Idiopathic recurrent acute pancreatitis

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Idiopathic recurrent acute pancreatitis is clinically challenging and has substantial socioeconomic consequences. Investigations are expensive and often reveal little about the cause of the disease. Little is known about the interaction between genetic, environmental, anatomical, and other factors that contribute to the disease. Data on the efficacy, safety, and long-term outcomes of endoscopic therapies are scarce. The effect of idiopathic recurrent pancreatitis on quality of life is often underestimated. A more thorough examination of the causes of the disease and the roles of other associated risk factors is needed, as are well designed clinical studies with robust and objectively measurable outcomes. Ideally, evaluation of the causes of disease and therapy should be done only in specialised centres, should follow a protocol, and all outcomes should be formally assessed.

Introduction

Acute pancreatitis is one of the most common causes of acute hospital admission, and substantially contributes to morbidity, mortality, and health-care costs.[1,2] Recurrent acute pancreatitis (also known as relapsing acute pancreatitis) is defined as two or more discrete episodes of acute pancreatitis, and has an estimated annual incidence of 8–10 per 100 000 and a prevalence of 110–140 per 100 000 worldwide.[3]

Acute pancreatitis has several aetiological factors, some of which are readily recognised as causative, whereas others are not. Most cases of acute pancreatitis are caused by either gallstones or alcohol.[1] When biliary factors and alcohol are ruled out, 25% of patients with acute pancreatitis subsequently develop recurrent acute pancreatitis.[4] Routine investigations identify a cause in up to 80% of cases; however, in up to 20% of cases, the cause of disease remains unclear—this is known as idiopathic recurrent acute pancreatitis. Both the sequence of testing and treatment options for patients with idiopathic recurrent acute pancreatitis are not clear, and have been subject to debate.[1,5] In at least 7% of cases, more than one causative factor can be identified (eg, in an individual who is genetically predisposed to recurrent acute pancreatitis, a toxic or obstructive cause can be an additional contributing factor).[6] Although some causes are obvious, data on the role of genetic or environmental factors are scarce, and, more importantly, the interplay between the factors that contribute to pancreatitis is not well understood. If the underlying cause is not corrected, recurrences of acute pancreatitis or chronic pancreatitis could occur.[7] However, invasive techniques such as endoscopic retrograde cholangiopancreatography (ERCP) can cause complications, including further episodes of pancreatitis.[8] In this Review, we address the issues associated with idiopathic recurrent acute pancreatitis; management of acute pancreatitis and chronic pancreatitis are beyond the scope of this Review.

Defining acute pancreatitis and recurrent acute pancreatitis

Acute pancreatitis is defined as a condition in which at least two of the following three criteria are present: abdominal pain, elevations in serum amylase and lipase concentrations that are equal to or greater than three times the upper limit of normal, and cross-sectional imaging (typically CT or MRI) or ultrasound findings that suggest pancreatitis.[9] Recurrent acute pancreatitis is generally defined as a condition in which at least two well documented episodes of acute pancreatitis have occurred, with resolution of symptoms between each episode, and absence of morphological criteria for chronic pancreatitis. Notably, appearance of the gland on imaging studies and symptoms in patients with proven chronic pancreatitis correlate poorly.[10,11] Clinically, patients do not always present immediately after the onset of pain, and some of the symptoms, clinical investigations, and findings can vary, making evaluation and assessment of clinical outcomes (including prevention of another episode of pancreatitis, disease progression, improvement in pain, and quality of life) challenging. Patients with chronic pancreatitis or other syndromes short of well defined recurrent acute pancreatitis can present with substantial pain, but with an amylase or lipase elevation that is less than three times the upper limit of normal. Sometimes, inflammatory changes persist well after initial presentation. Pancreatologists increasingly recognise that these symptoms can be considered more as a syndrome than as a disease. Patients with hyperenzymaemia and pain with or without abnormal imaging have been classified as having pancreatic type 2 sphincter-of-Oddi dysfunction, and patients with pain have been classified as having pancreatic type 3 sphincter-of-Oddi dysfunction, although the utility of such classifications is doubtful. With the paucity of outcome data, invasive treatments should not be offered to patients outside research protocols, and, when offered, should be confined to highly specialised centres.[7,12]

Does idiopathic recurrent acute pancreatitis represent early chronic pancreatitis?

In acute pancreatitis, once inflammation resolves, the pancreas is expected to return to normal function and morphology. However, available data suggest that recovery might not necessarily be complete, and ductal changes can persist without any signs or symptoms of acute or chronic pancreatitis.[13,14] In some cases, pain persists with inflammatory changes that are apparent on

imaging; this type of pancreatitis is often referred to as smouldering pancreatitis. Smouldering pancreatitis is thought to represent a prolonged course of acute pancreatitis with persistent pancreatic symptoms, inflammatory changes on cross-sectional imaging, and pancreatic enzyme elevation in the absence of systemic or local complications, such as pancreatic or peripancreatic fluid or necrotic collections.[15] Although the aetiopathogenesis of smouldering pancreatitis is unclear, this type of pancreatitis can occasionally be related to a functional obstruction of the pancreatic sphincter from oedema, which offers a possible role for endoscopic therapy such as pancreatic duct stenting.[16] Smouldering pancreatitis should be differentiated from chronic pancreatitis, in which morphological changes in the pancreas gland suggest chronicity and impairments of exocrine pancreatic function are often detectable by pancreatic function testing.

