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Management of pancreatic collections: an update

Ana García García de Paredes, Sergio López-Durán, José Ramón Foruny, Agustín Albillos and Enrique Vázquez-Sequeiros

Department of Gastroenterology and Hepatology. Hospital Universitario Ramón y Cajal. Universidad de Alcalá. IRYCIS. Madrid, Spain

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Correspondence: Enrique Vázquez-Sequeiros. Department of Gastroenterology and Hepatology. Hospital Universitario Ramón y Cajal. Universidad de Alcalá. IRYCIS. Carretera de Colmenar, km. 9,100. 28034 Madrid, Spain

e-mail: evazquezse@gmail.com

ABSTRACT

Pancreatic fluid collections frequently occur in the context of moderate and severe acute pancreatitis, and may also appear as a complication of chronic pancreatitis, pancreatic surgery or trauma. It is essential to adhere to the Atlanta classification nomenclature that subclassifies them into four categories (acute peripancreatic fluid collections, acute necrotic collections, pseudocysts, and walled-off necrosis) since it has an impact on prognosis and management. Pseudocysts and walled-off pancreatic necrosis are encapsulated pancreatic fluid collections characterized by a surrounding inflammatory wall, which typically develops three to four weeks after the onset of acute pancreatitis. Most pancreatic fluid collections resolve spontaneously and do not require intervention. However, when they become symptomatic or complicated drainage is indicated, and endoscopic ultrasound-guided drainage has become first-line treatment of encapsulated collections. Drainage of pseudocysts is relatively straightforward due to their liquid content. However, in walled-off necrosis the presence of solid necrotic debris can make treatment more challenging and therefore

multidisciplinary management in experienced centers is recommended, being a step-up approach the current standard of care. In this review, we aim to address the management of pancreatic fluid collections with an especial focus on endoscopic drainage.

Keywords: Pancreatic fluid collection. Pseudocyst. walled-off necrosis. Drainage. Lumen apposing metal stents.

INTRODUCTION

Pancreatic fluid collections (PFC) are common complications of interstitial and necrotizing moderate or severe acute pancreatitis, and may also develop as a complication of chronic pancreatitis, pancreatic surgery or trauma. Most PFC remain asymptomatic and resolve spontaneously with no need for intervention. However, drainage is required when they become symptomatic or complicated. The treatment of PFC has notably evolved over the past years, moving from open surgery to minimally invasive techniques, and a step-up approach is currently the standard of care. In this review, we aim to overview the management of PFC with a particular focus on endoscopic drainage, which has emerged as the leading treatment.

DEFINITIONS OF PANCREATIC COLLECTIONS

The revised Atlanta classification categorizes PFC into acute and chronic collections (Fig. 1) according to the development of a well-defined wall (1). Acute necrotic collections and walled-off necrosis (WON) occur in the setting of necrotizing pancreatitis and acute peripancreatic fluid collections and pseudocysts in that of interstitial pancreatitis. However, pseudocysts may also develop in necrotizing pancreatitis in the context of disconnected duct syndrome. In the past, all these lesions were indifferently referred to as pseudocysts. It is crucial to adhere to the updated Atlanta classification and use proper nomenclature as the treatment may differ and to standardize results.

PFC are diagnosed based on imaging findings in the appropriate clinical setting. Computerized tomography (CT) scan underestimates the existence of solid component

within the PFC compared to magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) (2,3). Differential diagnosis with other cystic lesions such as pancreatic cystic neoplasms is essential, especially when incidentally found out of the setting of acute or chronic pancreatitis. Comparison with prior imaging tests when available is helpful, and if the diagnosis persists uncertain, EUS with fine needle aspiration may be necessary to avoid misdiagnosing and mistreating (4,5).

