Review Article

Idiopathic acute pancreatitis (IAP)—a review of the literature and algorithm proposed for the diagnostic work-up of IAP

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Background and Objective: This narrative review addresses idiopathic acute pancreatitis (IAP) and its epidemiology, diagnosis, clinical course and treatment during the last decade. As there is no previously validated protocol for finding the aetiology of acute pancreatitis (AP), the primary aim of this study is to find, describe and unify evidence about the diagnostic work-up of AP to diagnose the true IAP. By finding the aetiology with the highest possible yield it may be possible to reduce recurrent AP (RAP) episodes and related morbidity and thereby decrease health care costs and possibly improve patients' quality of life.

Methods: This narrative review includes articles retrieved from PubMed search with publications from 2013–2023. Cross references were used when found relevant.

Key Content and Findings: The rates of aetiologies of AP and the diagnostics performed behind these numbers vary widely between different studies, time periods and different geographical regions, as there is no unified algorithm in diagnostic work-up of IAP. In this study, we describe an up-to-date summary of epidemiology, diagnostic course and treatment of IAP, and propose an algorithm of IAP diagnostics in light of recent scientific studies and their outcomes and address possible treatments of IAP.

Conclusions: Although aetiology is key for AP management, there is still no validated protocol for aetiological diagnosis. IAP is relevant due to its recurrence rate and possible evolution to chronic pancreatitis. We still need more studies addressing this topic and evaluating new diagnostic protocols with advanced tests and treatment strategies in true IAP.

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Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal diagnoses leading to hospital admissions across the United States (1). For over three decades, the incidence of AP has increased throughout Europe. Most cases are attributed to well-defined aetiologies of biliary lithiasis and alcohol abuse, and thereafter, other infrequent causes (2). The diagnostic journey typically involves a thorough examination of personal and family history coupled with blood tests and different imaging examinations. However, without detection of an apparent risk factor as the leading cause the pancreatitis episode remains idiopathic, unclassified and unanswered for both the clinicians and patients.

Idiopathic acute pancreatitis (IAP) has a higher recurrence rate compared to the classified cases (3). Better knowledge on the different aetiologies and diagnostic follow-up for IAP might lessen the burden on healthcare systems and increase the quality of life. Yet, the lack of a standardized protocol leaves the etiological workup to local practice and expertise. Variability in the availability of paraclinical examinations further complicates the diagnostic landscape.

This review aims to give an overview of IAP and to improve the systematic approach in the management of patients with AP of unknown origin. We present this article in accordance with the Narrative Review reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-125/rc).

Methods

This narrative review was performed within the study group of Pancreas 2000, an educational programme of the European Pancreatic Club. The publication search details are reported in *Table 1*. Cross-references were used when found relevant. At least two independent investigators analyzed and agreed on the studies to be included in the literature database.

Totally, 1,746 titles and abstracts were screened and classified manually into the following topics: aetiologies, prevalence, diagnostic workup, treatment, follow-up, and disease course.

Definitions

In accordance with the revised Atlanta classification of 2012, the diagnosis of AP is confirmed when at least two out of the three criteria are met: typical abdominal pain, serum amylase or lipase levels > three times the upper limit of normal, and characteristic findings from abdominal imaging (4). Typically, the pain associated with AP manifests as constant epigastric or left upper quadrant discomfort, with radiation to the back, chest, or flanks (5). In patients where diagnostic uncertainty persists, abdominal imaging, such as contrast-enhanced computed tomography (CECT), is recommended (6).

Venu *et al.* defined IAP as the absence of abnormalities detectable through careful history and conventional diagnostic tests. In 1989, these included blood test, upper gastrointestinal X-rays, transabdominal ultrasonography (US), and computed tomography (CT) examination of the abdomen (7). Wilcox *et al.* outlined thorough examination including physical examination and review of all medications, both prescription and over-the-counter in search for a specific cause in case of IAP (3). The American College of Gastroenterology (ACG) defined IAP as pancreatitis missing a classified aetiology, with normal findings in initial laboratory (including lipid and calcium levels) and imaging (transabdominal US and CT in the appropriate patient) (5).

The Dutch Pancreatitis Study Group divided IAP into “original”, “presumed”, and “true” based on evaluations seeking the unknown aetiology, excluding genetic testing from the criteria. Presumed IAP necessitated standard evaluation as mentioned including the exclusion of trauma/invasive procedures, and US on admission and after discharge. True IAP was assigned when additional CT, endoscopic retrograde cholangiopancreatography (ERCP), bile examination, endoscopic ultrasonography (EUS) or magnetic resonance cholangiopancreatography (MRCP) were normal (8).

