Endoscopic Retrograde Cholangiopancreatography for Management of Chronic Pancreatitis

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KEYWORDS

- Chronic pancreatitis • Endoscopic retrograde cholangiopancreatography
- Pancreatic stones • Pancreatic strictures • Pancreatoscopy-guided lithotripsy
- Extracorporeal shock wave lithotripsy

KEY POINTS

- Endoscopic therapy is the first-line therapeutic approach to pancreatic drainage in chronic pancreatitis (CP) for long-term management of pain.
- Endoscopic retrograde cholangiopancreatography (ERCP) and extracorporeal shock wave lithotripsy (ESWL) are the mainstay therapeutic modalities to manage symptomatic pancreatic duct stones in CP.
- Endoscopic treatment of pancreatic strictures by insertion of pancreatic stents aims to alleviate pain by decompression and remodeling of the stricture.

Video content accompanies this article at http://www.giendo.theclinics.com.

INTRODUCTION

Chronic pancreatitis (CP) is a persistent pathologic fibroinflammatory syndrome of the pancreas leading to irreversible parenchymal injury and destruction of the functional pancreatic tissue, resulting in permanent loss of function. The most common etiology is alcohol, followed by smoking, and other less common including autoimmune disease, genetic disorders, recurrent acute pancreatitis, obstructive causes, or idiopathic.[1] CP is a debilitating condition with a global incidence of 1.6 to 23 per 100.000 people.[2] The dominant symptom is abdominal pain, with other symptoms such as

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exocrine pancreatic insufficiency and endocrine dysfunction developing at variable rates.

The pathophysiology of pain in CP is multifactorial making management often challenging. One of the earliest proposed mechanisms for the development of pain is increased main pancreatic duct (MPD) pressure caused by ductal hypertension, which is suggested to be triggered by increased ductal stretch and parenchymal ischemia secondary to obstruction from stones or stricture. In these cases, decompressing therapies can be attempted to relieve the pain. Additionally, it has been suggested that pain can arise from chronic inflammation and central sensitization by neuropathic changes including structural changes to the intrapancreatic nerves and functional changes in both pancreatic nociceptive neurons and spinal and central neurons.[3,4] Due to its neuropathic involvement, as well as increase narcotic dependence among CP patients, pain may persist or relapse despite endoscopic interventions and MPD decompression.

Abdominal pain is often associated with a lower quality of life (QoL), higher rates of disability, and increased burden to the hospital system and healthcare costs, therefore it is the target for therapy. For decades, management was primarily surgical, however with recent technological advancements and more available endoscopic tools, the management has rapidly evolved to a less invasive approach. This article will focus on standard endoscopic retrograde cholangiopancreatography (ERCP) decompressive techniques for the management of CP complications.

APPROACH TO MANAGEMENT

To determine the best approach to pain management in CP, patients should be evaluated by an interdisciplinary team early in the course of the disease. A pre-interventional evaluation including cross-sectional imaging to tailor the best treatment strategy for the individual patient is crucial. The first step suggested to relieve pain includes lifestyle modifications and pharmacotherapy. Interventional therapy is recommended for patients with refractory pain and characteristics mentioned later in this article. Early studies have suggested that complete resolution of pain was more likely to be achieved from surgery than from endoscopic therapy.[5,6] The ESCAPE trial was a randomized controlled trial (RCT) that compared early surgery versus endoscopy-first approach and replicated these findings.[7] Although these studies have their limitations including the subjectivity of the pain score and no sham-control, data favor that surgical intervention at an earlier stage may help alleviate disease progression, leading to improved pain management, and the preservation of pancreatic function.[7]

A systematic review and meta-analysis concluded that surgical intervention provided long-term pain relief without significant difference in short-term relief when compared to endoscopy. Adverse events (AEs) and length of hospital stay were similar between groups.[8] Although data suggest that surgical interventions are superior to endoscopy for long term management of pain, endoscopic advancements have led societies to favor ERCP and/or extracorporeal shock wave lithotripsy (ESWL) as first-line approach to pancreatic drainage in view of its minimal invasiveness and low AE rate (**Table 1**).[9–12] Surgery should be reserved if endoscopic approaches have been exhausted or unsuccessful. Characteristics suggestive of long-term clinical success with ERCP and/or ESWL include absence of a pancreatic duct (PD) stricture, short disease duration, improved pain (with decreased narcotic use), smoking and alcohol cessation, pancreatic head stones, lack of PD divisum, if stenting was required, and steatorrhea.[10] In addition, patients with inflammatory

Table 1
Society guidelines on endoscopic management of painful uncomplicated chronic pancreatitis with obstructed main pancreatic duct

Society	Endoscopic Management to Relief Pain in Chronic Pancreatitis	Endoscopic Management of Pancreatic Stones	Endoscopic Management of Pancreatic Strictures
ESGE	1st line: ET and/or ESWL with evaluation of clinical response at 6–8 w; if unsatisfactory, discuss in a multidisciplinary team + consider surgery	1st line: ESWL for radiopaque >5 mm head/ body stones and ERCP for small <5 mm or radiolucent stones. ERCP following ESWL if no spontaneous clearance of stone fragments. POP-directed lithotripsy when ESWL is not available or for refractory stones after ESWL.	1st line: single 10 Fr PS for 1 uninterrupted year if symptoms improve after initial successful drainage. Stent should be exchanged based on symptoms or signs of stent dysfunction in follow-up imaging every 6 m. Refractory stricture: Multidisciplinary discussion to consider multiple PS. FCSEMSs needs further evaluation due to potential complications.
ASGE	1st line: ET in centers with this expertise, reserving surgery for cases of failure and/or recurrent symptoms.	ESWL + ERCP for symptomatic pancreatolithiasis refractory to standard ERCP techniques.	1st line: ERCP + dilation and/or PS placement after multidisciplinary article considering ET as the preferred initial therapy
ICGCP	Endoscopic or surgical treatment should be offered to patients with CP with persistent severe pain. Intervention is not recommended in asymptomatic patients to improve pancreatic exocrine and/or endocrine function or prevent cancer.	1st line: ESWL for MPD stones who do not get adequate pain relief with conservative management although a stent placement may be done first to relieve pain. ERCP for small stones or stone fragments after ESWL.	1st line: Straight PS across the stricture depending on the caliber of the stricture. Exchange or remove every 2–3 m. Multiple PS vs FCSEMS may be considered for refractory strictures. Surgical intervention for failed endoscopic procedures.
AGA	Surgical intervention > ET for long- term painful obstructive CP. For suboptimal surgical candidates or less invasive approach, ET is a reasonable alternative.	RCP with conventional stone extraction maneuvers for $\leq$5 mm MPD stones. For larger stones, ESWL and/or pancreatoscopy with intraductal lithotripsy may be required.	Prolonged stent therapy (6–12 m) for symptoms and remodeling MPD strictures. Preferred approach: place and sequentially add MSP in parallel (upsizing). Emerging evidence suggests that FCSEMS may have a role for this indication but additional research is necessary.

