Updates in endoscopic management of pain in chronic pancreatitis

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Purpose of review
This manuscript reviews recent updates on the management of pain in chronic pancreatitis, an entity that remains difficult to manage. In a time when opioid use disorder is on the rise, advanced endoscopists should be aware of the nonopioid options available to patients to help manage their pain.

Recent findings
Although there is no standardized approach in the management of pain in chronic pancreatitis, societal guidelines and recommendations have recently been updated to help guide physicians in this matter. However, the available endoscopic approaches have remained relatively unchanged in recent years. Studies are underway to determine whether one endoscopic approach is superior to another, depending on the suspected mechanism of pain.

Summary
Endoscopic management of pain in chronic pancreatitis remains challenging given the complex mechanisms at play. Surgery remains the most effective durable approach, though with significantly more morbidity and mortality compared to endoscopic options, which include endoscopic retrograde cholangiopancreatography (ERCP), extracorporeal shock wave lithotripsy (ESWL), pancreatoscopy-directed lithotripsy, and endoscopic ultrasound-guided celiac plexus block (EUS-CPB), depending on the predominant suspected cause of pain.

Keywords
endoscopic retrograde cholangiopancreatography, endoscopic ultrasound-guided celiac plexus block, extracorporeal shock wave lithotripsy, pain in chronic pancreatitis, pancreatoscopy-directed lithotripsy

INTRODUCTION

Chronic pancreatitis is a progressive, irreversible inflammatory disease that leads to distortion of pancreatic architecture, resulting in exocrine dysfunction and endocrine insufficiency. This complex, multifactorial condition, with rates as high as 150 cases per 100 000 people, is often underdiagnosed [1▪–3▪,4]. A variety of factors play a role in the development of chronic pancreatitis, ranging from modifiable exposures to genetic and idiopathic causes, with sequelae from acute pancreatitis remaining a significant contributor. The predominant modifiable risk factors for developing chronic pancreatitis in developed nations are alcohol and tobacco use, carrying an attributable risk of 40 and 31–38%, respectively. Nonmodifiable risk factors include autoimmune diseases, malignancies, gene mutations coding for proteases, protease inhibitors, and specific lipases [2▪]. Acute pancreatitis, which is most commonly caused by gallstone migration, progresses to chronic pancreatitis in roughly 30% of patients; however, the cause of chronic pancreatitis is often idiopathic [5,6].

Pathophysiologically, the inflammatory nature of chronic pancreatitis causes fibrosclerotic changes of the pancreatic tissue, leading to calcifications and impairment of both exocrine and endocrine pancreatic functions. As a result, patients often experience malabsorption, steatorrhea, weight loss, and glucose intolerance [5]. Recent studies have explored the complex molecular mechanisms of the inflammatory cascade that lead to pancreatic acinar cell damage and resulting fibrosis. These mechanisms provide potential targets for novel therapies [2▪,7].

Pain remains the most frequent and debilitating symptom of chronic pancreatitis, occurring in up to 90% of patients and significantly decreasing overall quality of life [8]. However, this disease process is inherently complex, and not all patients present or

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KEY POINTS

- Management of pain in chronic pancreatitis remains challenging in recent years given multifactorial and complex mechanisms hypothesized to be responsible.
- If pancreatic duct hypertension is thought to be the primary driver of pain, the recommended endoscopic approaches include ERCP with or without stent placement, ESWL, or pancreatoscopy-directed lithotripsy. Specific approach should be selected based on the size or presence of pancreatic calculi, as well as patient-specific anatomy and comorbidities.
- If pain is refractory, or thought to be primarily due to neuropathic changes, EUS-CPB can be considered, though lack of efficacy should be discussed with patients. Repeat treatments are also not recommended if initial intervention fails to provide pain control.

respond to treatment in similar manners [1▪]. The most widely accepted classifications of pain related to chronic pancreatitis subdivide patients into two categories: type A and type B. Type A is described as intermittent, with pain lasting a few days followed by longer pain-free episodes lasting months to years. Type B is continuous pain complicated by severe exacerbations [8].