Often, additional EUS and genetic investigation in

Table 1 The search strategy summary

Items	Specification
Date of search	October 4, 2023
Database	PubMed
Search terms	(acute pancreatitis AND aetiology) OR (idiopathic pancreatitis)
Timeframe	2013 to October 4, 2023
Inclusion and exclusion criteria	Inclusion: English language; studies regarding rates, diagnostics or prognostics in IAP
	Exclusion: non-English language; study population <18 years
Selections process	All 1,746 titles underwent screening by a minimum of two authors and were subsequently categorized based on review headings, including aetiology, prevalence, diagnostic workup, treatment, follow-up, and disease course. If one of the authors deemed a study's title appropriate for inclusion in the review, the abstract (if provided) or main text was then analyzed by two authors. If both agreed on its inclusion, the paper was selected. In cases of disagreement between the two initial authors, a vote among all other review authors was conducted. Cross-references were also consulted

IAP, idiopathic acute pancreatitis.

patients will be performed after the pancreatitis episode is classified as IAP as described in the International Association of Pancreatology/American Pancreatic Association (IAP/APA) guideline (9). If relevant findings appear, the patient should be reclassified, accordingly. While biliary aetiology is considered common in IAP, there is no consensus on distinguishing between biliary sludge and microlithiasis (10). In some patients, an aetiology may eventually be found, yet in others, no definite cause is ever established after all examinations and therefore, can be defined as true IAP (5,11). In this manuscript, the definition of IAP follows the guidelines of the IAP/APA (9). True IAP is classified when no aetiology has been found after all diagnostic workup is performed.

Recurrent idiopathic acute pancreatitis (RIAP) is defined as two or more distinct episodes of AP with resolution of symptoms in between, without a determined cause (11,12).

Possible aetiologic factors for AP

By determining the aetiology of AP and removing the cause, it is possible to reduce recurrences and improve patient outcomes. Biliary and alcohol are the most common causes of AP. However, there are other less frequent possible causes of AP that need to be evaluated when a patient is admitted, such as hypertriglyceridemia, hypercalcemia, post-ERCP, malignancy, sphincter of Oddi dysfunction (SOD), anatomical anomalies, drugs, genetic factors, and infectious agents (13,14).

Biliary

Gallstones are the main aetiological factor of AP, globally and across Europe, according to a review and meta-analysis that included 46 studies from 36 countries between 2006 and 2017 (15). The incidence of gallstones in Western countries is 10–20%, and more frequent among women (16). The incidence of AP in patients with gallstones is 0.3–1%. The risk of getting AP is increased in the presence of microlithiasis, stones <5 mm and high number of stones (17). The exact mechanism for biliary induced pancreatitis is not known, but impairment of pancreatic juice outflow could be one contributing factor (18). Biliary acids have also been shown to increase the intra-acinar concentration of calcium and further induce cytokine synthesis (19).

Alcohol

The global estimate of alcohol-induced AP is 21% (15). The mechanisms that cause alcohol-induced AP are multifactorial, including direct and metabolite-induced toxic effects, and cumulative effects are suggested to sensitize the pancreas to damage (20). Alcoholic pancreatitis is typically found in patients around 35–55 years of age (21). According to a case-control nationwide study from Japan (22), daily alcohol use of less than 20 g/day does not increase the risk of pancreatitis, and above this the risk of AP is increased dose-dependently. However, only a small percentage of heavy drinkers develop AP, so there might be other factors

besides alcohol involved in the disease (23).

There is no data showing that moderate alcohol intake or binge drinking (>80 g/day) in abstainers lead to an increased risk of developing AP (23). Moderate alcohol intake (1–2 doses/day) is suggested to be a protective factor against AP according to a large prospective cohort study (24) and this J-shaped association between alcohol intake and pancreatitis has been also demonstrated in a recent Danish cohort (25). In this cohort, they also found an increased risk in patients with daily drinking, binge drinking and problematic alcohol use, especially when drinking beer and spirits in large amounts (25).

Smoking

The association between smoking and AP has been supported in three different meta-analysis studies (26-28). Smoking precipitates the progression for alcohol-induced AP (29,30) and is regarded as dose-dependent risk factor for AP in Western population. The pathophysiology of smoking-induced AP is suggested to be caused by the imbalance of pancreatic proteases and their inhibitors in many ways similar to alcohol (31).

Obstructive AP

Obstructive AP is caused by calcifications and/or the mass effect caused by tumors, mainly pancreatic ductal adenocarcinoma (PDAC) and intraductal papillary mucinous neoplasm (IPMN). Other pancreatic tumors can also cause AP, including solid pseudopapillary tumor, and other less common focal lesions of the pancreas (32).

PDAC is the most common malignant tumor of the pancreas, which originates from the epithelial cells of the pancreatic ducts. In approximately 80% of patients, it is located in the head of the pancreas. It occurs with a slight predominance in men, usually between the ages of 70 and 80 years (33,34). An early symptom of pancreatic cancer may be newly diagnosed diabetes or the first episode of AP (35). The first symptom of PDAC, similarly as in AP, is an inflammatory reaction of the pancreatic parenchyma in response to the blockage of the outflow of pancreatic juice by the tumor mass (36).

AP is a frequent presenting symptom of IPMN. In the study by Morales-Oyarvide *et al.*, history of AP was found in as high as 21% of patients resected because of IPMN. Of those, 48% experienced a single episode of AP. In this study, AP was associated with the intestinal subtype of IPMN [odds ratio (OR) 4.69], malignant IPMN (OR 1.97), and main duct involvement (OR 1.87) (37).

