Emerging Role of Endoscopic Ultrasound in the Diagnostic Evaluation of Idiopathic Pancreatitis

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Abstract: *Background:* "Idiopathic pancreatitis" is diagnosed when clinical, laboratory and conventional radiologic methods do not provide a clear etiology for the episode. Given its associated morbidity and mortality, it is important to determine the cause of pancreatitis to provide early treatment and prevent recurrence. *Methods:* The aim of this systematic review was to evaluate the utility of endoscopic ultrasound (EUS) in determining an etiology in patients classified as having idiopathic pancreatitis and to assess how EUS performed compared with other modalities. A PubMed search for relevant articles (January 2000–November 2014) was performed using the search terms "(pancreatitis or idiopathic pancreatitis or unexplained pancreatitis) and (EUS or endoscopic ultrasound)." *Results:* The search yielded a total of 963 articles, and 13 studies were included in the final review. In some studies, the yield of EUS was higher than magnetic resonance cholangiopancreatography in idiopathic pancreatitis. EUS more accurately detected biliary stones, whereas magnetic resonance cholangiopancreatography more often identified pancreatic duct abnormalities. The yield of EUS was lower in patients postcholecystectomy but was not influenced by gender, severity of pancreatitis, or recurrent disease. The most frequent diagnoses by EUS for those with idiopathic pancreatitis were biliary tract disease (41%). Overall, EUS identified additional diagnostic information in 61% of patients with idiopathic pancreatitis. *Conclusions:* Given the high incidence of microlithiasis and/or biliary sludge as a cause of idiopathic pancreatitis as well as the safety and high accuracy, EUS should be considered 1st for evaluation of idiopathic pancreatitis if conventional cross-sectional radiography fails to reveal a cause.

Key Indexing Terms: Endoscopic; Ultrasound; Idiopathic pancreatitis; Pancreatitis; Endoscopic ultrasonography. **[Am J Med Sci 2015;350 (3):229–234.]**

Alcohol and gallstone disease are responsible for most cases of acute pancreatitis. Patients are classified as having idiopathic pancreatitis after clinical (history), laboratory studies (triglyceride and calcium level) and conventional radiological methods (transabdominal ultrasound and computed tomography [CT]) do not reveal an etiology of the pancreatitis. Idiopathic pancreatitis is diagnosed in 10% to 30%[1–4] of acute pancreatitis episodes. Recent studies have suggested that microlithiasis is a cause of unexplained pancreatitis in up to 75% of patients with an intact gallbladder.[5] Microlithiasis, defined as a stone less than 3 mm in diameter,[1] may be undetected by transabdominal ultrasound. Sphincter of Oddi dysfunction (SOD) can be identified in up to 30% of patients with idiopathic pancreatitis.[6] Given the associated morbidity and mortality, it is important to determine the cause of pancreatitis to provide therapy early and prevent further recurrence. Pancreatitis with or without a known cause may recur in 30% of patients with a bout of pancreatitis, and up to 30% of these cases remain undiagnosed.[3]

Endoscopic ultrasonography (EUS) has a high diagnostic accuracy for biliary pathology including cholelithiasis, biliary sludge and choledocholithiasis,[7] pancreatic disease and pancreatic divisum[8] but lacks in diagnosing SOD.[3] Magnetic resonance cholangiopancreatography (MRCP) with secretin administration is a promising and suitable alternative diagnostic modality but may not be widely available.[9] Endoscopic retrograde cholangiopancreatography (ERCP) can be used in combination with bile crystal analysis with or without sphincter of Oddi manometry and such an approach has led to identifying the underlying etiology in 30% to 60% of cases, but ERCP carries a risk of pancreatitis.[4]

To better understand the diagnostic role of EUS in identifying an etiology of idiopathic pancreatitis, the authors reviewed studies that included patients with idiopathic pancreatitis and used EUS with or without a comparator such as MRCP, ERCP, and/or bile crystal analysis to establish a cause of the pancreatitis. Second, we sought to identify clinical factors (previous cholecystectomy, single versus recurrent pancreatitis) that may affect the diagnostic yield of EUS.

METHODS

Review Protocol and Study Eligibility

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist[10] served as a guideline and was used by 2 authors (I.S. and C.W.) for the execution of this systematic review.

Eligibility Criteria

Definitions

Idiopathic pancreatitis was defined as acute pancreatitis after clinical, laboratory, and conventional radiological methods failed to reveal an etiology.