Many mechanisms are hypothesized to explain the complex pain response related to chronic pancreatitis. These include ductal hypertension as a result of strictures and calculi, neuropathic changes, peripheral sensitization, development of pseudocysts, and biliary strictures [9]. Main pancreatic duct strictures occur in roughly 50% of patients with chronic pancreatitis and can lead to the development of pancreatic ductal hypertension [10]. Pancreatic calculi can manifest in ducts or within the parenchyma as a consequence of stagnant secretions and protein plugs secondary to underlying inflammation [3▪]. Neurobiological changes also contribute to the heterogeneous nature of pain in chronic pancreatitis, as numerous molecular and morphological changes occur at both intra-pancreatic and extra-pancreatic nerve sites resulting in alteration of pain perception. As a result, pain in chronic pancreatitis has been historically challenging to classify and treat [1▪,2▪,4,7].

The treatment goal in chronic pancreatitis is to relieve pain, preserve quality of life, and reduce the risk of complications [7,11▪▪]. This review focuses on updates in endoscopic management of pain related to chronic pancreatitis including pancreatic sphincterotomy, pancreatic duct stenting, lithotripsy, and endoscopic ultrasound-guided celiac plexus block (EUS-CPB) [11▪▪,12].

MANAGING PANCREAS DUCT OBSTRUCTION

The paradigm of endoscopic intervention to treat pain by addressing local mechanisms in chronic pancreatitis remains relatively unchanged over the last several years. Pancreatic duct hypertension is hypothesized to increase the ductal and parenchymal pressures within the pancreas, thereby eliciting pain that is classically postprandial and intermittent. The mechanism is thought to be related to repeated inflammation causing a fibro-inflammatory response which in turn results in the formation of strictures and decreased pancreatic secretion [3▪,11▪▪,13▪]. While this mechanism may seem intuitive, studies have failed to show a strong correlation with pancreatic duct hypertension and symptoms, and decreased ductal pressures have not consistently lead to improvement in pain [14▪▪,15,16]. What has remained consistent among various society guidelines is that surgical intervention is preferred to endoscopic therapy for long-term pain relief in obstructive chronic pancreatitis, especially after endoscopic interventions have been unsuccessful [15,17–19,20▪▪].

Thus, the decision to perform a specific endoscopic therapy lies with each individual endoscopist. Several factors must be weighed, including ongoing pancreatic injury from reversible causes, underlying anatomical variations such as pancreas divisum, and prior interventions [17]. Cross-sectional imaging is critical for procedural planning, especially when considering if attempted pancreatic duct decompression would improve symptoms. Endoscopists should note any aberrant anatomy (such as parenchymal loss or presence of strictures), ductal diameter, presence of ductal calculi or parenchymal calcifications, and presence of possible obstructive lesions. Computed tomography and MRI are both helpful, though MRI with secretin is the ideal modality to best assess the pancreatic duct [14▪▪].

SPHINCTEROTOMY

Pancreatic sphincterotomy performed via endoscopic retrograde cholangiopancreatography (ERCP) serves two primary functions: relieve papillary sphincter stenosis and facilitate pancreatic duct access for further instrumentation and intervention. If papillary stenosis is thought to be the primary driver of pain, sphincterotomy alone is a viable therapeutic strategy. However, sphincterotomy of the major papilla is commonly associated with a secondary intervention such as mechanical lithotripsy and calculus extraction, pancreatic duct stent deployment, dilation, or direct pancreatoscopy [14▪▪,18].

STENTING

Pancreatic duct stenting remains as one of the most utilized interventions intended to decompress the main pancreatic duct and address abnormalities such as strictures or calculi (Fig. 1). While stents have demonstrated efficacy as high as 98% in decreasing pancreatic duct dilation and remodeling of strictures, high-quality data demonstrating a positive correlation with symptom improvement and optimal stent placement are lacking [12,13▪,14▪▪]. Most data are observational cohort studies which demonstrate pain relief in up to 60–80% of patients [14▪▪,21]. In 2019, the European Society of Gastrointestinal Endoscopy (ESGE) made a weak recommendation with low quality of evidence to place a single plastic stent as an initial approach for presumed dominant main duct strictures, but multiple plastic stents in parallel versus a self-expandable metal stent could be reasonable for refractory strictures [18]. Similarly, the American Gastroenterological Association (AGA) released updated guidelines in 2022, which recommended 6–12 months of prolonged stent therapy to treat the symptoms of chronic pancreatitis and facilitate remodeling of main pancreatic duct structures. The recommendation to sequentially increase the caliber or number of plastic stents is based on observational studies with notable risk of bias [15]. In 2024, the American Society for Gastrointestinal Endoscopy (ASGE) recommended surgical evaluation prior to endoscopy in patients with pain and an obstructed main pancreatic duct, though ERCP was recommended in poor surgical candidates or those who prefer a less-invasive approach [20▪▪].