Hypertriglyceridemia

Hypertriglyceridemic AP is the third most common cause of AP. It is generally thought to be responsible of 5% of AP episodes, but as high portion as 22% has been reported (38). It is usually seen in patients with other secondary factors (uncontrolled diabetes, alcoholism, pregnancy, medications) and genetic predisposition (39). The risk for AP with triglycerides (TG) >1,000 mg/dL (>11.3 mmol/L) is similar (around 5%) to that of the risk of heavy drinkers (40) and much higher (10–20%) in patients with TG >2,000 mg/dL (>22.6 mmol/L) (39). The suggested mechanism for pancreatic injury in hypertriglyceridemia-induced AP is promoted through free fatty acid formation, the activation of inflammatory response mechanisms and gene polymorphism (41).

Post-ERCP AP

ERCP is associated to development of AP. The post-ERCP pancreatitis (PEP) rate varies between 2–10% and could be up to 30–50% in selective high-risk cases (42). PEP is the result of mechanical obstruction and causes early activation of pancreatic enzymes, leading to inflammation (43). Obstruction can be caused by oedema or trauma to the papilla. Hydrostatic injuries, perforation of the pancreatic duct, electrocautery and reaction to the contrast agent might also contribute to development of PEP (44). In the study of Park *et al.*, post-ERCP risk prediction model for PEP was proposed. Independent risk factors for the development of PEP included: age (≤65 years), female sex, previous AP, and malignant biliary obstruction (45).

Hypercalcemia

Hypercalcemia is a rare cause of AP, estimated to account for 3% of AP episodes. It usually results from hyperparathyroidism, different malignant diseases, familial causes, or parenteral nutrition (46). Elevated calcium levels lead to intracellular activation of digestive enzymes that leads to pancreatic injury (47-49).

Drugs

Drug-induced AP is suggested to account for 3.6% of AP episodes (50). World Health Organization has listed more than 500 drugs that have pancreatitis as an adverse event (51). The most common causes of drug-induced AP have been reported to be azathioprine, hydrochlorothiazide and doxycycline according to a study by Chadalavada *et al.* (50). In addition, during the last decade, a lot of attention has been paid to certain novel diabetes medicines such as glucagon-like peptide 1 (GLP-1) agonists such as semaglutide (52-58) and dipeptidyl dipeptidase 4 (DPP-4) inhibitors such as saxagliptin (59-61), but no association to higher risk for AP has been shown. The pathophysiological and pharmacokinetic mechanisms are still partly unclear, but suggested mechanisms for pancreatic injury depends on the drug. A thorough evaluation of patient's medication should be made during admission investigating a possible association to AP.

Genetic

Genetic aetiology should be considered in the case of early-onset AP with no other obvious aetiology found, or when there is a positive family history. Most common genetic alterations are related to serine protease 1 (*PRSS1*), cystic fibrosis transmembrane conductance regulator channel (*CFTR*), serine protease inhibitor Kazal type 1 (*SPINK1*), and chymotrypsin C (*CTRC*) genes (62,63). These four genes are associated to trypsin activity in the pancreas and their mutation is linked to impaired trypsin inactivation and risk of idiopathic recurrent AP (RAP) due to continuous digestive enzymes activation (64).

In a cohort study by Ballard *et al.*, 18% of patients with unexplained pancreatitis (n=370) had a genetic mutation, with 6% of them being of high risk (65). Other genetic polymorphisms as the ones found in some interleukines (i.e., IL-8, IL-10) or alcohol dehydrogenase 1-c have also been suggested to increase risk of AP (66-73).

Evaluating the other possible risk factors in patients with genetic mutations is important, as by changing behaviours, such as alcohol consumption and smoking, we may be able to prevent AP episodes or progression towards chronic pancreatitis (74).

Infectious

Various microorganisms may cause AP, especially in patients with immunosuppression. It is suggested to be responsible of 10% of AP episodes. Possible organisms include viruses such as cytomegalovirus or hepatitis viruses, bacteria such as mycoplasma or salmonella, severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), fungi such as aspergillus and parasites such as toxoplasmosis. The underlying mechanisms to cause AP are multifactorial and every organism is thought to have a unique pattern of function (75).

Autoimmune pancreatitis

Autoimmune pancreatitis is a rare cause of AP, with an incidence of approximately 1.4:100,000 per year (76,77). Autoimmune pancreatitis is an inflammatory disease of the pancreas, characterized by infiltration and fibrosis leading to organ damage (78). There are two main types of autoimmune pancreatitis based on the histopathological picture. Type 1, lymphoplasmacytic sclerosing pancreatitis (LPSP), is associated with increased concentration of IgG4 antibodies and is the pancreatic manifestation of a systemic autoimmune process—an IgG4-dependent disease. Type 2, granulocytic epithelial lesion (GEL), is less frequently diagnosed and is characterized by frequent co-occurrence of inflammatory bowel diseases (IBD) (79). The diagnosis of autoimmune pancreatitis and IgG4-related disease is based on a comprehensive assessment of the clinical picture, laboratory, imaging, histopathological test results, and response to steroid therapy (78).

