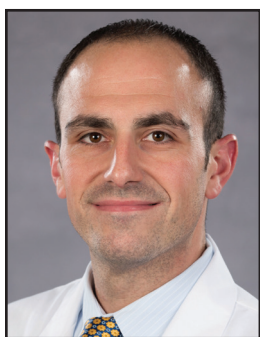


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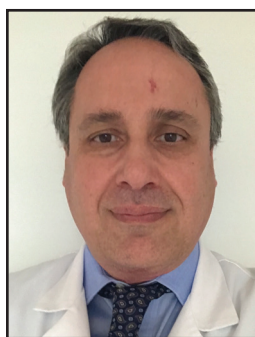
## Pancreatic Duct Strictures: Evaluation and Management



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### INTRODUCTION

**A**ccurate classification, diagnosis and management of pancreatic duct (PD) strictures can pose significant challenges to the treating endoscopists for a variety of reasons, including previously limited diagnostic options, compounded by the underlying disease processes which led to the stricture. The roles of endoscopic intervention are to first evaluate the stricture to firmly exclude a malignant etiology, and second, to provide interventional options aimed at ductal decompression, most commonly for pain relief. In benign disease such as that caused by chronic pancreatitis (CP), PD stones may form independently or be associated with a CP stricture. This may lead to clinical symptoms due to ductal obstruction further complicating the clinical picture. Furthermore, traumatic pancreatic injury related strictures sometimes have leaks associated with them, leading to recurrent collections, which are by themselves difficult to manage.

The primary aim of this review is to provide a concise differential diagnosis of the etiologies

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of PD strictures and to understand the diagnostic and therapeutic endoscopic management options. Secondary aims include exploring the management options for the secondary processes that can be associated with PD strictures, including PD stones, leaks and collections. Lastly we will explore the role of surgery for these disease processes.

### The Importance of Anatomy

To appropriately understand the PD anatomy, and plan any pancreatic endotherapy, it is imperative to dive into the embryology of the pancreas. The pancreas arises from 2 endodermal outpouchings (called “buds”) from the primitive duodenum. The small ventral bud forms the inferior (lower) portions of the head/uncinate, whereas the majority of the pancreas including the superior (upper) portions of head/uncinate, as well as the body and tail arise from the dorsal bud. The duct from the distal portion (body/tail) of the dorsal bud unites with the ventral bud duct to form the main PD (of Wirsung), and the residual proximal duct (head) of dorsal bud remains as the accessory PD (of Santorini). The normal anatomy allows the majority of the pancreas to be drained via a single duct, which opens at the ampulla of Vater. The presence of variant ductal anatomy, including

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pancreas divisum or ansa, is important to consider before planning any pancreatic endotherapy. If the dorsal duct does not unite with the ventral duct in the pancreatic head, pancreas divisum results, where the majority of pancreatic secretions drain via the minor ampulla.

Defining location of the stricture is critical to formulating an effective management strategy. Location in either the dorsal or the ventral duct, in relationship to dorsal-ventral confluence, may influence the initial ductal access approach, via either the major or minor papilla. Furthermore, anatomic location of the stricture in the main PD should be distinctly defined as in head, genu, body, or tail, with the knowledge that strictures more distal in the duct may be more challenging to manage endoscopically, via the traditional transpapillary approach.