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Table 1
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Society	Endoscopic Management to Relief Pain in Chronic Pancreatitis	Endoscopic Management of Pancreatic Stones	Endoscopic Management of Pancreatic Strictures
ACG	Surgery > ET in obstructive CP for the long-term relief of pain if first- line endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful.		Sequentially adding MPS in parallel (upsizing) for 6–12 m for symptom treatment and remodeling of the stricture. FCSEMS may have a role for this indication, but additional research is needed.

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; CP, chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; ESGE, European Society of Gastrointestinal Endoscopy; ESWL, extracorporeal shock wave lithotripsy; ET, endoscopic therapy; FCSEMS, fully-covered self-expanding metal stent; ICGP, International Consensus Guidelines on Chronic Pancreatitis; MPD, main pancreatic duct; MPS, multiple plastic stents; PD, pancreatic duct; POP, per oral pancreatoscopy-directed lithotripsy; PS, plastic stent; SEMS, self-expanding metal stents.

masses might be difficult to treat endoscopically.[13] Favorable prognostic factors include complete stone clearance and remodeling of the stricture after stenting.[10]

Pain Characteristics that Require Intervention

- Pain related to large PD disease
- Persistent and continuous pain with or without exacerbations
- Refractory pain to medical treatment
- Pain lasting more than 3 months

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY FOR PANCREATIC STONES

Intraductal stones account for 50% of the cases of CP with PD obstruction, 18% by stones alone and 32% by a combination of stones and stricture, with an increase in prevalence over time after disease onset.[14,15] In a multicenter survey of 879 patients with either newly diagnosed or long-standing CP, stones were more frequent in men, heavy drinkers, and heavy smokers.[16] These seem to arise as evenly calcified stones or as radiolucent protein plugs that may or may not become calcified during progression of the disease.[17] The vast majority are calcified and radiopaque, solitary, located in the pancreatic head, with a mean size of 10 mm, and in 50% of the cases are associated with an MPD stricture.[10] Those seen in the nonalcoholic and idiopathic type of CP are usually larger and denser than those seen in the alcohol related type, which are typically small, irregular, and with hazy margins.[18]

Over the course of the last several decades, endoscopic techniques have been the mainstay therapeutic modality to manage symptomatic pancreatic stones (PS) by lowering the intraductal pressure and restoring drainage of the MPD. An increase in ductal pressure that causes pain indicates a dilation of the MPD of greater than 5 mm in diameter.[2] In these selected patients, with marked ductal changes, endoscopic therapy with PD clearance, either with or without ESWL, dilation, and stenting are approaches for PD decompression. This is justified by the belief that endoscopic drainage causes an increase in pancreatic juice flow resulting in a decrease in ductal pressure with relief of pain as a result. However, not all stones can be managed similarly for which selection of the ideal candidate is important to achieve successful treatment and prevention of AEs. In addition, these techniques can be challenging due to underlying MPD strictures and the difference between the size of the stone and the downstream PD.

The success of ERCP-guided treatment is largely influenced by the type, size, number, and location of the stone. In addition, the operator's skill set and the availability of equipment also plays an important role for successful stone clearance. Conventional ERCP with standard techniques including pancreatic sphincterotomy and balloon sphincteroplasty followed by balloon or basket extraction is often reserved for smaller (<5 mm) and radiolucent stones.[10,19] Additionally, patients with less than 3 stones in the head or body with a dilated MPD of greater than 5 mm are better candidates for standard ERCP.[2]

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY TECHNIQUE FOR STONE EXTRACTION

Before attempting stone extraction, a pancreatic sphincterotomy is first performed using a sphincterotome over a guidewire. This can be performed at the minor papilla if evidence of pancreas divisum. Subsequently, balloon sphincteroplasty up to 4 to 6 mm can be performed in case of a stricture in the pancreatic head.[2,20,21] After achieving adequate PD access, baskets/balloons can be used to extract the stones. One of the most common AEs is a trapped or broken basket during stone extraction[22],for which balloon has shown to be safer, as they can be detached if trapped.[23] Nonetheless, often these stones sharp edges puncture and destroy both dilation and extraction balloons easily. Other factors associated with failed stone clearance include size greater than 10 mm, diffuse location, underlying downstream stricture, and stone impaction.[24,25]

Larger stones (>5 mm) are often more challenging to extract by standard ERCP only, and in 70% to 90% of the cases additional treatment methods for stone fragmentation is required to facilitate extraction.[19] The reported success rate with the use of Dormia basket is only 9%.[26] Mechanical lithotripsy is often not effective because of the hardness of the stones and also by the challenge of manipulating the larger basket in a tortuous and thin caliber MPD along with impaction of the stone. Due to the higher risk of failure and AEs related to fracture of basket wires and duct injury, it is used less frequently than biliary stone lithotripsy.[22] Lithotripsy is often utilized for fragmentation and options include mechanical lithotripsy, ESWL, and intraductal therapy with pancreatoscopy.

