Diagnosis and Management of Pancreatic Pseudocysts: What is the Evidence?

Jeremy W Cannon, MD, SM, FACS, Mark P Callery, MD, FACS, Charles M Vollmer Jr, MD, FACS

Pancreatic pseudocysts represent organized collections of enzyme-rich fluid that persist after an episode of acute pancreatitis (AP), an exacerbation of chronic pancreatitis (CP), or pancreatic trauma. These mature collections require accurate diagnosis and expert management by a multidisciplinary team of dedicated surgeons, gastroenterologists, and radiologists to minimize morbidity and mortality. Although most data on the topics of diagnosis and management of pseudocysts are classified as level IV evidence, prospective studies and cohort data have recently appeared in the literature, calling our historic understanding of this problem into question. Using the Oxford Levels of Evidence and Grades of Recommendation as recently reviewed by Ridgway and Guller,[1] this review critically evaluates the current surgical literature on the diagnosis and management of pancreatic pseudocysts in the context of a series of clinically oriented questions.[2] Each question concludes with the authors' recommendation and a grade assigned to that recommendation based on the quality of the supporting literature.

Does the cause of pancreatitis influence the probability of pseudocyst formation?

First described in 1761 by Morgagni, pancreatic pseudocysts represent a widely recognized result of both inflammatory and traumatic pancreatic ductal disruption. Based on existing case series, most pseudocysts develop after alcoholic pancreatitis, with gallstone pancreatitis ranking a close second. But numerous case series and reports indicate that any cause of pancreatic injury can lead to pseudocyst development. Patients with CP who develop acute exacerbations appear to have a higher incidence of pseudocyst formation than patients with AP[3-5] while patients with biliary AP seem to have the lowest incidence[6] (Grade: C).

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From the Departments of Surgery, Wilford Hall Medical Center, San Antonio, TX (Cannon) and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (Callery, Vollmer).

Correspondence address: Charles Vollmer Jr, MD, Department of Surgery, Stoneman 9th Floor, 330 Brookline Ave, Boston, MA 02215.

What features of an acute fluid collection indicate it will progress to a pseudocyst rather than resolve?

Pancreatic pseudocysts develop when the main pancreatic duct or one of its radicals is disrupted, excreting pancreatic secretions into the retroperitoneum or the peripancreatic tissue planes. A number of different terms are used to describe this accumulated fluid depending on the chronicity of the collection and the underlying pancreatic pathology. In 1992, the Atlanta Classification was proposed (Table 1).[7] Although this terminology is well known, a recent study showed it has not been universally applied in the literature.[8] These investigators called for refinement of the original system to reflect the many variations on imaging and clinical features that exist in patients with pancreatitis. In addition, an interobserver agreement study designed to evaluate a series of nine morphologic descriptors of acute pancreatitis as seen on CT has been reported.[9] This study showed a high degree of interobserver agreement on seven terms evaluated including *presence of a collection, relation of the collection with the pancreas, content, shape, mass effect, loculated gas bubbles*, and *air-fluid levels*. It has been proposed that such terms should supplant the clinical terminology presently in use. But because this updated scheme remains in the developmental phases, the following review will adhere to the original Atlanta Classification where possible.

According to this system, within the first 4 weeks of formation, accumulated peripancreatic fluid is labeled an acute fluid collection. The majority of these collections resolve spontaneously, but in 5% to 15% of patients with AP and in as many as 40% of patients with CP, the fluid persists. In these patients, the acute collection produces a profound inflammatory response along the serosal surfaces of the adjacent organs, resulting in a fibrous pseudocapsule. This process takes between 4 and 8 weeks, at which point this collection becomes a pseudocyst. A pseudocyst that forms after an episode of AP is an acute pseudocyst; one that develops in the setting of CP is labeled a chronic pseudocyst. Although this latter term was not included in the original Atlanta Classification, because it describes a unique clinical entity and has been used liberally in the recent literature,[10,11] we include this term in this review.

In the absence of glandular necrosis, these terms readily apply. But the Atlanta Classification unfortunately does not address fluid collections that develop in the setting of

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Abbreviations and Acronyms

AP = acute pancreatitis
CP = chronic pancreatitis
ERCP = endoscopic retrograde cholangiopancreatography
EUS = endoscopic ultrasound
MRCP = magnetic resonance cholangiopancreatography

pancreatic necrosis—either sterile or infected. Consequently, numerous terms such as *walled off pancreatic necrosis*, *collection in evolution*, *organized necrosis* and *necroma* have spawned to fill this void (Fig. 1). In this review, all pseudocysts are considered to be associated with an otherwise viable gland.

