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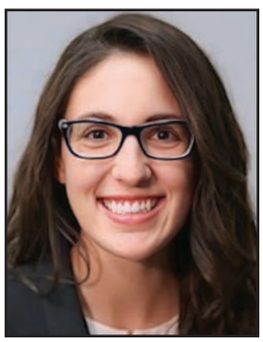
Pancreatic Duct Leaks



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INTRODUCTION

Pancreatic duct (PD) leaks can occur in the setting of acute or chronic pancreatitis, trauma, or pancreatic resection. Their clinical manifestations vary widely depending on the underlying etiology and the site and extent of PD disruption. Sequelae of PD leaks include peripancreatic and pancreatic fluid collections (PFCs), as well as internal and external pancreatic fistulas. Small PD leaks may resolve with conservative management alone, but other therapeutic options include endoscopic, radiologic, surgical, and combined approaches necessitating a multidisciplinary care team. The role of endoscopic retrograde cholangiopancreatography (ERCP) is primarily to provide a therapeutic intervention to PD leaks and their sequelae. Over time, the role of endoscopic therapy for PD leaks has expanded with comparable effectiveness to surgical and radiologic approaches. Currently, the mainstay of endoscopic therapy involves transpapillary pancreatic duct stenting to bridge the site of PD disruption. In this article, we review the pathophysiology, epidemiology, clinical manifestations, diagnosis, and approach to endoscopic management of PD leaks. (See Figure 1.)

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PATHOPHYSIOLOGY AND CLASSIFICATION

PD leaks result from disruption of the pancreatic ductal system, which can be seen in the setting of acute or chronic pancreatitis, abdominal trauma, and as a complication of pancreatic resection or peripancreatic surgery. (See **Figure 2.**) Activation of proteolytic enzymes, pancreatic autodigestion, and the production of proinflammatory cytokines are felt to play key roles in the pathogenesis of acute pancreatitis.[1] While the exact mechanism is unknown, pancreatic duct disruption is likely a secondary effect of pancreatic inflammation in patients without trauma or prior instrumentation. Disruption of the PD results in the leakage of pancreatic fluid, which may contribute to autodigestion of pancreatic parenchyma.[1] PD leaks can also occur in the setting of chronic

Key Points

- Sequelae of PD leaks include pancreatic and peripancreatic fluid collections, internal pancreatic fistulas, and external pancreatic fistulas.
- CT, MRI/MRCP, and EUS play a key role in the evaluation of PD leaks and their sequelae.
- ERCP is typically reserved for cases where endotherapy is considered.
- The mainstay of endoscopic therapy involves transpapillary pancreatic duct stenting to bridge the site of PD disruption.

Figure 1. Indomethacin suppositories as commonly used in patients undergoing ERCP.

Causes of Pancreatic Duct Leaks

- Acute pancreatitis (most common)
- Chronic pancreatitis
- Abdominal trauma
- Post-surgical

Figure 2.

pancreatitis either because of superimposed acute pancreatitis or increased intraductal pressure from obstructing PD stones or strictures. Lastly, PD leaks can occur as a result of direct injury to the PD from abdominal trauma, pancreatic resection, or inadvertent pancreatic injury during abdominal surgery. The American Association for the Surgery of Trauma grading system grades pancreatic injury based on the location of PD injury and degree of ductal involvement.[2] Postoperative pancreatic fistulae are defined and graded based on the 2016 International Study Group of Pancreatic Fistula consensus definitions.[3]

Persistent leakage of pancreatic fluid can erode into neighboring structures and spaces resulting in the formation of PFCs and pancreatic fistula. The classification of PFCs has changed over time and is currently based on the time that they develop in relation to pancreatitis onset and the presence of necrosis.[4] Pancreatic fistula are abnormal connections between the pancreatic ductal epithelium and another epithelial surface. Fistula are traditionally classified as internal or external, as well as anatomically based on the site of involvement. Internal pancreatic fistula can result from pancreatic fluid erosion into the peritoneal space (pancreaticoperitoneal fistula), pleural space (pancreaticopleural fistula), mediastinum (pancreaticomediastinal fistula), pericardial space (pancreaticopericardial fistula), bronchial tree (pancreaticobronchial fistula), biliary tract (pancreaticobiliary fistula), stomach (pancreaticogastric fistula) and nearby small or large bowel (pancreaticoenteric or pancreaticocolonic fistula). External pancreatic fistula, or pancreaticocutaneous fistulas, result from communication between the pancreas and the skin, and are most commonly iatrogenic secondary to drains placed via interventional radiology or surgery.

