Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Title:
Etiological diagnosis of recurrent acute pancreatitis

Authors:
Alberto Gómez Pérez, Ana Aparicio Serrano, Francisco Javier Serrano Ruiz

DOI: 10.17235/reed.2024.10404/2024
Link: PubMed (Epub ahead of print)

Please cite this article as:
Gómez Pérez Alberto, Aparicio Serrano Ana, Serrano Ruiz Francisco Javier. Etiological diagnosis of recurrent acute pancreatitis. Rev Esp Enferm Dig 2024. doi: 10.17235/reed.2024.10404/2024.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

10404 editorial

Etiological diagnosis of recurrent acute pancreatitis

Alberto Gómez Pérez, Ana Aparicio Serrano, Francisco Javier Serrano Ruiz

Gastroenterology Clinical Management Unit. Hospital Universitario Sofía. Córdoba, Spain

Author contributions: Writing-original draft: A. G. P., A. A. S., and F. J. S. R.

Conflict of interest: the authors declare no conflict of interest.

Artificial intelligence: the authors declare that they did not use artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

INTRODUCTION

Acute pancreatitis (AP) is highly prevalent worldwide, necessitating a comprehensive approach to identify and treat its underlying factors in order to prevent recurrence. Despite early intervention, one-third of patients experience recurrent acute pancreatitis (RAP) (1). Many of the recognized etiological factors associated with RAP are treatable and are usually already present at the time of the first episode. Identifying and addressing these factors may substantially reduce the likelihood of recurrence in a significant percentage of patients (2).

RAP is defined as two or more well-documented episodes of AP with complete resolution between episodes, lacking morphological criteria for chronic pancreatitis (CP), and separated by at least 3 months (2). RAP is notably observed in males aged 30-40 years, in smokers and in those with excessive alcohol consumption. Additionally,

it is also observed, albeit to a lesser extent, in patients with underlying biliary disease. Notably, RAP exhibits lower morbidity and mortality rates when compared to individuals experiencing a single episode, which is likely attributable to reduced pancreatic injury resulting from the acinar cell loss and fibrosis developed during previous AP episodes (3).

Approximately 25-50 % of RAP cases may progress to CP within 10 years, with various risk factors influencing this progression. Alcoholic etiology, smoking, AP severity, and male sex are factors that have been associated with a higher risk of developing CP in the context of RAP (1,4).

ETIOLOGY

Various factors contribute to RAP (Table 1), including microcholelithiasis (in up to 10 % of RAP cases) (5), alcohol abuse, tobacco use, hypertriglyceridemia, drug-induced cases, autoimmune pancreatitis, and genetic mutations.

In the context of alcohol consumption, the risk for RAP is intricately linked to factors such as quantity of alcohol consumed, duration of consumption, and cumulative exposure (6). Research indicates that lithiasic disease and alcohol abuse contribute significantly to 60-70 % of RAP cases (5). Moreover, the combined use of tobacco and alcohol exacerbates the risk of RAP, with tobacco acting both synergistically and independently as a risk factor (7). There is a positive association between smoking and non-gallstone-related pancreatitis but not gallstone-related pancreatitis in current smokers (8).

Hypertriglyceridemia emerges as a well-established cause of RAP with a direct correlation between triglyceride levels and risk. The likelihood of developing acute pancreatitis in individuals with hypertriglyceridemia exceeding 1000 mg/dL is approximately 5 %, escalating to 10-20 % when levels surpass 2000 mg/dL (9).

Among the limited number of drugs implicated in RAP through clinical trials, azathioprine, 6-mercaptopurine and didanosine have demonstrated potential roles (10).

Other diseases have been associated with an increased risk of RAP, such as type-2 autoimmune pancreatitis, known as idiopathic duct-centric pancreatitis (11); celiac disease, which heightens the risk of AP by sensitizing pancreatic acinar cells to gut hormone alterations and papillary inflammation (12,13).

Genetic factors also play a pivotal role, with mutations in the PRSS1 gene (linked to hereditary CP), as well as in the SPINK1, CFTR, and CTRC genes (14), resulting in recurrent episodes of acute pancreatitis.

Additionally, various pathologies leading to pancreatic duct obstruction such as pancreaticobiliary tumors, annular pancreas, post-necrosis stenosis, common bile duct cyst type 3, and intraductal papillary mucinous tumor, contribute to the occurrence of RAP (13). Anatomical variants, including pancreas divisum (PD) or sphincter of Oddi dysfunction, also stand out as potential causes of RAP (15).

