Etiology of acute pancreatitis

Review Article

Tomas Ratia Gimenez*, Alberto Gutierrez Calvo, Javier Granell Vicent

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Abstract: Acute pancreatitis is a common disease with a benign course in the majority of patients, but it is associated with serious morbidity, and mortality close to 20% in up to 20% of cases. The incidence of acute pancreatitis seems to be rising in western countries. About 75% of all cases are caused by gallstones or alcoholism. The relative rate of gallstones versus alcohol as etiology depends on the age and the area of enrolment. A thorough evaluation allows cause identification in another 10% of cases, leaving about 15-20% as idiopathic. The most common causes, and a growing list of less frequent and sometimes very rare and controversial etiologies, are reviewed in this article. A classification on the pathogenic mechanisms of causes of acute pancreatitis based is used in this Review. The approach, or suggested plan of investigations, to determine the etiology of acute pancreatitis, based on the most recently published Guidelines is outlined.

Keywords: Acute pancreatitis • Etiology • Guidelines • Pathogenesis

1. Introduction

Acute pancreatitis is an inflammatory disease of the pancreas that resolves without serious complications in 80% of cases, but may cause morbidity and mortality in up to 20% of patients. It is a disorder that has numerous causes, a complex, not fully understood pathogenesis, and often an unpredictable outcome [1].

Being a common disorder, accurate assessment of its incidence and mortality is difficult as mild pancreatitis may be subclinical and deaths may occur before diagnosis in fulminant cases. It represents 0.15-1.5% of all diagnosis in emergency room. Its prevalence varies in different countries and even in different areas inside a given country; it ranges from 200-300 cases/million inhabitants a year [2].

In the United States more than 300,000 patients are admitted per year for pancreatitis [3].

Over the last four decades, the overall incidence of acute pancreatitis seems to be increasing, not only in the United States, but also in different European countries: England, Scotland, Denmark, Sweden, Finland, Germany and the Netherlands [1,3-5].

In the Netherlands the incidence of acute pancreatitis increased by 28% between 1985 and 1995. In the United Kingdom the incidence of acute pancreatitis rose by a factor of ten from 1960 to the 80s [5]. Population studies from Europe and the United States have described the epidemiology of first attacks of acute pancreatitis, mostly in a retrospective way; only few report etiology-specific incidence trends. This increase has been attributed to a rise in the incidence of gallstone pancreatitis. A population study in California found that the incidence of gallstones increased 32% from 1994 to 2001 [6].
In contrast to gallstones pancreatitis, the trend for acute alcoholic pancreatitis differs among studies. Reports from the United Kingdom, Sweden, and Finland indicate an increase in alcoholic pancreatitis correlating with an increase in the per capita alcohol consumption [5,7,8].

The overall mortality in hospitalized patients is about 10% (range 2 to 22%), with a mortality that may be as high as 30% in the subset of severe acute pancreatitis [1].

2. Etiology of acute pancreatitis.

The etiology and pathogenesis of acute pancreatitis has been investigated for centuries. In 1856 Claude Bernard suggested that bile reflux into the pancreatic duct could induce acute pancreatitis [9]. In 1889 Reginald Fitz described many of the modern clinical and pathologic characteristics of severe acute pancreatitis [10]. In 1901 Eugene Opie wrote about the association between gallstones and pancreatitis, proposed the theory of migration of stones in the common bile duct, as the main cause of acute pancreatitis [11]. In 1917, alcohol was considered an important pathogenic factor for acute pancreatic inflammation [12].

About 70-80% of acute pancreatitis cases are caused by gallstones or alcohol abuse.

In the United States, Asia and Western countries gallstones are the most common cause of acute pancreatitis accounting for 45% of cases. Alcohol, the second most common etiology, causing about 35% [13].

The variability in the distribution of etiologies for acute pancreatitis in different geographical areas is shown in Table 1 [14-16].

Etiology of acute pancreatitis, as has been shown in a Swedish study has an important influence on the incidence or relapse over a period of ten years: 48% for alcoholic, 21% for gallstones, 18% for idiopathic cases [15].

Although some of the causes for acute pancreatitis besides gallstones and alcohol, are certainly very uncommon, they deserve being known and considered to aminorate the percentage of cases considered as idiopathic. The Classification of causes of acute pancreatitis that will be used in this Review is shown in Table 2.

A thorough evaluation of the patients allows for the determination of the cause in most cases of acute pancreatitis; as it is but still, 10-20% of cases remain idiopathic. In the UK Guidelines for the management of acute pancreatitis published in 2005, states that no more than 20% of cases should be classified as idiopathic [17]. This number should be reduced by better expertise in new diagnostic technologies, and improved knowledge of this disease.

