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TOPIC HIGHLIGHT

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Review of idiopathic pancreatitis

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Abstract

Recent advances in understanding of pancreatitis and advances in technology have uncovered the veils of idiopathic pancreatitis to a point where a thorough history and judicious use of diagnostic techniques elucidate the cause in over 80% of cases. This review examines the multitude of etiologies of what were once labeled idiopathic pancreatitis and provides the current evidence on each. This review begins with a background review of the current epidemiology of idiopathic pancreatitis prior to discussion of various etiologies. Etiologies of medications, infections, toxins, autoimmune disorders, vascular causes, and anatomic and functional causes are explored in detail. We conclude with management of true idiopathic pancreatitis and a summary of the various etiologic agents. Throughout this review, areas of controversies are highlighted.

Key words: Idiopathic pancreatitis; Recurrence; Etiology; Endoscopic retrograde cholangiopancreatography; Magnetic resonance cholangiopancreatography; Sphincter of Oddi dysfunction

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INTRODUCTION

Pancreatitis is a relatively common disorder with a myriad of etiologies all resulting in a common end result of inflammation within the pancreas. Acute pancreatitis (AP) results in acute inflammation typically presenting as abdominal pain with elevated levels of pancreatic enzymes[1]. Chronic pancreatitis (CP) is defined as a clinical syndrome of progressive inflammatory changes in the pancreas leading to permanent structural damage with subsequent impairment of both exocrine and endocrine function[2]. Chronic pancreatitis is often preceded by recurrent bouts of acute pancreatitis, however, occasionally it can present in a 'silent' fashion.

The label of "idiopathic pancreatitis" (IP) was originally designated to cases of pancreatitis wherein a diagnosis could not be made through a thorough history, physical examination, laboratory studies, and noninvasive imaging modalities such as abdominal ultrasonography/computerized tomography. Previously, this nomenclature had accounted for 8%-44% of cases being termed "idiopathic"[3-9]. Recent new laboratory and technological advances have been able to shred the enigmatic veils of IP to a point wherein with extensive evaluation it is possible to reveal the etiology in 79%-80% of patients previously labeled as having "idiopathic pancreatitis"[10,11]. More modern imaging investigations include, but are not limited to fine cut computerized tomography, endoscopic retrograde pancreatography, magnetic resonance pancreatography as well as endoscopic ultrasound.

EPIDEMIOLOGY

Longitudinal data on incidence trends report an increase in AP[12] which may be attributable to increases in all causes of pancreatitis as well as improved detection methods. The fatality rate for pancreatitis has continued to range between 3%-10%[13-18] despite a marked decrease in pancreatitis case fatality presumably secondary to early recognition of severity and complications as well as improved intensive care management[14,15]. Thomson[6] and others[7,17] have noted that in AP mortality rates are greater when the etiology is IP (14.1%)[6], compared with gallstone pancreatitis (7.2%)[6]. In addition, the clinical impact of IP is further highlighted by the fact that 40 percent (the largest subgroup) of all AP fatalities are attributable to IP[19, 20]. The incidence of IP ranges from 4.21 per 100 000[21] to as high as 45.33 per 100 000[9] depending on the population studied and the time in which data was collected with a trend toward high incidence in populations studied more recently[12,13,22]. The incidence appears to be

Table 1 Etiologies of acute or acute recurrent pancreatitis

Category	Agent/Diagnosis
Vascular	**Atheroembolism**
	Intraoperative hypotension
	Hemorrhagic shock
	Vasculitis (systemic lupus erythematosus and polyarteritis nodosa)
Infectious	**Viral**
	Mumps
	Coxsackievirus type B
	Hepatitis B
	Cytomegalovirus
	Herpes simplex
	Varicella-zoster
	HIV
	Rubella (probable)
	Bacterial
	Legionella
	Leptospira
	Salmonella
	Mycoplasma
	Brucella
	Mycoplasma
	Salmonella typhi
	Fungal
	Aspergillus
	Parasites
	Toxoplasma
	Cryptosporidium
	Ascaris lumbricoides
Trauma	Blunt or penetrating abdominal injury
	Post-ERCP pancreatitis
	ERCP sphincterotomy
	Manometry of sphincter of Oddi
	Iatrogenic operative complication
Metabolic	Hypertriglyceridemia (types Ⅰ, Ⅳ, Ⅴ)
	Hypercalcemia
	Hyperparathyroidism
Toxins	Ethyl alcohol
	Scorpion venom
	Methyl alcohol
	Organophosphorous insecticides
Medications	**Antimicrobial agents**
The following drugs were definitely associated with pancreatitis	Metronidazole, Stibogluconate, Sulfonamides, Tetracycline, Nitrofurantoin, Erythromycin, Isoniazid
	HIV Therapy
	Didanosine, Pentamidine
	Diuretics
	Furosemide, Thiazides
	Commonly used Gastroenterology Medications
	5-ASA, Sulphasalazine, Cimetidine, Ranitidine, Mercaptopurine, Proton pump inhibitors
	Cardiac Agents
	Procainamide
	Immunosuppressives or Chemotherapeutics
	L-asparaginase, Azathioprine, Cytosine arabinoside, Dexamethasone
	Neuropsychiatric Agents
	Valproic Acid, αMethyl Dopa
	Other Commonly Used
	Acetaminophen, Salicylates, Sulindac, Calcium, Ethinylestradiol, Norethindrone
Mechanical	Gallstones
	Microlithiasis and Biliary Sludge.
	Sphincter of Oddi dysfunction
	Pancreas divisum
	Annular pancreas
	Autoimmune pancreatitis
	Pancreatobiliary Tumours
	Cholodochocele
	Duodenal stricture or obstruction
	Ascariasis
Miscellaneous	Post ERCP
	Renal transplant
	Hyper IgG4 disease
Genetic	CFTR
	Serine protease inhibitor Kazal type 1 mutation
	Cationic trypsinogen gene PRSS1 mutation
Autoimmune	Sjogren's syndrome
	Primary biliary cirrhosis
	Renal tubular acidosis

equal between the two sexes and tends to increase with age in both before starting to plateau around 70 years[18].