A recent meta-analysis compared outcomes between multiple plastic stents and fully covered self-expandable metal stents (FCSEMS) used to treat main pancreatic duct strictures. One hundred and ninety-two patients received FCSEMS, and 106 received multiple plastic stents. Although there were no statistical differences in pain improvement or stricture recurrence, the FCSEMS population experienced significantly more adverse events (39 versus 14%) such as stent migration, biliary obstruction, and de novo pancreatic duct stricture formation [22]. Another prospective study conducted at a single center in India had similar findings for FCSEMS used to treat refractory main pancreatic duct strictures in 36 patients, with 86.1% of patients having symptom improvement but 36.1% experiencing some adverse event [23]. Sherman *et al*. [13▪] performed a prospective multicenter trial, which failed to show significant reduction in pain with the use of FCSEMS in chronic pancreatitis, but again demonstrated numerous adverse events, namely stent migration in 47.7% of patients. With these data in mind, the endoscopist should consider the risk and benefit profile when choosing between plastic stents and FCSEMS.

When transpapillary pancreatic duct stenting is difficult or fails, another option is transmural (either transgastric or transduodenal) approach with the use of endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD). EUS-PD can facilitate primary transmural stenting or rendezvous in which a guidewire is advanced antegrade from the main pancreatic duct to the duodenum where endoscopic retrograde pancreatography can be attempted. With technical success rates from 63 to 100%, it should be considered in the hands of an experienced endoscopist. This approach can be helpful in instances where pancreatic duct access is restricted by strictures, calculi, or obstructive mass lesions. Adverse events are common and include stent migration, pancreatitis, perforation, and pancreatic duct disruption [24].

MECHANICAL STONE EXTRACTION

Pancreatic calculi are composed of a sulfur and chloride core with sequential outer layers made up of rigid, high-density calcium carbonate [25]. They can develop in up to 60% of patients suffering from chronic pancreatitis, more commonly in men and those with heavy tobacco and alcohol use [15]. Mechanical stone extraction may be performed with the assistance of fluoroscopy and a retrieval balloon or dedicated stone retrieval basket, especially for calculi measuring less than 5 mm [3▪].

LITHOTRIPSY

For pancreatic duct calculi larger than 5 mm, available data support the use of extracorporeal shock wave lithotripsy (ESWL) given its more than 90% efficacy in fragmentation, as these calculi are typically impacted and difficult to extract (Fig. 2) [11▪▪,15]. Smaller and lower density calculi are associated with higher rates of clearance using ESWL combined with ERCP, so intervention earlier in the disease course is recommended [2▪,3▪]. Although this is the oldest and most studied intervention for the treatment of refractory pancreatic duct calculi, it is not widely available in the United States of America currently (Fig. 3) [14▪▪]. Recently, two randomized controlled trials (RCT) were completed, one in China (NCT04628273) and the other in Belgium and Italy (NCT00133835). The former ended in 2020 and aimed to evaluate the efficacy of ESWL in treating pancreatic calculi, while the latter was completed in 2022 and focused on comparing pain relief and calculus clearance between ESWL alone versus ESWL with ERCP. In addition, there are at least two ongoing RCTs investigating the effects of ESWL