EPIDEMIOLOGY

PD disruption and its sequelae are most commonly seen in the setting of severe acute pancreatitis, though the true incidence of PD leaks is unknown as small leaks may be clinically silent.[5–7] Disconnected pancreatic duct syndrome (DPDS) represents the most severe form of PD disruption with complete transection of the main PD resulting in a portion of the pancreas (usually the tail) becoming isolated from the remainder of the pancreas.[8,9] It is most commonly seen in the setting of necrotizing pancreatitis with up to 10-30% of patients developing DPDS, though the true incidence is not known.[5,6]

PD leaks can also occur post-operatively after pancreatic resection or inadvertent pancreatic injury during surgery of nearby organs such as the spleen, left kidney, colon, and left adrenal gland. (See **Figure 3.**) In the setting of pancreatic resection, PD leaks can complicate up to 5-29% of cases depending on the health of the underlying pancreatic tissue, extent of pancreatic resection, and main PD diameter.[10–13]

Lastly, PD leaks can be seen in the setting of pancreatic injury from abdominal trauma. The incidence of pancreatic injury is up to 5% after blunt abdominal trauma and up to 30% after penetrating abdominal trauma, with the most common complication being pancreatic fistula.[14–19]

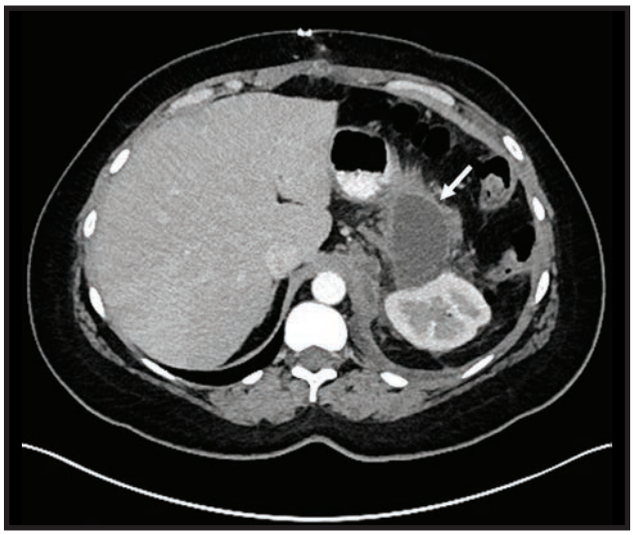

Figure 3. CT demonstrating a 5.8 cm rim-enhancing peri-pancreatic fluid collection (arrow) three weeks after left adrenalectomy with distal pancreatectomy and splenectomy

CLINICAL MANIFESTATIONS

The clinical manifestations of PD leaks vary widely and are driven by the underlying etiology, the site of the PD leak, the extent of PD disruption, rate of secretion of pancreatic fluid, and the presence of pancreatic fistula.[20] (See **Figure 4.**) In acute pancreatitis, the initial presentation is largely driven by the etiology and severity of the pancreatitis, whereas the sequelae of PD disruption play a greater role as the clinical course evolves. Generally, low-grade leaks can be asymptomatic, precipitate pancreatitis, or evolve to become pseudocysts whereas severe leaks and their sequelae are more likely to be symptomatic. Depending on the size, location, and presence of superinfection, PFCs may present as nonspecific gastrointestinal symptoms, sepsis/septic shock, gastric outlet obstruction, or biliary obstruction. DPDS typically presents as a refractory PFC or pancreatic fistula, as the isolated portion of the pancreas continues to secrete pancreatic fluid that is unable to be secreted appropriately into the GI tract.

The clinical manifestations of pancreatic fistula are highly variable depending on the distant site of communication. Pancreaticocutaneous fistulas are usually the most obvious, as they present with visible leakage of pancreatic fluid from the skin with or without skin excoriation. Pancreaticoperitoneal fistulas result in pancreatic ascites with varying degrees of abdominal symptoms and can be complicated by peritonitis. Pancreaticoenteric fistulas can present with gastrointestinal (GI) bleeding, diarrhea, or malabsorption. Thoracopancreatic fistulas can result in cough, dyspnea, chest pain, dysphagia, mediastinitis, and pneumonia depending on the site of involvement. Because pancreatic fluid is high in bicarbonate and protein, PD leaks can cause a metabolic acidosis, dehydration, and malnutrition, especially in the setting of high-grade leaks.

Manifestations of Pancreatic Duct Leaks

- Smoldering pancreatitis
- Pancreatic or peripancreatic fluid collections
  - Pseudocyst
  - Walled off necrosis
- Internal pancreatic fistula
  - Pancreaticoperitoneal fistula (pancreatic ascites)
  - Pancreaticoenteric fistula (upper or lower GI tract)
  - Pancreaticobiliary fistula
  - Pancreaticopleural fistula (pancreatic pleural effusions)
  - Pancreaticobronchial fistula
  - Pancreaticomediastinal fistula
  - Pancreaticopericardial fistula
- External pancreatic fistula
  - Pancreaticocutaneous fistula

Figure 4.