Identification of Relevant Studies

A systematic search was conducted on PubMed to identify articles published between January 1, 2000, and November 1, 2014. The following search terms were used: ("pancreatitis" [MESH] OR "idiopathic pancreatitis" [MESH] OR "unexplained pancreatitis" [All Fields]) AND ("EUS" [MESH] OR "endoscopic ultrasound" [All Fields]). Two authors (I.S. and C.W.) independently searched and abstracted the data according to standard methods.[11] Additionally, the references in each of the selected articles were searched to identify any missed references.

Study Selection

Eligible studies could be either retrospective or prospective and had to have enrolled at least 5 patients with

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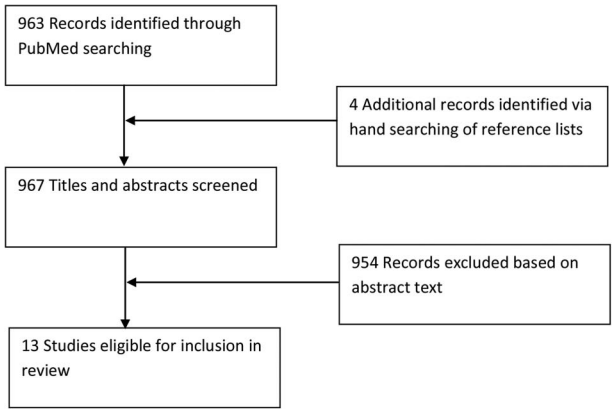

FIGURE 1. Flowchart of the search strategy and selection of studies eligible for inclusion in review.

idiopathic pancreatitis who underwent EUS to further investigate the etiology of the acute or recurrent attack when CT, ERCP, MRCP, ultrasound, and/or repeated ultrasound had failed to reveal a cause of pancreatitis.

Data Extraction and Analysis

Two investigators (I.S. and C.W.) performed the searches and reviewed the articles for appropriateness of inclusion into the study. The data extracted from the studies included authors, year of publication, number of patients included in the study, imaging before EUS, mean age, gender, follow-up duration in months, and EUS-quantified determined causes. Total number of patients was defined as those with idiopathic pancreatitis that were included in the study of which a defined number had to undergo EUS for further investigation. For each study, we calculated the overall yield of EUS in attaining a diagnosis for patients with idiopathic pancreatitis.

RESULTS

A total of 963 records were initially identified in the literature search (Figure 1). Four additional records were identified by means of hand searching of reference lists. All 967 records were screened based on title and abstract. After careful review and using the aforementioned inclusion and exclusion criteria, 13 studies were included in the final review.[1,4,7,8,12–20] Table 1 outlines studies evaluating EUS in idiopathic pancreatitis and Table 2 shows the EUS-identified causes of the pancreatitis. Representative images are demonstrated in Figures 2–6. The most frequent diagnosis after EUS in patients with idiopathic pancreatitis was biliary tract disease (biliary stones, microlithiasis and sludge) (41.1% ± 23.7%). EUS detected pancreatic disease (chronic pancreatitis, pancreatic divisum, pancreatic mass, pancreatic cancer, pancreatic parenchymal change and/or pancreatic ductal change) in 22.1% ± 26.6% of patients with idiopathic pancreatitis. Overall, EUS identified additional diagnostic information in 61.0% ± 18.0% of patients with idiopathic pancreatitis, with 41% having biliary tract disease. In one series, EUS demonstrated a high yield for occult gallbladder disease (6%) as well as the importance of chronic pancreatitis (45%).[4] Refer to Figure 2 for a proposed approach to the evaluation of idiopathic pancreatitis.

Single Versus Multiple Attacks

Overall, the yield of EUS was not influenced by recurrent disease. In the study by Yusoff et al,[8] chronic pancreatitis was the most commonly identified abnormality found (16.4%–42.0%) and was approximately twice as frequent in patients with recurrent episodes versus a single episode of idiopathic pancreatitis (no-cholecystectomy: 42.0% versus 21.6%, $P = 0.0008$; post-cholecystectomy: 38.6% versus 16.4%, $P = 0.008$). In one study, biliary pancreatitis (cholelithiasis, choledocholithiasis and microlithiasis) was the most common etiology of recurrent acute pancreatitis (37%).[21] In another study, the probability of harboring occult gallstones was also significantly associated with age, recurrent pancreatitis and altered liver function tests results during an index episode.[22] In contrast, in one study, the yield of positive EUS findings did not differ between single or recurrent idiopathic pancreatitis.[8] In another study, the yield of EUS was not influenced by sex, severity of pancreatitis or recurrent disease.[13]

