Modern Management of Pancreatic Fluid Collections

Iman Andalib, MD, Enad Dawod, MD, and Michel Kahaleh, MD, FASGE

Abstract: The last decade has seen dramatic shift in paradigm in the management of pancreatic fluid collections with the rise of endoscopic therapy over radiologic or surgical management. Endosonographic drainage is now considered the gold standard therapy for pancreatic pseudocyst. Infected pancreatic necroses are being offered endoscopic necrosectomy that has been facilitated by the arrival on the market of large diameter lumen-apposing metal stent. Severe pancreatitis or failure to thrive should receive enteral nutrition while pancreatic ductal disruption or strictures are best treated by pancreatic stenting.

Key Words: pseudocyst, pancreatic necrosis, pancreatic fluid collection, endoscopic necrosectomy, lumen-apposing metal stent

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Pancreatic fluid collections (PFCs) may result from pancreatic trauma, acute and chronic pancreatitis, and pancreatic surgery.[1,2] In 1993, the Atlanta International Symposium on Acute Pancreatitis allowed to further characterize and manage PFCs. This classification was further revised in 2012 with addition of acute peri-PFCs, pancreatic pseudocysts, acute necrotic collections (ANCs), and walled-off pancreatic necrosis (WOPN).[2,3] This revision was carried out to update terminology and facilitate treatment planning among multidisciplinary teams including radiologists, gastroenterologists, and surgeons. A pancreatic pseudocyst often results from acute peri-PFCs and usuallymatures after 4 weeks.[1,2,4,5] Pseudocysts arise from ~10% to 26% of acute pancreatitis and about 20% to 40% of chronic pancreatitis.[5] They are encapsulated collection of amylase-rich fluid with well-defined inflammatory wall, which contain no necrosis. WOPN is a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis which typically occurs >4 weeks after an acute episode of necrotizing pancreatitis.[2] These collections differ from acute peri-PFCs and ANCs which are yet to develop a well-defined wall and often resolve with conservative management.[5] Currently, the diagnosis is best made by computed tomographic (CT) scanning or magnetic resonance imaging.[6] Endoscopic ultrasound (EUS) can also further characterize these collections.[7] Ultimately, as these collections mature, differentiation may become more difficult; thus, the final diagnosis should correlate with the clinical condition of the patient.

INDICATION FOR DRAINAGE

The indication and the time for drainage have also become an important controversy in the past few years.[8,9] Most acute PFCs such as acute peri-PFCs and ANCs will resolve spontaneously without any intervention. However, Pancreatic pseudocysts and WOPN might require intervention if causing symptoms or complications such as gastric obstruction, biliary obstruction, infection, or rapid increase in size. In the past, surgery has been the primary method of treatment; however, with more technical development and experience, endoscopic drainage has now become the preferable approach at numerous centers, with fewer adverse events, higher cost effectiveness, shorter hospital stays, similar efficacy, when it is compared with surgical cystogastrostomy.[10,11]

The time and the preferred method of drainage for pancreatic pseudocysts have been a debate over the past few years. In the past, pancreatic pseudocysts that were ≥6 cm and/or persistent (≥6 wk) would require drainage.[4] Some recent studies have suggested that longer periods of observation are safe and effective in permitting spontaneous resolution if the patient is stable.[5] However, if drainage is required, then it should be performed if possible after 4 weeks to allow for encapsulation and to reduce possible adverse events. In 2011, Van Santvoort et al[12] demonstrated that mortality was reduced as the time from hospital admission to intervention of the PFC was increased (0 to 14 d: 56%; 14 to 29 d: 26%; and >29 d: 15%; $P < 0.001$).

However, other studies have advocated that prolonged waiting is unnecessary for pseudocysts and suggested that a pseudocyst is unlikely to resolve spontaneously if there are evidence of chronic pancreatitis, a thick wall surrounding the pseudocyst, pancreatic duct (PD) anomaly, or persistence >6 weeks.[9,13] Recently, American Society for Gastrointestinal Endoscopy (ASGE) prepared a guideline to further address this controversy; based on this report, the time for drainage is accepted after 4 weeks to allow for better encapsulation and to diminish adverse events postdrainage. This is in the absence of an infected collection, which mandate drainage, if suspected.

