

Peripancreatic Fluid Collections: A Review

Goyal J*

Department of Medicine, University of Alabama at Birmingham, Birmingham Alabama, USA

*Corresponding author: Jatinder Goyal, University of Alabama at Birmingham, Medicine, USA, Tel: 4109082942; E-mail: jatinaiims@gmail.com

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Abstract

Peripancreatic fluid collections arise as a complication of pancreatitis and pancreatic injury. Surgery has been the traditional treatment modality of choice for management of peripancreatic fluid collections though endoscopic, laparoscopic and transcutaneous techniques offer alternative drainage approaches. Endoscopic ultrasound has enabled real-time access and drainage of fluid collections which were previously not amenable to transmural drainage. There is limited data from randomized clinical trials including that on direct comparisons between different treatment approaches. In this review, we have summarized the existing evidence on endoscopic drainage of peripancreatic fluid collections from published studies. The final treatment approach should be chosen taking into consideration anatomic characteristics, patient preference, comorbidity profile of the patient, and physician discretion.

Keywords: Endoscopic ultrasound; Pancreatic pseudocyst; Peripancreatic fluid collection; Walled-off pancreatic necrosis

Introduction

Peripancreatic Fluid Collections (PFCs) are a diverse group of enzyme-rich fluid collections formed by pancreatic ductal disruption leading to secretion of pancreatic secretions in the retro-peritoneum or pancreatic tissue planes. Due to the wide discrepancy in the way these fluid collections were previously defined, the 1992 Atlanta Classification was proposed to provide structure and uniformity of nomenclature [1]. A revised classification has been recently proposed to reflect the enhanced understanding of these lesions [2]. Table 1 summarizes the original and revised Atlanta classification systems. According to the revised classification on acute pancreatitis, pancreatic pseudocysts are defined as well-circumscribed encapsulated collections of fluid surrounded by nonepithelial wall of fibrous or granulation tissue usually situated outside the pancreas without any necrotic material. It is important to differentiate pseudocysts from acute peripancreatic fluid collections which are homogenous collections of fluid adjacent to the pancreas and are characterized by the absence of a definable wall encapsulating them. These are usually seen within the first 4 weeks of interstitial edematous pancreatitis with no associated peripancreatic necrosis [2]. The presence of any solid necrotic material points towards a diagnosis of acute necrotic collections or Walled-Off Pancreatic Necrosis (WOPN). Walled-off pancreatic necrosis is defined as a mature, encapsulated collection of pancreatic or peripancreatic necrosis that has developed a well-defined inflammatory wall. These lesions usually develop more than 4 weeks after the onset of necrotizing pancreatitis [2]. Acute necrotic collections differ from WOPN by acute development and the absence of a definable wall around the fluid.

Effective management requires accurate diagnosis and treatment by a multidisciplinary team of expert gastroenterologists, surgeons and radiologists working in tandem to minimize morbidity and mortality. Traditionally, surgical debridement was considered to be the standard

of care, but was marred by poor outcomes along with considerable morbidity and mortality [3]. Percutaneous puncture with aspiration under radiological guidance has also been employed with some success but the high rates of recurrence limits clinical utility of this approach [4,5]. A step-up approach employing percutaneous drainage of necrotizing pancreatitis, followed by minimally invasive retroperitoneal necrosectomy has shown improved outcomes as compared to open necrosectomy [6]. Nevertheless, it has led to an increasing interest in less invasive endoscopic drainage techniques. Recent progress in the field of conventional endoscopy and Endoscopic Ultrasound (EUS) has resulted in substantial improvement in clinical outcomes. Through this review, we will critically evaluate existing evidence on endoscopic management of pancreatic fluid collections along with commenting on the challenges that lie ahead in the future.

Incidence and Etiology

The incidence of pseudocysts in published literature ranges from 5% to 16% in acute pancreatitis, [7-9] and 20% to 40% in chronic pancreatitis [10-12]. whereas alcohol was noted to be the etiological agent in 64% of chronic pancreatitis patients, it was only responsible for 26% of acute pancreatitis cases. Gallstone disease by comparison was responsible for 26% of acute and 11% of chronic pancreatitis patients respectively [13]. However, there is a geographic variation in the causes of acute and chronic pancreatitis across the world, especially in countries where alcohol abuse is less common [14]. Pancreatic pseudocysts account for a majority of all pancreatic cystic lesions, and differentiating pseudocyst from pancreatic cystic neoplasms, retention cysts and congenital cysts can be a challenging task. Although a preceding history of pancreatitis could be useful in distinguishing pancreatic pseudocysts from the rest, warshaw and colleagues found that as many of 37% of cases were misdiagnosed as pseudocysts before being confirmed as malignant neoplasms post-surgery [15].

1992 Atlanta Classification	Revised 2012 Classification
Acute Fluid Collections: Peripancreatic fluid collections occurring early in the course of acute pancreatitis and lacking a wall of granulation or fibrous tissue.	Interstitial Edematous Pancreatitis: Acute inflammation of the pancreatic parenchyma and Peri-pancreatic tissues without recognizable tissue necrosis.
Acute Pseudocysts: Collection of pancreatic juice enclosed by a fibrous or granulation wall; usually round or ovoid and occurring about 4 weeks after pancreatitis or pancreatic trauma.	Necrotizing Pancreatitis: Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis.
Pancreatic Necrosis: Diffuse or focal area of nonviable pancreatic parenchyma; nonenhanced pancreatic parenchyma >3cm or involving more than 30% of the area of the pancreas.	Acute Peripancreatic Fluid Collection: Peripancreatic fluid associated with interstitial edematous pancreatitis within the first 4 weeks with no associated peripancreatic necrosis.
Pancreatic Abscess: Circumscribed intra-abdominal collection of pus in the proximity of the pancreas, containing little or no pancreatic necrosis, occurring 4 or more weeks after onset of acute pancreatitis or pancreatic trauma.	An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis usually occurring more than 4 weeks after the onset of interstitial edematous pancreatitis.
	Acute Necrotic Collection: A collection containing variable amounts of both fluid and necrosis of the pancreatic and/or peripancreatic tissues associated with necrotizing pancreatitis.
	Walled-Off Pancreatic Necrosis: A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that have developed a well defined inflammatory wall usually occurring more than 4 weeks after the onset of necrotizing pancreatitis.