Elucidating the etiology of pancreatitis, if possible is paramount as it guides therapy and may theoretically subsequently improve patient outcomes, thereby preventing relapses. Some studies have shown that over 50% of untreated patients with acute IP experience recurrent episodes[23-25]. This contrasts with other studies where only 1 of 31 patients with a first episode of unexplained AP suffered another attack during a median follow up of 36 mo[26]. These conflicting results may reflect different patient populations, perhaps even within the same category known as IP.

Aside from the initial objective to decrease acute patient mortality and morbidity, repeated insults to the pancreas may progress to chronic pancreatitis with irreversible morphologic and functional changes[2,24,27]. This concern typically results in aggressive investigation for those patients with more than one episode of AP. This approach is supported by a study by Kaw and Brodmerkel in a study that included 126 patients with two or more episodes of IP. They demonstrated that investigations including bile for microlithiasis, a secretin stimulation test, and sphincter of Oddi manometry (SOM) was able to clarify the etiologies in 79 percent of patients[11]. In this study they were able to offer 75% of these patients treatment that resulted in the absence of AP in over 60% of cases over a 30 mo follow-up period[11].

However there is ongoing debate against aggressive evaluation. The Kaw and Brodmerkel study confirmed previous morbidity data demonstrating that SOM is not a benign procedure and that complications occur[11]. Additionally, many aggressive techniques for diagnosing the etiology of pancreatitis, including SOM, may not be routinely available. Therefore the generalizability of this study has been brought into question.

This article will examine some of the etiologies that must be excluded prior to a diagnosis of IP. An attempt will be made to highlight the areas of controversy, and make suggestions based on the best available evidence. For the purpose of this IP article, gallstones and alcohol related pancreatic disease will not be discussed as their presentation is usually easily determined. For a more comprehensive list of all etiologies of pancreatitis please refer to Table 1.

PANCREATITIS ETIOLOGIES OFTEN LABELLED AS IDIOPATHIC PANCREATITIS

Microlithiasis and biliary sludge

Biliary sludge refers to the viscous suspension in gallbladder bile formed by modification of hepatic bile by the gallbladder mucosa that may contain small stones (< 5 mm in diameter)[28]. Microlithiasis refers to stones of < 3 mm in diameter and is often used interchangeably at times with "microcrystals" and sometimes with biliary sludge[28-30]. Microscopy of bile in patients with sludge often shows cholesterol monohydrate crystals, calcium carbonate microspheroliths, or calcium bilirubinate granules[31]. A known risk factor for the development of sludge typically includes prolonged fasting states as well as some antibiotics (ceftriaxone)[32]. Microlithiasis has been suggested to be the most common causes of IP[31,33] with a prevalence ranging from 6%-73%[11,25,31,33,34].

It has been demonstrated that treatment with cholecystectomy, endoscopic sphincterotomy, or ursodiol significantly reduces further attacks of IP[31,33]. Therefore it was inferred that in the absence of other identifiable risk factors, the presence of microlithiasis was enough to cause IP[11,26,35]. The caveat to interpreting these studies is that combined, they involved only 74 patients who had IP and treatments were clearly not double blinded[31,33].

An Indian study published earlier this year evaluating 51 patients with recurrent IP found that microlithiasis accounted for a mere 13 percent of these patients (using duodenal bile samples)[36]. In the setting of suspected biliary pancreatitis up to 88% of patients will have microlithiasis demonstrating the difference between these two patient groups[37]. It is speculated that there may be some gender, age, racial, and procedural differences in bile sample collection and analysis as these are not well standardized.

The pathogenesis of AP *via* microlithiasis remains unclear however it is thought that the microlithiasis may transiently impact the papilla, cause pancreatic duct obstruction and thereby pancreatitis[29,37,38]. The diagnostic workup for microlithiasis includes routine abdominal ultrasound (US) which has limited sensitivity when looking for stones less than 3 mm in diameter[28,39]. Endoscopic US (EUS) may be considered as well as it carries a lower risk of complications than endoscopic retrograde cholangiopancreatography (ERCP)[34,40-45]. On average, EUS is able to identify gallbladder sludge in up to 75 percent of IP cases[40-45]. All patients with recurrent IP should have microlithiasis excluded and there is even some evidence that it should be excluded for patients who have their first IP[41-43].

It remains to be clarified which method of bile collection for microscopic analysis is clinically the best and there are no standardized methods or recommendations at this time[46-48].

Cholecystectomy is recommended for patients with biliary sludge/microlithiasis once they recover from their episode of pancreatitis as it reduces the relapse rates[31,33]. In patients who are poor surgical candidates, ERCP with biliary sphincterotomy or ursodeoxycholic acid may be alternative forms of treatment[31,33].

Sphincter of Oddi dysfunction

At times referred to as hypertensive or fibrotic SOD, SOD causes diminished transphincteric flow of bile and/or pancreatic juice due to either organic obstruction (stenosis) or functional obstruction (dysmotility)[3,35,49]. SOD often causes recurrent pain with or without abnormalities of either hepatic/pancreatic profiles as well as duct dilation. It is thought that SOD causes pancreatitis as a result of bile reflux into the pancreatic duct or from pancreatic duct outflow obstruction[25,50]. SOD is considered to cause up to one third of all cases of IP[25,30,51,52].

In order to diagnose SOD, one often needs to perform sphincter of Oddi manometry (SOM)[53,54]. The diagnostic gold standard is a water-perfused catheter system that can be inserted into the common bile duct or pancreatic duct with the positive finding being a hypertensive sphincter of Oddi pressure greater than 40 mmHg[53]. Unfortunately whether ERCP in patients with suspected SOD is done for diagnostic SOM or therapeutic purposes it is undeniable that there have been high complication rates, particularly pancreatitis[51,55-59]. Additionally "severe" pancreatitis that is associated with death has even been quoted in 1-3% in SOM[15,25,51]. Despite this, ERCP with SOM has been advocated for the evaluation of recurrent IP[25,60]. In patients who have normal biliary manometry, pancreatic sphincter manometry may be reasonable to perform[61,62] which does carry a higher risk of pancreatitis[54] that may be reduced by aspirating through the middle port of the triple lumen manometry catheter[63].