NUTRITIONAL SUPPORT

Early nutritional support has been proven to significantly reduce mortality and systemic infection and its use has been a part of management of acute pancreatitis for almost 2 decades. In 2010, a meta-analysis assessed all the randomized trials comparing enteral nutrition versus TPN in severe pancreatitis and showed that enteral feeding was superior to TPN in reducing mortality. Enteral nutrition and its early initiation have been evaluated extensively in the treatment of PFCs with similar results.[3] In 2013, Li et al[14] demonstrated that patients who received early initiation of enteral nutrition (defined as within 48 hours of admission) had a significantly lower rate of complications. However, the literature still lacking studies on which type of enteral nutrition formula would be superior.

PD DISRUPTION

PD disruption has also been associated with increased risk of recurrent pancreatitis, recurrence of PFCs and decreased rate of PFC resolution after drainage.[3,15–19]

From the Department of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY.

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Address correspondence to: Michel Kahaleh, MD, FASGE, Weill Cornell Medical College, 1305 York Avenue, 4th Floor New York, NY 10021 (e-mail: mkahaleh@gmail.com).

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Therefore, exploring the PD for any disruption via ERCP or MRCP plays an important factor in treatment success. In 2009, Nealon et al[16] showed that PD disruption decreased the rate of spontaneous resolution of pseudocyst. The authors were able to show that ductal changes predict patients with necrotizing pancreatitis who are most likely to have immediate and delayed complications.

In addition, in 2010, Trevino et al showed improved PFC resolution in patients who underwent PFC drainage with PD stenting compared with PFC drainage alone (97.5% vs. 80%).[2,17]

MANAGEMENT OF PANCREATIC PSEUDOCYSTS

Surgical Drainage

In the past, surgical drainage was the primary method in the management of pancreatic pseudocysts with reported recurrence rates between 2.5% and 5% postsurgical drainage as well as complication rates up to 30% in several studies[3,20] Open or laparoscopic surgical cystogastrostomy includes an anastomosis between the lumen of the PFC and the stomach or small intestine using suturing or stapling device.[3,14]

However, with continuous advancements in endoscopic devices, surgical approach is falling out of favor. During recent years, multiple studies have compared endoscopic and surgical drainage of the pseudocysts; based on these studies, the endoscopy success rates ranged from 82% to 100% and a mortality rate of $\leq 1\%$.[21] Recently, a single-center randomized trial compared endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in 40 patients; with the primary endpoint being pseudocyst recurrence after a 2-year follow-up period. By the end of the 2-year follow-up, none of the patients in the endoscopy group had recurrence. In addition, authors were able to show that the endoscopic drainage was linked with shorter length of hospital stay and more cost effective than surgery.[11,22]

Percutaneous Drainage

Percutaneous drainage is achieved by insertion of a drainage catheter into the PFC by ultrasound or CT guidance.[23] Multiple studies have compared percutaneous approach with surgical drainage. In 2005, Morton et al[24] in the largest study so far that included more 14,000 patients (surgical: 6409 and percutaneous: 8121) were able to show surgical drainage has less complications, length of stay, and inpatient mortality in comparison with percutaneous drainage (5.9% vs. 2.8%; $P < 0.0001$). Although, a risk of selection bias may be apparent in this study, as the patients who were poor surgical candidates received percutaneous drainage. Similarly, Heider et al[25] showed patients who underwent percutaneous drainage had a higher complication rate (64% vs. 27%), a longer hospital stay (45 ± 5 vs. 18 ± 2 d) and higher mortality (16% vs. 0%) than patients treated by surgery. These results contradict with results from older and smaller studies which favored percutaneous approach.[26,27] Other studies have been conducted to compare this technique with endoscopic approach. In 2014, in a single-center retrospective study, Akshintala and colleagues, directly compared percutaneous drainage (40 patients) with endoscopic drainage (41 patients). There were no significant differences in technical success rate (97.5% vs. 90.2%; $P = 0.36$), clinical success (72.5% vs. 70.7%; $P = 0.86$) and adverse events (15% vs. 14.6%; $P = 0.96$) between percutaneous approach and endoscopic approach, respectively. However, shorter length of hospital stay (6.5 ± 6.7 vs. 14.8 ± 14.4 d; $P = 0.001$) and lower rates of reintervention (9.8% vs. 42.5%; $P = 0.001$) were found in patients who underwent endoscopic drainage.[28] In a time, where patient satisfaction and health care cost have been scrutinized, it would be very difficult to justify percutaneous drainage of an endoscopically reachable collection.

