a level greater than 1000 mg/dl is associated with pancreatitis, but recent studies suggest that the risk increases at levels as low as 177 mg/dL.[72] Hypercalcemia is a rare cause pancreatitis, and a true association is debated.[73]

The causal relationship between pancreas divisum alone and pancreatitis is controversial. Since pancreas divisum is common in the general population (up to 5–10%)[74], additional factor(s) may be needed in these subjects to increase the risk of pancreatitis. One such factor may be *CFTR* mutations, which were noted to be over represented among patients with RAP and CP when compared with controls and pancreatitis patients with other etiologies.[75] These data however need to be replicated in other studies. The relationship between sphincter of Oddi dysfunction with RAP and CP is also controversial. Results of the EPISOD trial have empirically shown that addressing sphincter hypertension does not alleviate pain symptoms with presumed or proven sphincter of Oddi dysfunction.[76] Similarly, elevated sphincter pressures are highly prevalent in patients with idiopathic RAP, raising the possibility that this is likely the result of RAP and CP rather than the cause.[77, 78]

Other causes are considered rare. Over 100 drugs can cause AP by different mechanisms, and if not discontinued, can cause recurrent episodes. Medications do not cause CP.[79] Patients with celiac disease have 2- to 3-fold greater risk of developing pancreatitis (AP or CP) when compared with the general population; the highest risk of such diagnosis is within the first year of detection.[80] In celiac disease, the pancreas is sensitized by altered levels of autoregulatory enteric hormones and papillary inflammation.[81] Features of RAP or CP have also been demonstrated in patients with autoimmune pancreatitis (AIP), more commonly in patients with type 2 than type 1 AIP.[82, 83]

Natural history

The natural history in RAP patients could take one of the following three clinical scenarios – i) some may have none or more attack(s) of AP with preserved exocrine and endocrine function; ii) some may in addition develop varying combination of abdominal pain symptoms, functional derangement but do not progress to develop morphological changes of CP; and, iii) some may have varying combination of AP attack(s), abdominal pain symptoms and functional derangement and develop morphological progression to CP.

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In observational studies of patients after the first-attack of AP, among patients who had at least one recurrence, 36% subsequently progress to CP.[10] The probability of transition from RAP to CP can be highly variable; known predictors include underlying etiology, ongoing alcohol and tobacco use, burden of RAP episodes, and presence of pancreatic necrosis during AP attacks.[7, 11, 42, 50, 84–87] The prevalence and pattern of pain and functional derangement in RAP patients who do not develop morphological changes of CP is not well studied. While these data provide a good summary of the natural history, a study of RAP patients based on specific etiologies is more illustrative.

Following the first episode of alcoholic pancreatitis, 25 to 50% progress to RAP.[11, 42, 50, 86] Of those with RAP, 42 to 80% may progress to CP.[50, 84, 86] The risk of disease progression is linked to continuation of drinking and smoking habits.[11, 42, 50, 86] A Japanese study found that in patients who continued to drink at the same level, the risk of subsequent recurrences and progression to CP was the greatest at 58% and 41% respectively, and was the lowest (20% and 13%) among those who stopped drinking completely.[50] Observations in a cohort from Finland found similar results, and in a randomized trial they demonstrated a beneficial effect of abstinence on disease recurrences.[88, 89]

Progression from AP to CP is also high in the presence of genetic susceptibility factors. Hereditary pancreatitis related to *PRSS1* mutation, though an uncommon cause of RAP and CP, has the greatest risk of transition from AP to CP. Overall, ~80% subjects carrying the mutation have at least one episode of AP, and about half of them progress to CP, usually after one or more attacks of RAP.[43, 44] The risk of AP, RAP and CP in subjects who are heterozygote for *CFTR* mutations, homozygote for milder mutations in the CF gene, and with mutations in other genes, such as *SPINK1*, *CPA1*, *CASR*, *CTRC* has not been well quantified.

The natural history of idiopathic pancreatitis differs based on the age at disease onset - this distinction has been well described for CP[46], but not for RAP. Patients with early-onset idiopathic CP have disease course similar to patients with genetic susceptibility factors. In observational studies, between 20–50% of patients with idiopathic RAP progress to CP.[78, 87, 90] Endoscopic therapy in these patients does not appear to alter the risk of progression to CP.[78, 87]

A recent retrospective study in a cohort of patients with HTG and pancreatitis reported the prevalence of RAP and CP to be 53% and 17%; and the risk of progression from RAP to CP to be 33%.[91] The risk of recurrences is directly linked to serum TG control, i.e. tight control is associated with reduced recurrences.[92] Therefore, counseling for diet and lifestyle modification, diabetes control, and medical therapy could prevent disease progression.[93]

Compared to RAP, the natural history in patients with established CP has been well defined. Abdominal pain occurs in approximately 90% of patients at some time during the disease course. In a large US cohort of CP patients, 67% reported severe pain, 53% constant pain, and 16% no pain in the year preceding study enrollment.[22] Exocrine insufficiency and type-3 diabetes can develop in up to 87% and 80% respectively during the disease course.[94] Pancreatic calcifications and ductal dilation can be present in ~60% of patients.[14] The course