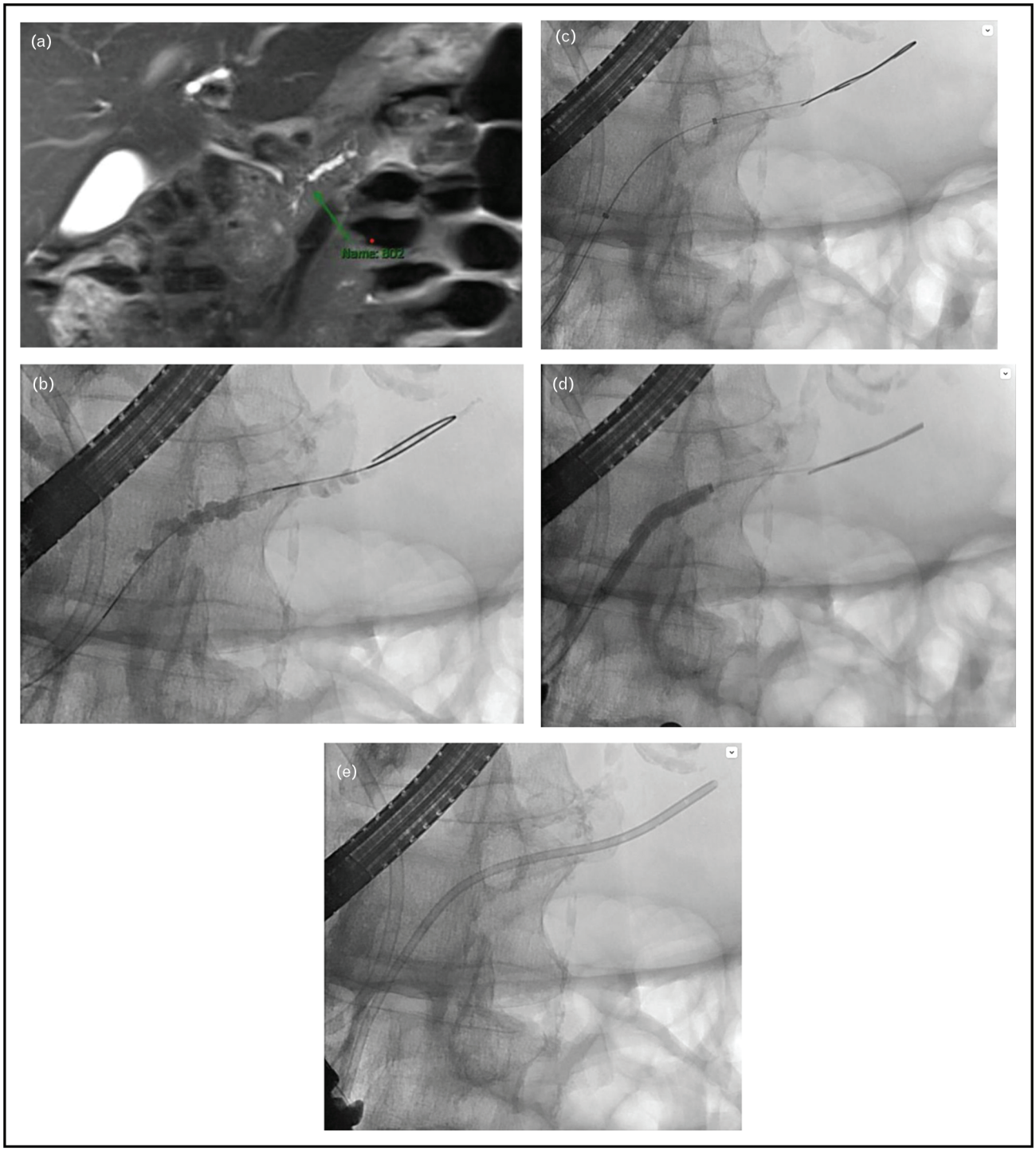

FIGURE 1. (a) Magnetic resonance cholangiopancreatography (MRCP) of a patient with chronic pancreatitis demonstrating a pancreatic duct stricture at the body and neck of the pancreas. (b) A pancreatogram reveals a dilated and irregular pancreatic duct in the body and tail upstream from the stricture. A wire has been placed into the duct. (c) A dilating balloon has been placed over the stricture. Radiopaque markers designate the distal and proximal ends of the balloon. (d) The dilating balloon is inflated to dilate the pancreatic duct stricture and facilitate pancreatic duct stent placement. (e) A 7 Fr plastic pancreatic duct stent is inserted to bridge the stricture and facilitate drainage and decrease pancreatic duct hypertension.