### Etiologies of PD Strictures

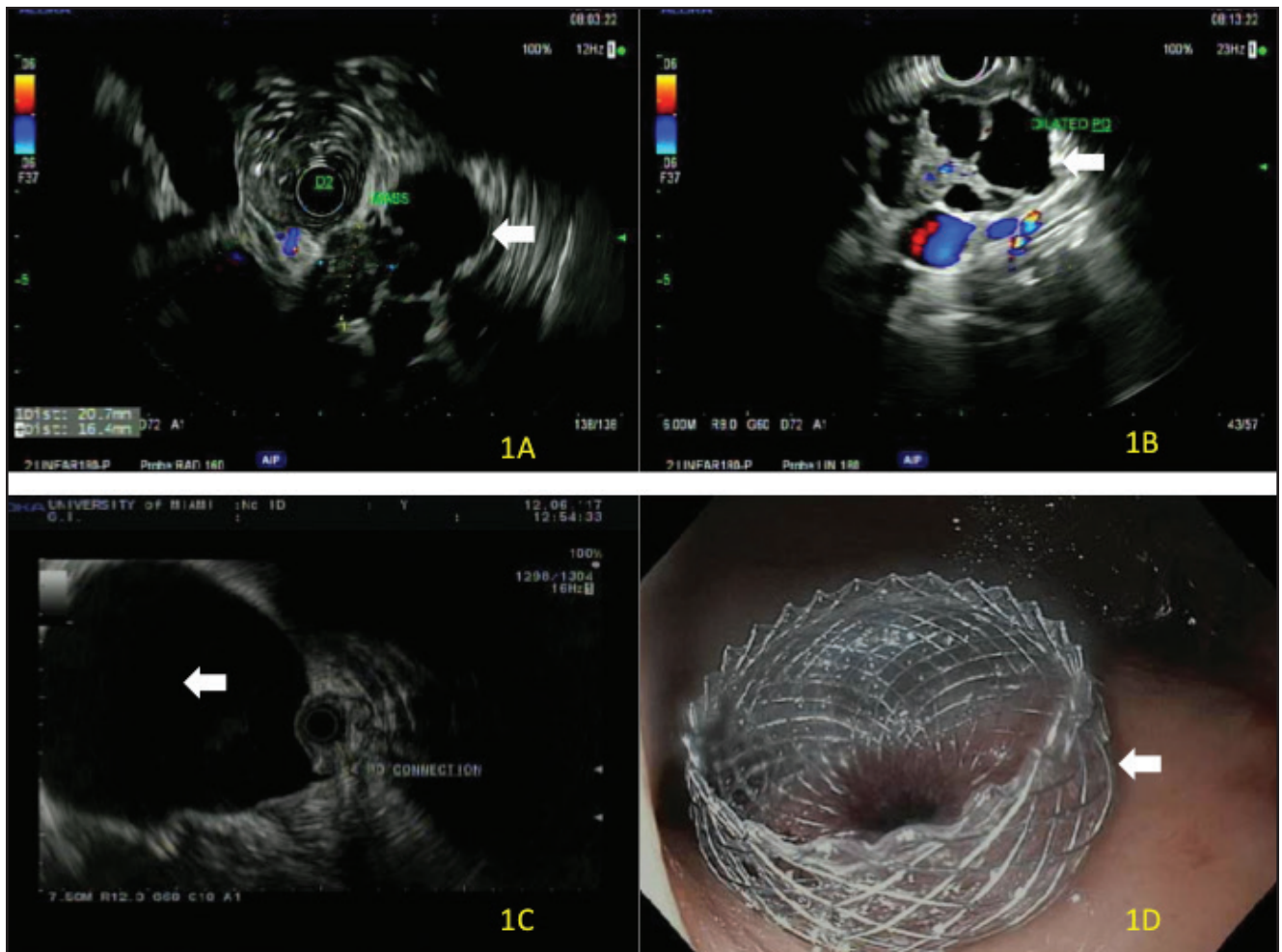
PD strictures can be categorized into three main etiologic groups: malignant, autoimmune, and benign, i.e. secondary to acute pancreatitis (AP), CP, or trauma. The algorithm to determine its etiology begins with a meticulous history and physical examination, followed by cross sectional imaging with computed tomography (CT), magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP), or EUS, or any combination of these modalities, to accurately evaluate the pancreatic anatomy, parenchyma and the ductal system.<sup>1</sup> It is noteworthy at the outset that EUS is the only modality allowing tissue acquisition, making it most optimal in the diagnostic algorithm of PD strictures.

PD strictures secondary to malignancy can either directly involve the duct or extrinsically compress the duct due to mass effect. Primary pancreatic ductal adenocarcinoma can obstruct the main PD (MPD) and cause symptoms of AP or exocrine pancreatic insufficiency (EPI). Approximately 2% of patients with “newly-diagnosed” CP may have underlying pancreatic malignancy.<sup>2</sup> Moreover, up to 10% of patients with intraductal papillary mucinous neoplasms (IPMNs), which are pre-malignant lesions, may be initially incorrectly diagnosed with CP.<sup>3</sup> Patients

over the age of 40 years, with an unexplained attack of AP need be screened for underlying pancreatic malignancy.<sup>4,5</sup> Hence, careful diagnostic workup should be pursued in those with high clinical suspicion for malignancy, and especially in patients over 40 years old who have unexplained AP and/or EPI.<sup>4,5</sup>

Autoimmune pancreatitis (AIP) and Immunoglobulin G4 (IgG4) related sclerosing cholangitis (IgG4-SC) may lead to PD strictures, and IgG4-SC may also lead to biliary strictures. In addition to the typical features of AIP on cross-sectional imaging of the pancreas or endoscopic ultrasound (EUS) showing diffuse glandular enlargement or a discrete mass, PD strictures can result from AIP. PD strictures associated with AIP may cause diffuse irregular MPD narrowing, may be long (> 1/3 length of MPD) and lack upstream MPD dilation (MPD size < 5mm).<sup>6-11</sup> In these cases, EUS-guided pancreatic parenchymal biopsy may be performed to confirm AIP on histology and to exclude malignancy. EUS-guided parenchymal biopsy has a sensitivity of approximately 80% for diagnosis of AIP via histology alone, but does carry a minimal resultant risk of AP from performance of parenchymal biopsy.<sup>12</sup>