DRAINAGE INDICATIONS

The majority of acute PFC remain asymptomatic and resolve spontaneously. Pseudocysts also resolve without drainage in over 70 % of patients, and up to 50 % of WON, even when infected, resolve with conservative treatment (6,7). Indications for drainage are no longer based on size or persistence of the collection over time but on the presence of symptoms or complications. Drainage of PFC is recommended in the following situations: persistent abdominal pain, gastrointestinal obstruction, biliary obstruction, vascular compression, bleeding, rapidly enlarging collection, recurrent acute pancreatitis, and, most frequently, confirmed or suspected infection (5, 8, 9). Infection can be suspected based on clinical deterioration, persistent systemic inflammatory response syndrome, inflammatory biomarkers, or radiological signs. Procalcitonin has been suggested as the best predictor of infection, with a cut-off value of 3.5 ng/mL offering a sensitivity and specificity of 90 % (10). It is no longer recommended the routine sample of the PFC to confirm infection (8). Considering that PFC resolve spontaneously in most cases and that drainage is not exempt from risks, observation is recommended out of the aforementioned situations.

One of the most important considerations when managing patients with PFCs is deciding when to intervene. It has long been observed that earlier intervention is associated with increased morbidity and mortality (11). Drainage of PFC should be avoided in the early phase and, if possible, delayed until a mature wall has formed which usually occurs three-four weeks after the onset of acute pancreatitis. This is essential for endoscopic and surgical drainage. Endoscopic drainage before four weeks is feasible when indicated, but doing it over 4 weeks decreases mortality (12). If the

clinical circumstances do not allow delaying drainage, percutaneous drainage should be performed (5,8,9).

THERAPEUTIC ALTERNATIVES: A STEP-UP APPROACH

Management of PFC, especially WON due to its necrotic compound, may be challenging and should be preferably carried out at referral centers with experienced teams. WON is associated with significant morbidity and mortality, lower treatment success and higher complications and recurrence rates compared to pseudocysts (13). Therefore, it usually requires a multidisciplinary approach including experts in intensive care, nutrition, interventional radiology, therapeutic endoscopy and pancreatic surgery.

Medical management

Antibiotic treatment

Prophylactic antibiotics to prevent infection are not recommended (9). In patients with suspected infection, empiric intravenous treatment with antibiotics that penetrate into the pancreas (carbapenems, quinolone, and metronidazole) is recommended, as it may delay or even avoid drainage (8,11). If blood or PFC cultures result positive, empiric antibiotic therapy should be tailored accordingly. The duration of antibiotic therapy is not well established and should be monitored by clinical, analytical and radiological evolution (8). Even though routine use of antifungal agents is not recommended, fungal superinfection is a frequent cause of clinical deterioration in these patients and a high index of suspicion is essential (9).

Nutrition

Optimizing the nutritional status of the patient with dietary supplements or artificial nutrition when necessary is imperative to avoid infections and ensure the success of drainage treatments. Enteral feeding is strongly encouraged over parenteral nutrition as it decreases the risk of infected necrosis, the need for surgery, and even mortality. Thus, parenteral nutrition should be reserved for patients who do not tolerate enteral feeding (14). Also, in extensive necrotizing pancreatitis exocrine pancreatic

insufficiency is frequently encountered and must be searched for and treated with pancreatic enzymes (15).

Proton pump inhibitors (PPI)

A recent retrospective study suggested that patients with an endoscopically drained WON receiving PPI may need more sessions of endoscopic necrosectomy to achieve clinical success (16). The proposed mechanism is that PPI may prevent the stomach acid to enter the WON, where it dissolves the solid necrotic debris easing the drainage through the stent and patients on PPI may need more endoscopic necrosectomy sessions to achieve success. Further studies are required before a firm recommendation may be given.

Drainage

Percutaneous drainage

The placement of a percutaneous catheter under CT scan or ultrasound guidance may be an effective treatment for WON in up to 35 % of patients (17). The draining catheter should be removed when it produces less than 50mL/day and the effluent is clear (8). However, this approach has significant disadvantages. First of all, obstruction of the catheter with necrotic material is relatively frequent, and may be prevented by flushing the catheter with saline serum every eight hours (18). In addition, another drawback of the percutaneous treatment is the risk of pancreaticocutaneous fistula formation, which may be reduced by combination with endoscopic drainage (19,20). Nevertheless, it remains an essential modality for WON treatment in certain situations: a) drainage in the early period before a mature wall is formed; b) location inaccessible for endoscopic drainage; c) combination with endoscopic drainage in difficult to treat collections that extend into the pelvis and the paracolic gutters; or d) lack of local expertise to perform endoscopic drainage (9,20).