TABLE 1. Studies evaluating EUS in idiopathic pancreatitis

Study	No. of patients	Year	Overall yield of EUS, %	Follow-up, month	Imaging before EUS	Mean age, year	Gender (female), %
Liu et al[12]	18	2000	78	22 (median)	CT, ERCP, US, repeated US	*	*
Ardengh et al[1]	36	2010	75	*	CT, US	47.1	58.4
Vila et al[13]	44	2010	79	29 (mean)	CT, US	61.5	29.5
Yusoff et al[8]	370	2004	59	*	CT, US	53.4	55.4
Tandon and Topazian[4]	31	2001	68	16 (mean)	CT, US, MRI, MRCP, EUS	48.8	61.2
Frossard et al[14]	168	2000	78	25 (mean)	US	50.0	39.0
Norton and Alderson[15]	44	2000	73	3–28 (range)	US	53.5 (median)	54.5
Thevenot et al[16]	41	2013	29	22 (mean)	CT, US	55.3	37.5
Zhang et al[17]	33	2011	42	*	CT, US, MRCP	46.5	60.6
Kim et al[18]	31	2011	42	36 (mean)	US, CT, MRCP, ERCP, SOM	51.3 (median)	64.5
Ortega et al[7]	49	2011	51	16 (mean)	CT, US	58.0	51.0
Morris-Stiff et al[19]	42	2009	41	74 (median)	CT, US, ERCP, MRCP	53.0	40.5
Mariani et al[20]	44	2009	80	*	US, CT	48.9	54.5

* Follow up not provided.

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; SOM, sphincter of oddi manometry.

TABLE 2. EUS identified causes of idiopathic pancreatitis

EUS findings	Study												
	Liu et al[12]	Ardengh et al[1]	Vila et al[13]	Yusoff et al[8]	Tandon and Topazian[4]	Frossard et al[14]	Norton and Alderson[15]	Thevenot et al[16]	Zhang et al[17]	Kim et al[18]	Ortega et al[7]	Morris-Stiff et al[19]	Mariani et al[20]
Cholelithiasis, choledocholithiasis, microlithiasis, biliary sludge	14	29	25	50	5	103	26	6	11	5	15	16	8
Chronic pancreatitis			14	109	14	16	4	3		3	9	1	
Pancreatic divisum			3	27	2		1				1		6
Pancreatic mass			1	3			1						
Pancreatic cancer					1	4							
IPMT/cystic neoplasm			1	10		4		2			1		1
Other		4	2	18		4	2		1	2	1		33

IPMT, intrapancreatic mucinous neoplasm.

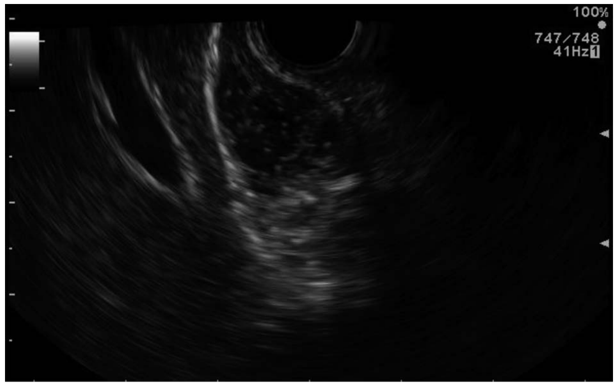

FIGURE 2. Linear echoendoscopic image of the gallbladder showing the classic "starry-sky" appearance of floating hyperechoic crystals.

Gallbladder Present Versus Postcholecystectomy

Based on the studies reviewed, it seems that patients with gallbladder and idiopathic pancreatitis are more likely to have a diagnosis on EUS than those without gallbladder and idiopathic pancreatitis. Importantly, for patients with recurrent idiopathic pancreatitis, prophylactic cholecystectomy did not affect the recurrence rate.[23] Patients younger than 65 years (age >65 or <65 years: 73.9% versus 95.2%; $P = 0.097$) and patients with gallbladder *in situ* (cholecystectomy versus non-cholecystectomy: 63.6% versus 90.9%; $P = 0.054$) showed a tendency to have positive EUS findings.[13] Chronic pancreatitis was the only abnormality in 30.9% of patients in the no-cholecystectomy group versus 26.6% of those in the post-cholecystectomy group ($P = 0.24$).[8] EUS's yield was lower in patients postcholecystectomy[13] (11% versus 60%, $P = 0.008$).[7]