The most common benign etiology of PD strictures is CP. Importantly, even in likely benign strictures associated with CP, malignancy should be ruled out with the appropriate diagnostic workup. Dominant MPD strictures in CP are defined by having at least one of the following criteria: upstream MPD dilation  $\geq$  6mm, prevention of contrast medium outflow next to a 6 French catheter placed upstream from the stricture, or abdominal pain with continuous infusion of 1 liter of saline over 12 to 24 hours via a nasopancreatic catheter placed upstream from the stricture.<sup>4,13</sup> Clinically, dominant PD strictures causing ductal obstruction result in pain or superimposed episodes of acute on chronic pancreatitis.<sup>5</sup> While CP itself may lead to strictures, resultant PD stones may further perpetuate damage. In a large, multicenter cohort of over 1000 patients with CP and MPD obstruction managed with pancreatic endotherapy, PD strictures accounted for the most common etiology (47%), while PD stones led to 18%; and a combination of stricture and stones accounted for an additional 32%.<sup>14</sup> Mechanistically, PD stones are thought to



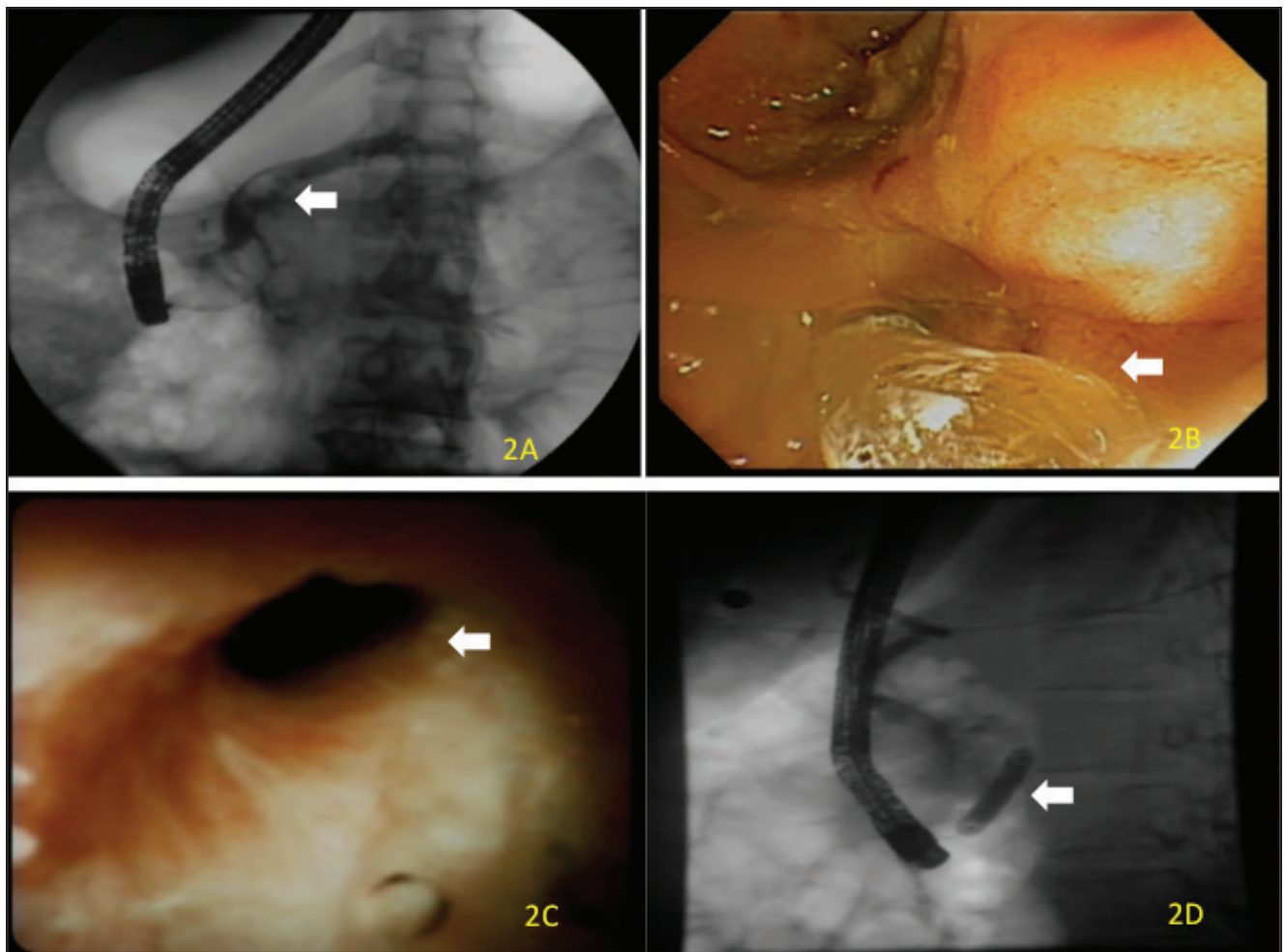
**Figure 1.** (A and B): EUS images of a patient with pancreatic ductal dilation seen on cross sectional imaging – Patient was found to have a PD stricture associated with a mass (20 x 16 mm seen in A) with upstream dilated PD (marked with white arrow, seen in B). Biopsy of this stricture-mass confirmed moderately differentiated adenocarcinoma. (C): EUS image of CP patient referred for recurrent pseudocyst (white arrow), as seen on image-1C. He was found to have a PD stricture in the neck of pancreas, resulting in recurrence of collection close to body of pancreas, with connection to main PD. Patient was managed with endoscopic cystgastrostomy using Axios™ (as depicted by white arrow in image-1D) followed by PD stricture management with stent.

