

Role of endoscopic evaluation in idiopathic pancreatitis: a systematic review CME

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In approximately 20% of patients with acute pancreatitis, a cause is not established by history, physical examination, routine laboratory testing, and abdominal imaging. For those with a single unexplained attack, the role of invasive evaluation with endoscopic retrograde cholangiopancreatography is unsettled but has been generally limited to those patients with suspected bile duct stones or malignancy. Recent studies suggest that microlithiasis is causative in up to 75% of patients with an unexplained attack and gallbladder in situ, whereas sphincter of Oddi dysfunction is most prevalent in those with recurrent attacks who have previously undergone cholecystectomy. EUS has been shown to be highly accurate for the identification of gallbladder sludge, common bile duct stones, and pancreatic diseases. Given this apparent diagnostic utility, an EUS-based strategy may be a reasonable approach to evaluate patients with a single idiopathic attack. ERCP and sphincter of Oddi manometry should generally be reserved for patients with multiple unexplained attacks and negative EUS results, especially for those patients who have previously undergone cholecystectomy. (*Gastrointest Endosc* 2006;63:1037-45.)

Acute pancreatitis is a common condition generally requiring hospitalization, most frequently caused by gallstones or alcohol, and whose incidence may be increasing.¹⁻⁷ In most cases, a diagnosis can be established by a careful history, routine laboratory studies, transabdominal US, and CT scanning. However, despite this initial workup, an etiology remains undefined in 2%⁸ to 30% of cases.^{9,10} After a single episode of unexplained pancreatitis, the role of invasive evaluation with ERCP is unsettled. Some investigators limit this procedure to those with a more severe attack, when common bile duct stones are highly suspected or those at risk for pancreatic cancer^{11,12}; however, such an approach has never been rigorously tested. In contrast, others recommend ERCP routinely after only a single episode if no cause is found.^{12,13} Recent studies document the etiologic importance of gallbladder microlithiasis and biliary sludge in patients with either single or multiple idiopathic attacks with prevalence rates up to 70%.¹⁴⁻¹⁶ Given the importance of microlithiasis as a cause of acute pancreatitis coupled with the emergence of EUS as a minimally invasive highly accurate diagnostic tool for pancreaticobiliary disease, the appropriate diagnostic strategy for patients after an idiopathic attack, both single and recurrent, warrants reassessment.

Although recent narrative reviews summarize data on the etiologies of recurrent idiopathic pancreatitis (RIP)

and the role of ERCP in pancreatitis,¹⁷⁻²⁰ there has been little critical analysis of the yield of invasive diagnostic testing that includes the role of EUS in idiopathic pancreatitis.²¹ Therefore, the purpose of this review is 3-fold: first, to evaluate the data regarding the yield of endoscopic evaluation with both EUS and ERCP after a single attack of idiopathic acute pancreatitis and for those with RIP;

EUS should be considered to evaluate patients with a single attack of idiopathic pancreatitis. ERCP and sphincter of Oddi manometry should be reserved for patients with multiple unexplained attacks of pancreatitis who have negative results on EUS, particularly for those post cholecystectomy.

second, on the basis of our review, to offer suggestions for the evaluation of idiopathic pancreatitis; and last, to suggest areas for further investigation.

METHODS

Our systematic review was conducted according to previously proposed criteria.²² We searched PubMed (1966–January 1, 2006; English language) using the search

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TABLE 1. Most frequently identified causes of unexplained pancreatitis after endoscopic evaluation

Ampullary lesions
Choledocholithiasis
Chronic pancreatitis
Gallbladder microlithiasis
Pancreas divisum
Pancreatic cancer
Sphincter of Oddi dysfunction

terms “idiopathic pancreatitis, unexplained pancreatitis, and recurrent pancreatitis.” We also searched using the term “genetic testing in idiopathic pancreatitis.” We retrieved potentially relevant articles and reviewed their reference list to identify studies that our search strategy may have missed. We also searched our personal archives to identify additional studies. We excluded studies that were case series of fewer than 3 patients, abstracts, studies that specifically examined a pediatric population, animal studies, and studies that were not published in English. When possible, cited literature was limited to those studies reporting on patients with unexplained pancreatitis. A total of 3340 abstracts or titles of articles were reviewed. For the purposes of this review, we defined idiopathic pancreatitis as the absence of a diagnosis after routine evaluation that included abdominal US and CT.