Determining the cause of acute pancreatitis is a critical component of the diagnostic evaluation. It affects therapy vitally. Different etiologies have diverse natural histories, complications, and implications. An etiologic diagnosis can result in elimination of the precipitating factor and prevention of recurrence. Certain causes of pancreatitis have long-term consequences (eg, pancreatic cancer associated with hereditary pancreatitis) [18].

Table 2. Classification of causes of Acute Pancreatitis.

- Obstructive
  - Gallstones
  - Biliary sludge and microlithiasis
  - Tumors
  - Parasites-Worms
  - Pancreas Divisum
  - Sphincter of Oddi Dysfunction
  - Other obstructive causes: choledocholes, duodenal diverticula, annular pancreas

- Alcohol, toxins, drugs
- Metabolic disorders
  - Hypertriglyceridemia
  - Hypercalcemia

- Post ERCP
- Trauma
- Infections
- Vascular-Ischemia
- Hereditary
- Miscellaneous

Table 1. Relative percentage of Acute Pancreatitis etiologies in different geographical areas.*

<table>
<thead>
<tr>
<th>Etiology</th>
<th>New York, USA (14)</th>
<th>Sweden (15)</th>
<th>New Delhi, India (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstones</td>
<td>32%</td>
<td>38.4%</td>
<td>49%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>20%</td>
<td>31.8%</td>
<td>23.6%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>18%</td>
<td>23.2%</td>
<td>16.5%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>29%</td>
<td>6.6%</td>
<td>10%</td>
</tr>
</tbody>
</table>


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3. Causes of acute pancreatitis

3.1. Obstructive

3.1.1. Gallstones
The most common obstructive cause of acute pancreatitis are gallstones: 40% of cases of acute pancreatitis. It is caused by migration of calculi from the gallbladder, towards the duodenum. Proposed mechanisms include biliary reflux into the pancreatic duct because transient obstruction of the ampulla during stone passage, and pancreatic ductal hypertension from either stone impacted at the ampulla or ampullary trauma by stone passage [19].

The increase in pancreatic duct pressure results in damage to the integrity of the duct system; bile reflux can activate trypsin and subsequent unregulated activation of trypsin within pancreatic acinar cells, and release of a series of inflammatory mediators [9,18].

Only 3-7% of patients with gallstones develop acute pancreatitis. It is more common in women than in men, because gallstones are more frequent in women. Older age and female sex are frequent characteristics of acute pancreatitis of biliary origin. However the risk of developing pancreatitis in gallstones patients is higher in the male sex [19].

The probability of stones causing acute pancreatitis are inversely proportional to its size. It is more probable when stones are less than 5 mm in diameter, because they more easily pass through the cystic duct and cause ampullary obstruction or trauma [20].

A prior history of biliary colic suggests this diagnosis. Abnormal liver function tests have been classically associated with a biliary origin. An elevated serum alanine aminotransferase (ALT) concentration of 150IU/L or more had a positive predictive value of 95% for the diagnosis of biliary acute pancreatitis [2].

Besides that, all patients in the first episode of acute pancreatitis should have an abdominal ultrasound to look for gallstones, choleodochal stones or signs of extrahepatic biliary obstruction. After one negative ultrasound examination the most sensitive test for diagnosis of gall stones remains a further ultrasound exam. The advent of endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) increase the range of tests available to search for duct stones or microlithiasis [17].

3.1.2. Biliary sludge and Microlithiasis
Biliary sludge is a viscous suspension in the gallbladder bile that may contain small stones (<3mm); it is a mixture of particulate solids precipitated from bile. This sediment consists of cholesterol crystals, calcium bilirubinate pigment, and other calcium salts [21]. Biliary sludge is usually detected on transabdominal ultrasonography: produces a mobile, low amplitude echo, without acoustic shadow. Microscopy of aspirated bile and EUS are far more sensitive. Biliary sludge is typically found when there is functional or mechanical bile stasis; it may be associated with prolonged fasting or total parenteral nutrition, or in the presence of distal common bile duct obstruction.

Biliary sludge has been observed in pregnancy; and with rapid weight loss in the obese. It has also been associated with drugs such as as ceftriaxone and octreotide; and with bone marrow or solid organ transplantation. Its clinical expression is variable. It is usually asymptomatic but may cause biliary colic, cholangitis and acute pancreatitis [22]. Cholecystectomy is indicated if symptoms or complications appear. It is found in 20 to 40% of patients of acute pancreatitis without a known cause. The gold standard for diagnosis of microlithiasis is microscopic analysis of gallbladder bile, obtaining the bile through an endoscope, tube or catheter. Although there is no universally accepted method for analyzing bile for microlithiasis. EUS may have a sensitivity of about 90% for microlithiasis [23,24].