DIAGNOSIS

Accurate identification and characterization of PD disruption is important in guiding the approach to management. Currently, there are no consensus guidelines for the diagnosis of PD leaks. ERCP is traditionally considered the gold standard for confirming the presence, severity, and site of PD disruption, which is defined by contrast extravasation from the pancreatic ductal system.

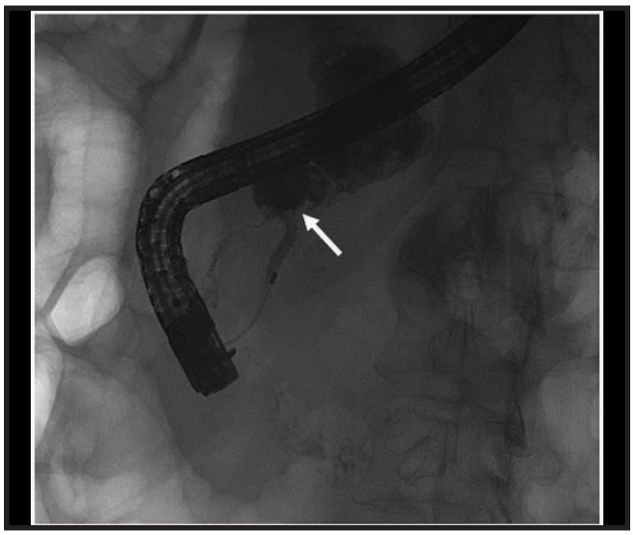

Figure 5. ERCP demonstrating the collection that communicates with the main pancreatic duct (arrow)

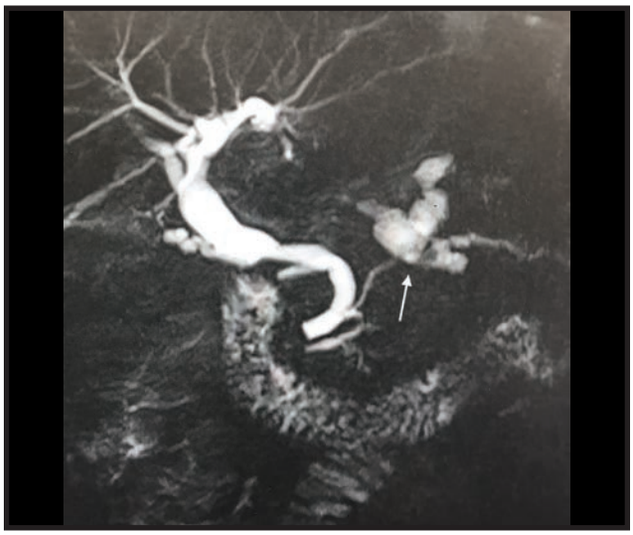

Figure 6. MRI demonstrating contrast extravasation (arrow)

(See **Figures 5-7.**) The potential for ERCP to cause pancreatitis and superinfection, and the improvement in noninvasive imaging modalities, has resulted in ERCP being primarily reserved for cases where endotherapy is warranted in the setting of a diagnostic evaluation.[21] Generally, the diagnostic approach is determined by the clinical presentation.

In the setting of acute pancreatitis, contrast-enhanced computerized tomography (CT) is often obtained as part of the initial diagnostic workup. Clinical worsening should prompt repeat CT imaging to evaluate for the development of PFCs and pancreatic necrosis. Identification of a PFC suggests that a PD leak is present, and its location may suggest the site of PD disruption. (See **Figure 8.**) Serial imaging demonstrating a persistent or enlarging PFC further supports the presence of an ongoing PD leak, which can be confirmed with magnetic resonance cholangiopancreatography (MRCP), secretin-enhanced MRCP (S-MRCP), or ERCP. In the setting of DPDS, S-MRCP has high sensitivity for identifying the site of ductal disruption and may additionally visualize the disconnected portion of the pancreas.[22] In the setting of chronic pancreatitis, CT is often used in the initial diagnosis of chronic pancreatitis and to evaluate for calcified PD stones, PD strictures, and sequelae of PD leaks in the case of symptom progression.[23]

Similarly, internal pancreatic fistula can be suggested by findings on cross-sectional imaging and, in the case of pancreatic ascites and pancreaticopleural fistulas, can be confirmed by the presence of a high fluid amylase in the peritoneal and pleural fluid, respectively. (See **Figure 9.**) The diagnosis of external pancreatic fistula and post-operative PD injury is often more straightforward, as they typically present as persistent fluid output from a percutaneous or surgical drain. Fluid analysis demonstrating a fluid amylase that is >3x upper limit of normal (ULN) supports the diagnosis, and a fistulogram is rarely necessary for diagnostic purposes.[3]

Occasionally, sequelae of PD disruption may present in the absence of a clear inciting event. If a patient presents with a PFC in the absence of preceding pancreatitis, a general approach involves obtaining cross-sectional imaging (CT or MRI) with or without EUS for fluid analysis to rule out a neoplasm.