The exact factor that sets off this continuous process of inflammation and necrosis and the number of episodes that occur before gland function is lost are not clear. The widely believed hypothesis is the sentinel acute pancreatitis event (SAPE) hypothesis, which defines pancreatitis as a disease spectrum. According to the SAPE hypothesis, a sentinel event triggers a necrosis–fibrosis sequence, and subsequent episodes of pancreatitis are either due to continuous exposure to the triggering causative factor, or to an aberration in the processes of repair or in the inhibition of ongoing inflammation, which leads to chronic pancreatitis.[17] This hypothesis has been further supported by clinical studies, leading to the belief that acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis are a continuum of the same disease.[3,4,18] Regardless of the cause of disease, recurrent acute pancreatitis is independently associated with the development of chronic pancreatitis, but the true incidence and prevalence of this complication outside of recurrent alcoholic pancreatitis is unknown.[19–21]

A meta-analysis based on 11 studies estimated the crude prevalence of recurrent acute pancreatitis to be 22% of patients with acute pancreatitis.[18] Although 10% (95% CI 6–15) of patients develop chronic pancreatitis after a single episode of acute pancreatitis, 36% (95% CI 20–53) of patients with recurrent acute pancreatitis were subsequently diagnosed with chronic pancreatitis.[18] The subset of patients with recurrent acute pancreatitis that could progress to chronic pancreatitis is also unclear. A study involving 669 patients who survived a first episode of acute pancreatitis defined independent risk factors for the development of chronic pancreatitis after the index episode of acute pancreatitis and recurrent acute pancreatitis. Per episode, recurrent acute pancreatitis had an odds ratio (OR) of 2·90 (95% CI 2·07–4·05) for progression to chronic pancreatitis. In patients with recurrent acute pancreatitis, the other independent risk factors for progression to chronic pancreatitis include alcohol (OR 4·85, 2·04–11·52) and development of necrotising pancreatitis (OR 8·78, 4·09–18·86).[19,20] Recognition of this continuum is of clinical relevance to the development of aetiology-based preventive strategies to interrupt the natural course of progression to chronic pancreatitis.[20]

New and sensitive testing, including secretin-stimulated magnetic resonance cholangiopancreatography (S-MRCP), endoscopic ultrasound, and secretin-stimulated endoscopic pancreatic function testing should be considered in the initial evaluation of the patient, since these methods can identify early chronic pancreatitis and some causative factors (eg, microlithiasis, choledocholithiasis, pancreas divisum, occult malignancies, and choledochocoele).

Recurrent acute pancreatitis leads to an impairment in quality of life similar to that in chronic pancreatitis, especially in patients with daily pain or narcotic use.[22] Strategies for management of recurrent acute pancreatitis should have a broad focus beyond simply reducing hospital admissions for acute flares of pancreatitis.[23]

Aetiological considerations

As mentioned previously, some of the aetiological factors associated with recurrent acute pancreatitis are widely accepted to be causative, whereas others are debated, and some of the invasive testing techniques that are used for the assessment of the cause, and even the treatments themselves, pose an additional risk of pancreatitis. The problem is compounded by the fact that there is often more than one causative factor, and correction of an apparent cause might not lead to an alteration in outcome because of genetic susceptibility or environmental factors that co-modify the disease.

As previously mentioned, alcohol and gallstones are known to cause recurrent acute pancreatitis; however, since the focus of this Review is idiopathic recurrent acute pancreatitis, these factors are not discussed in detail. Importantly, interventions to eliminate alcohol ingestion after the index episode have been shown to reduce the risk of subsequent pancreatitis episodes.[24] The widely accepted and popular classification of the causes of acute pancreatitis is the TIGAR-O classification; these causes are discussed below.[25]

Toxic metabolic causes

Toxic metabolic causes of both acute and recurrent acute pancreatitis include alcohol, especially its continuous consumption. A study showed that smoking is an independent risk factor for acute pancreatitis, and that it augments the effect of alcohol on risk; age of onset and recurrence of acute pancreatitis can further contribute to progression to chronic pancreatitis.[1,26,27] Additionally, hypertriglyceridaemia is a known risk factor for acute pancreatitis and recurrent acute pancreatitis, specifically above concentrations of 1000 mg/dL. Non-causative elevations can be seen in acute pancreatitis due to alcohol. Hypercalcaemia and hyperparathyroidism are

uncommon causes of acute pancreatitis, and can be readily identified with tests that measure serum concentrations of calcium and parathyroid hormone.

Medications

Medications have long been thought to cause recurrent acute pancreatitis, although cause and effect are difficult to establish, and episodes of pancreatitis associated with medications are often idiosyncratic. Several commonly used medications, such as paracetamol, furosemide, hydrochlorothiazide, enalapril, simvastatin, and erythromycin, have been identified as potential causative agents. Several other drugs are also thought to be associated with recurrent acute pancreatitis; these medications and, when possible, alternative medications have been previously reviewed.[28,29]

Genetic factors

Gene mutations are increasingly being shown to be associated with acute and chronic pancreatitis. These mutations have an important role in the cause, clinical course, and outcomes of pancreatitis. In a cohort of patients younger than 30 years with idiopathic pancreatitis, mutations in *PRSS1*, *SPINK1*, and *CFTR* genes were present in up to 32% of patients.[30] In a study in the North American population, gene mutations such as *SPINK1* Asn34Ser polymorphisms were associated with recurrent acute pancreatitis, but not with sentinel events.[31] An increasing number of other gene mutations have been associated with recurrent acute pancreatitis and chronic pancreatitis, such as those affecting *CTRC*.[32] CTRC clearly has an important role in protecting the pancreas from injury by prematurely activated trypsin. In the NAPS2 study,[33] the *CTRC* Gly60Gly variant significantly increased the risk of alcohol-associated, smoking-associated, and *CFTR*-associated and *SPINK1*-associated chronic pancreatitis, but not recurrent acute pancreatitis. Thus, unlike *PRSS1* or *CFTR*, which serve as acute pancreatitis susceptibility factors, *CTRC* variants are disease modifiers that trigger rapid progression to chronic pancreatitis.[33] Mutations in other genes such as the calcium-sensing receptor and carboxypeptidase genes also increase susceptibility to pancreatitis, but precise estimates of risk of recurrent acute pancreatitis and chronic pancreatitis with these mutations is unclear.