There are no case-control or cohort studies that define salient risk factors for pseudocyst development. One frequently referenced study suggests significant pancreatic necrosis (≥25%) as a risk factor for pseudocyst development, but this study was a retrospective case series designed to evaluate the utility of endoscopic retrograde cholangiopancreatography (ERCP) in AP.[12] Extrapolations of these data should be made with caution (Grade: D).

What features of an established pseudocyst indicate it will persist or become symptomatic?

One early observational report found that the majority of pancreatic pseudocysts larger than 6 cm in diameter, which persist longer than 6 weeks, result in significant clinical symptoms and complications.[13] But subsequent case series have found that approximately half of acute pseudocysts remain asymptomatic regardless of size or duration.[6,14-16] The other half either manifest symptoms or become complicated by infection, rupture, hemorrhage, vascular thrombosis, or obstruction of adjacent structures. To date, no comprehensive cohort study has been conducted to evaluate the true incidence of pseudocysts or their natural history. Consequently, no prospective indicators have been identified that reliably predict the natural history of an already established pseudocyst (Grade: D).

What preinterventional studies reliably differentiate pancreatic pseudocysts from cystic pancreatic neoplasms?

Before treating any peripancreatic fluid collection, an accurate diagnosis must be established. Most importantly, a pseudocyst must be distinguished from a cystic pancreatic neoplasm.[17] Making this distinction requires a comprehensive assessment of the patient: understanding the history of the disease process, reviewing available imaging studies, and in some cases, performing biochemical and cytologic analysis of the peripancreatic fluid.

Table 1. Summary of 1992 Atlanta Classification Terminology[7]

Pathology	Characteristics
Acute fluid collections	Occur early in the course of AP, are located in or near the pancreas, and always lack a wall of granulation or fibrous tissue.
Pancreatic necrosis	Diffuse or focal area(s) of nonviable pancreatic parenchyma, which is typically associated with peripancreatic fat necrosis; nonenhanced pancreatic parenchyma >3cm or involving more than 30% of the area of the pancreas.
Acute pseudocysts	Collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue, which arises as a consequence of AP, pancreatic trauma, or CP; usually round or ovoid and have a well-defined wall; require 4 or more weeks from the onset of AP.
Pancreatic abscess	Circumscribed intraabdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of AP or pancreatic trauma; occurs later in the course of severe AP, often 4 weeks or more after onset; the presence of pus and a positive culture for bacteria or fungi, but little or no pancreatic necrosis, differentiate a pancreatic or peripancreatic abscess from infected necrosis.

AP, acute pancreatitis; CP, chronic pancreatitis.

When an episode of AP results in an acute fluid collection that persists on serial imaging over a period of weeks, the diagnosis of an acute pseudocyst is assured. This direct link between pancreatitis and development of a peripancreatic fluid collection may be more difficult to establish in the setting of CP. In addition, cystic pancreatic neoplasms may result in a low-grade chronic inflammatory process that mimics CP. It is important for the clinician to review the patient's complete radiographic history because earlier axial imaging may define the presence or absence of the cystic lesion over time. If a clear-cut diagnosis of an inflammatory versus a neoplastic process cannot be made on clinical grounds alone and there is no evidence for a preexisting lesion, further imaging is indicated.

MRI or endoscopic ultrasound (EUS) may reveal septations, solid components within the cyst(s), or a communication between the cyst and the main pancreatic duct. If the diagnosis still remains uncertain, more invasive diagnostic measures should be undertaken. Typically this involves aspiration of the cyst for cytology and biochemical testing. One multicenter, retrospective case-controlled study divided 112 cases of cystic pancreatic lesions that were ultimately surgically resected into mucinous and nonmucinous groups and compared pre-resection EUS, cytology, and fluid tumor marker levels between the groups.[18] A