Table 1: Summary of 1992 Atlanta Classification and the revised 2012 classification of acute pancreatitis

A CT scan or Magnetic Resonance Imaging (MRI) is essential prior to any intervention for a suspected pancreatic pseudocyst as it yields the highest sensitivity and specificity with an overall efficacy of 88% to 94% [16,17]. Morphological characteristics seen on CT or MR imaging can help differentiate these lesions. While rim calcification would suggest neoplasm, dependent debris within the lesion is indicative of pseudocyst. MRI can be particularly helpful in patients who can't receive iodinated contrast material due to allergic reactions. Furthermore, Magnetic Resonance Cholangiopancreatography (MRCP) can provide important information about pancreatic parenchyma and pancreatic ductal integrity. However, it has been reported that as many as 10% of pseudocysts have ill-defined features on radiographic imaging that overlap with characteristics of cystic neoplasms, and thus cannot be completely relied upon [18]. EndoscopicUltrasound (EUS) is being increasingly employed in this role as it has been shown to possess superior diagnostic sensitivity for cystic lesions less than 2 cm in diameter because of better spatial resolution [19]. This has led many authors to believe that EUS should be employed in all patients with small peripancreatic fluid collections prior to endoscopic intervention.

Pancreatic Pseudocyst

Most pancreatic pseudocysts undergo spontaneous resolution. An early observational study had recommended that pseudocysts larger than 6 cm in size which persist for more than 6 weeks are likely to cause symptoms and should be treated [20]. However, recent evidence suggests that these parameters are arbitrary and pseudocysts can remain asymptomatic regardless of size or duration [9,21]. Spontaneous resolution is seen in a large proportion of these lesions with reports varying from 7% to 60% of patients [22].

Surgical intervention has been the traditional gold standard of treatment in patients with pancreatic fluid collections. However, this trend seems to be changing. In a recent publication by Varadarajulu et al., the authors reported a significant increase in the proportion of patients with pancreatic pseudocysts being treated endoscopically from 2008 to 2010 as compared to 2004 to 2007 (100% vs 84%,

p=0.001) [23]. The authors noticed a 'changing of guard' from surgical techniques to a preference for endoscopic procedures for treatment of pancreatic pseudocysts at their institution. Much of this change is credited to the ability of EUS to access small lesions not causing luminal compression which would have required surgical intervention traditionally. Other authors have also suggested a similar trend at their institutions [24].

Ever since the first published reports of successful drainage of pseudocyst, endoscopic approaches have gained widespread recognition as the preferred treatment approach. These collections can be drained through the conventional transmural or transpapillary endoscopy. Endoscopic transmural drainage entails the creation of a fistulous tract between the pseudocyst and the gastric (cystogastrostomy) or the duodenal lumen (cystoduodenostomy). The transpapillary approach is employed in patients with pseudocysts which directly communicate with the pancreatic duct. Endoscopic ultrasound (EUS) allows real-time intervention in fluid collections without a distinct luminal bulge.

Pseudocysts occurring in association with acute pancreatitis should be kept under observation as they are expected to undergo spontaneous resolution. However, intervention is indicated when pancreatitis fails to resolve with conservative management. The observation period before which decompression is indicated is a subject of much debate. Decompression is usually indicated for symptomatic relief from space-occupying chronic cystic lesions compressing neighboring organs. This includes chronic dull pain, early satiety, weight loss and persistent fevers. Other symptomatic indications include infection of the pseudocyst, gastric outlet obstruction, and biliary obstruction, rupture of the pseudocyst into the peritoneal cavity, hemorrhage into pancreatic pseudocyst, development of pancreaticopleural fistula or vascular thrombosis leading to sinister hypertension. Erosion of the pseudocyst into adjacent vessels may also lead to pseudoaneurysm formation and/or life-threatening hemorrhage. According to a study, the prevalence of bleeding pseudoaneurysms in patients with pancreatic pseudocysts was 3.2% [25]. Some of these evolving complications pose an

immediate threat to life and preemptive intervention maybe necessary. Although symptomatic large cysts need intervention, there is less clarity regarding treatment in asymptomatic collections. Finally, individualized decisions should be made based on patient condition, etiology, symptom burden and clinical course in a multidisciplinary setting.

Endoscopic transpapillary drainage

Recent technological advancement has led to the development of an array of nonsurgical minimally invasive modalities including endoscopic techniques for treatment of these lesions. The transpapillary route is an attractive choice if the pseudocyst communicates with the pancreatic duct, if there is stricture or disruption in the pancreatic duct, if transmural drainage is not feasible due to distance (>1cm from the enteric lumen), or is contraindicated (e.g. significant coagulopathy). Pancreatic duct sphincterotomy followed by judicious dilation of downstream pancreatic duct strictures allows cannulation, and a guidewire is directed through the duct into the pseudocyst cavity. After this, a plastic stent of 5F or 7F is passed over the guidewire preferably into the pseudocyst cavity or across ductal disruption [26,27]. Transpapillary stents are left until the pseudocyst resolves or undergoes significant reduction in size as seen by CT scan, usually after a period of 6 to 8 weeks. When pseudocysts are found to have heterogeneous contents in the form of debris, necrosis, or a suspected abscess, the transpapillary route allows the insertion of a nasocystic catheter with repeated aspiration and rinsing of the pseudocyst content.

Catalano et al. achieved successful transpapillary stenting in all patients (n=21) with 33 endoprosthesis for the treatment of symptomatic pseudocysts communicating directly with the main pancreatic duct [28]. Initial resolution of pseudocysts was seen in 17 patients, 16 of whom were free of recurrence at a mean follow-up of 37 months. Factors predictive of success included presence of strictures, size of pseudocyst greater than or equal to 6 cm, location in the body of the pancreas, and duration of pseudocyst less than 6 months. The required duration of stenting depends on the time taken by pseudocysts to resolve. In the current study, the authors exchanged stents every 6 to 8 weeks till resolution of pseudocysts was achieved. In another series, the authors presented their data on endoscopic transpapillary pancreatic cyst drainage in 30 patients [29]. Pancreatic stents were successfully placed into the cysts in 12 patients, and as close as possible to the cyst in the remaining 18 patients. Additional endoscopic cystenterostomy was done in 10 patients. Complete resolution of pseudocyst was achieved in 26 patients (87%), but 7 patients' required surgical procedures. Complications were reported in only 4 patients and were minor in nature. Endoscopic transpapillary nasopancreatic drainage has also been successfully employed in patients with large and multiple pancreatic pseudocysts with a reported success rate of 91% in one study [30] no recurrences were seen over a follow up period of 20 months.