Once the diagnosis of SOD is made, endoscopic sphincterotomy is the treatment of choice as it is believed to decrease the risk of recurrent pancreatitis[25,60,64-66].

The Geenen-Hogan (Milwaukee) criteria was devised to predict the overall probability of response to biliary sphincterotomy taking into account the presence of abnormal liver chemistries and dilated bile ducts[44]. On the basis of this, patients with pain and both abnormalities (type Ⅰ) are definitely recommended to have sphincterotomy as they have high response rates ranging from 90%-100% regardless of SOM[67,68]. Along this stratification, type Ⅱ patients have either abnormal liver chemistry or dilated bile ducts. If SOM is abnormal in type Ⅱ patients they will have a response rate to sphincterotomy of 60%-91%[64,67,69] and thus this would be a reasonable course of action. On the contrary, type Ⅲ patients do not have objective biliary abnormalities and even if they have abnormal SOM they have poor response rates of 6-58 percent[69-71], making sphincterotomy of questionable benefit (Table 2) .

If a diagnosis of pancreatic sphincter dysfunction is made in patients who have had biliary sphincterotomy the answer to who best benefits from pancreatic sphincterotomy is less clear. A study by Freeman *et al*[72] this year treated suspected SOD with biliary sphincterotomy with additional pancreatic sphincterotomy at initial or subsequent ERCP if there was abnormal pancreatic manometry in conjunction with pain refractory to biliary sphincterotomy, continuous pain, or a history of amylase elevation. In this study of 121 predominantly female (92%) and post cholecystectomy (87%) patients, all patients underwent biliary sphincterotomy while 40 percent also

Table 2 Sphincter of Oddi dysfunction (Geenen and Hogan Classification)

Biliary type	Pancreatic type
Type Ⅰ	**Type** Ⅰ
Biliary-type pain	Pancreatic-type pain
LFT elevation	Amylase/lipase elevation
CBD dilation	PD dilation
Delayed drainage	Delayed drainage
Type Ⅱ	**Type** Ⅱ
Biliary-type pain	Pancreatic-type pain
One or two of above criteria	One or two of above criteria
Type Ⅲ	**Type** Ⅲ
Biliary-type pain only	Pancreatic-type pain only

CBD: Common bile duct; LFT: Liver function tests; PD: Pancreatic duct.

underwent pancreatic sphincterotomy regardless of the modified Milwaukee biliary classification[72]. The result from this study was that a positive response at final follow up was reported in 69 percent of patients and that this response was not significantly different between biliary types Ⅰ, Ⅱ, and Ⅲ[72]. Freeman *et al*[72] concluded that patient characteristics of pancreatic manometry, delayed gastric emptying, daily opioid use, and age < 40 were significant as predictors of outcomes as opposed to the Milwaukee classification. Indeed it is becoming more accepted that a lack of improvement after biliary sphincterotomy may be representative of a failure to relieve pancreatic sphincter pressure[61,62,73-77].

Noninvasive strategies such as a low-fat diet, analgesics, anticholinergics, calcium-channel blockers, nitrates, and proton pump inhibitors are unfortunately seldom effective[78,79].

Pancreas divisum

In Pancreas divisum it is thought that 80%-95% of pancreatic juice volume flows *via* the dorsal duct through the smaller minor papillary orifice *via* the dorsal duct of Santorini as opposed to the more common route through the major papilla *via* the ventral duct of Wirsung[66]. It is postulated that the mechanism is that of relative minor papilla outflow obstruction leading to pancreatitis[23,80-82].

Pancreas divisum occurs as an anatomic variant in 5%-7.5% of patients[23,82]. There are those who are skeptical of the obstructive theory as fewer than 5% of patients with pancreas divisum develop pancreatitis[83-86]. It also appears that the incidence of pancreas divisum is the same in patients with and without pancreatitis[86]. Nonetheless there is consensus that while most individuals with pancreas divisum live normally, a few unfortunate patients are predisposed to develop recurrent AP[23-25,35] and that it accounts for 20 percent of the IP cases[23-25].

One explanation of why some patients with pancreas divisum are more likely to be affected was the smaller than usual minor papillary orifice causing a disproportionately high intrapancreatic dorsal ductal pressure especially during times of active secretion. In this situation a cascade of inadequate drainage leading to ductal distension and eventually pancreatitis could occur[23,87-89]. This theory is supported by at least one surgical study that demonstrated relief of pain as well as diminished attacks of AP with sphincteroplasty[87].

Recently, Choudari *et al*[90] found that prevalence of the cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations was similar in patients with pancreas divisum with recurrent acute pancreatitis and true idiopathic recurrent acute pancreatitis. Interesting, this study also found that the prevalence of CFTR gene mutations in patients with pancreas divisum but without recurrent AP was similar to controls without pancreatitis[90]. The significance of CFTR will be discussed in more detail under "Genetic Causes and Contributions" below, however, these genetic studies call into question the true role of pancreas divisum in IP.

At present, it is accepted that patients who present with severe pancreatobiliary type symptoms or recurrent IP should however be evaluated for pancreas divisum[35,48]. The diagnosis of divisum can be made either by ERCP or magnetic resonance cholangiopancreatography (MRCP)[91,92]. ERCP may be preferred to conventional MRCP as it has a higher sensitivity and specificity[91,92] and can offer therapy albeit with a complication rate that is higher than in MRCP. Secretin may be given intravenously to aid in finding the minor papillary orifice at ERCP[93], finding functional outflow obstructions[94-96], and assessing the relative obstruction of the minor papilla[94-96]. In settings where secretin is either contraindicated or does not produce a visible increase in pancreatic juice flow, a dilute (1:10) methylene blue solution can assist in the location of the minor papilla[97]. Confirmation is recommended to rule out pseudodivisum caused by a tumor.

An emerging area is the role of EUS as it is a minimally invasive tool for the general workup of IP and recurrent IP[48]. It appears that EUS is able to detect pancreas divisum but more research in comparing ERCP to EUS specific to divisum is needed before recommendations are made.

