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REVIEW

Pancreatic pseudocyst: The past, the present, and the future

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Abstract

A pancreatic pseudocyst is defined as an encapsulated fluid collection with a well-defined inflammatory wall with minimal or no necrosis. The diagnosis cannot be made prior to 4 wk after the onset of pancreatitis. The clinical presentation is often nonspecific, with abdominal pain being the most common symptom. If a diagnosis is suspected, contrast-enhanced computed tomography and/or magnetic resonance imaging are performed to confirm the diagnosis and assess the characteristics of the pseudocyst. Endoscopic ultrasound with cyst fluid analysis can be performed in cases of diagnostic uncertainty. Pseudocyst of the pancreas can lead to complications such as hemorrhage, infection, and rupture. The management of pancreatic pseudocysts depends on the presence of symptoms and the development of complications, such as biliary or gastric outlet obstruction. Management options include endoscopic or surgical drainage. The aim of this review was to summarize the current literature on pancreatic pseudocysts and discuss the evolution of the definitions, diagnosis, and management of this condition.

Key Words: Pancreatic pseudocyst; Pancreatic fluid collection; Cystic pancreatic lesions;

Pancreatitis; Endoscopic ultrasound

Core Tip: Surgery was the mainstay of treatment for pancreatic pseudocysts in the past until other modalities such as endoscopic and percutaneous drainage emerged as viable alternatives. Endoscopic drainage is currently the preferred modality for drainage of pseudocysts unless indications for surgical intervention are present. Not all pancreatic pseudocysts require intervention, and most can be treated with supportive measures. Intervention is indicated if the patient is symptomatic or if complications are present.

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INTRODUCTION

A pancreatic pseudocyst is an encapsulated fluid collection with a well-defined inflammatory wall with minimal or no necrosis, usually maturing at least 4 wk after the onset of pancreatitis[1]. A pseudocyst may arise as a consequence of acute pancreatitis, chronic pancreatitis (due to progressive ductal obstruction), or pancreatic trauma[2].

Morgagni[3] provided the earliest descriptions of pseudocysts of the pancreas in 1761. Historically, all peripancreatic fluid collections were referred to as "pancreatic pseudocysts"[4]. The variety of terminology used to describe the complications of acute pancreatitis has caused considerable confusion prior to the 1992 Atlanta classification, which first classified peripancreatic fluid collections secondary to acute pancreatitis as acute pancreatic fluid collections (PFCs), pseudocysts, and pancreatic necrosis[5]. In the following two decades, there was a discrepancy in the nomenclature being used among surgeons, gastroenterologists, and radiologists due to the increasing availability of high-quality cross-sectional imaging. An improved understanding of the nature and pathophysiology of PFCs then led to a revision of definitions in 2012 (the revised Atlanta classification). As shown in Table 1, the 2012 revised Atlanta classification of acute pancreatitis classifies PFCs as acute peripancreatic fluid collection, acute necrotic collection, pancreatic pseudocyst, and walled-off necrosis[1].

In 1882, Bozeman[6] reported the first successful surgical removal of a 10 kg pseudocyst from a 41-year-old female. Surgical drainage had traditionally been the predominant treatment for pancreatic pseudocysts, but with the advent of ultrasonography (US) or computed tomography (CT)-guided percutaneous drainage, as well as endoscopic techniques, traditional operative treatment has become uncommon[3,7]. This paper reviewed the current literature on pancreatic pseudocysts and discussed the evolution of its diagnosis and management.

EPIDEMIOLOGY AND ETIOLOGY

Pancreatic pseudocysts affect up to 1 per 100000 adults per year, and their incidence ranges from 1.0%-4.5% among patients with pancreatitis, regardless of etiology[8-10]. Imrie *et al*[11] reported a 7% incidence of pancreatic pseudocyst among their group of patients with acute pancreatitis. Moreover, pseudocysts tend to be more prevalent in chronic pancreatitis as compared to acute pancreatitis[12], with a reported incidence of 30%-40%[13]. Since 1970, the application of US and CT has led to the more frequent discovery of fluid collections associated with pancreatitis. Prior to 1970, upper gastrointestinal series such as barium studies were an inaccurate means of detecting pseudocysts, only detecting pseudocysts large enough to compress on adjacent viscera. However, the increased use of US and CT led to a more sensitive and precise means of characterizing pseudocysts as well as an increased recognition of other cystic lesions of the pancreas[14,15].

The etiology of pancreatic pseudocysts parallels that of pancreatitis. In countries where there is high alcohol consumption, alcoholic pancreatitis is the most common cause, accounting for 59%-78% of all pancreatic pseudocysts[16]. However, alcohol itself does not lead to a greater predisposition to pseudocyst formation[17]. According to data gathered from admissions for pancreatic pseudocysts in a United States hospital, the causative factors include alcohol consumption (70%), idiopathic trauma (16%), gallstone disease (8%), blunt trauma (5%), penetrating trauma (1%), and surgery (0.3%)[18].

PATHOPHYSIOLOGY

A pancreatic pseudocyst is a consequence of inflammatory or obstructive processes within the pancreas, which result in pancreatic duct disruption and the leakage of enzyme-rich pancreatic juice into the retroperitoneum, with ensuing autodi-

Table 1 Definitions of pancreatic fluid collections according to the 2012 Atlanta classification[1]

Collection type	Definitions
Acute peripancreatic fluid collection	Peripancreatic fluid seen within the first 4 wk after onset of interstitial edematous pancreatitis, with no associated peripancreatic necrosis or features of a pseudocyst
Pancreatic pseudocyst	An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. It usually takes more than 4 wk for it to mature after the onset of interstitial edematous pancreatitis and contains amylase-rich fluid with no solid debris
Acute necrotic collection	A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis within the first 4 wk. The necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues
Walled-off necrosis	A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis with a well-defined inflammatory wall. It usually matures 4 wk after the onset of necrotizing pancreatitis

gestion of the surrounding tissue[9,19]. In cases of pancreatic parenchymal necrosis of the neck or body, a viable distal pancreatic remnant is still present and continues to secrete pancreatic juice[20]. This enzymatic activity promotes further inflammation and produces a cyst wall with abundant granulation tissue but no true epithelial lining[4,9]. Subsequently, against the background of the inflammatory process, this fluid accumulation is separated by the deposition of fibrin and the formation of a granulation shaft, leading to the formation of a fibrous connective tissue wall.

The persistence of an acute fluid collection beyond 4 wk and formation of a well-defined wall define a pancreatic pseudocyst[12]. Over time, the cyst wall becomes more organized, and a dense fibrous capsule is formed. With this mechanism, the cysts are considered to be degenerative due to aseptic autolysis of pancreatic parenchymal tissue. Thus, in the course of its development, pancreatic pseudocysts go through several stages in the early period: (1) Progression of the inflammatory infiltrate; (2) acute fluid accumulation; and (3) formation of an encapsulated fluid accumulation, rich in pancreatic enzymes and confined to fibrous peritoneal tissue and/or the retroperitoneal space and serous membrane of adjacent organs. The absence of epithelium allows differentiation of pseudocysts from true cysts and cystic neoplasms.

In chronic pancreatitis, a pseudocyst may develop from an acute exacerbation of the underlying disease according to a previously described mechanism[12]. It can also be a result of pancreatic ductal obstruction by stones, strictures, or protein plugs, leading to increased intraductal pressure and localized rupture of the pancreatic duct or ductules, with extravasation of pancreatic juice[13,19,21].

Pseudocysts are commonly located in the lesser sac adjacent to the pancreas. However, they have also been reported to involve the liver[22], neck[23], mediastinum[24,25], pelvis, and scrotum[26] because of the enzymatic activity present in inflammatory collections of pancreatic origin. Complications may occur during the formation and progressive course of pancreatic pseudocysts. Suppuration, perforation, and rupture into the abdominal cavity or hollow organs can occur, with subsequent formation of internal and external fistulas. Other complications include erosive bleeding into the pseudocyst cavity that can mimic a splenic artery pseudoaneurysm[27], obstruction of the gastrointestinal tract due to compression of the stomach or duodenum, secondary portal hypertension, pleuropulmonary complications[28], diabetes mellitus, and exocrine insufficiency.