The finding of sludge can be difficult to interpret because it may represent the consequence rather than the cause of pancreatitis. Empiric cholecystectomy may be considered in patients with gallbladder in situ and recurrent attacks of pancreatitis where other etiologies have been ruled out [23,24].

3.1.3. Tumors
This etiology should be considered especially in recurring acute pancreatitis in non alcoholic men older than 40. It should be considered when worrisome features such as as weight loss, new onset of diabetes, and older age are present in patients with unexplained acute pancreatitis. In such patients cross sectional imaging of the pancreas and pancreatic duct is appropriate: CT with pancreas protocol or MRCP. Alternatively EUS can be used [24].

The most common neoplasm with this presentation is intraductal papillary mucinous neoplasm (IPMN). This tumor often presents with recurrent episodes of acute pancreatitis caused by temporary pancreatic duct obstruction by highly viscous mucus [25].

Ampullary tumors can occasionally obstruct the pancreatic duct and cause acute recurrent pancreatitis [26].

Pancreatic adenocarcinoma has been described as cause of acute pancreatitis in a small percentage of patients [27-29].
Metastases from other primary tumors (lung and breast) in the pancreas may also cause obstructive acute pancreatitis [30].

Neuroendocrine tumors of the pancreas has been described as associated with acute pancreatitis [31].

3.1.4. Parasites-Worms

In Kashmir, India, ascariasis is the second most frequent cause of acute pancreatitis. Worms migrate in and out of the biliary and pancreatic ductal systems [32].

Acute pancreatitis caused by Clonorchis infestation has also been described [19].

3.1.5. Pancreas divisum

It is considered as a controversial cause of acute pancreatitis by many authors. Pancreas divisum is the most common congenital malformation of pancreas occurring in 5-10% of the general healthy population. The proximal dorsal pancreatic normal regresses while the rest of the dorsal duct fuses with the ventral pancreatic duct to produce a single duct that empties through the major papilla. In pancreas divisum normal fusion fails to occur: the dorsal duct drains most of the pancreas through the minor papilla and the ventral duct drains only the head of the pancreas through the major papilla. Pancreas divisum is diagnosed by pancreatography either by ERCP or MRCP [18,33,34].

The association is controversial because 95% of patients who have pancreas divisum do not suffer from pancreatitis. A minority of patients with pancreas divisum becomes symptomatic with recurrent acute pancreatitis, chronic pancreatitis or chronic abdominal pain without evidence of pancreatitis. Some referral centers report that patients with recurrent acute pancreatitis have a higher incidence of pancreas divisum than general population [19,35].

In a recent cross-sectional population study, from Japan, made to determine (non biased by endoscopical selection) the prevalence of pancreas divisum in a community population, and to investigate this malformation on idiopathic pancreatitis using non invasive magnetic resonance studies. It described their association with idiopathic pancreatitis, concluding that pancreas divisum should be considered as predisposing factor to recurring pancreatitis [34].

The underlying mechanism in those cases is thought to be the relative obstruction to the flow of pancreatic juice through the minor papilla due to a true or relative stenosis. The finding of chronic obstructive changes confined to the dorsal pancreatic duct supports this hypothesis. Surgical sphincteroplasty as well as endoscopic interventions as endoscopic minor papillotomy, insertion of dorsal duct stents, dilation and injection of botulinum toxin into the minor papilla have been applied with variable success in symptomatic patients. However, data is limited and there is a lack of long term follow-up studies; but it seems that pancreas divisum patients with well-defined bouts of pancreatitis are more likely to benefit from endoscopic minor papillotomy than patients with continuous pain or when this is not associated to hyperamylasemia [36,37].

3.1.6. Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction (SOD) has also been considered as controversial cause of acute pancreatitis [18,19,24,33,38]. The sphincter of Oddi is a segment of circular and longitudinal muscle 6 to 10 mm long encircling the distal common bile duct and pancreatic duct. A resting pressure is maintained to allow the gallbladder to fill during fasting and prevent retrograde reflux of duodenal contents into the choledochus. Sphincter relaxation allows coordinated release of bile and pancreatic secretions into the duodenum to digest intraluminal contents and neutralize the gastric acid in duodenal lumen [18,33,38].