MANAGEMENT

PD leaks and their sequelae can result in fluid and electrolyte imbalance, malnutrition, and sepsis; thus, conservative medical therapy plays a key role in management and may result in resolution of low-volume PD leaks. A multi-disciplinary approach is

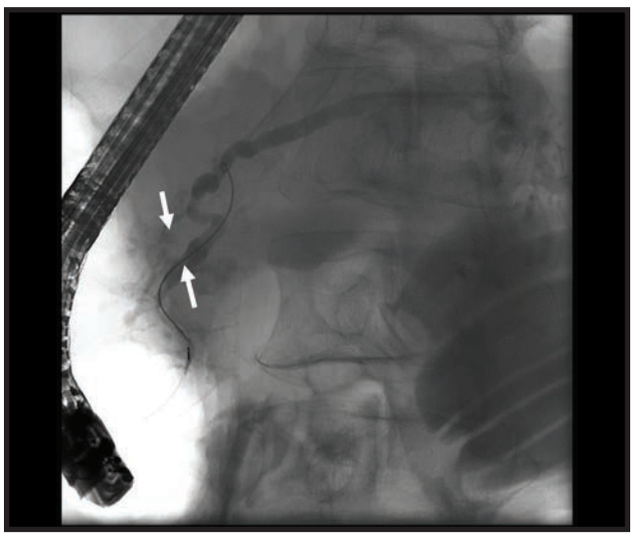

Figure 7. Pancreatogram demonstrating PD leak with contrast extravasation (arrow) at the pancreatic neck

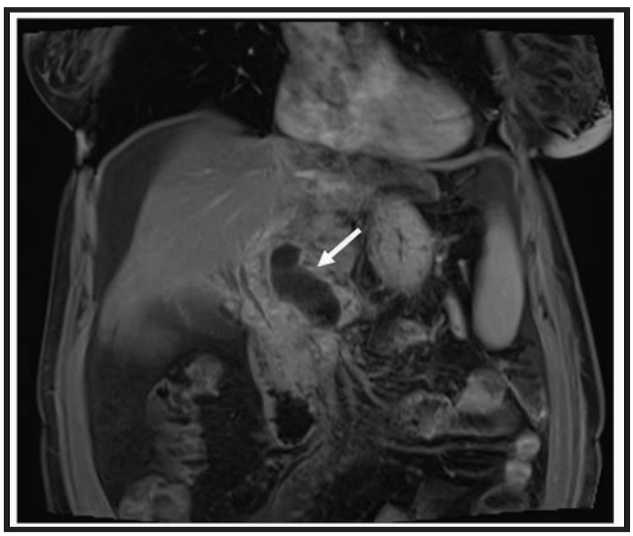

Figure 8. MRI demonstrating an enlarging fluid collection from a pancreatic duct leak at the pancreatic neck (arrow)

essential to identify patients that might benefit from endoscopic, radiologic, surgical, or multimodal therapy.

Overview of Endoscopic Therapy

ERCP can be used to effectively treat PD leaks and their sequelae. The presence of a PD leak is not a strict indication for endotherapy, as low-grade leaks may resolve with conservative management alone; thus, a key step is to identify patients that would benefit from an endoscopic approach to management. Still, in practice, most patients with PD leaks come to endotherapy at some point in their clinical course. Important considerations include whether there is evidence of an ongoing PD leak, PFC, or necrosis.

Relative indications for endotherapy of presumed or definite PD leaks and their sequelae include:

1. Persistent or worsening PD leak despite conservative management
2. Symptomatic PFC
3. Superinfected PFC

The mainstay of endoscopic therapy for PD leaks and their sequelae involves transpapillary pancreatic duct stenting to bridge the site of PD disruption and/or transmural drainage of associated PFCs. If a leak cannot be crossed with endoscopic transluminal stenting, which usually occurs in the setting of DPDS, surgery or interventional radiology approaches may be indicated. (See **Figure 10.**)

Transpapillary Drainage

Transpapillary drainage involves an ERCP with insertion of a PD stent that bridges the site of PD disruption. (See **Figures 11-13.**) Bridging the site of PD disruption with a PD stent promotes physiological flow of pancreatic fluid into the duodenum rather than through the site of PD disruption and correlates with successful outcomes.[24,25] Additionally, PD stents can be used to bypass areas of ductal obstruction due to PD stones and strictures. The stent diameter depends on the PD diameter and should not exceed the diameter of the upstream PD.[26] While pancreatic sphincterotomy is not required for stent insertion, it can be used to facilitate stone extraction and PD stricture dilation and is often performed if the need for repeated PD access is anticipated in the future. Optimal stent duration/indwell time is unclear and depends on the etiology of the PD leak and operator preference. In cases where the upstream portion of the PD is unable to be accessed, a shorter stent can be placed, with a plan to re-attempt ERCP to bridge the leak at a later date. In most case series, PD