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of clinical, functional and morphologic features varies with disease etiology - alcoholic CP has a more aggressive course when compared with other etiologies. Almost all patients with alcoholic and early-onset idiopathic CP have pain, while approximately half of those with late-onset idiopathic etiology have a painless course. [46, 94] End-stage features develop after a median of 5–10, 10–20, 20–30, and 30–40 years from the onset of symptoms in alcoholic, late-onset idiopathic, early-onset idiopathic, and hereditary CP, respectively. [43, 46, 84, 94]

Survival

Several population studies evaluating the long-term survival after diagnosis of established CP have demonstrated a 2 to 5-fold greater risk of death when compared with the sex- and age-matched population controls.[32, 95, 96] Long-term survival after a first episode of AP was evaluated in a Danish population study with a 30-year follow-up.[97] This study demonstrated that mortality rate in patients who did or did not progress to CP was 6 and 1.6 times the expected rate in the background population, respectively. Unfortunately, comparisons were not reported between AP patients who had recurrent attacks during follow up and those who progressed to CP. There are no data on long-term survival in patients with RAP. In another Danish study, mortality rate in patients with probable CP was 2.1 to 2.7-fold greater when compared with the background population.[95] Since probable CP is an intermediary stage for CP, and a subset of these patients have RAP, these data suggest that mortality rate for RAP may be greater than expected, but lower when compared with CP patients.

The causes of death during long-term follow-up of patients with RAP have not been studied. In CP, the most common causes of death include cancer (22–23%), cardiovascular disease (12–21%), and diseases of the alimentary tract (15–23%).[32, 96, 98] Many of these are linked to lifestyle factors and comorbidities in CP patients.[96] When compared with general population, CP patients have a 13-folds greater lifetime risk of pancreatic cancer, and also an increased risk of other malignancies (e.g. liver cancer, small intestinal cancer, lung cancer) and chronic conditions (e.g. chronic kidney disease, chronic pulmonary disease, cerebrovascular disease).[96, 99]

Quality of life (QOL)

The effect of CP on QOL has been evaluated using different validated generic instruments (SF-36, SF-12, and EORTC QL-C30/QLQ-PAN26). A disease specific QOL instrument for CP has been developed and validated (PANQOLI), but has not been widely used yet.[100] This 18 item-scale evaluates physical function, role function, emotional function, and self-worth (e.g. economic health, body image, stigma, and overall health). No validated disease specific instruments are available for RAP.

CP has a significant impact on QOL. In a study from the NAPS2 cohort, CP had an independent effect on both physical QOL and mental QOL when compared with controls with no pancreatic disease.[101] In CP patients, pancreatic pain, especially constant, seems to be the predominant factor causing this impairment.[102, 103] Poor QOL may be a contributing factor for the high rates of unemployment, work absenteeism, and low annual personal income seen in these patients.[104] There are no data on the effect of RAP on QOL.

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Conclusions and future directions

Studies in the past few years have convincingly demonstrated that AP, RAP and CP represent a disease continuum. RAP represents a high-risk group, comprised of individuals at varying risk of progression. Although many clinical factors have been identified, accurately predicting the disease course in individual patients remains difficult. Future studies should focus on providing more precise estimates of the risk of disease transition in a cohort of patients, quantification of clinical events during the natural course of disease, and discovery of biomarkers associated with different stages of disease. Availability of clinically-relevant endpoints and linked biomarkers will allow accurate prediction of disease course over an intermediate or long term based on characteristics of an individual patient. These endpoints will also provide objective measures for use in clinical trials of interventions that aim to alter the natural course of disease.

Acknowledgments

Dr. Yadav is supported in part by NIH (UO1 - DK108306).

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Key findings/future unmet needs/implications

- Acute pancreatitis (AP), recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) represent a disease continuum.
- Disease progression is dependent on clinical factors, such as etiology, ongoing risk factors, and local complications.
- Future studies should provide more precise estimates of the risk of disease transition in a cohort of RAP and CP patients, and quantify clinically relevant outcomes during disease course. This approach combined with collection of biological samples at different stages of diseases will allow discovery of biomarkers of disease progression.
- Information on clinically relevant endpoints and biomarkers of disease will provide objective measures to use for interventions that aim to alter the natural course of disease.

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Table 1

Causes of recurrent acute and chronic pancreatitis

Cause (%)	**Approximate frequency**	
	RAP	**CP**
Gallstones	10–30	Rare
Alcohol	25–50	40–70
Idiopathic	10–30	20–30
Genetic- *CFTR, SPINK1, PRSS1, CTRC, CPA*	5–10	10–15
Hypertriglyceridemia	3–5	1–2
Autoimmune Pancreatitis	2	2
Celiac disease	1	1
Other autoimmune diseases	1	1
Post-necrotic	Unknown	3
Obstructive causes (e.g. stricture, tumor)	<5%	<5%
Pancreas divisum	Controversial	Controversial
Sphincter of Oddi dysfunction	Controversial	Controversial
Hypercalcemia	Rare	Rare
Drugs	Rare	0