CLASSIFICATION

In 1991, D'Egidio and Schein[29] proposed a classification of pancreatic pseudocysts according to whether they develop following acute or chronic pancreatitis, with an emphasis on the presence of any pancreatic ductal pathology. They believed that both the presence of pancreatic ductal strictures and communication between the pseudocyst and pancreatic duct affect management significantly. Type I pseudocyst is defined as a post-necrotic pseudocyst associated with acute pancreatitis. Type II pseudocyst is a post-necrotic pseudocyst occurring after an episode of acute-on-chronic pancreatitis, without a ductal stricture (though there may be a pseudocyst-duct communication). Furthermore, type III pseudocyst is defined as a "retention" pseudocyst that occurs due to chronic pancreatitis and is associated with ductal stricture and pseudocyst-duct communication. Nealon and Walser[30] based their classification in 2002 on pancreatic ductal anatomy and endoscopic retrograde cholangiopancreatography (ERCP) findings. The categories of ductal abnormalities that formed their classification are detailed in Table 2.

CLINICAL PRESENTATION AND LABORATORY INVESTIGATIONS

Patients with even a large pancreatic pseudocyst may be asymptomatic. In symptomatic patients, epigastric pain is the most common symptom. The pain may be referred to the left hypochondrium or radiate to the back[16]. Pain may be aggravated by eating food, which may explain the marked weight loss experienced by some patients. Other symptoms include early satiety, nausea or vomiting, and less commonly jaundice (due to bile duct compression)[12,31]. Anorexia may occur with or without abdominal pain[16]. In patients presenting with incidentally discovered pancreatic cysts on imaging, eliciting a history of pancreatitis is crucial. Physical examination may reveal abdominal tenderness or occasionally a palpable abdominal mass. Patients with infected pancreatic pseudocysts may be febrile. A pleural effusion is an

Table 2 Classification by Nealon and Walser[30]

Classification	Description
Type I	Normal duct, no communication between duct and pseudocyst
Type II	Normal duct, with communication between duct and pseudocyst
Type III	Otherwise, normal duct with stricture and no communication between duct and pseudocyst
Type IV	Otherwise, normal duct with stricture and communication between duct and pseudocyst
Type V	Otherwise, normal duct with presence of complete cut-off along its course
Type VI	Chronic pancreatitis, no communication between duct and pseudocyst
Type VII	Chronic pancreatitis, with communication between duct and pseudocyst

uncommon finding[31].

Laboratory investigations have limited diagnostic value. Serum amylase and lipase levels are often elevated, while elevated bilirubin raises the suspicion of biliary pancreatitis. Other laboratory tests, such as triglyceride or serum calcium levels, may be done to elucidate the etiology of pancreatitis[12]. Carbohydrate antigen 19-9 (CA 19-9) in the serum and pseudocyst fluid can be elevated and masquerade as a malignancy[32].

Cystic lesions of the pancreas are common incidental findings on imaging. As such, it is important to differentiate pancreatic pseudocysts from other cystic lesions such as intraductal papillary mucinous neoplasm, serous cystadenoma, mucinous cystic neoplasm, and solid pseudopapillary neoplasm[12]. Other differential diagnoses include pancreatic tumor with cystic degeneration, duplication cyst, pseudoaneurysm, or a lymphocele[33].

IMAGING MODALITIES

The imaging appearance of pancreatic pseudocysts depends on size, location, and presence of necrosis or hemorrhage.

Transabdominal US

On US, a pancreatic pseudocyst appears hypoechoic or anechoic and is associated with distal acoustic enhancement (Figure 1). In the early stages, there can be varying degrees of internal echoes due to the presence of necrotic debris, especially after acute necrotizing pancreatitis[12]. Pseudocysts may also appear more complex when there is internal hemorrhage or in the presence of a secondary infection. Doppler US should always be performed to exclude pseudoaneurysms. The sensitivity of US for the detection of pancreatic pseudocysts ranges from 75%-90%[16]. Its sensitivity may be decreased by the presence of overlying bowel gas. Moreover, the interpretation of US findings is operator dependent.

CT scan

A contrast-enhanced CT scan can demonstrate a well-circumscribed, thick-walled, rounded fluid collection, which is typically peripancreatic (Figure 2)[12]. CT scan is the investigation of choice in the acute setting since the sensitivity of US is decreased with an increased amount of bowel gas, which may be a result of ileus or obstruction. More information on the surrounding anatomy can also be gathered from CT scans, and additional pathologies can be demonstrated, such as common bile duct dilatation, choledocholithiasis, main pancreatic duct dilatation, pancreatic necrosis, and pancreatic calcifications[12]. The sensitivity of CT for the diagnosis of pseudocysts is 90%-100%[16]. The limitations of CT scans include the relative inability to distinguish pseudocysts from cystic neoplasms of the pancreas[14] as well as the risk of intravenous contrast-induced nephropathy.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) provide valuable information for the further characterization of cystic lesions of the pancreas due to better soft tissue resolution[34]. MRI and MRCP have high sensitivity in the diagnosis of pancreatic pseudocysts and also have greater sensitivity than CT in the detection of solid debris or hemorrhage within PFCs[35]. MRI T2-weighted sequences typically appear bright with high signal intensity for a fluid-filled cystic lesion. MRI or MRCP is the preferred modality to delineate the pancreatic duct and biliary systems and are more sensitive than CT or US to detect choledocholithiasis[12].

ERCP

Some authors advocate for the use of ERCP if operative intervention for pancreatic pseudocyst is being considered, in light of the study by Nealon and Walser[36] that evaluated the use of ERCP as a means of assessing the pancreatic ductal anatomy to guide the decision between nonoperative and operative management as well as the modality of intervention. However, with the availability of multiple alternative modalities such as CT, MRI, and endoscopic US (EUS), most patients do not require ERCP to guide management[12].

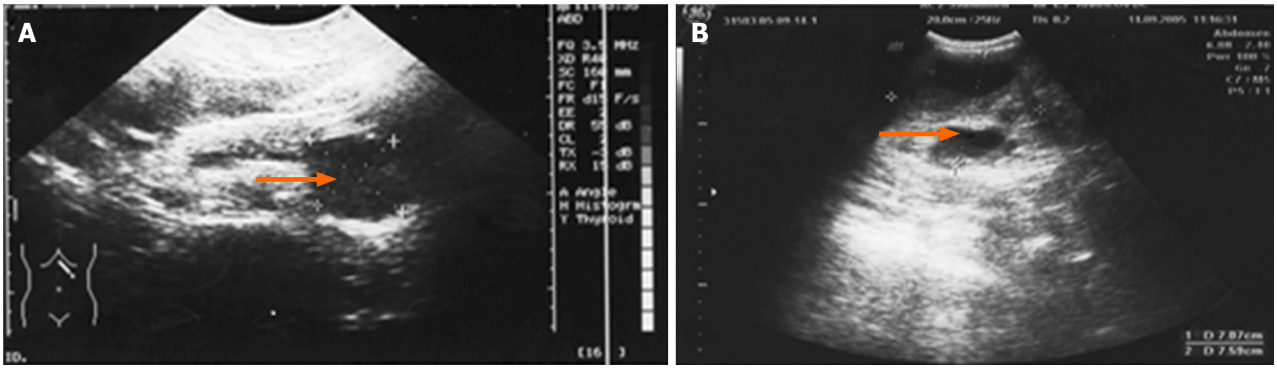

Figure 1 Transabdominal ultrasonography. A: Pseudocyst of the body-tail of the pancreas in the setting of chronic pancreatitis (indicated by an arrow); B: Pseudocyst of the head of the pancreas (indicated by an arrow).