It is crucial to consider less common causes of RAP, such as metabolic conditions (hyperparathyroidism or hypercalcemia), systemic diseases such as systemic lupus erythematosus or vasculitis (polyarteritis nodosa), and toxins such as pesticides (2).

Despite an adequate initial etiological study, in approximately 10-30 % of patients a specific cause cannot be identified, leading to their classification as having idiopathic RAP. Recent meta-analyses have highlighted the efficacy of advanced diagnostic tests such as magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) in unveiling the cause in about 50 % of cases previously deemed idiopathic. Notable causes identified through these advanced diagnostic methods include microcholelithiasis, unknown underlying CP, and pancreaticobiliary tumors (16).

DIAGNOSIS

Physicians managing AP should prioritize an accurate etiological diagnosis to facilitate optimal treatment, and minimize the risk of recurrent episodes, cumulative-damage, and unnecessary invasive procedures. A systematic, rational study is imperative for identifying the causative agent in RAP, considering the multifactorial nature of its origin (Fig. 1).

For patients experiencing a first episode of AP, a thorough anamnesis and physical examination is essential. Questioning should cover the pertinent family and patient history, including biliary disease, inflammatory bowel disease (IBD), celiac disease, familial hyperlipidemia, and family history of pancreatitis, cystic fibrosis, or pancreatic cancer. Additionally, investigations into drug use, alcohol consumption (quantity and duration) and tobacco use are crucial, along with an assessment of any history of biliary colic and of gastric or pancreaticobiliary surgery.

A comprehensive blood test, encompassing parameters such as hemogram, liver function, transaminases, cholestasis, triglycerides, cholesterol, and indirect markers of alcohol consumption should be conducted. Abdominal ultrasound should be performed in all patients with AP to identify potential gallstones and schedule cholecystectomy to prevent recurrent attacks as well as potential biliary sepsis (17,18). In case of poor image quality, significant inflammatory component or unidentified etiology, a repeat ultrasound after 5-7 days is recommended, given that cholelithiasis may be diagnosed even months after an initial AP episode (17,19).

While this initial approach may identify an etiology in up to 70-80 % of cases (2,20,21), managing RAP remains a challenge because of scarce evidence, with most studies being retrospective, and an absence of clinical guidelines. Despite this, it is advisable to perform advanced imaging studies (abdominal CT/MRCP/EUS) during the first AP episode. The choice of an imaging test should be based on patient profile, test availability, and clinical suspicion. Contrast-enhanced CT is typically the initial cross-sectional imaging test, especially in situations suggestive of pancreatic cancer (18-20).

If a new episode of AP occurs, repeating the initial basic study is recommended. If not performed during the first AP episode, a contrast-enhanced abdominal CT scan should be performed to rule out a biliopancreatic malignancy, especially in patients with unexplained weight loss, severe abdominal pain, jaundice, or recent diabetes or glycemic decompensation.

In cases where abdominal CT reveals no abnormal findings, and basic studies were performed during the initial AP episode, these should be cautiously examined according to clinical suspicion. If blood tests, alcohol consumption, and abdominal ultrasound are normal, MRCP/EUS are recommended. EUS is especially useful for

gallbladder patients as it allows an evaluation of microlithiasis, biliary sludge, anatomical changes, solid or cystic pancreatic lesions, and unrecognized underlying CP (19,22).

EUS emerges as an accurate, safe method for assessing idiopathic AP. Its accuracy in detecting microcholelithiasis and cholelithiasis, particularly when previous tests were inconclusive, highlights its diagnostic value (23). It also allows the diagnosis of choledocholithiasis, ampullary lesions, pancreatic duct abnormalities, and pancreatic cysts (2). Given its high yield and low risk of complications, and being the most sensitive technique for the diagnosis of pancreatic tumors smaller than 2 cm (24), it is recommended as the primary technique for studying idiopathic RAP.

MRCP, a non-invasive technique, allows examination of the pancreatic parenchyma and biliary and pancreatic ductal anatomy. MRCP is superior to EUS in identifying biliary strictures and PD, while EUS excels in detecting choledocholithiasis, microcholelithiasis and biliary mud (25).

Intravenous secretin administration with MRCP (MRCP-S) enhances visualization of the main pancreatic duct and of anomalies such as PD and incipient ductal stenosis. It outperforms conventional MRCP in diagnosing ductal anomalies in RAP patients. In addition, MCRP-S facilitates the evaluation of pancreatic exocrine function and indirect assessment of sphincter of Oddi motility. However, it is contraindicated in patients with recent AP. Integrating MRCP-S into the study of patients with RAP is recommended, but its limited availability in clinical practice should be taken into account (2,26).