DEFINING IDIOPATHIC PANCREATITIS

There are no agreed-on criteria for what constitutes an appropriate evaluation before an attack is labeled as being idiopathic. Generally, an attack is considered idiopathic after history, physical examination, laboratory studies, and US and CT imaging reveal no cause. Intuitively, the prevalence of idiopathic pancreatitis will necessarily depend on the epidemiologic setting, the criteria used to define specific causes, and the extent of the diagnostic evaluation. Nevertheless, for unclear reasons, even older series where ERCP is not routine and sphincter of Oddi manometry (SOM) not performed may have a low frequency of idiopathic cases.¹¹ As with any clinical situation, however, the evaluation should be tailored to the patient. For example, in older patients without risk factors for pancreatitis and with normal US results, excluding pancreatic cancer is prudent, whereas ERCP may be indicated when common bile duct stones are strongly suspected by the liver chemistry profile and imaging studies. Given the potential morbidity of any invasive test, especially ERCP, an invasive evaluation must always balance risk versus benefit. Prospective studies from experienced centers report complication rates of ~10% for ERCP,^{23,24} whereas

complications from EUS are very low (<1%) even when fine-needle aspiration is performed.^{25,26} The most frequent diagnoses established after endoscopic evaluation of patients with unexplained pancreatitis are listed in Table 1.

ROLE OF MICROLITHIASIS

Although gallstones have been recognized as a cause of acute pancreatitis for about a century, only recently have biliary sludge and microlithiasis been linked to acute biliary pancreatitis.²⁷⁻³⁰ Microlithiasis is often referred to as small stones less than 3 mm in diameter.^{27,28,30,31} Biliary sludge is defined as a suspension of crystals (usually cholesterol monohydrate), mucin, glycoproteins, cellular debris, and proteinaceous material within bile.¹⁶ Sludge may be visualized by abdominal US and by EUS, whereas microscopic examination of bile is required to identify crystals.

Multiple lines of evidence support a definitive link among sludge, microlithiasis, and acute pancreatitis that can be summarized as follows: (1) Epidemiologic and case-control studies demonstrate a heightened risk of pancreatitis for those with small gallbladder stones^{30,32-36} and a low relapse rate after cholecystectomy.^{27,28,34,37} (2) Microlithiasis can be identified in most patients (88%) early after suspected biliary pancreatitis by sampling bile from the common bile duct and performing microscopic analysis for biliary crystals; the density of crystals is highest soon after the attack.³⁸ (3) Despite negative US results, bile duct crystals can be found by microscopic examination of bile aspirated from the common bile duct by ERCP in the majority of patients (80%) with suspected (by clinical and laboratory criteria) biliary pancreatitis.³⁹ (4) Patients with either one or multiple recurrent idiopathic attacks and no stones on US often have microlithiasis identified by one of the following: collected duodenal bile samples after stimulated gallbladder contraction,⁴⁰⁻⁴³ bile obtained from the bile duct at ERCP, gallbladder sludge on US (found in 33%-48% of patients),^{16,44} or in the gallbladder at surgery.¹¹ For these patients, cholecystectomy or administration of ursodeoxycholic acid considerably reduces the pancreatitis recurrence rate compared with those not undergoing these interventions.^{15,16} (5) EUS may identify gallbladder sludge in up to 75% of patients with acute unexplained pancreatitis.⁴⁵⁻⁴⁹ (6) Biliary sphincterotomy or cholecystectomy reduces the relapse rate of RIP for patients with suspected biliary pancreatitis but no stones on US.^{28,50} Although these data suggest that biliary sludge and microlithiasis should be excluded in all patients with RIP and an intact gallbladder, a more limited data set also suggests its importance for those with a single idiopathic attack.^{46,47}