Surgical drainage

Once the only option for cure, at present open surgery has been relegated to the last step of the treatment algorithm. Nevertheless, surgery still plays an important role in

the treatment of WON after less invasive therapies have failed. In the absence of improvement after endoscopic drainage, minimally invasive surgical necrosectomy, frequently video-assisted retroperitoneal debridement, is the next step. Resolution of necrosis with this technique is achieved in 23-47 % of patients (19). If necessary, then a transgastric laparoscopic or open debridement should be performed. Retroperitoneal laparoscopic or open necrosectomy should probably be the last step, after failure of the previous modalities. If the patient condition allows it, cholecystectomy in cases of biliary pancreatitis can be performed in the same act. A multicenter randomized trial compared primary open necrosectomy versus a step-up surgical approach (percutaneous drainage followed if necessary by minimally invasive retroperitoneal necrosectomy) and found a lower rate of major complications and death in the minimally invasive step-up approach (17). A subsequent long-term follow-up study reevaluating the patients from the previous trial found a lower rate of incisional hernias, pancreatic exocrine insufficiency, and endocrine insufficiency in the minimally invasive group, with similar need for reintervention in both groups (21).

Endoscopic drainage

Management of PFC has considerably changed over the past years and, at present, a step-up approach is broadly recommended being endoscopic drainage the first-line treatment (5,8,9) (Fig. 2). Compared to percutaneous treatment, endoscopic drainage offers better tolerability and avoids pancreaticocutaneous fistula (22). A recent systematic review comparing percutaneous versus endoscopic drainage found a higher clinical success, a lower re-intervention and need of surgery rate and a shorter hospital stay (23). The benefits of endoscopic management over surgery in the treatment of pseudocysts was confirmed in a randomized control trial that showed a shorter hospital stay, lower cost and better quality of life (24). Focusing on WON, endoscopic treatment reduced inflammatory response, measured by lower postprocedural interleukin-6 levels in a pilot comparative study (25). Recently, a prospective randomized superiority study carried out by the Dutch Pancreatitis Study Group compared an endoscopic step-up approach (EUS-guided drainage followed, if necessary, by endoscopic necrosectomy) versus a step-up surgical approach

(percutaneous drainage, followed, if necessary, by minimally invasive retroperitoneal necrosectomy and open necrosectomy). The endoscopic approach was not superior in reducing complications or death, but it had a lower rate of pancreatic fistula and a shorter hospital stay (19). Another recent single-center randomized trial comparing minimally invasive surgery *versus* endoscopic step-up approach found a significantly lower risk of major complications, a reduced cost, and an increased quality of life in the endoscopic group (26).

ENDOSCOPIC TREATMENT: PRACTICAL CONSIDERATIONS

Endoscopic drainage of a pancreatic pseudocyst was first described in 1987 and since then the technique has significantly evolved (27).

Procedure

Before the procedure

- If a pancreatic disruption is suspected, a magnetic resonance colangiopancreatography (MRCP) is recommended (3). If confirmed, a combined approach with an endoscopic retrograde cholangiopancreatography (ERCP) to insert a pancreatic stent together with drainage of the collection should be considered to avoid an ongoing leakage that will lead to PFC recurrence after stent retrieval. Some authors recommend performing MRCP (preferably secretin-enhanced) after drainage and prior to stent removal (8).
- If a pseudoaneurysm of the splenic artery is suspected (unexplained drop in hemoglobin, sudden expansion of the PFC or radiological suggestive findings) a contrast-enhanced CT scan is recommended and, if confirmed, treatment with embolization before endoscopic drainage is strongly recommended (28). Severe hemorrhages have been reported following endoscopic drainage in patients with unsuspected pseudoaneurysms (29).
- If the collection is not infected at the time of drainage, antibiotic prophylaxis before and after the procedure is recommended (30).
- It is important to assure that the collection is encapsulated to decrease the risk of free perforation and to ease the adherence to the gastrointestinal lumen. Also,

proximity of the PFC to the gastrointestinal lumen (< 1 cm) is required (5).

