

Endoscopic Management of Acute Pancreatitis

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KEYWORDS

- Pancreatic pseudocyst • Walled-off pancreatic necrosis • Endoscopic ultrasound
- Endoscopy • Management • Acute pancreatitis

KEY POINTS

- Endoscopic direct pancreatic necrosectomy has become an essential tool in the step-up approach to treatment of acute necrotizing pancreatitis.
- Step-up approach results demonstrated a lower frequency of multisystem organ failure, major complications, and death compared with the open necrosectomy approach.
- Effective use of endoscopic therapy for treatment of acute pancreatitis eventually depends on determining optimal timing of transmural access to necrotic collections and perfecting the tools to assist in safe pancreatic debridement.

Patients presenting with acute pancreatitis can be complex on a multitude of different levels. Associated mortality rates can be 5% to 10% or more in these patients because of sepsis and multiorgan system failure.¹ Having a multifaceted approach to these patients is often necessary with radiographic, endoscopic, and surgical modalities all working to benefit the patient. Major surgical intervention can often be avoided or augmented by therapeutic and diagnostic endoscopic maneuvers. Endoscopic intervention, however, can be a double-edged sword because there is an associated risk of procedure-related acute pancreatitis. Although the quantity of information relating to the management of patients with acute pancreatitis is substantial, the data for the therapeutic role of endoscopy in patients with acute pancreatitis, in contrast to therapy for chronic pancreatitis, is less.

The diagnostic role of endoscopy in patients presenting with acute idiopathic pancreatitis can help define specific causative factors and ameliorate symptoms by endoscopic maneuvers. Etiologies of an acute pancreatitis episode, such as choledocholithiasis with or without concomitant cholangitis, microlithiasis or biliary sludge, and anatomic anomalies, such as pancreas divisum (PD) and pancreatobiliary ductal anomalies (anomalous pancreatobiliary duct junction [APBDJ], periampullary

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diverticulae, ampullary tumors, and choledochoceles), often improve after endoscopic therapy. Many of these anatomic anomalies are difficult to diagnose without endoscopic techniques, and concomitant or isolated physiologic abnormalities, such as sphincter of Oddi dysfunction, can often be diagnosed and treated endoscopically.

CAUSATIVE FACTORS OF ACUTE PANCREATITIS AND ENDOSCOPIC THERAPY

Despite a multitude of diagnostic and therapeutic advances, acute pancreatitis continues to affect more than 200,000 patients per year.² Most of these patients never come to procedural intervention and can be managed expectantly.³ It has been determined that patients younger than 40 years of age having a mild first episode of pancreatitis can be followed without endoscopic intervention.³ Should these patients have multiple episodes, or if they are older than 40 years, or have a very severe first attack then further evaluation may be considered. The severity of the initial pancreatitis episode is important to evaluate, and there are several different scoring systems to aid in objectifying a patient's severity (Ranson criteria, APACHE II, Balthazar, BISAP, Glasgow, and so forth). Severe acute pancreatitis is estimated to occur in up to 20% of patients and it is associated with sterile or infected necrosis, sepsis, and eventually progressive organ failure with a mortality rate approaching 15%.

The most common causes of acute pancreatitis especially in the Western hemisphere are related to alcohol intake and choledocholithiasis, microlithiasis, or biliary sludge. Other less common causes can be physiologic or environmental factors: hyperlipidemia with hypertriglyceridemia, drug-induced pancreatitis, autoimmune pancreatitis, and hypercalcemia. Much of these aforementioned causes, in addition to such genetic abnormalities as CFTR, PRSS1, and SPINK1 gene mutations, are discussed elsewhere in the literature. In addition, certain congenital anomalies of pancreatobiliary anatomy can contribute to recurrent episodes of acute pancreatitis, such as PD, annular pancreas, anomalous pancreatobiliary junction, and periampullary tumors.

Although much progress has been made in identifying causative factors contributing to acute pancreatitis, approximately 5% to 10% of patients still present with an undefined cause after careful evaluation.⁴ The percentage of idiopathic pancreatitis has continued to decline from almost 40% historically, now down to 5% in some studies.⁵ This can most likely be attributable to advances in the knowledge base, such as genetic sequencing; technologic advances, such as improved noninvasive radiographic imaging; and alternate techniques to evaluate the pancreatobiliary junction, such as endoscopic ultrasound (EUS).¹ The management of idiopathic pancreatitis can often be complex because more invasive diagnostic modalities can sometimes contribute to the very pancreatic inflammation one is trying to treat. Less invasive evaluation with magnetic resonance imaging (MRI) and EUS have certainly improved the diagnostic capabilities of modern day pancreatologists.

ENDOSCOPIC MANAGEMENT OF ACUTE BILIARY PANCREATITIS

The most common causes of acute pancreatitis in Western countries can be attributed to alcohol abuse and gallstone disease. Acute biliary pancreatitis can be exhibited in approximately 45% to 50% of patients presenting with pancreatitis.⁶ Diagnosing gallstone pancreatitis can be made on serologic, radiographic, and clinical parameters. It has been shown that a patient presenting with an elevated alanine aminotransferase that is measured greater than three times the upper limit of laboratory normal approximately 1 to 2 days after the onset of symptoms is a strong predictor of biliary pancreatitis.⁷ This can also be substantiated by elevated pancreatic amylase and lipase

levels; typical pain patterns in these patients; and computed tomography (CT) and MRI exhibiting biliary ductal dilation, periampullary inflammation, and choledocholithiasis with or without concomitant cholelithiasis. The severity of pancreatitis is usually based on admission criteria, with no true gold standard. The modified Glasgow criteria, Ranson criteria, APACHE II scores, among other scoring systems help to differentiate those suspected of having either mild or severe disease.

THE ROLE OF URGENT ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY IN THE SETTING OF ACUTE BILIARY PANCREATITIS

After acute biliary pancreatitis has been proved or suggested on a clinical basis, the issue then becomes the appropriate management of this patient. Because these stones pass spontaneously soon after admission to the hospital in up to 70% of patients, the importance of early endoscopic or surgical exploration and removal of this obstructive cause has been examined in multiple randomized, controlled trials. One of the initial evaluations from Neoptolemos and colleagues⁸ in 1988 examined 121 patients with acute pancreatitis thought to be caused by gallstones documented by ultrasound. These patients were randomized to either early endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy within the first 72 hours of admission or to conservative treatments. Although there was no significant difference in overall mortality rates between the experimental and control groups, there were significant reductions in complications (7% vs 19%) and length of hospital stay (9.5 vs 17 days) in the treatment group in this landmark study. It should be noted that gallstones were confirmed in 50 of 59 patients in the experimental group, and in 53 of 62 in the control group. Fourteen patients in the control group ultimately underwent ERCP between 6 and 30 days later, but none were done in the first 72 hours. Of these 14 patients, 3 were confirmed to have choledocholithiasis at the time of ERCP.