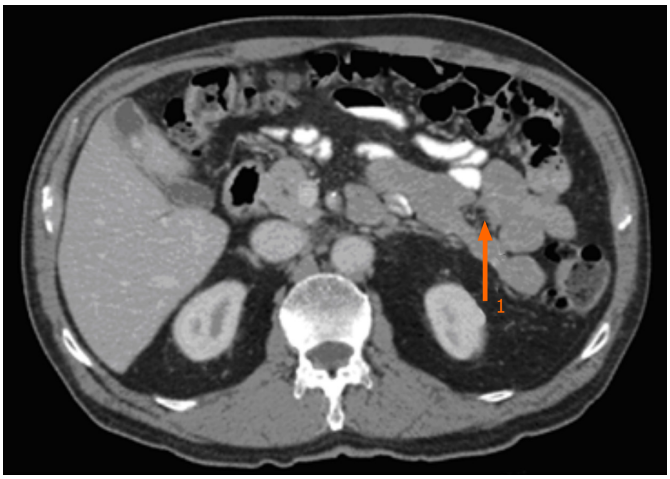

Figure 2 Computed tomography scan image showing pseudocyst at the tail of the pancreas (indicated by an arrow).

EUS

EUS is used as an additional imaging modality when diagnosis is uncertain, either because the clinical setting is unclear or when findings from other imaging modalities are atypical. EUS is useful for differentiating between pseudocysts and other cystic lesions of the pancreas[12,37]. As the pancreas lies posterior to the stomach, a US transducer can be placed in close proximity to the pancreas to provide detailed images of the cyst wall, septations, and presence of masses or nodules [38]. The following features raise suspicion of a malignancy: A cyst wall thickness of 3 mm or greater; macroseptation (when all cyst compartments are more than 10 mm in diameter); presence of a mass or intramural nodule; or cystic dilation of the main pancreatic duct[37]. Studies on the sensitivity and specificity of EUS morphology alone for identifying malignant cystic lesions or differentiating between mucinous cystic neoplasms and non-mucinous cystic lesions have shown mixed results[37,39]. Figure 3 shows EUS images of a pancreatic pseudocyst and fine-needle aspiration (FNA) being performed.

Furthermore, EUS-guided FNA can obtain cyst fluid for the analysis of cytology and molecular markers. Cumulatively, these investigations are more sensitive and specific than imaging[40]. High cyst fluid carcinoembryonic antigen (CEA) levels indicate a higher possibility of either malignancy or a mucinous cystic lesion[38,40]. Hammel *et al*[41] studied 91 patients with cystic lesions of the pancreas and found that a CEA level of greater than 400 ng/mL had 57% sensitivity and 100% specificity for distinguishing mucinous tumors and cystadenocarcinomas from pseudocysts, while a CEA level of less than 4 ng/mL had 100% sensitivity and 93% specificity for distinguishing serous cystadenomas from mucinous cystadenomas, cystadenocarcinomas, and pseudocysts. The same study also reported that CA 19-9 levels of greater than 50000 U/mL had 75% sensitivity and 90% specificity for distinguishing mucinous neoplasms from other cystic lesions. However, fluid from pancreatic pseudocysts can exhibit high CA 19-9 levels, which is not surprising given that this marker may also be elevated in the serum of patients with pancreatitis[40].

One prospective study reported that high relative viscosity of 1.6 or greater and CEA greater than 480 ng/mL are features of mucinous cystadenomas and mucinous cystadenocarcinomas, while low viscosity and low CEA suggest benign lesions[38]. A pooled analysis by van der Waaij *et al*[42] showed that a CEA level of greater than 800 ng/mL strongly suggests mucinous cystic neoplasm or mucinous cystadenocarcinoma, while CEA levels < 5 ng/mL or CA 19-9 < 37 U/mL suggest the presence of a serous cystadenoma or pseudocyst.

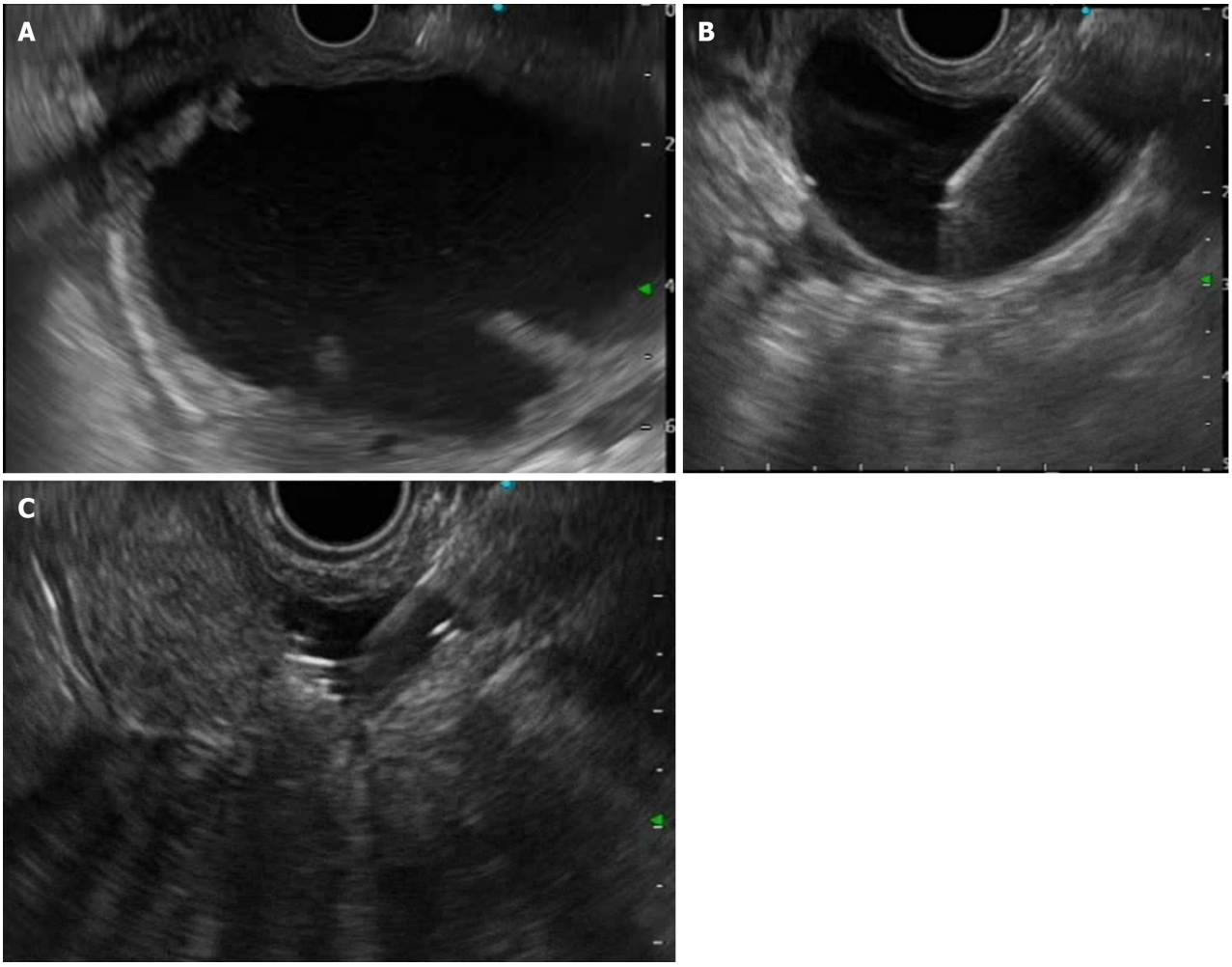

Figure 3 Endoscopic ultrasound utility in diagnosis and management of pancreas pseudocyst. A: Appearance of pseudocyst on endoscopic ultrasound; B: Endoscopic ultrasound-guided fine-needle aspiration of pseudocyst; C: Decrease in size of pseudocyst after aspiration of cyst fluid.

A high amylase level suggests a pseudocyst or retention cyst, and this is due to the cyst fluid being in communication with the pancreatic ductal system. Fluid amylase is usually low in serous cystadenoma[12], whereas an amylase level less than 250 U/L makes a diagnosis of pseudocyst unlikely[42]. However, there have been case reports of elevated amylase levels in patients with cystic neoplasms[43,44]. High lipase levels are generally observed in pseudocysts, whereas cystic tumors tend to exhibit low lipase levels. Similar to amylase, lipase values are unreliable in isolation, but may be useful when interpreted in conjunction with other cyst fluid parameters[40]. Linder *et al*[38] reported 91.3% sensitivity and 100% specificity in predicting pseudocysts when considering the combined criteria of relative viscosity less than 1.6, lipase greater than 6000 U/L, and CEA less than 480 ng/mL.