- Endoscopic drainage is a high-risk hemorrhagic procedure. Therefore, it is recommended to discontinue anticoagulants and antiplatelet agents (other than aspirin). International normalized ratio should be < 1.5 and platelet count > 50.000/µL (5).

During the procedure

There are no studies that compare sedation versus general anesthesia for PFC drainage. Considering that most PFC that require drainage will typically present a significant size, in most institutions this procedure is performed under orotracheal intubation.

There are two approaches for the endoscopic drainage of pseudocyst: transpapillary or transmural. Transpapillary drainage by ERCP (placing a pancreatic stent, with or without pancreatic sphincterotomy) is reserved to small collections that communicate with the main pancreatic duct (5). Placement of a transpapillary stent provides continuous drainage of pancreatic fluid and facilitates the resolution of the pancreatic ductal disruption that is responsible for the pseudocyst. Conversely, the majority of pseudocysts and all WON are drained via a transmural approach. There is no benefit to routinely combine transpapillary and transmural drainage (31).

Focusing on transmural drainage, the procedure starts with the identification of the collection through EUS. EUS-guided drainage allows a safer and more effective treatment and it is recommended over “blind” access (8). EUS helps to exclude alternative diagnosis such as pancreatic cystic neoplasms, avoid puncturing perigastric vessels in the setting of segmental portal hypertension, identify pseudoaneurysms, and measure the distance from the collection to the intestinal lumen to target the optimal site for puncture (32,33).

The procedure consists on the creation of a fistula tract between the gastric or less commonly the duodenum wall and the collection, and for that purpose, a stent is placed to maintaining the fistula permeable and allow progressive emptying. The procedure steps are depicted in figure 4. Insufflation with CO2 is recommended to reduce the risk of gas embolism (5, 8). Different types of stents have been employed

and there is still an on-going debate about which is the optimal stent. Initially plastic stents were used. Later, metal stents were introduced, first straight stents, mostly fully covered biliary stents but also esophageal stents, and finally lumen apposing metal stents (LAMS) which were specifically designed for PFC drainage to provide anchorage across luminal structures. The use of LAMS has become further simplified with the development of an electrocautery-enhanced system which allows puncture of the collection using the integrated cautery at the catheter tip. LAMS simplify the procedure, as they obviate the need for prior tract dilatation for stent insertion and reduce over the wire exchanges.

Each stent has its own advantages and disadvantages (Fig. 3). Plastic stents accumulate decades of experience and present good results in terms of efficacy and safety. Metal stents have shown a high rate of clinical success with relatively low adverse events in the Spanish registry (34). A limitation of most studies that evaluate the different stents is that they include both pseudocysts and WON. It is likely that the type of PFC influences the choice of the stent, as drainage of predominantly liquid collections is relatively straightforward with high rates of treatment success (> 80 %) irrespective of the type or size of stents. A randomized study did not show superiority of metal biliary stents over plastic stents for pseudocyst drainage, and a recent meta-analysis found no differences in clinical success or adverse events in patients treated with plastic or metal stents (35,36). Contrarily, the treatment of WON is much more challenging due to the presence of solid necrotic content (13). In this scenario, clinical success may be influenced by the type of stent and drainage may not be enough in some patients that will require debridement of necrotic tissue. There is a large number of studies that evaluate the type of stent in WON, most of them retrospective, single-center and non-comparative, which have reported excellent results regarding clinical success and safety of LAMS. A systematic review of 41 studies with over 2000 patients with WON treated endoscopically found a higher clinical success rate of metal stents versus plastic stents (92 % vs. 80 %) (37). This is probably due to their small lumen that may result in stent occlusion by necrotic debris, needing further interventions to achieve adequate drainage. However, there is a randomized trial that found no superiority of LAMS compared to plastic stents regarding clinical success, number of procedures and