Gene mutations appear to have a role in recurrent acute pancreatitis even when certain obvious anomalies such as pancreas divisum are present. In a study from North America, the prevalence of *CFTR* gene mutations was increased in people with pancreas divisum presenting with recurrent acute pancreatitis.[34] These data also highlight the role of genes as probable disease modifiers and cofactors for recurrent acute pancreatitis.

Hereditary or familial pancreatitis due to *PRSS1* mutations is a well known genetic disorder causing recurrent acute pancreatitis. This disorder is autosomal dominant with penetrance rates of about 80%. *PRSS1* gene mutations can result in impaired activation of trypsin and continuous activation of digestive enzymes. The disease often presents in childhood as recurrent acute pancreatitis and progresses to chronic pancreatitis with morphological changes, chronic pain, exocrine and endocrine insufficiency, and an elevated lifetime risk of pancreatic cancer of up to 40%. Genetic testing and family history confirm the diagnosis. Genetic counselling is important for both the patient and family members. Therapy can consist of medical support, endoscopic therapy for selected individuals, and increasingly, total pancreatectomy with islet autotransplantation (TPIAT) early in the disease course, which improves clinical outcomes and decreases lifetime cancer risk.[35,36] The presence of an identified predisposing genetic factor alone does not preclude response to endoscopic therapy or warrant radical surgery such as TPIAT, but does affect the trajectory of the disease, symptom burden, and response to less invasive interventions.

Autoimmune pancreatitis

Autoimmune pancreatitis is a chronic fibroinflammatory steroid-responsive disease of the pancreas with two distinct subtypes based on distinct natural history, clinical features, and histological features.

Type 1 autoimmune pancreatitis (also known as lymphoplasmacytic sclerosing pancreatitis) is the pancreatic manifestation of multiorgan immunoglobulin (Ig) G4-related disease, whereas type 2 autoimmune pancreatitis (also known as idiopathic duct-centric pancreatitis) has a different histopathology and clinical presentation. Type 1 autoimmune pancreatitis typically presents as obstructive jaundice in men aged at least 60–70 years, with a male-to-female ratio of 3:1. Serum IgG4 concentrations can be elevated in type 1 autoimmune pancreatitis. Type 2 autoimmune pancreatitis can present in up to 50% of cases as acute pancreatitis, but rarely as recurrent acute pancreatitis. A history of clinical manifestations of inflammatory bowel disease was seen in most patients with type 2 autoimmune pancreatitis.[37] Type 1 autoimmune pancreatitis is associated with histological features of lymphoplasmacytic acinar inflammation and storiform fibrosis, and pancreatic tissue of patients with this type of pancreatitis usually stains positive for high concentrations of IgG4. The pathological process of type 2 autoimmune pancreatitis differs from that of type 1 autoimmune pancreatitis, and involves granulocyte epithelial lesions. These lesions can be observed on histopathology, although obtaining a histopathological diagnosis is difficult because a fine needle biopsy is required, and this method can be challenging and has a higher complication risk than fine needle aspiration. Diagnosis of type 2 autoimmune pancreatitis is difficult because no biomarkers for the disease are known, and diagnosis is often presumed in the absence of histopathological results, particularly when associated with inflammatory bowel disease or

other radiological features such as pancreatic ductal strictures.[38,39] The sensitivity of serum concentrations of IgG4 for diagnosis of autoimmune pancreatitis is relatively low in the North American population, and a normal serum IgG4 concentration should not be used as a sole criterion to exclude diagnosis.

The presence of three of four key histopathological findings is considered to provide the highest diagnostic reliability: lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and more than ten IgG4-positive cells per high-powered field. However, the methods used to investigate these histopathological features have several limitations. The main limitation of fine-needle aspiration cytology is that it does not provide information on tissue architecture to allow for histopathological diagnosis. Although existing guidelines list core biopsy and surgical biopsy as methods that can provide a histological diagnosis of autoimmune pancreatitis, endoscopic ultrasound-guided trucut core-biopsy needles have high advancement resistance, leading to safety concerns that preclude their widespread use. A novel technique that involves piecing together fragments of tissue obtained during 22-gauge fine needle aspiration to reconstruct a large piece of pancreatic tissue has been reported.[40] Pancreatic tissue samples with at least one high-powered field were obtained by endoscopic ultrasound-fine needle aspiration from approximately 80% of patients, and nearly 60% of patients were diagnosed with type 2 autoimmune pancreatitis level 2 or higher.[40] In another study, endoscopic ultrasound sampling with a new fork-tip needle (SharkCore Fine Needle Biopsy System; SharkCore, Medtronic, Sunnydale, CA, USA) was shown to be reliable for diagnosis of autoimmune pancreatitis.[41]

Standard mucosal biopsies of ampullary tissue for IgG4 staining have been reported to have high specificity, although this method provides low (50% or less) sensitivity for type 1 autoimmune pancreatitis. Additionally, this technique requires careful avoidance of the ampullary orifice to avoid causing pancreatitis.[42]

Treatment of autoimmune pancreatitis is usually initiated with corticosteroids or other steroid-sparing agents such as rituximab, whereas maintenance of remission can be achieved with azathioprine or other immunosuppressive agents. Relapses are fairly common with type 1 autoimmune pancreatitis but less common with type 2 autoimmune pancreatitis, and can be reduced by use of immunosuppressant drugs, such as azathioprine.[37,39]