EXTRACORPORAL SHOCK WAVE LITHOTRIPSY FOR PANCREATIC STONES

As an alternative to conventional endoscopy, stone fragmentation with ESWL was introduced. It can be performed with or without subsequent ERCP to clear stone fragments from the PD. ESWL is based on the principle of shock wave energy, initially introduced in the early 1980s for the treatment of urinary stones and a few years later expanded to biliary/pancreatic stones (PS).[27,28] Over the years, studies have supported the use of ESWL and it is currently the cornerstone treatment modality for patients with painful uncomplicated CP and large stones that are not amenable to extraction by standard ERCP.[10,12]

The goal of ESWL is to achieve stone fragmentation to lesser than 3 mm in size or demonstrate a decrease in density of the stone mass.[29] Small fragments can either pass off spontaneously or are extracted with subsequent ERCP. Criteria for technical success of MPD clearance following ESWL are classified as complete (clearance of > 90% of stone volume), partial (clearance 50%–90%), and unsuccessful (<50%). Clinical success is usually based on pain relief, decreased use of pain medication, decreased need for hospitalization, and improvement in QoL. ESWL has been associated with a highly effective stone fragmentation rate with complete clearance rates reported between 70% and 90%[30] and with decreased number of ERCPs required to complete treatment.[30,31]

The first case series of ESWL alone, reported in 1996 from Japan, showed pain relief in 79% of the patients at 3.5 years follow-up.[32] A large prospective single-center series (N = 1006) evaluated ESWL for large PSs not amenable to extraction with ERCP. The stones were fragmented to lesser than 3 mm size and then cleared by endotherapy within 24 to 48 hours with stenting when indicated. The authors observed that 90% of patients needed lesser than 3 sessions of ESWL and at 6 months, 84% had significant pain relief with a decrease in analgesic use.[33] The same group later published one of the largest ESWL studies, which included the 1006 cases reported previously, showing complete stone clearance rate of 72.6% with most of the patients requiring 3 sessions of ESWL and only 4% requiring 5 to 8 sessions to achieve stone clerance.[34] In a more recent meta-analysis of 3868 patients, complete stone fragmentation and ductal clearance was achieved in 86.3% and 69.8% respectively, resulting in absence of pain in over 50%.[35] In studies evaluating relapse, most patients with complete stone clearance who remained pain-free at a 2-year follow-up rarely experienced pain relapse thereafter.[35]

A long-term study of patients with CP undergoing ESWL followed by ERCP demonstrated that after 14 years of follow-up 66% of patients had long-term clinical benefits with decrease in hospitalization rate and delayed impairment in exocrine pancreatic function.[36] Furthermore, this study highlighted the importance of environmental factors such as smoking cessation for achieving superior clinical outcomes. Similar long-term benefits were noted in patients undergoing ESWL combined with ERCP with 60% of patients having absence of abdominal pain more than 60 months after undergoing treatment.[37] Interestingly, most of the patients in this study were young (<40 years old) for which the authors concluded that early intervention, especially in young patients, may alter the course of the disease and possibly prevent the need of surgery in the future.

EXTRACORPORAL SHOCK WAVE LITHOTRIPSY WITH OR WITHOUT ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

The use of ERCP following successful and complete fragmentation of stones by ESWL versus ESWL as standalone therapy has been a topic of debate. Studies have shown that if ESWL is performed adequately, the fragments may spontaneously clear obviating the need for ERCP.[32,38] Vaysee and colleagues demonstrated that ERCP did not provide additional benefit compared to ESWL alone.[39] An RCT comparing ESWL alone versus ESWL followed by ERCP demonstrated equal efficacy between the 2 arms, but the cost of the procedure was 3 times higher in patients who underwent both the procedures.[40] The authors concluded that ESWL is safe, but the addition of ERCP added to the cost without improving the outcome of pain control. However, other studies have reported that ESWL alone is not cost effective due to the need for multiple sessions (>10) to ensure adequate fragmentation and spontaneous clearance with an increased risk of impacted stone fragments at risk for pancreatitis.[41,42] In clinical practice, ERCP is routinely performed after ESWL as complete stone clearance is associated with improved abdominal pain. Both the European Society for Gynocological Endoscopy and International consensus guidelines recommend that patients with MPD head/body stones greater than 5 mm should undergo ESWL, followed by ERCP for duct clearance, if there has not been spontaneous clearance after adequate fragmentation.[10,11]

TIMING OF EXTRACORPORAL SHOCK WAVE LITHOTRIPSY WITH ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

The optimal timing of ESWL in relation to ERCP is not clearly defined and most institutions that offer ESWL have implemented their own protocols. It has been argued that delaying ERCP after ESWL helps reduce papillary and tissue edema and improves the success of stone clearance.[43] Theoretically, edema around the papilla after ESWL can potentially affect PD cannulation and immediate ERCP after ESWL may cause a “double attack on the pancreas”, increasing post-ERCP pancreatitis.[44] Nonetheless, same-day sessions may include faster clearance and relief of abdominal pain, decrease appointments, and travel burden with potential cost savings.[41]

In a small retrospective series, 30 patients were divided between early-ERCP (up to 2 days after ESWL) and delayed-ERCP (>2 days after ESWL) and found that 82% in the delayed group achieved stone clearance compared to 16% in the early group. The authors concluded that timing had a significant impact on the ability to clear the MPD and recommended delaying ERCP to allow tissue recovery.[43] However, this study only included patients who had initially undergone unsuccessful ERCP and required subsequent ESWL. Contradictory results were observed in a retrospective analysis that divided patients in 3 different groups according to the interval time between ESWL and ERCP: lesser than 12 hours, 12 hours to 36 hours, and greater than 36 hours.[44] The authors found that cannulation and stone clearance rates were similarly successful in patients with a history of ERCP, regardless of the timing. However, in those with a native papilla, delaying ERCP improved outcomes, as ESWL can increase the risk of AEs due to difficult cannulation.[44] On the contrary, a recent retrospective study found that delaying ERCP to allow peripancreatic tissue recovery does not affect outcomes and same-day ERCP after ESWL is safe and effective even in those with prior pancreatic sphincterotomy.[41] At the moment, there are no guidelines addressing this issue for which timing is usually left at the discretion of the institution.

SUCCESS, ADVERSE EVENTS, SAFETY, AND LIMITATIONS

Some factors associated with successful endoscopic clearance of stone fragments after ESWL include solitary stones, location at the pancreatic head, density of lesser than 820.5 Hounsfield units on CT scan, secretin injection during the procedure and pre-ESWL pancreatic stent placement.[42,45–49] Other predictive factors include absence of MPD stricture, short disease duration, non-severe pain, and less frequent pancreatitis attacks.[10] These factors may explain the different results between the studies.