Endoscopic transluminal drainage

Transpapillary drainage has its disadvantages as the stent caliber is small; placing an endoprosthesis into the collection may cause ductal disruption and lead to a longstanding fistula formation and result in recurrence. The transluminal approach is an alternative option in patients where pseudocysts are directly adjacent to the gastroduodenal wall and produce a visible bulge in the gastric or duodenal wall. Endoscopic needle localization confirms the most appropriate location

for cystenterostomy which can be achieved by diathermic puncture [31] or the Seldinger technique [32]. Diathermic puncture involves inserting a needle-knife or a Cremer Cystostome (Cook Endoscopy, Winston-Salem, NC) into the gut wall at a 90-degree angle at the site of maximum gastric or duodenal bulge. A needle-knife is advanced through the bulge with application of cautery, a gush of cystic fluid is encountered following which, a guidewire is inserted into the cystic cavity. The Cremer Cystostome employs a single catheter for needle knife cyst entry followed by cyst-enterostomy creation with an electrocautery ring, and subsequent stent deployment [33]. The Seldinger method has been shown to have encouraging outcomes in the form of reduced bleeding and perforation rates but comparable efficacy to the diathermic puncture technique [32]. This method involves cyst puncture by an 18-gauge needle followed by wire passage into the pseudocyst, balloon tract dilation, and stent placement. After cystenterostomy is achieved, one or two 10F catheter double pigtail stents are deployed into the pseudocyst. The pigtail stents prevent displacement into the pseudocyst or into the gastrointestinal tract. Transmural stents are usually kept in place and are subsequently removed when repeat CT scanning shows complete resolution of the pseudocyst after at least 2 months and patient's symptoms have improved or resolved [34]. It is generally expected that a chronic fistulous tract from the cyst to the stomach has been formed and will remain patent allowing continuous drainage.

While initial technical success rates of transpapillary and transmural endoscopic drainage of pancreatic pseudocysts are between 92% and 100%, final success rates have been reported to be in the range of 65% to 80% [27-29,35]. Factors like unclear transluminal bulge, failed insertion of the drain, bleeding, and gallbladder puncture have been found to be increase predisposition to treatment failure. In a retrospective study, the authors reported their experience with endoscopic drainage of pseudocysts in 37 patients with chronic pancreatitis [35]. While technical success was achieved in 34 patients (92%), complete resolution of pseudocyst could be achieved in only 24 patients (65%). Recurrence of pseudocyst was seen in 3 patients. In another series of 53 patients, transpapillary drainage was attempted in 33 patients with pseudocysts that communicated with the main pancreatic duct and transmural drainage of cysts in 20 patients that were found to be in contact with the stomach or duodenal wall [27]. The authors reported successful drainage in 50 patients (94%) with complete pseudocyst resolution in 47 patients. At a mean follow-up of 22 months, pseudocyst recurrence was seen in 11 patients (23%), 7 of whom underwent successful endoscopic re-treatment.

Hookey et al. presented their experience in 116 patients who underwent endoscopic drainage of PFCs by transpapillary route in 15 patients, transmural in 60, and both in 41 patients [36]. No difference in outcomes was seen between the two drainage techniques. Weckman and colleagues reported an 86% success rate in 165 patients with only a 5% recurrence rate at a mean follow-up period of 25 months [37]. In another study, Cahenet al. reported a technical success rate of 97% in 92 patients undergoing endoscopic drainage [38]. Other authors have also reported high rates of success with transpapillary and transmural drainage of pancreatic pseudocysts [39-41]. However, some studies have reported relatively high rates of recurrence on long term follow-up. An Italian study on 49 patients with pseudocysts reported a recurrence rate of 21% after initial endoscopic drainage [42]. Causes of recurrence included obstruction of a cystenterostomy or stent obstruction in the presence of persistent pancreatic disease or ductal stricture. Cyst location in the head of the pancreas, multiple stent insertion, and stent insertion for more than 6 weeks were found to be

independent predictors of successful outcomes while presence of residual necrosis or moderate abscess debris predicted failure [38,43,44]. Outcomes from studies described above and other studies [45-51] have been described in Table 2.