The best diagnostic method for biliary sludge and microlithiasis, such as duodenal sampling with microscopic examination for biliary crystals, intraductal bile aspiration

at ERCP, repeat US, EUS, or some combination, remains undefined; additional comparative trials are needed. Two trials^{42,51} suggested the superiority of EUS for sludge over duodenal aspiration for biliary microscopic examination for biliary crystals, whereas in another study⁴⁷ microlithiasis could be found in 46% of patients by duodenal bile aspirate after a negative EUS. Last, the optimal laboratory techniques for performing microscopic examination for biliary crystal analysis, the importance of cholecystokinin stimulation before duodenal or common bile duct sampling for those with a gallbladder in situ, the quantity of bile to be obtained, and the value of bile duct bile compared with duodenal bile remain to be better defined.

YIELD OF ENDOSCOPY FOR A SINGLE ATTACK OF UNEXPLAINED PANCREATITIS

ERCP

As noted above, current practice has traditionally been to more aggressively evaluate patients after multiple attacks rather than after the first idiopathic attack, presumably because of the inherent complications of ERCP.^{23,24} However, to our knowledge, there have been only 2 studies, only one of which was prospective, whose primary focus was evaluating such a cohort, and in only one was follow-up reported. In the earliest study, Ballinger et al⁵² retrospectively identified 31 patients with acute idiopathic pancreatitis from 1989 to 1994. Some of these patients were culled from an ERCP database. The evaluation paralleled those outlined above, but, in addition, 20 patients (65%) had undergone nondiagnostic ERCP at the discretion of the physician; sphincterotomy, microscopic examination for biliary crystals, and SOM were not performed. At a median follow-up of 36 months, only 1 patient had a further episode of acute pancreatitis, again idiopathic, 9 months later. Thus, this widely quoted series, often cited to argue for a conservative approach, in fact used invasive testing with ERCP (without manometry) at the time of the index evaluation. Interestingly, however, a very low recurrence rate was shown with such an approach.

In contrast, Maes et al¹³ prospectively evaluated all cases of acute pancreatitis at a single center over a 1-year period (1994-1995) with routine history, metabolic evaluation, infectious serologic screen (not further defined), US, and CT. If no cause was found, CT and screen for infectious diseases were repeated. ERCP with common bile duct sampling for biliary crystals or EUS were also performed, whereas SOM was not performed. Three of 19 patients (16%) had had previous attacks of idiopathic pancreatitis. Before ERCP, pancreatitis was labeled as idiopathic in 16%, but after ERCP an additional 11 patients had a diagnosis made, including biliary tract disease (4) and malignancy (3); thus, with the addition of ERCP, the true idiopathic pancreatitis rate fell from 16% to 7%. No complications from ERCP were reported, but long-term

follow-up was not performed. This study suggests that incorporating ERCP with bile sampling for sludge into the evaluation after a single attack may reduce the number of patients with idiopathic disease. The results of this study are hampered by the inclusion of patients with RIP, by the fact that the role of EUS before ERCP was neither well defined nor was EUS performed in all patients, and by the fact that follow-up was not provided.

Several studies report on ERCP findings in patients after a single unexplained attack.^{10,53-57} However, in these reports patients were often poorly characterized, the evaluation preceding ERCP was incomplete or not reported, and many of the studies were before the era of spiral CT and application of SOM.

