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CLINICAL REVIEW

Idiopathic acute pancreatitis: a review on etiology and diagnostic work-up

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Abstract
Acute pancreatitis (AP) is a common disease associated with a substantial medical and financial burden, and with an incidence across Europe ranging from 4.6 to 100 per 100,000 population. Although most cases of AP are caused by gallstones or alcohol abuse, several other causes may be responsible for acute inflammation of the pancreatic gland. Correctly diagnosing AP etiology is a crucial step in the diagnostic and therapeutic work-up of patients to prescribe the most appropriate therapy and to prevent recurrent attacks leading to the development of chronic pancreatitis. Despite the improvement of diagnostic technologies, and the availability of endoscopic ultrasound and sophisticated radiological imaging techniques, the etiology of AP remains unclear in ~ 10–30% of patients and is defined as idiopathic AP (IAP). The present review aims to describe all the conditions underlying an initially diagnosed IAP and the investigations to consider during diagnostic work-up in patients with non-alcoholic non-biliary pancreatitis.

Keywords Acute pancreatitis · Endoscopic ultrasonography · Idiopathic pancreatitis · MRCP · *PRSS1*/*SPINK1*/*CTRC* mutations

Introduction

Acute pancreatitis (AP) is the most common gastrointestinal disease requiring hospitalization, and is associated with high morbidity and, in the case of necrotizing pancreatitis, high mortality ranging from 10 to 20% of patients [1–3]. The incidence of AP in Europe varies from 4.6 to 100 per 100,000 population, and has shown an increasing trend in the last decade [2, 3]. The main causes of AP, accounting for ~ 60–80% of all cases, are gallstones and alcohol abuse, which have the highest incidence in southern and eastern Europe, respectively [2]. In the remaining patients, even after an extensive evaluation of history, physical examination, laboratory tests and imaging studies, etiology remains unexplained. In these patients in whom no underlying condition could be identified, AP is labeled as idiopathic AP (IAP). IAP has been defined as a condition in which the etiological cause of an AP is not detectable after an accurate anamnesis excluding drug abuse, alcohol abuse, history of infection, an evaluation of metabolic disorder, including hypertriglyceridemia and hypercalcemia, genetic mutation and at least two second-level imaging techniques including EUS and MRCP to exclude abnormality of pancreatic gland, pancreatic or biliary and gallbladder lithiasis [4–8].

Two clinical patterns of IAP have been described: a form with an episode of acute inflammation of the pancreas with no further recurrence, accounting of 10–19% of AP expressing with an isolated episode; and an IAP characterized by two or more attacks of AP, defined as idiopathic recurrent acute pancreatitis (IRAP), accounting of 3–59% of all cases of recurrent AP [8–11].

Since this definition, a highly variable incidence of IAP has been reported, ranging from 8 to 44% [12, 13]. This large variability is very likely due to missed diagnosis of underlying conditions that are not immediately evident. Once all possible causes have been explored, the actual incidence of IAP was recently hypothesized to account for 10% of AP [9]. Despite the body of literature on this condition has grown over the last ten years, IAP is the third most frequent form of AP and still remains a clinical challenge [4, 14–18].

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The present review describes the possible etiological factors (Table 1) underlying an initially diagnosed IAP and the investigations to consider during diagnostic work-up in patients with non-alcoholic non-biliary pancreatitis.

Possible etiological factors responsible for non-alcoholic/non-gallstone-related acute pancreatitis

Microlithiasis and sludge

Microlithiasis or biliary sludge is a common cause of AP, in the absence of frank biliary obstruction due to gallstones [4]. The term microlithiasis refers to the presence of clusters of cholesterol monohydrate crystals, calcium bilirubinate granules, and/or calcium carbonate microspheroliths in bile duct or in gallbladder, without any detectable biliary stones. Biliary sludge was previously defined as the presence of low-level echoes that layer in the gallbladder without acoustic shadowing on ultrasonography [18]. Biliary sludge is composed of cholesterol monohydrate crystals, calcium bilirubinate granules, calcium carbonate salts or small gallstones (< 2 mm). The incidence of microlithiasis and sludge in the presence of AP varies from 28 to 80% [4, 14, 15, 18–22]. This wide range is probably due to the use of different diagnostic techniques. Endoscopic ultrasound (EUS) is a safe and minimally invasive technique able to detect microlithiasis (Fig. 1) with a diagnostic yield varying between 29 and 80% in IAP [9, 16, 22–24]. In addition, EUS sensitivity in diagnosing biliary microlithiasis in patients with AP was reported to be higher than contrast tomography (CT) scan or magnetic resonance cholangiopancreatography (MRCP) [9]. EUS should, therefore, be considered as a first-choice investigation in the diagnostic work-up of AP.

As microliths are predominantly composed of cholesterol, treatment with ursodeoxycholic acid (usually 12 mg/kg/day) was shown to have good efficacy in patients with recurrent AP [4, 24–26]. Endoscopic biliary sphincterotomy during endoscopic retrograde cholangiopancreatography (ERCP) either alone or in combination with cholecystectomy was reported to be curative in patients with IAP possibly associated with microlithiasis [9, 24, 25]. In a randomized prospective trial [27] including patients with recurrent acute pancreatitis (RAP) probably secondary to microlithiasis, laparoscopic cholecystectomy was found to be effective in preventing relapse of AP after exclusion of all other possible causes.

Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction (SOD) is a clinical syndrome due to dyskinesia (functional) or anatomic (mechanical)

Table 1 Conditions associated with idiopathic acute pancreatitis

Mechanical	Autoimmune diseases	Toxic–metabolic	Infections and Infestations	Miscellaneous
Microlithiasis	Autoimmune pancreatitis	Diabetes	Viruses (EBV, CMV, HSV, HAV, HBV, HCV, HEV, H1N1, HIV)	Genetic mutations (*PRSS1*, *CFTR*, *SPINK1*, *CTRC*)
Sphincter of Oddi dysfunction	Mitochondrial disorders	Hypercalcemia	Bacteria (*Mycoplasma pneumoniae*, *Legionella pneumoniae*, *Brucella*, *Campylobacter jejuni*, *Yersinia enterocolitica*)	Hereditary pancreatitis
Anatomical anomalies	Rheumatic diseases	Hypertriglyceridemia	
Pancreatobiliary tumors	Vasculitis	Drugs (6-mercaptopurine, angiotensin converting-enzyme inhibitors, azathioprine, didanosine, mesalamine, valproic acid)	
Trauma		Cannabis, cocaine, opiates	Parasites (*Ascaris lumbricoides*)
		Mushrooms	
		Organophosphates	
		Poisoning	

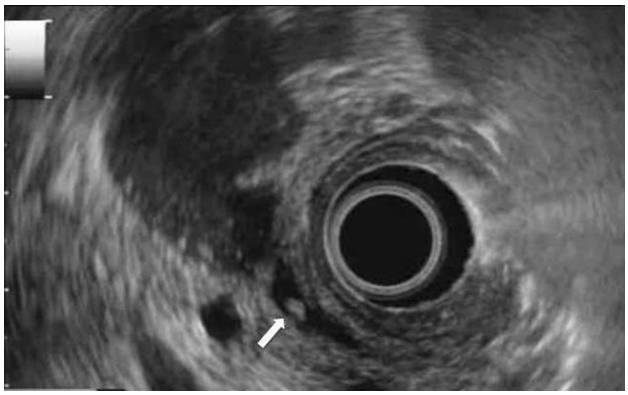

Fig. 1 Endoscopic ultrasound in a patient with idiopathic acute pancreatitis. Examination with a radial echoendoscope revealed microlithiasis (arrow) in the common bile duct

abnormality of the biliary and/or pancreatic sphincter causing intermittent or continuous obstruction to bile/pancreatic juice flow, associated with abdominal pain, elevation of liver or pancreatic enzymes, and dilation of common bile duct or pancreatic duct [28, 29]. The estimated prevalence of SOD is 1.5% in the general population and may be as high as 72% in patients with idiopathic recurrent pancreatitis based on small cohort studies [29]. The clinical presentation of SOD depends on whether only one or both sphincters are involved. The Milwaukee classification of SOD proposed by Hogan and Geenen [30] distinguishes between biliary-type and pancreatic-type SOD, and each SOD type is also sub-classified into three forms according to symptoms, laboratory tests and radiological imaging (Table 2). Although widely accepted for the classification of patients with suspected SOD, the Milwaukee classification has several limitations, primarily because it is often difficult to determine whether the origin of the pain is biliary or pancreatic. Conditions predisposing to SOD include cholecystectomy [31], agenesis of the gallbladder [32], preoperative cholelithiasis, gallstone lithotripsy, and liver transplantation [28]. Hypothyroidism has been associated with a delayed emptying of the biliary tract, suggesting that it might be another risk factor for SOD [33, 34].

SOD may be diagnosed by sphincter of Oddi manometry (SOM), which reveals a hypertensive sphincter of Oddi pressure, with a basal biliary or pancreatic sphincter pressure > 40 mmHg in 15–72% of patients with RAP initially diagnosed as idiopathic [17]. Although considered the gold standard test for SOD diagnosis, the use of SOM is controversial as it requires skilled endoscopists and highly specialized equipment not widely available, it is associated with up to 30% of post-manometry pancreatitis, and is not confirmatory in ~ 13–40% of patients ultimately diagnosed with type I SOD [26]. Therefore, SOM is nowadays rarely employed [8].

The first treatment proposed for SOD was surgery, although it has been suggested that endoscopic treatment with biliary endoscopic sphincterotomy alone or in combination with pancreatic sphincterotomy (dual endoscopic sphincterotomy) may be more effective in the prevention of RAP. However, a prospective randomized controlled trial [35] showed no difference between dual endoscopic sphincterotomy and biliary endoscopic sphincterotomy alone in preventing RAP. In another randomized controlled trial [36] on patients with abdominal pain after cholecystectomy possibly related to SOD, sphincterotomy was not found to be more effective than sham therapy (placebo) in reducing symptoms. These findings seem to support the hypothesis that patients with SOD, in particular those with type III, may have a functional abdominal pain syndrome related to visceral hypersensitivity [30].

Table 2 Milwaukee classification of sphincter of Oddi dysfunction

Biliary-type SOD	Pancreatic-type SOD
Type I	Type I
Typical biliary-type pain	Pancreatic-type pain
Liver enzymes (AST, ALT or ALP) > 2 times normal limit documented on at least 2 occasions during episodes of pain	Amylase and/or lipase > 2 times normal limit documented on at least 2
Dilated CBD > 12 mm in diameter	occasions during episodes of pain
Prolonged biliary drainage time (> 45 min)	Dilated pancreatic duct (head > 6 mm, body > 5 mm)
Type II	
Biliary-type pain and One or two of the above criteria	Prolonged pancreatic drainage time (> 9 min)
Type III	Type II
Biliary-type pain only	Pancreatic-type pain and One or two of the above criteria
	Type III
	Pancreatic-type pain only

ALP Alkaline phosphatase, *ALT* alanine transaminase, *AST* aspartate transaminase, *CBD* common bile duct, *SOD* sphincter of Oddi dysfunction

In these patients, treatment with nitrates and nifedipine, antidepressant drugs such as amitriptyline, or antispasmodics has been proposed [29, 37, 38]. Botulinum toxin injection into the papilla of Vater was also suggested [39] as an alternative medical procedure, but its efficacy and safety have not been investigated in clinical trials.