obstruct the PD leading to increased PD pressure, causing inflammatory cascade activation resulting in further fibrosis.<sup>15</sup> Similarly, PD strictures can cause the same ductal hypertension and activate the same inflammatory cascade.<sup>15</sup> Other causes of benign PD strictures may include trauma, as well as iatrogenic triggers from placement of a PD stent, instrumentation during endoscopic retrograde cholangiopancreatography (ERCP), or surgery, particularly at an anastomosis after pancreatic surgery.

### Imaging of Pancreatic Strictures

There is a clear role for cross-sectional imaging

in the evaluation and non-invasive management of patients with CP, and possible PD strictures. CT with dedicated pancreatic protocol is currently the first-line recommended imaging modality for evaluation of the pancreatic parenchyma by the European guidelines.<sup>4</sup> CT with pancreatic protocol has the benefit of being highly sensitive for detection of parenchymal calcifications and specifically masses.<sup>4,5</sup> CT does, however, have the drawback of repeated radiation exposure, which needs to be considered over time for this chronic condition. Further, CT, while beneficial for the parenchyma, is not as efficacious as MRCP for evaluation of the ductal systems of the pancreas and biliary tree.



**Figure 2.** (A): ERCP image of a patient with chronic pancreatitis and PD stricture in head-neck with an upstream large stone (white arrow in image-2A) referred for management. After sphincterotomy followed by balloon dilation of ampulla (sphincteroplasty, as seen in image-2B), a digital pancreatoscope is introduced into PD, which reveals no mass, and rather benign appearance of stricture (white arrow in image-2C). This PD stricture in head of pancreas is then dilated using balloon (white arrow in image-2D), to advance the pancreatoscope deeper into the PD for further therapeutics.

MRCP has excellent performance characteristics for delineation of ductal abnormalities including strictures, dilation, and intra-ductal stones.<sup>16,17</sup> Given the reliability of MRCP findings and the fact that MRCP is noninvasive, ERCP has largely shifted to primarily a therapeutic procedure offering the endoscopist the modality to intervene upon the findings of noninvasive imaging technologies, often including EUS.

EUS is utilized to evaluate both the pancreatic parenchyma and PD. EUS can diagnose the presence of CP using, for example, the expert-consensus based Rosemont Classification, which is a combination of features including the presence of parenchymal lobularity, hyperechoic foci

and strands, and honeycombing, as well as PD changes including calculi, tortuosity, dilation, and hyperechoic PD walls.<sup>18</sup> EUS for diagnosis of CP is limited however by varying degrees of interobserver agreement.<sup>19,20</sup> EUS has the added benefit of tissue sampling when indicated, and is particularly useful if malignancy, and in some cases AIP, is suspected for both imaging diagnosis and tissue acquisition (Figure 1A, B). A meta-analysis of 33 studies of 4,984 patients from 1997 to 2009 estimated the sensitivity of EUS with malignant cytology to be 85% and specificity of 98% for detection of solid pancreatic neoplasms.<sup>21</sup> These figures are likely to improve over time as imaging

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technologies and EUS needles for tissue acquisition via fine needle aspiration for cytology or fine needle biopsy for histology continue to advance.

### Management Strategies for Pancreatic Duct Strictures

There are multiple tools in the armamentarium to approach PD strictures including medical, endoscopic, and surgical options. Perhaps the easiest strictures to manage are those caused by AIP or IgG4-SC, in which treatment is primarily medical with steroid administration.<sup>5,6</sup> Medical therapy in CP should be focused on removal of any potential offending agents, such as alcohol and smoking in an effort to minimize further damage, and use of pancreatic enzyme replacement therapy in those who have EPI,<sup>5,22</sup> which may additionally help with pain as well. It is important to remain cognizant that not all PD strictures need treatment, and endoscopic techniques should be reserved for carefully selected symptomatic patients, where expected benefits outweigh the risks of pancreatic endotherapy.