EUS

There are growing data on the utility of EUS for patients with a single unexplained attack. Tandon and Topazian⁴⁸ evaluated 14 patients with a single episode of idiopathic pancreatitis and reserved ERCP on the basis of the results of EUS. Overall, a diagnosis was made by EUS in 50% (3 alcoholic chronic pancreatitis, 3 microlithiasis, 1 pancreas divisum), and after a mean follow-up of 16 months, symptoms recurred in 5 patients but the diagnosis changed in only one. Yusoff et al⁴⁷ prospectively evaluated 201 patients after a single unexplained attack. EUS made a presumptive diagnosis in 31%; chronic pancreatitis and sludge were most common in those with a gallbladder, whereas chronic pancreatitis and pancreas divisum were most prevalent after cholecystectomy.

Unfortunately, in most series, patients with a single attack are compiled with those with RIP. In a study by Liu et al⁵⁸ of 89 patients with an attack of acute pancreatitis, 72% had stones on conventional radiologic studies. In this series, 13 (15%) patients were evaluated for a single attack. Of the 18 patients classified as having idiopathic pancreatitis after a negative results on US scan, all but one patient had either gallbladder sludge (14 patients) or bile duct stones (3 patients) identified by EUS, which were subsequently confirmed by either ERCP or cholecystectomy. Follow-up showed no additional attacks. Norton and Alderson⁴⁶ evaluated 44 patients with idiopathic pancreatitis by EUS, 10 (23%) of whom had had a prior episode. Gallbladder sludge or stones were the most common cause, found in 22 patients (50%). There were 2 false-positive results and one failed examination because of intolerability of intubation.

In aggregate, these studies suggest a high yield of EUS in patients with a single episode of unexplained pancreatitis. Biliary sludge and chronic pancreatitis are the most frequent diagnoses made by EUS. Patients who have had prior cholecystectomy and who have an attack of unexplained pancreatitis are at low risk for bile duct stones; these patients represent a minority of the patients studied to date. Further study is required for confirmation of

TABLE 2. Studies evaluating ERCP in recurrent idiopathic pancreatitis

Reference, y	No.	Diagnosis (%)			Overall yield (%)	Follow-up (mean [range])
		SOD	Divisum	CBDS		
62, 1973	25	ND	0	8	60	19 mo (3-42)
63, 1981	35	ND	23	3	46	— (6-36 y)
10, 1982	11	ND	0	9	50	19 mo (3-56)
54, 1984*	73	ND	7	11	32	22 mo (10-48)
55, 1986	101	ND	1	18	64	ND
59, 1989	116	15	9	0	38	ND
60, 2000	40	35†	7.5	27.5	70	>12 (27-73)
53, 2002	66	30	19	‡	80	ND
61, 2002	126	33	7	5	79	29.6 (18-33)

SOD, Sphincter of Oddi dysfunction; CBDS, common bile duct stone; ND, not done.

*Not all patients had both endoscopic retrograde cholangiography and endoscopic retrograde pancreatography.

†Sphincter of Oddi dysfunction types 1, 2.

‡Overall "biliary" cause including cholelithiasis, choledocholithiasis, and biliary crystals in ~18%; raw data not provided.

these observations, but the data do support the potential utility of EUS examination in this setting.

YIELD OF ENDOSCOPIC EVALUATION OF RECURRENT IDIOPATHIC PANCREATITIS

ERCP

Studies performed early on after the birth of ERCP suggested a potential role for pancreatography in patients with idiopathic pancreatitis,⁵⁶ and a number of centers worldwide have now reported their experience with ERCP in RIP^{10,53-55,59-64} (Table 2). Many of the initial studies are flawed by the inclusion of patients with only a single attack^{11,54} or inclusion of those with gallbladder stones⁵⁵ and outdated by the technologic infancy of US and CT and by failure of cannulation of the biliary and pancreatic ducts, which in some studies was as high as 35%.⁵⁴ Furthermore, only recently has the importance of sphincter hypertension as a cause of pancreatitis been shown at the time of ERCP by SOM.^{59,65-68} In one of the first studies to report SOM in recurrent pancreatitis, Toouli et al⁶⁵ examined 28 patients with RIP and diagnosed SOD, defined as an elevation of basal pressure, in 57%. Venu et al⁵⁹ retrospectively evaluated 116 patients with at least 2 episodes of RIP and routinely performed pancreatic SOM. The overall diagnostic yield of ERCP was low (38%), but sphincter of Oddi dysfunction was found to be the most common cause (15%), followed by pancreas divisum (9%); 7% of patients had cholelithiasis and ampullary lesions were found in 6%. Microscopic examination for biliary crystals was not performed.