ESWL is considered a safe procedure with an overall low AEs rate of 6% to 10% with mild pancreatitis the most common reported.[50,51] Pancreatitis has been reported in up to 4% but it is unclear if it is attributable to the same-day ERCP session[19,34,35] with similar incidence when compared with ESWL plus ERCP versus ERCP alone.[29] Other common AEs include pain and ecchymosis at the site of shockwave, abdominal pain, and fever.[50] Perineal hematoma, biliary obstruction, splenic rupture, bowel perforation, and liver trauma have been rarely reported.[19] Contraindications include non-correctable coagulation disorders, pregnancy, and presence of bone, calcified vessels, or lung tissue in the shockwave path.

Although ESWL is considered standard of care and first-line therapy for large stones, it has some limitations. Failure of stone fragmentation has been reported in approximately 10% of patients with a recurrence of 23% on long-term follow-up.[19,34] Extracorporeal shock wave lithotripsyby itself cannot address concurrent dominant PD strictures, thus additional endoscopic procedures are needed in this setting. In addition, fluoroscopy can detect only radiopaque stones. For radiolucent stones, an intraductal stent prior to ESWL may be placed to target the stones. Other disadvantages include cost, lack of reimbursement, variable efficacy depending on the experience of the operator (most services are provided by urologists), and limited availability in the United States (U.S), impacting generalizability of this approach. Extracorporeal shock wave lithotripsyshould be avoided in patients with extensive calculi involving multiple PD areas, presence of moderate/severe ascites, and suspected pancreatic head mass.[29] Stones in the tail of the pancreas are usually avoided due to risk of splenic rupture.[52]

PER-ORAL PANCREATOSCOPY

Per-oral pancreatoscopy (POP) with intraductal lithotripsy has emerged in recent years as a safe therapeutic alternative for the endoscopic management of PSs. POP has been available since the 1990s, but never gained widespread acceptance due to the technical difficulties, the requirement for 2 operators, and poor imaging quality.[50] With the introduction of the single operator cholangiopancreatoscopy system (SOCP) (SpyGlass DVS; Boston Scientific) in 2007, some of these problems were elucidated but still was underutilized due to suboptimal fiber optic imaging.[53] Later, in 2015, this system was upgraded to a digital version (SpyGlass DS; Boston Scientific) with a 60% wider field of vision, a larger working channel (13 mm), specialized irrigation channel, and improved image quality. Pancreatoscopy-guided lithotripsy (PGL) has been suggested as an alternative to ESWL for PD stones that are refractory to conventional ERCP and/or when ESWL is not available.

PER-ORAL PANCREATOSCOPY-GUIDED FRAGMENTATION SYSTEMS

Pancreatoscopy-guided lithotripsy uses 2 different intraductal fragmentation techniques, electrohydraulic lithotripsy (EHL) and laser lithotripsy (LL), both with different mechanisms of action. EHL consists of a charge generator and a bipolar probe that produces a spark at its tip in an aqueous solution. The sparks produce vapor plasma and subsequently an oscillating cavitating bubble, generating high-amplitude hydraulic pressure waves, which are absorbed by the stones resulting in their fragmentation. In LL, laser light of a specific wavelength is concentrated on the stone's surface to produce wave-mediated fragmentation. The neodymium: yttrium-aluminum-garnet (Nd: YAG) laser breaks stones through the initial formation of plasma on the stone surface which subsequently absorbs the infrared light energy powerfully and generates a strong shockwave. The holmium: YAG laser lithotripsy occurs primarily by a photothermal mechanism where energy is directly transmitted from the laser to the stone.[54] In both mechanisms, the probe needs to be directed at the stone at a distance of greater than or equal to5 mm without making contact. If the probe is not deployed near the stone and away from the duct wall, the shock waves may induce damage or even perforation to the wall.[55]

PER-ORAL PANCREATOSCOPY-GUIDED LITHOTRIPSY TECHNIQUE

The pancreatoscope has a small diameter (3.3 mm/10 Fr) and can be introduced through the working channel of a duodenoscope. It has its own working channel, through which accessories (minimum diameter 1.2 mm/3.2 Fr) can be introduced. When performing PGL, a pancreatic sphincterotomy and/or a sphincteroplasty of 4 mm are necessary to enter the MPD.[2] Once deep wire access is obtained, the pancreatoscope can be advanced to the stone, the guidewire removed, and lithotripsy is performed under direct vision. Stone fragments can be then removed with standard ERCP techniques including balloon sweep and basket retrieval. If a stricture is encountered downstream to the stone, a step-up-dilation up to 10 Fr should be performed prior to attempting POP.[2] It has been suggested that after PGL, a PS (9–10 Fr) should be placed if there is an underlying stricture.[56] Saline irrigation should be reduced to a necessary minimum and the patient should receive nonsteroidal anti-inflammatory suppositories and intravenous hydration as high pressure in the MPD can increase the risk of post-ERCP pancreatitis (PEP).[56] In addition, prophylactic antibiotic use is recommended in all cases due to risk of systemic bacterial translocation during saline irrigation.[55] Video 1 shows a case of effective PD stone fragmentation with EHL.

PER-ORAL PANCREATOSCOPY-GUIDED LITHOTRIPSY OUTCOMES

In recent years, several retrospective studies have demonstrated a stone clearance rate ranging from 43% to 100% with recent larger studies showing rates between 80% and 90%.[50,51,57–60] This variability can be explained by the retrospective designs of the studies, small sample sizes, short follow-up, and varied patient selection and treatment protocols. In a retrospective review, patients who underwent ERCP with POP had higher technical success than those with ERCP alone (n = 129, 98.9% vs 87.6%, $P < .001$), but required more ERCPs (3.1 vs 1.9). ERCP with POP was associated with larger stone size (8.9 vs 6.1 mm, $P = .001$), more stones per case, and more impacted stones.[61]

In a meta-analysis that included 16 studies, the overall technical and clinical success rates were 76% and 77% respectively. Factors influencing lower technical success included multiple or impacted stones, size greater than 17 mm, strictures, difficulty in cannulating the PD due to angulation, poor visibility, and equipment failure.[62] On direct comparative analysis, LL had higher overall rates of technical and clinical success with comparable AE rates and less procedure time.[62] The advantage theoretically was explained by the ability of LL to fragment denser stones. The presence of 3 or more stones has been reported as a significant independent risk for failure of PGL.[50] Contrary, increased stone burden has led to higher technical success rates as these patients had higher probabilities of having smaller stones which are easier to clear compared to larger stones.[61]