MCRP Versus EUS

The most frequent diagnoses for EUS were cholelithiasis and biliary sludge (24%) and for MRCP was pancreatic divisum (8%).[10] EUS more accurately detected biliary stones, whereas MRCP identified pancreatic duct abnormalities such as intraductal papillary mucinous neoplasm (IPMN) of the pancreas or chronic pancreatitis.[16] EUS and/or MRCP led to an etiology of pancreatitis in 50% of patients.[16] The diagnostic yield of EUS was higher than for MRCP (29% versus 10.5%) ($P = 0.09$).[16] The combination of these 2 procedures and the subsequent

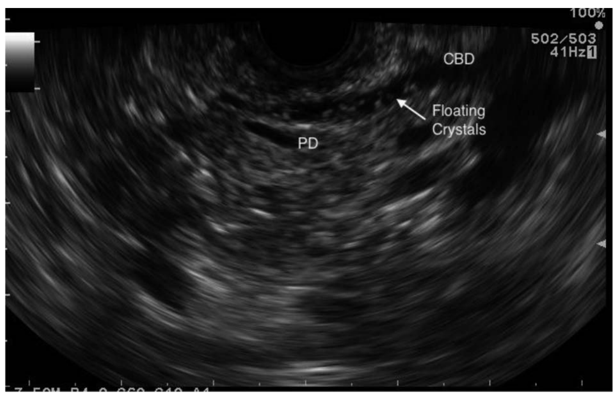

FIGURE 3. Linear echoendoscopic elongated view of the undilated bile and pancreatic ducts in the head of pancreas. The bile duct showed mobile hyperechoic microcrystals.

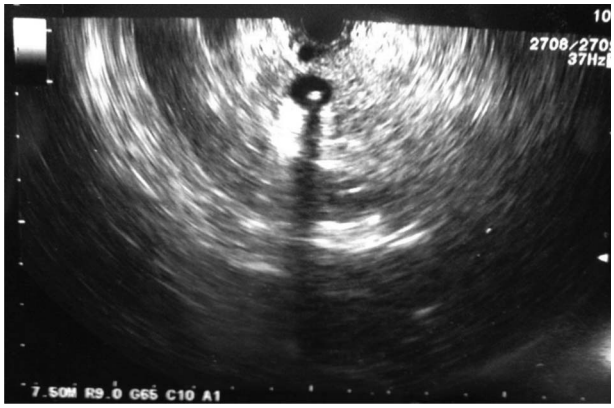

FIGURE 4. Linear echoendoscopic image of a 3.7-mm hyperechoic bile duct calculus casting an acoustic shadow.

follow-up reduced the rate of idiopathic pancreatitis by 66%.[16] EUS and MRCP with secretin were superior to ERCP for detecting pancreatic ductal abnormalities.[20] EUS and MRCP with secretin combined could have explained the cause for the recurrence of pancreatitis in 63.6% of patients.[20] The yield of EUS was significantly higher compared with MRCP in acute idiopathic pancreatitis (51% versus 20%, $P = 0.001$).[7]

Follow-up

Follow-up duration and follow-up findings varied greatly between studies. Although EUS had a yield of 61% in the studies reviewed, an alternate diagnosis on follow-up included but was not limited to pancreas divisum, SOD, pancreatic duct stone and IPMN. In one study, during a follow-up period of 16 months, EUS diagnosis was unchanged in 87% of patients.[4] ERCP changed the diagnosis in 4 of the 12 (33.3%) patients in whom it was performed, detecting one additional case of pancreas divisum, one previously undetected pancreatic duct stone, one IPMN and one case of SOD.[4] In another study,[15] 2 false positives and one failed examination due to intolerability of intubation were seen. In another study, no recurrences were