Trauma

Pancreatic trauma, blunt or penetrating force, may be a cause for AP, although infrequent (80). Post-traumatic damage of the pancreas occurs in <2% of trauma cases mainly in patients with multiple injuries after motor vehicle accidents. Postoperative AP has recently been defined by the International Study Group of Pancreatic Surgery (ISGPS) (81). Colonoscopy has also been reported as a rare cause of traumatic AP (82).

SOD

The pathophysiology of SOD as a cause of AP is not yet fully understood. Presumably, the main physiopathological mechanism involves constant or intermittent, obstructed outflow of pancreatic juice or bile, not related to lithiasis (83). It is reported that the incidence of SOD in the general

population is approximately 1.5%, while in patients with RIAP it may reach up to 72%. However, due to difficult diagnosis, factual incidence of SOD as a risk factor for AP is unknown (84).

Anatomical anomalies

Pancreatic anomalies that may be the cause of AP include pancreas divisum and annular pancreas. Pancreas divisum is the main anatomical variation and it occurs in 5–10% of the population. It occurs when the dorsal and ventral ducts of the pancreas fail to join during gestation (85). The main route of outflow of pancreatic juice in this case is the dorsal duct of Santorini draining via the minor papilla (86). In the study by Takuma *et al.*, RAP occurred in 19% of the subjects, and the highest recurrence of AP episodes concerned pancreaticobiliary malformation, including pancreas divisum, and reached up to 80% (87). Although we can find pancreas divisum in a high percentage of patients with IAP, it remains controversial whether this is the real cause or just another factor influencing AP development. In fact, recent genetic studies have associated pancreas divisum to some of the main genetic alterations, as SPINK1 or CFTR associated to AP (88,89).

Annular pancreas is also an anomaly that occurs during gestation due to abnormal rotation of the abdominal pancreatic bud that surrounds the second portion of the duodenum, usually around the major papilla and affects less than 1% of the population, with an incidence of 1 in 20,000 newborns (90). One-third of the cases are also associated to pancreas divisum (91). Although the main symptom is usually duodenal obstruction, it may cause AP or RAP (92). Annular pancreas is a rare cause of AP estimated between 15 and 400 cases per 100,000 adults (93).

Rate of IAP

Regarding the rates of IAP, a meta-analysis by Zilio *et al.* analysed 38 studies up until the year 2017 and reported an estimated mean proportion of IAP to be 18% (15). There were also substantial differences between geographic regions with Africa (7%) and Latin America (12%) displaying the lowest numbers, followed by Europe (18%) and Asia (19%), while Oceania (26%) and US (35%) had the highest proportion of IAP.

The proportion of AP patients diagnosed with IAP varies considerably between studies (*Table 2*) and despite increasing availability of advanced diagnostic tests, such as EUS and MRCP, there is no clear trend of decreasing IAP proportion. That being said, Culetto *et al.* reported that IAP rate decreased from 48.5% to 21% after secondary investigations with EUS, MRCP and genetic testing (111). Also, Rashidi *et al.* reported an IAP rate of 29.7% in a retrospective cohort and only 7% in a prospective cohort (107). Of note, more patients in the prospective *vs.* the retrospective cohort had CT (78.9% *vs.* 53.1%) and MRCP (56.1% *vs.* 33.5%) performed. The largest retrospective study was performed in the US and included more than 800,000 episodes of IAP (119). The authors report quite a high overall IAP rate (36.5%), although they noted it had a decreasing tendency from 41% in 1998 to 30% in 2007. The second largest retrospective study with 4,359 IAP cases also reported a high IAP rate of 29.5% (117). The largest prospective cohort with 579 IAP patients (22.4%) was reported in the PANC study (94). In this cohort IAP was as common in women as it was in men, in contrast to some earlier retrospective studies (98,119).

Diagnostic workup

After the first attack of AP, recurrence rate is three times higher in patients without an identified aetiology compared to the ones with an identifiable cause (43% *vs.* 15%) (121). In order to reduce RAP, patients with AP need to be evaluated in detail.

Main causes of AP should be ruled out during admission. This first evaluation usually includes anamnesis and blood tests (with liver enzymes, calcium and TG) and abdominal US according to different guidelines (admission assessment in *Figure 1*) (5,9,74). When the aetiology of AP is not defined after the first evaluation, it is classified as IAP according to different guidelines (5,9), but aetiology workup should continue.