SOD refers to sphincter spasm or uncoordinated contractions. Manometric features include an elevated basal sphincter pressure that decreases with smooth muscle dilators, rapid bursts or sphincter contraction, retrograde phasic contractions, and a paradoxical increase in its pressure after administration of cholecystokinin octapeptide.

In cases of recurrent acute pancreatitis where Oddi sphincter manometry is performed, a basal sphincter pressure >40mmHg has been the most common abnormal finding described, in 35-40% of patients. Delayed drainage of contrast in ERCP and a dilated pancreatic duct are also features suggestive of SOD as a potential cause of pancreatitis.

Numerous observational series report the elimination of recurrent attacks of acute pancreatitis after endoscopic pancreatic sphincterotomy, or surgical sphincteroplasty.

But the lack of prospective controlled blinded trials in the treatment of this disorder; the short duration of follow up in the observational reports and the high risk of acute pancreatitis (25-35%) associated with sphincter of Oddi manometry and pancreatic sphincterotomy in this setting, make the association of acute pancreatitis and SOD difficult to be determined. Careful selection of patients is required to identify those who may benefit from manometry and subsequent treatment. Type I patients of pancreatic SOD, according the contemporary classification, (recurrent pancreatitis, elevated amylase or lipase, dilated pancreatic duct or delayed emptying) would be the patients where endoscopic or surgical...
intervention in the sphincter of Oddi, should be more successful in avoiding recurrent acute pancreatitis [39].

### 3.1.7. Other obstructive causes
Coledochoeles types V [13,19], periampullar duodenal diverticula [40], annular pancreas [41].

### 3.2. Alcohol, toxins, drugs

#### 3.2.1. Ethyl alcohol
Ethyl alcohol is the most common toxin causing acute pancreatitis, and the second most frequent cause of acute pancreatitis overall: 30-35%. It is the most frequent etiology of chronic pancreatitis [1,13,19].

Identification of the alcoholic origin of an episode of acute pancreatitis is relevant in order to avoid the use of non-necessary diagnostic tools. It is well known that information obtained by asking the patient or relatives is often inadequate, and questionnaires developed to estimate the intake of alcohol have a low sensitivity and specificity [2].

There may be several pathogenic mechanisms involved: sphincter of Oddi spasm, precipitation of insoluble protein plugs in pancreatic ductules, activation of pancreatic proteases, and overstimulation of pancreatic secretion by cholecystokinin. Failure to inhibit trypsin activity or to wash active trypsin into pancreatic ducts might promote alcoholic pancreatitis [42].

In relation to its pathogenesis, it is well known that alcohol alone is not sufficient to cause pancreatitis. In animal models it has been shown that in addition to alcohol another stimulus is required to initiate pancreatic injury. Only a very small proportion of alcohol abusers (5-10%) ever develop pancreatitis. In addition to alcohol other factors are important in the development of alcoholic pancreatitis. It might be affected by both genetic and environmental factors, or their interaction [42].

Well defined cofactors to alcohol in pancreatitis pathogenesis are: Smoking, more than 90% of patients with alcoholic pancreatitis are also chronic smokers [43]; Race, there is a higher risk of alcoholic pancreatitis among African Americans compared to whites; Diet and Drinking pattern, with conflicting data on the influence of high-fat, high-protein diet; and the influence of binge alcohol drinking is also unclear. The known genetic variations in cystic fibrosis transmembrane gene (CFTR), the cationic trypsinogen gene (PRSS1) and the serine protease inhibitor Kazal type 1 (SPINK1), and polymorphisms in alcohol metabolizing pathway do not seem to play an important role in alcoholic pancreatitis [42,44].

Alcoholic acute pancreatitis is more frequent among males (male/female ratio 2.5/1). It occurs in a pancreas already damaged by prior toxicity, and it has been published that chronic pancreatitis develops in 70% of patients 10 years after the initial episode of acute pancreatitis. The main controversy regarding alcohol related pancreatitis is whether the acute episodes represent exacerbations of chronic pancreatitis or if there are truly recurrent attacks of acute pancreatitis [1].

In relations to etiology-specific severity and mortality in alcoholic acute pancreatitis, data is mixed. A population-base study from California found that the odds of dying from acute alcoholic pancreatitis were higher compared with gallstones and idiopathic, after controlling demographic factors. The pancreas of alcoholics may be at higher risk of ischemic injury or segmental necrosis because it is already under metabolic stress and has a decreased reserve and tolerance for injury [6,46,47].

#### 3.2.2. Other Toxins
Methyl alcohol, Trinidad, and Brazil Scorpion venom (massive cholinergic hyperstimulation of the pancreas) [19], methyl alcohol, organophosphorous insecticides have been reported to induce acute pancreatitis. Smoking, until recently considered only as a cofactor associated to alcohol, however some studies suggest smoking as an independent risk factor for acute and chronic pancreatitis [48].