Pancreas divisum

Pancreas divisum is a congenital anomaly in which the dorsal and ventral pancreatic ducts do not fuse during the embryonic stage, which results in drainage of most of the exocrine pancreas through the minor papilla. In some cases, drainage through the minor papilla has been postulated to result in outflow obstruction of pancreatic secretions and clinical pancreatitis.[43] Pancreas divisum is prevalent in about 7% of the population of high-income countries. However, only a few individuals (up to 5%) with pancreas divisum present with symptomatic pancreatic disease, including chronic pancreatitis.[44] Identification of pancreas divisum is often made with MRCP or S-MRCP. S-MRCP could help to identify subsets of patients who might respond to endoscopic therapy, as shown by dilation of the dorsal pancreatic duct by 1–2 mm, or by the presence of a saccular dilation of the minor papilla (termed santorinicele), indicating possible obstructive pathology.[45] Use of ERCP for diagnostic purposes alone should be avoided. Endoscopic ultrasound not only identifies pancreas divisum, but also helps to assess the pancreatic parenchyma and search for other possible causes, including those responsible for chronic pancreatitis.

Although many experts believe that endoscopy is therapeutic, the cause–effect relationship between pancreas divisum, recurrent acute pancreatitis, and chronic pancreatitis is questionable. In one of the few prevalence studies, the frequency of pancreas divisum was similar in patients with idiopathic pancreatitis and controls, based on MRCP, suggesting that pancreas divisum by itself is not a cause of pancreatitis. The frequency of pancreas divisum was higher in patients with genetically mediated pancreatitis, especially in those with *CFTR* mutations or polymorphisms (47%), than in controls, suggesting a cumulative effect of genetic mutations and pancreas divisum.[46] The authors hypothesised that impaired pancreatic ductal drainage through the smaller minor papillary orifice and *CFTR* mutations increase the pancreatic juice viscosity and precipitate an excessive host inflammatory response in patients with pancreas divisum, resulting in ductal obstruction.

Because there is no consensus on its role in pancreatic disease, the role of endoscopic or surgical intervention for pancreas divisum remains unclear. Surgical sphincteroplasty or endoscopic therapies, including minor papillotomy, have been done with variable results, and the data—which do not include randomised controlled trials with long-term follow-up or quality-of-life measures—on these types of intervention are scarce.

To date, only one small randomised controlled trial[47] has been done, in which 19 patients with pancreas divisum and recurrent acute pancreatitis were randomly assigned to either a dorsal duct-stent placement group or a control group and followed up for 1 year. Although no patients from the stent group required hospital admission or emergency room visits for abdominal pain during or following the treatment period, five hospital admissions and two emergency room visits for abdominal pain were required in the control group.[47]

Some experts believe that a subset of patients with pancreas divisum with focal obstruction of the minor

papilla and resulting dilation of the dorsal pancreatic duct improve with minor papillotomy. In a small study, such patients had an improvement in quality of life, narcotic use, hospital admissions, and pain scores after minor papillotomy.[48]

A systematic review[49] concluded that the technical success of endotherapy ranged from 17% to 86%, and the median overall estimated response rate was 62%. The highest response rate was seen in patients with recurrent acute pancreatitis without chronic pancreatitis (median 76%), and the rate of pancreatitis after ERCP was 18%, with 90% of pancreatitis cases being mild and self-limiting.[49] However, all the studies included in the systematic review are limited by retrospective design and variable endpoints, except for the small randomised controlled trial mentioned previously.[47]

Although available data suggest that endoscopic therapies might be a reasonable choice for individuals with pancreas divisum and recurrent acute pancreatitis, the optimal approach is not clear. Primary stent therapy is not recommended since this method is temporary and can cause ductal and parenchymal changes, including chronic pancreatitis.[50] The role of genetics and other covariables is unknown.[12] At this time, pancreas divisum should be considered only as a possible cause of recurrent acute pancreatitis. Endoscopic therapies should be offered only by centres with substantial experience, and preferably under a research protocol with defined outcomes. A prospective sham-controlled randomised trial of minor papillotomy is being initiated (NCT03609944).

Sphincter-of-Oddi dysfunction

High pressure in either the biliary or pancreatic sphincters (or both) has been proposed to result in outflow obstruction, and could cause recurrent acute pancreatitis or chronic pancreatitis. This hypothesis is debated, because supporting data are scarce. Abnormal sphincter-of-Oddi manometries have been reported in 30–65% of people having manometry for recurrent acute pancreatitis, but the clinical significance and implications of these results are unclear. Relief of symptoms after sphincterotomy is not well studied, but data suggest no advantage to pancreatic sphincterotomy in addition to biliary sphincterotomy.[51] Most data favouring sphincterotomy for recurrent acute pancreatitis are derived from small uncontrolled studies with little follow-up, and no studies include validated quality-of-life measures, which is often the most important aspect of any intervention. Larger sham-controlled studies that also include evaluation of genetic and other covariable factors are needed. Endoscopic sphincterotomy does not appear to alter the natural history of recurrent acute pancreatitis.[52] Furthermore, the risk of complications, including pancreatitis after ERCP, is high in this subgroup.[7] At this time, ERCP with sphincterotomy for recurrent acute pancreatitis should be avoided unless performed as part of a research protocol.