If no aetiology is found, a second abdominal US to rule out biliary aetiology improves accuracy by 20% (from 66% to 83% and even till 87% if there is elevated alanine transaminase (ALT) if performed after recovery (first line follow-up test in *Figure 1*) (9,121,122). There is lack of evidence on when to perform this second abdominal US. In a study from Signoretti *et al.* abdominal US was performed one week after admission improving biliary detection even after this short period after the AP episode (122). In similar studies assessing the role of an additional abdominal US, the time elapsed from the onset of AP until second US was not specified (9,121). Therefore, there is not enough evidence to provide a clear recommendation regarding the

Table 2 IAP rate among different studies from 2013–2023

Reference	Year	Country/countries	Study type	Number of AP patients	Number of IAP patients	IAP proportion (%)
(94)	2023	UK	Prospective	2,580	579	22.4
(95)	2022	USA	Retrospective	878	338	38.5
(96)	2023	Finland	Retrospective	1,084	215	21
(97)	2020	China	Retrospective	3,028	412	13.6
(98)	2020	Japan	Retrospective	2,908	555	19.1
(99)	2019	UK (England)	Prospective	283	65	23
(100)	2019	Singapore	Prospective	391	82	20.9
(101)	2019	Iceland	Retrospective	1,102	283	26
(102)	2017	Korea	Retrospective	1,110	148	13.3
(103)	2017	USA, India, Lithuania, Romania, Greece, Italy, Paraguay, Argentina, Mexico	Prospective	509	87	17
(104)	2017	Thailand	Retrospective	250	37	15
(105)	2017	Jamaica	Retrospective	91	12	13.2
(106)	2017	China	Retrospective	3,260	543	16.7
(107)*	2016	Norway	Retrospective	613	182	29.7
(107)*	2016	Norway	Prospective	57	4	7
(108)	2016	Netherlands	Prospective	669	108	15
(109)	2016	Hungary	Prospective	600	98	16.3
(110)	2015	Australia	Retrospective	932	239	25.6
(111)	2015	France	Prospective	66	32	48.5
(112)	2015	Slovenia	Retrospective	139	16	11.5
(113)	2015	China	Retrospective	2,461	479	19.46
(114)	2015	Sweden	Retrospective	1,457	432	29.6
(115)	2015	Korea	Retrospective	153	24	15.7
(116)	2014	Oman	Retrospective	174	37	21
(117)	2014	UK (Wales)	Retrospective	10,589	4,359	29.5
(118)	2013	Iceland	Prospective	126	15	12
(119)	2013	USA	Retrospective	2,242,731	818,025	36.5
(120)	2013	Croatia	Retrospective	922	13	1.4

*, (107) has two cohorts, a retrospective and a prospective one that are analysed and shown separately. IAP, idiopathic acute pancreatitis; AP, acute pancreatitis.

time to perform the second abdominal US. Nevertheless, even with the diagnostic yield of 20%, excellent safety, wide availability and low cost, this second US is performed in less than half of the patients when searching aetiology after an AP episode (121,122).

If risk factors are present (>40 years old, alarm symptoms, prolonged course) a CECT should also be performed (first line follow-up test in *Figure 1*) (5,9,74). It adds a diagnostic