### Traditional Endoscopic Techniques

Endoscopically, ERCP with use of its associated devices and technologies are the mainstay of pancreatic endotherapy. The initial endoscopic approach to PD strictures is often pancreatic sphincterotomy, followed by guidewire passage through the stricture and then stricture dilation followed by placement of a PD stent. These techniques result in good overall technical success.<sup>15,23,24</sup> Stricture dilation can be performed with either balloon or bougie dilators, as well as with the Soehendra stent retriever as a rescue option if the dilator cannot traverse the stricture.<sup>4,25</sup> Dilation alone, without stenting, is not recommended based on the most recent ASGE guidelines, as dilation alone is not typically effective for these tight and resilient PD strictures.<sup>5</sup>

Endoscopic ductal stenting can be performed in strictures that involve either short or long segments of PD. Current ASGE guidelines recommend the use of plastic stents for MPD strictures, which can be either a single large caliber stent or multiple smaller caliber stents placed in a side-by-side configuration.<sup>5</sup> Stent size selection should be at

least as large as the PD diameter and long enough to traverse the stricture while not going far beyond the strictured area to minimize collateral damage to the PD.<sup>26</sup> There are no published trials to date evaluating placement of a single larger diameter (10 French) plastic stent compared to placement of multiple side-by-side smaller diameter plastic stents for PD stricture therapy.<sup>5</sup> Stents may become occluded over time and require replacement, which can be done on a scheduled basis every 2-3 months or as needed based on return of symptoms. While both methods have been studied, there is no clear head-to-head comparison favoring one schedule over another.<sup>15,27,28</sup> Stenting may be pursued for a number of months to years for therapy. When stents are placed, larger diameter 10 French plastic stents resulted in significantly fewer hospitalizations for abdominal pain than plastic stents of 8.5 French diameter or less.<sup>29</sup> When dilation and stenting are performed in PD strictures without the presence of intraductal stones, abdominal pain decreased in 65 to 84% of CP patients.<sup>23,30</sup> The long-term efficacy of PD stenting for relief of pain in CP appears to be in the range of 52% to 90% with less than 30% of patients requiring surgery.<sup>24,31,32</sup> Predictors of good clinical outcomes to nonsurgical interventions in painful CP are obstructive ductal calcifications located in the pancreatic head, short disease duration, and low frequency of pain attacks prior to the planned intervention.<sup>33</sup>

From a technical perspective, placement of multiple side-by-side stents may be challenging depending on patient ductal anatomy. While stenting has traditionally been performed with plastic stents, fully covered metal stents may be used as well, and are an emerging field of investigation. A 2014 systematic review of 5 studies of 80 patients with chronic pancreatitis revealed comparable technical success rates for refractory PD strictures using multiple plastic stents (94.7%) compared to fully covered self-expandable metal stents (FCSEMS) (100.0%;  $p=ns$ ), comparable stent migration rates (10.5% vs 8.6%), and comparable pain relief rates (84.2% vs 85.2%).<sup>34</sup> There was, however, a 26.2% reported complication rate in the metal-stents group and no reported complications with plastic stents. Notably, sample size was low in both groups (19 patients in plastic stents vs. 61 patients

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with metal stents). When complications occur, they are most commonly pain, mild pancreatitis and stent migration, but may also include stent occlusion, infection, bleeding, perforation and stone formation.<sup>5</sup> Further, placement of any type of stent may induce periductal damage and scarring leading to development of further strictures.<sup>35,36</sup>

Two recent studies have raised concern over the long-term outcomes of FCSEMS for benign pancreatic strictures. In a study of 10 patients followed for 35 months after 3 months of FCSEMS stent placement, the rate of recurrent stricture was 38%.<sup>37</sup> Further, in a second study of 15 patients followed for 15.9 months with refractory PD strictures secondary to chronic pancreatitis, there was a 27% rate of new stricture development secondary to placement of the metal stent itself.<sup>38</sup> At this time, the jury is still out, and choice of pancreatic stent should be made with caution, based on provider expertise on a case-by-case basis. The exception is pancreatic cancer induced biliary strictures causing biliary obstruction, in which guidelines recommend use of uncovered self-expanding metal stents for palliation, if life expectancy is greater than 6 months in unresectable patients.<sup>39-41</sup>