Khalid *et al*[45] published a prospective study in 2005 on the utility of molecular analysis of EUS-guided aspirates of pancreatic cyst fluid and found that malignant cysts can be differentiated from premalignant cysts based on fluid CEA, quality of DNA, number of mutations, and sequence of mutations acquired. The pattern of a first hit *K-ras* mutation followed by allelic loss was the most predictive of a malignant cyst, with sensitivity of 91% and specificity of 93%. Molecular analysis can serve as an additional tool for the evaluation of cystic lesions of the pancreas.

Cytology may be useful for differentiating mucinous from non-mucinous cysts and can even provide evidence of a malignancy. However, cytology cannot reliably distinguish pseudocysts from serous cystadenoma. Furthermore, a negative cytology result does not exclude malignancy, as some neoplastic cyst fluids may contain no tumor cells[40]. Van der Waaij *et al*[42] analyzed 11 studies and reported that cytology has a sensitivity of 48% in the detection of malignant cystic lesions, and different studies yielded drastically different sensitivities in terms of cytologic examination. In their study, rare forms of pancreatic cystic neoplasms such as solid pseudopapillary neoplasms were excluded. It is our recommendation that management decisions are made after clinician-led multidisciplinary discussions with radiology and pathology teams to support the search for diagnostic clarity to provide high quality patient-centered care.

COMPLICATIONS OF PANCREATIC PSEUDOCYST

Infection

Infection of a pancreatic pseudocyst may be due to translocation of bacteria from the gastrointestinal tract, secondary infection of an intracystic hematoma, or iatrogenic infection after EUS-FNA or ERCP[46]. Surgery had been the preferred modality of treatment historically, but nowadays endoscopic treatment is advocated. EUS-guided internal drainage of infected pancreatic pseudocysts is safe and effective[47]. In the event that the patient is unstable and not fit for surgical or endoscopic drainage, external drainage may be required[12].

Rupture

Spontaneous rupture complicates less than 3% of pancreatic pseudocysts. Aside from perforation into the peritoneal cavity, there have also been reports of perforation into the stomach, duodenum, colon, abdominal wall, portal vein, and pleural cavity[48,49]. If the adjacent hollow viscus is involved by such an episode of spontaneous pseudocyst rupture, life-threatening hemorrhage may ensue. As such, these cases may require urgent surgical intervention[12,48].

Hemorrhage

Hemorrhage is a significant complication of pancreatic pseudocysts and is associated with high morbidity and mortality. Mechanisms of hemorrhage include variceal bleeding (secondary to obstruction of the portal or splenic veins by the pseudocyst), hemobilia, intraperitoneal hemorrhage, and intracystic hemorrhage, with conversion of the pseudocyst to a pseudoaneurysm[21]. Interventional radiologists play a crucial role in both localization of the source of bleeding and therapeutic angioembolization of the bleeding vessel. Arterial embolization can also be an effective temporizing measure to provide the surgeon time (in the following 72 h) to plan definitive surgical treatment[50].

The presence of signs of bleeding warrants catheter angiography to confirm diagnosis and plan therapeutic embolization to achieve hemostasis[51]. Angiography demonstrates contrast medium into the duodenal lumen in patients where the presence of acute bleeding from a vessel into the pancreatic pseudocyst cavity communicates with the main pancreatic duct (Figure 4). One of the differentiating criteria between true and pseudoaneurysms is the intensity of contrast in the aneurysm cavity. In a true aneurysm, it is close in density to the aorta, whereas in a pseudoaneurysm, the intensity is lower than the density of the aorta. Outside of the bleeding period, the pseudocyst cavity may not have filled with contrast medium, and the only angiographic sign may be a "cut off" in the contrast of the feeding vessel and also the presence of an avascular area in the pseudocyst projection (Figure 4B).

Splenic complications

Splenic involvement by a pancreatic pseudocyst is of two types. Firstly, pseudocyst proximity to the splenic vessels can lead to vascular involvement and secondly the splenic parenchymal pathological sequalae following the vascular involvement. The splenic arterial pseudoaneurysm has a potential for massive hemorrhage that can be within the pseudocyst, retroperitoneum, intragastric, or free intraperitoneal[27]. The splenic venous involvement can lead to thrombosis with features of left-sided portal hypertension and splenic infarction in advanced situations[52,53]. As the tail of the pancreas is in close relation to the hilum of the spleen, sometimes a pancreatic pseudocyst can be indistinguishable from a splenic cyst and present as a left upper quadrant mass[12]. CT aids the confirmation of splenic involvement, and angiography should be performed to detect pseudoaneurysm formation[52]. The splenic vessels will necessarily be in contact with an intrasplenic pseudocyst; hence, the splenic artery is particularly vulnerable to erosion and hemorrhage. For a pseudocyst that is located at the tail of the pancreas, distal pancreatectomy with splenectomy can be curative[54].

Portal hypertension

A pancreatic pseudocyst can rarely cause compression of the splenic vein or portal vein, either alone or in conjunction with underlying chronic pancreatitis, leading to portal hypertension[55]. Splenic vein occlusion can increase the risk of development of esophageal or gastric varices by reversing the flow of blood on the left side of the portal system through promoting the formation of collateral channels between the splenic vein and the gastric or gastroepiploic veins. Variceal bleeding can potentially be massive. Surgical intervention, such as splenectomy with or without pancreatectomy, is indicated in symptomatic patients[56].

Biliary obstruction

Pancreatic pseudocysts in the vicinity of the pancreatic head may cause common bile duct obstruction, leading to obstructive jaundice. However, patients with chronic pancreatitis, who form the majority of those with pancreatic pseudocysts, commonly have other causes of intrapancreatic common bile duct obstruction, the most prominent being a fibrotic stricture. Hence, drainage of the pseudocyst alone may be insufficient to relieve biliary obstruction[57]. ERCP is valuable in this situation to delineate the anatomical alterations of the pancreatic duct as well as common bile duct, with the option of biliary stenting. Surgery is indicated if a pseudocyst causes biliary obstruction by compression, and cystoduodenostomy is one of the methods used. After surgical drainage of the pseudocyst, if there is concern regarding the patency of the common bile duct, obtaining an intraoperative cholangiogram is prudent[58].

Gastric outlet obstruction

Large pancreatic pseudocysts that cause external compression are a well-documented cause of gastric outlet obstruction. Endoscopic drainage is a viable treatment option and is currently the first-line modality of treatment. However, if there is