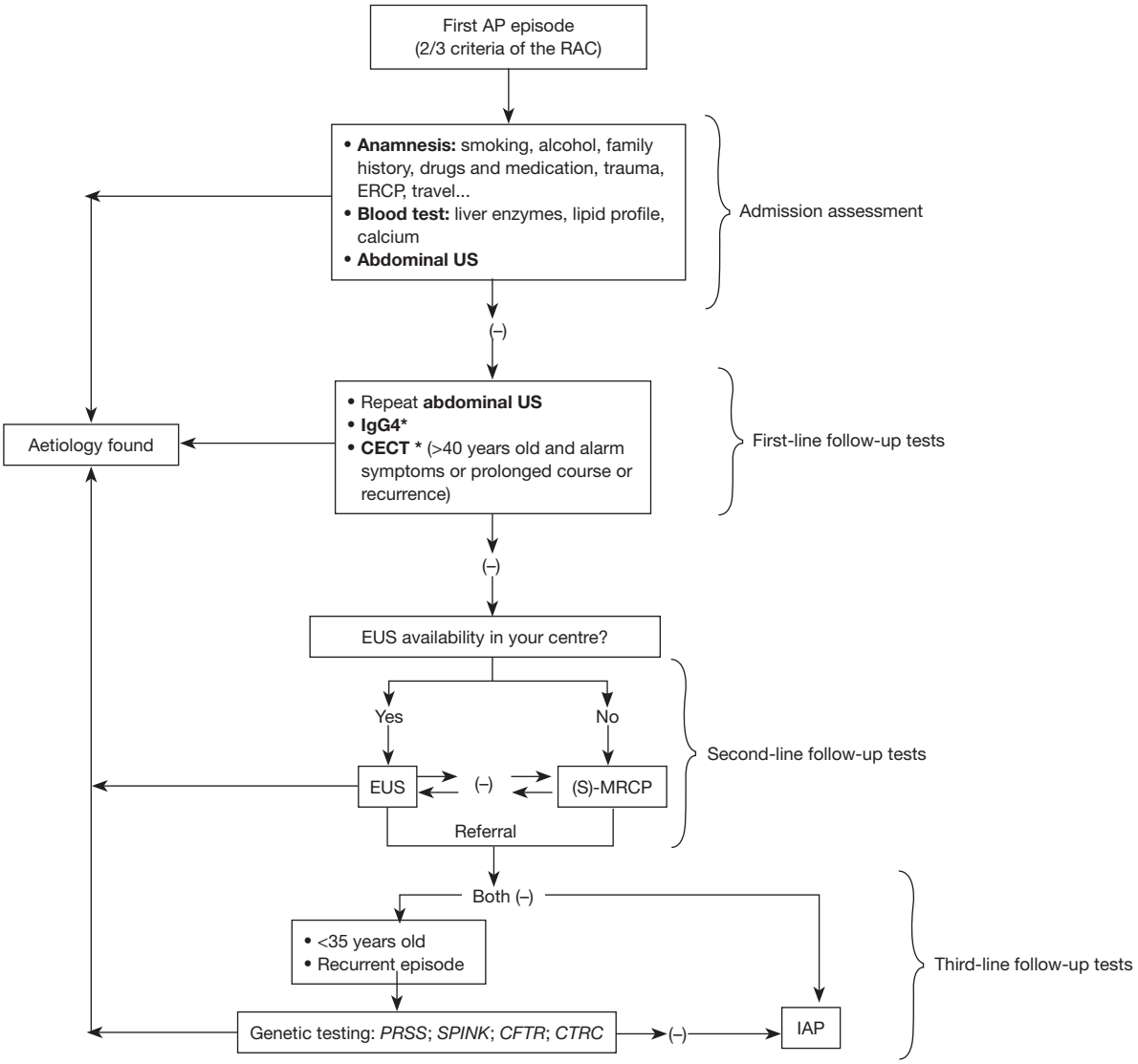

Figure 1 Algorithm proposed for the diagnostic work-up of IAP. *, serum IgG4 could also be done during admission. AP, acute pancreatitis; RAC, Revised Atlanta Classification; ERCP, endoscopic retrograde cholangiopancreatography; US, ultrasonography; CECT, contrast enhanced computed-tomography; EUS, endoscopic ultrasonography; (S)-MRCP, secretin-magnetic resonance cholangio-pancreatography (if available, preferably with secretin); PRSS, serine protease 1; SPINK, serine protease inhibitor Kazal type 1; CFTR, cystic fibrosis transmembrane conductance regulator channel; CTRC, chymotrypsin C; IAP, idiopathic acute pancreatitis.

yield of 8–10% after admission assessment mainly detecting tumors as a cause of AP (122).

All these complementary tests are available in most hospitals. Therefore, these tests are considered to be performed during admission or as first line follow-up tests to improve diagnosis of AP aetiology. However, a recent study has shown the low rate of an accurate diagnostic initial workup (25–29%) (123).

After initial assessment and first-line follow-up tests (*Figure 1*), some possible causes of AP might be missed. For these patients, more advanced techniques such as EUS or MRCP are beneficial and for some of them, genetic testing is also of value. These options are not widely available, and because of that we consider them as second or third line tests, but according to guidelines, patients should be referred to tertiary hospitals to complete the evaluation to rule out all relevant aetiologies (9,74,124). Nevertheless, a complete assessment of patients with IAP is only performed

in <5% according to some recent data (123).

In the last few years, evidence about the use of EUS as an advanced tool for the diagnostic workup of AP has risen (3,124-134). In a recent systematic review and meta-analysis (126), EUS demonstrated an overall diagnostic yield of 59%, with the most common causes being biliary (30%), chronic pancreatitis (12%) and pancreatic tumors (2%). Diagnostic yield was better after recovery of AP episode (61%) compared to its diagnostic yield during ongoing AP (48%) and it was not affected by being the first episode or not. This is in line with other studies (3,131,135). EUS performed better when no cholecystectomy had been performed earlier, and this was also in agreement with a previous study (134). Patients with higher severity score CT index will need more than six weeks to recover before performing the EUS, but in less severe AP it can be performed around four weeks after recovery (3,125). Although there is no evidence regarding the timing of MRCP after AP, similar time intervals to EUS should be considered.

Recently, two multicenter prospective studies have shown that EUS has an ability to detect aetiology after a first episode of IAP of 32–35% (122,127). This is a lower rate than previously described, but EUS was only performed after a thorough initial workup based on the IAP/APA 2013 guidelines (9). The aetiology one of these studies (127) ended up being biliary in almost 24% of the cases, 7% chronic pancreatitis and 3% tumours. Recurrence rate in EUS negative IAP was 17% compared to 6% in the EUS positive and treated patients (127). This emphasizes the importance of aetiologic diagnosis to decrease recurrence rate of AP by treating its cause. Also, exclusion of pancreatobiliary abnormalities on EUS has an important prognostic value for absence of new episodes of AP (3,129).

Compared to MRCP (136), EUS has a higher diagnostic accuracy and it should thus be preferred when biliary aetiology or chronic pancreatitis needs to be excluded. However, recent studies show that the superiority of EUS is minimal if a thorough diagnostic workup is performed prior (diagnostic yield for EUS 35% *vs.* 33% for MRCP) (122,127).

Based on this data, we suggest that after a first episode of AP with unknown aetiology, the first advanced test should be EUS. However, MRCP could also be a good option with high diagnostic yield (up to 33%), depending on EUS availability. Nevertheless, EUS should be performed in case of inconclusive MRCP and vice versa to rule out different aetiologies (*Figure 1*). Secretin(S)-MRCP was superior to MRCP or EUS detecting anatomical abnormalities such as pancreas divisum. If available, this option may exclude additional anatomical causes compared to traditional MRCP (127).