The results of Neoptolemos' group were subsequently re-evaluated by Fan and colleagues⁹ in 1993. In this prospective, randomized trial, 195 patients underwent either urgent ERCP with sphincterotomy within 24 hours of admission (97 patients) or initially conservative treatment (98 patients). In patients in whom stones were discovered and endoscopically treated, there were fewer overall complications compared with the control group (16% vs 33%). Additionally, there was an overall reduction in mortality rate observed in the treatment group (5% vs 9%). The studies by Fan and Neoptolemos failed to exhibit a true difference in the rate of complications seen in patients with mild pancreatitis treated with early ERCP versus conservative treatment. Nowak and colleagues¹⁰ then examined this cohort of patients and demonstrated a benefit of early ERCP in severe and mild pancreatitis. The overall complication rate (17% vs 36%) and mortality (2% vs 13%) was reduced in the treatment group. This was the first study to exhibit a clear difference between the treatment group and the control group with respect to mild and severe pancreatitis rather than just the patients with severe disease.

In contrast to the aforementioned three randomized, controlled trials that were from a single institution, the German study group with Fölsch and colleagues¹¹ evaluated early ERCP with sphincterotomy defined as within 72 hours of onset of symptoms versus conservative treatment across a 22-institution multicenter trial. Moreover, this multicenter study excluded patients who had either jaundice or cholangitis in contrast to the previously published reports. A total of 126 of 238 patients were randomized to the treatment group, and 112 were assigned to the control group. Early ERCP was successful in 121 of the 126, and 58 patients were found to have stones that were successfully extracted. Twenty-two of the 112 patients in the control group

were ultimately treated with ERCP because of concern for choledocholithiasis, and 13 of these patients were found to have stones. The overall rate of complications was found to be similar between the two groups, but the patients in the treatment group had a higher incidence of respiratory failure and severe complications. This was the first study to dispute the use of early ERCP in patients presenting with acute biliary pancreatitis in the absence of obstructive jaundice. This study has been criticized for 19 of the 22 centers contributing less than two patients to the study, and flaws in the design and randomization process contributing to the results that differed from prior studies.

Oría and colleagues¹² again examined early endoscopic intervention compared with conservative management in patients with acute biliary pancreatitis and obstructive jaundice in one of the most recent randomized, controlled trials. Of 238 patients admitted within 48 hours after the onset of acute biliary pancreatitis, 103 were found to have biliary ductal dilation (≥ 8 mm) and obstructive jaundice (total serum bilirubin ≥ 1.20 mg/dL). These 103 patients were then randomized to receive either ERCP with endoscopic sphincterotomy (51 patients) or conservative management. Those patients with concomitant acute cholangitis were excluded from this study. The incidence of bile duct stones in the treatment group was 72%, and 40% of the patients in the conservative management group were found to have stones at the time of elective cholecystectomy. This study failed to exhibit clear benefit of early endoscopic intervention in patients with purported acute biliary pancreatitis caused by stone obstruction in the absence of acute cholangitis. There were no significant differences observed with regard to mean organ failure scores, CT severity index, incidence of local complications, and overall morbidity and mortality. Early endoscopic intervention can be detrimental, especially if the pancreatitis is unsure to be caused by stone disease or if the stone has already passed. Acute pancreatitis can often alter periampullary anatomy making ductal cannulation more difficult and can potentially contribute to a worsening of the pancreatic inflammation, increase the risk of retroperitoneal perforation, or lead to hemorrhage.

Given the results of these studies, most clinicians currently agree that patients presenting with acute biliary pancreatitis with concomitant cholangitis or suspected impacted bile duct stones benefit from early ERCP and sphincterotomy. The definition of early ERCP certainly differs, but most agree that within the first 72 hours is sufficient. The complexity arises in the preprocedural predictability of pancreatitis caused by stone disease. There is little dispute as to the benefit of early ERCP in patients with elevated liver function tests and obstructive jaundice with a septic-appearing picture and severe disease graded by an accepted scoring system, especially in those patients that have not had a cholecystectomy.

ENDOSCOPIC EVALUATION AND MANAGEMENT OF INTRINSIC ANATOMIC ABNORMALITIES CONTRIBUTING TO PANCREATITIS

Endoscopic cannulation, ultrasound, and helical CT or MRI can often reveal intrinsic anatomic abnormalities that can contribute to episodes of recurrent acute pancreatitis and eventual chronic pancreatitis. Such anomalies as PD, type 3 choledochal cysts (choledochoceles), and APBDJ all have a role in potentially leading to symptomatic acute pancreatitis that may benefit from endoscopic management.

PANCREAS DIVISUM

PD is the most commonly encountered ductal anomaly involving the pancreas. PD and other anomalies involving a dominant dorsal pancreatic duct require a keen

knowledge of embryology and pancreatobiliary development. PD is defined as the lack of union of the ventral and dorsal pancreatic ducts seen in the primitive foregut of all infants. It has been estimated to occur in approximately 5% to 10% of the Caucasian population,¹³ but it can be found in any race. Additionally, because of the complex migration of the ventral pancreatic bud around the primitive embryologic foregut, several variants of dorsal duct anatomy can occur.

Of the population that possesses PD, only 5% or less are symptomatic because of this ductal anomaly.¹³ It is hypothesized that pancreatitis caused by PD stems from ductal hypertension and inadequate secretory drainage by the minor papilla. Although this theory of ductal hypertension makes sense and applies in the realm of other causes of acute pancreatitis, direct evidence to support this theory still remains vague and determination of which patients with PD progress to clinical symptoms is certainly multifactorial with genetic and environmental factors contributing. Moreover, the clinical picture can often be confusing because, although the signs and symptoms of chronic abdominal pain experienced by these patients seem to be pathognomonic for pancreatitis, they often do not have enzyme elevation or radiographic changes characteristic of parenchymal inflammation, so-called minimal change disease.

The clinical presentation of patients with PD varies from vague abdominal complaints to recurrent episodes of acute pancreatitis. Most of these patients are female and in the fourth decade of life.¹⁴ The most common complaint on presentation is pain, often in the subxiphoid region with radiation around the right or left upper quadrants and to the back. This pain may or may not be associated with elevations of the patient's serum amylase, lipase, leukocyte count, or C-reactive protein. The group of patients with PD that present with chronic abdominal pain without clinically objective evidence of pancreatitis can be difficult to treat.

The diagnosis of PD can sometimes present as a challenge. Helical CT can rarely identify PD unless there is actual ductal dilation. MRI with magnetic resonance cholangiopancreatography (MRCP), with or without secretin stimulation, has a higher yield at identifying PD with a diagnostic accuracy estimated to be approximately 73%.¹⁵ EUS and the "cross sign" seen on sonography can also aid in the diagnosis.¹⁶ However, if the clinical suspicion is great enough, ERCP with pancreatogram still remains the most sensitive, albeit invasive method to identify PD. The diagnosis by ERCP is often confirmed by a 1- to 4-cm ventral duct that is quite diminutive in size with prominent side-branching that is often finely tapered and draining a portion of the pancreatic head and uncinata process, as would be expected from the embryologic remnant of the ventral pancreatic bud (**Fig. 1**). Cannulation of the dorsal pancreatic duct through the minor papilla is essential in the diagnosis of PD, exhibiting the typical appearance of dominant ductal drainage by the minor papilla.