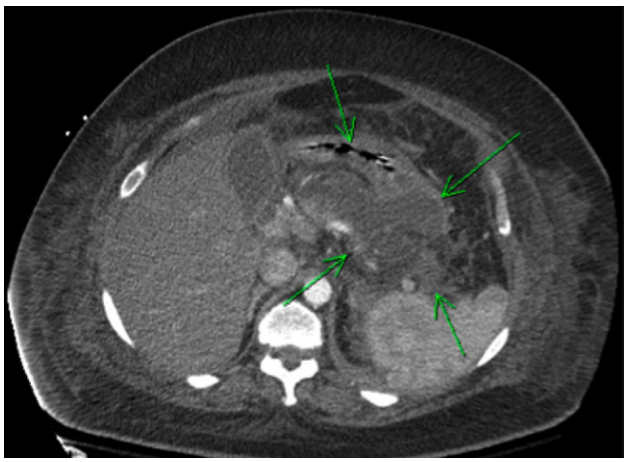

Figure 1. Complex lesser-sac fluid collection abutting the stomach (lumen demonstrated with superior arrow) in the setting of extensive necrosis of the distal pancreas after an episode of gallstone pancreatitis 2 weeks earlier. The nomenclature for this entity is poorly defined and contributes to confusion among practitioners and difficulty in developing comparative studies to address this condition.

CEA level of 192 ng/mL was found to distinguish mucinous from nonmucinous pathologies more accurately than EUS morphology and cytology (79% accuracy versus 51% for EUS morphology and 59% for cytology) (Grade: C).

Do endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography have any role in planning the management of patients with symptomatic pseudocysts?

Once the diagnosis of a pancreatic pseudocyst is made, evaluation of the ductal architecture may affect management. Several schemes for classifying pancreatic ductal anatomy in the setting of a veritable pseudocyst have been developed, but no consensus exists on patient selection for imaging, the optimal timing of imaging studies, or the preferred imaging modality. ERCP and magnetic resonance cholangiopancreatography (MRCP) have both been applied. If considering surgical versus percutaneous drainage, one case series suggests preintervention ERCP should be performed to guide clinical management.[19] Another retrospective assessment of an ERCP-based treatment algorithm showed fewer adverse events in patients in whom the treatment algorithm was applied.[20] But the benefit of defining the ductal anatomy with ERCP must be weighed against the risk of potentially infecting a sterile fluid collection. Because of this concern, ERCP is often performed immediately before a planned intervention. MRCP offers a noninvasive alternative and can now be paired with secretin injection to provide a functional assessment of the ductal architecture and physiologic capacity of the parenchyma. To date, however, there are no studies directly comparing the quality of diagnostic information obtained by MRCP versus ERCP in the setting of pancreatic pseudocysts (Grade: C).

What is the risk of expectant management of an established, asymptomatic pancreatic pseudocyst?

In contrast to traditional management guided by arbitrary size and duration parameters, current evidence indicates that intervention should be reserved for patients who manifest symptoms or who develop a pseudocyst-related complication. But existing management guidelines are based solely on a few level III and IV studies, making the strength of these recommendations limited at best.[11] Currently, only one registered trial on pseudocyst management is enrolling patients,[21] which suggests this field remains ripe for clinical investigations. Because of the limited numbers of eligible patients, though, multicenter collaboration will be necessary to accrue sufficient power to answer this question.

For acute fluid collections, no intervention is required because the majority of these resolve. If the acute collection persists to form a pseudocyst, current knowledge suggests that these can still be managed expectantly unless symptoms manifest or complications develop (Grade: D). Symptoms generally stem from the local mass effect of the pseudocyst or the associated inflammatory response. These include abdominal pain, early satiety, weight loss, and persistent fevers. Potential complications include infection of the pseudocyst, biliary or gastric outflow obstruction, free rupture of the pseudocyst into the peritoneal cavity, or vascular thrombosis leading to sinistral hypertension. Pseudocyst erosion into adjacent vessels may result in pseudoaneurysm formation or even catastrophic hemorrhage into the gastrointestinal tract or peritoneal cavity. In addition to intervening once a complication develops, an experienced pancreatic surgeon should not hesitate to intervene preemptively if imaging features suggest an imminent complication such as erosion into the splenic hilum, a threatening pseudoaneurysm, or evolving sinistral hypertension.

Is endoscopic drainage of pseudocysts as safe and effective as surgical drainage?