Endoscopic Drainage

Endoscopic procedures are being increasingly used for drainage of PFCs. Currently, these approaches are transmural and transpapillary route.[29,30] Multiple factors such as location of the PFC or ductal communication with the fluid collection play a role in the management. The transmural approach involves creating a tract through the gastric or duodenal wall with subsequent balloon dilation and placement of ≥ 1 stents (typically double-pigtailed plastic stents). However, due to their narrow lumen, these stents may cause premature occlusion in up to 18% of cases requiring placement of additional stents or repeat stent exchange.[3] In addition, placement of multiple stents into the PFC can be technically challenging and time consuming specially using a 10 F stents.[31] Fully covered, self-expanding metal stents (SEMSs) with a larger lumen diameter (> 10 mm) offered more rapid drainage and less likelihood of stent occlusion.[32] However, these stents could migrate, with potential leakage and inefficient drainage. Because of these concern, some endoscopists place an anchoring plastic double pigtail stent within the covered SEMS to avoid migration.[2,33] Until recently, there was no strong data to support that plastic stents are inferior to SEMSs for resolution of these cysts.[34] In 2015, a large retrospective study directly compared the technical and clinical outcomes, success rates, and adverse events of EUS-guided PFC drainage by using double-pigtailed plastic stent and metal stents. The authors demonstrated that complete resolution of PFCs by using metal stents was higher compared with plastic stents.[31]

It is estimated that in 42% to 48% of the cases, there is no bulging impression, limiting the safety and efficacy of direct endoscopic drainage.[35] Because of these limiting factors, EUS-assisted approach drainage has become the gold standard. Indeed, EUS allow localization of the PFC when the luminal compression is absent, avoid vascular structure and confirms the components in the PFC such as solid or necrotic materials.[36–38]

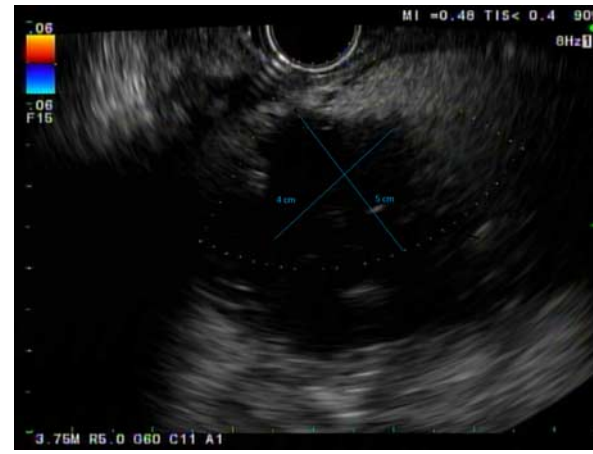

FIGURE 1. Endosonographic measurement of pancreatic fluid collection from the stomach before puncture. full color online

FIGURE 2. EUS-guided 19 G needle puncture. full color online

Lumen-apposing metal stents (LAMS), which are deployed under EUS guidance, have been added to our arsenal to facilitate PFC drainage. In the recent years, the safety and efficacy of this device has been evaluated in various studies. In 2015, Shah and colleagues demonstrated a technical success rate of 91% and a PFC resolution rate of 93% using this type of stents. Following this study, few studies compared the lumen-apposing stents to conventional double-pigtailed plastic stents, which mostly showed similar efficacy; however, LAMS include single-step deployment and minimal stent migration.[39]

The approach to endoscopic drainage of PFCs is transpapillary approach. If there is evidence that the pseudocyst communicates with the PD, then a transpapillary stent can be placed directly into the collection via PD. This approach can be performed during an ERCP.[23] However, most expert now, recommend treating the duct by either sealing a PD leak or crossing a ductal stricture.[40] Studies have showed that complete bridging of the leak has greater resolution rate for collections in the body and tail compared with the pancreatic head.[41] Indeed, transpapillary drainage offer inadequate drainage of larger PFCs, stent-induced scarring of the PD and/or ERCP-related pancreatitis.[2,42,43] Tervino et al showed a higher clinical success rates for transmural drainage in those patients who received transpapillary stents for duct disruption.