In the setting of recurrent AP, once divisum is diagnosed, ERCP therapy to relieve minor papillary obstruction is recommended to decrease the rate of recurrent pancreatitis[98-101], particularly in patients with a dilated pancreatic duct who may be the most likely to benefit from therapy[98]. The rate of decrease of recurrent pancreatitis is quoted to range from 70%-90%[99,100] with a 40%-60% response rate in patients with CP also demonstrated[102]. The ERCP therapy involves a minor papillotomy usually with temporary stenting[98-101,103]. In one study, more favorable long-term results were achieved with minor papilla sphincterotomy than with repeated stenting in terms of both recurrence and fewer complications (25% *vs* 44% respectively)[98]. Some endoscopists are particularly cautious about endoscopic stenting as the procedure may cause permanent damage to the pancreatic ducts, possibly promoting the development of chronic pancreatic disease[104,105].

Anomalous union of pancreaticobiliary duct

Anomalous union of pancreaticobiliary duct (AUPBD) is defined as an anomalous junction of bile duct and

pancreatic duct at an abnormal proximal site of these ducts[35]. The precise location of the junction is outside the duodenal musculature and independent of the sphincter of Oddi. This independence from the contractility of the sphincter of Oddi results in regurgitation of the pancreatic juice into the biliary tract and vice versa[106]. AUPBD is frequently associated with choledochal cysts which in itself has been linked to IP (see below)[107] and is more common in East Asia[35].

It is thought that in AUPBD reflux of bile into the pancreatic duct may cause recurrent AP[106,108] and that in cases with a dilated common channel the stasis of pancreatic secretion can occur in the common channel leading to pancreatitis[109,110]. Moreover it has also been found that SOD (see above) is sometimes associated with AUPBD[111].

The diagnosis of AUPBD is usually made during ERCP evaluation for IP when one notes a pancreatic duct and choledochus connecting with a long common channel of > 15 mm in adults[112]. Similarly AUPBD is also seen during MRCP[91]. The length of the common channel alone is not an absolute diagnostic criterion as other factors like the form of union, direction, and age and stature of patients need to be considered[108,113]. An alternate method of diagnosis, more importantly a 'clue' to the presence of AUPBD, may be the presence of high amylase levels in aspirated bile[114,115].

In AUPBD, endoscopic biliary sphincterotomy has been shown to prevent further attacks of AP[112] by a postulated mechanism of decreasing resistance at the major duodenal papilla[35]. Due to the fact that AUPBD has a propensity to increase gallbladder and biliary duct cancer[114,116-118], prophylactic cholecystectomy has been recommended in these patients[116]. As well, at this time there is some evidence that patients with AUPBD and choledochal cyst should have an extensive resection of the extrahepatic bile duct inclusive of the cyst in hopes of preventing development of biliary duct cancer[108] which may be relevant in 5% of patients[116]. It is reiterated that the understanding of AUPBD, its pathophysiology and therapy is very limited[35].

Choledochocele

Choledochocele is classified as a type Ⅲ choledochal cyst that represents a prolapse or herniation of the intramural segment of the distal common bile duct into the duodenal lumen which may be either congenital or acquired[35,119]. Pancreatitis and recurrent AP is an important complication occurring in choledochoceles occurring in 12%-30% of patients[120,121]. Choledochoceles do not represent a common cause of IP, especially in adults[25,35,120].

It is thought that the choledochocele may create an obstruction to the pancreatic duct intermittently when the choledochocele becomes distended and that this may lead to reflux of bile into the pancreatic duct[121-123].

A characteristic "bulging" appearance of the papilla at ERCP and a soft "pillow" sign with pressure applied at the catheter tip suggests a choledochocele[120,124]. A CT or US in isolation may miss this diagnosis[120]. The role of MRCP in adults to diagnose this is still undefined[91,125,126].

Treatment can be initiated with endoscopic sphincterotomy combined with "unroofing" of the choledochocele with a papillotome with the goal of creating effective drainage of bile and pancreatic juice[120,127]. Patients that fail this treatment may be considered for a surgical sphincteroplasty[128]. Reports in the surgical literature about choledochal cysts in general recommend a single stage surgery usually comprising of complete cyst resection, cholecystectomy and Rou-en-Y hepatojejunostomy[129-131]. Malignancy is noted in 3-5 percent which may in some cases warrant prophylactic surgery[131,132].

Annular pancreas

Annular pancreas is a congenital condition that represents a band of pancreatic tissue partially or completely encircling the duodenum that is usually at the level of or immediately proximal to the major duodenal papilla[133]. It is thought that this defect occurs in utero due to the failure of the ventral bud to rotate with the duodenum[133]. This abnormality is rare and is detected in 1/7000-1/20 000 autopsies[133,134] and in 1/1500 ERCPs[135-137].

Clinically it usually manifests in childhood with intractable vomiting[136,137] and is thought to result from descending duodenal narrowing leading to duodenal obstruction or recurrent AP[138]. In adults annular pancreas may present with abdominal pain, acute recurrent IP, CP, peptic ulcer disease, postprandial fullness, vomiting, or biliary obstruction[137,139]. Associated congenital anomalies such as Down's syndrome, cardiac defects, tracheoesophageal fistula, Meckel's diverticulum, and imperforate anus may be present[133,136]. If the diagnosis is made in adults it usually occurs between the ages of 20 to 50[140].

From a diagnostic view, barium studies, abdominal CT, or MRCP may suggest the diagnosis but an ERCP is recommended for confirmation[135,136,141]. A typical ERCP is that of the duct of the pancreatic annulus encircling the duodenum[24] and in one third of cases a pancreas divisum is also present[139]. The annular duct may communicate with the central duct but rarely drains into the dorsal duct, common bile duct, or independently into the duodenum[135,139]. In cases where ERCP may not be feasible, an EUS may offer an alternative means of diagnosis[142]. Recently some data has also become available on the role of MRCP which appears encouraging as a non-invasive method of diagnosis[143-145].

Surgery is the procedure of choice in patients in whom symptoms can be attributed to annular pancreas with the goal to relieve duodenal or gastric outlet obstruction[137,146].