Traditional open surgical approaches to acute, symptomatic pseudocysts include cyst-gastrostomy, cyst-duodenostomy, Roux-en-Y cyst-jejunostomy, and, in rare cases, external drainage. No studies exist to guide patient selection or type of operation, although anatomic cyst topography is a critical factor. Recent advances in endoscopic capabilities have led to the development of an array of nonsurgical drainage methods that bear consideration as well. To date, randomized comparison of endoscopic management of pseudo-

cysts versus surgical management has not been performed, so the advantages of one approach over the other cannot be stated with certainty. A recent retrospective study compared 79 patients who suffered complications from percutaneous drainage, endoscopic drainage, or both, with 100 patients who underwent surgical intervention alone.[22] Although this study suggested that fewer complications occur in patients undergoing primary surgical intervention, these groups cannot be directly compared because the number of patients undergoing successful nonsurgical intervention is unknown. Another retrospective cohort study of 10 patients who underwent surgical cyst-gastrostomy versus 20 who underwent endoscopic transgastric drainage demonstrated no difference in treatment success, procedural complications, or reintervention, although the study was underpowered to detect clinically important differences in these measures.[23] But it did demonstrate a significantly shorter hospital length of stay in the endoscopic group (2.65 versus 6.5 days, $p = 0.008$) and a mean cost savings of $5,738 per patient for endoscopic drainage.

Endoscopic drainage has been applied to both acute and chronic pseudocysts and pancreatic necrosis.[24] In this retrospective review, resolution of the fluid collection was achieved in 113 of 138 patients (82%), with a median time to resolution of 40 days. Patients with chronic pseudocysts were more likely to have resolution (59 of 64 patients, 92%) than those with acute pseudocysts (23 of 31 patients, 74%, $p = 0.02$) or necrosis (31 of 43 patients, 72%, $p = 0.006$). Complications were greatest in patients with necrosis (37%) versus chronic pseudocysts (17%, $p = 0.02$), with a similar trend versus acute pseudocysts (19%, $p =$ NS). After a median of 2.1 years, recurrence occurred in 18 of 113 patients (16%), with the greatest recurrence seen in patients with necrosis (29%), which was higher than with chronic pseudocysts (12%, $p = 0.047$) and acute pseudocysts (9%, $p =$ NS). On multivariate analysis, chronic pseudocysts were a marker for successful drainage; necrosis was a marker for unsuccessful drainage, complications, and recurrence. These authors demonstrated viability of this technique for treating symptomatic pseudocysts, which has led to further development of this approach. For pancreatic necrosis, however, surgical debridement remains the standard, although efforts to refine this technique for patients with necrosis continue.[25]

Endoscopic pseudocyst drainage has been described using both a transpapillary and a transenteric approach. Not surprisingly, increased endoscopic experience with these procedures correlates with improved patient outcomes.[26] In this retrospective study, performance of 20 or more endoscopic drainage procedures afforded improved rates of resolution (93% versus 45% for more than versus less than 20 procedures, respectively) and fewer days to resolution (33.5 days versus 50 days) in patients with chronic pseudocysts. The transpapillary approach requires that the pseudocyst communicate with the main pancreatic duct and that it have few septations to permit complete drainage. Pancreatic ductal strictures, if identified, may be balloon dilated, after which a single 5–7 F stent is placed within the pancreatic duct.

The transenteric endoscopic approach requires either an endolumenal bulge or EUS evidence of adherence between the gastric or duodenal wall and the cyst without associated necrosis, but such simplicity rarely exists. Navigation with EUS theoretically permits localization and avoidance of adjacent vessels that could lead to significant hemorrhage if injured during attempted endoscopic drainage. After identifying the pseudocyst, aspiration confirms access to the cyst cavity. A contrast injection can be performed for further confirmation if required. Once access is established, a pseudocystotomy is performed and the tract balloon dilated. One or more double pigtail stents can then be deployed to maintain patency of the cyst-enterostomy. One recent randomized, prospective study suggests that premature removal of these stents leads to pseudocyst recurrence.[27] Fifteen patients were randomized to have their stents left in place indefinitely; 13 underwent stent retrieval after a median of 2 months. The primary pseudocyst recurred in five patients after stent removal at a median of 6 months after initial drainage versus none in the group with persistent stent-facilitated drainage ($p = 0.013$). Although small and potentially underpowered to detect recurrence in the stent maintenance group, this study suggested that removal of endoscopically placed transenteric stents increases the rate of recurrence, likely from obstruction or premature closure of the cyst-enterostomy. An ongoing trial using a surgical stapling device to create the endoscopic cyst-enterostomy may address this limitation of endoscopic pseudocyst management by creating a larger opening for cyst decompression.[21] At present, without clear data to guide treatment selection, the approach used is often dictated by the skill set of the physician caring for the patient (Grade: C).