Anatomical anomalies

Pancreas divisum

Pancreas divisum (PD) is the most common anatomical variation and the most frequent congenital anomaly of the pancreatic duct, occurring in almost 5–10% of individuals [40]. PD is characterized by a malfusion of ventral and dorsal duct during gestation. Three different variations have been described: complete (the most common), incomplete, and dorsal duct PD. Although symptomatic PD is often detected in patients with IAP, whether PD is the primary cause or predisposes to AP for other reasons remains controversial [41]. Recent genetic studies [40, 42] found an association between PD and mutations in two genes, serine protease inhibitor Kazal type 1 (*SPINK1*) and the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, in > 20% of patients with pancreatitis, suggesting that PD may not be the main cause of AP. As far as the diagnosis of PD is concerned, the role of ERCP has recently become more limited due to its invasiveness and possible complications [11, 23]. MRCP and EUS are able to detect PD in > 90% of cases [9]. In two recent systematic reviews [43, 44] comparing MRCP with secretin-enhanced MRCP (S-MRCP), S-MRCP showed greater accuracy in diagnosing PD. Overall, sensitivity and specificity have been estimated to be 69–95% and 97% for EUS, 83–86% and 97–99% for S-MRCP, 59–73% and 97–99% for MRCP, 37–90% and 97% for CT scan [43, 45].

Therefore, in the case of suspected PD in IAP patients, EUS and S-MRCP should be preferred as first-line investigations, if available. First-line therapeutic approach to PD is ERCP with minor papilla sphincterotomy, dilatation, stenting, or a combination of these procedures. However, a long-term follow-up study reported high recurrence rates of AP in patients with PD, despite endoscopic therapy [23]. In a recent systematic review [46], surgery (pancreatic head resection, pancreaticojejunostomy, or pancreas left resection) was found to be more effective than endoscopic treatment in terms of success, complication, and re-intervention rates. However, no randomized trials comparing endoscopic and surgical procedures have yet been conducted to clarify which is the best treatment for PD-associated AP.

Annular pancreas

Annular pancreas is an anomaly occurring during gestation, consisting in a band of pancreatic tissue which partially or completely surrounds the second portion of the duodenum, in most cases at the level of or proximally to the major papilla [47]. This pancreatic anomaly affects approximately 1 in 20,000 newborns [48] and incidence in adults varies from 0.005 to 0.015% [49]. Six variants of annular pancreas are described [50]. The most frequent variants are type I, where the main pancreatic duct in the annular pancreas opens into the duct of Wirsung, and type II, where the main pancreatic duct encircles the duodenum. In the other types, the duct of Wirsung opens into the duct of Santorini or the bile duct. Clinical manifestation with intractable vomiting due to duodenal obstruction may occur during childhood. Adults, more frequently (65%) males, begin to suffer from abdominal pain, postprandial fullness and vomiting between the age of 30 and 50 years [50, 51]. Frequent complications secondary to annular pancreas include peptic ulcer, chronic pancreatitis, idiopathic RAP (IRAP), or biliary obstruction. One-third of patients with annular pancreas also present PD [51]. CT, MRCP and ERCP may reveal the presence of a ring surrounding the descending part of the duodenum. EUS, a less invasive approach, was reported to be effective in diagnosing annular pancreas [52, 53] and, together with fine-needle aspiration, pancreatic carcinoma involving annular pancreas [54]. The treatment of annular pancreas is a by-pass operation such as gastrojejunostomy or duodenojejunostomy with pancreaticoduodenectomy [55].

Pancreatobiliary tumors

AP caused by pancreatic duct obstruction may occasionally be due to tumors. Recurrent AP was reported in 7–67% of patients with intraductal pancreatic mucinous neoplasm (IPMN) of the pancreas [56, 57] and in up to 14% of patients with pancreatic adenocarcinoma [58]. Cystic pancreatic tumors, serous cystadenomas, mucinous cystadenomas, and mucinous cystadenocarcinomas may be premalignant or malignant and require surgery. IPMN of the pancreas is a cystic tumour characterized by the papillary proliferation of epithelial cells producing excess mucin and cystic dilatation of the main duct, the branch pancreatic ducts, or both. Patients with IPMN may occasionally present with recurrent AP due to intermittent obstruction of the main pancreatic duct by secreted mucin [59]. Pancreatic sphincterotomy was recently reported as safe and effective in reducing episodes of IPMN-associated AP [57].

Ampullary adenoma is a premalignant lesion also causing recurrent AP with a reported prevalence of 0.04–0.12% [60, 61]. As ~30% of ampullary adenoma may progress to adenocarcinoma [62], complete removal of adenoma is

essential for curative therapy [63]. It is agreed that an adenoma confined to the ampullary region may be successfully treated by endoscopic papillectomy [64], with success rates of up to 89% [65]. When the tumor extends into the biliary common duct > 10 mm, endoscopic treatment is not indicated and surgery is mandatory, especially when dysplasia is found in biopsy specimens and EUS revealed ductal dilation with no ductal invasion. However, baseline evaluation of ampullary tumor may not be conclusive and the choice between endoscopic papillectomy and surgery can be challenging. In a systematic review and metanalysis comparing complete primary resection, primary success, and recurrence outcomes of endoscopic papillectomy and surgery, the surgical approach achieved significantly better results with comparable complication rates compared to the conservative (endoscopic) approach [66]. If endoscopic management is the preferred treatment, surveillance and random biopsies should be performed.

CT and MRI are essential in identifying pancreatobiliary tumors. ERCP is indicated for palliative/preoperative treatment of jaundice [12]. EUS, especially when combined with fine-needle aspiration, nowadays plays a crucial role as it may provide useful information for histological diagnostic and staging purposes [diventano 67].