Conversely, a meta-analysis evaluating POP with either LL or EHL for the treatment of difficult PD stones defined as failure of conventional ERCP, showed high technical success rates (91%) but no significant difference between EHL and LL.[63] Currently, there is no comparative study evaluating which of these 2 techniques is more effective in pancreatic stone fragmentation. In most of the studies, POP was performed after unsuccessful stone fragmentation with standard ERCP and in some ESWL, highlighting POP as an alternative option when first-line therapies fail.[62,63] However, can this be a promising first-line treatment for CP patients with obstructive stones? In a prospective, single-center study evaluating the efficacy and safety of EHL as a first-line treatment for stones in the head/neck of the pancreas, authors reported a technical success rate of 70.6%, which was mainly limited by the inability to achieve deep cannulation of the PD. When POP was successful, the success rate increased to 92.3% with complete stone removal in 80% of the patients with a median of 2 ERCP and 1 EHL procedure. Clinical success was achieved in 72% of the patients, with greater than 50% pain score and opioid use reduction over a 6-month follow-up period.[64] However, there was a trend towards higher pain scores and more opiate use at 6 months, suggesting that its benefit may not be long-lasting. A recent prospective multicenter trial also demonstrated high technical success rates (92%) with persistent stone clearance and pain-relief (82%) at 6 month follow-up.[56] However, this data must be carefully interpreted and might not represent both lithotripsy techniques, as only 1 patient underwent LL while the rest underwent EHL. A retrospective 4 center study evaluated LL for PD stones in 28 patients who underwent 1 to 4 POP-LL sessions. Prior history of ESWL or EHL not excluded. The authors demonstrated a total stone clearance of 79% and a clinical success rate of 89% at a median of 13 months with improvement in pain, decreased narcotic use, or reduced hospitalizations. It was concluded that LL could complete stone clearance but at least 1 subsequent PGL or ERCP is needed for additional stone extraction and/or stricture therapy.[57] More prospective studies are needed to assess direct comparison and cost-effective analysis when POP is undertaken.

PER-ORAL PANCREATOSCOPY-GUIDED LITHOTRIPSY ADVANTAGES, ADVERSE EVENTS

Although studies are still sparse, one of the advantages of PGL is direct stone visualization, facilitating precise fragmentation, and confirming clearance of the PD. In addition, concomitant strictures can be assessed and combined with other interventions including stricture dilation, and/or stenting in a single session. Although direct visualization can reduce duct injury, it is important to avoid long periods of PD exposure to high energy levels in a single session, given the risk of thermal injury to the duct wall. Some of the limitations include significant costs, the need for device expertise to achieve cannulation, as well as the need for longer procedure durations, and moderate success rates when compared to conventional strategies.[63] Additionally, the success of a pancreatoscopy will largely depend by the MPD anatomy, strictures, or obstructing stones. For cephalic stones, PGL could be challenging due to device instability and/or difficulty visualization. Compared to standard ERCP or ESWL, PGL is more technically challenging as it is often difficult to advance the pancreatoscope catheter even in a normal caliber PD with some authors suggesting that an MPD diameter of 4 to 5 mm is necessary to allow passage.[55] Compared to EHL, LL is more expensive, needs special precautions, and the equipment is less compact.[62] The overall AE rates after PGL have been reported at 10% to 12%[10,60] and mostly consisted of mild pancreatitis; similar findings when compared to ESWL.

Although PGL appears to be effective, its precise role in the treatment of difficult stones remains unclear. Upcoming devices suitable for the single-operator cholangiopancreatoscopy could open new additional option for therapeutic procedures. Currently there are no standardized protocols or treatment strategies, thus more studies are needed to validate its role in the therapeutic algorithm of CP. However, according to available studies and societies recommendations, PD stones in CP can be managed as suggested in the algorithm illustrated in **Fig. 1**.

MAIN PANCREATIC DUCT STRICTURES

Benign strictures of the MPD occur in CP because of inflammation and/or fibrosis. They can present as single or multiple and classified as dominant, or nondominant.

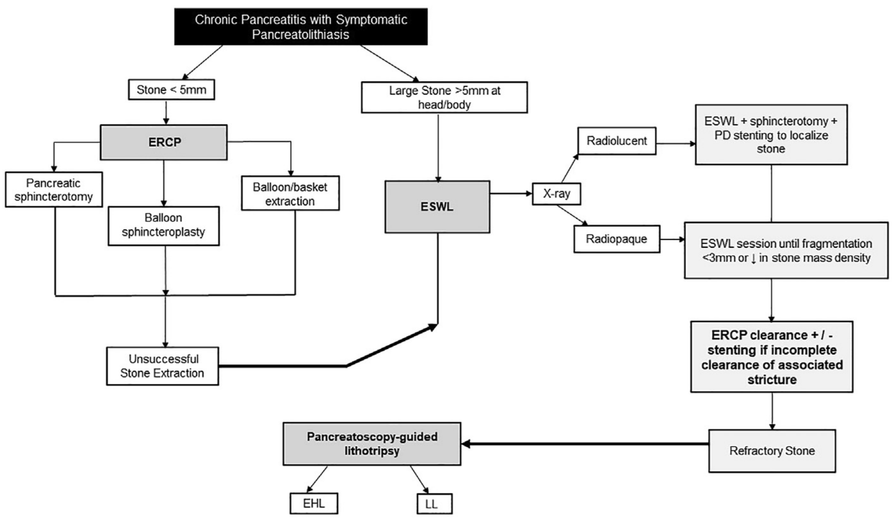

Fig. 1. Suggested flowchart for the management of chronic pancreatitis with symptomatic pancreatolithiasis. EHL, electrohydraulic lithotripsy; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; LL, laser lithotripsy; PD pancreatic duct.