costs. This study raised some safety concerns due to an elevated delayed bleeding rate occurring about three weeks after the procedure. However, it is noteworthy that most of these bleedings occurred in patients with pseudoaneuryms, a rare condition, and that adverse events were much higher in this single-center study than previously reported. There is an ongoing multicenter randomized trial comparing LAMS with plastic stents for WON drainage in Spain (NCT03100578) and its results will hopefully shed some light on this topic. Therefore, the optimal stent for WON drainage remains to be established and at this point both plastic or LAMS are recommended (8). However, even though no definite study has proven them to be superior, metal stents and specifically LAMS with electrocautery-enhanced system are, in our opinion, probably a more favourable option for WON therapy. The theoretical advantages include their easier deployment with shorter procedure time, lower risk of migration due to its design, their wider lumen which could provide more effective drainage of the solid content and may obviate the need for necrosectomy or facilitate necrosectomy if necessary.

Endoscopic necrosectomy consists on removing necrotic debris using different devices such as polypectomy snares or baskets (Fig. 5). A novel tool specifically designed for endoscopic necrosectomy is available but further studies are required to validate its use (38). Direct endoscopic necrosectomy consists on inserting a gastroscope inside the cavity for mechanical clearance of the necrotic tissue. There is no consensus regarding when to perform necrosectomy and whether to perform it in a scheduled or on-demand manner. Initially, it was widely performed but nowadays the need for endoscopic necrosectomy is controversial. On one side, the improvements in the drainage technique and the use of stents with wider diameter has led to higher clinical success. On the other hand, the safety of necrosectomy is increasingly debated, with an adverse event rate of 36 %, mostly bleeding, and a 6 % mortality rate in a recent meta-analysis (39). Currently, the debridement of the necrotic content within the collection should probably be relegated to WON which fail to improve after appropriate drainage (8,9). Predictive factors of need of necrosectomy include large size and higher amount of solid debris (40).

Different strategies have been proposed in order to reduce the need for endoscopic necrosectomy. Even though they lack sufficient evidence to be routinely recommended, its use should be considered individually in difficult cases. The placement of a nasocystic catheter to irrigate the cavity with normal saline, commonly a daily volume of 500-1000mL, has been associated with a lower occurrence of stent occlusion and a higher resolution, especially in collections with high amount of necrotic debris (8,41). Also, some authors have proposed an approach consisting in creating multiple transluminal fistula, with a high treatment success and should be considered in patients with multiple or large (> 12 cm) WON (8,42). Another option is the combination of transluminal and percutaneous drainage, especially in patients with WON that extend to the pelvis or paracolic gutters (20). Local instillation of antibiotics inside the collection together with systemic antibiotherapy has also been explored with promising results (43). The use of hydrogen peroxide to irrigate the cavity and facilitate necrotic tissue dislodgement has been reported in case series with apparently low adverse events (44).

Adverse events

Complications of endoscopic drainage are uncommon, being more frequent in WON treatment compared to pseudocysts (13). They can be endoscopically managed successfully in most patients, being exceptional the need for radiological or surgical rescue therapy (45). Complications may include:

1. Bleeding from the fistula tract or from inside the PFC due to erosion of a large blood vessel which may be challenging. The high delayed bleeding rate with LAMS reported by Bang et al. was not confirmed in a recent large muticenter retrospective study designed to evaluate complications of LAMS (45). A retrospective study that evaluated whether the placement of a coaxial double-pigtail plastic stent within LAMS improved safety reported lower rate of bleeding with its use (46).
2. Perforation which is more likely when the wall is poorly defined or has a distance of greater than 1 cm from the intestinal lumen.
3. Stent migration into the PFC or towards the gastrointestinal lumen, which was higher with biliary stents motivating the need to place a coaxial double-pigtail plastic

stent to minimize this risk. It can be managed by endoscopic removal of the stent.

4. Stent occlusion with secondary infection of the PFC. It usually requires endoscopic revision to unblock the drainage by retrieving the solid necrotic material occluding it.

Follow-up

One unresolved issue is the duration of stenting, as a short time may increase recurrence of the PFC and longer time may be associated with complications. A follow-up CT scan is usually performed 4-6 weeks after drainage to assess PFC resolution and if a significant reduction of PFC is noted, together with clinical resolution of symptoms, then the stent should be removed (5). The high bleeding rate of the aforementioned trial motivated current guidelines recommendation to retrieve LAMS within four weeks of placement (8). Double-pigtail plastic stents can be left in place for longer time, and it is especially advisable in patients with disconnected pancreatic duct syndrome (8).