FIGURE 2. Extracorporeal shock wave lithotripsy setup demonstrating C-arm for targeting and delivering shocks.

on pain in chronic pancreatitis (NCT03966781, NCT04490083) [11▪▪]. Results of these studies are not yet published.

ESWL is contraindicated in pregnancy and certain coagulopathies that cannot be corrected, and caution is advised in patients with implantable devices. Adverse events in ESWL, such as skin erythema and local discomfort, are mainly because of the inability to precisely align the calculi with the focal point of energy release. Pancreatitis is the most common severe adverse event internationally, with rates estimated between 2.5 and 4.4% [3▪].

Pancreatoscopy-directed lithotripsy employing electrohydraulic lithotripsy (EHL) or laser lithotripsy are promising alternatives to ESWL. Pooled technical success rates of EHL and laser lithotripsy have been observed to be 91–92%, with complete pancreatic duct clearance rates as high as 62–80% in one session. Pancreatoscopy with lithotripsy is associated with lower number of procedures and shorter procedure times when compared to ESWL [26]. While data from small observational studies often combine EHL and laser lithotripsy, there is a trend toward technical success and improved pain scores [27]. A recent retrospective study looked at patients with difficult main pancreatic duct calculi. Patients were included if they initially underwent ESWL followed by ERCP but had persistent calculi. Of the 27 patients included, 11 underwent laser lithotripsy and 16 continued to receive ESWL and ERCP. Technical and clinical success, as well as mild adverse events, were similar between the groups [28]. The ASGE recommends consideration of ERCP with or without pancreatoscopy for pancreatic duct calculi more than 5 mm, post ESWL without spontaneous calculi clearance, or in patients with contraindications to ESWL [20▪▪].

Given the need for specialized equipment, EHL and laser lithotripsy are currently considered second-line therapies when ESWL fails, though they have the advantage of stone extraction and stricture treatment during the same procedure. Adverse event