Study	Study design and year	No. of patients	Technical success	Clinical success	Recurrence	Complications
Conventional endoscopy						
Binmoller [27]	Retrospective (1995)	53	50 (94%)	47 (89%)	11 (23%)	6 (11%)
Catalano et al. [28]	Retrospective (1995)	21	21 (100%)	17 (81%)	1 (6%)	1 (6%)
Barthet [29]	Retrospective (1995)	30	30 (100%)	26 (87%)	3 (12%)	4 (13%)
Bhasin et al. [30]	Retrospective (2006)	11	10 (91%)	7 (64%)	0 (0%)	1 (9%)
Smits [35]	Retrospective (1995)	37	34 (92%)	24 (65%)	3 (12.5%)	6 (16%)
Hookey et al. [36]	Retrospective (2006)	116	-	108 (93%)	19 (16%)	13 (11%)
Weckman [37]	Retrospective (2006)	165	-	146 (86%)	8 (5%)	16 (10%)
Cahen et al. [38]	Retrospective (2005)	97	89 (92%)	79 (86%)	4 (5%)	31 (35%)
Vitale et al. [39]	Retrospective (1999)	36	31 (86%)	31 (86%)	5 (14%)	1 (3%)
Sharma [40]	Retrospective (2002)	38	38 (100%)	38 (100%)	7 (16%)	5 (13%)
Libera et al. [41]	Retrospective (2000)	25	21 (84%)	20 (80%)	1 (4%)	6 (28%)
De Palma et al. [42]	Retrospective (2002)	49	43 (88%)	-	9 (21%)	12 (25%)
Baron [45]	Retrospective (2002)	64	59 (92%)	52 (81%)	7 (12%)	11 (17%)
Cremer [46]	Retrospective (1989)	33	30 (91%)	28 (85%)	30 (91%)	3 (9%)
Sahel [47]	Retrospective (1991)	37	36 (97%)	31 (86%)	2 (5%)	5 (14%)
Kozarek et al. [48]	Retrospective (1991)	14	-	11 (79%)	2 (14%)	3 (21%)
Bejanin et al. [49]	Retrospective (1993)	26	-	19 (73%)	4 (15%)	4 (15%)
EUS-guided endoscopic drainage						
Giovannini [52]	Retrospective (2001)	15	15 (100%)	15 (100%)	0	1 (7%)
Antillon [54]	Retrospective (2006)	33	31 (94%)	24 (82%)	1 (3%)	2 (6%)
Ahlawat [55]	Retrospective (2006)	11	11 (100%)	9 (82%)	2 (18%)	0 (0%)
Lopes et al. [56]	Retrospective (2007)	51	48 (94%)	48 (94%)	18%	21 %
Puri et al. [57]	Retrospective (2012)	40	40 (100%)	39 (98%)	1 (3%)	4 (10%)
Norton et al. [58]	Retrospective (2001)	17	13 (77%)	14 (82%)	1 (7%)	3 (18%)
Kruger [59]	Retrospective (2006)	35	30 (88%)	33 (94%)	4 (12%)	0
Varadarajulu et al. [61]	Prospective (2007)	21	21 (100%)	21 (100%)	0	0
Varadarajulu et al. [89]	Retrospective (2011)	95	89 (94%)	-	-	5 (5%)

Table 2: Endoscopic drainage of pancreatic pseudocysts

EUS guided drainage

Endoscopic ultrasound allows real-time intervention and drainage of pancreatic fluid collections. It provides an accurate assessment of the size, location and wall thickness of these lesions especially those which do not compress the luminal wall. It also allows identification of any intervening vessels before puncture to avoid major hemorrhagic complications. Through these data, the most optimal site for

pseudocyst puncture can be determined, thereby improving outcomes and reducing morbidity. There are two possible techniques of employing EUS for endoscopic drainage of PFCs: the EUS-endoscopy technique where EUS is only employed in the initial step to locate the site of puncture of pseudocysts, and the EUS single-step technique, where the whole procedure relies on EUS [51]. The EUS-endoscopy technique employs a radial echoendoscope to evaluate and

characterize the lesion including a Doppler assessment. Features like size, distance from the gut wall, presence of solid debris inside the cyst, relationship of the cyst to adjacent vessels, communication of the cyst with the pancreatic duct and presence of biliary ductal disease are studied. Based on the findings from the initial testing, the most optimal site of puncture is determined. The echo endoscope is then exchanged for a duodenoscope and transmural drainage performed as described.

A linear array echoendoscope is then introduced as far as the stomach or the duodenum and the best site of puncture is finalized. A 19 G needle is then introduced through the working channel of the endoscope following which the pseudocyst is punctured. Cyst fluid can be aspirated during this time for analysis. A guidewire is subsequently introduced through the needle into the pseudocyst and its position is confirmed using ultrasonography and fluoroscopy. The needle is then removed and balloon dilatation is performed over the wire to create the fistula followed by stent placement as outlined in the previous section on conventional endoscopy. A success rate of 89% using this technique in 35 patients with pancreatic pseudocysts and abscesses was reported from a retrospective French study [52].

First described in 1998 by Vilmann et al. the EUS-single step technique employs an all in one stent introduction system, containing a 0.035-inch needle-wire suitable for cutting current, 5.5 F guiding catheter and a pushing catheter with a back-loaded straight stent [53]. After initial assessment as described above, the needle-wire is then introduced into the intestinal wall and cyst wall is penetrated under continuous pressure and cutting current. After entering the cyst, the rigid part of the needle is removed and the soft wire is inserted into the cyst followed by the dilator catheter and finally the straight plastic endoprosthesis. This technique avoids the need for any wire exchanges. However, this accessory is not widely available and outcome studies are lacking. Antillon and colleagues had demonstrated encouraging results with an 82% success rate using the single-step EUS guided transmural endoscopic drainage of pancreatic pseudocysts [54]. Similar success rates were reported in another study with only two recurrences seen in 4 months, one of which underwent repeat drainage while the other was managed with surgical cystogastrostomy [55]. A retrospective series on 51 symptomatic patients reported an initial treatment success in 48 patients (94%) though recurrence was seen in 18% [56]. Placement of an additional stent in pancreatic abscess was associated with a reduced complication rate. In a modified technique, EUS guided pancreatic pseudocyst drainage using a combination of endoprosthesis and nasocystic catheter placement, successful resolution was achieved in 39 out of 40 patients (97.5%) [57]. Recurrence was seen in one patient requiring a repeat of the procedure. Outcomes from these and other studies [58,59] have been summarized in Table 2.

Direct comparison between the two EUS techniques has also been done. In a small series comprising 21 patients, Mangiavillano et al. compared the one-step EUS guided drainage procedure with the two-step technique [60]. Technical success was achieved in 12/13 (92%) in the one-step group as compared to 6/8 (75%) in the two step group. Clinical success was achieved in all patients in the first group and 5 of the 6 patients in the second group ($p < 0.05$). Although the authors concluded that the one-step technique had superior results, the study with its small sample size was underpowered to draw such conclusions.

In a prospective nonrandomized study, conventional transmural drainage was found to be successful in 30 out of 36 patients (83%) with

PFCs in the head and body of the pancreas and failed in all 17 patients with PFCs located in the tail [61]. The causes of failed endoscopic were absence of luminal compression in 20, difficulty with scope positioning in 2, and bleeding with attempted drainage (portal hypertension) in 1 patient. EUS-guided drainage was successful in draining the PFCs in all the patients who had failed the initial drainage procedure especially those located in the tail of the pancreas. Only 1 complication in the form of bleeding occurred in a patient who underwent conventional drainage.