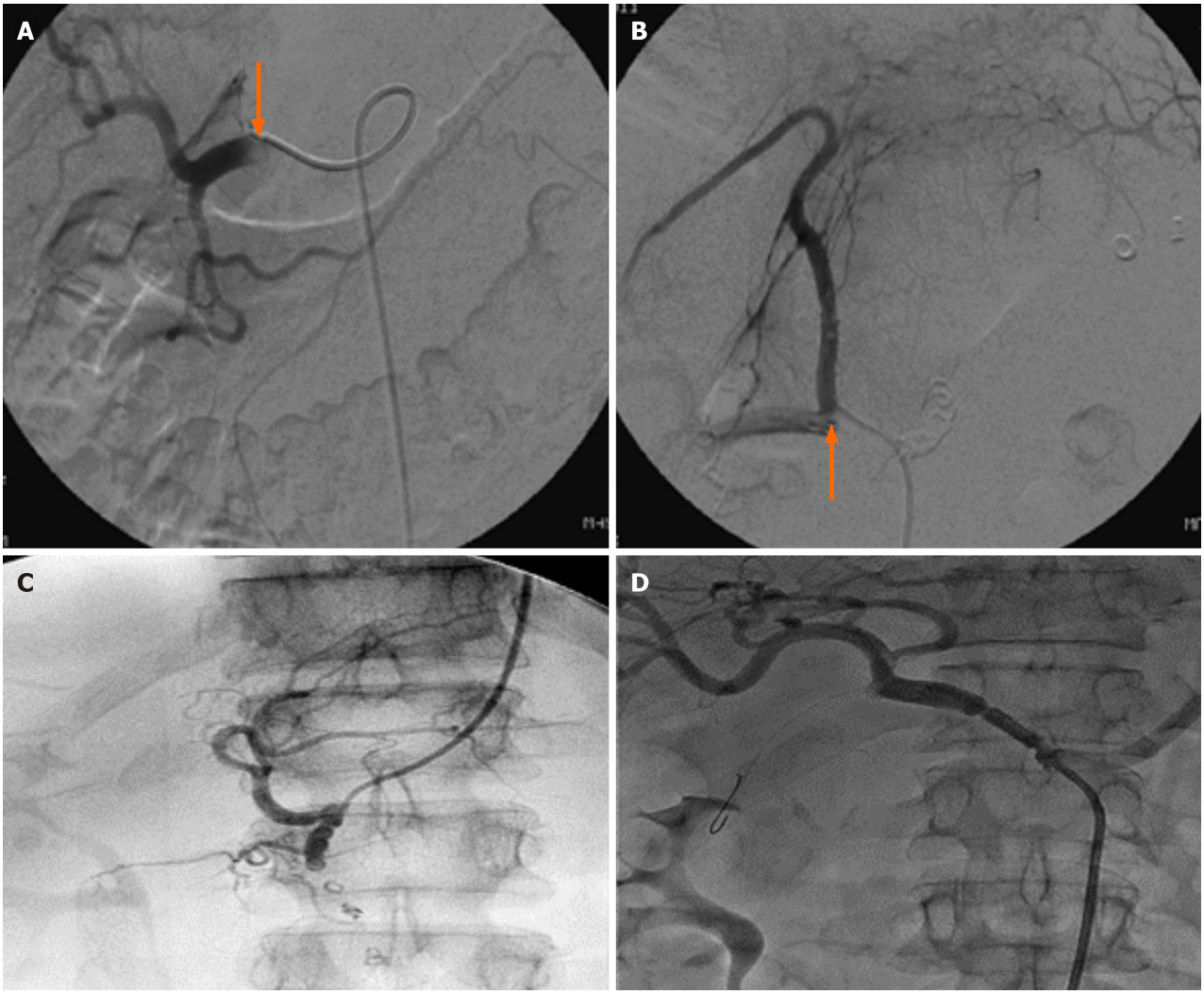

Figure 4 Angiogram. A: Bleeding into the pseudocyst cavity from gastroduodenal artery (indicated by an arrow); B: Bleeding into the pseudocyst cavity ("cut off" of the left gastric artery, indicated by an arrow); C: Embolization was performed distal and proximal to the erosion zone; D: A stent graft was placed in the common hepatic artery.

a lack of endoscopic expertise or if the patient presents with a recurrence or failure of endoscopic therapy, surgical drainage can be considered[59].

MANAGEMENT

The management of pancreatic pseudocysts is guided by the symptomatology, presence of any complications, and the characteristics and location of fluid collection. With regard to PFCs in general, the American College of Gastroenterology and the International Association of Pancreatology/American Pancreatic Association guidelines recommend no intervention if asymptomatic and an absence of infected necrosis, regardless of the size, location, and extension of the PFC[60,61]. Surgery, traditionally the mainstay of treatment for pancreatic pseudocysts, is now reserved only for select cases, given the low morbidity of minimal access endoscopic modalities that provide equivalent clinical success[62]. The availability of resources and expertise, as well as the technical factors of the pseudocyst, are essential in making treatment decisions[63]. Management requires a multidisciplinary approach that involves surgeons, gastroenterologists, and interventional radiologists. In addition, allied health specialists such as nutritionists are also an important part of the clinical care team.

Supportive treatment

Intravenous fluids, analgesia, and antiemetics are administered as per the clinical judgment. Symptoms related to pancreatic pseudocysts, such as nausea and early satiety, may limit oral intake and affect nutritional status. For patients who are able to tolerate diet, a low-fat diet consisting of small frequent meals is recommended. Enteral feeding is strongly encouraged over parenteral nutrition[62]. We advocate using a functional gastrointestinal system to prevent its malfunction[64]. If the patient is unable to tolerate oral administration, nasoenteric feeding can be initiated, with total parenteral

nutrition being an alternative option. There is currently no evidence to suggest one option over the other in the setting of pancreatic pseudocysts[12]. In our opinion, both approaches are complementary and not competing. Some authors have suggested a role for somatostatin analogues such as octreotide in promoting pseudocyst resolution on the basis that it may reduce pancreatic secretions; however, the evidence for octreotide is limited to case series[65,66].

Most pancreatic pseudocysts resolve with supportive care. Some clinicians adhere to the prior dictum of treating non-resolving pancreatic pseudocysts greater than 6 cm in size that have been persisting for at least 6 wk, even though the patient may be asymptomatic, on the grounds of preventing future complications[21,67]. However, other studies have shown that size is not a significant factor in determining the likelihood of spontaneous resolution. Vitas and Sarr[68] followed 114 patients over 5 years of age, 68 of whom were initially treated conservatively. Resolution of the pseudocyst occurred in 57% of these patients, and severe complications occurred in only 6 patients (9%) over a mean duration of 46 mo. Surgery (on an elective basis) was eventually required for 19 patients.

Maringhini *et al*[69] found that 65% of pancreatic pseudocysts that developed after an episode of acute pancreatitis resolved within 1 year, though they noted that pseudocysts less than 5 cm or involving the tail of the pancreas had a higher rate of spontaneous resolution. A 2013 prospective multicenter study[70] showed that 84.2% of pseudocysts, including some that were larger than 10 cm, showed spontaneous improvement with just conservative management. In our opinion, size alone should not be the indication to intervene, and imaging findings must be considered along with the patient's clinical progress. A pancreatologist has a duty to treat the patient rather than the radiographic image.

Endoscopic drainage

There are indications for drainage of a pancreatic pseudocyst with persistent symptoms and the presence of complications. Endoscopic drainage is the preferred approach for drainage because it is a less invasive option than surgery and does not require an external drain, all while achieving comparable cyst resolution outcomes with surgery[2,12]. Endoscopic drainage is becoming the most commonly used modality as it reduces hospital length of stay and associated costs[71].

Endoscopic drainage can be performed using either a transmural (Figure 5) or a transpapillary approach. Transmural drainage is preferred and is suitable for a pseudocyst that is directly adjacent to the gastroduodenal wall. Relative contraindications for endoscopic drainage are a distance of more than 1 cm between the gastric or duodenal wall and cyst wall or the presence of varices or large intervening vessels[72]. During the procedure, access to the cyst cavity can be obtained through an incision in the stomach wall (transgastric) or duodenum (transduodenal).

The transpapillary approach is recommended in the presence of communication between the pseudocyst and main pancreatic duct. The incidence of this is 36%-69% in patients with pseudocysts[2]. For patients with main pancreatic duct strictures, EUS-guided transmural drainage can be performed alone or in combination with ERCP-guided transpapillary stent placement and drainage[73]. However, a large multicenter study of 174 patients found that transmural drainage had a 97% success rate compared to 44% for combined transmural and transpapillary drainage, mainly due to failed transpapillary drainage[74]. A meta-analysis by Amin *et al*[75] showed that combined drainage demonstrated no additional benefits over transmural drainage in terms of technical success, clinical success, recurrence, or complications. Therefore, routine transpapillary drainage should be reserved for cases whereby there is a communication between the pseudocyst and main pancreatic duct or when there is failure of the initial transmural approach[76].

In terms of the choice of stents to be deployed during endoscopic drainage, the use of newer lumen-apposing, covered, and self-expanding metal stents have become increasingly popular. Lumen-apposing metal stents (LAMS) have significant advantages compared to traditional plastic stents, such as the integration of modern LAMS to facilitate single-step deployment minimizing device exchanges as well as enabling the procedurist to perform direct endoscopic debridement with minimal stent migration[77-79]. EUS-guided transmural drainage using LAMS has a clinical success rate of 98% for pseudocyst drainage[80]. Figure 6 illustrates the use of endoscopic techniques for pancreatic pseudocysts and walled-off necrosis.