Choledochocoele

Cystic dilation of the extrahepatic or intrahepatic bile duct is considered to be a choledochal cyst. According to the Todani classification, choledochocoeles (also known as type 3 choledochal cysts) represent a uniquely obstructive and endoscopically treatable variant of choledochocoele, involving cystic dilation of a sac confined to the intraduodenal segment of the bile duct, into which the bile and pancreatic ducts drain separately without anomalous pancreaticobiliary junction. Diagnosis is best accomplished by MRCP. In patients with a choledochocoele, sludge or stones can superimpose, causing outflow obstruction, which can result in recurrent acute pancreatitis. Endoscopic unroofing of the choledochocoele, with or without biliary or pancreatic sphincterotomy, usually results in definitive therapy. Unlike other types of choledochal cysts, choledochocoeles are associated with a negligible risk of cholangiocarcinoma.[53]

Anomalous pancreaticobiliary junction

Anomalous pancreaticobiliary junction is a congenital anomaly that can contribute to recurrent acute pancreatitis, and is usually associated with choledochal cysts other than choledochocoeles. Anomalous pancreaticobiliary junction involves an abnormally long common channel (≥1·5 cm) between the bile duct and the pancreatic duct. The resultant obstruction and reflux can cause recurrent acute pancreatitis, and the associated pancreaticobiliary reflux is thought to increase the risk of biliary tract malignancies, especially in people with an associated choledochal cyst.[53] Diagnosis is best made by MRCP. The role of endoscopic therapy by sphincterotomy in reducing the risk of recurrent acute pancreatitis or malignancies is unclear, but this treatment option is usually ineffective, because the anomalous junction is above the limit of the endoscopic extent of sphincterotomies. Surgical management typically involves wide resection of the bile duct down to the pancreas.[53,54]

Annular pancreas

An annular pancreas is a rare congenital deformity of the pancreas due to failure of rotation of the ventral bud of the pancreas along with the duodenum. This anomaly results in band-like pancreatic tissue that surrounds and constricts the duodenum. Clinically, an annular pancreas presents as recurrent acute pancreatitis or as duodenal obstruction. Diagnosis is often made with cross-sectional imaging such as CT or MRI, or on endoscopic ultrasound. Endoscopic therapy has a small role, if any, for treatment of the condition. Duodenal obstruction usually requires definitive enteric bypass surgery.[7] Data on TPIAT in severe chronic pancreatitis are scarce.[55]

Ampullary neoplasms

Ampullary neoplasms of various histology, including adenomas, adenocarcinomas, and neuroendocrine tumours, can cause recurrent acute pancreatitis by

obstructing pancreatic ductal outflow. Ampullary neoplasms are usually identified by endoscopic investigation for recurrent acute pancreatitis, or during surveillance of individuals who are at a high risk of the condition or for other types of upper gastrointestinal neoplasia. Ampullary adenomas and other benign tumours are typically resected or ablated endoscopically if the lesions do not extend into the pancreas or deep into the bile duct, or if the patient is a poor candidate for surgical resection because surgical risks exceed the benefits (eg, patients who are elderly, or those who have comorbidites). Surgical resection, usually in the form of a pancreaticoduodenectomy, is the treatment of choice for locally invasive or malignant lesions. Local excision by either surgery or endoscopy has recurrence rates of up to 20%, and therefore needs long-term surveillance. When endoscopic ampullectomy is done, prophylactic pancreatic stents reduce the risk of pancreatitis after ERCP.[56]

Pancreatic tumours

Pancreatic tumours can present as recurrent acute pancreatitis, especially in older patients (aged at least 40 years). Solid tumours, such as adenocarcinoma, neuroendocrine tumours, and intraductal papillary mucinous neoplasms can present as recurrent acute pancreatitis. Despite advances in imaging, small lesions can be missed by CT scans and MRCP. Endoscopic ultrasound has a high sensitivity for the detection of small lesions, and hence is recommended for evaluation of unexplained pancreatitis, especially in patients aged 40 years or older, with or without any abdominal pain or weight loss.[57]

Evaluation

As with any illness, a proper history and physical examination are needed to assess recurrent acute pancreatitis. A review of medications and assessment of risk factors including smoking and alcohol use are important. Family history of pancreatic disease and congenital hyperlipidaemia should be obtained. Routine serum chemistries are useful, including obtaining serum calcium and fasting triglyceride concentrations. Alanine aminotransferase concentrations that are two-to-three times greater than normal, and alanine aminotransferase concentrations that are higher than those of aspartate aminotransferase, strongly favour a biliary cause. Triglyceride concentrations can be transiently elevated during an episode of alcoholic pancreatitis, although a concentration higher than 1 mg/dL should favour hypertriglyceridaemia as a cause. Care should be taken to review patient records, including lipase and amylase concentrations, if the individuals had previous episodes of pancreatitis, to document that the patient's previous episodes meet the true definition of recurrent acute pancreatitis, as defined previously.

Imaging studies including transabdominal ultrasound are widely available, and should be the first step for patients with an intact gallbladder to assess the presence of gallbladder stones or sludge. If the results available from transabdominal ultrasound are limited during an acute episode because of poor visualisation secondary to ileus, ultrasound should be repeated once acute inflammation is resolved. Most institutions perform a CT scan to assess abdominal pain and pancreatitis. Preferably, CT scans should be done with contrast following a pancreas protocol. For unexplained pancreatitis, especially in patients older than 40 years, endoscopic ultrasound should be performed once the acute inflammation resolves. Endoscopic ultrasound can identify gallbladder disease that has been missed by transabdominal ultrasound, and can identify small parenchymal and ampullary tumours missed by CT scanning or MRI, and allows visualisation of periampullary lesions that are not identified by MRCP. In a meta-analysis of the available data on recurrent acute pancreatitis, endoscopic ultrasound was better than MRCP at identifying biliary disease and chronic pancreatitis.[58]

MRCP is non-invasive and has supplanted ERCP for diagnostic purposes. MRCP not only allows for detailed visualisation of ductal anatomy, but also provides information regarding parenchymal pathology.[3] Three-dimensional reconstruction of the ductal anatomy is possible, and aids targeted therapy if needed. However, MRCP is not as sensitive as endoscopic ultrasound for identifying periampullary lesions and chronic pancreatitis. S-MRCP is superior to MRCP for diagnosis of pancreatic ductal disease. A meta-analysis of 34 studies concluded that the diagnostic yield of endoscopic ultrasound (64%) in the investigation of idiopathic acute pancreatitis was higher than that of MRCP (34%), and the most frequent diagnosis in patients who had endoscopic ultrasound was biliary disease (34%). S-MRCP showed a better diagnostic performance (43% of cases diagnosed) than did MRCP (24%), and the technique was better at diagnosing pancreas divisum than was endoscopic ultrasound (12% *vs* 2%).[58]

On the basis of our experience, endoscopic ultrasound and MRCP should both be used in the diagnosis of idiopathic acute pancreatitis as complementary techniques. ERCP for diagnostic purposes should be avoided, and in fact is associated with a high risk of complications. Furthermore, ERCP should be avoided for bile crystal analysis, since this type of analysis is difficult to do and might not be reliably associated with microlithiasis.