Medicines, drug abuse and toxic substances

Medicines are responsible for < 5% of all cases of AP. Although several pharmaceuticals have been implicated (Table 1), it is sometimes difficult to identify the specific drug causing AP, especially in patients on multi-therapy regimens [68].

Drug abuse (cocaine, cannabis, opiates) has been associated with occurrence of AP, although the pathophysiology of AP following assumption of illegal substances is still unknown. Cocaine may promote inflammation and pancreatic damage by inducing vasoconstriction, by interacting on cannabinoid pancreatic receptors, or through induction of SOD [68–71]. Cannabis is described as a possible risk factor for AP and RAP, primarily in patients aged < 35 years; a recent metanalysis [72] reported 26 cases of cannabis-induced AP. Toxicology screening should be considered in all patients with IAP, especially when young adults.

Ingestion of toxic substances containing organophosphates is also a rare cause of AP, possibly due to cholinergic hypersecretion [73, 74]. Cases of AP were reported following ingestion of *Lactarius volemus*, an edible mushroom [75].

Thus, all patients with AP of unknown etiology should be carefully questioned about lifestyle, including the use of medicines, substance abuse, occupation and diet to identify the intake of toxic substances possibly responsible for triggering the disease.

Metabolic disorders

Hypertriglyceridemia

Hypertriglyceridemia (HTG) is responsible for 2–5% of AP patients in Western countries [76] but the corresponding figure is 7.8–25.6% and tends to increase in China [77]. The role of HTG in inducing AP is widely debated. There is no consensus on a clear threshold above which triglycerides are associated with AP. According to the guidelines of the American College of Gastroenterology and of the Endocrine Society [78], a triglyceride level > 1000 mg/dL (> 11.3 mmol/L) should be considered as a risk factor for AP. Non-fasting mild/moderate HTG was recently proposed [79] as a possible cause of AP. The primary diagnostic workup of the etiology of AP should, therefore, include evaluation of serum triglycerides at hospitalization. However, triglyceride levels may fall rapidly within 24–48 h after the onset of AP because of fasting. Thus, if triglyceride assessment on admission was not performed is missing or may be considered unreliable due to fasting, diagnosis could be missed and AP labeled as idiopathic. In addition, the detection of hyperlipidemia facilitates dietary and pharmacologic treatment to prevent recurring attacks of AP. Weight reduction and cessation of alcohol intake should be recommended for the prevention of AP relapse. In the case of severe RAP due to hyperlipidemia, plasmapheresis should be considered as an additional treatment [80]. Of great importance is HTG-induced AP secondary to genetic mutations. Five genetic variants have been involved in the regulation of plasma lipid metabolism, namely *LPL* (encoding lipoprotein lipase, which catalyzes hydrolysis of TG-rich lipoproteins), *APOA5* (encoding apolipoprotein A-V, which stabilizes the lipoprotein–LPL complex), *APOC2* (encoding apolipoprotein C-II, which acts as an essential LPL activator), *GPIHBP1* (encoding glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1, which mediates the transmembrane transport and binding of LPL), and *LMF1* (encoding lipase maturation factor 1, which is involved in the folding and expression of LPL). However, the etiology of HTG in most cases is complex and likely involves gene–gene and/or gene–lifestyle interactions [81].

Hypercalcemia

Hypercalcemia as a cause of pancreatitis is very rarely reported, with an incidence of 0.4% [82]. Increased plasma levels of calcium may lead to AP through a block of enzymatic secretion and accumulation of digestive zymogens within the pancreatic acinar cells [83]. Common causes of hypercalcemia include hyperparathyroidism, malignancy (bone metastases, multiple myeloma, parathyroid carcinoma), vitamin D toxicity, sarcoidosis, familial

hypocalciuric hypercalcemia, and total parenteral nutrition [84, 85].

Diabetes

Patients affected by type 1 or type 2 diabetes mellitus have a greater probability to develop AP in respect to non-diabetic population, with an odds ratio of 1.86 in patients with type 2 diabetes. The incidence rate stated in different series ranges from 54 to 475/100,000 person-year [86]. Not only a severe episode of ketoacidosis [87, 88] but also the coexistence of comorbid risk factor factors has been associated with the occurrence of AP in diabetic patients [86].

Autoimmune disorders

Autoimmune pancreatitis

Autoimmune pancreatitis (AUIP) is rare, with a prevalence of < 1 to 4.6 per 100,000 individuals and an incidence of 1.4 per 100,000 [89–91]. AUIP is clinically characterized by presentation with obstructive jaundice sometimes associated with a pancreatic mass. Typical histopathological features are lymphoplasmacytic infiltrate and fibrosis [92]. Diagnostic criteria were described in 2011 and, on the basis of histopathological features, two distinct forms of AUIP were defined by the International Association of Pancreatology [92].

Type 1 AUIP: Lymphoplasmacytic sclerosing pancreatitis Lymphoplasmacytic sclerosing pancreatitis (LPSP) is the most common type of AUIP, with a greater incidence among Asiatic population groups aged > 50 years. Typical histological findings are dense lymphoplasmacytic infiltration, consisting mainly in CD4 + T lymphocytes, fibrosis without granulocytic infiltration, storiform fibrosis, obliterative phlebitis and > 10 IgG4-positive plasma cells/HPF. Clinically, LPSP is characterized by obstructive jaundice and/or pancreatic mass, and seems to be a pancreatic manifestation of an IgG4-related systemic disease. Extrapancreatic organs frequently involved at onset include the biliary tree (sclerosing cholangitis), chest (lung nodules, mediastinal fibrosis, adenopathy), retroperitoneum (retroperitoneal fibrosis, chronic periaortitis), salivary glands (sclerosing sialadenitis), kidneys (interstitial nephritis) and orbits (pseudolymphoma). Bowel involvement is rare. Elevated serum IgG4 levels are described in approximately two-thirds of patients. Late presentation is with pancreatic atrophy, calcification, ductal dilatation, and other features of advanced painless chronic pancreatitis. Patients may complain of recurrent mild pain, if present.