More recent studies have demonstrated higher diagnostic yields of ERCP. Coyle et al⁵³ retrospectively evaluated 90 patients with idiopathic pancreatitis, 24 (27%) of whom were studied after only a single attack. Approximately 50% of patients had a prior cholecystectomy, and 38 patients (42%) had previously undergone diagnostic ERCP. With SOM and selective use of microscopic examination for biliary crystals obtained directly from the bile duct or duodenum after cholecystokinin administration and EUS in 62%, the most commonly identified causes were sphincter of Oddi dysfunction (31%) and pancreas divisum (20%); as with other studies, stone disease was uncommon. Kaw and Broadmerkel⁶¹ prospectively evaluated 126 patients with a minimum of 2 episodes of RIP. ERCP was performed in all patients, including SOM followed by direct aspiration of bile for microscopic analysis. In this study, important differences in final diagnosis were shown on the basis of prior cholecystectomy. Overall, sphincter of Oddi dysfunction was demonstrated in 39% and was the most frequent diagnosis in postcholecystectomy patients (47%). No postcholecystectomy patients had crystals identified or bile duct stones; these results parallel those of Yusoff et al.⁴⁷ For the 54 patients with gallbladder in situ, biliary sludge was identified in 50% and was found in conjunction with papillary stenosis in 6 (11%) and sphincter of Oddi dysfunction in 9 (17%), with an overall cause identified in 79%. Long-term follow-up was not reported for the patients for whom no cause was found. Other studies using SOM have likewise documented sphincter of Oddi dysfunction.⁶⁶⁻⁶⁸ Raddawi et al⁶⁶ reported sphincter of Oddi dysfunction in 29% of patients with unexplained pancreatitis. In a large

retrospective study of all patients undergoing SOM, Eversman et al⁶⁷ reported a 72% frequency of sphincter of Oddi dysfunction in patients with RIP. This high frequency could be related to the fact that patients with pancreas divisum, bile duct stones, or pancreatic malignancy were excluded.

Excluding bile duct stones is a common management theme, especially in a community setting. As noted above, overall, common bile duct stones are an infrequent cause of RIP. The yield for these stones may be higher in those with a biochemical liver profile suggesting stones.¹¹ Elevation of liver test results in biliary pancreatitis has also been documented with biliary sludge⁶⁹; however, because no filling defect may be observed radiographically at cholangiography, ERCP may be falsely interpreted as normal.³⁸

Testoni et al⁷⁰ examined 40 consecutive patients with RIP and an intact gallbladder, performing diagnostic ERCP followed by biliary or minor papilla sphincterotomy depending on the clinical and endoscopic findings. If no abnormalities were found, the patients received long-term ursodeoxycholic acid therapy. If pancreatitis recurred, main pancreatic duct stenting and pancreatic sphincterotomy were performed. An underlying cause was found in 70%, including sphincter of Oddi dysfunction type II (35%), biliary sludge (27.5%), and pancreas divisum (7.5%). By use of this protocol, with follow-up in all patients exceeding 27 months, 11 patients (27.5%) had recurrent pancreatitis. Ultimately, only 3 patients failed after therapeutic ERCP or bile acid therapy. This study shows that sphincter ablation, which should treat sphincter of Oddi dysfunction, and medical therapy for biliary sludge are effective and thus indirectly suggests these two entities as important causes of RIP.