Genetic testing

Whether gene mutations in themselves cause acute recurrent pancreatitis is unclear. Some gene mutations are common in patients with acute recurrent pancreatitis, and whether these gene mutations act in the presence of other factors such as pancreas divisum to modify disease severity or treatment response remains unclear. Many hypotheses about the role of gene mutations in acute recurrent pancreatitis are speculative. Data clearly indicate

Search strategy and selection criteria

We searched PubMed from Jan 1, 2008, to March 1, 2018, for the term "acute recurrent pancreatitis". We included all clinical trials and all clinical studies, consensus development conferences, and reviews. We limited our search to core clinical journals in English. Any older publications that were cross-referenced were reviewed and included.

that pathogenic genetic variants of *PRSS1*, *SPINK1*, *CTFR*, and *CTRC* are present in 58% of people with acute recurrent pancreatitis, and in 63% of people with an unexplained first episode of pancreatitis. Mutations in genes such as *SPINK1* have also been shown to cause progression to chronic pancreatitis.[59] Additionally, genetic testing is indicated for individuals with early onset of acute recurrent pancreatitis without any obvious cause, and this subset of patients includes those with pancreas divisum.[60] Genetic testing has the potential to identify a genetic cause. Although therapy targeted specifically at gene mutations is not yet available, the information from genetic testing is useful for appropriate counselling, family screening, and to identify cofactors for other anomalies such as pancreas divisum; this information can also influence the decision to use more aggressive long-term surgical therapies such as TPIAT. On the basis of consensus statements and available evidence, obtaining at least genetic counselling, if not necessarily testing, for individuals with two episodes of pancreatitis without a definite cause is reasonable.[61]

Role of laparoscopic cholecystectomy

In clinical practice, empirical laparoscopic cholecystectomy has been done in patients with recurrent acute pancreatitis to treat presumptive microlithiasis not detected on conventional imaging. Although this technique is commonly used, no evidence supports its use. A retrospective study has shown a decrease in recurrence of pancreatitis after cholecystectomy in patients with idiopathic recurrent acute pancreatitis.[62] However the authors of the study did not have any information on the genetics, medications, or triglyceride concentrations of the patients.[62] In another randomised trial in 80 patients, empirical cholecystectomy significantly reduced recurrence of pancreatitis compared with the control group. However, endoscopic ultrasound was not included as part of the evaluation.[63] Endoscopic ultrasound is sensitive for the detection of microlithiasis, and should be considered before contemplating cholecystectomy, both to document gallbladder disease and to rule out other causes, such as neoplasia. Larger studies that take into account cofactors including genetics are needed.

Disease management

Every episode of acute pancreatitis should be managed, irrespective of the cause, with supportive measures, including aggressive hydration, adequate analgaesia, and other interventions as appropriate.[61] Metabolic abnormalities should be corrected. CT scanning is recommended, typically at least 48–72 h after presentation, for severe episodes, to allow any necrosis to develop. Transabdominal ultrasound should be considered when no CT abnormalities or laboratory testing point to a diagnosis. Endoscopic ultrasound and MRCP are reasonable next steps in the evaluation of acute pancreatitis, and should be considered once acute inflammation resolves. Endoscopic ultrasound is especially desirable in older patients of at least 50 years and in patients with an intact gallbladder to rule out a tumour or microlithiasis. Given the scarcity of adequate data, empirical cholecystectomy or sphincter-directed endotherapy is generally not recommended outside the context of clinical trials, and only after a thorough discussion of the uncertain benefits and high risks. ERCP is indicated when there is evidence of an obstructive process. Although bilirubin concentrations are generally elevated in acute pancreatitis, partial obstruction can occur when bilirubin concentrations are normal. Endoscopic ultrasound can guide further management, including potential surgery. When done, ERCP should be performed after the acute episode resolves to minimise further inflammation related to pancreatitis after the procedure. In patients with recurrent acute pancreatitis, genetic testing and counselling is recommended. A single study has suggested that TPIAT is a reasonable option for people with intractable and disabling daily pain that is refractory to medical and endoscopic management.[23]

Current problems and future trends

Recurrent acute pancreatitis represents an important problem with respect to patient disability and health-care burden. Recurrent acute pancreatitis generally presents with abdominal pain and elevations in lipase or amylase concentrations that are more than three times the upper limit of normal. Clinically, these problems are compounded when patients do not have a classic clinical presentation. Understanding of the disease is impaired by scarcity of natural history data and knowledge of the cofactors associated with recurrent acute pancreatitis, including genetic factors and environmental influences. Available data are scarce and are difficult to interpret because of the absence of common definitions regarding pancreatitis, time to recurrent event, and influence of interventions. There are no specific validated quality-of-life instruments for patients with recurrent acute pancreatitis or for those with frequent or daily symptoms. The roles of pancreas divisum and sphincter-of-Oddi dysfunction in development of recurrent acute pancreatitis are questionable. A large multinational consensus conference on recurrent acute pancreatitis emphasised the relative paucity of data on assessment, and particularly on therapeutic interventions, for recurrent acute pancreatitis.[64] Adequately powered

multicentre studies that use measurable outcomes and factor in the effects of covariates and multiple interventions are needed.