In patients in whom PD access cannot be achieved via ERCP with a transpapillary approach, EUS-guided PD access and drainage is feasible. EUS can then guide traditional transpapillary drainage (rendezvous technique where the PD is punctured with needle under EUS guidance, and a guidewire is placed into the PD and then passed through the papilla), or EUS can be used to provide transmural drainage into the stomach or duodenum.<sup>1,42-44</sup> Lastly, in patients who have a peri-pancreatic fluid collection associated with a stricture such as in the case of patients with ductal trauma, endoscopic drainage of only the collection will not fix the ductal leak, giving rise to the fluid collection. Endoscopic drainage of the collection can be attempted using a transpapillary approach or using EUS guidance for drainage using a transgastric or transduodenal approach.<sup>1</sup> In these cases, similar to patients with bile leaks due to bile duct injury, endoscopic therapy to address the stricture preferably with stenting to decrease the ductal pressure gradient is necessary

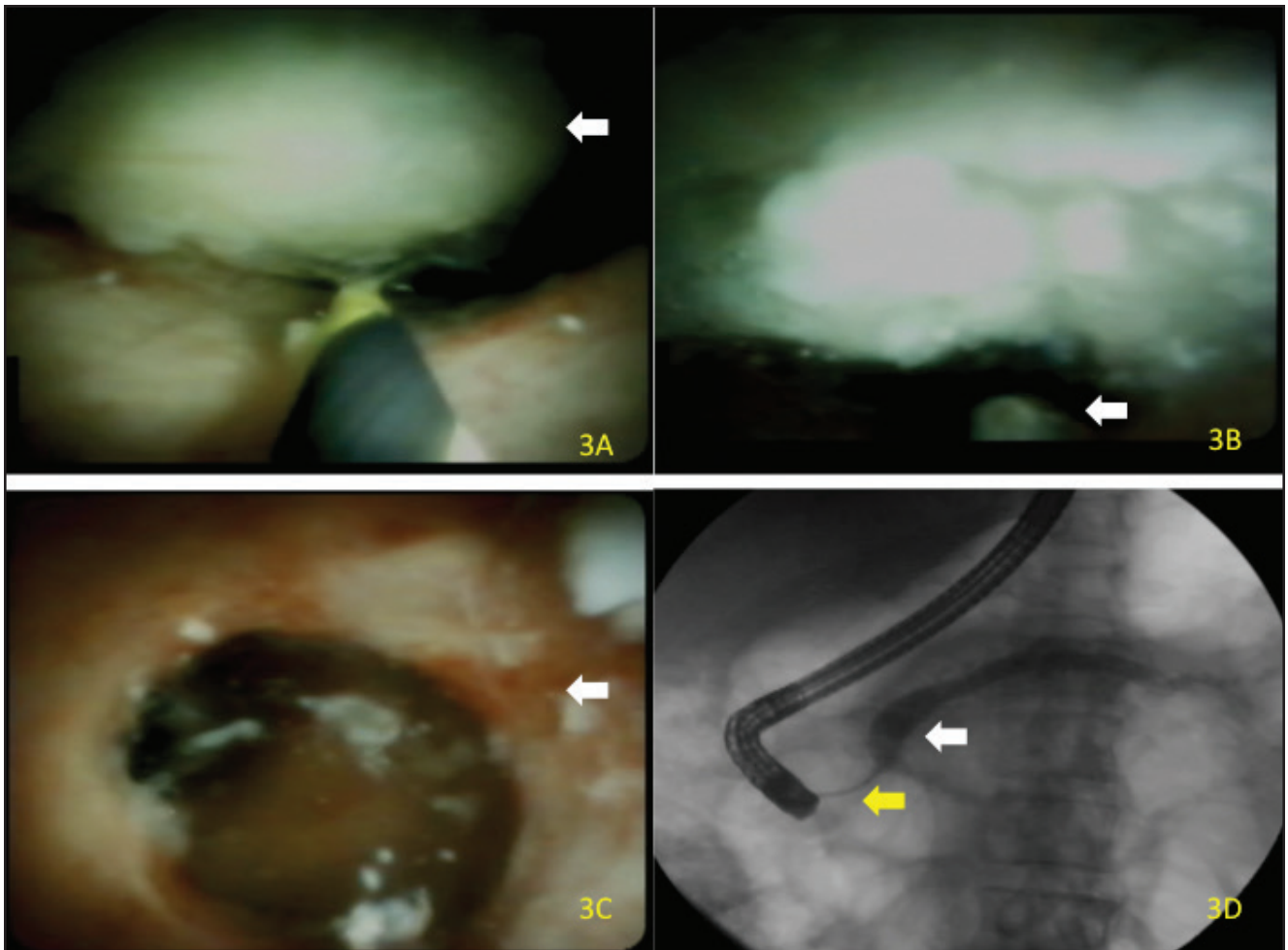
to prevent re-accumulation of the peri-pancreatic fluid collection after initial drainage (Figure 1C, D).