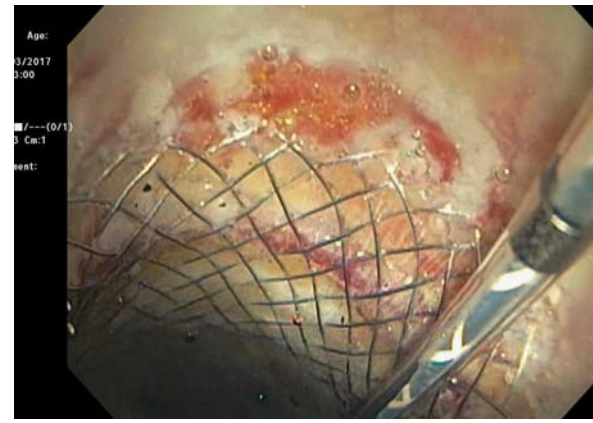

FIGURE 4. Lumen-apposing metal stent Balloon dilation.

MANAGEMENT OF WOPN COLLECTIONS

WOPN is a mature, encapsulated collection, which contained solid necrotic debris with or without fluid that occurs >4 weeks after an acute episode of necrotizing pancreatitis.[44] A large percentage of WOPN would not resolve spontaneously and require intervention if symptomatic. Traditionally, these patients would undergo an open surgical debridement. However, this approach has been associated with complication rates as high as 72%.[45–47]

Because of these high complication rates, minimally invasive surgeries have been developed for the treatment of WOPN. There are multiple small studies throughout recent years looking at the safety and efficacy of these laparoscopic techniques with a survival rate as high as 85%.[46,48] The current laparoscopic techniques have been associated with lower complications compared with open surgeries; however, none of those technique address the PD and only few studies actually compared this technique with conventional open necrosectomy.[47,49] On the basis of a meta-analysis that was published in 2013 by Cirocchi et al[50] mortality was 30% after open necrosectomy versus 17% after laparoscopic technique (odds ratio 0.43; 95% CI, 0.01-8.60; $P=0.06$), which is still very high.

Given the high morbidity and lack of convincing data, the management of these types of collections has been changed over the past few years. Percutaneous drainage was therefore proposed for the management of WOPN as initial therapy. The percutaneous drain can be placed in a retro peritoneal or

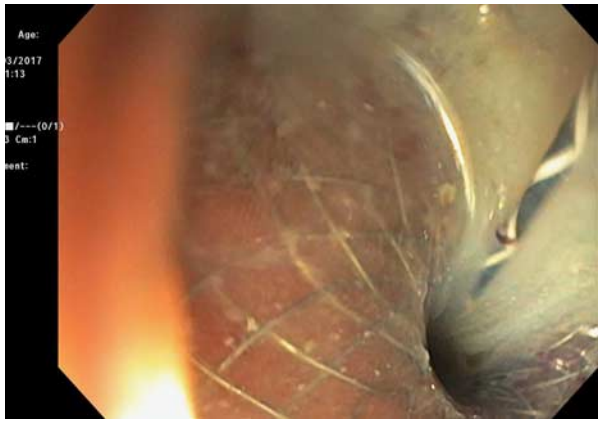

FIGURE 3. Transgastric deployment of Lumen-apposing metal stent through the created fistula.

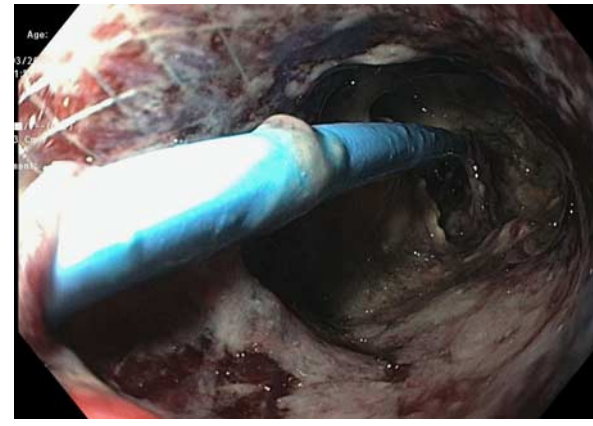

FIGURE 5. Endoscopic visualization of the necrosis through the Lumen-apposing metal stent.