After PD has been identified, the severity of symptoms and resultant pancreatitis must be assessed clinically. Like other causes of pancreatitis, patients with PD can be managed expectantly if their symptoms are mild. The sheer aspect of possessing separate dorsal and ventral pancreatic ducts does not dictate the need for intervention. The patients that have more severe episodes, exhibit clear and reproducible chronicity of symptoms, have an elevation of the pancreatic enzymes at the time of symptoms, or have a dilated dorsal duct on imaging studies may benefit from endoscopic management.

Endoscopic evaluation of PD takes a stepwise approach that often truly helps some patients long-term, whereas others have more of a diminishing return with each endoscopic intervention. There are data to suggest that those patients who possess evidence of outflow obstruction seen on ductal imaging by EUS or MRI before and after intravenous bolus of secretin may benefit from accessory sphincterotomy or

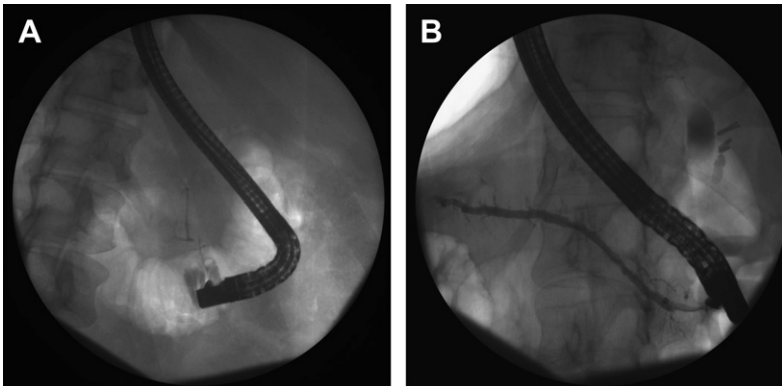


Fig. 1. Pancreatograms in pancreas divisum. (A) Ventral duct pancreatogram by way of major papilla. (B) Dorsal duct pancreatogram by way of minor papilla.

operative sphincteroplasty.^{17,18} Outflow obstruction from stenosis of the minor papilla is defined by persistent dilation greater than 3 mm of the dorsal pancreatic duct above the patient's baseline 10 minutes after secretin injection by MRCP in patients younger than 60 years.¹⁷

Endoscopic therapy for patients with PD is quite challenging. The small minor papillary orifice is often difficult to identify and cannulate. In experienced hands, cannulation of the minor papilla in patients with PD is achievable in approximately 95% of cases.^{19–26} Once cannulated, there are many minor papillary manipulations that can occur: sphincterotomy, papillary dilation, stent placement, or a combination of these techniques. Isolated pneumatic balloon dilation of the minor papillary orifice without concomitant sphincterotomy or dorsal ductal stent placement has been largely abandoned because of subsequent traumatic pancreatitis.

It is the authors' practice to begin with minor papillary endoscopic sphincterotomy, with or without balloon dilation of the minor papillary orifice and stent placement. Often the ductal anatomy dictates a smaller-caliber stent be placed (5F or 7F catheter). At subsequent stent exchanges (usually done at 8-week intervals), the dorsal duct is balloon dilated and the stent is up-sized to a larger-caliber, 10F catheter stent. We continue to vary the stent lengths to minimize ductal stricture formation. If clinical symptoms improve or resolve, then the stents are removed at follow-up endoscopy. If the patient's symptoms fail to resolve after 8 weeks with a 10F catheter minor papillary stent and the duct demonstrates good contrast drainage at the time of endoscopic pancreatography, then continued endoscopic therapy is largely abandoned for alternate therapies, such as thoracoscopic splanchnicectomy or operative parenchymal resection based on their observed symptoms. We have also examined the result of endoscopic stent placement in 32 patients with symptomatic pancreatitis caused by PD during a 12-year period. Twenty-four patients were followed for approximately 60 months with a decline in pain scores, number of hospital admissions, pain medication usage, and improvement in associated symptoms, such as nausea and vomiting, observed in this study group.¹³

Minor papillary stent placement may not be entirely necessary. Stent placement may cause or exacerbate the degree of pancreatitis and complications, such as stent migration, stent occlusion, and ductal stricture with downstream pancreatic ductal dilation may result in nonresolution of symptoms. There is clear evidence to suggest that the use of minor papilla sphincterotomy alone has a favorable response in

patients with acute pancreatitis caused by PD.^{19–26} At a follow-up of 22 to 44 months, fewer attacks of pancreatitis and hospitalizations were shown in 76% to 94% of patients after endoscopic intervention with sphincterotomy alone.²⁷ Moreover, the type of sphincterotomy done (standard pull technique sphincterotomy vs a needle knife) has not exhibited any difference in treatment outcomes in a retrospective review.²⁷

Early series published in the 1990s reported approximately a 20% recurrence rate of stenosis of the minor papilla after endoscopic sphincterotomy alone.¹⁷ Multiple other studies have been performed subsequent to this to address the issue of maintaining sphincter patency with most contemporary series reporting the use of endoscopic sphincterotomy with concomitant pancreatic dorsal duct stent placement for up to approximately 18 months.²⁷ A retrospective evaluation comparing patients undergoing sphincterotomy alone with those undergoing sphincterotomy with dorsal duct stenting was performed. Stents were exchanged at 4-month intervals and sizes varied according to the anatomy encountered.²³ There were more treatment-related complications in the group that underwent sphincterotomy and stent placement but both groups had a decrease in the degree of chronic abdominal pain. Stenosis occurred in four patients with sphincterotomy alone and in three patients with concurrent stent placement calling into question the use of endoscopic therapy. Although this evaluation of 24 patients was small and likely underpowered, most endoscopists still consider placement of a stent into the dorsal duct as an integral part of the management of chronic abdominal pain caused by PD.

Although the focus of this article is more on endoscopic management, it is the authors' observation that those patients that benefit from ductal stenting will most likely also do well with surgical sphincteroplasty. If symptoms are relieved with stent placement, there may be a role for early transduodenal sphincteroplasty or lateral pancreaticojejunostomy if pain recurs. Many patients receive some degree of relief after dorsal duct stenting but endoscopic intervention ultimately becomes ineffective. It is the authors' observation that patients with continued pain that is not relieved after resolution of pancreatic ductal hypertension by endoscopic stenting often possess parenchymal and ductal side-branch changes more consistent with chronic pancreatitis. In these patients the authors tend to proceed with partial, if not complete, pancreatic parenchymal resection with a pancreaticoduodenectomy; subtotal pancreatectomy with pancreaticojejunostomy to drain the remaining head of the pancreas in a retrograde fashion (Duvall modification); or total pancreatectomy with or without autoislet cell transplantation.