#### 3.2.3. Drugs
Drugs are an infrequent but important cause of acute pancreatitis. About 2% of cases are due to this etiology. The diagnosis of drug induced acute pancreatitis is often difficult to establish. Drug induced pancreatitis tends to be mild and self limited; besides general measures cessation of the offending drug is critical [18,49].

More than 120 drugs have been implicated. Drug induced pancreatitis rarely is accompanied by clinical or laboratory evidence of a drug reaction, such as rash or eosinophilia. The association between a drug and pancreatitis is strengthened by the number of reported cases, and the quality of these individual cases. Acute pancreatitis has to occur during drug exposure, other causes excluded, resolution of pancreatitis after drug withdrawal, and recurrence of pancreatitis with drug rechallenge, but a pancreatic hypersensitivity reaction after re-exposure to the drug may be dangerous [19].

Several different mechanisms of drug induced acute pancreatitis have been proposed [50]. These include immunologic or hypersensitivity reactions, that usually occur 4 to 8 weeks after starting the drug and is not dose related. On rechallenge pancreatitis appears within hours or days. In this group are 6-mercaptopurine and Azathioprine, that are among the drugs with a highest
incidence of associated acute pancreatitis. Other drugs in this group: Aminosalicylates, sulfasalazine, metronidazole, tetracycline.

A second group of drugs cause acute pancreatitis by accumulation of toxic metabolites, usually after several months of use. In this category are valproic acid, didanosine and pentamidine. Some drugs may induce hypertriglyceridemia (e.g., thiazides, isotretinoin, tamoxifen).

An overdose of some drugs like acetaminophen and erythromycin may cause acute pancreatitis by its intrinsic toxicity.

In Table 3, Drugs with the greatest evidence of causing acute pancreatitis are shown; those with challenges, or with relatively predictable latency [51].

### Table 3. Drugs associated with acute pancreatitis.

<table>
<thead>
<tr>
<th>Definite association</th>
<th>Probable association</th>
<th>Possible association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminosalicylates</td>
<td>Chlorthalidone</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>Cyclosporine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Ethacrynic acid</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Didanosine</td>
<td>FK-506</td>
<td>Carbamazepine</td>
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<tr>
<td>Estrogen</td>
<td></td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Furosemide</td>
<td></td>
<td>Cholestyramine</td>
</tr>
<tr>
<td>Probable association</td>
<td></td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Definite association</td>
<td>Probable association</td>
<td>Contrast media</td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>Probable association</td>
<td>Danazol</td>
</tr>
<tr>
<td>(Sulfasalazine, Mesalamine)</td>
<td>Probable association</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>Probable association</td>
<td>Diphenoxylate</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Probable association</td>
<td>Ergotamine</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Probable association</td>
<td>Pentamidine</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Probable association</td>
<td>Sulfonamide</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Probable association</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Probable association</td>
<td>Probable association</td>
<td>Thiazides</td>
</tr>
<tr>
<td>Definite association</td>
<td>Probable association</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>Probable association</td>
<td>Vinca alkaloids</td>
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<tr>
<td>L-asparaginase</td>
<td>Probable association</td>
<td>6 mercaptopurine</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Probable association</td>
<td>HMG-CoA reductase inhibitors</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Probable association</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Probable association</td>
<td>Ritampin</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Probable association</td>
<td>Steroids</td>
</tr>
</tbody>
</table>


### 3.3. Metabolic disorders

#### 3.3.1. Hypertriglyceridemia

Hypertriglyceridemia causes about 2-5% of cases of acute pancreatitis. Its association with this disease is particularly well defined in children with rare hereditary disorders of lipoprotein metabolism: congenital types I, II and V hyperlipidemia [52].

Serum triglyceride level greater than 1000mg/dL may precipitate attacks of acute pancreatitis. The release of free fatty acids by lipase may damage acinar cells or capillary endothelium.

Alcoholic pancreatitis sometimes is associated with hypertriglyceridemia, but rarely is higher than 1000mg/dL. Alcohol itself increases serum triglyceride concentrations in a dose-dependent manner.

The triglyceride level should be measured early after clinical symptoms of acute pancreatitis, because that elevation declines rapidly due to fasting during hospitalization, insulin therapy and restoration of fluid and electrolyte balance [53].