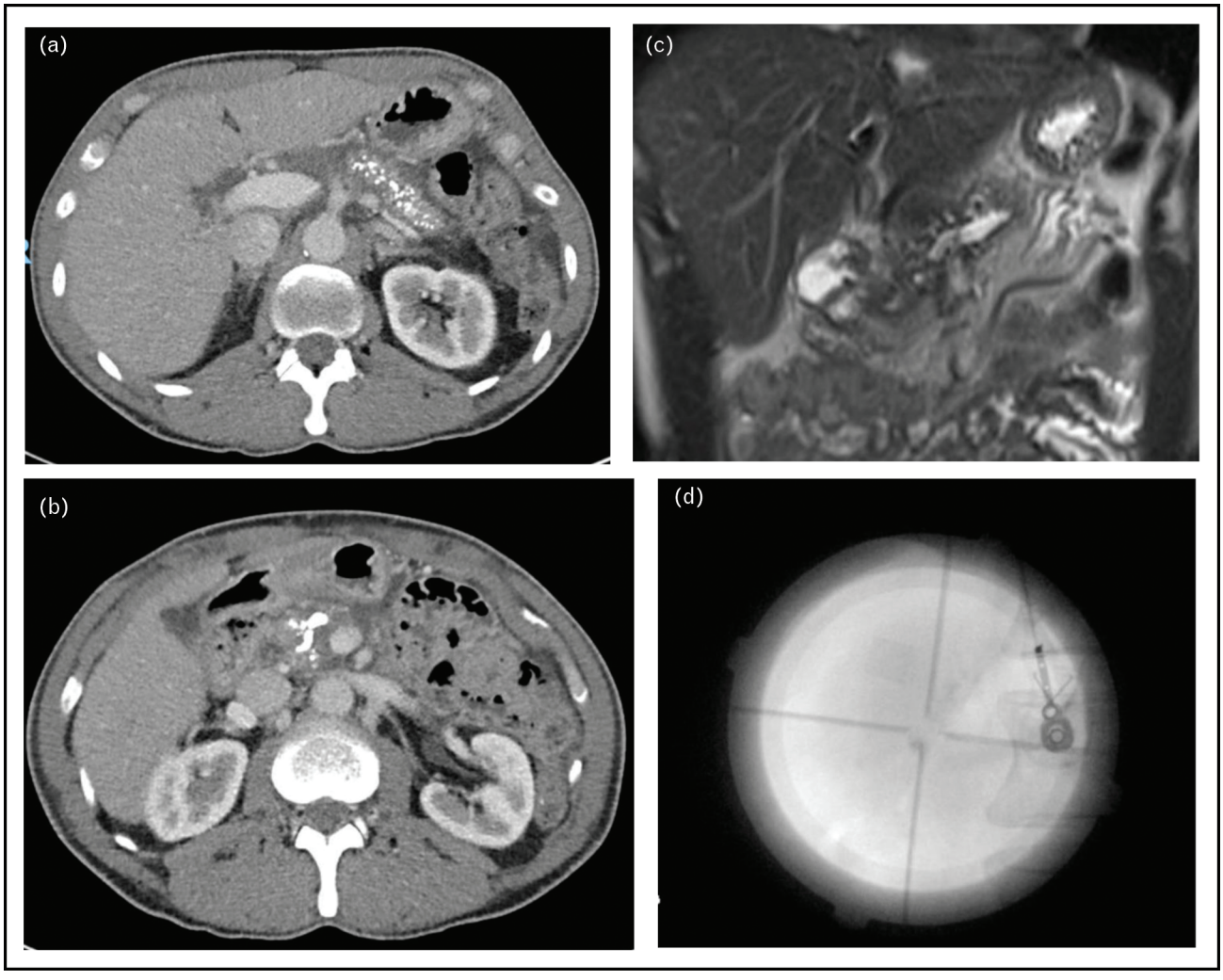

FIGURE 3. (a) Sagittal computed tomography (CT) revealing numerous pancreatic body and tail parenchymal calcifications in a patient with chronic pancreatitis. (b) Sagittal computed tomography (CT) imaging showing a large calcification/stone in the neck of the pancreas, which obstructs the pancreatic duct. (c) MRI demonstrating upstream dilation of the main pancreatic duct in the body and tail secondary to obstruction by the pancreatic calculus. (d) Fluoroscopy is used to triangulate the calculus and determine a target for energy delivery. Lithotripsy is then performed to fragment the calculus.

rates are higher compared to ESWL alone, with post-procedural pancreatitis reported in 8–28% of patients [27,29]. It is important to counsel patients on these risks in the context of managing difficult pancreas duct calculi refractory to ESWL and ERCP, as the alternative to EHL or laser lithotripsy would be surgery.

CELIAC PLEXUS BLOCK

The ganglia network known as the celiac plexus relays sensory afferent fibers to the pancreas. Gress *et al*. first described the celiac plexus block (CPB) technique in 1999, whereby bupivacaine and triamcinolone are injected into the axis to decrease pain (Fig. 4) [30]. Most data on the efficacy of CPB in providing palliation in patients with chronic pancreatitis are over a decade old. Since then, little has changed in terms of technique or data. New RCTs to validate the effectiveness of this intervention are finally on the way.

A publication by Pfau [31▪] recently reviewed the top tips for EUS-CPB and celiac plexus neurolysis (CPN), the latter used in palliation of pain in pancreatic cancer. This review includes the different injectates and techniques of performing CPB. As the plexus surrounds the celiac artery, instead of injecting the bupivacaine and triamcinolone on one side of the take-off, known as the unilateral approach, some advocate for injection of ½ of the injectant on both sides of the celiac artery (bilateral approach). No robust data favor either the unilateral