Pancreatobiliary tumors

Any mass that obstructs the main pancreatic or biliary ducts, benign or malignant can result in acute pancreatitis. It has been estimated that 5%-14% of patients with pancreatobiliary tumors, benign or malignant, present with apparent IP[147-150]. Pancreatic cancer should be suspected in any patient older than 40 years with IP especially with a prolonged or recurrent course[3,5]. Neoplasia should be suspected in a patient with weight loss, steatorrhea, ductal dilation, new onset diabetes, or evidence of a solid

or cystic pancreatic mass[24,149,150]. In younger patients lesions such as curable islet cell tumors should be in the differential whereas in the elderly they may have potentially curable lesions such as cystic neoplasms[24].

It is well known that CT, MRI, ERCP, and EUS have a role in identifying pancreatobiliary neoplasms[151-154]. It is recommended that if there is any clinical suspicion of malignancy that aggressive investigation including ERCP be performed even on the first attack of IP in older patients. In patients who are less than 40 years old, a CT may be sufficient in first attacks of AP[24]. If a malignancy is suspected, EUS is a favorable technique that can be used for diagnostic and staging purposes[155,156] especially when combined with fine needle biopsy[157,158].

Intraductal papillary mucinous neoplasm of the pancreas (IPMN) is a distinct pathologic entity formed of papillary proliferations of mucin-producing epithelial cells with or without excessive mucus production and or cystic dilation of the pancreatic duct. IPMN represents a precancerous lesion with a well described adenoma and carcinoma sequence that causes recurrent acute IP with symptoms suggestive of chronic obstructive pancreatitis due to intermittent obstruction of the pancreatic duct with mucus plugs[159]. It is worth noting this entity has an insidious nature and lack of awareness often delays diagnosis[160-163]. On ERCP, in cases of main duct involvement, the papilla is patulous and resembles a "fish-eye" frequently with mucus extruding from the orifice[161,164,165]. In terms of management, since the ten-year actuarial risk of high grade dysplasia and invasive cancer is significant[166] surgery is usually recommended, particularly for main duct disease[159,167-169]. It should also be noted that patients with IPMN may be at increased risk for extrapancreatic malignancies and because of this gastricadenocarcinoma and colorectal cancer should be screened for using endoscopy[170,171]. Patients with branch type disease may be at a lower risk of malignancy and theoretically can be monitored in regards to mural wall thickening, size of branch cystic lesion and tumor markers.

Cystic pancreatic tumors including IPMN, serous cystadenomas, mucinous cystadenomas, and mucinous cystadenocarcinomas, can be premalignant or malignant and surgery is generally indicated[172-174]. Tumor markers such as CA 19-9, CA 15-3, CA 72-4, and carcinoembryonic antigen in aspirated cystic fluid along with fluid viscosity and amylase level may be used to increase the diagnostic yield of cyst fluid cytology[175-179].

Ampullary adenomas are premalignant and in general, indicate the need for close monitoring and eventual removal[180,181]. In general, ampullary tumors have a more favorable prognosis than pancreatic tumors and pancreatoduodenectomy has historically been recommended[182-184]. An emerging development for ampullary tumors is the use of endoscopic techniques such as endoscopic ampullectomy for management of patients with small benign lesions or for carcinoma *in situ*[185-188] which appears to be safe and efficacious on long term follow up[188]. If endoscopic management is selected it has been recommended that surveillance and random biopsies be performed[24].

GENETIC ASSOCIATIONS AND CAUSES

An exciting development is the recognition of genetic mutations that are associated with pancreatitis.

CFTR

The cystic fibrosis transmembrane conductance regulator (CFTR) and its gene mutations cause cystic fibrosis in an autosomal recessive pattern. It is well established that CFTR mutations cause disease of the exocrine pancreas[189]. The CFTR gene encodes a chloride-channel protein that is regulated by cAMP. Bicarbonate ion is secreted into the duct lumen by the action of CFTR in the apical membranes and this sets up a gradient in which water follows[190]. In the absence of CFTR, the pancreatic duct cells cannot secrete fluid and bicarbonate and hence CF of the pancreas develops[191].

The actual mechanism that mutations in the CFTR gene causes recurrent AP or CP[90,192-194] is unknown. It may be that mutant CFTR channels are inefficient at flushing digestive enzymes out of the pancreatic duct and thereby limiting the major mechanism that prevents trypsin-associated injury within the pancreatic duct[195]. Along the same lines, it may be that mutant CFTR can limit bicarbonate secretion that can interfere with trypsin activation[195]. What is clear is that CFTR mutations have a demonstrated increased incidence in patients with CP, IP, and alcohol induced CP[194,196-201]. One recent study of 381 patients diagnosed with either CP or recurrent IP that used expansive CFTR genotyping showed mutant CFTR genes in 11% (43/381) of these patients[195]. This frequency is in keeping with previous reports of 28%-45% of IP patients being either heterozygous or homozygous for a CFTR gene mutation[202,203]. One study in Poland showed that the frequency of mutations in CFTR alleles was similar to controls (4.9% *vs* 5%, $P = 0.587$) but this study only looked at 3 CFTR defects[204].

Testing for this gene mutation may be considered in younger patients presenting with recurrent IP who have a positive family history of cystic fibrosis or IP[66,195,205]. If testing is to be done, a broad mutation panel to look for a multitude of mutations of CFTR is recommended[195].

SPINK1

The N34S mutation of the serine protease inhibitor Kazal type 1 (SPINK1) has been reported to be strongly associated with IP and hereditary/familial pancreatitis[206-208]. SPINK1 is a specific trypsin and trypsin activated trypsin like inhibitor expressed within the pancreas that provides a defense against prematurely activated trypsinogen[209,210]. It has been suggested that SPINK1 mutations are disease modifiers in that they lower the threshold for pancreatitis from other genetic or environmental factors[207]. For example this mutation was found in one study to be associated with CP and recurrent IP in 7.7% and 10% respectively[204]. Likewise, a larger study showed that 15.7% of patients with CP or recurrent IP carried at least one SPINK1 mutation[195].