ANOMALOUS PANCREATICOBILIARY DUCT JUNCTION AND CHOLEDOCHOCELES

Choledochal cysts are believed to result in part from anomalies involving the junction of the biliary and pancreatic ducts. An APBDJ is usually defined as a long common channel. The pancreatic duct enters the common bile duct between 1 and 1.5 cm proximal to where the common bile duct reaches the ampulla of Vater in patients with APBDJ.²⁸ Greater than 90% of patients with choledochal cysts have demonstrated anomalous ductal junctions.^{29,30} It is believed that the long common channel of APBDJ contributes to the reflux of pancreatic exocrine secretion into the common bile duct, and these pancreatic enzymes can be activated in the alkaline environment of the biliary system thereby resulting in degradation of the ductal mucosa and weakening of the wall of the bile duct.³⁰ This focal weakening can then lead to cystic degeneration of the biliary system, with multiple permutations possible. However, patients with choledochal cysts can have a normal pancreatic ductal anatomy and therefore

this theory of reflux and mucosal breakdown does not always apply. It is also believed that embryologic causes contribute to the formation of these cysts because of alterations during organogenesis.

Choledochal cysts present at any age, and most are diagnosed incidentally with radiographic imaging for another purpose. The presenting symptom of these cysts often does depend on age, with obstructive jaundice being the most prominent symptom in children and abdominal pain seen in adults.³⁰ The Todani³¹ and Alonso-Lej³² classifications of choledochal cysts from I to V is fairly well known. Surgical resection is the mainstay in treatment of patients with extrahepatic biliary cysts because of the potential of malignant degeneration to cholangiocarcinoma observed in this population. The role of endoscopy in these patients is limited to diagnostic purposes. Therapeutic endoscopic maneuvers are limited to those patients with recurrent acute pancreatitis caused by type 3 choledochal cysts (choledochoceles), with or without an APBDJ.

Endoscopic diagnosis of a type 3 choledochal cyst can be difficult. Distinguishing between a true choledochal cyst compared with just mechanical dilation of the bile duct caused by other extrinsic factors is the main diagnostic hurdle. There have been certain criteria that had been established for the diagnosis of a type 3 choledochal cyst outlined by Park and colleagues³³: a radiolucent halo and bulbous end to the distal common bile duct and dynamic sequential morphologic changes with cannulation. The patients that meet at least two of these criteria are believed to have a choledochoceles by fluoroscopy. There are other endoscopic findings on duodenoscopy that are suggestive of a choledochal cyst: a cystic protrusion or bulging of the duodenal lumen that has a soft, ballotable overlying mucosa and is seen to visibly enlarge during contrast infusion with cannulation is nearly pathognomonic (**Fig. 2**). It is often difficult to distinguish between choledochoceles and congenital duodenal duplication cysts unless the mucosal lining is examined histologically, but duplication cysts tend to not alter their morphology with injection of the biliary system after cannulation.

Treatment of most choledochal cysts is largely surgical. Resection, irrespective of the age of the patient, is the preferred modality of treatment. This not only obviates the need for long-term surveillance for potential malignant degeneration, but also aids in improved biliary ductal drainage and often thwarts the long-term sequelae of ductal stone disease or recurrent acute pancreatitis. However, rather than surgical resection, endoscopic management is the method of choice for patients with uncomplicated type 3 choledochal cysts (see **Fig. 2**). Patients with type 3 choledochal cysts, with or without a concomitant APBDJ (usually seen in ~90%), often benefit from just endoscopic sphincterotomy alone.³⁰ Choledochal cysts do carry a risk of potential malignant degeneration up to 30% even if resected, but the risk associated with choledochoceles is minimal. It has been theorized that in patients with APBDJ the enzymatic activation of exocrine secretion of the pancreatic duct by the alkaline environment of the common bile duct predisposes to altered pancreatic ductal drainage, stricture formation, calcification and potential stone formation, and pancreatic ductal hypertension. This in turn contributes to recurrent episodes of pancreatitis that are often ameliorated with endoscopic sphincterotomy.

PERIAMPULLARY DIVERTICULAE

Morphologic abnormalities at the ampulla of Vater may contribute to recurrent episodes of acute pancreatitis because of impaired drainage of exocrine secretions from the pancreatic duct. These patients present like any other case of relapsing

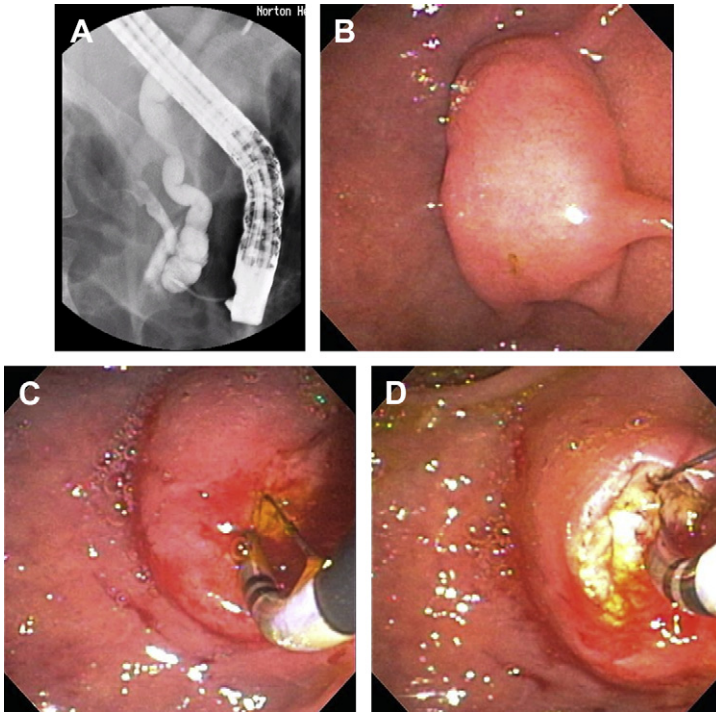


Fig. 2. Endoscopic management of a type 3 choledochal cyst (choledochocele). (A) Initial fluoroscopic view. (B) Initial endoscopic view. (C, D) Endoscopic sphincterotomy and opening of the cyst.

acute idiopathic pancreatitis. Radiographic evaluations with CT and MRI with MRCP can occasionally exhibit periampullary abnormalities, but diverticulae and ampullary tumors are often only diagnosed by endoscopic techniques, namely EUS and ERCP.