TABLE 1. Characteristics of Studies Using Lumen-apposing Metal Stents (Single Arm)

References, Country	Design	N	Age	Males	Etiologies	Type of PFC	Dimensions (cm)	Location of PFC	Stent Name and Sizes	Tract Dilation	Follow-up
Lakhtakia et al,[64] India	Retrospective	205	34.8	181	Gallstones 55 Alcohol 91 Idiopathic 52 Other 7	WON 205	10.77 ± 2.81	NR	Nagi 10×20 mm 12×20 mm 14×20 mm 16×20 mm	6 F cystotome and balloon dilator (6 mm)	12 mo
Sharaiha et al,[65] USA	Retrospective	124	54.2	75	Gallstones 59 Alcohol 25 Idiopathic 16 Trauma 6 Autoimmune 4 Others 14	WON 124	10.5 ± 43.2	Head 14 Body/tail 110	AXIOS 15×10 mm 10×10 mm	Balloon dilator (4 or 6 mm) 13 cases used cystotome also	4 mo
Gornals et al,[66] Spain	Retrospective	13	52.6	9	Gallstones 5 Alcohol 5 Idiopathic 3	WON 13	12.4 ± 2.94	NR	AXIOS 15×10 mm 10×10 mm	6 F cystotome and balloon dilator (10 mm)	13 mo
Rinninella et al,[67] International	Retrospective	93	60	71	Gallstones 28 Alcohol 23 Chronic pancreatitis 13 Postsurgical 5 Idiopathic 17 Other 7	WON 52 PP 18 PA 19 APFC 4	10 median	NR	Hot AXIOS 15×10 mm 10×10 mm	Hot AXIOS	10 mo
Walter et al,[63] Netherlands	Prospective	61	55	38	Gallstones 19 Alcohol 22 Postsurgical 6 Idiopathic 9 Other 5	WON 46 PP 15	9 median	Head 7 Neck 4 Body 35 Tail 11 Entire 2	AXIOS 15×10 mm 10×10 mm	Cystotome or balloon dilator	NR
Shah et al,[39] International	Prospective	33	53	18	Gallstones 6 Alcohol 6 Postsurgical 4 Idiopathic 15 Other 2	WON 11 PP 22	9 ± 3.3	NR	AXIOS 15×10 mm 10×10 mm	Bougie or balloon dilator	NR

APFC indicates acute pancreatic fluid collection; NR, not reported; PFC, pancreatic fluid collection; PP, pancreatic pseudocysts; RCT, randomized controlled trial; WON, walled-off pancreatic necrosis.

transperitoneal approach under ultrasound guidance or CT guidance. There have been many studies looking at the safety and efficacy of this technique with success rate, which varies from 30% to 50% and mortality rate up to 15%.[51] This technique has been associated with multiple complications such as pancreaticoenteric/pancreaticocutaneous fistulas.[51–57] Therefore, a step-up approach has been designed to improve the rate of clinical success. Initially a percutaneous drain is placed followed by minimally invasive retro peritoneal necrosectomy. This approach was evaluated in the PANTER trial where patients with WOPN assigned to either primary open necrosectomy or a step-up approach.[52] The authors in this trial demonstrated that the step-up approach was associated with a lower rate of major complications and mortality when compared with open necrosectomy. However, there is still risk of developing a chronic pancreaticocutaneous fistula with this approach.[53]

Because of these unsatisfactory results, endoscopic methods were examined for further managing these types of collections. Baron and colleagues first described endoscopic necrosectomy in 1996. This was performed with deployment of plastic stents and placement of a nasocystic drain without direct mechanical debridement in 11 patients. The overall success rate was 81% and complication rate was 36%.[58] Following this study, direct endoscopic necrosectomy (DEN) was introduced as the new modality for the treatment of these collections. Using EUS, the collection can be accessed safely through the gastric or duodenal wall via a fistulous tract. Subsequently, the tract is dilated to allow the mechanical debridement of the necrotic tissues under direct visualization of the endoscope.[58] Seewald et al[59] first described this technique with a 91% WOPN resolution rate in 13 patients. During DEN, hydrogen peroxide in a 1:5 or 1:10 dilution with normal saline can be used to dissolve necrotic debris.[3] DEN can be performed every 48 to 72 hours until complete removal of all necrotic debris.[60] This technique is proven to be safe but complications such as perforation, self-limited pneumoperitoneum and bleeding have also been reported.[3] In a multicenter study of 93 patients undergoing DEN, Seifert et al[61] showed 80% clinical success rate, with a 23% complication rate and 7.5% mortality rate. In 2012, in a randomized control trial, Bakker et al[62] were able to show DEN resulted in lower complication rate when compared with surgical necrosectomy. Furthermore, the authors were able to show that DEN reduced the levels of inflammatory markers (post-procedural IL-6) as well as the adverse events ($P = 0.03$) when compared with surgical drainage ($P = 0.004$).[62]