Dominant strictures are associated with upstream MPD dilation and often lead to pain and superimposed acute on CP. Endoscopic treatment of PD strictures by insertion of pancreatic stents aims to alleviate pain by decompression and steadily stricture dilation to a size that will allow stent removal without recurrence. Long-term clinical success is achieved when the patient remains pain free during the year following stent removal. Technical success has been defined as successful stent insertion across a dominant MPD stricture or the most distal (tail) stricture when multiple strictures are present.[10] Studies have reported a technical success rate of 90% of a first stent insertion.[6,65,66] Nonetheless, these strictures are often tight and difficult to treat for which dilation prior to stenting is recommended, relieving abdominal pain in more than 50% of patients.[65] **Fig. 2** illustrates a case of a severe head/neck PD stricture where dilation was performed prior to stenting.

A greater extent of dilation and stricture remodeling can be achieved by upsizing the caliber of the stent or by sequential placement of multiple side-by-side plastic stents (PS).[67,68] However, this requires multiple interventions, as durable stricture remodeling usually takes up 6 to 12 months of incremental replacement and upsizing of stents. Refractory strictures, defined as symptomatic dominant strictures that persist or relapse after greater than 1 year of single 10 Fr stent insertion,[10] may be treated by multiple side-by-side PS or self-expandable metal stents (SEMS).[69]

For pancreatic stenting to be successful, it is paramount to understand the cause of the stricture, as well as to evaluate the anatomy with dedicated pancreatic imaging. If the etiology of the stricture is not evident, excluding malignancy with cytology brushing should be initially performed.[12] Some of the PD stricture studies discussed later are summarized in **Table 2**.

SINGLE PLASTIC STENTS

Insertion of a single PS has been used as the initial endoscopic therapy for symptomatic MPD stricture caused by CP.[10] Several stenting designs have been proposed, including, straight, curved, wedge or single pigtail but, the presence of side holes to allow drainage of side branches are the distinguishing feature of dedicated pancreatic stents. Their ends also vary with 1 or 2 internal flanges to prevent migration and 2 external flanges or pigtail to prevent inward migration.[70] To improve pancreatic stenting, a nonflanged, multi-fenestrated PS with an ultra-tapered tip (Johlin Wedge Stent; Cook Medical, Winston-Salem, NC) was developed. These are made of a soft polymer blend material that minimizes injury by the tip and can be customized per patient to a

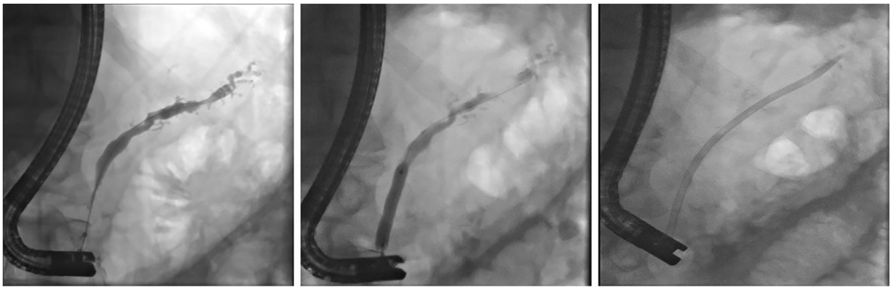

Fig. 2. Pancreatogram with evidence of severe chronic pancreatitis, classified as Cambridge grade 5. Notable stricture in the pancreas head. Ballon dilation to 6 mm of the strictured portion of the MPD followed by the placement of a 10 Fr PS across the stricture. MPD, main pancreatic duct; PS, plastic stent.

Table 2
Key studies comparing the different modalities and types of stents for MPD strictures in CP

		Key Findings							
Type of Stent	Patient Group	Type of Study	Stent Duration (m)	Long-Term Outcomes	Median Follow-up	Pain Relief	Complications	Comments	Related Study
PS vs surgery	Painful CP with MPD strictures predominantly head/body. N = 140 Randomization: 76 underwent surgery 64 treated endoscopically 33/64 stented	Prospective	16 (exchange every 2–4)	Technical success: 62/64 (97%)	5 y	Complete or partial pain relief after ET at 5 follow-up in 65% (of 64 ET patients) ↓ Melzack score	Post-ERCP complications: 5/64 (8%) bleeding: 2 pancreatitis:2 pancreatic abscess: 1 mortality: 0	Pseudo-randomization High bias risk Not an ITT analysis.	Díte et al,[5] 2003
Johlin-JPWS® stent (Cook®)	Painful CP N = 13	Retrospective	4.5 ± 3 (0.5–3.5)	91% clinical success rate at the end of follow-up	11 ± 7 m (1.5–24)	11/13 patients ↓analgesic +/−reduction in the frequency of pain	Uncomplicated acute pancreatitis (10%) No stent migration		Boursier et al,[71] 2008
Single PS temporary pancreatic stenting vs non- stenting	Severe CP with dominant MPD stricture Stenting: N = 20 Non-stenting: N = 22	Prospective, non-randomized	15.2 (exchange every 2–3)	Re-stenting: 2/20 vs 3/22	5.2 y	Pain relapses: Stenting: 3/20 Non-stenting: 11/22	NA		Seza et al,[65] 2011

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Table 2
(continued)

		Key Findings							
Type of Stent	**Patient Group**	**Type of Study**	**Stent Duration (m)**	**Long-Term Outcomes**	**Median Follow-up**	**Pain Relief**	**Complications**	**Comments**	**Related Study**
MPS after single PS refractory stricture	Severe CP requiring pancreatic stenting N = 19	Prospective	7 (5–11)	84% asymptomatic at 38 m mean follow-up	38 m (17–55)	Symptom-free period: longer after removal of MPS than by single PS	10.5% symptom recurrence	First study to assess the placement of MPS within the PD for CP dominant strictures in the head of the pancreas	Costamagna et al,[68] 2006
Multiple vs SPS	Painful CP and distal MPD obstruction N = 85 Divided in 3 groups: A: exclusively one stent B: 1 or 2 PS C: 2 PS during the stenting period	Observational	A:14.5 (9–27) B:23 (16–33) C: 22.5 (15–31)	Median procedures A: 3 (1–3) B: 4 (3–5) C: 3 (2–3) Clinical success: Group C:50% Group A:88.2% Group B:74.2%	89 m (64–108)	Refractory stricture with MPS: pain recurrence after PS:10 patients (29%)	Stent migration: A: 3 (17%) B:9 (26%) C: 6 (19%) post-ERCP pancreatitis: 2 duodenal perforation: 1	Initial single stenting deployment was associated with a higher rate of clinical success compared to patients with initial placement of 2 stents.	Papalavrentios et al,[101] 2019
MPS after refractory PS	CP and refractory single PS N = 48	Retrospective analysis of a previous prospective study	6.8 (6–18)	83.3% MPD stricture resolution after stent removal 100% refractory strictures re-treated and 37.5% cured	9.5 y (0.3–15.5)	74.4% remained asymptomatic after initial stricture resolution	Pancreatitis recurrence or pancreatitis type pain: 25% Refractory stricture:10.4%		Tringali et al,[67] 2019