Once a comprehensive assessment has failed to reveal a causative agent, if no new AP episodes occur, conservative management may be a reasonable approach. Alternatively, if recurrent episodes persist, an expanded etiological study should be undertaken considering less frequent causes. The initial basic workup should be repeated, including immunoglobulin IgG4 and antinuclear antibody levels to rule out autoimmune pancreatitis and vasculitis, and metabolic causes should be investigated. In addition, a CT or MRCP scan should be performed; the choice of either test depends on which one was previously used. For suspected autoimmune pancreatitis, obtaining histological material may aid in the differential diagnosis, especially to exclude

pancreatic adenocarcinoma (27).

Genetic studies play an important role, particularly in younger patients where a biliary or alcoholic etiology was reasonably ruled out. Genetic counseling and testing may be considered for younger patients (< 30 years of age) with recurrent episodes (> 1 episode) of idiopathic acute pancreatitis, especially if there is a family history of pancreatic disease (17,19). Certain genetic mutations are prevalent among patients with RAP, and it remains unclear whether these mutations act in the presence of other factors such as PD to modify disease severity or response to treatment. Research suggests that genetic variants within the PRSS1, SPINK1, CTFR and CTRC genes may be present in approximately 58 % of patients with RAP classified as idiopathic (28).

Recurrent acute pancreatitis represents an important problem regarding patient disability and health care burden. In order to avoid new episodes of AP, the study should focus on making an accurate etiological diagnosis. For this reason, it is paramount to perform a systematic and rational study, from an initial basic study including anamnesis and physical examination, blood tests and abdominal ultrasound, to advanced diagnostic tests such as EUS or MRCP. EUS is to be preferred for patients with the gallbladder in place because of its superior performance for small tumors and microcholelithiasis. Genetic counseling (not necessarily genetic testing) may be considered for younger patients (< 30 years of age) when no cause is apparent and a family history of pancreatic disease is present.

REFERENCES

1. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol 2019;16(3):175-84. DOI: 10.1038/s41575-018-0087-5

2. Guda NM, Muddana V, Whitcomb DC, et al. Recurrent Acute Pancreatitis: International State-of-the-Science Conference with Recommendations. Pancreas 2018;47(6):653-66. DOI: 10.1097/MPA.0000000000001053

3. Mallick B, Shrama DJ, Siddappa P, et al. Differences between the outcome of recurrent acute pancreatitis and acute pancreatitis. JGH Open 2018;2(4):134-8. DOI: 10.1002/jgh3.12060

4. Ahmed 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):738-46. DOI: 10.1016/j.cgh.2015.12.040

5. 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):1959-62. DOI: 10.1111/j.1572-0241.2002.05907.x

6. 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. DOI: 10.1016/j.ebiom.2015.11.023

7. Andriulli A, Botteri E, Almasio PL, et al. Smoking as a cofactor for causation of chronic pancreatitis: a meta-analysis. Pancreas 2010;39(8):1205-10. DOI: 10.1097/MPA.0b013e3181df27c0

8. Aue D, Mahamat-Saleh Y, Norat T, et al. Tobacco smoking and the risk of pancreatitis: A systematic review and meta-analysis of prospective studies. Pancreatology 2019;19:1009-1022. DOI: 10.1016/j.pan.2019.09.004

9. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis. JAMA Intern Med 2016;176(12):1834-42. DOI: 10.1001/jamainternmed.2016.6875

10. Saini J, Marino D, Badalov N, et al. Drug-Induced Acute Pancreatitis: An Evidence-Based Classification (Revised). Clin Transl Gastroenterol 2023;14(8):e00621. DOI: 10.14309/ctg.0000000000000621

11. De Pretis N, Frulloni L. Autoimmune pancreatitis type 2. Curr Opin Gastroenterol 2020;36(5):417-20. DOI: 10.1097/MOG.0000000000000655

12. 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):1136-42 e3. DOI: 10.1016/j.cgh.2012.06.023

13. Guda NM, Romagnuolo J, Freeman ML. Recurrent and relapsing pancreatitis. Curr Gastroenterol Rep 2011;13(2):140-9. DOI: 10.1007/s11894-011-0176-x

14. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology 2013;144(6):1292-302. DOI: 10.1053/j.gastro.2013.01.069

15. 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):311-7. DOI: 10.1038/ajg.2011.424