The typical clinical profile of adults with hyperlipemic pancreatitis is a patient with preexisting lipid abnormality along with the presence of a secondary factor (e.g., poorly controlled diabetes, alcohol use, or a medication) that can induce hypertriglyceridemia. It is more unusual to find a patient with isolated hyperlipemia (type V or I) without a precipitating factor presenting with pancreatitis [54].

The clinical manifestations of hypertriglyceridemia acute pancreatitis are similar to other causes of acute pancreatitis, but elevations in serum amylase are minimal. Its severity has a tendency to be more severe than biliary or alcoholic acute pancreatitis. Routine management should be similar to that of other causes. A thorough family history of lipid disorders should be obtained, and an attempt to identify secondary causes should be made [55].

#### 3.3.2. Hypercalcemia

Acute pancreatitis has been considered a complication of primary hyperparathyroidism [56]. The prevalence of acute pancreatitis in that disease has been estimated to be between 1.5 and 13%. However, not all the studies have shown an increased incidence of pancreatitis in patients with primary hyperparathyroidism. In a population-based study done in Minnesota is suggested that the relationship between acute pancreatitis and primary hyperparathyroidism is a chance association. That contradicts reports based primarily upon surgical or hospital based cohorts, which likely selects the most severe cases [57,58].

Proposed mechanisms are calcium deposition within the pancreatic duct; or de novo trypsinogen activation to trypsin induced by calcium. Sudden, brisk elevations of
Acute pancreatitis is the most common complication of ERCP; it happens in approximately 5% or ERCPs, with a range of 2-7% depending on the criteria for defining pancreatitis [18,19]. A higher incidence is reported after therapeutic ERCP, 7%, and especially high incidence, 25% when SOD is suspected or with history of previous post-ERCP pancreatitis. Although mild in most cases, 5-10% are severe because complications and prolonged hospitalization [60].

In some reviews this etiology is classified under the Trauma category, but we will discuss it as a separate entity, as we think post ERCP acute pancreatitis has its specific characteristics.

Asymptomatic hyperamylasemia occurs after 35% to 70% of ERCPs.

Post ERCP acute pancreatitis is multifactorial, involving chemical, hydrostatic, enzymatic, mechanical and thermal factors. Two pathophysiologic theories have been proposed, and the two may act synergistically. First, traumatic intubation of the ampulla can cause sphincter spasm, delayed pancreatic drainage, and pancreatic duct hypertension. Second, excessive hydrostatic pressure in contrast injection may injure the pancreatic duct and parenchyma [18].

In general, the more likely a patient is to have an abnormal bile or pancreatic duct, the less likely the patient will develop post-ERCP pancreatitis [61].

Early recognition of post-ERCP pancreatitis is possible by evaluating serum amylase or lipase after the procedure. Bedside assessment alone has been shown to be suboptimal in diagnosing acute pancreatitis. A combined clinical and laboratory assessment has been shown to be most sensitive and specific. A post ERCP serum amylase or lipase drawn 2-4 h after the procedure greater than 4-5 times the reference values, is a relatively rapid and reliable predictor of pancreatitis [62].

3.5. Trauma

Blunt or penetrating trauma can damage the pancreas. In most cases there is also injury to adjacent viscera. In penetrating trauma laparotomy is necessary for assessment and treating all intrabdominal injuries [19,63].

Blunt trauma results from compression of the pancreas by the spine. It can range from mild contusion to a severe crush injury or transection of the gland, with disruption of pancreatic ductal system. The diagnosis of traumatic pancreatitis is difficult, requiring a high degree of suspicion. Serum amylase may be increased in abdominal trauma whether or not the pancreas has been injured. Diagnosis is highly dependent on CT or MRCP, which may show enlargement of the gland, or fluid in the anterior pararenal space, typically associated to ductal disruption. It has to be remembered that the CT may be normal during the first two days despite significant pancreatic trauma. If there is strong clinical suspicion of pancreatic injury, or if CT scan or MRCP show an abnormality, ERCP will be required to define whether there is pancreatic duct injury [64,65].

3.6. Infections

Acute pancreatitis has been associated with multiple infections: viruses, bacteria, fungi and parasites [1,18,66]. Mumps and coxsackie B virus are the most common causes of infectious pancreatitis among immunocompetent patients. Other viral causes include Hepatitis B, Hepatitis C, Cytomegalovirus, Herpes simplex, and Varicella Zoster, Epstein-Barr, the vaccine that contains attenuated measles, mumps, and rubella viruses [18,67-70].


In acquired immunodeficiency syndrome (AIDS) infectious agents causing acute pancreatitis include Cytomegalovirus, Mycobacterium avium, Mycobacterium tuberculosis, Pneumocystis carinii and Candida species. Often they are associated with widespread opportunistic infections [71,72].