FCSEMS (sustained response after removal)	CP strictures refractory to PS N = 6	Prospective	3 (87–100 d)	Recurrent PD stricture in 3/5 patients after 1-and 4-m post removal	4 w after stent removal	>50% pain relapse after stent removal, which later resolved after re-stenting for 3 m	No complications reported	Limitations: Pilot study	Sauer et al,[86] 2008
FCSEMS for refractory PD strictures	Previously drained stents for CP N = 33	Retrospective Multicenter (USA experience case series)	14	Recurrence rate 0% in 8 m	8 m	Using VAS pain score:87.1% significant pain reduction with reduced narcotic use	Cholestasis after stent placement: 6.06% Worsening abdominal pain: 8.2%		Sharaiha et al,[100] 2019
Investigational 4- 6-cm-long soft pancreatic FC-SEMS	CP with PS placement within 90 d of FCSEMS N = 67	Prospective, multicenter	6	Clinical success rate: 6.1%	6 months after FC-SEMS removal	Pain reduction 6 mo after FC-SEMS: 26.1%	Procedure-related SAEs occurred in 31.3% (21/67) Study stent migrations occurred in 47.7% (31/65)	Clinical success rate was lower than the performance goal set for the study (53%)	Sherman et al,[85] 2023
FCSEMS vs PS	CP with persistent MPD strictures after SPS N = 80 FCSEMS N = 26 PS N = 54	Retrospective	FCSEMS: up to 6 m PS- 3–6 m	MPD stricture resolution rate: FC-SEMS: 87% PS: 42%	FCSEMS: 33.7 m PS: 36.2 m	Using VAS pain score: FCSEMS: 76.9 PS: 53.7	Spontaneous stent migration FCSEMS: 26.9% PS: 3.7%	FCSEMS had favorable clinical efficacy (pain relief), but > spontaneous migration 1and de novo strictures	Lee SH, Kim YS et al,[79] 2021

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Table 2
(*continued*)

		Key Findings							
Type of Stent	**Patient Group**	**Type of Study**	**Stent Duration (m)**	**Long-Term Outcomes**	**Median Follow-up**	**Pain Relief**	**Complications**	**Comments**	**Related Study**
MPS vs FCSEMS	106 MPS vs 192 FCSEMS patients from 13 studies refractory to single PS	SRMA	Mean range for SEMS: 2–7 for MPS: 6.6–23.7	Weighted pool rates (WPR) for pain recurrence after MPS: 11.8% after SEMS: 14.8%	Mean range between 5.5–34 m between studies	WPR of pain improvement resolution after SEMS: 88% after MPS: 89%	Risk of stent migration was higher with FCSEMS	Meta-analysis for safety and efficacy did not show any advantage of SEMS over MPS in refractory PD strictures Limitations: all studies were observational, increasing risk of bias	Sofi et al,[80] 2021

Abbreviations: CP, chronic pancreatitis; ET, endoscopic therapy; FCSEMS, fully-covered self-expanding metal stent, ITT, intention-to-treat; mo, months; MPD, main pancreatic duct; MPS, multiple plastic stents; PD, pancreatic duct; PS, plastic stent; SAEs, severe adverse events; SEMS, self-expanding metal stents; SRMA, systematic review and meta-analysis.

length of less than or equal to 22 cm. A single-center retrospective study by Boursier and colleagues evaluated this stent and concluded that it is effective for the immediate and medium-term pain relief and may result in less frequent replacements.[71] The deployment of PS is like biliary stents and whether a pancreatic sphincterotomy should be performed has not been addressed but it should be considered when placing larger caliber stents (>8.5 Fr).[10,70]

Current guidelines recommended index placement of a single 10 Fr PS for 1 uninterrupted year.[10,12] In a retrospective study, patients who were treated with lesser than 8.5 Fr stents were more likely to be hospitalized for abdominal pain than those who received 10 Fr stents.[72] Stents can be exchanged until stricture resolution in a regular time interval or an as-needed basis according to clinical manifestations or suggestion of stent malfunction.[10] In clinical practice most centers favor a regular stent exchange after 3 month as previous studies showed less septic complications when compared to “on-demand” stent exchange or longer intervals.[5,65,66,71,73–77] At this time, a new stent should be inserted if the stricture remains significant.

MULTIPLE SIDE-BY-SIDE PLASTIC STENTS

For refractory strictures, placement of multiple plastic stents (MPS) can be considered. This technique can avoid blockage of a side-branches compared to a single large caliber stent. In a study of 19 patients with refractory strictures, a median of 3 PS were placed and removed after 6 to 12 months. During a mean follow-up of 38 months after stent removal, 84% of patients were asymptomatic, and 10.5% had symptomatic recurrences. The authors concluded that this approach allows for shorter resolution time with fewer stent exchanges.[68] More recently, the same group re-evaluated the long-term results in 48 patients with 89.5% achieving stricture resolution after a single session and 77.1% pain relief during a mean follow-up of 9.5 years.[67]

SELF-EXPANDABLE METAL STENTS

The use of fully covered self-expandable metal stent (FCSEMS) of 6mm-10 mm in diameter as a treatment option for refractory PD strictures has been of recent interest. Currently, none are approved by the U.S. Food and Drug Administration for the PD and most of the U.S and Europe studies have typically used off-label biliary FCSEMS. A meta-analysis including 10 studies with 163 patients treated with FCSEMSs showed a stricture resolution rate of 93% with a recurrence rate of 5%.[78] Similarly, a retrospective study of patients with persistent PD strictures after at least 3 months of initial single PS, showed that FCSEMSs had statistically higher stricture resolution rate compared to PS, but with higher AEs such as spontaneous migration and de novo strictures.[79] A recent systematic article and meta-analysis that compared FCSEMSs and MPS found no differences in pain improvement or stricture recurrence, and like prior studies, it showed higher rate of serious AEs with FCSEMSs.[80]