Moreover, patients with post-surgical anastomotic strictures may present a completely different set of challenges for the endoscopists, including identification and intubation of afferent limb, and later identification and cannulation of pancreatico-jejunal (P-J) anastomosis. The etiologies of P-J stricture may be benign post-surgical changes or inflammation, or recurrence of malignancy. EUS may have a role in this situation to assist in identification of the PD and sometimes perform rendezvous or direct drainage of the PD.

### New Endoscopic Technologies

Intraductal pancreatoscopy previously was limited in its technological abilities with cumbersome systems of mother-daughter scopes and low overall image quality. The newest platform is the SpyGlass DS™, single-operator, single-use cholangiopancreatoscopy system (Boston Scientific, Natick, Massachusetts, USA), which provides high-quality images to guide diagnostic and therapeutic interventions. Digital pancreatoscopy can directly image a stricture to assist with determination of malignant potential, take small biopsies as opposed to conventional brushings, and may enable therapeutics especially for stone removal with targeted endoscopic lithotripsy.<sup>45</sup> Pancreatoscopy may further characterize the etiology of indeterminate PD strictures and pathology, including main duct intraductal papillary mucinous neoplasms and malignancy both by endoscopic appearance and improved sampling via biopsy with sensitivities of up to 91%.<sup>46-48</sup> With increased time on the market, we can expect larger series in the future to further evaluate the impact of this technology on pancreatobiliary pathology.

There are several technical considerations of using digital pancreatoscopy, of which endoscopist must remain cognizant. First, based on the width of the probe, the PD must be dilated to > 4mm, and have a relatively non-tortuous course in the head of pancreas, to allow safe passage of the probe (Figure 2C, D). The probe should be advanced over a long guidewire, traditionally 0.035-inch x 450 cm long, which can then be removed once the scope is stabilized within the duct, so as to not interfere with



**Figure 3.** (A): Advancement of a pancreatoscope upstream of already dilated stricture reveals a large stone (white arrow in image-3A). This stone was fragmented using electrohydraulic lithotripsy (EHL) technique (tip of EHL probe shown with white arrow in image-3B). After complete fragmentation of the stone, and removal of debris with balloon sweeps, repeat pancreatoscopy shows improved stricture and no upstream stone. Mild inflammation at the site of stone impaction is still seen (white arrow in image-3C). Final fluoroscopic image shows clearance of stone, which was seen previously at site marked with white arrow, and no remnant stone in remainder of the PD. The PD stricture in head of pancreas (depicted with yellow arrow in image-3D) was managed using successive PD stenting protocol.

visualization.<sup>45</sup> Additionally, even with favorable caliber and contour of PD, stones downstream to the stricture may have to be managed first (as discussed below), pancreatic sphincterotomy may need to be initially performed to facilitate MPD access, and strictures may require dilation to allow passage of the probe for full characterization of the stricture as well as management of upstream stones/pathology.<sup>45,49</sup> Last, it is of utmost importance to remember that there is an associated increased risk of post-ERCP pancreatitis (PEP) when performing pancreatoscopy secondary to pancreatic manipulation, and appropriate PEP prophylaxis

measures should be utilized.<sup>50</sup>

Additional newer technology for PD stricture evaluation includes confocal laser endomicroscopy (CLE). CLE uses a low-power laser light which is focused on a single point to create a microscopic field of view, with the goal of creating real-time digital histology to enable the operator to characterize the nature of lesions.<sup>51</sup> Use of intravenous fluorescein sodium as a contrast agent may enhance CLE image quality. The current CLE mini-probe available for pancreatobiliary disorders is the CholangioFlex miniprobe (Mauna Kea Technologies, Paris, France), and is passed through

the working channel of the endoscope. Needle based systems are also available for cystic and mass lesions. It was initially utilized for evaluation of indeterminate biliary strictures, first applying the Miami Classification and subsequently the Paris Classification systems.<sup>52-54</sup> However, no such rubric exists for evaluation of PD strictures. Small case series and studies have shown promise for probe-based CLE in the evaluation of PD strictures but larger studies will need to be performed to further progress this technology.<sup>55-59</sup> If CLE is proven to be useful in PD stricture evaluation on a larger scale, standardized classification systems specifically for PD strictures will need to be established as most work to date has focused on biliary stricture classification.