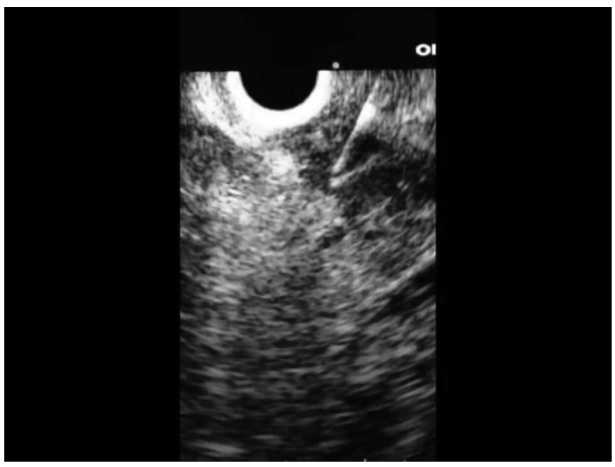

FIGURE 5. Linear EUS view of a 5 × 5-mm hypoechoic mass lesion arising from the dorsal pancreatic duct in a patient with pancreas divisum. A fine needle aspiration was performed that proved to be positive for adenocarcinoma confirmed at surgery. Computed tomography in this patient showed a dilated pancreatic duct with no obvious mass lesion.

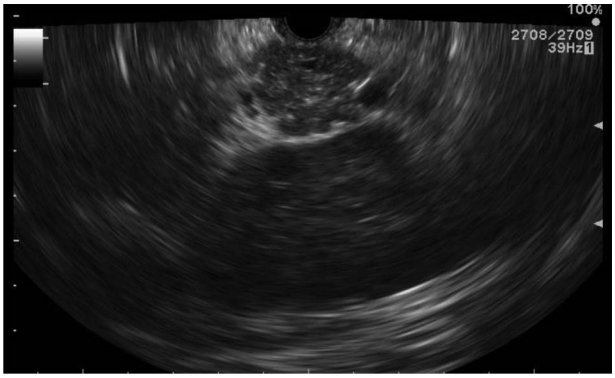

FIGURE 6. Linear EUS view of the pancreatic parenchyma showing lobulations, hyperechoic foci, with a hyperechoic marginated pancreatic duct suggestive of chronic non-calcific pancreatitis.

observed.[12] The etiological diagnosis was changed in 2 patients lowering the diagnostic yield of EUS to 79%.[13] In 13 (8%) patients, the results of EUS and the final diagnosis disagreed after follow-up[14]; 5 of these patients, who had a normal EUS examination, had biliary stones demonstrated at surgery or bile crystal analysis; 1 patient who was diagnosed with a biliary stone had a choledochal cyst at the time of surgery; and 1 patient diagnosed with pancreatic cancer had focal chronic pancreatitis at surgery.[14] Finally, EUS misdiagnosed 5 patients as having biliary stones and 1 patient as having pancreatic intraductal tumor in whom the final diagnosis was idiopathic pancreatitis (diagnosed by surgery [5 patients] or ERCP[1]).[14] Three patients (7.3%) had acute pancreatitis recurrence.[16] Recurrent pancreatitis did not develop in 7 of these 8 patients (87.5%) with bile duct stones or sludge after extracting the stone or sludge.[18] Two false-negative results were seen including a patient with severe acute pancreatitis in whom the gallbladder was not clearly observed by EUS but in whom the presence of cholesterol microcrystals was identified in the duodenal aspiration obtained by endoscopy.[7] No patients with a normal EUS was subsequently reinvestigated and diagnosed with cholelithiasis.[19]

DISCUSSION

The sensitivity of conventional ultrasonography in the detection of cholelithiasis ranges from 87% to 98%.[15] In our systematic review, when conventional radiological techniques (transabdominal ultrasound, CT, and occasionally MRCP and ERCP) showed no stones, the diagnostic yield of EUS in idiopathic pancreatitis was 61%. The most frequent diagnoses for EUS were biliary tract disease (biliary stones, microlithiasis and sludge) (41%).

It has been suggested that it is the smaller stones that transiently impact the ampulla of Vater[15] causing pancreatitis. Microlithiasis in some studies was the leading cause of idiopathic pancreatitis[4] and was observed in up to 75% of idiopathic pancreatitis in patients with a gallbladder present.[5] Among idiopathic acute pancreatitis, 20% to 50% present with microcalculi and tend to have recurrences with high morbidity and mortality rates.[1] EUS is thought to be the best diagnostic technique for gallbladder microlithiasis, but bile duct microlithiasis was rarely detected or may not have a pathogenic role in acute pancreatitis in those who are postcholecystectomy.[24] In our review, EUS detected calculi/biliary tract disease missed by other modalities in 41%,[1,4,7,8,12–20] which is comparable with