EUS-guided transmural drainage is the first-line option for the treatment of pancreatic pseudocysts when drainage is indicated[76,81]. The advantage of EUS is that it does not require the pseudocyst to produce an obvious bulge into the lumen of the stomach or duodenum to be amenable for drainage and allows for a safer needle puncture under ultrasonic guidance. EUS can help to exclude the presence of intervening blood vessels (using real-time color Doppler) and detect the presence of debris within the pseudocyst cavity[2], as shown in Figure 7. The presence of solid debris in the cavity guides management in terms of type and size of stents used or placement of additional drains.

The success rate of endoscopic drainage as evidenced by regression of the pseudocyst is approximately 62%-90%, with a recurrence rate of 4.8%-20.9% and a complication rate of 11%-34%[82-89]. Hookey *et al*[89] found no significant difference in the success of endoscopic drainage when comparing between different drainage techniques (transmural, transpapillary, or combined) or location of fluid collection (pancreatic head, body or tail, and extrapancreatic). On the other hand, the success rate of endoscopic drainage of necrotic collections (25%) was significantly lower than that of other types of fluid collections such as acute peripancreatic fluid collections and pseudocysts (92.6%).

A 2009 meta-analysis comparing the outcomes of endoscopic and laparoscopic approaches showed no significant difference in the overall success rate, incidence of adverse events, or recurrence rate[90]. However, endoscopic treatment has the advantage of shorter operative time, blood loss, and length of hospital stay compared with laparoscopic surgery [91]. Similarly, a randomized trial by Garg *et al*[92] that included both symptomatic pseudocysts and walled-off necrosis showed that laparoscopic drainage had an initial success rate of 83.3% and that of endoscopic drainage was 76.6%, while both had similar overall success rates of 93.3% and 90.0%, respectively. A randomized trial in 2013 compared the outcomes of endoscopic drainage and open surgical drainage (cystgastrostomy) and found that endoscopic cystgastrostomy is noninferior to surgical cystgastrostomy in terms of recurrence after 24-mo follow-up[93]. A systematic review comparing the outcomes of endoscopic, percutaneous, and surgical pseudocyst drainage showed that the clinical success and

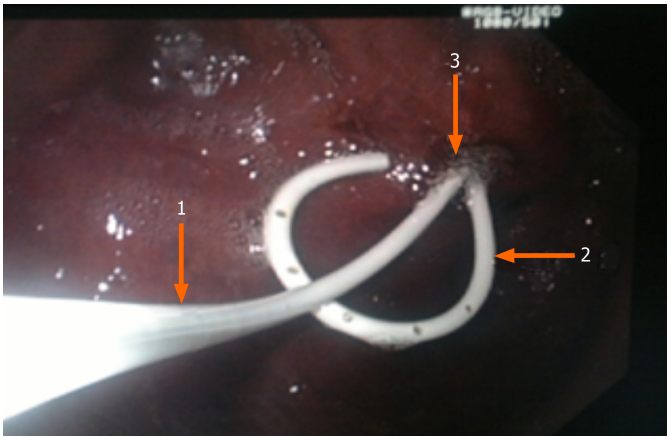

Figure 5 Transmural cystogastroanastomosis with external-internal drainage. Arrow 1 shows cystonasal drainage, arrow 2 shows internal stent, and arrow 3 shows cystogastroanastomosis.

rate of adverse events were comparable between EUS-guided and surgical drainage; however, the EUS approach was able to shorten length of hospital stay, reduce cost, as well as improve the patient's quality of life[94].

Percutaneous drainage

Pancreatic pseudocysts can be drained externally with the placement of a pigtail catheter percutaneously into the pseudocyst cavity under CT or US guidance (Figure 8). The drain may be left in place for several weeks, and the decision for drain removal is guided by drainage output, among other factors such as clinical and radiological improvement. Apart from cross sectional imaging such as CT, the size of the residual cavity can also be monitored by contrast injection into the cyst cavity, as shown in Figure 8C. Contraindications to percutaneous drainage include the presence of main pancreatic duct strictures or cysts containing solid material[29]. If there is communication between the pseudocyst and pancreatic duct or a downstream obstruction of the main pancreatic duct, there is a high risk of pancreatic fistula formation, and percutaneous drainage should be avoided in such situations[13,29]. Both types of situations are common in patients with chronic pancreatitis. In patients with severe sepsis and who are medically unfit for operative intervention, percutaneous drainage can be a useful alternative, especially in the acute setting, as there is no need to wait for maturation of the pseudocyst wall[63].

There are two options for percutaneous intervention: (1) Percutaneous cystgastrostomy; and (2) percutaneous cystostomy (percutaneous drainage). Henriksen and Hancke[95] successfully performed percutaneous cystgastrostomy under US guidance and reported pain reduction and weight gain with minimal morbidity. Adams and Anderson[96] found that surgical intervention resulted in a significantly higher mortality rate of 9% as compared with 1% for percutaneous drainage. The disadvantages of percutaneous drainage include a prolonged external pancreatic fistula and catheter site infection. vanSonnenberg *et al*[97] reported a 90.1% success rate for percutaneous drainage of pancreatic pseudocysts, with a mean duration of drainage of 19.6 d.

However, some studies have shown less optimistic results, with Heider *et al*[98] reporting a success rate of 42% for percutaneous drainage as well as a significantly higher complication rate (64% *vs* 27%), longer hospital stay, and higher mortality rate (16% *vs* 0%) than patients treated by surgery. A retrospective study directly comparing percutaneous drainage with endoscopic drainage found a lower treatment success rate and a higher recurrence rate with the percutaneous approach[99]. Moreover, a recent meta-analysis showed that percutaneous drainage has a lower clinical success rate and a higher recurrence rate than endoscopic drainage or surgery[100]. Therefore, percutaneous drainage is not the first-line treatment for pancreatic pseudocysts unless the patient's medical comorbidities preclude definitive surgery or endoscopic management.

Endovascular therapy

Leaking pancreatic enzymes lead to autodigestion and pseudoaneurysm formation. Pseudoaneurysm and pseudocyst coexist in some patients and catastrophic bleeding can be life threatening. Diagnostic and interventional radiological capabilities are critical to the successful management of these pathologies. Endovascular embolization for bleeding into the pancreatic pseudocyst cavity is usually performed using the "sandwich technique" distal and proximal to the erosion zone (Figure 4C) to exclude retrograde filling using metal coils and polyurethane emboli as well as the stent graft placement (Figure 4D). Emergent surgery is indicated if endovascular embolization is unsuccessful.

Surgery

Historically, open surgical drainage of pancreatic pseudocysts had been considered the "gold standard." Surgical approaches can generally be divided into internal drainage, pancreatic parenchymal resection, and in rare cases external drainage. Internal drainage is achieved by the creation of a communication between the pseudocyst cavity and the stomach, duodenum, or jejunum, known as a cystgastrostomy, cystduodenostomy, or cystjejunostomy, respectively[4,101]. The cystenterostomy is placed to allow gravity-dependent drainage, and the resultant stoma can remain patent for