A machine-learning model to predict sludge or microlithiasis in EUS in the setting of IAP has recently been presented (128). Until further data is available, it cannot be recommended in a clinical setting, but it may aid in the future to better select patients who undergo EUS.

ERCP cannot be recommended nowadays in the diagnosis of IAP and should merely be used for therapeutic purposes (74).

Autoimmune pancreatitis should also be ruled out. Measuring serum IgG4 should be done when dealing with an IAP, although its isolated elevation is not diagnostic of autoimmune pancreatitis and although it is not a marker of disease in type 2 (137). There is no clear data on when to perform IgG4. In a recent study, IgG4 helped to classify the aetiology of a first episode of IAP after initial assessment in 13% of the patients (121). Although it is not necessary during admission (9) we recommend IgG4 should be determined during the follow-up of patients with unknown origin of their AP, probably before or at the same time than "second line tests" (*Figure 1*). This could support imaging findings to diagnose autoimmune pancreatitis in some patients, even when it is not a recurrent episode (121).

In patients with negative EUS and MRCP, and all other previous workup being negative, genetic testing should be performed in the group of patients with a first AP episode and <35 years old (111,138), as well as in patients with RIAP (9,138). The minimum gene investigation to perform in these patients includes PRSS1, SPINK1 and CTRC, which are associated to trypsin activation and CFTR (139) although more genetic mutations have been established to play a role in susceptibility for AP (139,140). In patients <35 years old with IAP, we can find an alteration in these genes that varies between 10–63% of patients depending on the series (94,138) and in RIAP between 34–58% (138,141).

In RIAP, using a complete gene sequencing identifies significantly more mutations (5-fold, 42.2% *vs.* 8.1%) and high-risk mutations (12-fold) than other tests. However, not all mutations found with a complete gene sequencing are well characterized in terms of clinical relevance (65).

Based on the literature discussed above, we propose the following work-up algorithm (*Figure 1*) to be used to rule out definable causes of AP, and end up with the cases of true IAP.

Disease course of IAP

The mortality of IAP is reported to be low; 3.5% in Sweden (142), 5.4% in Korea (102), 2.5% in Iceland (101), 1.2% in US (95) and 3.6% in UK (94). This seems a bit higher compared to other aetiologies, but without statistical significance.

IAP recurrence after the initial attack is significant, with reported rates of 16–43% (102,114,121,143). The 30-day readmission rate of 22.3% in IAP patients is not different compared to non-IAP aetiology, despite the fact that 61.5% of IAP patients had a previous history of pancreatitis (95). In contrast, Bolourani *et al.* reported that IAP accounts for 3% of all AP hospital readmissions, which is lower than for alcoholic or biliary aetiology (144). Some studies report a tendency for IAP to recur more frequently—a significantly higher five-year IAP recurrence rate when compared to non-IAP was reported in an IBD cohort (143). Earlier studies from Italy (145) and the Netherlands (108) reported an association between idiopathic aetiology and recurrent pancreatitis. However, this was not confirmed by other studies (101,114,146). Instead, alcoholic aetiology, male gender and smoking were most often associated with the recurrence risk. Most IAP cases are mild, and the rate of severe pancreatitis varies between 0% and 12.7% (94,95,101,102,106,109,143). These results are similar between IAP and non-IAP.

The rate of AP local complications tends to be lower in IAP. Anderson *et al.* and Garcia Garcia de Paredes *et al.* reported local complication rates in IAP of 26.3% (95) and 13.1% (143) respectively, which was not different from that seen in other aetiologies. However, there are some studies that found lower local complication rate in IAP than in alcoholic aetiology (19.4% *vs.* 37.1%) (114) or other aetiologies (101).

Regarding the development of chronic pancreatitis in IAP, Bertilsson *et al.* reported that 5.8% of IAP patients developed chronic pancreatitis over a nine-year period, which was higher than with biliary aetiology, but significantly lower than with alcoholic aetiology (114). The strongest predictors for developing chronic pancreatitis were episodes of RAP, alcoholic aetiology, smoking, systemic and local complications. This is in line with Magnusdottir *et al.* that alcoholic AP, RAP, organ failure and local complications predict the development of chronic pancreatitis (101). On the other hand, a prospective study in the Netherlands found that IAP patients had an increased risk of developing chronic pancreatitis that is higher than the risk in biliary AP, but still, the highest risk was associated with alcoholic AP and smoking (108). A retrospective study in an IBD population with a five-year follow-up reported that 5.2% of IAP patients developed chronic pancreatitis which is comparable to previous results (143). However, the authors found that this is significantly higher than the chronic pancreatitis rate in other aetiologies (0.6%). The most likely explanation is that because the study was conducted in a specific subset of patients (IBD cohort), the majority of AP pancreatitis cases were not true IAP but drug-induced (59%) while the amount of alcoholic AP was disproportionately low (1%). These results further illustrate that alcohol is one of the main factors in the development of chronic pancreatitis.