The usage of the LAMSs has also been assessed for the drainage of WOPN. The addition of these stents have allowed for a larger drainage lumen allowing access to the necrotic material with the endoscope (Figs. 1–5). In 2015, a prospective multicenter study evaluated 46 patients with WOPN who undergone EUS-guided drainage with AXIOS (Boston Scientific, Natick, MA) showing a clinical success rate of 81%, with an overall major complication rate of 9% due to stent occlusion.[63] Additional studies have looked at the safety and efficacy of LAMS in WOPN management with similar conclusions (Tables 1–3).[3]

CONCLUSIONS

The last decade has seen a shift of paradigm in the management of PFC. Endoscopic drainage has become the preferable approach for the management of symptomatic fluid collections at various centers, with fewer adverse events, higher cost effectiveness, shorter hospital stays and similar

TABLE 2. Summary of Results From Included Studies Using Lumen-apposing Metal Stents (Single Arm)

References	Technical Success	Clinical Success	Adverse Events	DEN	Stent Removal	Quality
Lakhtakia et al,[64] 2016	203	198	2 major bleeding 2 Perforation 2 symptomatic internal migration 3 symptomatic external migration 21 occlusions with endoscopic interventions	23	198	Good
Sharaiha et al[65]	124	107	2 major bleeding 7 infection that required endoscopic intervention 7 migration during DEN that required stent replacement or repositioning 7 occlusion that required stent deocclusion or repositioning	78	124	Good
Gornals et al[66]	13	13	1 migration/infection 1 occlusion/infection 2 major bleeding	13	13	Fair
Rinninella et al[67]	WON 51 PP 18 PA 19 APFC 4	WON 47 PP 18 PA 19 APFC 4	1 massive bleeding 1 perforation 1 pneumoperitoneum 1 stent migration during DEN 1 infection	33	83	Good
Walter et al[63]	60	WON 35 PP 13	4 infection/occlusion 1 perforation	15	47	Good
Shah et al[39]	30	27	1 partial occlusion that lead to stent removal 1 dislodgment during DEN that lead to precut and surgical debridement 1 fever that prolonged hospitalization 1Abd pain requiring endoscopy	11	29	Good

APFC indicates acute pancreatic fluid collection; DEN, direct endoscopic necrosectomy; NR, not reported; PFC, pancreatic fluid collection; PP, pancreatic pseudocysts; RCT, randomized controlled trial; WON, walled-off pancreatic necrosis.

TABLE 3. Characteristics of Included Studies Comparing LAMS Versus Plastic Stents

References and Country	Design	Groups	N	Age	Male	Type of PFC	Technical Success	Clinical Success	Adverse Events	DEN	Quality
Siddiqui et al,[68] USA	Retrospective	LAMS	86	51.5	77	WON	84	77	6 bleeding, 1 suprainfection, 3 perforation, 3 occlusion with infection, 1 other		Good
		Plastic	106	56.3	38	WON	105	86	2 bleeding, 5 suprainfection, 1 perforation, 23 occlusion with infection, 6 other		
Bapaye et al,[69] India	Retrospective	LAMS	72	43.8	62	WON	72	68	2 infection, 2 delayed bleeding, 2 deaths (due to persistent sepsis)	24	Good
		Plastic	61	40.6	54	WON	61	45	16 sepsis, 2 symptomatic migration, 5 bleeding, 4 deaths (due to persistent sepsis).	29	
Ang et al,[70] Singapore	Retrospective	LAMS	12	50	7	WON 4 PP 8	12	11	None	4	Fair
		Plastic	37	56	18	WON 10 PP 27	37	24	1 perforation, 2 bleeding, 1 pneumoperitoneum, 1 infection	15	
Mukai et al[71]	Retrospective	LAMS	43	54.4	37	WON	43	42	1 perforation		Good
		Plastic	27	55.9	21	WON	27	25	3 bleeding, 1 mediastinal emphysema, 1 symptomatic migration, 2 deaths due to sepsis		
Bang et al[72]	Retrospective	LAMS	20	50.7	11	WON 13 PP 7	20	19	2 infection, 2 symptomatic migration	NR	Good
		Plastic	40	52.9	25	WON 26 PP 14	40	37	5 infection, 1 symptomatic migration	NR	
Bang et al[73]	Interim analysis from RCT	LAMS	12	NR	NR	WON	NR	NR	3 bleeding, 1 buried stent, 1 stricture	NR	Methods not reported
		Plastic	9	NR	NR	WON	NR	NR	None	NR	