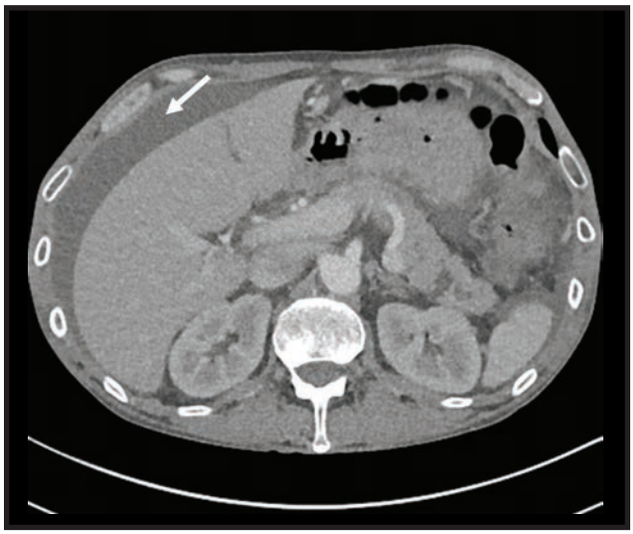

Figure 9. CT demonstrating new ascites in a patient found to have pancreatic ascites

stents were left in place for 4-8 weeks with shorter durations being associated with an increased risk of recurrence or failure and longer durations being associated with stent occlusion and ductal changes in a previously otherwise normal PDs, but this has not been universally reported.[24,25,27–29] Importantly, many patients need, and tolerate, long PD stent indwell times without any evidence of duct injury. Lastly, transpapillary drainage can be used to drain PFCs that communicate directly with the main PD. This technique involves placing the distal aspect of the stent directly into the PFC and is supported by case-series that have demonstrated its effectiveness, though it is not the preferred route of drainage.[30,31] (See **Figure 14.**) Even if the PD does not clearly communicate with the PFC, a PD stent can still help to prevent backfilling of the PFC and can promote resolution.

Transmural Drainage

Transmural drainage directs PFC contents into the stomach or duodenum, which decompresses the PFC and promotes healing of the PD leak. This technique involves transmural puncture of a mature PFC through the gastric wall (cystgastrostomy) or duodenal wall (cystenterostomy) and placement of one or more stents to allow for drainage of the contents into the GI tract. (See **Figure 15**) Transmural drainage is performed during esophagogastroduodenoscopy (EGD) with or without EUS guidance, although in current practice the use of EUS is almost universal. EUS allows for the identification of blood vessels and solid debris and is the preferred approach, especially in the absence of an obvious area of extrinsic compression.[32,33] Effective drainage of liquefied PFCs has been reported with the placement of double-pigtail plastic stents, biliary SEMS, or lumen apposing metal stent (LAMS).[34–41] Currently, there are no consensus guidelines for stent selection and duration and, thus, this is left at the discretion of the endoscopist. Typically, cross-sectional imaging is performed 4-8 weeks later to confirm PFC resolution followed by stent removal 6-8 weeks after radiographic resolution of the PFC.[21] If percutaneous drains were also placed, they are typically removed before the transmural drains to minimize the risk of developing external PF. If the PFC contains solid necrotic material, this can also be debrided endoscopically via direct endoscopic necrosectomy (DEN).

Pancreatic Leak from Acute Pancreatitis

In the setting of acute pancreatitis, PFCs are classified according to the time they develop in relation to onset of pancreatitis and the presence of necrosis.[4] Briefly, acute PFCs are seen earlier in the course of pancreatitis, lack a definable wall, and are either predominantly fluid-filled (acute PFCs) or contain some component of solid necrotic debris (acute necrotic collections).[4] Most acute collections resolve spontaneously but if drainage is necessary, endoscopic drainage is often not recommended in the absence of a definable outer wall. Occasionally, acute collections evolve into pancreatic pseudocysts or WON which contain a well-defined wall.[4] Distinguishing between pseudocysts and WON is important, as this will inform therapeutic management.