The relative efficacy of endoscopic transmural drainage and EUS-guided drainage has been explored in prospective studies including randomized controlled trials. Table 3 summarizes the findings from these studies. In one such prospective study, a total of 99 consecutive patients with pancreatic pseudocysts underwent endoscopic management according to a predetermined algorithm [43]. Patients with bulging lesions without obvious portal hypertension underwent endoscopic transmural drainage (53 patients) while the remaining patients underwent endoscopic ultrasound guided drainage (46 patients). On statistical analysis, the two groups were similar regarding short-term (94% vs 93%) and long-term success (91% vs 84%). The complication rates were also not statistically different between the two groups. The authors inferred that there was no difference in efficacy or safety between the two treatment modalities and the approach should be decided based on individual preference and local expertise at the treatment center. In another study utilizing an almost similar predetermined algorithm, 50 patients with pseudocyst underwent either conventional endoscopic transmural/transpapillary drainage, or EUS-guided transmural drainage [62]. The group reported impressive results in the form of technical success in 49 of the 50 patients (98%), clinical success in 90%, and disappearance of pseudocysts in 96% of cases without significant differences between the three groups. Morbidity was seen in 9 cases overall along with one death from late bleeding which occurred in the conventional transmural drainage group.

In a landmark prospective randomized trial, Varadarajulu et al. compared the efficacy of EUS and conventional endoscopy for transmural drainage of pancreatic pseudocysts at a tertiary referral center [63]. While technically successful drainage was achieved in all patients within the EUS cohort (100%), endoscopy was successful in only 5 of 15 (33%) of patients. The remaining 10 patients underwent successful drainage on crossover to EUS. Even after adjustment for luminal compression and sex, technical success was found to be better for EUS than endoscopy. On further analyses, there was no difference in the rates of treatment success in the two groups, either on intention-to-treat analysis (100% vs 84%, $p = 0.48$) or as-treated analysis (95.8% vs 80%, $p = 0.32$). No significant differences were found in the complication rates between the two groups. The authors recommended that EUS with its better technical success rates should be opted over conventional endoscopy whenever available.

In another randomized prospective trial exploring the issue, the authors compared the technical success and clinical outcomes of EUS-guided drainage and conventional endoscopic transmural drainage of pancreatic pseudocysts [64]. The investigators randomized 31 patients to the EUS group and 29 patients to the endoscopy group. On analysis, it was found that the rate of technical success was higher in the EUS group (94% vs 72%, $p = 0.039$). The two groups did not differ in terms of rates of complications with 7% of EUS and 10% of endoscopy patients developing complications from the procedures ($p = 0.67$). Comparing pseudocyst resolution rates between EUS and

conventional endoscopy, both short-term (97% vs 91%, p=0.565) and long-term (89% vs 86%, p=0.696) analyses did not reveal statistically significant differences in the clinical outcomes. Based on their findings, the authors opined that though both conventional

endoscopic and ultrasound guided drainage should be considered first line, those with non-bulging pseudocysts should be preferentially drained using EUS.

	Study design and year	No of patients	Technical success	Clinical success	Complications	Comment
Kahaleh et al. [43]	TMD vs EUD (2006)	46 vs 53	93% vs 94%	84% vs 91%	19% vs 18%	No differences
Mangiavillano et al. [60]	1-step vs 2-step EUD (2012)	13 vs 8	92% vs 75%	100% vs 83%	0% vs 12.5%	1-step technique superior
Barthet et al. [62]	EUD vs TMD vs TPD (2008)	28 vs 13 vs 8	100%	89 % vs 925 vs 100%	25% vs 15% vs 0%	No differences in outcomes. Overall success in 90%
Varadarajulu et al. [63]	EUD vs Endoscopic (2008)	15 vs 15	100% vs 33%*	100% vs 87%	0% vs 13%	Technical success rate higher with EUD
Park et al. [64]	EUD vs TMD (2009)	31 vs 29	94% vs 72%	89% vs 86%	7% vs 10%	Technical success rate higher with EUD

EUD: Endoscopic ultrasound guided drainage; TMD: Transmural drainage;
 TPD: Transpapillary drainage ; Represents statistically significant difference

Table 3: Studies comparing conventional endoscopy with endoscopic ultrasound guided drainage of pancreatic pseudocysts

Despite proven benefits, many authors have questioned the necessity of using EUS for endoscopic drainage [65]. In addition to enabling patients with non-bulging fluid collections to be endoscopically drained, EUS also reduces complication rates by locating the safest site for initial puncture. Furthermore, performing EUS prior to drainage can help in better characterization of neoplastic cystic lesions which might be misinterpreted as pseudocysts lesions [65,66]. Overall, endoscopic drainage for pancreatic pseudocysts has shown impressive results with complete resolution of pseudocysts in 65% to 95% of cases, complication rates of 0% to 37%, and minimal mortality associated with the procedure [67].

In a recent publication, the authors compared endoscopic and surgical cystogastrostomy for pseudocysts on an open-label, single center randomized controlled trial [68]. The authors randomized 20 patients in each group who were compared for rates of recurrence at a 24 month follow-up period. The authors reported no differences between the two groups in terms of treatment successes, complications, or re-interventions. However, the endoscopic cohort of patients had superior outcomes in other ways. The length of hospital stay was shorter in the endoscopy group (2 days vs 6 days, p < 0.001). Also, these patients performed better on physical component scores (p=0.19) and mental component scores (p=0.025) on longitudinal follow up despite being equal at baseline with the surgical group. Furthermore, on cost-effectiveness analysis, the endoscopy group fared better with a lower mean cost as compared to the surgical group (\$7011 vs \$15,052, p=0.003). Another study comparing surgical and endoscopic approaches for pancreatic pseudocysts did not find any differences in complications or resolution rates between the two [69].

Complications during endoscopic drainage can occur either directly related to the procedure or as an indirect consequence of placement of stents and drains [27,35]. Major complications of endoscopic pseudocyst drainage include infections (0%-8%), bleeding (0% - 9%), and retroperitoneal perforation (0% - 5%)[67]. In patients with suspected infected cases, wide opening of the cyst enterostomy is necessary to reduce the incidence of infected cyst complications

[34,39]. Bleeding from accidental injury of the arterial or variceal blood vessels during transmural penetration of the gut wall can have catastrophic consequences and requires emergent surgery or sclerotherapy. Use of EUS guidance with Doppler imaging can also decrease the risk of inadvertent vascular puncture. The transpapillary approach has been associated with complications like pancreatitis, sepsis, as well as abscess formation [27]. Stent related complications include dislocation and clogging with the possibility of subsequent infection.