A genetic test for SPINK1 should be done in any younger patient presenting with recurrent AP or CP and a family history of IP or CP-particularly if they have had

prior negative workup with ERCP. When genetic testing is done, it is advised to perform a concomitant CFTR and PRSS1 mutation screen[195].

Cationic trypsinogen gene PRSS1

Two missense mutations R12211[211] and N291[212] in the human cationic trypsinogen gene [protease serine 1 (trypsin 1); PRSS1] were first detected in patients with hereditary pancreatitis and appear to manifest as autosomal dominant mutations[213]. Since the discovery of the first two genes many other PRSS1 mutations have been reported[214-219]. Pathophysiologically this mutation leads to impaired trypsin autolysis and degradation, impairment of SPINK1 defense mechanism, and promotion of auto-activation of trypsinogen all of which can cause AP and lead to CP[211,220].

Symptoms typically arise in childhood but may be delayed until the mid 30 s[221]. These usually include symptoms associated with CP[221]. The lifetime risk of pancreatic cancer is 40% and reportedly 75% with paternal inheritance[222]. Whereas in cases of CFTR and SPINK1 are associated with IP and CP, PRSS1 defects seem to be causative for AP[204].

As in CFTR and SPINK1, the diagnosis is usually suspected if younger patients with affected family members present with CP or recurrent IP. Complications of CP are usually dealt with endoscopically but given the high risk of malignancy surgical resection may be preferred[24].

Celiac disease

The frequent familial occurrence and the remarkably close association with the HLA-DQ2 and/or DQ8 gene locus suggests that celiac disease as an immune disorder that is triggered by an environmental agent, gliadin, in genetically predisposed individuals[223,224]. Intriguingly, recurrent pancreatitis can be caused by celiac disease[225,226]. The mechanism appears to be duodenal inflammation and associated papillary stenosis causing pancreatitis[225]. Endoscopic treatment is recommended at this time to relieve the obstruction.

There are consensus guidelines to the role of genetic testing in IP although they are evolving as our knowledge expands in the area[227].

MEDICATIONS

The list of medications that are associated with or that cause pancreatitis is increasing[228-230]. In one German study 1.4% of all acute pancreatitis was related to medications[231]. Another study reported an even lower association of 0.3%[232]. Drugs with the highest incidence of pancreatitis are azathioprine and mercaptopurine (incidence, 3 to 5%)[233] and didanosine (23%)[234].

Most medication related to pancreatitis is due to idiosyncratic response or a direct toxic effect. A high index of suspicion and astute drug history is crucial for making the diagnosis.

A few areas of medications causing pancreatitis will be highlighted. Firstly, physicians should be aware of a recent development showing an association of proton pump inhibitors and pancreatitis[235-237]. Secondly, some medications, such as pentamidine, valproic acid, and didanosine, appear to cause injury weeks to months after exposure, possibly through the accumulation of a toxic metabolite[238]. Hypersensitivity reactions have been implicated in other drugs, such as azathioprine, mercaptopurine, metronidazole, aminosalicylates, and sulfonamides, and these drugs characteristically lead to pancreatitis within one month after exposure[238]. Lastly, some medications like acetaminophen may cause pancreatitis with a single dose[239].

A complete list of medications that are classified as being definitely associated with pancreatitis derived from multiple references is shown in Table 1[228-230,240-242].

TOXINS

Toxins that have been linked to pancreatitis include the most common alcohol. The more deadly methanol can also cause AP[243]. Although exceedingly rare scorpion bites from Trinidad have been known to cause AP[244,245]. Another rare cause of IP is organophosphorous poisoning[246].

INFECTIOUS CAUSES

A plethora of infectious agents have been associated with AP[247]. A full list of definite and probable etiologic agents is provided in Table 1 from data gathered from Parenti *et al*[247]. It is unclear how often an infectious etiology is responsible for IP but many appear to be associated with it[247].

A clinician must be suspicious of an infectious etiology in the characteristic syndrome caused by the particular infectious agent notwithstanding that this was evident in only 70% of patients in the prior review for definite cases[247]. A routine search for an infectious cause in IP is not recommended unless there is a strong clinical suspicion.

Ascariasis is an important cause of infectious obstructive AP in India where it is the second most common cause of AP[248]. At times this may also present with associated biliary tree infestation requiring endoscopic decompression[249].

An infectious group worth discussing in greater detail is HIV infections and their relation to AP[250]. One large series revealed that 4.7% of hospitalized patients with HIV had AP[251]. While primary HIV infection itself can be a cause of AP[252,253] it is more commonly attributable to a complication of medications taken as part of HIV treatment or medications for opportunistic infections such as Pneumocystis carinii and Mycobacterium avium-intracellulare[250].

METABOLIC

Hypertriglyceridemia

Serum triglyceride concentrations above 11.3 mmol/L are capable of causing AP although admittedly the pathogenesis of inflammation is unclear[254]. It is thought that hypertriglyceridemia represents 1.3%-3.8% of AP

cases[255]. The incidence has been best defined in children with inherited disorders of lipoprotein metabolism that is associated with severe hypertriglyceridemia which are 35%, 15%, and up to 40% in hyperlipidemia types Ⅰ, Ⅱ, and Ⅴ respectively[256,257]. Other acquired causes of hypertriglyceridemia include obesity, diabetes mellitus, hypothyroidism, pregnancy, estrogen or tamoxifen therapy, glucocorticoid excess, nephritic syndrome, and beta blockers[258-260,255].

Drug-induced disease is more likely to occur in patients with underlying hypertriglyceridemia[256]. It is important to not neglect the lactescent serum as it is a vital clue to the diagnosis[255].

Controversy surrounds the contribution of hyperlipidemia in causing AP in alcoholics[261] but it is thought that in most alcohol abusers the moderate elevations of triglyceride levels are transient and likely to be an epiphenomenon rather than a causative agent of pancreatitis[262].

Hypercalcemia

Occurring in uncommon frequency, hypercalcemia of any cause is a known cause of AP[263,264]. Postulated mechanisms include calcium deposition in the pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma[265,266].