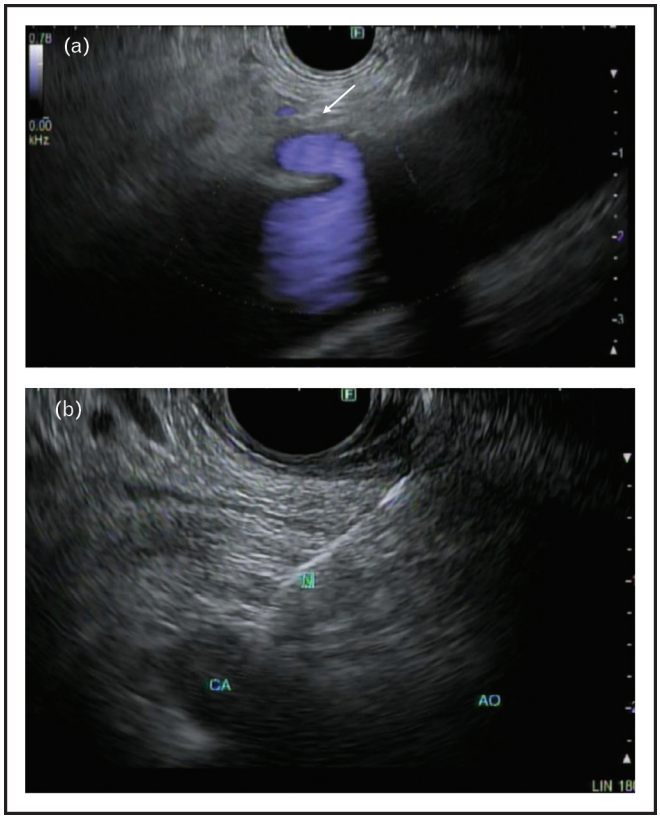

FIGURE 4. (a) Linear endoscopic ultrasound image showing blood flow of the aorta and celiac artery take off. The area above the take off (arrow) is the celiac axis. (b) Linear endoscopic ultrasound (EUS) image of a 22-gauge needle inserted into the celiac axis during a celiac plexus block.

or bilateral approach. When reviewing the sparse data for CPB and CPN in a prospective trial of 160 patients, bilateral injections were found to be more effective [32]. Pain relief was 70.4% on day 7 in the bilateral vs. 45.9% in the unilateral arm. However, another prospective randomized trial showed no difference in duration or time to onset of pain relief [33].

As robust data regarding the efficacy of EUS-CPB are lacking, a recent AGA Clinical Practice Update states that CPB should not be routinely performed to manage pain due to chronic pancreatitis. The decision to proceed with CPB in selected patients with debilitating pain in whom other therapeutic measures have failed can be considered on a case-by-case basis, but only after discussion of the unclear outcomes of this intervention and its procedural risks [15]. The recent ASGE guideline on endoscopy's role in managing chronic pancreatitis recommends that EUS-CPB be performed over the percutaneous approach because it is more efficacious, though the recommendation was made conditionally with low-quality evidence [20▪▪].

More recent studies provide more favorable data on CPB in managing chronic pancreatitis pain. Han *et al.* examined the impact of pancreatic endotherapy on QOL in chronic pancreatitis, where 49.2% of 120 patients underwent pancreatic duct stenting, 33% EUS-CPB, and 16.7% pancreatic duct stone lithotripsy. Significant QOL score improvement was noted up to 12 months after pancreatic endotherapy. Significant improvement in pain scores was reported at 1 and 6 months, but not at 12 months [34▪]. Furthermore, a systematic review and meta-analysis examining the efficacy of EUS-CPB for chronic pancreatitis pain was recently published. The study included five RCTs and seven observational studies from 1999 to 2022. The authors concluded that EUS-CPB is well tolerated and effective for pain lasting weeks to months. The adverse event rate was 4.2%, with diarrhea being the most common. There was no reported mortality [35▪].

There is a desperate need for current RCTs to perfect the technique and understand its true efficacy. Wilcox *et al.* are currently performing a two-armed randomized sham-controlled trial (CPB or sham saline injection into the gastric lumen) in patients with pancreatic pain to determine if CPB should be routinely performed for chronic pancreatitis pain. Until these data are available, the evidence for the efficacy of CPB in this setting is low at best [36].

CONCLUSION

Management of pain in chronic pancreatitis is challenging given the multifactorial and complex mechanisms responsible. Although surgery is recommended as the most durable option for patients, this approach comes with significant risks compared to endoscopic options. If ductal hypertension is suspected to be the cause of pain, addressing strictures or pancreatic duct calculi via ERCP, ESWL, or pancreatoscopy-directed lithotripsy remain the preferred endoscopic approaches. Refractory or neuropathic pain can be addressed with EUS-CPN, though data are mixed on efficacy and duration of effect. There are ongoing studies to better determine the efficacy of these endoscopic options, though novel approaches to address pain in chronic pancreatitis are lacking and necessary.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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