Is there any role for percutaneous drainage of pancreatic pseudocysts?

Percutaneous pseudocyst drainage has also been used. But a recent cohort study showed percutaneous drainage was associated with higher mortality, longer hospital stay, and greater complications than surgical drainage.[28] This result and numerous observational studies indicate that percutaneous drainage, although seemingly convenient for the practitioner and the patient, should be performed only in patients with an acute pseudocyst and radiographically

proven normal ductal anatomy or in cases in which comorbid conditions or physiologic exhaustion make surgical intervention ill advised. Predictors of failure of percutaneous drainage include a pancreatic duct cut-off, direct communication of the pseudocyst with the pancreatic duct, and underlying CP, according to one case series.[19] Another retrospective case series compared 66 patients with pseudocysts who underwent percutaneous drainage with 41 patients who were observed and 66 who underwent surgical therapy.[29] Of those who underwent initial percutaneous drainage, 38 of 66 (58%) failed as compared with 3 of 41 (7%) who were observed and 8 of 66 (12%) who underwent operations. Of the 38 who failed percutaneous drainage, 33 (87%) required operations and 4 died.

The practice of using percutaneous drainage to treat a pancreatic abscess in order to avoid the theoretic risk of progression to retroperitoneal sepsis has not been well studied. Percutaneous drainage has been used in early infected necrosis as a guide for minimally invasive surgical intervention either immediately[30] or in a delayed fashion in patients who fail to resolve.[31] Such an approach has merit in cases of early necrosis with uncontrolled sepsis because the patient may resolve with percutaneous drainage or with subsequent minimally invasive removal of the necrotic debris. In contrast, patients with a symptomatic or infected pseudocyst (ie, a pancreatic abscess) are typically physiologically stable and are best managed with a single surgical or endoscopic procedure without the preamble of percutaneous drainage (Grade: B).

Is there any advantage to laparoscopic drainage over open surgical drainage?

Laparoscopic drainage of pseudocysts has been performed where the minimally invasive surgical approach essentially mimics traditional open cyst-enteric drainage techniques. A number of case series have been reported that suggest this approach is safe, although definitive evidence is lacking (Grade: D).

What features of pseudocysts indicate a predilection for developing complications?

Management of pseudocyst complications has not been well studied to date. Consequently, current approaches are based primarily on observational data and surgeon experience. Infection of the pseudocyst resulting in a pancreatic abscess can rapidly progress to retroperitoneal sepsis, so early recognition and prompt intervention are required. But distinguishing those clinical features associated with peripancreatic inflammation from infection of the pseudocyst poses significant challenges. Imaging findings such as rim enhancement or gas within the pseudocyst clearly suggest an infection (Fig. 2). In the absence of such findings, the treating physician may consider percutaneous fine-needle aspiration to evaluate for infection. But this invasive diagnostic test should be pursued only if the patient can tolerate a major surgical intervention based on the results. In such cases, infection of the pseudocyst can be definitively managed with direct surgical drainage into the enteric system. This approach is especially important in the case of the "disconnected pancreatic segment," in which the drainage of the distal gland is completely disrupted (Fig. 3). Although percutaneous drainage has been recommended by some for treatment of pancreatic abscess, as indicated above, this strategy should be used with caution because it typically only forestalls the inevitable surgical intervention.

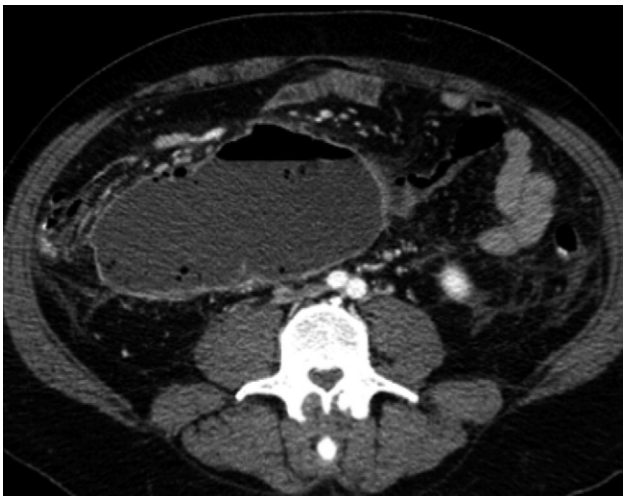

Figure 2. Infected pancreatic pseudocyst. This well-circumscribed lesion, in direct connection with a viable pancreatic head (not shown), illustrates evidence of a gas-forming infection 5 weeks after an attack of alcohol-induced pancreatitis.