APFC indicates acute pancreatic fluid collection; DEN, direct endoscopic necrosectomy; LAMS, lumen-apposing metal stents; NR, not reported; PFC, pancreatic fluid collection; PP, pancreatic pseudocysts; RCT, randomized controlled trial; WON, walled-off pancreatic necrosis.

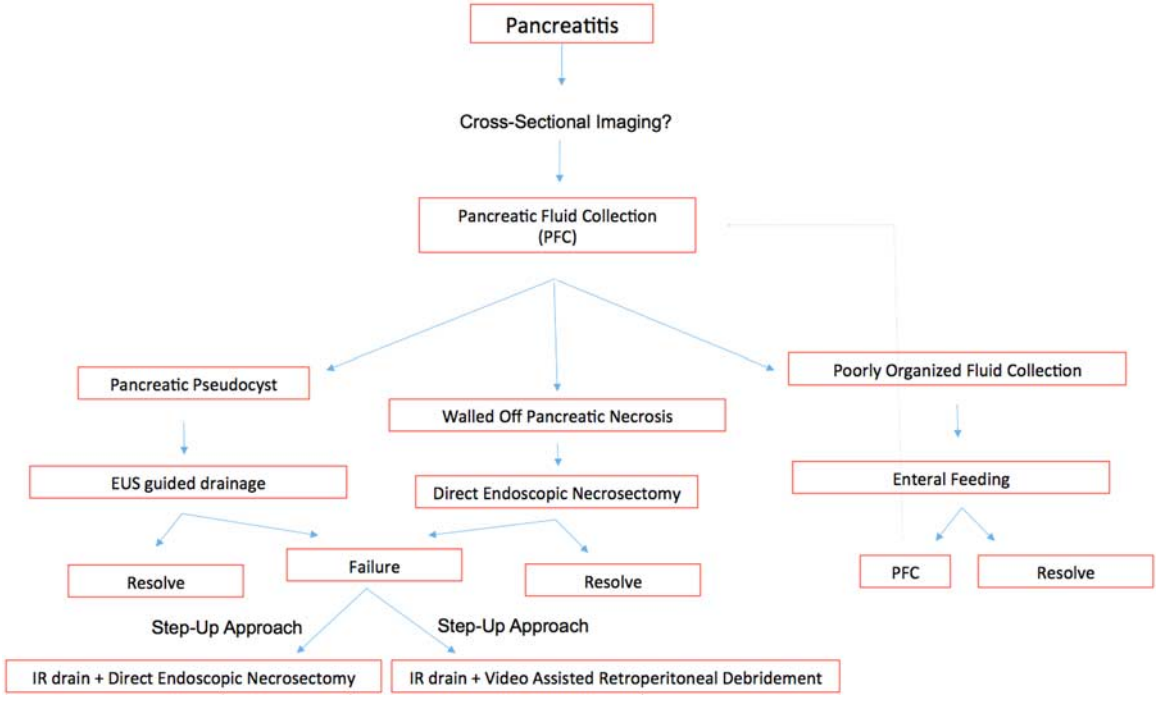

FIGURE 6. Algorithm summarizing modern management of pancreatic fluid collections. EUS indicates endoscopic ultrasound. full color online

efficacy when compared with surgery.[10,11] Poorly organized fluid collection are best managed with pancreatic rest using enteral feeding. Symptomatic pseudocysts require drainage, while WON require debridement (Fig. 6). Finally PD disruption needs to be ruled out in all patients with MRCP or ERCP to decrease the recurrence rate and to increase the resolution rate.

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