Options for the endoscopic management of pseudocysts include transpapillary drainage, transmural drainage, or a combination of the two.[21] The approach depends on the collection's size, proximity to the gastric or duodenal wall, and communication with the main PD. Smaller pseudocysts (≤ 6cm) that communicate with the main PD can be effectively managed with

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transpapillary drainage alone.[42,43] Outcomes have otherwise been variable due to heterogeneity in PFC nomenclature and varying patient populations. More recently, evidence has emerged regarding the lack of additional benefit with transpapillary drainage among individuals with successful transmural drainage of PFCs.[44,45] Transmural drainage has become increasingly popular over time, with SEMS and especially LAMS being widely utilized with excellent reported outcomes.[39,40] Percutaneous drainage can also be performed but is associated with pancreaticocutaneous fistulae (which can become chronic); thus, it is typically reserved for PFCs that are either immature or not amenable to transmural drainage because of their location.[21] In regards to timing, endoscopists may choose to perform an ERCP and place a PD stent if there is an active PD leak either at the time of transmural drainage or later in the patient's course, as transmural drainage alone may result in healing of the leak.[44]

Whereas pseudocysts are predominantly fluid filled, WON contains solid debris which cannot be effectively drained with a transpapillary approach. The preferred approach to endoscopic management is transmural drainage and necrosectomy with a "step-up" approach to potentially include percutaneous drainage and/or surgical debridement, although this last step is rarely required.

Manifestations of Pancreatic Duct Leaks

- A multidisciplinary team is essential for management.
- Conservative medical therapy is recommended and may result in resolution of low-volume PD leaks.
- The mainstay of endoscopic therapy is transpapillary pancreatic duct stenting to bridge the site of PD disruption.
- Transmural drainage can be used for drainage of pancreatic fluid collections.
- The management of DPDS has not been standardized and there is no consensus regarding optimal nonsurgical management. Transmural drainage is an option for DPDS-associated pancreatic fluid collections and if attempted, it is important to consider a step-up approach for patients who fail minimally invasive therapy. Pancreatic or peripancreatic fluid collections

Figure 10.

Pancreatic Leak from Chronic Pancreatitis

In the setting of chronic pancreatitis, PD disruption can occur from either an episode of acute on chronic pancreatitis, or ductal obstruction secondary to PD stones or strictures. The most common indication for endotherapy in chronic pancreatitis is to alleviate abdominal pain that is felt secondary to PD obstruction and to treat PD leaks, and is supported by international consensus guidelines.[46] Similar to PD leaks from acute pancreatitis, PD stents can bridge the site of PD disruption and bypass areas of obstruction, thus restoring endoluminal flow of pancreatic duct secretions.

External Pancreatic Fistula

External pancreatic fistula are most commonly iatrogenic due to surgery or percutaneous drainage of PFCs, and are rarely due to penetrating abdominal trauma. Endoscopic therapy is typically reserved for persistent pancreaticocutaneous fistulae despite initial attempts at conservative management, as the majority of low-volume leaks will close with conservative therapy. Conservative management includes enteral feeding, which has been shown to improve fistula closure rates.[47] The use of

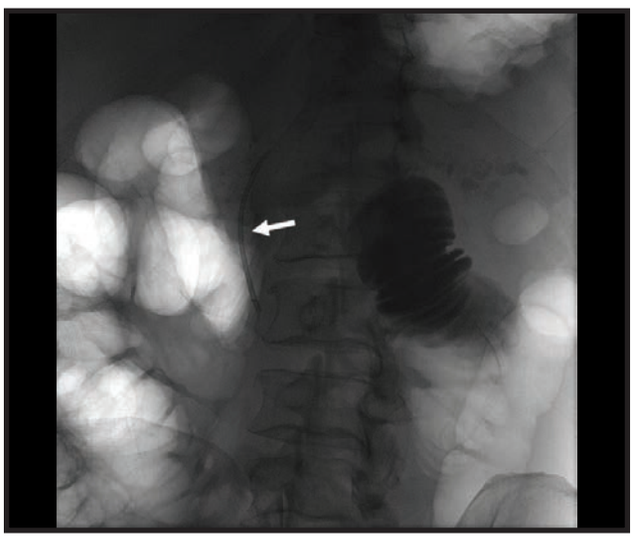

Figure 11. PD leak crossed with a pancreatic duct stent (arrow)

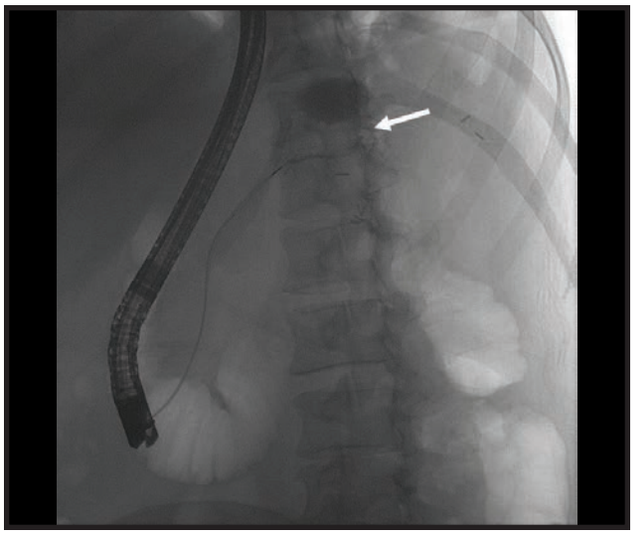

Figure 12. Pancreatogram with contrast extravasation (arrow) at the surgical edge