Other complications, including hemorrhage and rupture, can present as life-threatening emergencies. Pseudocyst-associated hemorrhage generally should be controlled with endovascular embolization of the affected vessel—most often a branch of the splenic or gastroduodenal artery. Some pseudocysts, including those in the pancreatic tail, which incorporate into the splenic hilum, carry an especially high risk of acute hemorrhage and should be treated prophylactically with surgical resection. Although rare, free rupture of the pseudocyst typically results in peritonitis and requires emergency open surgery with abdominal washout and external drainage of the pseudocyst cavity. Predictors of these events have not been evaluated in the literature because of their relative infrequency.

Giant pseudocysts have been variably defined as greater than 15 cm[32] or greater than 10 cm.[33] Initial observations that patients with pseudocysts larger than15cm require a unique management approach have not been corroborated with case-

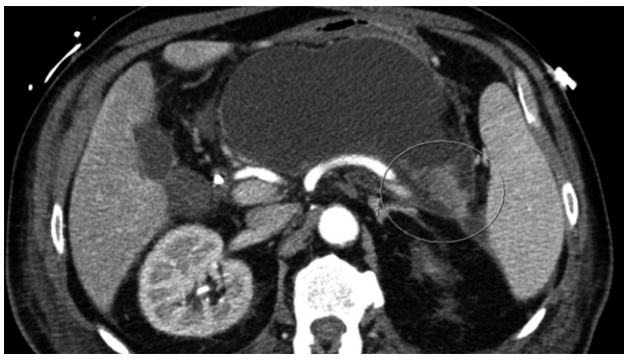

Figure 3. Disconnected pancreatic segment. This well-developed pseudocyst progressed in size over 6 weeks, leading to early satiety. Notice the viable (enhancing) remnant of pancreatic parenchyma in the tail (circle). The drainage of this segment is in discontinuity with the pancreatic head and is the source of persistent enlargement of the cyst over time.

controlled or cohort data. In the case-control study by Soliani and colleagues,[33] 41 patients with pseudocysts greater than 10 cm (including 19 greater than 14 cm) were compared with 30 patients with pseudocysts smaller than 10 cm. No differences in morbidity, mortality, or recurrence were detected after treatment, although this study was arguably underpowered to detect clinically significant differences. Based on these limited studies, it appears that there are no reliable clinical indicators or anatomic features that predict pseudocyst complications, including pseudocyst size (Grade: C).

What treatment approach should be used for a chronic pancreatic pseudocyst?

Chronic pseudocysts—those arising in the setting of chronic pancreatitis—bear special consideration because they are often associated with an underlying stricture or obstruction in the main pancreatic duct. In these cases, the pancreatic ductal pathology must be addressed either endoscopically or surgically to avoid pseudocyst recurrence from a persistent distal obstruction. Because of this intrinsic difference between acute and chronic pseudocysts, the status of the underlying gland should be firmly established on clinical grounds or with confirmatory imaging before any planned intervention.

Once the diagnosis of a chronic pseudocyst has been made, treatment options include transampullary stenting as described earlier, longitudinal pancreaticojejunostomy, pseudocyst-enteric drainage, or resection. Endoscopic treatment is generally used as a first line treatment in patients without chronic pain, biliary obstruction, or large chronic pseudocysts involving the pancreatic tail. Patients with a large main pancreatic duct (≥7mm) can be treated with a longitudinal pancreaticojejunostomy. One recent study indicates that adding a separate pseudocyst drainage procedure to the longitudinal pancreaticojejunostomy increases operative time, hospital days, complications, and transfusion requirements with no benefit added.[34] In other words, drainage of the ductal system alone suffices. In patients with a chronic pseudocyst in the pancreatic head with or without biliary or gastric outlet obstruction, pancreaticoduodenectomy or duodenal-preserving pancreatic resection should be considered. Finally, as described above, pseudocysts in the pancreatic tail carry a risk of rupture into the spleen or splenic vasculature, resulting in catastrophic hemorrhage, so operative removal is advised. In addition, in patients with associated splenic vein thrombosis, the effects of sinistral hypertension can lead to upper gastrointestinal bleeding. Consequently, distal pancreatectomy and splenectomy should be strongly considered for these select patients. Because of the variability in pseudocyst location and ductal anatomy, chronic pseudocyst treatment cannot be narrowly proscribed because the treatment must be tailored to the individual clinical situation (Grade: C).