Various studies have examined the rates of complications for EUS guided procedures as well. In one such study on 148 patients, the authors reported that complications were rare with EUS guided drainage of PFCs [70]. Perforation at the site of puncture was only seen in two patients who underwent transmural stenting for a pseudocyst in the uncinate region. Not surprisingly, PFCs located in the uncinate process were at a higher risk of perforation (50% vs 0%, p=0.0005).

Novel methods

Success with endoscopic techniques described above has ushered an era of unprecedented clinical progress. Newer and more advances procedural techniques are being increasingly reported and hold the promise of improved patient outcomes in the future. Natural Orifice Transluminal Endoscopic Surgery (NOTES) is one such technique that has garnered considerable attention in recent times. One study described successful NOTES-stapled pseudocystogastrostomy with a peroral flexible stapler in six patients [71].

Transenteric drainage of pseudocysts with poor adherence to the bowel wall risks leakage and perforation. Fully Covered Self Expanding Metal Stents (FCSEMS) avoid the need for tract dilatation and may therefore improve safety. In a study evaluating their efficacy in 18 patients with indeterminate adherence of PFC to the bowel wall, the authors achieved technical success in 100% patients and cyst resolution in 78% [72]. Successful placement of self expanding stents

was achieved in all seven cases in another study with achievement of complete resolution in 9/10 cysts [73]. Another study verified their safety and efficacy in infected pancreatic fluid collections [74]. Novel uncovered lumen apposing, metallic stents have been developed in Japan for serial access to pseudocysts and have shown promising results in their pilot study [75].

Walled-Off Pancreatic Necrosis

Walled off pancreatic necrosis (WOPN) are heterogeneous collections of pancreatic fluid with necrotic debris surrounded by an encapsulating wall that comprise of less than 5% of peripancreatic fluid collections [76]. These represent the mature encapsulated form of acute pancreatic necrosis resulting from insufficient perfusion of pancreatic parenchyma necessary to support metabolic requirements. CT scans have been shown to effectively differentiate WOPN from pseudocysts [77]. Larger size, extension to paracolic space, irregular wall definition, presence of fat attenuation debris in PFC, pancreatic deformity or discontinuity were found to be associated with WOPN. In contrast, presence of pancreatic ductal dilation was associated with pancreatic pseudocyst. This study found that using a CT score of 2 or more as threshold, CT differentiated WOPN from pseudocyst with an accuracy of 79.5 – 83.6%. It is generally recommended to defer treatment until these lesions have an encapsulated wall around them as premature intervention has been associated with poor outcomes [77]. Until very recently; surgical debridement was the gold standard for WOPN. Success with endoscopic drainage of other PFCs encouraged the development of transluminal endoscopic techniques to remove retroperitoneal pancreatic necrotic collections under direct visual control. Ever since the first report of a direct transgastric endoscopic debridement of WOPN by Seifert et al. [78] minimally invasive endoscopic techniques have continued to evolve. Transluminal access can be gained either through conventional techniques or by using EUS. Since EUS is associated with higher efficacy and lower complication rates in non-bulging collections, it could be preferentially employed wherever feasible.

Endoscopic ultrasound can be used to determine the appropriate site for gaining access, following which the enterostomy site is dilated with low-profile controlled radial expanding balloons, biliary dilating catheters, or a Soehendra stent extractor. Experts have recommended a fistulous tract of 20 mm diameter at the time of initial drainage [79]. Formation of the fistulous tract is followed by fluid aspiration for Gram stain and culture which can be used to direct antibiotic therapy. Direct necrosectomy can then be performed by driving a forward viewing endoscope into the gut wall and subsequent removal of necrotic debris using snares, baskets, and water jets. Hydrogen peroxide is employed to liquefy the debris which can then be removed through serial procedures. Stents are left after each procedure to aid in maturation of fistulous tract to allow debridement by gastric and bile acids. In case the draining cyst fluid is thick or contains debris, the endoscopist should place additional large-bore stents and nasocystic tubes. These nasocystic tubes can be lavaged every 3 to 4 hours or flushed continuously with sterile normal saline for several days to weeks depending on patient tolerance and the amount of debris. It is noteworthy that direct endoscopic necrosectomy does not have to be done at the time of the index drainage procedure. Once temporary drainage is established, subsequent debridement can be performed through a mature tract on repeat endoscopic procedures.

Outcomes with endoscopic procedures

In a retrospective review of 53 patients who underwent endoscopic transmural drainage/debridement of WOPN after pancreatic necrosis, the authors reported a final success rate of 81% (43 of 53 patients) while 10 patients (19%) had persistence of WOPN at a median follow up of 6 months [80]. Open operative intervention was required in 12 patients (23%) at a median of 47 days after initial endoscopic drainage. On further analysis, preexisting diabetes mellitus, size of WOPN, and extension of WOPN into the paracolic gutter were found to be predictors for need for subsequent open operative treatment. In one of the largest multicenter studies on the role of direct endoscopic necrosectomy in patients with WOPN, Gardner and coworkers examined the outcomes in 104 patients from six tertiary medical centers [81]. Successful resolution was achieved in 95 patients (91%) with a mean time to resolution of 4.1 months from the initial procedure. These patients required a median number of 3 procedures with 2 debridements. Complications were seen in 14% of patients which included 5 retrogastric Perforations/pneumoperitoneum, all of which were managed nonoperatively. On univariate analysis, a body mass index > 32 was found to be associated with a failed endoscopic procedure.