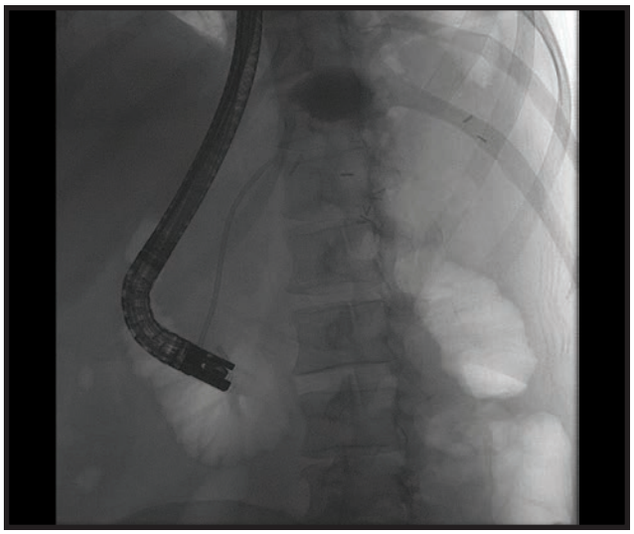

Figure 13. Transpapillary single pigtail pancreatic duct stent placement

somatostatin analogs for prevention and treatment of pancreatic fistula has been extensively studied with mixed results; thus, it is typically reserved for patients with high-output fistulas in the absence of contraindications.[48,49] If fistula output fails to decrease with conservative management, MRCP or S-MRCP should be performed prior to evaluate for DPDS. In the absence of DPDS, transpapillary stent placement can be performed to facilitate closure of external PF and is supported by case series.[50–55] In addition, case series have described combined endoscopic and percutaneous rendezvous approaches to internalizing external fistulae but this should only be attempted at expert centers.[56] Surgery is rarely necessary and typically reserved for inaccessible superinfected PFCs, bleeding from pseudoaneurysms, failure of endoscopic methods, and clinical instability.

Internal Pancreatic Fistula

As previously discussed, internal pancreatic fistulae can communicate with the peritoneum, pleural space, bowel, biliary tree, or other thoracomediastinal spaces. The approach to therapy depends on the type of fistula and whether or not there is an associated pseudocyst. Pancreatic ascites and high-amylase pleural effusions were initially managed with conservative management consisting of bowel rest, diuretics, octreotide, and large-volume paracenteses and thoracenteses with suboptimal success and recurrence.[57–59] Transpapillary stenting has proven to be effective in multiple case series, so long as the site of PD disruption can be bridged with the stent.[27,60–64] In the presence of a concomitant pseudocyst, transmural drainage alone may result in resolution of pancreatic ascites and pleural effusions.[65] Surgical options include partial pancreatectomy, enteropancreatic anastomosis, or Roux-en-Y cystojejunostomy if concomitant pseudocysts are present, but is associated with up to 10% mortality and 15% recurrence rates.[12,57,66,67]

Pancreatic fistulization into the bowel can also occur. While pancreaticoenteric fistulas in the upper GI tract appear to be effectively managed with conservative therapy, pancreaticocolonic fistulas are associated with higher mortality rates due to associated sepsis and/or GI bleeding.[68,69] For stable patients, endoscopic therapy can be considered, as case series have reported acceptable rates of success with transpapillary stent placement and transmural drainage of associated PFCs.[70,71] Of note, specialized centers have described the use of transcolonic necrosectomy, SEMS placement, and over-the-scope clip closure of pancreatoenteric fistulas but this should only be attempted at expert centers.[72–74] Surgical management, which often includes diverting ileostomy or colostomy, should be considered in patients who fail endoscopic therapy or develop clinical instability or GI bleeding.