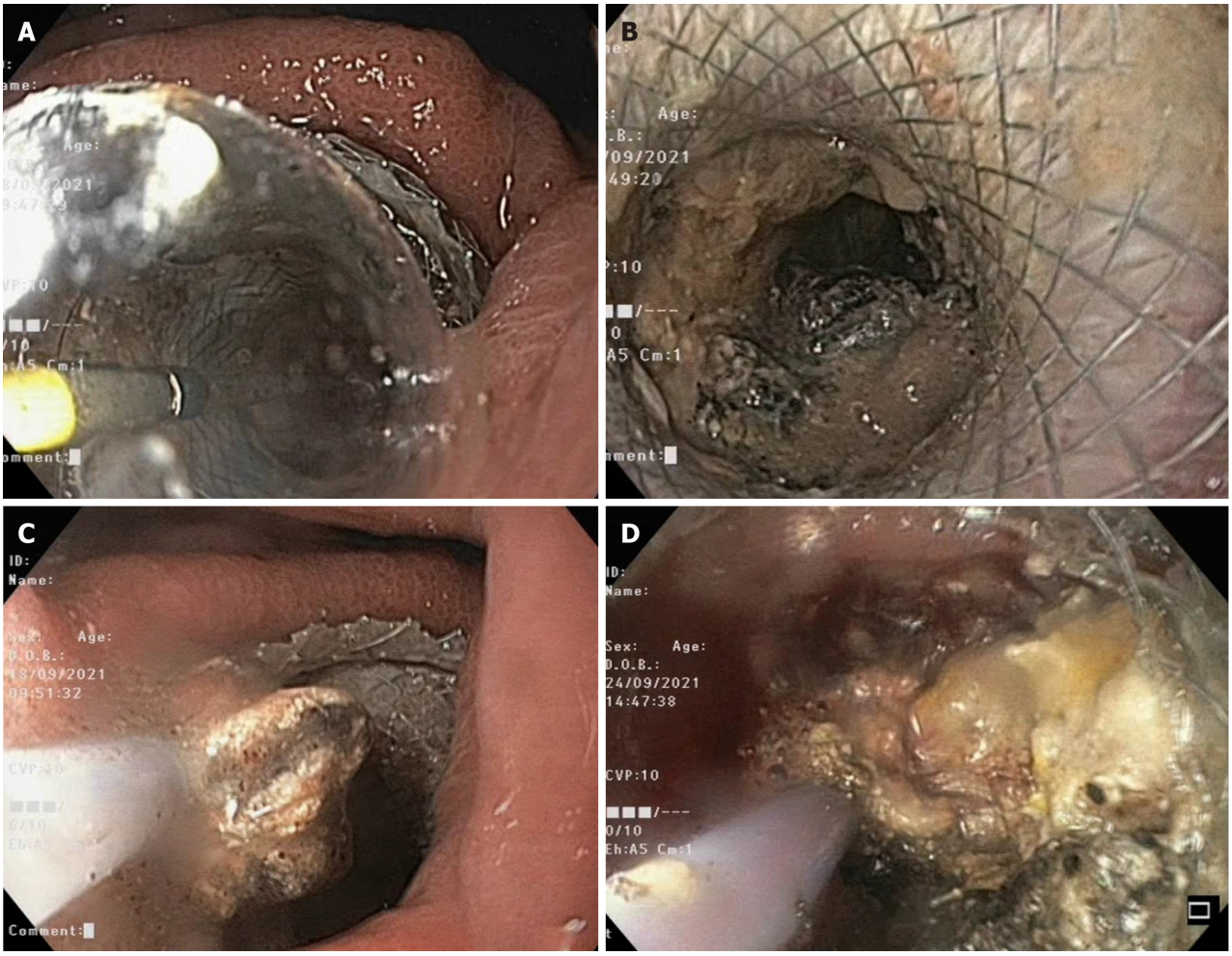

Figure 6 Endoscopic images. A: Balloon dilatation of a lumen-apposing metal stent; B: The view inside the walled-off necrosis cavity after cystgastrostomy; C: Direct endoscopic necrosectomy with removal of debris using an endoscopic snare device; D: Bleeding within walled-off necrosis cavity during direct endoscopic necrosectomy.

months[12]. Surgical drainage of pancreatic pseudocysts is indicated if the patient has recurrent pseudocysts despite endoscopic and/or percutaneous intervention. Other indications include pseudocysts with associated duodenal stenosis, bile duct stricture, and pancreatic ductal abnormalities such as strictures or a dilated main pancreatic duct[16]. Furthermore, an advantage of surgery is that cholecystectomy can be performed at the same setting as internal drainage of the pseudocyst, thereby also addressing the issue of gallstones as an underlying etiology of pancreatitis.

The choice of surgical approach is influenced by various factors such as the location and size of the pseudocyst, the extent of inflammatory changes, vascular complications, and the presence of ductal ectasia[3]. Internal drainage establishes a controlled fistula in the gastrointestinal tract and is the method of choice for uncomplicated pseudocysts. There are no significant differences in the morbidity and mortality rates between cystgastrostomy, Roux-en-Y cystjejunostomy, or cystoduodenostomy, with a mortality rate of 4.9% reported in a series of 1280 cases[102]. Mitty *et al*[103] reported a 6% recurrence rate after cystjejunostomy, 3% after cystgastrostomy, and 8% after cystoduodenostomy, while Newell *et al*[104] found no difference in the incidence of recurrence, morbidity, or mortality between cystgastrostomy and cystjejunostomy.

More recent data from Ye *et al*[105] in 2021 found no significant differences in cure rate, reoperation rate, and mortality between patients who underwent cystgastrostomy and Roux-en-Y cystjejunostomy, while the cystgastrostomy group had a shorter operation time, less intraoperative bleeding, and lower cost. Cystjejunostomy offers more flexibility in maximizing dependent drainage based on the location and geometry of the pseudocyst, with the Roux-en-Y technique preferred because enteral nutrition is not interrupted in the event of an anastomotic leak requiring percutaneous drainage. Overall, the method of internal drainage is at the discretion of the surgeon and depends on what is most convenient, as long as gravity-dependent drainage can be achieved.

Once the decision for surgical internal drainage has been made, the timing of the procedure is critical in determining the likelihood of success. The inflammatory capsule of an acute pancreatic pseudocyst typically requires approximately 4-6 wk to become thick enough to have sufficient integrity for a safe anastomosis[101,106]. If the patient requires early surgical drainage but there has not been sufficient time for the formation of a mature pseudocyst wall, pancreatic resection or external drainage are alternative considerations.

Indications for pancreatic resection include the presence of pseudoaneurysms, multiple pseudocysts, pseudocysts located in the distal pancreas, associated main pancreatic duct dilatation, or inability to exclude malignancy[63]. Duct