Hyperamylasemia is common in patients who have AIDS and most of them do not have acute pancreatitis [18]. Drugs that are used in the treatment of opportunistic infections as trimethoprim or pentamidine, or drugs used to treat the HIV infection itself as didanosine can cause pancreatitis. Opportunistic infections may involve the pancreas in patients with AIDS, presenting as pancreatic infection or abscess and less commonly as acute pancreatitis.

3.7. Vascular-ischemia

Pancreatic ischemia is an infrequent cause of pancreatitis due to the rich perfusion of the pancreas from the superior and inferior pancreaticoduodenal artery [73,74].

serum calcium levels may increase the risk of pancreatitis [19,56].

Rarely pancreatitis has been associated with other causes of hypercalcemia: metastatic bone disease, total parenteral nutrition, sarcoidosis, vitamin D toxicity and infusions of calcium in high doses [59].

3.4. Post endoscopic retrograde cholangiopancreatography (ERCP)

Acute pancreatitis is the most common complication of ERCP; it happens in approximately 5% or ERCPs, with a range of 2-7% depending on the criteria for defining pancreatitis [18,19]. A higher incidence is reported after therapeutic ERCP, 7%, and especially high incidence, 25% when SOD is suspected or with history of previous post-ERCP pancreatitis. Although mild in most cases, 5-10% are severe because complications and prolonged hospitalization [60].

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In most cases it is mild, but fatal necrotizing pancreatitis may happen.

Ischemia may result from vasculitis (polyarteritis nodosa, systemic lupus erythematosus), atheromatous embolism of cholesterol plaques from the aorta after angiography, intraoperative hypotension, hemorrhagic shock, ergotamine overdose, cocaine use, transcatheter arterial embolization for hepatocellular carcinoma, or liver metastases; hypercoagulable disorders (antiphospholipid antibodies, factor V Leiden mutation [75-78].

Ischemia may be an explanation for pancreatitis after cardiopulmonary bypass [79,80]. Acute pancreatitis has been described in marathon runners, and explained on an ischemic pathogenesis [81].

3.8. Hereditary

Hereditary pancreatitis is related to mutations in different genes that may cause uncontrolled action of trypsin. While some of these mutations may be associated with acute pancreatitis, the primary presentation is chronic pancreatitis (or pancreatic malignancy) [24].

Serine protease 1 gene mutation (PRSS1): is the most common cause of autosomal hereditary pancreatitis. It is a dominant gain-of -function disorder related to mutations of the cationic trypsinogen gene which has an 80% penetrance. It causes premature activation of trypsinogen to trypsin. Alcohol, smoking, and dietary fat are triggers for acute pancreatitis [82-85].

Serine protease inhibitor Kazal type 1 gene mutations (SPINK1): also called pancreatic secretory trypsin inhibitor gene; there is an inability to inhibit intracellular trypsin in the acinar cells. A combination of genetic and environmental factors influences de development of pancreatitis. Patients with this mutation typically develop chronic pancreatitis in childhood [85,86].

Cystic fibrosis transmembrane conductance regulator gene mutations (CFTR): this gene regulates the elimination of Trypsin by flushing the pancreatic duct. Inherited in autosomal recessive pattern are important cause of chronic pancreatitis. While most of these patients are evaluated for unexplained chronic pancreatitis, some develop acute attacks [82,87].

Chymotrypsin C gene mutation (CTRC): Chymotrypsin C facilitates degradation of trypsin. A mutation in this gene has been associated to pancreatitis [83].

3.9. Miscellaneous

Penetrating peptic ulcer. It is a rare cause of acute pancreatitis. Hyperamylasemia in peptic ulcer disease is rather inespecific and not associated to acute pancreatitis. There are cases reported of posterior duodenal ulcers that penetrate into the pancreas causing pancreatitis, and even the communication between the ulcer and the pancreatic duct has been reported [88,89].

Aferent loop syndrome after gastrectomy [90].

Crohn’s disease. A case control study from Denmark found a 4-fold increase in the incidence of acute pancreatitis among patients with Crohn’s and a 1.5-fold increase among ulcerative colitis. Drugs used in the treatment of Crohn’s disease may cause acute pancreatitis [19,91].

Duodenal Crohn’s disease can cause obstruction in the pancreatic ductal system.

It can be considered an extraintestinal manifestation of inflammatory bowel diseases: autoimmune process can be the cause of pancreatitis in cases of extraduodenal Crohn’s disease [92].

Celiac disease. The relationship remains uncertain, although it has been described [93].

