Etiology of acute pancreatitis

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INTRODUCTION

Acute pancreatitis is an inflammatory condition of the pancreas characterized by abdominal pain and elevated levels of pancreatic enzymes in the blood. Acute pancreatitis is a leading gastrointestinal cause of hospitalization in the United States [1]. Several conditions are associated with acute pancreatitis. Of these, gallstones and chronic alcohol use disorder account for approximately two-thirds of cases.

This topic will review the etiology of acute pancreatitis and an approach to establishing the underlying etiology. Our approach is largely consistent with guidelines issued by the American Gastroenterological Association and American College of Gastroenterology and is outlined below. The pathogenesis, clinical manifestations, diagnosis, and management of acute pancreatitis are discussed separately. (See "Predicting the severity of acute pancreatitis" and "Management of acute pancreatitis" and "Pancreatic debridement" and "Pathogenesis of acute pancreatitis".)

EPIDEMIOLOGY

The reported annual incidence of acute pancreatitis in the United States ranges from 4.9 to 35 per 100,000 population [2]. The incidence of acute pancreatitis is increasing worldwide due to increased rates of obesity and gallstones [3]. Smoking may increase the risk for non-gallstone-related pancreatitis by mechanisms that are unclear and may potentiate alcohol-

induced damage to the pancreas [4-9].

Mortality in acute pancreatitis is usually due to systemic inflammatory response syndrome and organ failure in the first two-week period, while after two weeks it is usually due to sepsis and its complications [10,11]. In a systematic review of studies of acute pancreatitis, overall mortality was approximately 5 percent, with mortality rates in patients with interstitial, and necrotizing pancreatitis, of 3 percent, and 17 percent, respectively [12]. However, mortality rates in necrotizing pancreatitis may be lower in centers of expertise (range 6 to 9 percent) [10,13].

ETIOLOGY

Gallstones — Gallstones (including microlithiasis) are the most common cause of acute pancreatitis accounting for 40 to 70 percent of cases [14]. However, only 3 to 7 percent of patients with gallstones develop pancreatitis [15,16]. The mechanism by which the passage of gallstones induces pancreatitis is unknown. Two factors have been suggested as the possible initiating event in gallstone pancreatitis: reflux of bile into the pancreatic duct due to transient obstruction of the ampulla during passage of gallstones; or obstruction at the ampulla secondary to stone(s) or edema resulting from the passage of a stone [17,18]. Cholecystectomy and clearing the common bile duct of stones prevents recurrence, confirming the cause-and-effect relationship [15].

The risk of developing acute pancreatitis in patients with gallstones is greater in men; however, the incidence of gallstone pancreatitis is higher in women due to a higher prevalence of gallstones [15]. Small gallstones are associated with an increased risk of pancreatitis [19]. One study found that stones with a diameter of less than 5 mm were significantly more likely than larger stones to pass through the cystic duct and cause obstruction at the ampulla. (See 'Biliary sludge and microlithiasis' below.)

Alcohol — Alcohol is responsible for approximately 25 to 35 percent of cases of acute pancreatitis in the United States [20]. Approximately 10 percent of patients with chronic alcohol use disorder develop attacks of clinically acute pancreatitis that are indistinguishable from other forms of acute pancreatitis.

Alcohol may act by increasing the synthesis of enzymes by pancreatic acinar cells to synthesize the digestive and lysosomal enzymes that are thought to be responsible for acute pancreatitis or over-sensitization of acini to cholecystokinin [21,22]. However, the exact mechanism of pancreatic injury, the genetic and environmental factors that influence the

development of pancreatitis in patients with alcohol use disorder, and the reason why only a small proportion of patients with alcohol use disorder develop pancreatitis, are unclear. (See "Pathogenesis of acute pancreatitis".)

There is debate about the presence of underlying chronic pancreatitis in patients presenting with acute alcoholic pancreatitis. It was initially thought that alcohol causes chronic pancreatitis, and that patients with alcohol use disorder who present with clinically acute pancreatitis have underlying chronic disease [23]. However, long-term follow-up studies of patients with acute alcoholic pancreatitis have demonstrated that not all patients progress to chronic pancreatitis, even with continued alcohol use disorder [24]. This suggests that some patients with alcohol use disorder may have nonprogressive acute alcohol-induced pancreatitis [25].

The association of smoking with acute pancreatitis, both by itself and also with alcohol, is well recognized [26]. These results suggest that tobacco smoking increases the risk of acute and chronic pancreatitis and acute and chronic pancreatitis combined, and that there is a dose-response relationship between increasing number of cigarettes and pack-years and pancreatitis risk.