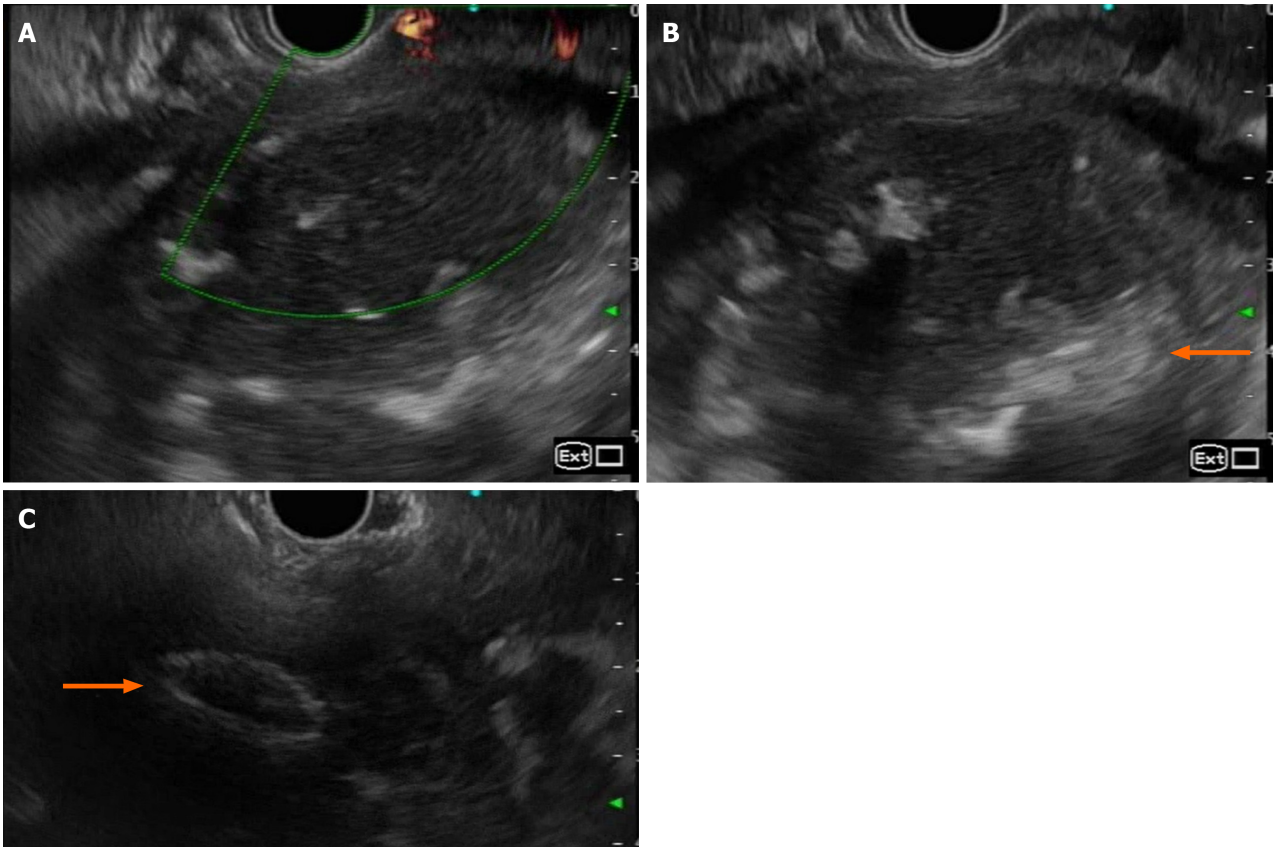

Figure 7 Endoscopic ultrasound images. A: Absence of Doppler signal within walled-off necrosis cavity, ruling out presence of vessels or pseudoaneurysm; B: Solid debris (labelled with arrow) seen within walled-off necrosis cavity; C: Post deployment of lumen-apposing metal stent (labelled with arrow).

abnormalities are also an indication for definitive surgery such as the Puestow procedure (longitudinal pancreaticojejunostomy)[29,107]. Another definitive operation is distal pancreatectomy[108]. Pancreatic resection can be challenging in the setting of dense adhesions between the pseudocyst and major vessels such as the portal vein and superior mesenteric vessels, especially for pseudocysts located in the neck and body of the pancreas[109].

Laparoscopic surgery is a safe and feasible option[110,111]. As surgeons have become more adept at intracorporeal suturing and laparoscopic surgical staplers have been developed, laparoscopic surgery now plays a more significant role in the treatment of pancreatic pseudocysts. The results of laparoscopic internal drainage are comparable to open surgery in terms of initial treatment success, complication rate, and recurrence rate on long-term follow-up, while laparoscopic surgery offers the additional benefits of faster recovery and reduced postoperative pain as compared to open surgery [112].

Laparoscopic cystgastrostomy or cystjejunostomy can be performed using either a linear endoscopic stapler or laparoscopic suturing techniques[113]. Laparoscopic cystgastrostomy using an intragastric approach has been described for retrogastric pancreatic pseudocysts with good outcomes[114]. It involves placement of transgastric ports through the fascia into the stomach with subsequent entry into the cyst cavity through the posterior wall of the stomach. A 2003 review by Bhattacharya and Ammori[115] showed that laparoscopic cystgastrostomy and cystjejunostomy can achieve adequate internal drainage with minimal morbidity, and the laparoscopic approach can also allow concomitant debridement of necrotic tissue.

FUTURE PERSPECTIVES, NOVEL TECHNICAL MODIFICATIONS, AND EMERGING TRENDS

Bartoș and Bartoș[116] reported a case series of endoscopy-assisted, single transgastric port, laparoscopic cystgastrostomy for large pancreatic pseudocyst (measuring 13-18 cm), with the aid of laparoscopic ultrasound. This illustrates the potential of using a hybrid technique combining laparoscopy with endoscopic guidance with the placement of a transgastric trocar, allowing for more complete debridement inside the pseudocyst by means of standard laparoscopic instruments.

Robot-assisted surgical drainage of pancreatic pseudocysts has been shown to be safe and feasible[117]. Marino *et al* [118] retrospectively analyzed the outcomes of 14 patients treated with robot-assisted surgery for pancreatic pseudocysts. Of these patients, 10 underwent cystgastrostomy and 4 underwent Roux-En-Y cystjejunostomy. They achieved a primary success rate of 85.7% after the index procedure, a major morbidity rate of 14.3%, and no 30-d mortality. The mean postoperative length of stay was 7 d, and 1 patient had recurrent pancreatic pseudocyst requiring endoscopic drainage.

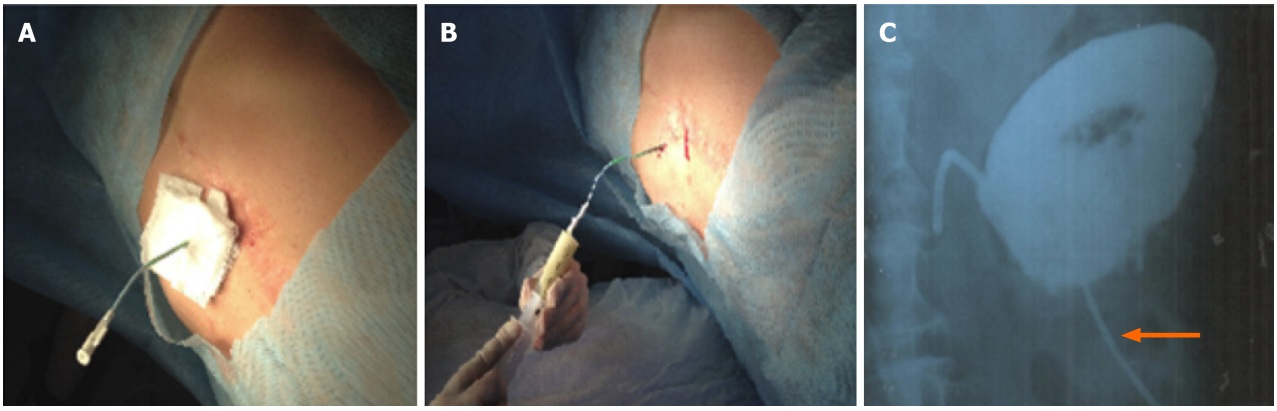

Figure 8 Percutaneous drain and dye study in pancreas pseudocyst management. A: Percutaneous drainage of an infected pancreatic pseudocyst *via* a pigtail drain; B: Lavage of the cavity of the infected pseudocyst; C: Cystography in which the cavity of the pseudocyst was visualized, and the pigtail drainage was established.

Robot-assisted surgery may offer certain advantages over traditional laparoscopic surgery, including the presence of endowrist instruments that enhance microsuturing capabilities as well as high definition three-dimensional visualization that facilitates anastomosis[118]. In our opinion, sustainable healthcare initiatives and patient informed consent are important considerations, and we caution against routine adoption of robotic surgical technology for the management of pancreatic pseudocysts[119-121]. However, with technological advances, it is possible that current limitations may be overcome in the coming decades.

CONCLUSION

Acute pancreatitis is an evolving condition, and its severity or complications may change during the course of the disease. The revised Atlanta classification has clarified the terminology of PFCs, including pancreatic pseudocysts. Both the definition and management of pancreatic pseudocysts have changed significantly over the years. The diagnosis of pancreatic pseudocysts has been greatly facilitated by advances in cross sectional imaging. EUS can enable a more precise characterization of morphological features to allow differentiation between pseudocysts and other cystic lesions of the pancreas. When combined with cyst fluid analysis, EUS can achieve high sensitivity and specificity.

In the management of pseudocysts, a tailored therapeutic approach considering patient preferences and the involvement of a multidisciplinary team comprising the surgeon, gastroenterologist, and interventional radiologist should be part of routine clinical practice. Good supportive treatment is essential for all patients and is likely to suffice for cases without persistent symptoms or complications. The decision on intervention for pancreatic pseudocysts rests heavily on the patient's clinical presentation. If drainage is indicated, endoscopic drainage under EUS guidance is preferred. Laparoscopic drainage is becoming an increasingly popular alternative when there are indications for surgical drainage.

FOOTNOTES

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