In summary, ERCP plays an important role in the management of RIP. In this setting, the reported diagnostic yield of ERCP varies from 38% to 79% and the overall yield is influenced by (1) the presence or absence of prior cholecystectomy and (2) referral bias because studies that include patients who previously underwent ERCP would thus decrease the number of patients with biliary stones. Sphincter of Oddi dysfunction and pancreas divisum are the most frequent diagnoses at ERCP, and the diagnostic yield may be further increased by common bile duct aspiration of bile for microscopic examination for crystals for those patients with a gallbladder. Common bile duct stones alone are an infrequent cause of pancreatitis in this setting. Whether EUS with or without duodenal bile sampling would have mitigated the need for ERCP in those studies using common bile duct sampling for crystals is unknown. The data do not support the use of diagnostic ERCP in the absence of the ability to perform SOM, treat pancreas divisum, or evaluate for biliary sludge either with common bile duct sampling for bile or duodenal aspiration after cholecystokinin administration. Patients after cholecystectomy with RIP warrant ERCP provided that SOM can be simultaneously performed.

TABLE 3. Studies evaluating EUS in recurrent idiopathic pancreatitis

Reference, y	No.	Diagnosis				Overall yield (%)
		GB sludge	Stone	CBD stone	CP	
45, 2000	168	7	31	6	7	78
46, 2000	44	45	0	14	9	73
58, 2000	18	—	78	17*	0	78
48, 2001	17	12	0	0	65	88
47, 2004	169	8	4†	†	41	68

GB, Gallbladder; CBD, common bile duct; CP, chronic pancreatitis.

*All had concomitant gallbladder sludge or stones.

†Provided as stones in gallbladder or common bile duct.

EUS

Given the accuracy of EUS for the identification of cholecystolithiasis and gallbladder sludge, common bile duct stones,⁷¹ and the ability to examine the pancreas for tumors, chronic pancreatitis, ductal dilation (which suggests obstruction), and ampullary lesions, EUS may represent an ideal minimally invasive tool for evaluation of unexplained pancreatitis.

In the earliest report, Frossard et al⁴⁵ studied 168 patients with idiopathic acute pancreatitis with EUS. It is unclear in this series how many patients underwent EUS after the initial unexplained attack or after multiple attacks. All patients had one or more nondiagnostic US examinations. Overall, the diagnostic yield of EUS was high (77%). Biliary tract disease was the most common diagnosis, with 50% having small gallbladder stones or sludge and an additional 12% having gallbladder sludge alone. Similar to the ERCP studies (Table 3), the prevalence of bile duct stones was low (10%). A subsequent series by Tandon and Topazian⁴⁸ confirmed the high yield for occult gallbladder disease but also demonstrated the potential importance of chronic pancreatitis. In this series,⁴⁸ ERCP was only performed for recurrent attacks. In another study using follow-up, Liu et al⁵⁸ also confirmed the diagnostic importance of EUS in patients with idiopathic pancreatitis. In this series of 89 consecutive patients, 15% of whom had multiple attacks, US, CT, and ERCP without SOM were performed on all patients with confirmed or suspected biliary pancreatitis. Twenty percent of patients had a negative results on US scan and, of these 18 patients, small gallbladder stones were found by EUS in 14 (72%), with 3 patients having small bile duct stones, all of which were confirmed by ERCP and sphincterotomy or cholecystectomy. At a median follow-up of 22 months, no recurrences were observed. As noted above, in this study the results were not specifically distinguished between those with a single or multiple unexplained attacks.

In the largest study published to date, Yusoff et al⁴⁷ evaluated 169 patients with RIP by EUS and, in a small subset, duodenal bile sampling for microscopic analysis for biliary crystal analysis. The overall yield of EUS was 68% for patients with RIP. Those patients with gallbladder in situ had sludge (12%), stones (5%), or pancreas divisum (6%) found most commonly, whereas chronic pancreatitis (39%) and pancreas divisum (10%) were most frequent after cholecystectomy. In this study, 5 EUS criteria were required for the diagnosis of chronic pancreatitis in contrast to 3 criteria in prior studies.^{45,48} ERCP was not performed to confirm the findings of pancreas divisum or chronic pancreatitis or to evaluate for sphincter of Oddi dysfunction. The importance of excluding microlithiasis by microscopic examination of duodenal bile for crystals after normal results from EUS warrants further study, given that Yusoff et al⁴⁷ found 46% of such patients to have crystals by duodenal aspiration. In all of the above studies, EUS was well tolerated and without significant complication.