What followup imaging should be obtained after treatment of a pancreatic pseudocyst?

After definitive treatment of pancreatic pseudocysts, surveillance imaging is often used but has not been studied or standardized with regard to either timing or imaging modality. Ultrasonography, CT, and MRI have all been described for this purpose. Although no consensus exists on the need for or timing of post-treatment studies, if the patient's symptoms do not improve shortly after treatment, followup imaging is obviously warranted. In addition, documentation of cyst resolution at some interval after treatment should also be considered. There is no clearly defined clinical or economic value for longitudinal followup in the asymptomatic, postintervention patient (Grade: D).

DISCUSSION

Existing studies on pancreatic pseudocysts are hampered by relative infrequency, inconsistent terminology, differences in methodology, selection bias, and lack of uniform management principles that limit the conclusions that can be drawn from them and preclude combining study groups for further analysis. With a paucity of randomized studies, the state of the art of pancreatic pseudocyst management hinges largely on observational data from case series. Nonetheless, a few contemporary studies afford some reliable insights into the correct approach for diagnosis and management of this challenging clinical problem and should serve as the foundation for future work in this field. In addition, this review has identified a number of areas for future study that bear summarizing.

Results of the limited case-control and cohort studies on topics related to pancreatic pseudocysts are presented in

Table 2. Summary of Pancreatic Pseudocyst Studies*

First author	Year	Level of evidence	Randomized groups, n	Intervention/design	Median followup	Major endpoint	Minor endpoint	Interpretations/comments
Brugge[18]	2004	IIIb		Retrospective analysis of mucinous (n = 68) versus nonmucinous (n = 44) pancreatic cysts including 27 inflammatory cysts	Unknown	Receiver-operator characteristic curves of tumor markers	Comparison of sensitivity, specificity, and accuracy of tumor markers with morphology and cytology	This retrospective case-control study provides the current best evidence for distinguishing neoplastic pancreatic cysts from benign cysts and suggests that CEA was more accurate than EUS morphology and cytology at making this distinction.
Ahearne[20]	1992	IIIb		Retrospective application of a treatment algorithm	Unknown	Adverse outcomes (persistent or recurrent pseudocyst or complication requiring additional treatment or hospitalization		In this retrospective algorithm assessment, the authors provide the first evidence that pancreatic ductal anatomy should guide therapy. Adverse events occurred in 6 of 14 patients who did not follow the algorithm (43%) versus 3 of 26 who did (12%, p = 0.04). This algorithm applied percutaneous drainage more liberally than those of subsequent investigators.
Morton[28]	2005	IIb		Cohort analysis of The National Inpatient Sample	Unknown	Complication rates, length of stay, disposition, inpatient mortality		This study includes 14,530 patients with pancreatic pseudocysts treated with either surgical or percutaneous drainage. After controlling for confounding variables, surgical versus percutaneous drainage had a lower mortality (2.8% versus 5.9%), shorter length of stay (15 versus 21 days), and many fewer complications. These data also indicated a protective benefit of ERCP (odds ratio 0.68, 95% CI 0.51–0.9).
Varadarajulu[23]	2008	IIIb		Nonrandomized retrospective review of patients undergoing surgical (n = 10) versus endoscopic (n = 20) cyst-gastrostomy		Treatment success, procedural complications, reinterventions, postprocedure length of stay, mean direct cost		This small retrospective, matched, case-controlled study compared the periprocedure outcomes, length of stay, and cost of endoscopic cyst-gastrostomy in 20 patients with surgical cyst-gastrostomy in 10 patients. There was no detected difference in periprocedural outcomes; length of stay (2.65 versus 6.5 d) and costs ($9,077 versus $14,815) were lower with endoscopic versus surgical intervention.
Baron[24]	2002	IIIb		Nonrandomized retrospective review of endoscopic drainage of acute pseudocysts (n = 31), chronic pseudocysts (n = 64), and pancreatic necrosis (n = 43).	2.1 y	Acute resolution, complications, and recurrence		This is a relatively large series of 138 patients with pancreatic pseudocysts and pancreatic necrosis who underwent attempted endoscopic drainage. Acute resolution was achieved in 113 of 138 patients (82%). Comparisons between groups showed that complications and interval recurrence were greater in patients with necrosis versus chronic pseudocysts, with similar trends for both when comparing necrosis with acute pseudocysts. Endoscopic management of pseudocysts warrants further study but such techniques should not be applied to patients with necrotic debris within the peripancreatic fluid.