Contributors

All authors contributed equally to the initial draft, review, and revisions of this manuscript.

Declaration of interests

NMG and MLF are consultants for Boston Scientific Corporation. GT declares no competing interests.

References

1 Lankisch PG, Apte M, Banks PA. Acute pancreatitis. *Lancet* 2015; **386:** 85–96.

2 Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology* 2015; **149:** 1731–41.

3 Machicado JD, Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. *Dig Dis Sci* 2017; **62:** 1683–91.

4 Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol* 2016; **14:** 738–46.

5 Wilcox CM, Seay T, Kim H, Varadarajulu S. Prospective endoscopic ultrasound-based approach to the evaluation of idiopathic pancreatitis: causes, response to therapy, and long-term outcome. *Am J Gastroenterol* 2016; **111:** 1339–48.

6 Sajith KG, Chacko A, Dutta AK. Recurrent acute pancreatitis: clinical profile and an approach to diagnosis. *Dig Dis Sci* 2010; **55:** 3610–16.

7 Guda NM, Romagnuolo J, Freeman ML. Recurrent and relapsing pancreatitis. *Curr Gastroenterol Rep* 2011; **13:** 140–49.

8 Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004; **59:** 845–64.

9 Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62:** 102–11.

10 Wilcox CM, Yadav D, Ye T, et al. Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. *Clin Gastroenterol Hepatol* 2015; **13:** 552–60.

11 Bahuva R, Walsh RM, Kapural L, Stevens T. Morphologic abnormalities are poorly predictive of visceral pain in chronic pancreatitis. *Pancreas* 2013; **42:** 6–10.

12 Romagnuolo J, Guda N, Freeman M, Durkalski V. Preferred designs, outcomes, and analysis strategies for treatment trials in idiopathic recurrent acute pancreatitis. *Gastrointest Endosc* 2008; **68:** 966–74.

13 Seidensticker F, Otto J, Lankisch PG. Recovery of the pancreas after acute pancreatitis is not necessarily complete. *Int J Pancreatol* 1995; **17:** 225–29.

14 Lankisch PG, Seidensticker F, Otto J, et al. Secretin-pancreozymin test (SPT) and endoscopic retrograde cholangiopancreatography (ERCP): both are necessary for diagnosing or excluding chronic pancreatitis. *Pancreas* 1996; **12:** 149–52.

15 Das R, Yadav D, Papachristou GI. Endoscopic treatment of recurrent acute pancreatitis and smoldering acute pancreatitis. *Gastrointest Endosc Clin N Am* 2015; **25:** 737–48.

16 Varadarajulu S, Noone T, Hawes RH, Cotton PB. Pancreatic duct stent insertion for functional smoldering pancreatitis. *Gastrointest Endosc* 2003; **58:** 438–41.

17 Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. *Gut* 1999; **45:** 317–22.

18 Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. *Gastroenterology* 2015; **149:** 1490–500.

19 Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. *Am J Gastroenterol* 2012; **107:** 1096–103.

20 Lankisch PG, Breuer N, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P. Natural history of acute pancreatitis: a long-term population-based study. *Am J Gastroenterol* 2009; **104:** 2797–805.

21 Cavestro GM, Leandro G, Di Leo M, et al. A single-centre prospective, cohort study of the natural history of acute pancreatitis. *Dig Liver Dis* 2015; **47:** 205–10.

22 Machicado JD, Amann ST, Anderson MA, et al. Quality of life in chronic pancreatitis is determined by constant pain, disability/unemployment, current smoking, and associated co-morbidities. *Am J Gastroenterol* 2017; **112:** 633–42.

23 Bellin MD, Kerdsirichairat T, Beilman GJ, et al. Total pancreatectomy with islet autotransplantation improves quality of life in patients with refractory recurrent acute pancreatitis. *Clin Gastroenterol Hepatol* 2016; **14:** 1317–23.

24 Nordback I, Pelli H, Lappalainen-Lehto R, Jarvinen S, Raty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. *Gastroenterology* 2009; **136:** 848–55.

25 Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001; **120:** 682–707.

26 Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med* 2009; **169:** 1035–45.

27 Munigala S, Conwell DL, Gelrud A, Agarwal B. Heavy smoking is associated with lower age at first episode of acute pancreatitis and a higher risk of recurrence. *Pancreas* 2015; **44:** 876–81.

28 Nitsche C, Maertin S, Scheiber J, Ritter CA, Lerch MM, Mayerle J. Drug-induced pancreatitis. *Curr Gastroenterol Rep* 2012; **14:** 131–38.

29 Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007; **5:** 648–61.

30 Joergensen M, Brusgaard K, Cruger DG, Gerdes AM, Schaffalitzky de Muckadell OB. Incidence, etiology and prognosis of first-time acute pancreatitis in young patients: a population-based cohort study. *Pancreatology* 2010; **10:** 453–61.

31 Aoun E, Muddana V, Papachristou GI, Whitcomb DC. *SPINK1* N34S is strongly associated with recurrent acute pancreatitis but is not a risk factor for the first or sentinel acute pancreatitis event. *Am J Gastroenterol* 2010; **105:** 446–51.

32 Zhou J, Sahin-Toth M. Chymotrypsin C mutations in chronic pancreatitis. *J Gastroenterol Hepatol* 2011; **26:** 1238–46.

33 LaRusch J, Lozano-Leon A, Stello K, et al. The common chymotrypsinogen C (*CTRC*) variant G60G (C.180T) increases risk of chronic pancreatitis but not recurrent acute pancreatitis in a North American population. *Clin Transl Gastroenterol* 2015; **6:** e68.