16. Umans DS, Rangkuti CK, Sperna Weiland CJ, et al. Endoscopic ultrasonography can detect a cause in the majority of patients with idiopathic acute pancreatitis: a systematic review and meta-analysis. Endoscopy 2020;52(11):955-64. DOI: 10.1055/a-1183-3370

17. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400-15;1416. DOI: 10.1038/ajg.2013.218

18. Crockett SD, Wani S, Gardner TB, et al. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology 2018;154:1096-101. DOI: 10.1053/j.gastro.2018.01.032

19. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1-15. DOI: 10.1016/j.pan.2013.07.063

20. Machicado JDaY, D. Acute Relapsing Pancreatitis. In: Domínguez-Muñoz JE, editor. Clinical Pancreatology for Practising Gastroenterologists and Surgeons; 2021. DOI: 10.1002/9780470987506.CH5

21. Strand DS, Law RJ, Yang D, et al. AGA Clinical Practice Update on the Endoscopic Approach to Recurrent Acute and Chronic Pancreatitis: Expert Review. Gastroenterology 2022;163(4):1107-14. DOI: 10.1053/j.gastro.2022.07.079

22. Leppaniemi A, Tolonen M, Tarasconi A, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg 2019;14:27. DOI: 10.1186/s13017 019-0247-0

23. Morris-Stiff G, Al-Allak A, Frost B, et al. Does endoscopic ultrasound have anything to offer in the diagnosis of idiopathic acute pancreatitis? J Pancreas 2009;10(2):143-6.

24. Iglesias-Garcia J, de la Iglesia-Garcia D, Olmos-Martinez JM, et al. Differential diagnosis of solid pancreatic masses. Minerva Gastroenterol Dietol 2020;66(1):70-81. DOI: 10.23736/S1121-421X.20.02646-X

25. 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):1180-8

e9. DOI: 10.1016/j.gie.2017.11.028

26. Sandrasegaran K, Tahir B, Barad U, et al. The Value of Secretin-Enhanced MRCP in Patients with Recurrent Acute Pancreatitis. AJR Am J Roentgenol 2017;208(2):315-21. DOI: 10.2214/AJR.16.16566

27. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011;40(3):352-8. DOI: 10.1097/MPA.0b013e3182142fd2

28. Jalaly NY, Moran RA, Fargahi F, et al. An Evaluation of Factors Associated with Pathogenic PRSS1, SPINK1, CTFR, and/or CTRC Genetic Variants in Patients With Idiopathic Pancreatitis. Am J Gastroenterol 2017;112(8):1320-9. DOI: 10.1038/ajg.2017.106