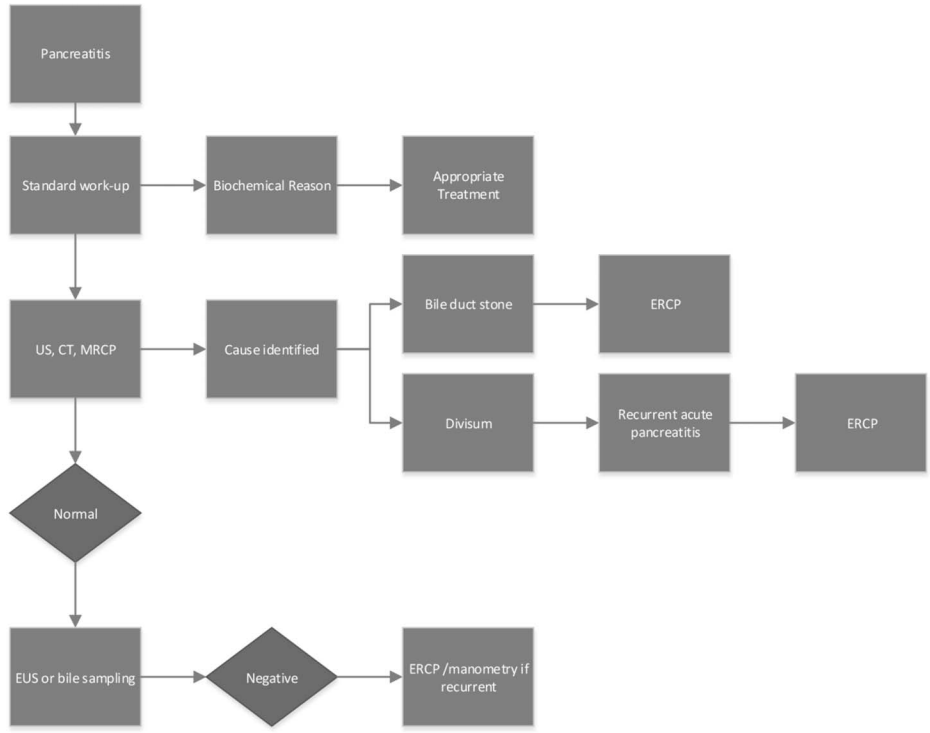

FIGURE 7. Proposed algorithm for the evaluation of idiopathic pancreatitis.

the overall figure (30.9%) reported in the review of Rösch et al.[25]

In several studies, EUS was compared with MRCP in the evaluation of idiopathic pancreatitis. The diagnostic yield for EUS was higher than for MRCP (29% versus 10.5%) and more accurately detected biliary stones.[16] MRCP more accurately identified pancreatic duct abnormalities.[16] Similarly, the diagnostic yield of EUS was higher than that of MRCP (51% versus 20%).[7] The most frequent EUS diagnoses were cholelithiasis and biliary sludge (24%) and that of MRCP was pancreas divisum (8%).[7] In the Kondo et al study,[26] EUS was superior to MRCP for detecting common bile duct stones <5 mm in size. Given these data, the choice of imaging may be center and expertise dependent. In addition, EUS may be an ideal choice if the gallbladder is *in situ*.

A prospective large patient long-term follow-up study should be conducted with idiopathic pancreatitis patients undergoing EUS being stratified based on their gallbladder status and whether their pancreatitis is a singular event or is a recurrent event. Also, it may be that multiple modalities may be needed to best exclude an etiology.

CONCLUSIONS

Given the high incidence of microlithiasis and/or biliary sludge as a cause of idiopathic pancreatitis and EUS's high accuracy of recognizing these diagnoses, EUS should be considered 1st for idiopathic pancreatitis after conventional radiography fails. Preventing recurrent episodes of pancreatitis and providing early treatment of pancreatitis is ideal and dependent on identifying a cause of the pancreatitis. In some studies, the yield of EUS did not differ among primary versus recurrent idiopathic acute pancreatitis. EUS should be used after the 1st bout of idiopathic pancreatitis. MRCP may also help to exclude pancreas divisum. ERCP can subsequently be used to evaluate and treat pancreatic divisum and to remove biliary stones but carries the risk of causing pancreatitis itself. Thus, ERCP should be reserved for those with recurrent episodes of pancreatitis with negative EUS, especially for those with previous cholecystectomy or need for endoscopic therapy as it offers additional information on SOD function (Figure 7).

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