Periampullary diverticulae are out-pouchings of the duodenal mucosa that are located within 2 to 3 cm of the ampulla of Vater.³⁴ There are varying data regarding the causative factors of these diverticulae contributing to recurrent pancreatitis, but most experts agree that alterations in the duodenal mucosa around the ampulla contribute to impaired ductal drainage. After a diverticulum has been diagnosed and believed to be symptomatic, endoscopic manipulation may be attempted but is often unsuccessful because of the inability to cannulate the ducts secondary to periampullary morphologic changes. If the ampullary orifice is able to be cannulated, then such treatments as endoscopic sphincterotomy offer symptomatic relief to some patients by improving ductal drainage. The efficacy of endoscopic sphincterotomy in the treatment of patients with acute pancreatitis caused by a periampullary diverticulum was examined in a retrospective cohort of patients from Greece.³⁴ A total of 344 patients who had undergone ERCP between 1994 and 2005 for investigation of acute pancreatitis were retrospectively evaluated and 11 were found to have acute relapsing pancreatitis associated with a diverticulum. All of these patients underwent endoscopic sphincterotomy and were subsequently followed for recurrent attacks of pancreatitis. No further episodes were reported in all 11 patients.

AMPULLARY TUMORS

Like periampullary diverticulae, ampullary tumors can also contribute to recurrent pancreatitis and are best diagnosed endoscopically. These tumors are often found incidentally on esophagogastroduodenoscopy for reasons other than pancreatitis, and initially biopsies are taken. When dysplasia or malignancy is identified, endoscopic treatment can be useful if the tumor is small. EUS and high-resolution CT imaging can sometimes provide aid in assessing the depth of the tumor and potential resectability. Most tumors less than 3 cm, without ductal invasion, and no signs of locally advanced or distant metastatic disease can be resected en bloc endoscopically. Those patients with larger tumors, multiple tumors (eg, in patients with familial polyposis syndromes), and those with a deeper level of involvement should be referred for surgical evaluation. In the absence of ductal invasion, snare polypectomy with sphincterotomy is successful in the removal of ampullary tumors in up to 90% of cases.^{28,35} Procedure-related pancreatitis has been reported in up to 30% of cases, but can be reduced by prophylactic stent placement. Although surveillance schedules differ between experts, all agree that these patients do need continued surveillance with random endoscopic biopsies.

SPHINCTER OF ODDI DYSFUNCTION AND ACUTE PANCREATITIS

Many of the aforementioned causes of recurrent acute pancreatitis are caused by mechanical or anatomic perturbations of the ampulla or pancreatic ductal orifice contributing to impaired drainage of exocrine secretions. Sphincter of Oddi dysfunction is a nonmalignant condition resulting in impairment in sphincteric physiology, leading to outflow obstruction. These patients exhibit the clinical symptoms of pancreatitis with abdominal pain, radiation, nausea, and vomiting. There is often serologic evidence of pancreatitis with elevated amylase and lipase levels, serum liver function tests, C-reactive protein, and erythrocyte sedimentation rate. These findings are frequently in the setting of a radiographically benign pancreatic parenchyma without dilated ductal anatomy and an absence of cholelithiasis. The diagnosis of Sphincter of Oddi dysfunction is confirmed by endoscopic sphincter of Oddi manometry. Selective pancreatic duct manometric pressures greater than 40 mm Hg have been found in 15% to 72% of patients with idiopathic pancreatitis.³⁶ Once recognized, the treatment is simply selective endoscopic sphincterotomy of the pancreatic ductal orifice, which leads to clinical improvement in up to 70% of patients.³⁷

ENDOSCOPIC TREATMENT OF COMPLICATIONS OF ACUTE PANCREATITIS

Endoscopic techniques have supplanted surgery in treatment approaches for complications of acute pancreatitis including the disrupted pancreatic duct syndrome, pancreatic pseudocysts, and pancreatic necrosis. Low complication and mortality rates and the high success rate of endoscopic drainage make this approach preferable to surgery. EUS approaches decrease risks associated with endoscopic drainage of pseudocysts and facilitate the safety of endoscopic necrosectomy.

ENDOSCOPIC TREATMENT OF THE DISRUPTED DUCT SYNDROME AND FISTULAS

Disrupted pancreatic duct syndrome occurs in attacks of acute pancreatitis leading to pancreatic duct injury or from chronic pancreatitis with upstream blowout of obstructing strictures or stones.³⁸ Manifestations include pancreatic ascites; internal fistulae (pseudocysts, pleural effusion); or external cutaneous fistulae.^{39,40} The disrupted duct syndrome demonstrates an abrupt cutoff of the pancreatic duct in patients

with suspected pancreatic fistula and viable tissue visualized upstream on cross-sectional imaging. Treatment of the disrupted duct necessitates bridging of the pancreatic leak with transpapillary stents or diverting pancreatic duct flow.⁴¹

Endoscopic transpapillary stent bridging of duct disruption has proved effective therapy. Varadarajulu and coworkers⁴² demonstrated fistula resolution of 56% with multivariate analysis showing that partial duct disruption and a bridging stent were associated with successful outcomes. Complete disruption of the pancreatic duct has less effective results with stenting as reported by Lawrence and colleagues⁴³ with a 59% failure of initial response or fistulae recurrence in patients with necrotizing pancreatitis. Complete duct disruptions are refractory to transpapillary stenting because the upstream disconnected segment maintains secretion without effective drainage into the duodenum.⁴⁴ Transmural drainage has arisen as the procedure of choice for complete duct disruptions that result in pseudocyst formation and fistulas to the pleura or cutaneous surface. EUS has also demonstrated effective transgastric drainage of the disconnected duct in upstream pancreatic segments resulting in pseudocysts and fistulae.⁴⁵ Further evolution of transmural EUS-assisted pancreatic duct drainage will facilitate improved outcomes in the endoscopic treatment and resolution of the disrupted duct syndrome.

PANCREATIC PSEUDOCYST DRAINAGE

Pseudocysts result from pancreatic duct disruption in up to 10% to 25% of acute pancreatitis and 20% to 40% of chronic pancreatitis cases.⁴⁶ Classification consists of fluid collections more than 4 weeks old surrounded by a nonepithelial wall of fibrous or granulation tissue (Atlanta International Symposium on Acute Pancreatitis 1993).⁴⁷ Evaluation should involve high-quality CT scan and a complete pancreatogram. Warsaw and coworkers⁴⁸ reported on experience with cystic neoplasms noting that 37% of lesions had been misdiagnosed as pseudocysts before operation. CT and MRI may help identify dependent debris suggesting pseudocyst or rim calcification indicative of neoplasm. External microlobulated morphology and internal septae were also more common in cystic neoplasms.⁴⁹ Chalian and coworkers⁵⁰ found that CT attenuation was significantly higher in pseudocysts than in mucinous neoplasms. EUS with fine-needle aspiration allows for tissue sampling and cyst fluid analysis to differentiate pseudocysts from neoplasm.⁵¹ Vander Waaij and coworkers⁵² determined in meta-analysis that carcinoembryonic antigen less than 5 ng/mL showed specificity of 95% for pseudocyst and serous cystadenoma as did carbohydrate-associated antigen Ca 19-9 concentrations of less than 37 U/mL with a specificity of 98%. Amylase was also found to be a specific predictor with a level of less than 250 U/L essentially excluding the diagnosis of pseudocyst.⁵³

Indications for drainage include initial observations of Bradley and coworkers⁵⁴ that complications occurred in up to 41% of patients during an observation period of 7 weeks with spontaneous cyst resolution occurring in only 20%. Recent studies suggest that periods of prolonged observation in asymptomatic patients are safe with spontaneous resolution in up to 86% with a 3% to 9% rate of serious complications.^{55,56} Data regarding pseudocyst size and outcomes are mixed, although a smaller size (<4 cm) is an important predictor of spontaneous resolution.⁵⁷ Nguyen and coworkers⁵⁸ and Cheruvu and coworkers⁵⁹ found that cyst size was not a predictor of surgical intervention resulting in recommendations that therapeutic decisions be based on symptoms of persistent pain, obstruction, ascites, pleural effusion, enlarging size, signs of infection, bleeding, or evidence of pancreatic neoplasia.