Hypertriglyceridemia — Serum triglyceride concentrations above 1000 mg/dL (11 mmol/L) can precipitate attacks of acute pancreatitis, although lower levels may also contribute to severity [27,28]. Hypertriglyceridemia may account for 1 to 14 percent of cases of acute pancreatitis [29,30]. Both primary (genetic) and secondary (acquired) disorders of lipoprotein metabolism are associated with hypertriglyceridemia-induced pancreatitis. Acquired causes of hypertriglyceridemia include obesity, diabetes mellitus, hypothyroidism, pregnancy, and medications (eg, estrogen or tamoxifen therapy, beta blockers). (See "Hypertriglyceridemia-induced acute pancreatitis".)

Post-endoscopic retrograde cholangiopancreatography (ERCP) — Acute pancreatitis occurs in about 3 percent of patients undergoing diagnostic ERCP, 5 percent undergoing therapeutic ERCP, and up to 25 percent undergoing sphincter of Oddi manometric studies [31]. Multiple operator, patient, and procedure-related factors increase the risk of post-ERCP pancreatitis. Important risk factors include lack of ERCP experience, sphincter of Oddi dysfunction, difficult cannulation, and the performance of a therapeutic (rather than diagnostic) ERCP. (See "Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis", section on 'Risk factors'.)

Genetic risk — Patients with genetic risk for pancreatitis may present as recurrent acute

pancreatitis, or childhood pancreatitis without a known cause and eventually progress to chronic pancreatitis. Gain-of-function mutations in the *PRSS1* gene, which encodes cationic trypsinogen, results in an autosomal dominantly inherited form of hereditary pancreatitis. Mutations in the *CFTR* gene have been associated with an autosomal recessively inherited pancreatitis. Pancreatitis has also been associated with low penetrance mutations in the *SPINK1*, which may act as a disease modifier and lower the threshold for developing pancreatitis from other genetic or environmental factors. Mutations in *CTRC* gene can cause pancreatitis with or without associated manifestations of cystic fibrosis [32]. The majority of "idiopathic" cases appear to have genetic risk, especially in younger patients (age <35 years). Other genes associated with recurrent acute pancreatitis are discussed in detail separately. (See "Pancreatitis associated with genetic risk factors", section on 'Genetics'.)

Medications — Pancreatitis due to medications is rare (<5 percent) [33-36]. The prognosis of drug-induced pancreatitis is generally excellent and mortality is low [37,38].

Mechanisms of drug-induced pancreatitis include immunologic reactions (eg, 6-mercaptopurine, aminosalicylates, sulfonamides), direct toxic effect (eg, diuretics, sulfonamides), accumulation of a toxic metabolite (eg, valproic acid, pentamidine, tetracycline), ischemia (diuretics, azathioprine), intravascular thrombosis (eg, estrogen), and an increased viscosity of pancreatic juice (eg, diuretics and steroids) [39,40].

Drug-induced pancreatitis is classified (class I-IV) based on the number of cases reported, demonstration of a consistent latency period (time from initiation of drug to development of pancreatitis), and reaction with rechallenge (table 1) [41]. Class I and II drugs have the greatest potential for causing acute pancreatitis (table 2). However, proving the association with a particular drug may not always be straightforward, even in suspected cases. Pancreatitis may develop within a few weeks after beginning a drug associated with an immunologically mediated adverse reaction; in this setting, the patient may also have a rash and eosinophilia. In contrast, patients taking valproic acid or pentamidine may not develop pancreatitis until after many months of use, presumably due to the chronic accumulation of toxic metabolic products. Thus, patients restarted on their medications should be closely monitored and the drug promptly discontinued if symptoms recur. Most of the published evidence is based on case reports and, hence, it is very important to rule out all other causes before attributing a drug as the cause of acute pancreatitis [42].

Pancreatic duct injury — Blunt or penetrating trauma can damage the pancreas, however, these injuries are uncommon due to the retroperitoneal location of the pancreas [43,44]. Trauma can range from a mild contusion to a severe crush injury or transection of the gland

where the pancreas crosses over the spine. Pancreatin injury can cause acute duct rupture and pancreatic ascites. Healing of pancreatic ductal injuries can lead to scarring and stricture of the main pancreatic duct, with resultant obstructive pancreatitis in the gland downstream from the stricture. (See "Management of pancreatic trauma in adults", section on 'Clinical evaluation'.)