CONCLUSIONS

The management of PFC has significantly changed over the past years. When we evaluate a PFC, it is of great importance to adhere to the Atlanta nomenclature as the terms pseudocyst and WON are not interchangeable and entail different prognosis and management. Not all PFC require drainage, in fact most resolve spontaneously. EUS-guided drainage is the first-line treatment of PFC when intervention is needed. A prerequisite for endoscopic treatment of a PFC is the presence of a well-defined mature wall that encapsulates the collection, which usually requires at least four weeks from the onset of acute pancreatitis. Pseudocysts present high treatment success irrespective of type of stent. However, management of WON is still challenging and a step-up approach is recommended. Despite the great progress made in recent years, there are still several unresolved questions regarding technical aspects of endoscopic PFC management.

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	ACUTE PERIPANCREATIC FLUID COLLECTION	ACUTE NECROTIC COLLECTION	PSEUDOCYST	WALLED-OFF NECROSIS
Onset	< 4 weeks (ACUTE COLLECTIONS)		≥ 4 weeks (CHRONIC COLECTIONS)	
Wall	NO		YES	
Type of acute pancreatitis	Interstitial edematous pancreatitis	Necrotizing pancreatitis	Interstitial edematous pancreatitis	Necrotizing pancreatitis
Content	Homogeneous, liquid	Heterogeneous, solid	Homogeneous, liquid	Heterogeneous, solid
			 	 

Fig. 1. Types of pancreatic fluid collections.

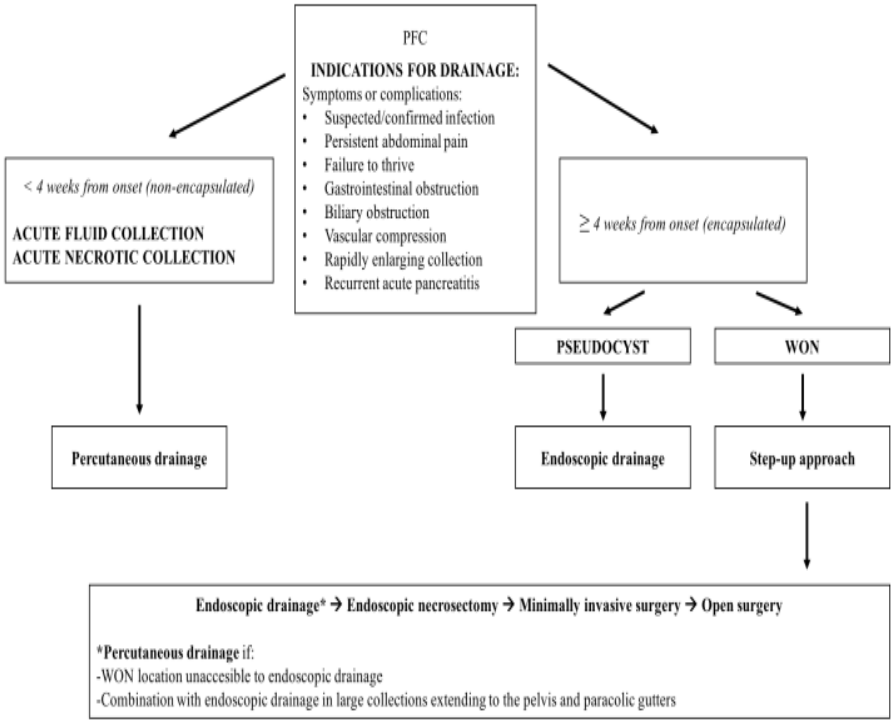

Fig. 2. Management of pancreatic fluid collections PFC: Pancreatic fluid collection; WON: Walled-off necrosis.