Type 2 AUIP: Idiopathic duct-centric pancreatitis Idiopathic duct-centric pancreatitis is a relatively recent form of AUIP observed in young (aged < 20) Europeans and Americans with no gender preponderance. It is also known as idiopathic duct-centric pancreatitis or AUIP with a granulocytic epithelial lesion. Intraluminal and intraepithelial neutrophils in medium-sized and small ducts, as well as in acini, often lead to the destruction and obliteration of the duct lumen. This form of AUIP seems to be a pancreatic-specific disorder rather than a systemic disorder like the type 1 form. It is not associated with high levels of IgG4, but ~ 30% of cases are associated with inflammatory bowel disease, such as ulcerative colitis [93]. Due to the lack of serological markers, pancreatic histology is frequently required for a definitive diagnosis of type 2 AUIP. EUS-guided tissue acquisition with a fine-needle biopsy is an emerging technique useful in clinical practice to obtain histological confirmation of AUIP [94].

In 2017, the treatment of AUIP was defined at an international consensus symposium [95]. Steroids remain the first-line agent in symptomatic patients, with an initial dose of 0.6–1.0 mg/kg/day for at least 12 weeks. Rituximab (anti-CD-20 antibodies) is recommended as an alternative therapy in patients in whom steroids are contraindicated [95].

Vasculitis

The gastrointestinal system may be involved in primary and secondary vasculitis, especially when small vessels are affected. A recent report described an uncommon pancreatobiliary involvement in pediatric patients with Henoch–Schönlein purpura [96]. A rare case of AP, associated with antineutrophil cytoplasmic antibody-related vasculitis, was also found in a 72-year-old man with suspected pancreatic tumor suffering from glomerulonephritis [97]. Finally, Wegener's granulomatosis was reported as a rare but possible cause of AP with rapid progression to severe multiorgan failure [98].

Rheumatic diseases

Systemic lupus erythematosus is an autoimmune multisystem disorder, which may involve the gastrointestinal tract. Lupus pancreatitis is usually associated with high systemic lupus erythematosus activity and has a relatively high mortality rate. Early diagnosis and timely intervention are crucial; administration of steroids and immunosuppressants was found to be effective in most patients [99]. AP was also reported in patients with rheumatoid arthritis [100]. Although the pathogenesis of AP in rheumatoid arthritis is unknown, treatment with oral glucocorticoids seems to reduce the risk of developing this condition.

Mitochondrial disorders

Patients with respiratory/non-respiratory chain mitochondrial disorders may very occasionally suffer from AP associated or not with diabetes and exocrine pancreas insufficiency [101]. This form of pancreatitis usually has a high risk of recurrence and presents exclusively with an increase in amylase or lipase without clinical manifestations or abnormalities on imaging. The pathogenesis is unknown, but a metabolic defect in exocrine pancreas cells promoting a defect in exocrine enzyme secretion has been speculated [101].

Hereditary pancreatitis and genetic mutations

Hereditary pancreatitis (HP) was first described in 1952 when recurrent AP in six family members across three generations was recorded [102]. Since then, more than 100 families with HP have been reported in the literature. The worldwide prevalence of HP has not been estimated, but European studies reported a prevalence ranging from 0.125 to 0.57 per 100,000 people [103]. HP clinically manifests with symptoms similar to those caused by other forms of pancreatitis, but has several distinguishing features. Compared to "mutation-negative" pancreatitis, HP was found (a) to have an earlier onset, often in the first two decades of life, and (b) to be associated with a higher cumulative risk of exocrine insufficiency and diabetes (60% and 68%, respectively) and pancreatic cancer, with a standardized incidence ratio ranging from 67 to 87 [103]. Several chromosomal markers on the long arm of chromosome 7 were identified in 1996, leading to the discovery of an HP gene [103]. Genetic mutations and polymorphisms have been extensively described, and are considered as causative agents or cofactors in determining the onset of acute/chronic HP pancreatitis. The prevalence of gene mutations in IRAP and idiopathic chronic pancreatitis ranges from 30 to 60% and from 12 to 43%, respectively [104–107]. Genetic etiology was associated with IAP, IRAP and idiopathic chronic pancreatitis in children with an incidence of 33, 45.4, and 54.4%, respectively [108]. A database of gene variants associated with pancreatitis has been assembled and four main genetic variants in the cationic trypsinogen (*PRSS1*), *CFTR*, *SPINK1* and chymotrypsin C (*CTRC*) genes have been described [109]. These four genes are mechanistically liked to control of trypsin activity within the pancreas and their mutation can lead to impaired trypsin inactivation, continuous activation of digestive enzymes, IRAP, chronic pancreatitis, and pancreatic cancer in about 40% of cases [110]. HP forms may be divided into autosomal dominant, recessive, or a multigenic inheritance. PRSS1 gene mutations cause a HP, with autosomal dominant inheritance, due to a prematurely activated or degradation-resistant trypsin promoting an increased autoactivation of mutant trypsinogens and higher intrapancreatic trypsin activity. HP related with SPINK1 mutations has an autosomal recessive pattern of inheritance. The defective SPINK1 gene expression impairs the synthesis of a strong trypsin inhibitor protecting the pancreas against premature trypsinogen activation. CFTR gene encodes an anionic channel involved in chloride and bicarbonate secretion in the duct cells of the lung, pancreas, digestive system, and other organs, allowing it to control intraluminal pH, thereby affecting the production of sweat, digestive fluids, and mucus. A dysfunction in the CFTR gene leads to failure of the alkalization of the acinar cells, resulting in retention of zymogens in the duct, where they can become active and begin digesting the surrounding pancreas tissue, thus leading to pancreatitis. Furthermore, the loss of alkalization can lead to the formation of protein plugs in the pancreatic ducts. The CTRC gene encodes chymotrypsin C, a digestive enzyme involved in trypsin regulation and sensitive to alterations in calcium concentrations. CTRC mutations disrupt trypsin destruction with an increased risk of pancreatitis. These genetic mutations were found in young patients, generally aged < 35, with a first episode of AP of unknown etiology [104, 107]. This finding led to the speculation that early genetic testing could contribute to defining the etiology of IAP in a subgroup of patients, thereby avoiding further unnecessary, costly and sometimes invasive investigations, especially in individuals with RAP [107]. Moreover, early identification of these genetic mutations possibly associated with AP can reinforce the decision to modify lifestyle behaviors, such as alcohol intake and smoking, to prevent a more aggressive form of the disease and/or reduce the risk of progression towards chronic pancreatitis and pancreatic cancer. There is no agreement on when and in which patients genetic testing should be performed, as it is expensive and not widely available. Subjects < 35 years with a family history of AP and no underlying condition favoring the occurrence of AP may be most likely to harbor pathogenic genetic variants and benefit from this technology. Gene therapy based on various techniques, including synthetic and viral vectors, molecular tools, and genome editing methods, has been proposed in several completed and ongoing clinical trials for the treatment of pancreatitis and other pancreatic disorders [111]. Among genetic therapies for genetic mutations-related AP, alipogene tiparvovec [AAV-LPL, (Glybera® uniQure N.V.,Amsterdam, The Netherlands)], an adeno-associated virus-based gene therapy containing a single nucleopolymorphism (SNP) of the LPL gene construct with an associated constitutive expression promoter (LPL^{S447X}), is included. Alipogene tiparvovec is the first gene therapy approved by the European Medicines Evaluation Agency for the treatment of patients with familial LPL deficiency and suffering from RAP despite dietary fat restrictions [112]. Alipogene tiparvovec showed to reduce