In summary, the diagnostic yield of EUS in RIP varies from 32% to 88%. The highest diagnostic yield, primarily for biliary sludge, was observed for those patients with gallbladder in situ. Chronic pancreatitis, identified by EUS, is emerging as a potentially important cause of RIP, although the diagnosis of chronic pancreatitis by EUS may lack specificity if secretin stimulation testing is used as the gold standard.⁷² Preliminary findings suggest that EUS may fail to identify biliary sludge, but duodenal sampling for bile with microscopic examination for biliary crystals,⁴⁷ in combination with EUS and, if results are negative, bile sampling may be the ideal approach.⁴² Preliminary observations⁴⁸ suggest that EUS may decrease the need for ERCP through the identification of microlithiasis and chronic pancreatitis.

RECOMMENDATIONS FOR EVALUATION

The majority of patients with acute pancreatitis will have a diagnosis established with use of routine investigations. Recent studies with EUS used after conventional evaluation underscore that the true prevalence of idiopathic pancreatitis depends on the extensiveness of the evaluation. Long-term follow-up has not been commonly performed in most studies and, thus, the true importance of some causes, on the basis of the recurrence of pancreatitis, remains less well defined.

On the basis of the prevalence of causes of pancreatitis and the diagnostic yield of imaging studies, the following evaluation can be recommended at the time of the index attack: careful history to exclude alcohol use, hereditary pancreatitis, drug-induced causes, possible infectious causes, recent abdominal trauma, and systemic diseases; US to exclude gallstone disease or sludge; and metabolic evaluation for hypercalcemia and hypertriglyceridemia.

Although not recommended for patients with mild pancreatitis by some,⁷³ at most centers abdominal CT is almost uniformly performed as the first imaging study on patients with clinical pancreatitis, and CT will not only confirm the diagnosis of acute pancreatitis but provide prognostic information by assessing severity.⁷⁴ Furthermore, CT may be diagnostically relevant by establishing the diagnosis of chronic pancreatitis, demonstrating gallbladder calculi, thus limiting the need for subsequent US if not already performed, and revealing a pancreatic neoplasm.⁷⁵ A rapid bolus contrast technique should be used to best highlight pancreatic necrosis, especially in those with predicted severe pancreatitis and small neoplasms.⁷⁴ Abdominal CT should be considered for patients with idiopathic pancreatitis at the index episode if the above evaluation, including US, fails to establish a diagnosis. Whether a workup for biliary sludge and microlithiasis for those with a gallbladder in situ is similarly warranted has not been well studied, but the data do suggest this to be an important cause.^{46,47} Some favor ERCP at the time of the initial idiopathic attack for those more than 40 years old to exclude malignancy,¹² but the diagnostic role of spiral CT with contrast⁷⁵ or EUS, which are accurate and have less morbidity, have not been appropriately compared with ERCP in this setting.

Approximately 20% to 50% of patients with acute pancreatitis will have a recurrence.^{7,9,76,77} When a patient with a history of a single attack of idiopathic pancreatitis has a recurrent attack, the data support the utility of an invasive evaluation because a diagnosis can be established in 38% to 76%.^{14,53,59-61} Depending on the elapsed time since the index attack, the above recommended evaluation should be again performed, and US should be repeated because multiple longitudinal examinations may be required to identify small gallbladder stones or sludge.^{40,78} Observations on the sensitivity of EUS for sludge suggest it may be ideal after a negative US scan and it could screen for those who may benefit most from ERCP by identifying common bile duct stones. Also, excluding biliary sludge by EUS coupled with duodenal bile sampling for microscopic examination for crystals should be considered before ERCP for those with a gallbladder in situ. Whether aspiration of duodenal contents by routine endoscopy for bile with microscopic examination should be done before EUS is uncertain. The value of microscopic examination for bile crystals obtained by duodenal sampling in patients after a negative EUS⁴⁷ requires further study but may be considered pending such data.