Other rare causes

Biliary sludge and microlithiasis — Biliary sludge is a viscous suspension in gallbladder bile that may contain small stones (<5 mm in diameter) [45]. Microscopic analysis of bile in patients with sludge often shows cholesterol monohydrate crystals or calcium bilirubinate granules [46]. Sludge is typically found in patients with functional or mechanical bile stasis, such as those undergoing a prolonged fast, with distal bile duct obstruction, or on total parenteral nutrition. Most patients with biliary sludge are asymptomatic. However, biliary sludge is found in 20 to 40 percent of patients with acute pancreatitis with no obvious cause. In the absence of any other etiology, biliary sludge should be suspected as the cause in patients with acute pancreatitis with a transient elevation in liver tests. (See 'Recurrent episodes' below.)

Biliary obstruction — Conditions causing obstruction of the ampulla that have been associated with pancreatitis include biliary ascariasis, periampullary diverticula, and pancreatic and periampullary tumors [47-49]. Autoimmune pancreatitis is a rare cause of acute pancreatitis; its usual presentation is weight loss, jaundice, and pancreatic enlargement on imaging, mimicking a neoplasm. In rare cases, duodenal inflammation and papillary stenosis secondary to celiac disease can cause recurrent episodes of acute pancreatitis [50]. (See "Autoimmune pancreatitis: Clinical manifestations and diagnosis" and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations".)

Hypercalcemia — Hypercalcemia of any cause can lead to acute pancreatitis but the incidence is low [51,52]. Proposed mechanisms include deposition of calcium in the pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma [51-54]. The low incidence of pancreatitis in patients with chronic hypercalcemia suggests that other factors (acute rise in serum calcium) are responsible in patients who develop acute pancreatitis [55]. An experimental model, for example, found that acute calcium infusions in rats led to hyperamylasemia and dose-dependent morphological alterations characteristic of acute pancreatitis [53]. (See "Etiology of hypercalcemia".)

Infections and toxins — Pancreatitis has been associated with the following infections [56,57]:

- **Viruses** – Mumps, coxsackievirus, hepatitis B, cytomegalovirus, varicella-zoster, herpes simplex, human immunodeficiency virus (HIV)
- **Bacteria** – *Mycoplasma, Legionella, Leptospira, Salmonella*
- **Fungi** – *Aspergillus*
- **Parasites** – *Toxoplasma, Cryptosporidium, Ascaris*

There are limited data regarding the frequency with which these infections lead to pancreatitis. In one series, acute pancreatitis occurred in 4.7 percent of 939 hospitalized patients who were seropositive for HIV [58]. Acute pancreatitis may be part of primary HIV infection but more frequently occurs as a complication of medications taken to treat the virus or opportunistic infections (eg, pentamidine), or due to the opportunistic infection itself (eg, Pneumocystis carinii, Mycobacterium avium-intracellulare) [57,59].

Only 70 percent of individuals have a characteristic syndrome caused by the infectious agent [56]. In addition, the value of treating the infectious agent to reverse pancreatitis remains unknown. Thus, the routine search for an infectious etiology in idiopathic pancreatitis is **not** recommended.

The venom of arachnids and reptiles (brown recluse spider, some scorpions, and the Gila monster lizard) have been associated with acute pancreatitis due to cholinergic stimulation. (See "Scorpion envenomation causing autonomic dysfunction (North Africa, Middle East, Asia, South America, and the Republic of Trinidad and Tobago)", section on 'Pancreatitis'.)

Vascular disease — Pancreatic ischemia is an uncommon cause of clinically significant pancreatitis. Ischemia with resultant pancreatitis has been reported in association with vasculitis (systemic lupus erythematosus and polyarteritis nodosa), atheroembolism, intraoperative hypotension, and hemorrhagic shock [60-64]. A porcine model of cardiogenic shock induced by pericardial tamponade found that pancreatic vasospasm was responsible for significant selective pancreatic ischemia [65].

Most patients have mild attacks of pancreatitis secondary to ischemia, although fatal necrotizing pancreatitis can occur. In one report, for example, 81 of 300 patients (27 percent) undergoing cardiac surgery developed hyperamylasemia and three patients subsequently developed necrotizing pancreatitis [63]. Preoperative renal insufficiency, postoperative

hypotension, and perioperative administration of calcium chloride were significant risk factors for the development of pancreatitis.