frequency and severity of LPL deficiency-induced RAP after a single treatment [113]. Albeit approved, the high cost limited the diffusion of alipogene tiparvovec into the clinical practice and the production of Glybera was stopped at the end of 2017. Studies on gene silencing therapy are ongoing in animal models of AP. SA100A9 gene silencing has been shown to inhibit the release of pro-inflammatory cytokines by blocking the IL-17 signalling pathway in mice with AP [114]. Further investigations are needed to clarify whether a AS100A9 gene-based therapy could be used in the treatment of patients with AP.

Infections and infestations

A variety of infectious agents (viruses, bacteria, parasites) are reported to induce AP in ~10% of patients via different mechanisms [115]. Symptoms and clinical signs of AP are frequently associated with symptoms and signs of acute infection. Microorganisms responsible for pancreatic damage are listed in Table 3.

Viral infections

Viral pancreatitis has been diagnosed both in immunocompetent and immunodeficient patients. In a review [116] evaluating 48 reports published between 1966 and 2016, acute symptomatic Epstein-Barr virus (EBV) infection was responsible for AP in 14 patients and acalculous cholecystitis in 37 patients. In all these subjects, clinical manifestations of pancreatitis or cholecystitis were synchronous with those of EBV infection. Viral AP related to herpes virus or cytomegalovirus (CMV) infection [117, 118] is common in immunocompromised individuals. CMV infection-related pancreatitis/hepatitis should, therefore, be considered in the diagnostic work-up of immunocompetent patients [119], especially when a recent viral-like illness is reported.

HIV infection is complicated by AP in ~40% of patients, due to either a direct effect of the virus in pancreatic tissue or an indirect effect of antiviral drugs [115]. AP was also described as a complication of hepatitis B virus (HBV) infection in several case reports [120–124]. Indeed, HBV infection-related AP is more frequently reported in post-transplant patients on immunosuppressive therapy [125]. The detection of HBsAg in pancreatic acinar cells and pancreatic juice in patients with AP [126] has led to suggest direct cytotoxic action by HBV or pancreatic damage secondary to a local immune response induced by circulating anti-HBV antibodies [122]. A systematic review found that hepatitis A virus (HAV) infection accounted for 54 cases of AP, most of them in Asia, with a frequency of 0.01% [127]. Patients are generally young, with a median age of 16 years, developing AP < 1 week after the onset of jaundice due to non-fulminant hepatitis A, with a more aggressive clinical course and a mortality rate similar to that of other causes of AP. Hepatitis E virus (HEV) infection accounted for at least 69 cases of AP, mainly males in the third decade living in Asian countries, with a mild to moderate course and good prognosis in most cases [128, 129]. Severe AP was also diagnosed in patients with H1N1 infection [130–134] and Coxsackie virus infection [135–137].