STENT TYPE	DIAMETER	ADVANTAGES AND DISADVANTAGES
PLASTIC STENTS	7-10 Fr	-Low cost -Low risk of migration -Technical complexity -Small diameter (risk of obstruction)
Double-pigtail plastic stents 		
METAL STENTS		
Straight biliary fully covered stents 	6-10 mm	-Large diameter -Less technical complexity -No anchoring (risk of migration, usually requiring a coaxial double-pigtail plastic stent)
Lumen-apposing stents AXIOS/HOT AXIOS™ NAGI™ SPAXUS™ 	10, 15, 20 mm	-Large diameter -Technical simplicity (reduced need of fluoroscopy) -Anchoring design (low risk of migration) -Eases access to collection (necrosectomy) -Higher cost

Fig. 3. Types of stents for endoscopic drainage.

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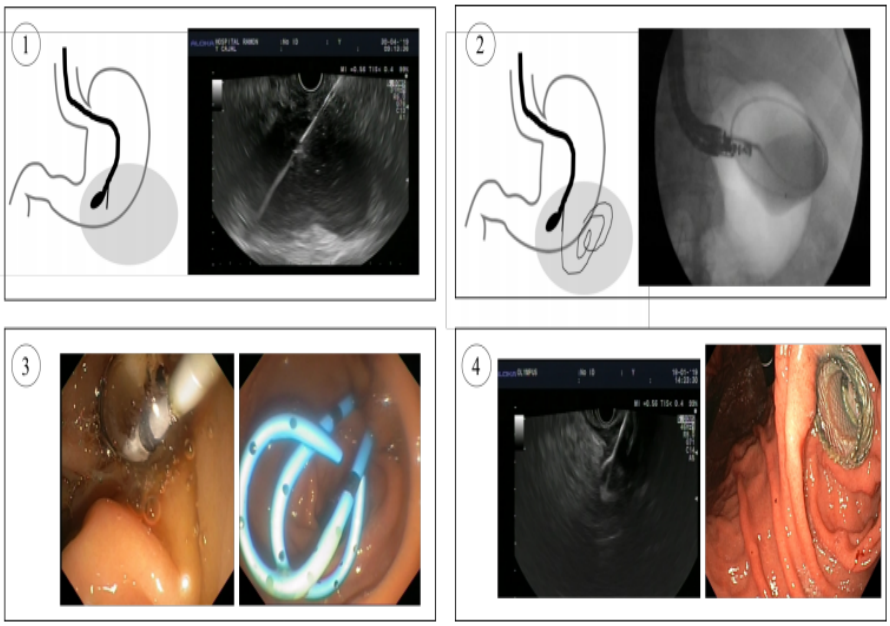

Fig. 4. Endoscopic drainage: Steps 1. A19G needle is used to puncture the collection under EUS control. It is recommendable to send the aspirated content for culture. 2. A through the needle guide-wire is advanced and coiled inside the PFC. 3. Placement of a double-pigtail plastic stent and metal stents usually requires to create a cystenterostomy with a needle-knife or cystotome and subsequent balloon dilation of the tract to allow stent deployment under fluoroscopy guidance. 4. LAMS with electrocautery-enhanced system allow puncture of the PFC by using the integrated cautery and obviate the need of prior tract dilatation (EUS: endoscopic ultrasound; G: Gauge; PFC: pancreatic fluid collection; LAMS: lumen-apposing metal stent).

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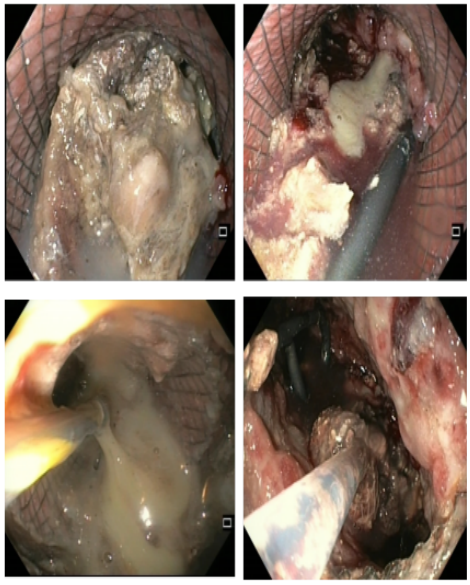

Fig. 5. Endoscopic necrosectomy of a walled-off necrosis through a lumen-apposing metal sten.