Investigators of the GEPARD study reported a similar success rate of 80% in 93 patients undergoing a mean of six interventions for WOPN after an attack of severe acute pancreatitis [82]. At the 30 day follow-up, complication rate in this study was 26% along with a mortality rate of 7.5%. Long term follow-up revealed impressive results in the form of sustained clinical improvement in 84% of patients. The Dutch Acute Pancreatitis Study group recently published their findings from the PENGUIN trial that randomized 22 patients with necrotizing pancreatitis to undergo either open surgical necrosectomy or transgastric endoscopic necrosectomy [83]. The primary endpoint of the study was the postprocedural Proinflammatory response measured by serum Interleukin-6 (IL-6) levels while secondary endpoint was a predefined composite endpoint of major complications or death. The investigators found that endoscopic necrosectomy reduced the postprocedural IL-6 levels as compared to the surgical technique ($p=0.004$). The composite clinical endpoint occurred less often after endoscopy with lower rates of complications in the form of new-onset multiple organ failure, intra-abdominal bleeding, pancreatic fistula and death. Direct transluminal endoscopic necrosectomy has therefore been shown to have impressive results though further optimization of endoscopic techniques is needed to reduce morbidity and mortality associated with the procedure.

Novel methods

Newer techniques and approaches are being consistently developed to treat these lesions in an effort to improve clinical outcomes. A report by Wehrmann et al. described successful endoscopic necrosectomy of infected pancreatic necrosis through dual access (gastric and duodenal) [84]. Multiple transluminal tracts for drainage of symptomatic WOPN have been shown to have a higher rate of success (92% vs 52%) than conventional single transluminal drainage technique [85]. Antillon et al. described a novel method of placing a much larger diameter removable metallic esophageal stent into the pancreatic necrotic cavity, successfully resolving patient symptoms [86]. Successful transduodenal endoscopic necrosectomy performed via pancreaticoduodenal fistula dilated to debride the necrotic tissue has also been reported [87].

Study	Study design and year	No. of patients	Clinical success	Complications	Comments
Papachristou et al. [80]	Retrospective (2007)	53	43 (81%)	12 (23%)	Diabetes, size of WOPN and extension into paracolic gutter predict operative therapy subsequently
Gardner et al. [81]	Retrospective (2011)	104	95 (91%)	15 (14%)	-
Seifert et al. [82]	Retrospective (2009)	93	74 (80%)	24 (26%)	Mortality rate of 7.5% at 30 days
Bakker et al. [83]	Endoscopic vs surgical necrosectomy (2012)	10 vs 12	-	20% vs 80%*	Endoscopy drainage associated with reduced IL-6 levels post-procedure, reduced incidence of multiple-organ failure and pancreatic fistula

*Represents statistically significant difference

Table 4: Endoscopic drainage of walled-off pancreatic necrosis

Experience from Comparative Studies

Endoscopic drainage has been used with variable degrees of success in all kinds of pancreatic fluid collections including walled off necrosis. Studies comparing their outcomes have enhanced our knowledge on the efficacy of endoscopic techniques in these lesions. Evidence from these studies have suggested that endoscopic drainage outcomes vary based on the type of pancreatic fluid collection with worse outcomes in patients with necrosis. In one such study, the comparative outcomes of pseudocysts (acute and chronic) and pancreatic necrosis after transmural and/or transpapillary endoscopic drainage in 138 patients were discussed [45]. The authors reported a success rate of 82% (113 or 138 patients) with a median time to resolution of 40 days. Patients with chronic pseudocysts were more likely to achieve complete resolution (59/64, 92%) than acute pseudocysts (23/31, 74%, p=0.02) or necrosis (31/43, 72%, p=0.006). The study also found a higher complication rate in patients with necrosis (16/43, 37%) than chronic (11/64, 17%, p=0.02) or acute pseudocysts (6/31, 19%, p = NS). When followed up over a median period of 2.1 years after successful endoscopic treatment, 18 out of the 113 patients (16%) were found to have a recurrence of pancreatic fluid collections. Interestingly, the rate of recurrence was higher in patients with necrosis (9/31, 29%) than acute pseudocysts (2/23, 9%, p = 0.07) or chronic pseudocysts (7/59, 12%, p=0.047).

Hookey et al. confirmed these findings and found that patients with organized necrosis did worse when compared to those with acute or chronic pancreatitis after undergoing endoscopic drainage [36]. Combined experience with EUS-guided endoscopic drainage and necrosectomy of pancreatic fluid collections in 80 patients was discussed in another study [88]. Endoscopic necrosectomy was carried out in 49/56 patients with abscesses and infected necrosis. Initial technical success was achieved in 78/80 (97.5%) and clinical resolution of collections was seen in 67/80 (83.8%) patients. Recurrence of fluid collections was seen in 9 of the 67 patients (13.4%). Over a mean follow-up of 31 months, long term success was seen in 58/80 patients (72.5%). Procedural complications included bleeding in 12, perforation in 7, and portal air embolism in 1 and Ogilvie Syndrome in 1 patient.

In one of the largest studies on patients with peripancreatic fluid collections, Varadarajulu et al. published their collective experience with endoscopic transmural drainage (conventional and ultrasound

guided) in 211 patients over a 7 year period [89]. In patients with pancreatic duct leakage, an ERCP stent was placed prior to endoscopic drainage. Among these 211 patients, 45% were found to have pseudocysts while 28% and 27% had abscess and necrosis respectively. The overall treatment success was 85.3% though when analyzed separately; it was found to be much higher for pseudocyst and abscess as compared to necrosis (93.5% vs. 63.2%, p<0.0001). Furthermore, complications developed in 17 patients (8.5%) and were higher for necrosis than pseudocyst or abscess (15.8% vs. 5.2%, p=0.02). Analyzing for predictors of treatment success, the group found that successful treatment was more likely for patients with pseudocyst or abscess than necrosis (adjusted OR = 7.6, 95% CI 2.9 - 20.1, p<0.0001). Based on their observation, the authors convincingly endorsed the use of endoscopic drainage in non-necrotic pancreatic fluid collections. Furthermore, patients with peripancreatic fluid collections who underwent pancreatic duct stenting did considerably better than those who did not (97.5% vs 80%, p=0.01) [90] (Table 4).