Anatomic or physiologic pancreatic anomalies — Biliary cysts (eg, some choledochal cysts types) may increase the risk for acute pancreatitis, presumably due to pressure and obstruction of pancreatic duct or anomalous pancreaticobiliary malunion with a long common channel. Other anatomic anomalies like pancreaticobiliary malunion, large juxta-ampullary diverticula, and annular pancreas have also been associated with acute pancreatitis, possibly due to mechanical obstruction at the ampullary level. (See "Biliary cysts", section on 'Types of biliary cysts'.)

Whether sphincter of Oddi dysfunction or pancreas divisum are a cause of acute pancreatitis is controversial. (See "Pancreas divisum: Clinical manifestations and diagnosis".)

Idiopathic — No obvious etiology is identifiable by history, laboratory tests, and gallbladder ultrasound in 25 to 30 percent of patients with acute pancreatitis. After an extensive work-up for recurrent pancreatitis (including magnetic resonance imaging/magnetic resonance cholangiopancreatography, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, analysis of bile for microlithiasis, and sphincter of Oddi manometry), approximately 15 to 25 percent of patients with acute pancreatitis are idiopathic. Emerging data indicates that the majority of patients with idiopathic acute and recurrent acute pancreatitis have underlying complex genetic risk profiles [66,67]. A meta-analysis found that cholecystectomy, after an episode of idiopathic acute pancreatitis, reduces the risk of recurrent pancreatitis [68]. This implies that the present approaches to establishing the etiology are insufficient to exclude a biliary cause and may label the patient as idiopathic acute pancreatitis.

APPROACH TO ESTABLISHING THE UNDERLYING ETIOLOGY

The etiology of acute pancreatitis can be established in nearly 75 percent of patients [14].

Initial evaluation

History — Key elements to the history include the following:

- Prior symptoms of gallstone disease (eg, biliary colic) or documentation of gallstones on prior imaging.
- Systemic symptoms including unexplained weight loss or new onset of diabetes.

- Amount and pattern of alcohol use. Alcoholic pancreatitis is unlikely to be the underlying etiology in the absence of a history of over five years of heavy alcohol consumption (>50 g per day).
- Medication use (prescription and nonprescription) including the time course of developing pancreatitis and the presence of associated symptoms (rash eosinophilia). (See 'Medications' above.)
- Prior surgery, endoscopic retrograde cholangiopancreatography (ERCP), or trauma.
- History of hypertriglyceridemia or hypercalcemia.
- Concomitant autoimmune diseases suggestive of autoimmune pancreatitis.
- Family history of recurrent acute pancreatitis, idiopathic chronic pancreatitis, childhood pancreatitis without a known cause and pancreatic cancer. (See 'Genetic risk' above.)

Laboratory evaluation

Routine tests in all patients — Routine tests in all patients with acute pancreatitis should include the following:

- **Triglyceride levels** – Serum triglyceride levels >1000 mg/dL (11.2 mmol/L) are required for hypertriglyceridemia to be considered the underlying etiology of acute pancreatitis. Hypertriglyceridemia may be missed if levels are obtained after prolonged fasting. Fasting triglyceride levels should therefore be rechecked once the patient has resumed a normal diet. (See "Hypertriglyceridemia-induced acute pancreatitis".)
- **Serum calcium levels** – Hypercalcemia may be missed during a severe attack because calcium levels can decrease. Calcium levels should be re-checked after few weeks of recovery, as is the case with triglycerides. However, hypercalcemia is an unusual cause of acute pancreatitis. Other causes should be excluded before concluding that hypercalcemia is the underlying etiology.
- **Liver biochemical tests** – The presence of elevated liver tests (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) in the setting of acute pancreatitis is suggestive of gallstone/biliary pancreatitis [69]. In one meta-analysis, a serum ALT concentration of 150 international units/L or more (approximately a threefold elevation) had a positive predictive value of 95 percent for the diagnosis of gallstone pancreatitis. The AST concentration was nearly as useful as, ALT, while the

total bilirubin and alkaline phosphatase concentrations did not assist in making the diagnosis.

Additional tests in selected patients

- In patients with acute pancreatitis at a young age (<35 years) or a family history of pancreatitis, we perform genetic testing for hereditary pancreatitis (eg, *PRSS1, SPINK1, CFTR, CTRC and CASR and Claudin-2,* if available). (See 'Genetic risk' above.)