Endoscopic drainage should be considered the first preference for treatment of mature pseudocysts (**Fig. 3**). Endoscopic transpapillary drainage is beneficial for pseudocysts that communicate with the pancreatic duct, which occurs in up to 44% of pancreatograms studied by Nealon and coworkers^{60,61} and when cyst size is relatively small (<6 cm). Endoscopic transmural drainage should be considered for larger cysts that fail to communicate with the duct and show signs of multiloculation and necrosis. Conventional transmural drainage can be safely performed when there is (1) evidence of gastric bulge or luminal impression, (2) absence of collateral

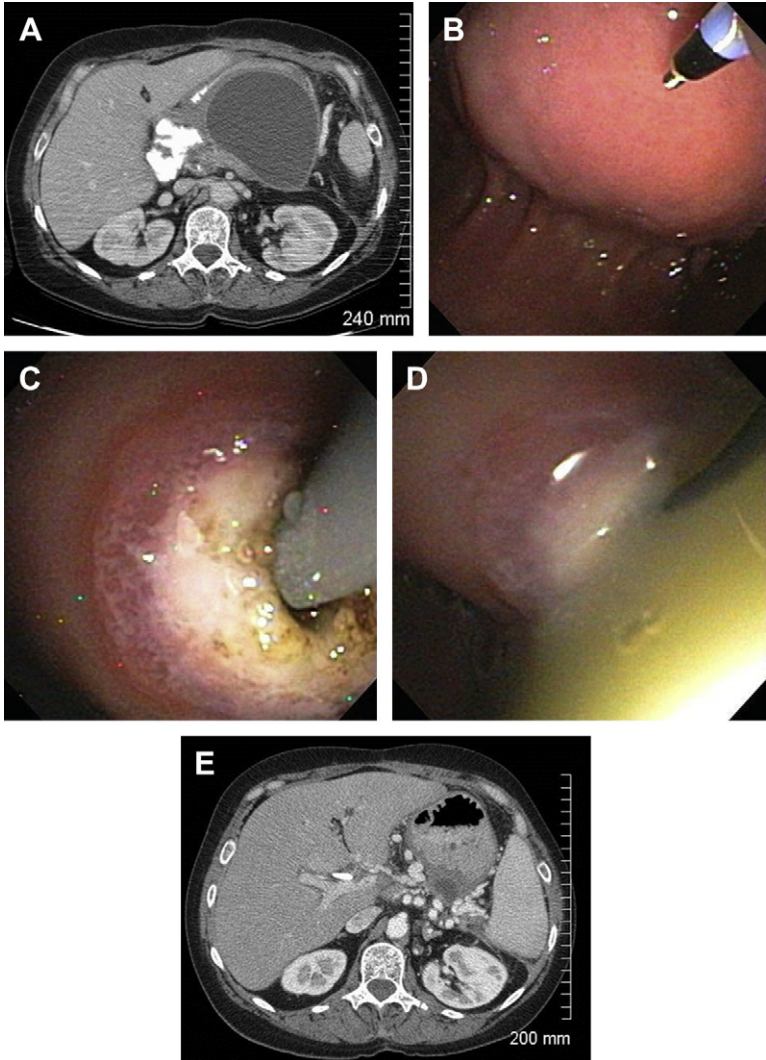


Fig. 3. Endoscopic transgastric pancreatic pseudocyst drainage. (A) Initial diagnostic CT with significant indentation into the stomach by the retrogastric pancreatic pseudocyst. (B) Endoscopic view of pseudocyst bulging into posterior gastric wall and cystotome. (C) Creation of cystgastrostomy and placement of wire-guided stent introducer. (D) Pseudocyst effluent. (E) Interval CT 3 months after endoscopic drainage.

blood vessels and varices, and (3) the distance from the pseudocyst to the gastric/duodenal lumen on imaging studies is less than 1 cm.⁶² When pseudocysts fail to meet such criteria EUS-guided drainage has been shown to be equally successful without increased risk of complications according to Kahaleh and coworkers.⁶³ Recent studies by Baron and coworkers⁶⁴ have demonstrated that pseudocyst drainage is associated with higher rates of failure in infected pseudocysts and in the presence of pancreatic necrosis.

TRANSPAPILLARY DRAINAGE

Transpapillary drainage involves initial duct decompression by sphincterotomy, first on the biliary sphincter and then selectively on the pancreatic sphincter. Ancillary interventions include minor papilla sphincterotomy and dilation of duct strictures. If the pseudocyst is demonstrated on contrast injection, transpapillary endoscopic drainage is possible with placement of a large-bore (7F catheter) stent across duct disruption or within the lumen of the pseudocyst.⁶⁵ If the tail of the pancreas is visualized beyond the origin of the pseudocyst, drainage of this portion of the duct may allow pseudocyst resolution by passing a stent as far into the tail as possible beyond the connection to the pseudocyst. Transpapillary stents are left until the pseudocyst resolves or significantly decreases in size by CT scan; stents should be removed and treatment options reviewed after 6 to 8 weeks.⁶⁵ The advantage of the transpapillary approach is that the risk of gastric wall hemorrhage and retrogastric perforation is eliminated.⁶⁰

TRANSMURAL DRAINAGE

Transmural endoscopic drainage is best indicated when pseudocysts indent the gastric or duodenal wall. Endoscopic needle localization confirms the appropriate location for cyst-enterostomy using two techniques described as a diathermic puncture and Seldinger technique.^{66,67} Diathermic puncture involves either inserting a needle knife or a Cremer Cystotome (Cook Endoscopy, Winston-Salem, NC) into the gut lumen at a 90-degree angle at the maximal endoscopic bulge. A needle knife can be used to open into a bulge in the stomach (2 or 3 mm); a gush of cyst fluid is encountered when the cyst is entered; and a guidewire is then passed into the cyst cavity. A sphincterotome is passed over the wire to enlarge the opening to a minimum of 1 cm. If the mucosa is prone to bleeding with the initial cut using the needle knife, a balloon can be used to dilate the opening.⁶⁶ The Cremer Cystotome allows needle knife cyst entry followed by cyst-enterostomy creation with an electrocautery ring, and stent deployment using a single catheter.⁶⁸ The Seldinger technique involves cyst puncture by an 18-gauge needle followed by wire passage into the pseudocyst, balloon tract dilation, and stent placement. The Seldinger technique has demonstrated comparable efficacy and fewer bleeding complications compared with diathermic puncture.⁶⁷