Autoimmune pancreatitis. It is an extremely infrequent cause of acute pancreatitis (prevalence, 0.82 per 100,000). These patients rarely present with acute pancreatitis, more commonly the present as chronic pancreatitis or a mass, which may be mistaken with pancreatic carcinoma. An elevation on serum immunoglobulin G subclass 4 levels is typical, as well as a bulky pancreatic head and long or multifocal strictures of the pancreatic duct in ERCP without significant dilation. This entity has been described in patients with different autoimmune disorders: primary sclerosing cholangitis, autoimmune hepatitis, Sjogren syndrome, and inflammatory bowel disease [94].

Severe Burns [95]
Renal transplantation [96]
Alpha 1 antitrypsin deficiency [97]
Pregnancy. Acute pancreatitis in pregnancy is a rare condition estimated to occur in 1 per 1000 to 1 per 12,000 pregnancies. The most frequent etiology in pregnancy is biliary, followed by hyperlipidemia and/or alcohol abuse. Non biliary causes are associated with worse prognosis. Abdominal ultrasound and endoscopic ultrasound are ideal imaging techniques for diagnosing disease because they have no radiation risk. In the last decades the outcome of acute pancreatitis in pregnancy is much better, and perinatal mortality is less than 5% [98].

Anorexia nervosa [99]
Postoperative [13,19]
4. Determining the etiology of acute pancreatitis

According to the UK guidelines for the management of acute pancreatitis (2005) no more than 20% of cases of acute pancreatitis should be considered as idiopathic. Investigations considered to be helpful determining the etiology of acute pancreatitis, distributed in different evolutive phases of the disease are [17]:

**History:** should focus on previous gallstones symptoms or documentation, alcohol intake, family history (genetic analysis indicated in the presence of a family history of one or more of the following: acute pancreatitis, recurrent undiagnosed abdominal pain, pancreatic carcinoma, or type 1 diabetes mellitus), drug intake, exposure to known viral causes or prodromal symptoms.

**Initial investigation (acute phase):** Pancreatic enzymes in plasma, liver function tests, ultrasound of gall bladder.

**Follow up investigations (recovery phase):** Fasting plasma lipids, fasting plasma calcium, viral antibodies titres, repeat biliary ultrasound, MRCP, CT (helical or multislice with pancreas protocol).

**Further investigations (usually appropriate for recurrent idiopathic acute pancreatitis):** Further ultrasound, Endoscopic ultrasound, autoimmune markers, ERCP (bile crystals-bile and pancreatic cytology), sphincter of Oddi manometry, pancreatic function tests to exclude chronic pancreatitis.

According the guidelines issued by the American Gastroenterological Association (2007), when common potential etiologies are excluded by history, laboratory studies, and imaging examinations, other more unusual conditions should be considered. In patients with intact gallbladder, occult cholelitiasis or microlithiasis is the most likely etiology. Missed cholelitiasis is best detected by repeating the transabdominal ultrasonography, or by EUS or MRCP [24].

Extensive or invasive evaluation is not usually recommended after a single episode of pancreatitis in patients younger than 40, but some recommend EUS even after one attack if the cause is not clear looking for ductal abnormalities, small tumors at or near the ampulla, microlithiasis, and early chronic pancreatitis. ERCP should not be performed after a single episode of acute pancreatitis in the absence of laboratory tests or imaging evidence of choledocolithiasis [24].

The consideration of malignancy as a potential etiology of unexplained acute pancreatitis would be appropriate in patients at risk, age older than 40 ys. and/or associated features (weight loss, new onset diabetes). In such patients, cross sectional imaging of the pancreas in indicated. Alternatively EUS could be used in that situation. MRCP are preferred before considering ERCP.

In patients with recurrent episodes of pancreatitis, at any age, EUS and/or ERCP should be considered. EUS is the preferred initial test. If etiology is not identified on ERCP, sphincter of Oddi manometry may be considered. Alternatively one could proceed to biliary and/or pancreatic sphincterotomies without measuring biliary and pancreatic pressures presuming a diagnosis of type 2 sphincter of Oddi dysfunction. Important limitations in diagnostic evaluation are the procedure related complications associated with invasive testing; that the relationship between some findings, such as pancreas divisum, SOD, microlithiasis, and pancreatitis are not always clear; methods for detection of microlithiasis have not been standardized [1,17,24]. An inherited cause of pancreatitis is looked in patients with an strong family history or with onset of symptoms at a young age (<35 years). All patients in whom genetic testing is done should have genetic counseling prior to, and after testing [24].

**Conflict of interest statement**

Authors state no conflict of interest.

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