- We do not routinely perform serologic testing for IgG4. Although autoimmune pancreatitis (AIP) can present with acute pancreatitis it is rare. AIP is also an extremely unlikely cause of recurrent acute pancreatitis. Serologic testing is not an important diagnostic feature, and if AIP is suspected, then the diagnosis is largely based on imaging, other organ involvement, and histology, if available. (See "Autoimmune pancreatitis: Clinical manifestations and diagnosis", section on 'Diagnostic approach'.)

Abdominal ultrasound — An abdominal ultrasound should be obtained on admission in all patients with acute pancreatitis to evaluate for cholelithiasis or choledocholithiasis or signs of extrahepatic biliary tract obstruction. The ultrasound should be performed regardless of whether liver tests are elevated.

If the initial examination is inadequate or if clinical suspicion for gallstones remains high, the abdominal ultrasound examination should be repeated after recovery. (See "Management of acute pancreatitis", section on 'Gallstone pancreatitis'.)

Subsequent evaluation for acute pancreatitis without a clear etiology — In patients with acute pancreatitis without a clear etiology despite initial testing, additional evaluation is required to identify other causes that may be missed during the initial evaluation.

Although pancreatic cancer is a rare cause of acute pancreatitis, it should be suspected in patients with acute pancreatitis who are older than 40 years of age, have unexplained weight loss preceding the attack of acute pancreatitis, new onset of diabetes, or a family history of pancreatic cancer in first-degree relative.

Isolated episode — In patients with an isolated episode of acute pancreatitis without a clear etiology we perform an endoscopic ultrasonography (EUS) to evaluate for pancreatic ductal abnormalities, small tumors at or near the ampulla, microlithiasis in the gallbladder or bile duct, and early chronic pancreatitis.

We perform magnetic resonance cholangiopancreatography (MRCP) with secretin

administration if the EUS does not reveal a cause or is unavailable. MRCP may sometimes unmask a dynamic obstruction or early chronic pancreatitis that may have been rarely missed on EUS. Computed tomography with pancreas protocol should be performed if MRCP and EUS are unavailable.

ERCP is not routinely recommended as a diagnostic test for idiopathic acute pancreatitis because of its complications. It is reserved for endotherapy in patients with abnormal MRCP/EUS findings (eg, choledocholithiasis, and pancreatic ductal stricture), to diagnose a small tumor in the terminal bile duct or pancreatic duct in patients with a suspected pancreatic neoplasm, to perform intraductal endoscopy in patients with a main duct intraductal papillary mucinous neoplasm.

Recurrent episodes — In patients with recurrent episodes of acute pancreatitis we perform an EUS. We collect bile for microscopic evaluation for cholesterol or bilirubinate crystals if EUS imaging is negative, especially if there is a strong suspicion for biliary pancreatitis (eg, due to elevated ALT). The bile sample is collected during the same endoscopic session as the EUS. (See "Overview of gallstone disease in adults", section on 'Bile microscopy' and 'Laboratory evaluation' above and 'Biliary sludge and microlithiasis' above.)

We perform MRCP with secretin administration if the EUS and bile microscopy do not reveal a cause or are unavailable. In patients with abnormal MRCP/EUS, ERCP is performed to confirm the diagnosis and/or endotherapy. In patients with normal MRCP and EUS, but recurrent episodes of pancreatitis (regardless of age), some experts perform ERCP to measure biliary and pancreatic pressures to evaluate for sphincter of Oddi dysfunction or to perform biliary and or pancreatic sphincterotomies, regardless of such measurements. However, it is important to note that there is significant controversy about whether sphincter of Oddi dysfunction is an underlying cause of idiopathic recurrent acute pancreatitis. Sphincterotomy has also not been demonstrated to reduce the risk of acute pancreatitis in patients with sphincter of Oddi dysfunction [70]. In addition, both ERCP and sphincter of Oddi manometry are associated with procedure-related complications. If ERCP is performed, it should only be performed by an endoscopist with experience in pancreatic endotherapy. (See "Pancreas divisum: Clinical manifestations and diagnosis".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute pancreatitis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Acute pancreatitis (The Basics)")
- Beyond the Basics topics (see "Patient education: Acute pancreatitis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Acute pancreatitis is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes in the blood. The reported annual incidence of acute pancreatitis in the United States ranges from 4.9 to 35 per 100,000 population. (See 'Introduction' above.)
- **Etiology** – A number of conditions are known to cause acute pancreatitis. Of these, gallstones and chronic alcohol use disorder account for approximately two-thirds of cases. Gallstones (including microlithiasis) are the most common cause of acute pancreatitis, however, only 3 to 7 percent of patients with gallstones develop pancreatitis. (See 'Gallstones' above and 'Alcohol' above.)
- **Determining the underlying etiology**
  - **Evaluation in all patients** – Initial evaluation to determine the etiology of acute pancreatitis, includes a history, laboratory evaluation (serum amylase or lipase, triglyceride level, calcium level, and liver biochemistries), and abdominal ultrasound

(repeated, if initially negative for gallstones). (See 'Initial evaluation' above.)