Several studies from Asia have used PD-specific 6-10 mm FCSEMSs that are more flexible with antimigration features.[81–84] In a long-term study using this type of stent, for refractory strictures, 23% patients experienced recurrence during the 11-year follow-up with a median time to recurrence of 2 years.[84] A novel short, saddle-shaped stent (BONASTENT M-intraductal; Standard Sci Tech Inc, Seoul, South Korea) was developed for targeted intraductal placement and easy retrieval by a lasso attached to the duodenal end.[82] In 25 patients treated with this stent, 100% achieved stricture resolution with only 2 patients developing recurrence at a median follow-up of 24 months following stent removal.[82] On the contrary, in a prospective multicenter study of 67 patients treated with a 4-cm to 6-cm-long soft pancreatic FCSEMS, only 26.1% achieved complete or partial pain relief by 6 months after stent removal and almost half of patients experienced stent migration.[85]

Duration of placement and exchange intervals are still unclear. A study by Sauer and colleagues, found that more than 50% of patients had pain relapse after FCSEMS removal, that later resolved after placement of another one for an additional 3 months.[86] Although studies are promising, prospective studies are needed to evaluate optimal patient selection, as well as long-term efficacy and safety, since most studies have used off-label biliary FCSEMS.

ADVERSE EVENTS OF ENDOSCOPIC PANCREATIC STENT THERAPY

The most common AEs associated with PS are pancreatitis and worsening abdominal pain with an average occurrence of 6%-10%, followed by sepsis, cholangitis, and post-sphincterotomy bleeding.[10,70] Severe pancreatitis is rarely documented. Stent migration, stent occlusion, and stent-induced strictures have also been reported. Proximal and distal migration have been reported in 2.7% and 3.6% of patients, respectively.[87] PD stenting can induce duct changes, including de novo strictures reported in up to 27% of patients who underwent stenting prophylactically (though many of these patients had a normal pancreas).[10,88] Higher rates of de novo-strictures have been reported with FCSEMS, likely related to their flared ends inducing ischemic injury from excessive compression of the MPD due to outward radial forces.[10,70,84]

BENIGN BILIARY STRICTURES

Benign biliary strictures (BBS) have been reported in 3%-46% of patients with CP.[89–91] The incidence may be higher as many of the cases remain asymptomatic. CP-related BBSs are often seen late in the course of the disease as progressive, irreversible pancreatic parenchymal fibrosis leads to stricturing of the distal bile duct. A study of 2153 CP patients aimed to develop a prognostic nomogram for BBS in CP patients. They found that some risk factors associated with the development of these strictures included smoking, MPD morphology, male gender, body mass index, and age of onset of CP, with the latter two and type of pain identified as risk factors for symptomatic strictures.[92] BBS can be present with asymptomatic elevation of liver functions test, jaundice, abdominal pain, and cholangitis.

ERCP for bile duct drainage is recommended in patients presenting with jaundice and subclinical cholestasis for greater than 1 month to prevent the development of secondary biliary cirrhosis. However, the data supporting the latter are notably absent. ERCP with stent placement is considered first-line therapy, unless the patient has a pancreatic head mass suspicious for malignancy[89,93] or if there is no resolution after 1 year or 3 sessions of endotherapy.[10] It is important to keep in mind that transient biliary obstruction can occur secondary to acute inflammation in the setting of edema from acute on CP. However, this usually resolves without specific treatment and does not require intervention.[94] Cholangitis is rare but can occur especially if history of previous biliary sphincterotomy and warrants urgent biliary drainage.[89]

Due to the fibrotic nature of BBS-related to CP, MPS are preferred over a single PS as it can provide gradual remodeling of fibrotic tissue.[95] However, if feasible, FCSEMS are recommended over MSP as they provide similar efficacy without the frequent need for stent exchange.[9,96,97] Currently, only 1 stent (WallFlex stent Boston Scientific) is FDA-approved with a 12-month dwell time for treatment of CP-related BBS. In a multicenter RCT, patients treated with FCSEMS for 12 months had similar stricture resolution rates compared with MPS (76% vs 77% respectively) but required significantly less reinterventions over 24 months.[98] A prospective study evaluating the long-term success and safety of FCSEMS showed that nearly 60% of the patients remain asymptomatic and stent free for up to 5 years after 1 FCSEMS was placed for 10 to 12 months. Severe CP and longer stricture length were identified as predictors of treatment failure.[99] From the data available, placement of a single FCSEMS should be considered as the first-line treatment in BBS related to CP.

CLINICS CARE POINTS

- Pain is the main indication for endoscopic therapy in CP, and in case of intraductal stones and/or strictures, endoscopic treatment can help reduce the intraductal pressure by restoring a sufficient drainage of the MPD.
- Standard ERCP with sphincterotomy, downstream stricture dilation, and balloon and/or basket retrieval may remove small stones but up to 50% of stones will be refractory to this approach.
- Extracorporeal shock wave lithotripsy is the standard of care for managing large stones (>5 mm) and those not amenable to extraction by standard techniques.
- Pancreatoscopy-guided lithotripsy using EHL or LL is a useful tool in treating ductal obstruction with a relatively higher success in cases not amenable to ERCP techniques or failure to ESWL but, more data are needed for better definition of indications and role in the current algorithms.
- Pancreatoscopy-guided lithotripsy can also be paired with an additional intervention, such as PD stricture dilatation and/or PD stenting, in a single session.
- For PD strictures, guidelines recommended index placement of a single 10 Fr PS for 1 uninterrupted year.
- For refractory strictures, MPS or FCSEMS have shown similar clinical and technical success rates, but higher risk of stent migration and de novo strictures with FCSEMS.
- ERCP with stenting in distal biliary strictures related to CP is recommended in patients presenting with jaundice and subclinical cholestasis to prevent the development of secondary biliary cirrhosis.

DISCLOSURE

The authors have nothing to disclose.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.giec.2024.02.004.

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