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

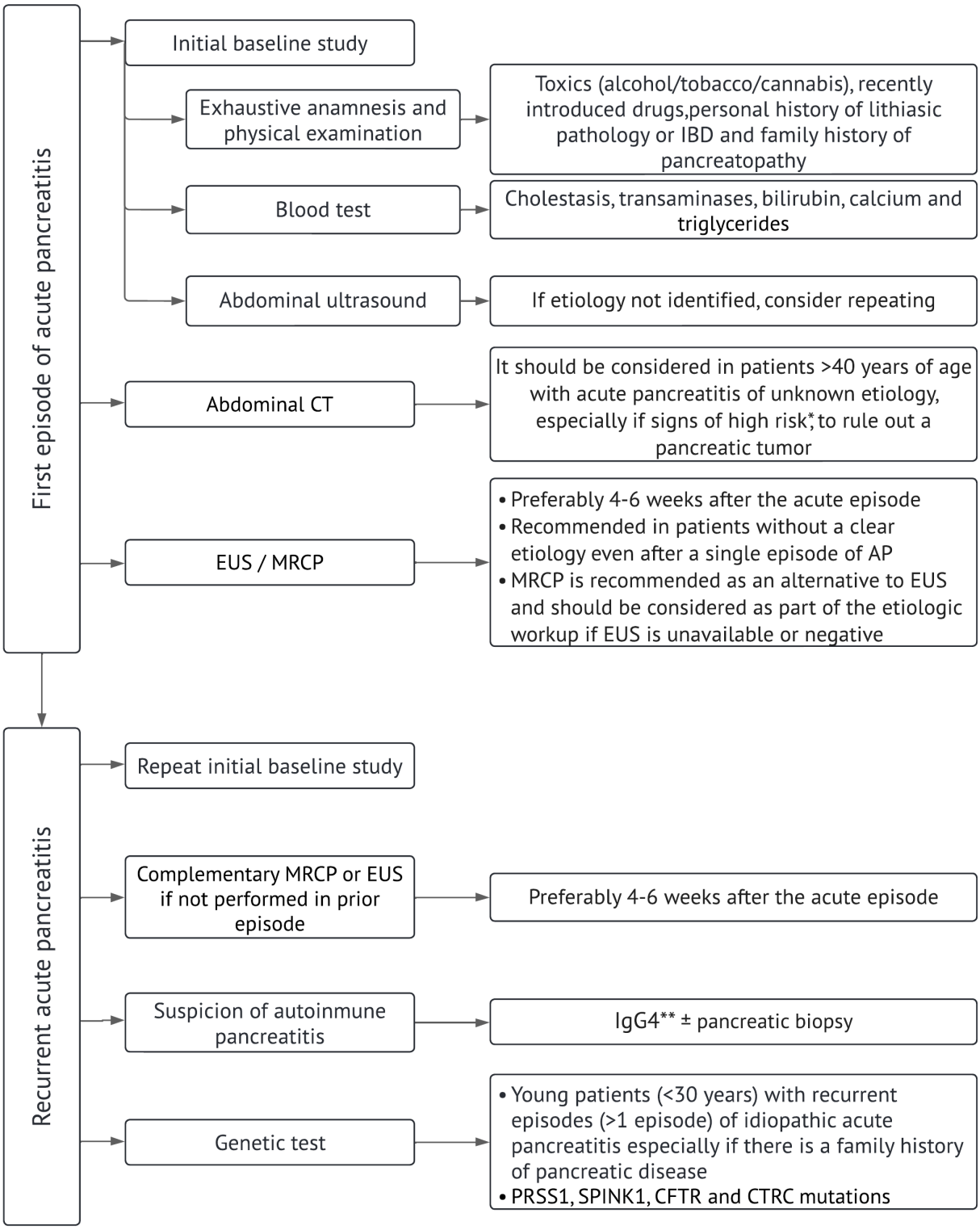

Figure 1. Recommendations for the etiological diagnosis of acute and recurrent acute pancreatitis. *Weight loss, jaundice, severe abdominal pain and new onset diabetes or glycemic decompensation. **Serum IgG4 determination is not routinely recommended as part of the etiological study (CE-CT: contrast-enhanced computed tomography; EUS:

endoscopic ultrasound; MRCP: magnetic resonance cholangiopancreatography; IBD: inflammatory bowel disease).

Table 1. Etiology of acute pancreatitis

Obstructive	Biliary lithiasis, pancreatic tumors, distal cholangiocarcinoma, ampuloma, sphincter of Oddi dysfunction, pancreas divisum*, duodenal diverticulum, duodenal stricture-obstruction, cholodochocele type IV, parasites (*Ascaris lumbricoides*)
Toxic	Ethanol, organophosphate poisoning, scorpion venom (only some species). Tobacco smoking is an important cofactor
Metabolic	Hypertriglyceridemia, hypercalcemia (primary hyperparathyroidism or iatrogenic infusion)
Iatrogenic	Post ERCP (acute pancreatitis is the most frequent post-ERCP complication), post PTC, post-surgical, peritoneal dialysis, renal transplantation, drugs (valproic acid, azathioprine, diclofenac, didanosine, ACE inhibitors, loop diuretics, thiazide diuretics, mesalamine, metronidazole, L-asparaginase, pentamidine, tetracycline, simvastatin)
Autoimmune	Type 1 and type 2 autoimmune pancreatitis
Genetic	CFTR, PRSS1, SPINK1, and other genetic mutations
Infectious	Hepatotropic viruses (hepatitis A, B, E), CMV, *Cocksackie*, varicella-zoster, HSV, HIV, *Legionella*, *Mycoplasma*, *Salmonella*, *Leptospira*, *Aspergillus*, *Toxoplasma*, *Cryptosporidium*
Other	Ischemia, vasculitis (polyarteritis nodosa, SLE), kinetic injury and other trauma (including seat belt injuries)

*Controversial. 5-ASA: 5-aminosalicylic acid; ACE: angiotensin-converting enzyme; CMV: cytomegalovirus; ERCP: endoscopic retrograde cholangiopancreatography; HIV: human immunodeficiency virus; HSV: herpes simplex virus; PTC: percutaneous transhepatic cholangiography; SLE: systemic lupus erythematous.

Revista Española
de Enfermedades Digestivas
The Spanish Journal
of Gastroenterology