There are questions however on hyperparathyroidism, a cause of hypercalcemia, and the link to pancreatitis rose in one large study of 1153 patients that found that AP occurred in only 1.5 percent of patients that was of a statistically non significant difference from that of the general population[267]. This finding was mirrored in two other studies[268,269]. This is still an open controversy however as other studies have supported at least an association and a significantly increased relative risk of AP in patients with hyperparathyroidism[270,271]. Until the debate is resolved it is recommended that the parathyroid be checked in recurrent IP if hypercalcemia is present.

VASCULAR DISEASE

Pancreatic ischemia is an uncommon but an established cause of pancreatitis reported in: (1) vasculitis (systemic lupus erythematosus, polyarteritis nodosa, and microscopic polyangiitis)[272-274], (2) atheroembolism[275,276], (3) hypotension and shock[277-279].

While it is true that most patients have mild attacks of pancreatitis secondary to ischemia, fatal necrotizing pancreatitis is a rare occurrence[277].

TRAUMATIC CAUSES

Blunt or penetrating abdominal injuries can cause pancreatitis although it is incredibly rare given the retroperitoneal location of the gland[280]. Types of trauma that cause pancreatitis can range from a mild contusion, severe crush injury, or transection of the gland[280].

Post ERCP pancreatitis remains the commonest severe complication of ERCP found to occur in 5%-7% of patients in a recent review[281]. It may be possible that prophylactic stenting of the pancreatic duct in selective cases and minimally traumatic cannulation techniques may prevent some cases[281] and indeed this has been shown to be cost effective in high risk patients[282]. Octreotide infusion does not prevent ERCP-induced pancreatitis or affect serum amylase levels[283]. Likewise, transdermal glyceryl trinitrate did not improve the rate of success in ERCP cannulation or prevent post-ERCP pancreatitis in either average or high-risk patient groups[284]. Allopurinol at high doses has been shown in a prospective randomized trial to lower the risk of post-ERCP pancreatitis[285] but this study requires further verification as other studies have shown no benefit[285,286]. Risk factors for post-ERCP pancreatitis have been well described[287].

AUTOIMMUNE CAUSES

Autoimmune pancreatitis is a more recently described type of chronic pancreatitis characterized by an autoimmune inflammatory process in which prominent lymphoplasmacytic infiltration with associated fibrosis of the pancreas causes organ dysfunction[288-290]. The reported prevalence of autoimmune pancreatitis is between 5 and 6% of all patients with chronic pancreatitis[291]. A series from the United States shows that 11% of patients (27 of 254) with chronic pancreatitis received a diagnosis of autoimmune pancreatitis based on histological findings[292].

Immunologic abnormalities including hypergammaglobulinemia, elevated serum IgG4 levels, and the presence of autoantibodies against carbonic anhydrase and lactoferrin are important markers of the disease[288]. In particular, autoantibodies against lactoferrin and carbonic anhydrase Ⅱ have been identified as potential serologic markers of autoimmune pancreatitis[293,294]. The finding of increased serum IgG levels or the presence of autoantibodies is supportive of the diagnosis, whereas an elevated serum IgG4 level is nearly diagnostic[288].

CP has also been found to be in association with Sjogren's syndrome, primary biliary cirrhosis, and renal tubular acidosis[295,296]. The diagnosis is usually based on clinical suspicion and serum autoantibody to a pancreatic antigen previously discussed. Inflammatory bowel disease is also occasionally associated with autoimmune pancreatitis[297].

Differentiating the focal form of autoimmune pancreatitis rather than pancreatic carcinoma can be very difficult on the basis of CT imaging only[288]. Diffuse pancreatic-ductal narrowing is highly diagnostic of autoimmune pancreatitis[288,289,291]. There are also nonspecific endoscopic findings in the stomach or colon in patients with autoimmune pancreatitis, foci of slightly pale, thickened mucosa with loss of visible vascular pattern were observed in some cases[298]. The role for MRCP is at this time undefined[288].

EUS is a key tool in the diagnosis of autoimmune pancreatitis and its differentiation from other pancreatic diseases. The most common finding on endoscopic ultrasonography is diffuse or focal pancreatic enlargement along with a diffusely hypoechoic parenchyma, similar to findings on transabdominal ultrasonography[299,300].

The use of corticosteroid therapy is not mandatory in autoimmune pancreatitis, as there are reports of the spontaneous resolution of a pancreatic mass, stricture, and jaundice[301,302]. When steroids are given the response is often dramatic and can be monitored *via* clinical, laboratory and radiological parameters[303-306].

MISCELLANEOUS CAUSES

Recent reports of a new disease known as hyper IgG4 disease has been linked to IP[307] but more data is required before further comment. It is unclear if this is an entirely separate entity from autoimmune pancreatitis.

In renal transplant cases pancreatitis can occur as a result of the procedure itself[308], immunosuppressant medications (see above 'Medications'), opportunistic infections[309] or through allograft pancreatitis[310].

CHRONIC PANCREATITIS

The aforementioned etiologies of IP can all theoretically lead to CP. The diagnosis is best made after considering the results of ERCP, pancreatic function tests, and EUS[24].

It has been suggested that pancreatic function testing may help establish the diagnosis of CP at an earlier stage[311]. It appears based on recent evidence that EUS may be the most sensitive test[311,312] for CP diagnosis with the caveat of false positives[313].

Mortality rates for CP are 3-4 times greater than in controls[314,315]. Pancreatitis in CP accounts for 20 percent of mortality but mortality is usually from non-pancreatic causes[314,315]. CP carries with it many complications such as pancreatic duct strictures, stones, pseudocyst, fistulas, pseudoaneurysm, or ascites[316-320].

TRUE IDIOPATHIC PANCREATITIS

In spite of extensive systematic investigations and exhaustive efforts, there will be patients with true IP (TIP). Recommendations are difficult to make given the heterogeneity of studies that have evaluated this problem. Generally there are 4 therapies that might be applicable in TIP taking into account that TIP most likely represents a group of heterogeneous disorders: antioxidants, ursodeoxycholic acid, pancreatic enzymes, and somatostatin or its analogue octreotide.