ERCP with SOM is recommended in the evaluation of RIP, and the data support its use in this setting. In clinical practice, however, ERCP without SOM is commonly performed presumptively to exclude common bile duct stones, yet their prevalence is low in RIP (<10%) and much less frequent than sphincter of Oddi dysfunction. Because of the substantial risk of pancreatitis after ERCP in patients with sphincter of Oddi dysfunction,²⁸ such

a practice is discouraged unless clinical, laboratory,^{11,79-81} and radiologic features strongly suggest choledocholithiasis as a likely cause. Therefore, in this setting, ERCP should be undertaken but only if there is the ability to perform SOM and endoscopically treat pancreas divisum. Although not studied, magnetic resonance cholangiopancreatography could be beneficial in such a circumstance to exclude bile duct stones or evaluate for pancreas divisum. Some have recommended empiric cholecystectomy,⁸² although no prospective studies have examined such an approach. The relative importance of autoimmune pancreatitis as a cause of RIP remains undefined.⁸³

Older patients warrant evaluation for pancreatic neoplasia, although the age at which to evaluate is not known but is suggested to be >40 years¹²; however, in most series the mean age of patients with pancreatic cancer presenting with pancreatitis is closer to 60 years.^{84,85} Although ERCP will typically show ductal stricture(s) in patients with cancer, tumors may also be found less invasively with contrast-enhanced CT.^{57,75,86} EUS may be useful for diagnosis with fine-needle aspiration and staging when the CT has negative results, even with small lesions.^{87,88} The additional value for the diagnosis of pancreatic cancer of ERCP after negative results from contrast-enhanced spiral CT and EUS has not been studied in this setting but likely is very low. The ability to visualize small lesions could, however, be hampered by significant peripancreatic inflammatory reactions, and thus close follow-up with repeat CT with contrast will be required.

For patients with idiopathic acute pancreatitis, selective use of genetic testing is appropriate. For the patient with RIP, especially in the setting of an appropriate family history, genetic testing for cationic trypsinogen gene (*PRSS1*) has been recommended and may be warranted before any endoscopic evaluation is done.⁸⁹ Other genetic abnormalities associated with idiopathic pancreatitis include the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) and mutations of the trypsin inhibitor (*SPINK1*) gene. The role of genetic testing for these mutations is less clear and it is controversial⁹⁰; thus the reader is referred to a recent review on this topic.⁹¹

AREAS FOR FUTURE INVESTIGATION

The data presented above clearly demonstrate the importance of biliary sludge in the genesis of idiopathic pancreatitis. Although duodenal sampling for crystal analysis and EUS have shown promise, additional studies are warranted to determine whether initial EUS and, if results are negative, microscopic examination of bile for crystals is the appropriate diagnostic strategy. Additional studies are also warranted to better determine the ideal method for microscopic examination of bile for crystals, particularly in a community setting. Studies evaluating the role of magnetic resonance cholangiopancreatography as a

noninvasive strategy in RIP to exclude bile duct stones in low-risk patients and to evaluate for pancreas divisum would be useful. Given the lingering concern regarding the importance of spincter of Oddi dysfunction and pancreas divisum as causes of RIP,⁹² long-term follow-up studies after endoscopic therapy would add further support to the importance of these diagnoses and thus endoscopic treatments. Given the potential diagnostic utility of EUS, prospective studies evaluating an EUS-based strategy for both a single attack and for those with RIP should be performed. Further studies will also better define the role of genetic testing.

DISCLOSURE

The authors have no disclosures to report.

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