After completion of the cyst-enterostomy one to two 10F catheter double pigtail stents are deployed into the pseudocyst. The pigtail stents prevent migration into the cyst or out into the gastrointestinal tract. Two stents are preferable, because they allow the cyst to drain alongside the stents and through them. Transmural stents generally remain in the cavity for up to 1 year, and then they are then removed after the cyst is entirely resolved for at least 3 months by CT. If there is a small persistent pseudocyst that remains unchanged over time, the stents can also usually be removed without high risk of recurrence. Often these small cysts become isolated from the stent and the pancreatic duct. If there is a tail of the pancreas duct identified by MRI, and it is not connected to the main pancreatic duct, then one should leave the transgastric stent to drain the tail for a more prolonged period depending on the CT and ERCP

anatomic findings.⁶⁹ Eventually the stent can be removed with expectation that a chronic fistula from the tail to the stomach will remain patent. It is the authors' practice to continue to evaluate patients with transpapillary, transgastric, or transduodenal stents placed for pancreatic pseudocysts with a CT scan periodically. After the cyst has resolved by imaging and the patient's symptoms have improved or resolved, then the stents are removed endoscopically. If the symptoms do not improve or if there is no diminution in the size of the cyst after at least 6 months, then surgical intervention is considered.

Pseudocysts that do not present with a luminal bulge or that present with perigastric varices are best drained under direct ultrasound guidance. EUS is used for direct needle-guided puncture of the pseudocyst with a 19-gauge needle followed by wire placement, dilation over the guidewire, and stent placement. Kahaleh and coworkers⁶³ demonstrated 93% effective drainage with EUS in patients lacking a luminal bulge or presenting with portal hypertension. A novel device for single-step cyst-enterostomy has been developed (Navix; Xlumena, San Francisco, CA), which permits needle puncture followed by entry of an anchoring and dilating balloon to allow double wire advancement for sequential stent placement.⁷⁰

Endoscopic drainage of pancreatic fluid collections has been demonstrated as effective in large retrospective patient series. Hookey and coworkers⁷¹ described results in 116 patients demonstrating equivalent efficacy between transmural and transpapillary drainage techniques. Antillon and coworkers⁷² demonstrated successful 82% single-step EUS-guided transmural endoscopic drainage of simple and complex pancreatic pseudocysts. Weckman and coworkers⁷³ demonstrated an 86% rate of successful pseudocyst drainage in 165 patients with a 5% recurrence rate during a 25-month follow-up. Cahen and coworkers⁶⁹ noted that independent predictors of successful outcomes included location of the cyst in the pancreatic head, insertion of multiple stents into the pseudocyst cavity, and stent drainage of the pseudocyst cavity longer than 6 weeks. Predictors of failure included the presence of moderate abscess debris. Large numbers of series have demonstrated that endoscopic drainage is successful with between 71% and 95% complete pseudocyst resolution, complications between 0% and 37%, and 0% and 1% procedure-related mortality.^{60,62,63,69,71-73}

Pancreatic abscesses can also be effectively treated with endoscopic drainage. According to the Atlanta classification pancreatic abscesses are circumscribed intra-abdominal collections of pus containing little or no pancreatic necrosis.⁴⁷ Necrotic residual debris has been described as the most important factor in predicting failure of endoscopic drainage.⁶³ Endoscopic abscess drainage was initially reported by Binmoeller and coworkers⁶⁰ demonstrating an 80% complete resolution rate. Vitale and coworkers⁷⁴ demonstrate an initial success rate of 94% for drainage of pancreatic abscesses followed by an overall success rate of 80% on long-term follow-up; there was a 20% recurrence that required surgery. Weckman and colleagues⁷³ noted similar efficacy between endoscopic pseudocyst and abscess drainage except that abscesses required multiple stents and repeated endoscopic drainage procedures. Baron (2002) described treatment of pancreatic fluid collections with necrotic debris defined as walled-off pancreatic necrosis (WOPN) with lower success rates of 71% and higher recurrence rates of 29%.⁶⁴ Effective measures to facilitate drainage of necrotic debris include placement of large-bore covered self-expanding metallic stents and nasocystic tubes for irrigation debridement.⁶⁸

On long-term follow-up, endoscopic drainage has a reported recurrence rate ranging from 8% to 20%, which compares favorably with recurrence rates reported after surgical cyst-enterostomy (5%–20%).^{62,63,69,75-78} After a 44-month follow-up,

Sharma and colleagues⁷⁵ reported the results of endoscopic drainage for 38 pseudocysts. Three patients had symptomatic recurrences, whereas three had asymptomatic recurrences; all had alcohol-induced pancreatitis. No recurrences were seen in the biliary pancreatitis and trauma group. With a median follow-up of 26 months, De Palma and coworkers⁷⁶ showed a 20.9% of recurrence rate. Causes of recurrent pseudocysts usually involve the obstruction of a cystoenterostomy or stent obstruction in the presence of persistent pancreatic disease or ductal stricture.

Complications of endoscopic pseudocyst drainage include retroperitoneal perforation, bleeding, and infection. Sharma and colleagues⁷⁵ report experience in 38 patients with endoscopic drainage. Massive bleeding in one patient required surgery, whereas stent blockage and pseudocyst infection in three patients and perforation in one patient were managed conservatively. De Palma and coworkers⁷⁶ also report an experience with 49 patients using an endoscopic approach. Twelve (24.5%) patients had complications: two patients had bleeding, two patients had mild pancreatitis, and eight patients had cyst infections. Five patients with infection had pancreatic necrosis and three patients had a clogged stent. In our experience, a wide opening of the cyst enterostomy (about 1–2 cm) is necessary in potentially infected cases to reduce the incidence of infected cyst complications.⁷⁴

ENDOSCOPIC NECROSECTOMY

Endoscopic access to pancreatic fluid collections has had limited efficacy in the presence of significant pancreatic necrosis leading to classifications of WOPN and techniques of endoscopic direct pancreatic necrosectomy.⁶³ The New Atlanta Classification of pancreatic fluid collections divides into acute phase (first 4 weeks) and chronic phase.⁷⁷ Chronic collections are divided into pseudocysts and WOPN, which comprise heterogeneous collections of necrotic debris and an encapsulating wall. Indications for endoscopic drainage of pancreatic fluid collections most importantly include suspected infection in patients with systemic clinical deterioration and multiple organ failure.⁷⁹ Interventions within the first few weeks of necrotizing pancreatitis generally have poor outcomes with a guiding principle to delay endoscopic pancreatic debridement until fluid collections have become encapsulated.⁸⁰ A recently published multicenter series demonstrated a 95% successful resolution rate for endoscopic necrosectomy for WOPN with a median duration between initial pancreatitis to endoscopic intervention of 46 days. Direct correlation was demonstrated between successful endoscopic therapy and the degree of encapsulation of WOPN.⁸¹