- **Additional evaluation in patients with acute pancreatitis without a clear etiology**

  - In patients with acute pancreatitis at a young age (<35 years) or a family history of pancreatitis, we perform genetic testing for hereditary pancreatitis (eg, *PRSS1, SPINK1, CFTR, CTRC, CASR and Claudin-2*). (See 'Additional tests in selected patients' above and 'Initial evaluation' above.)

  - In patients with an isolated episode of acute pancreatitis, if the initial evaluation does not yield an etiology, we perform an endoscopic ultrasonography (EUS). In patients with a negative EUS or if EUS is unavailable, we perform magnetic resonance cholangiopancreatography (MRCP) following secretin administration. Endoscopic retrograde cholangiopancreatography (ERCP) is not routinely recommended as a diagnostic test for idiopathic acute pancreatitis because of its complications. It is reserved for endotherapy in patients with abnormal MRCP/EUS findings (eg, choledocholithiasis, and pancreatic ductal stricture), to diagnose a small tumor in the terminal bile duct or pancreatic duct in patients with a suspected pancreatic neoplasm, or to perform intraductal endoscopy in patients with a main duct intraductal papillary mucinous neoplasm. (See 'Isolated episode' above.)

  - In patients with recurrent episodes of pancreatitis (irrespective of age), EUS is the preferred initial test. We collect bile for microscopic evaluation for cholesterol or bilirubinate crystals if EUS imaging is negative. We perform MRCP following secretin administration in patients with a negative EUS and bile microscopy. We do not routinely perform ERCP unless indicated for additional evaluation of abnormal MRCP/EUS findings or endotherapy. There is significant controversy about whether sphincter of Oddi dysfunction is an underlying cause of idiopathic recurrent acute pancreatitis and both ERCP and sphincter of Oddi manometry are associated with procedure-related complications. (See 'Recurrent episodes' above.)

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GRAPHICS

Classification system of drug-induced acute pancreatitis

Class Ia drugs
At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs
Class Ib drugs
At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out
Class II drugs
At least 4 cases in the literature
Consistent latency (≥75 percent of cases)
Class III drugs
At least 2 cases in the literature
No consistent latency among cases
No rechallenge
Class IV drugs
Drugs not fitting into the earlier-described classes, single case report published in medical literature, without rechallenge

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Summary of drug-induced acute pancreatitis based on drug class

Class Ia	Class Ib	Class II	Class III	
α-methyldopa	All-trans-retinoic acid	Acetaminophen	Alendronate	A h
Azodisalicylate	Amiodarone	Chlorothiazide	Atorvastatin	A
Bezafibrate	Azathioprine	Clozapine	Carbamazepine	B
Cannabis	Clomiphene	Didanosine	Captopril	B
Carbimazole	Dexamethasone	Erythromycin	Ceftriaxone	B
Codeine	Ifosfamide	Estrogen	Chlorthalidone	C
Cytosine	Lamivudine	L-asparaginase	Cimetidine	C
Arabinoside	Losartan	Pegaspargase	Clarithromycin	C
Dapsone	Lynestrenol/methoxyethinylestradiol	Propofol	Cyclosporin	C
Enalapril	6-mercaptopurine	Tamoxifen	Gold	C
Furosemide	Meglumine		Hydrochlorothiazide	C
Isoniazid	Methimazole		Indomethacin	D
Mesalamine	Nelfinavir		Interferon/ribavirin	D
Metronidazole	Norethindronate/mestranol		Irbesartan	D
Pentamidine	Omeprazole		Isotretinoin	D
Pravastatin	Premarin		Ketorolac	D
Procainamide	Trimethoprimsulfamethazole		Lisinopril	E
Pyritonol			Metolazone	F
Simvastatin			Metformin	Fi
Stibogluconate			Minocycline	5
Sulfamethoxazole			Mirtazapine	Fl
Sulindac			Naproxen	G
Tetracycline			Paclitaxel	Ir
Valproic acid			Ponatinib	K
			Prednisone	L
			Prednisolone	M
				N
				O
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Contributor Disclosures

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