34 Gelrud A, Sheth S, Banerjee S, et al. Analysis of cystic fibrosis gene product (CFTR) function in patients with pancreas divisum and recurrent acute pancreatitis. *Am J Gastroenterol* 2004; **99:** 1557–62.

35 Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996; **14:** 141–45.

36 Bellin MD, Prokhoda P, Hodges JS, et al. Age and disease duration impact outcomes of total pancreatectomy and islet autotransplant for PRSS1 hereditary pancreatitis. *Pancreas* 2018; **47:** 466–70.

37 Hart PA, Levy MJ, Smyrk TC, et al. Clinical profiles and outcomes in idiopathic duct-centric chronic pancreatitis (type 2 autoimmune pancreatitis): the Mayo Clinic experience. *Gut* 2016; **65:** 1702–09.

38 Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40:** 352–58.

39 Majumder S, Takahashi N, Chari ST. Autoimmune pancreatitis. *Dig Dis Sci* 2017; **62:** 1762–69.

40 Kanno A, Masamune A, Fujishima F, et al. Diagnosis of autoimmune pancreatitis by EUS-guided FNA using a 22-gauge needle: a prospective multicenter study. *Gastrointest Endosc* 2016; **84:** 797–804.

41 Bhattacharya A, Cruise M, Chahal P. Endoscopic ultrasound guided 22 gauge core needle biopsy for the diagnosis of autoimmune pancreatitis. *Pancreatology* 2018; **18:** 168–69.

42 Moon SH, Kim MH, Park DH, et al. IgG4 immunostaining of duodenal papillary biopsy specimens may be useful for supporting a diagnosis of autoimmune pancreatitis. *Gastrointest Endosc* 2010; **71:** 960–66.

43 Cotton PB. Congenital anomaly of pancreas divisum as cause of obstructive pain and pancreatitis. *Gut* 1980; **21:** 105–14.

44 Klein SD, Affronti JP. Pancreas divisum, an evidence-based review: part I, pathophysiology. *Gastrointest Endosc* 2004; **60:** 419–25.

45 Delhaye M, Matos C, Arvanitakis M, Deviere J. Pancreatic ductal system obstruction and acute recurrent pancreatitis. *World J Gastroenterol* 2008; **14:** 1027–33.

46 Bertin C, Pelletier AL, Vullierme MP, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. *Am J Gastroenterol* 2012; **107:** 311–17.

47 Lans JI, Geenen JE, Johanson JF, Hogan WJ. Endoscopic therapy in patients with pancreas divisum and acute pancreatitis: a prospective, randomized, controlled clinical trial. *Gastrointest Endosc* 1992; **38:** 430–34.

48 Lutzak GD, Gluck M, Ross AS, Kozarek RA. Endoscopic minor papilla sphincterotomy in patients with santoriniceles reduces pain and improves quality of life. *Dig Dis Sci* 2013; **58:** 2075–81.

49 Kanth R, Samji NS, Inaganti A, et al. Endotherapy in symptomatic pancreas divisum: a systematic review. *Pancreatology* 2014; **14:** 244–50.

50 Bakman YG, Safdar K, Freeman ML. Significant clinical implications of prophylactic pancreatic stent placement in previously normal pancreatic ducts. *Endoscopy* 2009; **41:** 1095–98.

51 Cote GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. *Gastroenterology* 2012; **143:** 1502–09.

52 Das R, Clarke B, Tang G, et al. Endoscopic sphincterotomy (ES) may not alter the natural history of idiopathic recurrent acute pancreatitis (IRAP). *Pancreatology* 2016; **16:** 770–77.

53 Soares KC, Kim Y, Spolverato G, et al. Presentation and clinical outcomes of choledochal cysts in children and adults: a multi-institutional analysis. *JAMA Surg* 2015; **150:** 577–84.

54 Samavedy R, Sherman S, Lehman GA. Endoscopic therapy in anomalous pancreatobiliary duct junction. *Gastrointest Endosc* 1999; **50:** 623–27.

55 Bellin MD, Freeman ML, Gelrud A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. *Pancreatology* 2014; **14:** 27–35.

56 Harewood GC, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. *Gastrointest Endosc* 2005; **62:** 367–70.

57 Munigala S, Kanwal F, Xian H, Scherrer JF, Agarwal B. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. *Clin Gastroenterol Hepatol* 2014; **12:** 1143–50.

58 Wan J, Ouyang Y, Yu C, Yang X, Xia L, Lu N. Comparison of EUS with MRCP in idiopathic acute pancreatitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2017; **87:** 1180–88.

59 Poddar U, Yachha SK, Mathias A, Choudhuri G. Genetic predisposition and its impact on natural history of idiopathic acute and acute recurrent pancreatitis in children. *Dig Liver Dis* 2015; **47:** 709–14.

60 Giefer MJ, Lowe ME, Werlin SL, et al. Early-onset acute recurrent and chronic pancreatitis is associated with *PRSS1* or *CTRC* gene mutations. *J Pediatr* 2017; **186:** 95–100.

61 Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; **13** (suppl 2): e1–15.

62 Shmelev A, Kowdley GC, Cunningham SC. Cholecystectomy following idiopathic pancreatitis: how much to look for stones? *J Gastrointest Surg* 2017; **21:** 1196–97.

63 Raty S, Pulkkinen J, Nordback I, et al. Can laparoscopic cholecystectomy prevent recurrent idiopathic acute pancreatitis?: a prospective randomized multicenter trial. *Ann Surg* 2015; **262:** 736–41.

64 Guda NM, Muddana V, Whitcomb DC, et al. Recurrent acute pancreatitis: international state-of-the-science conference with recommendations. *Pancreas* 2018; **47:** 653–66.