Table 3 Infectious causes of acute pancreatitis

Author	[Ref.]	Year	Agent	No. cases
Kottanattu	[116]	2016	Epstein-Barr virus (EBV)	14
Konstantinou	[117]	2009	Herpes simplex virus	1
Chan	[119]	2014	Citomegalovirus (CMV)	1
Jain	[120]	2007	HAV/HBV	3
Haffar	[127]	2017	HAV	54
Haffar	[128]	2015	HEV	53
Raji	[129]	2015	HEV	16
Blum	[130]	2010	H1N1	1
Baran	[131]	2012	H1N1	1
Rodríguez Schulz	[132]	2015	H1N1	3
Sánchez Bautista	[133]	2015	H1N1	1
Habib	[134]	2016	H1N1	1
Freeman	[138]	2010	Mycoplasma pneumoniae	9
Valdés Lacasa	[139]	2017	Mycoplasma pneumoniae	1
Franchini	[140]	2015	Legionella pneumonia	1
Suvak	[141]	2016	Brucella	21
Saebø	[142]	1992	Yersinia enterocolitica	8
Kobayashi	[143]	2014	Campylobacter jejuni	1
Khuroo	[144]	2016	Ascaris lumbricoides	256

Bacterial infections

Mycoplasma pneumoniae is one of the most common bacteria associated with infectious AP [138, 139]. This microorganism produces multiple extra-pulmonary manifestations, including AP. Infectious AP is generally reported in immunocompetent children and young adults. Patients usually present symptoms and signs of pancreatitis and pneumoniae infection. *M. pneumoniae* induces an altered immune modulation during the infection, which is responsible for an inflammatory response in different organs. Inflammatory changes are probably due to a direct effect of the bacteria in the blood stream, causing the local activation of inflammatory mediators, and an indirect effect through a systemic hypercoagulable state [138]. Legionellosis [140] and brucellosis [141] infections caused by gastrointestinal pathogens (*Campylobacter jejuni*, *Yersinia enterocolitica*) were reported in association with AP [142, 143].

Parasitic infestations

Parasitic infestations of the biliary tract are a common cause of biliary obstruction in tropical countries and may lead to serious complications, such as cholangitis and cholangiocarcinoma. Many types of parasitic infestation have been associated with AP. *Ascaris lumbricoides* is probably responsible for the most frequently reported parasitic-related AP in literature [144, 145]. *A. lumbricoides*, one of the most common parasitic infestations of the human gastrointestinal tract, normally resides in the jejunum and, thanks to its active motility, may pass thorough the papilla and migrate into the bile duct causing biliary obstruction. Almost 23% of patients with ascariasis suffer from AP [144]. Biliary ascariasis can be easily diagnosed by EUS in the diagnostic work-up of IAP [145, 146].

Post-traumatic pancreatitis

Post-traumatic damage of pancreas is a rare injury occurring in < 2% of trauma cases and mainly in connection with multiple injuries after motor vehicle or bicycle accidents. Pancreatic injury accounts for only 5% of directly related mortality, while acute pancreatitis, pseudocyst formation, abscesses and duct stricture are common sequelae which may lead to recurrent episodes of AP. Early diagnosis by imaging techniques (US, CT and MRI) may decrease morbidity related to post-traumatic pancreatic injury [147].

Importance of extensive diagnostic work-up in patients with IAP

Patients with AP need to be carefully evaluated at first attack to identify the most common causative conditions such as alcohol abuse or any form of biliary obstruction. If early (Phase I) investigations are not conclusive, the decision as to whether diagnostic work-up needs to be continued or not with more sophisticated techniques (Phase II) depends on several factors. Firstly, practical reasons may limit diagnostic work-up. EUS, MRCP, ERCP and genetic testing are usually readily available in third-level referred center. The ability to detect rare forms of AP may also differ greatly among tertiary level gastroenterology units depending on their experience with patients affected by these conditions. In addition, a complex multistep diagnostic work-up in patients with IAP may lead to a substantial increase in costs, and patients undergoing multiple investigations may be exposed to a greater risk of side effects or complications. Lastly, some concerns about performing a complex diagnostic work-up were raised in a study [148] describing low recurrence rates (1/39 patients, 2.56%) of IAP. In contrast, other studies reported recurrence of IAP varying from 14% to 24% [10, 23, 35, 149, 150] and, more recently, up to 35–52% [20]. Further, IAP was recently found to account for a mortality rate of up to 16% [77].

Taking into account all the above considerations, in our opinion, patients with IAP should be thoroughly investigated using more advanced techniques, if available, to detect an underlying condition. Identifying the etiology of initially diagnosed IAP could help to guide appropriate treatment which may, in the majority of cases, be curative and prevent further attacks of AP. The awareness of the frequency of the different possible underlying conditions may be helpful in choosing the investigations to be performed (Table 4).

Phase I At first episode of AP, essential investigations are serum biochemistry (including lipid profile and calcium), abdominal US and contrast-enhanced CT. Liver function tests above the normal range may indicate a biliary etiology of AP. Contrast-enhanced CT may confirm a frank biliary obstruction or reveal other conditions, including a pancreatic tumor.

Phase II Once no etiology of AP has been clearly ruled out by Phase I investigations, diagnostic work-up should continue with EUS and S-MRCP (Fig. 2) and ERCP. As far as ERCP is concerned, guidelines from the American College of Gastroenterology [78] suggest that endoscopic investigation of IAP should be limited, as the risk and benefits are unclear. In addition, in cases such as suspected PD where ERCP may be useful, EUS and/or MRCP should be preferred as non-invasive techniques with a similar diagnostic yield. Literature on the diagnostic yield of EUS in IAP

Table 4 Frequency of different etiological conditions related with acute pancreatitis

Conditions	Prevalence	References
Microlithiasis	28–80%	[4, 14, 15, 18–23]
Sphincter of Oddi dysfunction	< 1.5%	[33]
Pancreas divisum	5%	[46]
Annular pancreas	< 0.01%	[48, 49]
Pancreatobiliary tumors	7–67%	[56–58]
Medicines, drugs abuse, toxic substances	< 5%	[68–75]
Hypertriglyceridemia	2–25%	[76, 77]
Hypercalcemia	0.4%	[82]
Diabetes	Not stated[a]	
Autoimmune disorders	< 1–4.6%	[89–91]
Mitochondrial disorders	Occasional[b]	
Hereditary pancreatitis	0.0001%	[103]
Infectious agents	10%	[115]
Post-traumatic	< 2%	[147]