Role of Endoscopic Retrograde Cholangiopancreatography

Acute necrotizing pancreatitis can often result in pancreatic ductal disruption [91]. In such patients with partial pancreatic ductal injury or disconnected pancreatic duct syndrome, there is a high rate of recurrence of PFCs on follow-up. Endoscopic retrograde pancreatography can evaluate for pancreatic ductal injury/leak. Newer non-invasive techniques like MRCP can also provide such diagnostic information in patients with suspected pancreatobiliary diseases, and studies comparing ERCP with MRCP have been published [92,93]. However, ERCP provides the added option of therapeutic intervention in patients with pancreatobiliary stones and strictures, biliary leak and pancreatic endotherapy. It also allows diagnosis of pancreatobiliary malignancies through a combination of needle aspiration, brush cytology and forceps biopsy. Table 5 outlines the outcomes from studies on ERCP and stent placement in patients with pancreatic duct injury [48,94-97]. However, it is not routinely done in patients getting endoscopic transmural drainage of pancreatic fluid collections. In one study, the authors routinely performed ERCP in all patients after endoscopic cystogastrostomy for pancreatic pseudocysts to assess and treat pancreatic ductal leak [68]. During ERCP, leak from ductal disruptions were noted in 10 of 20 patients which were treated with placement of 5F transpapillary pancreatic duct stent. At follow-up at 8

weeks, resolution of duct leak was seen in 9 of 10 patients who underwent pancreatic stent placement. The pancreatogram was normal in 5 patients and disconnected duct was seen in the other 5. Transmural stents were left in place indefinitely in all 5 patients with

Disconnected Pancreatic Duct Syndrome (DPDS). At a median follow up of 39 months, no adverse events were recorded in any of these five patients.

Study	Study design and year	No. of patients	Clinical success	Complications
Kozarek et al. [48]	Retrospective (1991)	18	16 (89%)	4 (22%)
Kim et al. [94]	Retrospective (2001)	3	3 (100%)	2 (66%)
Telford et al. [95]	Retrospective (2002)	43	25 (58%)	4 (9%)
Varadarajulu et al. [96]	Retrospective (2005)	97	52 (55%)	6 (6%)
Bhasin et al. [97]	Retrospective (2012)	6	6 (100%)	

Table 5: Table showing outcomes of endoscopic retrograde cholangiopancreatography and stent placement in patients with pancreatic duct injury

Table 6 outlines the results from studies on endoscopic treatment in patients with disconnected pancreatic duct syndrome [98-101]. In one such study on patients with WOPN occurring in association with pancreatic ductal injury, the authors evaluated the consequences of long term indwelling transmural stent placement in 30 patients with WOPN and DPDS. They found that stent migration occurred in 5 patients (17%). However, it led to recurrence of symptoms and PFC in only patient whereas in the remaining 4 patients the stent migration

was asymptomatic [101]. The authors opined that long term stent indwelling stents reduces recurrence rates in these patients. These studies, justify the role of ERCP in patients with pancreatic fluid collections to assess for pancreatic ductal leak. However, the role of ERCP in these patients requires further validation on prospective trials with large cohort of patients with robust clinical follow up to help form.

Study	Study design and year	No. of patients	Clinical success	Complications
Devire et al. [98]	Retrospective (1995)	12	10 (87%)	2 (13%)
Lawrence et al. [99]	Retrospective (2008)	29	22 (76%)	16 (53%)
Pelaez-Luna et al. [100]	Retrospective (2008)	26	19 (73%)	7 (26%)
Rana et al. [101]	Retrospective (2013)	30	30 (100%)	5 (15%)

Table 6: Studies on the endoscopic management of disconnected duct syndrome

Unanswered questions

Since its initial use for drainage of pancreatic fluid collections, the field of endoscopic drainage of pancreatic fluid collections has come a long way notwithstanding the vast array of technical and clinical advancements in this field, certain questions still remain unanswered. The descriptive parameters defining various kinds of peripancreatic fluid collections need to be refined further. Furthermore, criteria defining the degree of necrosis still remain undefined. The optimal number of stents to be placed and the optimal duration of stent placement still need to be fully ascertained through well planned clinical studies. In a prospective randomized trial, the investigators recruited 28 patients who had undergone endoscopic transmural drainage of pancreatic fluid collections and randomized them into two groups [102]. While 15 patients had their stents left in place indefinitely, 13 patients underwent early stent retrieval after a median of 2 months. At a median follow up of 6 months, pseudocyst recurrence was seen in 5 patients who had their stents removed, as compared to none in the other group with persistent stent-facilitated drainage (p=0.013). Though the study has obvious drawbacks in the form of a small sample size, it does suggest that stent removal could

predispose patients to pseudocyst recurrence likely due to premature closure of cystenterostomy. Another issue of vital importance is the nebulous role of pancreatic necrosectomy after endoscopic drainage. It is still unclear when endoscopic procedures suffice and when a surgical intervention is needed. As shown in a recent study, a step-up approach utilizing percutaneous drainage of necrotizing pancreatitis followed by minimally invasive retroperitoneal necrosectomy has been shown to have better outcomes than open necrosectomy [6]. Also, the optimal technique of necrosectomy needs further exploration on trials. Furthermore, existing data has been mostly derived from studies employing endoscopes with an oblique-viewing endosonography. Though the forward viewing endoscope seems promising, evidence is still lacking on its efficacy in draining pancreatic pseudocysts.

Summary

Peripancreatic fluid collections are associated with significant morbidity and mortality. Recent advances in endoscopic technology have improved our understanding of these lesions and improved clinical outcomes. While conventional endoscopy is appropriate for patients with PFCs within easy endoscopic reach, EUS guided drainage

is considered the gold standard in patients with nonbulging PFCs and patients with portal hypertension. Not only does EUS reduce complication rate by localizing the safest site for puncture and drainage, it also maximizes the number of patients amenable to endoscopic drainage by treating collections which would have been hard to treat by the blind approach. However, most of the data available is from retrospective studies and is marked by obvious drawbacks in the form of inconsistent terminology, differences in methodology, selection bias and lack of uniform treatment guidelines. This means that this area is still ripe for further clinical investigation on randomized trials. Due to the low incidence and limited number of eligible patients, multicenter collaboration will be essential to accrue sufficient number of participants to allow a robust analysis. Effective use of endoscopic techniques to manage peripancreatic fluid collections will eventually depend on optimizing timing and localization of transmural access, duration of stent placement along with perfecting the tools to assist in safe drainage/debridement of these collections.

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