Lastly, pancreatobiliary fistulae are a rare

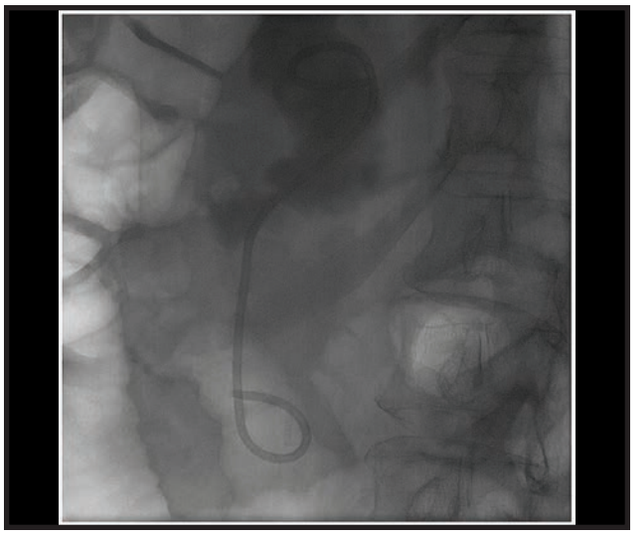

Figure 14. Placement of a transpapillary double pigtail plastic stent

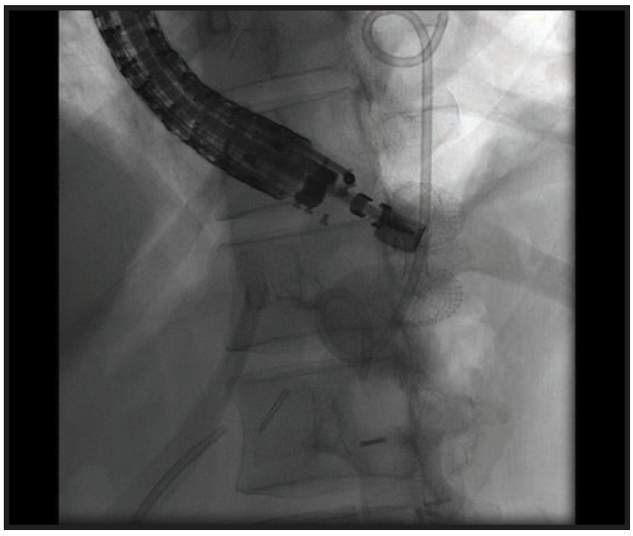

Figure 15. Cystgastrostomy of a pancreatic fluid collection with lumen apposing metal stent and double pigtail plastic stent

complication of PD leaks, which may result in cholestasis or cholangitis/sepsis. Similar to the above, case reports and case series have reported successful outcomes with different combinations of transmural drainage of associated PFCs, transpapillary PD stent placement, and biliary stent placement in the presence of cholestasis or cholangitis.[75,76] Based on limited case series, an endoscopic approach appears to be safe and effective, with surgical biliary reconstruction reserved for patients who fail endoscopic therapy.

Disconnected Pancreatic Duct Syndrome

DPDS most commonly manifests as a PFC or pancreaticocutaneous fistula that is refractory to conservative management. The management of DPDS is complex and has not been standardized. Traditionally, it involves distal pancreatectomy or internal drainage via Roux-en-Y pancreaticojejunostomy with the disconnected segment.[8] More recently, there has been interest in endoscopic and multimodal approaches.[77] For DPDS-associated PFCs, percutaneous drainage alone carries the risk of pancreaticocutaneous fistula formation. Alternatively, transmural drainage allows for enteral drainage of the upstream pancreatic secretions that are unable to drain transpapillary. In these instances, transmural drains are often left in place indefinitely with favorable outcomes.[8,78,79] Lastly, interventional radiology-guided percutaneous embolization of the disconnected portion of the PD with cyanoacrylate or other agents has been described in case series.[80] Currently, there is no consensus regarding optimal nonsurgical management in these patients due to a lack of robust comparative studies. Important limitations of previous studies are the inclusion of patients with partial duct disruption, which may skew the findings in favor of endoscopic therapy, and varying definitions of DPDS and endoscopic success. In a recent systematic review, endoscopic transmural drainage was found to be superior to transpapillary drainage with comparable success rates of >80% when compared to surgical management, analogous to previous systematic reviews and meta-analyses.[81–83] Should endoscopic therapy be attempted, it is important to consider a step-up approach for patients who fail minimally invasive treatment.

Traumatic PD Leaks

Traumatic PD leaks can present similarly to PD leaks from other etiologies. The role of ERCP in traumatic PD leaks has not been established. As with other clinical scenarios, ERCP is useful when the suspicion of PD disruption is high and endotherapy can be performed. Case series have described the utility of early ERCP to assess PD anatomy, which may influence immediate surgical management.[84,85] If the PD leak is identified at a later

presentation, they typically present as smoldering pancreatitis or a PFC, the management of which is described above.

CONCLUSION

It is important to be able to identify PD leaks and understand the indications and contraindications for endotherapy. While small PD leaks may resolve with conservative management alone, larger leaks often require additional therapy for which the options include endoscopic, radiologic, surgical, and combined approaches. The majority of PD leaks can be managed effectively without surgery, but a multidisciplinary approach to therapy is recommended to identify patients that require step-up therapy. The mainstay of endoscopic therapy for PD leaks and their sequelae involves transpapillary pancreatic duct stenting to bridge the site of PD disruption and/or transmural drainage of associated PFCs. Importantly, current evidence for the management of PD leaks is limited to case series, retrospective observational studies, and expert opinion; therefore, prospective studies are needed to inform clinical practice guidelines. ■

ACKNOWLEDGEMENTS

We would like to thank Drs. Ricardo Morgenstern, Kashyap Panganamamula, Nuzhat Ahmad, and Galen Leung for providing images.

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