To better understand the evolution of patients with true IAP, more prospective cohort studies with a longer follow-up are needed.

Treatment

There is no specific treatment for a true AP, unless treating the underlying aetiology. Therefore, the initial therapy is focused on ameliorating symptoms and precluding the occurrence of complications (147).

Since it has been suggested that a significant percentage of the IAP cases are in fact due to microlithiasis (121,127,148) therapeutic modalities have been proposed focused on that. However, there is a lack of sufficient evidence and lack of standardization of diagnostic work-up among the studies and no consensus has been achieved.

The definitions of biliary sludge and microlithiasis are still heterogenic and subject to controversy. In a recently published survey answered by experts, 40% of respondents agreed about their similar findings in both cases and 36% of respondents attributed up to 50% of IAP cases to biliary sludge or microlithiasis (10).

Based on the possibility that most of the so-called IAP are in fact biliary, caused by microlithiasis or sludge, some studies have been performed evaluating the role of cholecystectomy in IAP. A multicenter randomized Finnish trial (149) randomized patients after a first episode of IAP to undergo laparoscopic cholecystectomy (LCC) or conservative treatment. This study showed lower recurrence rate of IAP in the LCC group compared to conservative treatment, lower number of recurrences, even within a subgroup with normal liver values. The number needed to treat to avoid 1 episode of IAP was 5. At surgery, sludge or microlithiasis was found in 58% of all cases. These results are in line with

another retrospective study (150), which concluded that performing LCC after the first episode of IAP significantly reduces recurrence rate. However, it should be noted that in these studies, EUS was not part of the diagnostic work-up of IAP, and in the retrospective study information about hypertriglyceridemia and medication was not reported (151). Therefore, one may assume that by using EUS some unnecessary surgeries could be avoided. Nevertheless, a recent meta-analysis (8) performed to evaluate the role of cholecystectomy in this scenario, showed that even in patients diagnosed of IAP after EUS or MRCP, the recurrence rate was lower after cholecystectomy, compared to non-operative treatment. More prospective trials are needed on the role of cholecystectomy after a true IAP, where an accurate evaluation and exclusion of biliary aetiology is being performed (as recommended in the algorithm in *Figure 1*).

Another option that has been evaluated for the treatment of IAP is ERCP with biliary sphincterotomy, with or without pancreatic sphincterotomy. Coté *et al.* enrolled RIAP patients and performed sphincter of Oddi manometry. The patients with high pressure were randomized to receive either biliary sphincterotomy alone or accompanied with pancreatic sphincterotomy. They found no difference in the IAP recurrence between the groups, and concluded that adding pancreatic sphincterotomy to biliary sphincterotomy for patients with SOD does not add further benefit. They also evaluated patients with normal manometry, and these were randomized to biliary sphincterotomy or sham surgery without differences in recurrence between both groups (152). These results are in line with the study published by Das *et al.* which determined that for patients who had endoscopic sphincterotomy (biliary or dual sphincterotomy), the risk of RAP was not statistically different from the group with no sphincterotomy (153). For patients with RIAP and pancreas divisum, minor papilla sphincterotomy is also a treatment option with a clinical efficacy of 46–76% although the data is based on retrospective studies (154,155). In 2018, Coté and colleagues initiated the SHARP trial that aims to test whether ERCP with minor papilla endoscopic sphincterotomy will reduce the risk of RAP; the results have not yet published (156).

A small prospective randomized trial showed promising results for pancreatic stenting in the context of RIAP; yet, the pancreatic pain was recurrent in both groups (157).

Regarding the ursodeoxycholic acid treatment (UDCA), Testoni *et al.* stated that 75% of their patients that had no radiological lesions (evaluated by ERCP) responded to oral bile acid therapy, reinforcing the idea that the presence of sludge may have been the recurrence cause, although the study was performed before the EUS era (158). UDCA may be used for patients with demonstrated sludge or microlithiasis, who do not go for LCC or sphincterotomy (10).

Follow-up

No evidence-based guidelines have been established for outpatient follow-up care for IAP patients. At the beginning, follow-up should be focused on diagnostic work-up to rule out all the possible aetiologies that might have caused the AP episode (*Figure 1*) as with a true IAP, the risk for developing a recurrent episode or chronic pancreatitis is high. However, there is no clear evidence or recommendation regarding the follow-up of IAP. Further prospective studies are needed.

Conclusions

Careful search of AP aetiology remains a key to successful management. Only by identifying the aetiology, a suitable therapy may be planned, possibly leading to prevention of RIAP, improvement of prognosis and reduction of health care costs. However, no validated protocol on this topic exists, and the differences in the diagnostic work-up and management vary, also seen as different rates of IAP. With this review we aimed to collect evidence to improve the systematic approach in aetiological examinations of AP, focusing on classifying the aetiology of AP and thus reducing the amount of true IAP cases. We believe that the algorithm for the diagnostic work-up of IAP proposed herein will be beneficial for clinicians. In addition, we conclude that more studies addressing the strategies to determine the aetiology of AP and possible treatments of true IAP are needed.

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