Antioxidants (e.g., vitamin C, and E, beta carotene) have been shown to reduce the pain involved in IP[321]. It is postulated that patients with AP or CP may have a deficiency in antioxidants either locally within the pancreatic parenchyma or systemically[322]. A cocktail of antioxidants including 600 μg of selenium, 9000 IU of β-carotene, 0.54 g of vitamin C, 270 IU of vitamin E, and 2 g of methionine daily[321] was shown to have a statistically significant benefit in reducing attacks of pancreatitis. It is again stressed that these trials have limited power since the above study evaluated only 28 patients[321].

In patients who continue to have attacks of pancreatitis despite having cholecystectomy or endoscopic sphincterotomy, or patients with contraindications to surgical and endoscopic treatment, maintenance therapy with ursodeoxycholic acid has also been suggested with some benefit[31,323].

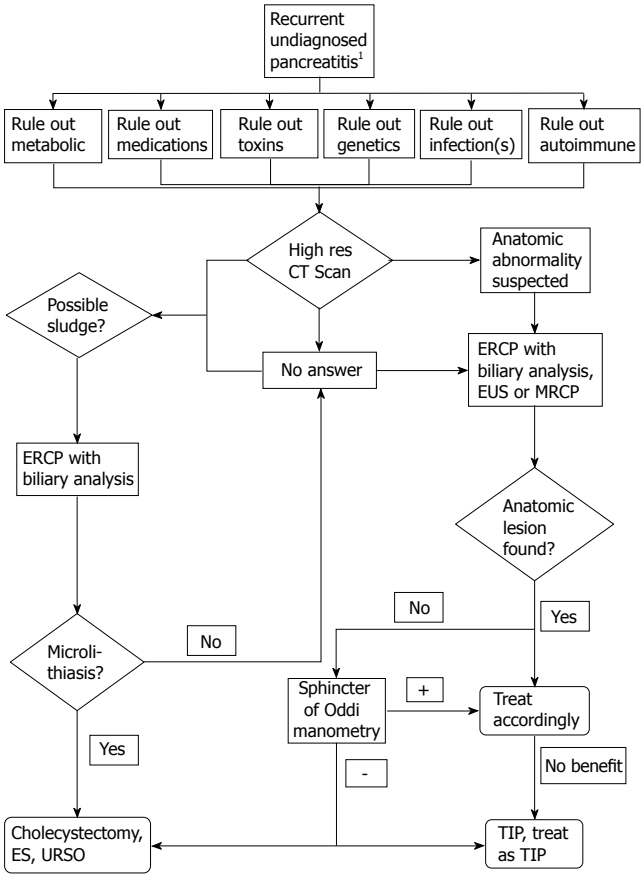

Figure 1 [1]To arrive at the label of recurrent undiagnosed pancreatitis, a history, physical exam, routine laboratory investigations, chest radiograph, abdominal ultrasound, and or computed tomography must fail to find the etiology of pancreatitis. Although sludge may be picked up on transabdominal ultrasound, the low sensitivity precludes exclusion of diagnosis of microlithiasis. ES: Endoscopic sphincterotomy; TIP: True idiopathic pancreatitis; EUS: Endoscopic ultrasound; CT: Computed tomography; URSO: Ursodeoxycholic acid.

Pancreatic enzyme therapy has recently been reviewed and the efficacy in IP or recurrent AP or CP is small[324]. However, given the low risk of enzyme therapy it has been suggested as a therapeutic trial in treating CP and IP[325,326].

Somatostatin or its analogue octreotide has been postulated to reduce pancreatic secretion and thereby be of benefit in the treatment of relapsing pancreatitis. This therapy entails either a continuous infusion or frequent injections in the past[327]. A 1 mo depot injection has recently become available and may make this therapy more attractive but data is limited with existing data on octreotide and somatostatin focused on altering outcomes during an index hospitalization of severe pancreatitis rather than preventing subsequent attacks[327].

APPROACH TO RECURRENT IP

The authors of this review propose the following systematic approach for patients who have had more than one attack of IP. The following is not validated and is meant to be only used as a guide. For specific details please refer to the aforementioned sections (Figure 1).

CONCLUSION

True IP is declining as knowledge and technology advances. IP has been found now to represent a myriad of etiologies that have been elucidated with the advancement of laboratory and endoscopic studies. It is thought that a thorough workup of these cases should reveal an etiology in up to 80% of cases. If genetic screening is applied it is suspected the etiologies may be explained in a much higher percentage of cases. There are still many controversies surrounding some of the IP etiologies and full consensus agreement is lacking in many areas. This review comprehensively outlined the latest evidence in the etiology, pathogenesis, diagnosis, and treatment strategies. It is felt that establishing a diagnosis is key, for it has the potential to direct management. It is recognized, however, that for many of the disorders (particularly genetic abnormalities) there are limited therapies. Elucidating all the causes of IP is a challenge that needs to be faced so that patients can avoid unnecessary morbidity and mortality from subsequent invasive testing.

The treating physician should perform a detailed history to rule out medication, metabolic, and toxin related etiologies. Moreover a detailed history should raise the possibility of genetic associations and causes as well as infectious etiologies so that further testing can be best directed. Celiac disease, vascular disease, and autoimmune causes of pancreatitis should be considered in evaluating the optimal approach to IP.

The most common causes of IP include microlithiasis and biliary sludge, sphincter of Oddi Dysfunction, and anatomic abnormalities. When there is any risk or suggestion of malignancy either as a cause or as an association of the etiology, as in choledochoceles, appropriate management including the necessary diagnostic workup and consideration of surgical excision when the diagnosis is made needs to be considered. In the aforementioned causes it is clear that both imaging techniques such as MRCP, EUS, high resolution CT, and interventional techniques as ERCP play their respective roles.

Indeed with further research additional causes of IP and associations of IP will be revealed. Even with exhaustive efforts and considering all the etiologies in this article there will still be a few patients who will continue to have true IP. In these patients non specific therapy including pain control is often unfortunately the only option. Certainly further advances in pancreatitis will be welcome.

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