[a]Prevalence in type 2 diabetes:54-475/100,000 person-year [see ref. 86]

[b]Occasional: the condition has been described in a limited number of case reports

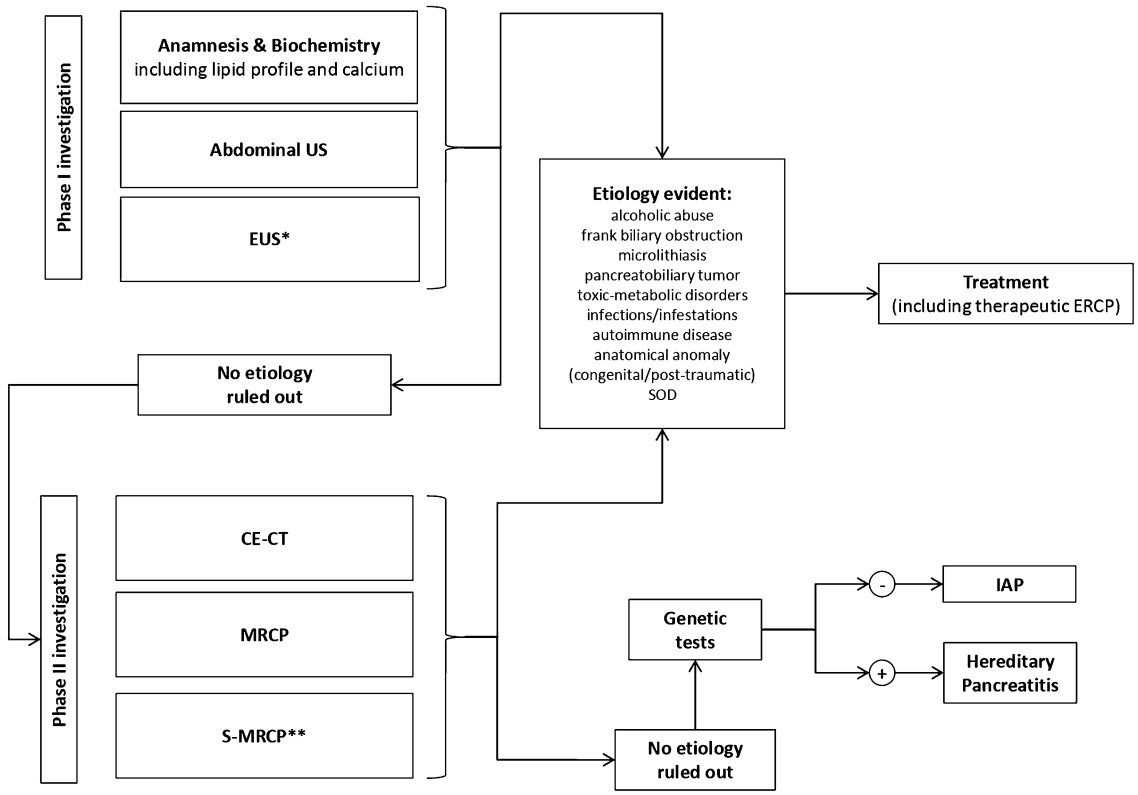

Fig. 2 Diagnostic work-up (Phase I and Phase II) in patients with suspected idiopathic acute pancreatitis. *CE-CT* Contrast-enhanced computed tomography, *EUS* endoscopic ultrasound, *IAP* idiopathic acute pancreatitis, *MRCP* magnetic resonance cholangiopancreatography, *S-MRCP* secretin-enhanced magnetic resonance cholangiopancreatography, *SOD* sphincter of Oddi dysfunction, *US* ultrasound. *if not available, MRCP; ** if available

has grown in the last few years. In a recent metanalysis [44] of 34 studies involving EUS and/or MRCP for the etiological diagnosis of IAP, EUS showed higher diagnostic accuracy than MRCP (64% versus 34%) for establishing possible biliary disease and chronic pancreatitis, whereas S-MRCP was more reliable than EUS and MRCP in diagnosing possible anatomical alterations in biliopancreatic ductal system, such as pancreas divisum. On the other hand, a negative EUS after a single attack of IAP may predict a low rate of recurrence of AP, while evidence of PD and SOD has a negative prognostic value, suggesting a recurrent course of the disease [23]. Thus, EUS seems to be the method of choice for investigating IAP as it is a minimally invasive technique able to reveal an underlying etiology in the majority of patients. Furthermore, EUS may provide important information for predicting the course of disease in patients with IAP. If EUS is not available, MRCP is the alternative of choice. The ideal diagnostic strategy is perhaps a combination of EUS and MRCP, as both may give complementary findings. In patients in whom EUS and radiological investigations failed to rule out any underlying condition, genetic testing may be recommended, particularly in patients aged < 35 and with a family history of AP.

Conclusions

In the case of AP unrelated to alcohol abuse or a frank biliary obstruction, all possible conditions promoting inflammation and pancreatic damage need to be considered. Diagnostic work-up should include a detailed patient history documenting family history, lifestyle, occupation, pharmaceuticals, substance abuse, and comorbidities, as well as a thorough physical examination. On the basis of clinical data and lifestyle information, specific laboratory tests, EUS and/or MRCP should be proposed. More specialized laboratory tests, namely tumor markers, IgG4 plasma levels, infective screening and genetic tests, should also be performed. This diagnostic algorithm may increase the probability of detecting a hidden cause of AP and is useful for defining the most appropriate treatment. A correct diagnosis and, therefore, suitable therapy may reduce the risk of recurrence of IAP.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest.

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