The advent of transmural endoscopic therapy for pancreatic necrosis began with the use of linear echoendoscopes. Siefert and coworkers⁸² reported the first cases of direct endoscopic necrosectomy with endoscopic cavitory debridement. Papachristou and coworkers⁸³ described early treatment of pancreatic necrosis for 53 patients with necrotic pancreatic fluid collections an average of 49 days after the onset of necrotizing pancreatitis with an 81% success rate. The largest series to date presents from six American centers with a resolution rate in WOPN of 91% with a mean number of 3.7 procedures with 2.5 debridements.⁸¹ This multicenter study demonstrated complications of pneumoperitoneum (13%) and bleeding (18%). Other reported complications include infection (undrained necrosis); pancreatitis; aspiration; stent migration; occlusion; pancreatic duct damage; and complications of sedation.⁸⁰ Overall complication rates for direct endoscopic drainage or direct pancreatic necrosectomy have been reported as between 15% and 25% for experienced practitioners.⁸⁴

Direct endoscopic necrosectomy uses multiple endoscopic tools to achieve adequate debridement usually resulting in serial procedures as pancreatic necrosis liquefies and patients experience worsening organ failure (Fig. 4).⁸⁵ Transmural access can be obtained using standard access techniques or under EUS guidance. EUS guidance is recommended in cases involving extensive necrotic debris for

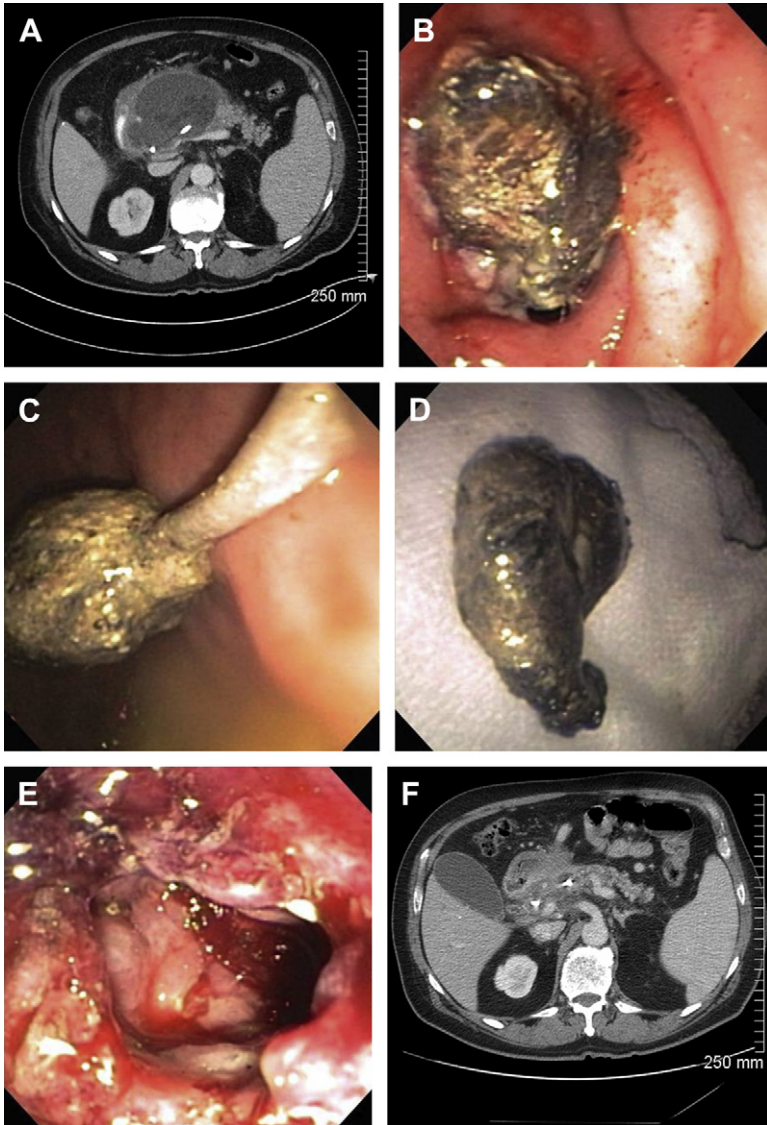


Fig. 4. Endoscopic transduodenal pancreatic necrosectomy. (A) Interval CT scan after initial ERCP with attempted transpapillary drainage. (B) Endoscopic view of pancreatic necrosus into first portion of duodenum. (C) Debridement and retrieval of pancreatic necrosus with Roth net. (D) Extracorporeal specimen of pancreatic necrosus. (E) Final endoscopic view of necrotic cavity after debridement. (F) Completion CT 3 months after necrosectomy.

adequate identification of mural blood vessels. Evidence suggests that EUS allows for higher efficacy and fewer complications for nonbulging collections, collections in the tail, and in patients with varices.⁶² The site for transmural access should be through a wall less than 10 mm in thickness. After the collection is accessed the enterostomy can be dilated with low-profile controlled radial expanding balloons, biliary dilating catheters, or a Soehendra stent extractor. The goal of dilation is to achieve a fistula tract of 20 mm diameter at the time of initial drainage.⁸⁵

Completion of the cyst-enterostomy or fistula is followed by fluid aspiration for Gram stain and culture to direct antibiotic therapy. A forward-viewing gastroscope can then be driven across the gastric or duodenal wall to perform direct necrosectomy. Necrotic pancreas can then be removed using snares, baskets, and water-jets. Hydrogen peroxide can also be used for irrigation to liquefy the debris.⁸⁴ Devitalized tissue is debrided serially removing as much tissue as safely possible at each session with deposition in the stomach or duodenum. Stents are left after each procedure to mature the fistula tract to allow debridement by gastric and bile acids. Uncovered metal stents have been used for fistula tract maturation. Recent case series from Japan have introduced a novel uncovered metallic stent for serial access to pancreatic pseudocysts and WOPN. This metallic stent allows serial access for necrosectomy and has a low profile, which prevents complications of stent migration and erosion.⁸⁶

Endoscopic direct pancreatic necrosectomy has become an essential tool in the step-up approach to treatment of acute necrotizing pancreatitis. The Dutch Acute Pancreatitis Study Group initially demonstrated the efficacy of the step-up approach where patients with pancreatic necrosis were randomized to open necrosectomy compared with minimally invasive retroperitoneal drainage therapies. Step-up approach results demonstrated a lower frequency of multisystem organ failure, major complications, and death compared with the open necrosectomy approach.⁸⁷ The Dutch group subsequently published the PENGUIN trial that randomized patients to endoscopic transgastric versus open necrosectomy. This study demonstrated improved outcomes in the endoscopic necrosectomy group with lower incidence of major complications to include new-onset multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula or pancreatic fistulas, or death when compared with the surgical group.⁸⁸ Effective use of endoscopic therapy for treatment of acute pancreatitis will eventually depend on determining optimal timing of transmural access to necrotic collections and perfecting the tools to assist in safe pancreatic debridement.

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