### Pancreatic Ductal Stones

PD stones occur in approximately 50% of CP patients, and can be located in both the parenchyma and PD.<sup>14</sup> Classically, removal of PD stones is performed with ERCP with a retrograde approach to the PD. PD stones are usually more difficult to manage than biliary stones, given their shape/morphology, high calcium and protein content resulting in harder stones, and the small caliber and usually tortuous contour of the PD in CP patients (Figure 2A, B). Once cannulation of the MPD is achieved, stones in the MPD can be removed using small balloons, retrieval baskets, or perhaps forceps. Pancreatic sphincterotomy may assist in removal of larger stones and debris.<sup>15</sup> In addition to conventional ERCP with mechanical stone extraction, larger stones (usually those over 5mm in size) or stones impacted in a stricture or in a side branch PD may be difficult to remove and require either endoscopic or extracorporeal shock wave lithotripsy (ESWL) for management.<sup>45,60-64</sup> Endoscopic techniques of stone fragmentation include electrohydraulic lithotripsy (EHL), which may be targeted using pancreatoscopy, and laser lithotripsy.<sup>45,63,64</sup> (Figure 3A-D). The specific performance, indications, efficacy, risks and benefits of each of these techniques are outside of the scope of this manuscript.

### Surgical Approach to Pancreatic Strictures

While endoscopy is the preferred initial approach for patients with symptomatic benign PD strictures,

in patients who fail endoscopic interventions, surgery should be considered.<sup>4,60</sup> Surgically, there are multiple options depending on stricture location, presence of additional parenchymal disease and stricture etiology. Surgical interventions can be divided into resection procedures, drainage procedures, or a combination thereof.<sup>65</sup> These include drainage procedures, i.e. the Puestow or Frye procedures as lateral pancreaticojejunostomies, and resection procedures including a traditional Whipple procedure primarily for disease confined to the head or proximal pancreas, a central or distal pancreatectomy, a total pancreatectomy, and most recently, a total pancreatectomy with islet cell autotransplantation to minimize the risk of post-operative diabetes.

When comparing endoscopic interventions to surgery specifically for painful CP, both methods appear to have suboptimal results, likely due to the complex nature of chronic pain in CP.<sup>4,66-69</sup> A 2015 Cochrane Database systematic review and meta-analysis comparing endoscopic (excluding any trials with ESWL) and surgical interventions for painful CP included two randomized controlled trials of 111 total patients showing significantly higher proportion of patients with pain relief in the surgical arm at both medium (2-5 years; Relative risk 1.62; 95% CI 1.22-2.15) and long-term ( $\geq$  5 years; Relative risk 1.56; 95% CI 1.18-2.05) follow up.<sup>65-67</sup> In this Cochrane review, surgery also resulted in improved medium-term quality of life and preserved exocrine pancreatic function; however, this effect was not durable at 5 years. Given the small number of patients in the two studies included, there were no differences in morbidity and mortality between the two arms but the review authors noted that the sample size was underpowered to detect such differences. In fact, in multiple other studies, surgical intervention for CP seems to carry substantially higher rates of morbidity and mortality compared to endoscopic interventions for CP (morbidity surgery 18-53% vs. endoscopy 3-9%; mortality surgery 0-5% vs. endoscopy 0-0.5%).<sup>4,14,61,70-73</sup>

### The Caveat: Post-ERCP Pancreatitis

Post-ERCP pancreatitis (PEP) is the most common and feared complications of ERCP, with

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an incidence of 3-10% in large series.<sup>74,75</sup> When planning ERCP for biliary access, PD cannulation is inadvertent; however, when PD cannulation is the goal of the procedure, the endoscopist must be increasingly mindful of PEP risk. Strategies to minimize PEP risk should be employed per protocol in all patients undergoing ERCP with intention of PD cannulation, unless there is a contraindication. The current strategy is a trifecta of intravenous fluid hydration (preferably with lactated ringer's solution), rectal indomethacin, and PD stenting.<sup>39,76-80</sup> Specifically, placement of a 3-French or 5-French, short, plastic stent can decrease PEP risk (39, 81). Interestingly, CP may actually confer a slight relative protection against PEP; however, a recent large study showed a PEP incidence of 4.5% in CP patients compared to 4.8% in non-CP patients.<sup>73,82,83</sup> Decisions on any interventions in this patient population or others should be made carefully after a clear discussion of risks, benefits, and alternatives with the patient

## CONCLUSIONS

PD strictures and upstream stones remain challenging for endoscopists to manage. There are, however, continually emerging diagnostic and therapeutic tools, techniques and procedural refinements at the endoscopist's disposal to approach these complex disease processes. The physician must always remember to exclude underlying malignancy, and subsequently move on to the perhaps far more daunting task of managing PD strictures and stones oftentimes associated with painful CP. While surgery remains an option in especially difficult cases and specifically for those with refractory painful CP, endoscopic management now includes a panacea of options to provide both short and long-term therapies. Careful discussion with the patient of risks, benefits, and alternatives should be had regarding all appropriately indicated diagnostic and therapeutic options in these often challenging cases, but fear not, for the future is bright. ■

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Answers to this month's crossword puzzle:

