

## The role of endoscopy in benign pancreatic disease

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*This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature was performed by using PubMed from January 1980 through October 2014 by using the keyword(s) "acute pancreatitis," "chronic pancreatitis," "autoimmune pancreatitis," "benign pancreatic disease," "gastrointestinal endoscopy," "endoscopy," and "endoscopic procedures." Pertinent studies published in English were reviewed, and additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence by using the GRADE criteria (Table 1).<sup>1</sup>*

*This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical deci-*

*sions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines.*

A variety of benign pancreatic disorders can be diagnosed and treated with endoscopy. Endoscopy may be useful in the evaluation of idiopathic acute recurrent pancreatitis, suspected chronic pancreatitis (CP), or differentiation of focal CP from malignancy. EUS and endoscopic retrograde pancreatography (ERP) are the 2 most common endoscopic procedures used to evaluate the pancreas. EUS provides high-resolution imaging of both the pancreatic parenchyma and ductal structures and can be used to guide FNA or other interventional procedures. ERP is a more invasive procedure that provides information about pancreatic duct (PD) structures, but not the pancreatic parenchyma. Compared with EUS, ERP is associated with a higher risk of pancreatitis and is often reserved for therapeutic indications such as management of CP-associated PD strictures, stones, leaks, and symptomatic fluid collections.

### ACUTE PANCREATITIS

Acute pancreatitis (AP) is most commonly due to gallstones or alcohol. History, physical examination, laboratory testing, and abdominal imaging can identify the cause in 80% of adults with AP.<sup>2</sup> For the remaining 20% with a single episode of unexplained or idiopathic pancreatitis, the role of endoscopic investigation is unclear. However, endoscopy may be indicated in select patients with a single episode or recurrent idiopathic pancreatitis to evaluate for choledocholithiasis, biliary sludge, pancreas divisum, sphincter of Oddi dysfunction (SOD), ampullary lesions,

**TABLE 1. GRADE system for rating the quality of evidence for guidelines**

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕○
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕○○
Very low quality	Any estimate of effect is very uncertain.	⊕○○○

Adapted from Guyatt et al.<sup>1</sup>

pancreatic cystic neoplasms, pancreatic cancer, or acute exacerbation of CP.<sup>2</sup>

Emerging data suggest that EUS may be beneficial for the investigation of a single episode of unexplained pancreatitis.<sup>3,4</sup> In a prospective study of 201 patients, EUS identified a cause of a single episode of unexplained pancreatitis in 31%.<sup>5</sup> The most common EUS findings in these patients are choledocholithiasis, biliary sludge, and CP, although the yield of EUS is lower in those who have undergone cholecystectomy.<sup>4</sup> Older patients with an initial episode of AP warrant investigation for pancreatic cancer, often with noninvasive cross-sectional imaging and/or EUS. Some authors suggest that all patients older than 40 years of age with idiopathic pancreatitis should be investigated for pancreatic neoplasia.<sup>6</sup> However, the mean age of patients with pancreatic cancer who present with AP is closer to 60 years.<sup>2,7,8</sup>

The utility of ERCP after a single episode of unexplained mild AP is not established and is generally not recommended.<sup>2,9</sup> Given the favorable safety profile of EUS (particularly with regard to ERCP-induced pancreatitis), there is a growing trend for an initial evaluation with EUS in these patients for the detection of biliary sludge and CP before consideration of ERCP.<sup>2,5,10,11</sup>

ERCP is generally reserved for the treatment of abnormalities found by less-invasive imaging techniques. However, in patients with idiopathic recurrent AP and negative imaging studies, ERCP has been reported to have a diagnostic yield of 38% to 79%.<sup>2</sup> When ERCP is performed for idiopathic recurrent AP, biliary and/or pancreatic sphincterotomy may be required. In this scenario, some centers perform manometry to evaluate for SOD and perform therapy accordingly.<sup>12,13</sup> Pancreas divisum in the setting of recurrent AP may be treated with papillotomy of the minor papilla.<sup>14</sup> In high-risk patient populations, placement of a pancreatic duct stent and/or the administration of rectal indomethacin reduces the risk of post-ERCP pancreatitis.<sup>15,16</sup>

### Choledocholithiasis and microlithiasis

Choledocholithiasis and microlithiasis are common causes of AP. Microlithiasis refers to stones less than 3 mm in diameter, whereas biliary sludge is a suspension of crystals, mucin, glycoproteins, cellular debris, and proteinaceous

material.<sup>2</sup> The reported prevalence of microlithiasis in the setting of idiopathic pancreatitis varies from 6% to 70% and is largely dependent on the testing methods and the timing of these tests relative to the onset of pancreatitis.<sup>17-20</sup> Microlithiasis and biliary sludge may develop as a consequence of biliary stasis secondary to pancreatitis and their presence does not confirm a causal role. Furthermore, microlithiasis and biliary sludge are more common in individuals with an intact gallbladder. Endoscopic methods for detection of microlithiasis and sludge include duodenal fluid sampling for the detection of biliary crystals by polarized microscopy, ERCP with or without intraductal bile aspiration, and EUS. The role of endoscopy in choledocholithiasis has been discussed extensively in a previous ASGE guideline.<sup>21</sup> Cholecystectomy is recommended for patients with recurrent AP thought to be secondary to microlithiasis.<sup>14</sup> Endoscopic biliary sphincterotomy may also be used to prevent recurrent biliary pancreatitis in patients with choledocholithiasis or microlithiasis but should be limited to individuals unable or unwilling to undergo cholecystectomy.<sup>22-24</sup>

### Pancreas divisum

Pancreas divisum is an anatomic variant characterized by the failure of fusion between the dorsal and ventral PDs. This variant is present in approximately 7% of the population. The role of divisum as a cause of recurrent AP or CP remains controversial, although there is a significant association between divisum and these disorders.<sup>25,26</sup> Magnetic resonance imaging (MRI) is considered sensitive for the detection of divisum, particularly when secretin is administered before the study.<sup>27</sup> However, the sensitivity of MRI for the detection of divisum is lower in those with CP.<sup>28</sup> EUS may be superior to multidetector CT or MRI without secretin for detection of divisum.<sup>27</sup> Pancreatography is considered the best method for establishing the presence of divisum; however, ERP via the minor papilla should not be offered only for diagnostic purposes. ERP with minor papillotomy may prevent further attacks of acute recurrent pancreatitis in certain patients with divisum, yet there are no prospective, randomized, controlled trials that confirm this hypothesis. In a retrospective series of 53 patients with pancreas divisum and recurrent pancreatitis treated with minor papillotomy, 60% of patients reported immediate

improvement in symptoms. Nevertheless, recurrent symptoms developed in half of these patients at a mean follow-up of 6 months after the procedure.<sup>29</sup> A long-term retrospective study of patients undergoing ERP with minor papilla endotherapy (papillotomy and/or stenting) demonstrated higher rates of improved pain scores and fewer hospitalizations for patients with divisum and acute recurrent pancreatitis (53%) than for patients with divisum and CP (18%) or those with divisum and chronic/recurrent epigastric pain (41%;  $P = .02$ ).<sup>30</sup> Limited data suggest that prolonged stenting of the minor papilla without sphincterotomy may produce results equivalent to minor papilla sphincterotomy, but this has not been widely adopted, as more data are needed.<sup>31-33</sup> Minor papilla manipulation may carry an increased risk of pancreatitis, and postprocedure administration of rectal indomethacin and/or PD stenting is recommended.<sup>15,16,34,35</sup>

### Sphincter of Oddi dysfunction

The modified Milwaukee classification categorizes pancreatic SOD into 3 types: type 1 with pain, abnormal pancreatic enzymes on 2 occasions, and a dilated PD; type 2 with pain and either abnormal enzymes or a dilated PD; and type 3 with “pancreatic type” pain alone.<sup>36</sup> Classically, individuals with type 1 SOD undergo ERCP with pancreatic sphincterotomy. However, the sphincter complex comprises a biliary sphincter, pancreatic sphincter, and a common sphincter. Depending on the contribution of the common sphincter to an individual’s pancreatic sphincter hypertension, a simple biliary endoscopic sphincterotomy, which cuts both the biliary and common sphincter, may be sufficient to substantially reduce pancreatic sphincter pressure. The endoscopic approach to individuals with type 2 SOD or those with idiopathic recurrent AP varies across institutions. Some centers perform ERCP with SOD manometry, with treatment based on manometric findings.<sup>37,38</sup> Other centers perform empiric biliary and/or pancreatic sphincterotomy for individuals with type 2 SOD or idiopathic recurrent AP. Others perform biliary sphincterotomy and reserve pancreatic SOD manometry for those who do not respond to biliary sphincterotomy alone.

SOD has been reported in as many as 72% of patients undergoing manometry for idiopathic recurrent AP in which divisum, bile duct stones, and pancreatic malignancy were excluded with ERCP.<sup>39</sup> A recent randomized trial of patients with recurrent idiopathic pancreatitis found that individuals with pancreatic SOD responded similarly to biliary sphincterotomy alone (51.5%) compared with combined biliary and pancreatic sphincterotomies (52.8%;  $P = 1.0$ ) for the prevention of recurrent episodes of AP.<sup>12</sup> Pancreatic SOD was found to be an independent risk factor for identifying patients at higher risk of recurrent AP. A randomized multicenter trial of individuals with abdominal pain after cholecystectomy attributed to SOD (type 3 SOD) found no diagnostic or predictive

benefit of biliary or pancreatic manometry. This same study failed to demonstrate a therapeutic benefit of biliary and/or pancreatic sphincterotomy over sham therapy.<sup>40</sup> The authors concluded that manometry or sphincterotomy for type 3 SOD are not recommended.<sup>40</sup>

### Autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is a distinct form of CP characterized by a fibroinflammatory process that readily responds to steroid therapy.<sup>41</sup> It is now recognized that there are 2 forms of AIP. Type 1 AIP is also referred to as lymphoplasmacytic sclerosing pancreatitis and is the pancreatic manifestation of immunoglobulin G4 (IgG4)-related disease. It is more commonly observed in Asia in older individuals and is associated with the histological features of storiform fibrosis, obliterative venulitis, preserved arterioles, increased serum IgG4 levels, and abundant infiltration of IgG4-positive plasma cells. Type 2 AIP has been termed idiopathic duct-centric pancreatitis and is more common in Europe and the United States. This type occurs in younger individuals and is associated with granulocyte epithelial lesions, absent or low levels of serum IgG4 and tissue IgG4-positive plasma cells, and absence of other organ involvement except inflammatory bowel disease. The role of endoscopy for the diagnosis of AIP has varied according to country based on the type of AIP most commonly encountered. For example, Japanese consensus guidelines and Asian diagnostic criteria mandate ERP as part of the imaging criteria for diagnosing AIP, yet pancreatography is not mandated by the Mayo Clinic’s HISORt diagnostic criteria.<sup>42-44</sup> In an attempt to unify diagnostic criteria, a panel of experts created the International Consensus Diagnostic Criteria for AIP.<sup>45</sup> These criteria suggest the use of ERP when CT findings are atypical for AIP. ERP findings suggestive of AIP include long, narrow strictures (more than one-third of the length of the PD), lack of upstream dilation (<5 mm), multiple strictures, and the presence of side branches arising from a strictured duct.<sup>46</sup> However, there is regional variability with interpretation of pancreatography. Experts from the United States demonstrate lower sensitivity for identifying AIP based solely on pancreatography images compared with Asian experts.<sup>46</sup> Cholangiography in addition to pancreatography (ERCP) may be necessary for the diagnosis of AIP in individuals with signs or symptoms of biliary strictures related to IgG4-related disease.<sup>47</sup> In this scenario, endobiliary sampling of the stricture is recommended to rule out malignancy and for IgG4 staining. Ampullary biopsies for IgG4 staining are also recommended by some at the time of ERCP. Carefully performed ampullary biopsies do not appear to increase the risk of bleeding or pancreatitis and have a sensitivity of 52% to 80% and a specificity of 89% to 100% for the diagnosis of AIP.<sup>47</sup> IgG4-related biliary strictures often respond promptly to treatment with corticosteroids. Therefore, ERCP with biliary stenting in AIP is

reserved for those biliary strictures that do not respond to steroid therapy.

There are no pathognomonic EUS imaging characteristics of AIP. However, classic EUS findings of AIP include diffuse gland enlargement with parenchyma that is hypoechoic, patchy, and heterogeneous.<sup>48-50</sup> The diagnosis of AIP should be strongly suspected when all these EUS features are present and may be seen in as many as 57% of patients.<sup>48,49</sup> Diffuse hypoechoic areas and pancreatic enlargement, a thickened bile duct wall, and peripancreatic hypoechoic margins are more common in AIP than in pancreatic cancer.<sup>51</sup> On the other hand, focal hyperechoic areas, focal enlargement, and marked biliary and PD dilation are more common in patients with pancreatic cancer. As the biliary tree is the most common extrapancreatic site of organ involvement, it is important to evaluate the bile ducts at EUS when type 1 AIP is suspected. In 38% of patients who underwent EUS for AIP, the extrahepatic bile duct and gallbladder wall were thickened.<sup>49</sup>

EUS can confirm the diagnosis of AIP through pancreatic tissue biopsy. EUS-guided tissue acquisition is important, particularly in the diagnosis of type 2 AIP, because pancreatic histology is one of the diagnostic criteria of International Consensus Diagnostic Criteria.<sup>45</sup> Standard FNA commonly yields small specimens for cytological review, most of which do not preserve tissue architecture. Although a few published reports advocate the use of FNA to diagnose AIP, there is no broadly accepted consensus for the cytological diagnosis of AIP, and most pathologists are reluctant to rely solely on FNA specimens.<sup>52-55</sup> In a series of 44 patients diagnosed with AIP, 43% were diagnosed based on histologic analysis from FNA with a conventional 19-gauge needle.<sup>56</sup> The greatest utility of EUS-FNA may be to exclude pancreatic cancer rather than diagnose AIP. However, one must be mindful of the 10% to 40% false-negative rate of FNA, which indicates that a negative result does not reliably exclude pancreatic adenocarcinoma.

To overcome the limitations of EUS-FNA, larger-caliber cutting biopsy needles have been developed that preserve tissue architecture for histological evaluation. A 19-gauge needle designed to capture a core tissue sample (Quick-Core; Cook Medical, Winston-Salem, NC) has been shown to help differentiate AIP from classic CP and pancreatic cancer.<sup>57-60</sup>

Elastography and contrast-enhanced EUS are newer technologies that may differentiate AIP from neoplastic processes.<sup>61,62</sup> Both of these image-enhancing techniques are still in an experimental phase, and routine use in evaluating possible AIP cannot be recommended at this time.

## CHRONIC PANCREATITIS

CP is an irreversible inflammatory process characterized by the destruction of pancreatic parenchyma and

ductal structures associated with fibrosis. Pain is the predominant symptom of CP and is often multifactorial.<sup>63</sup> Histologically, CP is characterized by fibrosis with a chronic inflammatory infiltrate and loss of acinar cells. Endoscopy, including EUS, ERP, and endoscopic pancreatic function testing (ePFT) can be used to establish the diagnosis of CP. However, these modalities should be reserved for patients in whom the diagnosis remains unclear after noninvasive imaging (CT or MRI with or without cholangiopancreatography).

Endoscopic therapy should be considered as part of a multidisciplinary approach to managing patients with CP. Optimizing medical management is paramount, with emphasis on abstinence from alcohol and tobacco, dietary modification, and the proper use of oral enzyme supplements, particularly in those patients with pancreatic exocrine insufficiency. Pancreatography should be primarily reserved to direct endoscopic therapy for patients with abdominal pain thought to be due to outflow obstruction of the PD. PD strictures and obstructing stones may result in PD hypertension, thereby contributing to the pain in patients with CP. Endoscopic therapy in these patients often requires multiple interventions that may be technically difficult. Endoscopic treatment should be weighed in the context of surgical options and is clinically successful in approximately 50% of patients with symptomatic CP.<sup>64</sup> Several randomized, controlled trials have compared operative intervention with endoscopic therapy and are discussed in detail later in this document. EUS-guided interventions can also be used to access the obstructed PD, drain pancreatic fluid collections, and deliver injections in and around the celiac plexus for treatment of chronic pain.

### Endoscopic diagnosis of CP

The clinical diagnosis of CP is obvious in patients with overt exocrine or endocrine dysfunction or in those with imaging demonstrating organ atrophy or calcification. However, a significant subset of individuals with suspected CP do not have symptoms of pancreatic insufficiency or radiographic abnormalities, making the diagnosis challenging. Endoscopic investigation has been suggested if noninvasive imaging is equivocal for the diagnosis of CP.<sup>65</sup>

### Endoscopic pancreatic function testing

Pancreatic function testing was first reported more than 60 years ago.<sup>66</sup> This technique can detect early CP with exocrine insufficiency.<sup>66</sup> One approach involves the placement of a double-lumen tube into the duodenum to collect pancreatic secretions at specific intervals after administration of secretin or cholecystokinin. Aspirates are evaluated for bicarbonate concentration or pancreatic enzyme levels. Limitations of the test that preclude wide use include (1) the need for fluoroscopy to confirm appropriate placement of the tubes and (2) the absence of conscious sedation for the entire procedure. ePFT is a newer method for

**TABLE 2. Endosonographic criteria for chronic pancreatitis**

	<b>Parenchymal changes</b>	<b>Ductal abnormalities</b>
Major A	Hyperechoic foci with shadowing	MPD calculi
Major B	Lobularity with "honeycombing": $\geq 3$ contiguous lobules measuring at least 5 mm in length	
Minor criteria	Lobularity without honeycombing	Irregular/ectatic MPD contour
	Hyperechoic foci without shadowing	$\geq 3$ dilated side branches
	Cysts	MPD dilation >3.5-mm body; >1.5-mm tail
	Hyperechoic stranding	Hyperechoic MPD margin

Consistent with chronic pancreatitis: 1 major A feature and  $\geq 3$  minor features, 1 major A and major B features, 2 major A features. Suggestive of chronic pancreatitis: 1 major A feature and  $\leq 3$  minor features, 1 major B feature and  $\geq 3$  minor features, any  $\geq 5$  minor features. Indeterminate for chronic pancreatitis: 3 or 4 minor features, major B feature alone or with  $< 3$  minor features. Normal:  $\leq 2$  minor features without major features.

MPD, Main pancreatic duct.

the detection of pancreatic exocrine insufficiency. During ePFT, EGD is initially performed, and all gastric and duodenal secretions are aspirated and discarded. Secretin is then administered intravenously. At 15, 30, 45, and 60 minutes after secretin administration, endoscopic duodenal aspiration is performed, and the contents are analyzed for bicarbonate concentration.<sup>67</sup> A peak bicarbonate concentration less than 80 mEq/L is considered abnormal and indicative of exocrine insufficiency. ePFT has an excellent negative predictive value, and CP is essentially excluded if the concentration exceeds 80 mEq/L.<sup>68</sup> A shortened duration of the procedure to 45 minutes may be adequate, although 15 minutes is insufficient, even with direct intraductal collection of secretions.<sup>69-71</sup>

## EUS

EUS provides high-resolution imaging of the pancreatic parenchyma and ductal structures. EUS parenchymal features in CP include hyperechoic foci, hyperechoic strands, lobularity, and cysts. Ductal features of CP include main duct dilation, duct irregularity, hyperechoic duct margins, visible side branches, and stones. In the traditional EUS diagnostic system, each parenchymal or ductal feature is weighted equally and counted as 1 point (on a scale of 0 to 9 points) with higher scores increasing the likelihood of disease. There is uncertainty as to the ideal threshold number of criteria necessary for diagnosing CP. Increasing the number of required EUS features improves the specificity but sacrifices sensitivity for the diagnosis of CP. Most agree that the presence of 5 or more features reliably diagnoses CP and that absence of all features reliably excludes CP.<sup>72</sup> However, there remains uncertainty, and practice patterns vary for patients demonstrating 1 to 4 EUS features. Some authors believe that 1 to 2 EUS features is indicative of a normal gland and that the presence of 3 to 4 criteria may indicate early or mild CP. This uncertainty highlights the need to correlate the EUS findings with clinical, structural, and functional analyses, particularly among patients with possible early or indeterminate

disease. One must be hesitant to diagnose CP based solely on minimal EUS criteria with otherwise negative or inconclusive findings.

Consensus-based criteria for EUS features of CP (Rosemont classification) were developed after a conference among 32 internationally recognized endosonographers (Table 2).<sup>73</sup> By using expert opinion, attendees assigned different weights to conventional parenchymal and ductal features of CP to optimize diagnostic accuracy. This classification scheme does not appear to increase interobserver agreement for the diagnosis of CP compared with the standard scoring system.<sup>74</sup> Defining the sensitivity of EUS criteria is challenging as a true criterion standard comparator has been difficult to identify because PFT, pancreatography, and histology may not recognize mild or moderate CP.

Caution must be exercised in several circumstances when using EUS for the diagnosis of suspected CP. First, recent or active AP can result in an overdiagnosis of certain criteria for CP including parenchymal hyperechoic strands and foci, lobularity, and hyperechoic duct walls. Moreover, acute inflammation can obscure an underlying mass on imaging; therefore, many endosonographers prefer to defer EUS for at least 4 weeks after an episode of AP. Second, pancreatic EUS findings that mimic CP are often seen as a result of normal aging, male sex, tobacco use, obesity, or alcohol use.<sup>75-78</sup> Third, although some studies have demonstrated good interobserver agreement among expert endosonographers for suspected CP, others have demonstrated relatively poor interobserver agreement.<sup>74,79</sup> Fourth, in contrast to AIP, data are insufficient to endorse the use of EUS-guided tissue acquisition for diagnosing CP at the present time.<sup>80,81</sup> Combining EUS with ePFT appears to improve the sensitivity for the detection of early CP as functional abnormalities before structural changes may develop in some individuals.<sup>82</sup>

## Pancreatography

ERP may detect PD changes associated with CP but cannot assess for pancreatic parenchymal changes. The

Cambridge Classification of pancreatographic findings has been the traditional method for diagnosing and grading severity of CP based on findings of main and branched duct abnormalities including dilation, irregularity, strictures, stones, and/or cavities.<sup>83,84</sup> However, variations in technique, such as underfilling of the PD, can affect the sensitivity of ERP for diagnosing CP. In addition, these pancreatography findings may not reflect CP because ductal changes can occur with normal aging and in those who consume alcohol but in whom CP is not suspected.<sup>85-87</sup> Injection of contrast during ERP may result in an overestimate of the main PD diameter by as much as 1.5 times relative to measurements made at MRCP.<sup>88</sup> ERP is an invasive study with a risk of AP as high as 15%.<sup>89</sup> Furthermore, the risk of post-ERCP pancreatitis is higher in younger individuals with chronic abdominal pain without an obvious diagnosis of CP (ie, those with possible minimal change CP). Consequently, diagnostic pancreatography has been replaced by noninvasive or less-invasive imaging modalities (ie, EUS or MRCP) that can evaluate the pancreatic parenchyma and ductal structures. ERP should be reserved for therapeutic indications.

### Differentiating CP from pancreatic adenocarcinoma

CP is associated with an increased risk of pancreatic adenocarcinoma. Approximately 2% of patients with a new diagnosis of CP have underlying pancreatic cancer.<sup>90</sup> In particular, malignancy should be excluded in patients older than 40 years of age without an extensive history of heavy alcohol or tobacco use before making a new diagnosis of CP. Standard CT scanning is insensitive for the detection of pancreatic adenocarcinoma in patients with CP. Therefore, triple-phase CT imaging is recommended (ie, pancreas protocol CT) for this indication. EUS alone has poor accuracy (<75%) for differentiating benign inflammatory masses from neoplasia.<sup>91,92</sup> EUS-FNA of lesions in the setting of CP is less sensitive (79% to 92%) for the diagnosis of malignancy compared with FNA of lesions in patients without CP.<sup>93-96</sup>

Elastography and contrast-enhanced EUS are 2 new technologies that may help improve detection of adenocarcinoma and differentiate malignant mass lesions from focal CP.<sup>97-99</sup> Elastography evaluates the relative stiffness of lesions compared with surrounding tissues with the expectation that malignant lesions consist of “harder” tissue than benign ones.<sup>100</sup> Contrast-enhanced techniques characterize the vascularity of lesions by imaging its microvessels and hypothesizes that malignancies are relatively hypoenhanced compared with benign lesions.<sup>97</sup> These technologies are at varying stages of development and study. Carefully designed studies are needed to determine their utility and role in the differentiation of malignant from benign disease.

### PD strictures

Benign strictures of the main PD occur in CP as a result of inflammation or fibrosis and may occur at anastomotic sites after pancreatic surgery. Dominant PD strictures resulting in ductal obstruction may lead to pain or superimposed AP on CP. At the time of endoscopic intervention, brushings for cytology can be performed to assess for occult malignancy. Confocal endomicroscopy is an emerging technology that may prove useful for the evaluation of indeterminate pancreatic strictures.<sup>101</sup>

PD strictures from CP are often tight and resilient. Therefore, endotherapy usually involves dilation before stenting, and treatment with dilation alone is not recommended. Endoscopic therapy with dilation and stenting for PD strictures without intraductal stones has been effective in reducing abdominal pain in 65% to 84% of patients.<sup>102-105</sup> Symptomatic improvement may persist after pancreatic stent removal despite persistence of the stricture.<sup>103,106</sup> PD stents are prone to occlusion and may require frequent exchange. When single stents are placed, use of 10F stents across the stricture has been recommended because single smaller-diameter stents have been associated with a higher risk of hospital admission for abdominal pain.<sup>107,108</sup> Multiple plastic stents are favored by some experts as a way to avoid blockage of side branches compared with using single larger-caliber stents. A single small series described placement of a median of 3 stents, which permitted 84% of the cohort to achieve persistent pain relief after a mean follow-up of 38 months.<sup>104</sup> There are no trials comparing the use of single larger stents to multiple stents for PD strictures in CP. The off-label use of fully covered self-expandable metal stents for PD strictures has been described, although this indication remains investigational. Adverse events associated with endotherapy for PD strictures include pain, AP, stent occlusion, stent migration, pancreatic infection, perforation, stone formation, and bleeding. In addition, PD stents may induce periductal damage and scarring, including the development of strictures or focal CP, particularly when used in near-normal glands.<sup>109,110</sup>

EUS-guided access and drainage of an obstructed main PD by 1 of 3 techniques has been described in cases of surgically altered anatomy or failed conventional transpapillary access. EUS-guided duct access may facilitate retrograde transpapillary drainage by using the “rendezvous” technique. Alternatively, direct anterograde duct puncture and transmural drainage or anterograde passage of a transpapillary stent may be considered. One series of 36 patients reported partial or complete pain relief in 69% of patients after intervention, but this benefit waned over time with only 20% remaining pain free after 450 days.<sup>111</sup> A recent series of 43 patients undergoing EUS-guided main PD stent placement described technical success in 74% and complete symptom resolution in 83% while PD stents were in place.<sup>112</sup> Due to potential significant morbidity (ie, perforation, bleeding, infection), the use of

EUS-guided main PD access and drainage remains limited to high-volume centers. These EUS-guided interventions should be performed in carefully selected patients managed by a skilled multidisciplinary team that fully considers endoscopic and surgical options.

### PD stones

Similar to PD strictures, obstructing pancreatic stones may result in abdominal pain or superimposed AP on CP. ERP-guided treatment of symptomatic pancreatolithiasis can be difficult due to underlying PD strictures or the difference between the size of the stone and the downstream PD. Extracorporeal shock wave lithotripsy (ESWL) may be required to fragment stones before endoscopic removal is attempted. Several studies have demonstrated encouraging short-term (77%-100%) and long-term (54%-86%) improvement in pain after pancreatic endotherapy for CP.<sup>113,114</sup> A multicenter study of 1000 patients with CP with a mean long-term follow-up of 4.9 years (range 2-12 years) found that pancreatic endotherapy of strictures, stones, or both improved pain in 65% of patients, but endotherapy in this group did not improve pancreatic function.<sup>115</sup> Twenty-four percent of patients in this series undergoing endoscopic therapy subsequently required some form of operative intervention for symptoms related to CP.

Other studies have demonstrated less-impressive results for ESWL combined with pancreatic endotherapy, with improvement in pain seen in as few as 35% of patients.<sup>116,117</sup> Furthermore, ESWL may require protracted therapy (>10 sessions) to obtain successful clearance of the duct.<sup>118</sup> A prospective study that randomized patients with chronic calcific pancreatitis to ESWL with endoscopic drainage or ESWL alone demonstrated that the number of patients with pain relapse was similar in both groups (45% vs 38%;  $P = .633$ ) 2 years after the intervention.<sup>119</sup> The authors concluded that ESWL is safe, but the addition of endotherapy added to the cost without improving pain control.

One small series demonstrated that the timing of ESWL in relation to ERP had a significant impact on the ability to endoscopically clear the main PD.<sup>120</sup> Eighty-two percent of patients undergoing ERP more than 2 days after ESWL achieved clearance of the main PD compared with 16% in the group undergoing ERP less than 2 days after ESWL ( $P = .001$ ).<sup>120</sup>

Another recent long-term study of patients with chronic calcific pancreatitis undergoing ESWL followed by ERP demonstrated partial pain relief in 85% and complete pain relief with no narcotic requirement in 50% of patients after a mean follow-up of 4.3 years.<sup>121</sup> Furthermore, 84% of patients in this study were able to avoid surgery. This study also highlighted the importance of environmental factors as smokers who quit had reduced narcotic requirements compared with those who continued smoking. Other investigators noted a similar long-term success rate with

60% of patients experiencing no abdominal pain more than 60 months after undergoing ESWL and ERP although 23% were noted to have recurrent calculi.<sup>122</sup> The use of a mini-lithotripter device followed by endoscopic clearance demonstrated similarly improved outcomes with complete pain resolution in 53% of patients and partial pain improvement in 87.5% of patients.<sup>123</sup>

Prospective, randomized trials have demonstrated surgery to be more effective and durable than endoscopic treatment for pain relief in patients with CP and PD obstruction.<sup>124,125</sup> A study of 140 patients undergoing surgery or endoscopic therapy demonstrated higher rates of complete pain relief with surgery (37% vs 14%;  $P = .002$ ) and similar rates of partial pain relief (49% vs 51%;  $P =$  not significant) at 5-year follow-up.<sup>124</sup> However, this study had several limitations that may have influenced study conclusions. First, efficacy was assessed in a nonblinded fashion based not only on the 72 randomized patients, but also on 68 patients who refused randomization. In the 72 patients who were randomized to surgery or endoscopic therapy, higher rates of complete relief (34% vs 15%;  $P = .002$ ) and similar rates of partial pain relief (52% vs 46%;  $P =$  not significant) were noted with surgery after 5-year follow-up. Second, the majority (80%) of patients taken to surgery underwent resection (pancreaticoduodenectomy, duodenum-preserving pancreatic head resection, and distal pancreatic resection), and only 20% were offered drainage (Partington-Rochelle pancreatojejunal anastomosis). Third, ESWL was not included in the endoscopic treatment protocol, which may explain the lower rates of pain relief in the endoscopic group compared with the rates observed in other studies. Another study randomized 39 patients with CP and downstream PD obstruction without a mass to endoscopic therapy including ESWL versus operative pancreatojejunostomy.<sup>125</sup> This study concluded that operative intervention resulted in a significantly higher rate of pain relief (complete or partial) compared with endoscopic intervention (75% vs 32%;  $P = .007$ ), with surgery ultimately required in 47% of patients initially treated endoscopically.<sup>125</sup> However, this study was also notable for the low overall technical success rate (53%) of endoscopic therapy. Long-term outcomes from the same cohort of patients after 5 years demonstrated higher rates of pain relief in the surgery arm compared with the endoscopy arm (80% vs 38%;  $P = .042$ ).<sup>126</sup> The same study noted no difference between groups in terms of hospital duration, pancreatic function, adverse event rate, or quality of life. Surgical drainage has an adverse event rate of 6% to 30% and may require repeat operative intervention with a mortality rate as high as 2%.<sup>125</sup> Due to the increased risks associated with various operative interventions, some experts have argued that despite the lower rate of pain relief with endoscopic treatments, endotherapy may be the preferred initial approach in centers with this expertise, reserving surgery for cases of failure and/or recurrent symptoms.<sup>124,127</sup> Factors

associated with long-term success with endoscopic therapy include location of an obstructing stone in the head of the pancreas, shorter disease duration with less-frequent attacks of pain, complete clearance of the main PD without a history of main PD stricture at the time of initial ERP, and discontinuation of alcohol and tobacco use.<sup>108</sup> For individuals with uncomplicated CP and a radiopaque stone 5 mm or larger obstructing the main PD, the European Society for Gastrointestinal Endoscopy recommends ESWL as the first step with subsequent ERP to clear stone fragments.<sup>108</sup> Intraductal laser and electrohydraulic lithotripsy are technically demanding procedures with varied rates of successful stone clearance ranging from 47% to 83% in small series.<sup>128-130</sup> These interventions should be considered after failed previous ESWL and ERP.<sup>108</sup> Surgery has been demonstrated to be effective in symptomatic relief in approximately 50% of patients who were not improved with previous endoscopic therapy.<sup>64</sup> Surgical intervention is favored whenever malignancy cannot be excluded or in the presence of coexisting pathology (eg, inflammatory mass, biliary or duodenal obstruction), certain types of strictures (long, complex, or multiple), certain types of stones (large, location in the pancreatic tail, or complex), and whenever endotherapy fails.

### **PD leaks, pancreatic fluid collections, and walled-off pancreatic necrosis**

The endoscopic management of pancreatic fluid collections has previously been summarized in ASGE documents and guidelines.<sup>131-133</sup> PD disruptions or leaks may occur as a result of AP, CP, trauma, or surgical injury and can result in pancreatic ascites and pseudocyst formation. Pancreatic fluid collections that communicate with the PD and incomplete PD disruptions may be amenable to transpapillary therapy stent therapy.<sup>134</sup> Although bridging the region of PD disruption is desirable, nonbridging transpapillary stent placement with or without pancreatic sphincterotomy may still benefit patients by reducing resistance to pancreatic juice flow.<sup>135</sup> In 1 study of 43 patients with PD disruption treated by PD stenting, 25 patients (58%) had resolution of their disruption. Factors associated with improved outcomes included successful bridging of the disruption and longer duration of stenting (~6 weeks).<sup>135</sup> There are no randomized studies that compare surgical with endoscopic therapy for PD injuries.

Smaller symptomatic pseudocysts that communicate with the PD can be drained via a transpapillary approach. PD stenting, pancreatic sphincterotomy, or a combination of these techniques can allow successful nonsurgical resolution. Large case series of pseudocysts drained by the transpapillary route have yielded success rates of nearly 90%.<sup>113,136-138</sup> Transmural drainage of peripancreatic fluid collections, including pseudocysts, is the preferred nonsurgical approach for larger cysts and/or those with significant debris.<sup>139</sup> Antibiotic prophylaxis is recommended for endoscopic drainage of sterile pancreatic fluid collections.<sup>140</sup>

In contrast to sterile pancreatic fluid collections, walled-off pancreatic necrosis responds more favorably to direct endoscopic necrosectomy than standard endoscopic transmural drainage alone.<sup>141</sup> A retrospective multicenter study has demonstrated endoscopic necrosectomy to have a highly successful rate of resolution (91%) of pancreatic necrosis and an acceptable adverse event profile without the need for additional operative or percutaneous intervention.<sup>142</sup> The endoscopic management of walled-off pancreatic necrosis is discussed in detail in a previous ASGE guideline.<sup>131</sup>

### **EUS-guided celiac block**

Chronic inflammation often leads to debilitating pain in CP, and long-term pain management in these patients remains challenging. The celiac plexus is located below the diaphragm, surrounds the origin of the celiac artery, and comprises a network of ganglia and interconnecting fibers. The plexus typically contains 1 to 5 ganglia that vary in diameter from 0.5 cm to 4.5 cm and in location from T12 to L2. The celiac plexus transmits pain sensation for the pancreas and most of the abdominal viscera. A number of potential routes and targets for injection have been reported. Celiac block may be performed endoscopically or via percutaneous routes by radiologists and anesthesiologists, either blindly or under radiographic guidance. Regardless of the delivery method, this technique involves injection of an anesthetic agent, usually in combination with a steroid to disrupt the signaling of painful stimuli. Although EUS-targeted intraganglia injection may theoretically offer enhanced pain relief, the absence of robust comparative data precludes assessment of the relative safety and efficacy of broad plexus therapy versus focused ganglia-directed therapy.

Most studies have shown only minimal relief of the intensity and duration of pain from celiac block in patients with CP. Recent systematic reviews estimate that celiac block provides pain relief in 51% to 59% of those with CP.<sup>143,144</sup> However, the relief is temporary, typically less than 24 weeks in duration.<sup>145</sup> Although limited data suggest that EUS-directed celiac block is more effective, less expensive, and preferred by patients compared with CT-guided therapy,<sup>146,147</sup> the methodological limitations of current studies limit firm conclusions. The multifocal nature of the pain and disease chronicity must also be considered and further limits the role of celiac block in this cohort. However, celiac block is occasionally offered to patients with severe pain that markedly impairs their quality of life after failing aggressive, closely monitored pharmacologic therapy. Some reserve EUS celiac block for hospitalized patients with refractory pain even though such therapy has never been proved to shorten the duration of hospitalization. EUS-guided celiac block has resulted in transient diarrhea, orthostasis, transient increase in pain, retroperitoneal abscess formation, and spinal cord infarction with paralysis.<sup>11</sup>



## RECOMMENDATIONS

1. We suggest EUS for the evaluation of idiopathic AP for patients older than 40 years of age if history, physical examination, laboratory testing, and abdominal imaging with MRI or CT are unrevealing. (⊕⊕○○)
2. We recommend against diagnostic ERCP for a single episode of AP. (⊕⊕⊕○)
3. We suggest that ERCP with sphincter of Oddi manometry may be considered for the evaluation of idiopathic acute recurrent pancreatitis (suspected type 2 pancreatic SOD) when findings on EUS and/or MRCP are normal and without suspicion for biliary stones, sludge, or CP. Alternate strategies include ERCP with empiric biliary and/or pancreatic sphincterotomy. (⊕⊕○○)
4. We recommend biliary and/or pancreatic sphincterotomy in patients with type 1 pancreatic SOD or patients with type 2 pancreatic SOD confirmed by manometry. (⊕⊕⊕○)
5. We recommend against the use of ERCP for the evaluation of recurrent or chronic abdominal pain interpreted as type 3 SOD. (⊕⊕⊕⊕)
6. We recommend the use of rectal indomethacin and/or PD stenting for the prevention of post-ERCP pancreatitis in high-risk patients. (⊕⊕⊕⊕)
7. We recommend EUS-guided tissue biopsy for suspected but unproved cases of AIP. Although FNA is useful for excluding underlying malignancy in older patients, larger gauge core tissue devices may be required to confirm the diagnosis of AIP. (⊕⊕⊕○).
8. We suggest ePFT and/or EUS without pancreatic biopsy for the diagnosis of CP not readily evident by previous noninvasive imaging. (⊕⊕○○)
9. We recommend ERP with dilation and/or plastic stent placement for the treatment of symptomatic dominant PD strictures for individuals in whom multidisciplinary review considers endoscopic therapy as the preferred initial therapy. (⊕⊕⊕⊕)
10. We recommend the adjunctive use of ESWL for patients with symptoms attributed to pancreatolithiasis refractory to standard endoscopic stone extraction techniques. (⊕⊕⊕○)
11. We recommend that ERP with stenting be the first-line therapy for the management of PD leaks. (⊕⊕⊕⊕)

## DISCLOSURE

*Dr Khashab is a consultant for and on the Medical Advisory Board of Boston Scientific, is a consultant for Olympus America, and has received research support from Cook Medical. Drs Chathadi and Muthusamy are consultants for Boston Scientific. Dr Fanelli is the owner and director of New Wave Surgical and an advisor for Via Surgical. Dr Hwang is a speaker for Novartis, a*

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*Abbreviations: AP, acute pancreatitis; AIP, autoimmune pancreatitis; CP, chronic pancreatitis; ePFT, endoscopic pancreatic function testing; ESWL, extracorporeal shock wave lithotripsy; IgG4, immunoglobulin G4; MRI, magnetic resonance imaging; PD, pancreatic duct; SOD, sphincter of Oddi dysfunction.*

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