(continued)

Table 2. Continued

First author	Year	Level of evidence	Randomized groups, n	Intervention/design	Median followup	Major endpoint	Minor endpoint	Interpretations/comments
Harewood[26]	2003	IIIb		Nonrandomized retrospective review of results before and after 20 endoscopic drainage procedures	Unknown	Pseudocyst resolution, time to resolution, procedure failure, complications, length of stay, recurrence		This study showed a significant improvement in frequency of resolution and decreased length of stay for endoscopic drainage of chronic pseudocysts when the endoscopist had performed over 20 procedures.
Aryanitakis[27]	2007	IIIb	2	Prospective case-controlled series	14 mo	Recurrence of the index pseudocyst		This is a well-designed study of 15 patients who had percutaneous endolumenal stents maintained versus 13 patients where the stents were removed on resolution of the cyst. Kaplan-Meier curves show a recurrence rate of 40% at 10 months in the latter group. Because of the small size of the endoscopic cyst-enterostomy, this result should come as no surprise.
Soliani[33]	2004	IIIb		Nonrandomized retrospective review of "necrotic pseudocysts" from an attack of acute pancreatitis	Unknown	Morbidity, mortality, and recurrence		This study does not clearly exclude patients with associated pancreatic necrosis. It does suggest, however, that patients with giant pseudocysts can safely undergo cyst-gastrostomy, although it is significantly underpowered to detect important differences in any of the endpoints.

*First author, Level IV studies excluded.
ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound.

Table 2. In summary, these studies show that in distinguishing pseudocysts from cystic pancreatic neoplasms, an elevated CEA level within the cyst fluid is the most accurate predictor of a neoplastic process.[18] In designing a treatment approach, ERCP-based management may improve outcomes by defining the pancreatic ductal architecture.[20] Percutaneous drainage is generally associated with worse outcomes than surgical management.[28] If an endoscopic management approach is attempted for an acute or chronic pseudocyst,[24] the endoscopist should have significant experience with the procedure,[26] and the endoscopically placed stent should not be removed immediately on pseudocyst resolution.[27] Finally, based on a small case-control series, management of giant pseudocysts with surgical cyst-gastrostomy did not result in worse clinical outcomes.[33]

Although these limited studies do provide some insight, to truly understand the natural history and multiple nuances of this disease process, a well-designed cohort study is required. A large dataset encompassing a sizable population with patients at risk (primarily patients who consume alcohol or who have cholelithiasis) would be required to identify sufficient numbers of affected patients. Such a study using standard terminology could define the incidence of acute fluid collections, the frequency with which these progress to form a pseudocyst, and the frequency with which established pseudocysts become complicated, manifest symptoms, or even regress.

Then, as noted earlier, a multicenter group of collaborating investigators should design and conduct studies to address existing controversies and questions related to the evaluation and management of established pseudocysts. Some of these unanswered questions include optimal management of pancreatic abscess, the accuracy of pancreatic ductal anatomy documented by MRCP, the merits of endoscopic versus surgical therapy for acute and chronic pseudocysts, defining clinical and imaging features that anticipate future complications in an asymptomatic pseudocyst, and the need for, and timing of, postintervention imaging of pseudocysts, just to name a few. As with many other clinical entities for which there are numerous treatment options, a clinical pathway for pseudocyst management should also be considered because this may allow for streamlined first-line therapy, accelerated recognition of treatment failures, and improved patient outcomes. As with many surgical problems, existing studies on the management of pancreatic pseudocyst have laid the groundwork for our current clinical thinking but in no way represent a scientifically robust definitive answer on how to approach this condition and all of its nuances. Future studies must seek to better define this clinical entity and its optimal management.

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