J Hepatobiliary Pancreat Sci (2014) 21:E75–E85
DOI: 10.1002/jhbp.146

TECHNICAL VIEW

Interventional endoscopy for the treatment of pancreatic pseudocyst and walled-off necrosis (with videos)

Shuntaro Mukai · Takao Itoi · Fuminori Moriyasu

Published online: 20 August 2014

Abstract Pancreatic pseudocysts and walled-off necrosis are typical late complications of acute pancreatitis, and they require drainage in symptomatic cases presenting with infection. Transgastrointestinal endoscopic treatment with endoscopic ultrasound-guided drainage has become common and yields a good treatment outcome for pancreatic pseudocyst. Walled-off necrosis, however, contains necrotic tissue, and thus many cases additionally require an invasive treatment that includes endoscopic necrosectomy. Methods that involve a procedure-specific large-diameter metal stent, additional endoscopic drainage techniques, and the hybrid approach method of adding percutaneous drainage have been described, and considerable advances in these methods have now made it possible to cure almost all cases of walled-off necrosis with endoscopic treatment alone. However, without being restricted to endoscopic treatments, a wide range of options including surgery should be considered as treatments for walled-off necrosis.

Keywords Endoscopic necrosectomy · Endoscopic ultrasound-guided drainage · Hybrid approach · Step-up approach · Walled-off necrosis

Introduction

Pancreatic pseudocysts (PPC) and walled-off necrosis (WON) are typical late complications of acute pancreatitis. Many terms have been used to refer to these lesions, such as "pancreatic pseudocyst" for those that contain only a fluid component and "pancreatic abscess" for infected pancreatic pseudocysts. All over the world these local complications of pancreatitis were once defined based on the Atlanta Classification [1], which was proposed in 1992. However, later clinical findings revealed that the course of treatment and even the need for treatment vary depending on whether the fluid is infected, and that the presence of peripancreatic necrosis or walled-off necrotic pancreatic tissue that contains liquefied necrotic tissue causes the effects of treatment to differ from those seen with pseudocysts that contain only fluid [2, 3]. This encapsulated, liquefied necrotic pancreatic or peripancreatic tissue is referred to as "walled-off necrosis" (WON). This was proposed as a new concept in the revised Atlanta Classification of 2007 [4], and the final version after an international consensus was obtained was published in the journal *Gut* in January 2013 [5].

The revised Atlanta Classification addresses the process by which local complications of pancreatitis occur and the duration of that process, the location of lesions, and signs of infection, and broadly classifies acute pancreatitis into four categories. First, it is classified as either interstitial edematous pancreatitis or necrotizing pancreatitis. Then, interstitial edematous pancreatitis is classified as either an acute peripancreatic fluid collection (APFC) or PPC when the APFC is encapsulated. Necrotizing pancreatitis is classified as either an acute necrotic collection (ANC) or WON when the ANC is encapsulated.

These local complications of acute pancreatitis must be treated in symptomatic cases presenting with infection; it is impossible to control infection with conservative treatment such as antibiotics alone when WON is infected and contains a large amount of necrotic tissue. Such cases can lead to multiple organ failure, making invasive drainage necessary. Endoscopic ultrasound (EUS)-guided transgastrointestinal drainage is now becoming common worldwide as a minimally invasive treatment for PPC/WON [6–11].

This paper will review advances in endoscopic treatments for PPC/WON based on the revised Atlanta Classification.

S. Mukai · T. Itoi (✉) · F. Moriyasu
Department of Gastroenterology and Hepatology, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan
e-mail: itoi@tokyo-med.ac.jp

Indication for treatment of PPC/WON

Asymptomatic PPCs can generally be managed by observation. The incidence of APFC after edematous pancreatitis is reported to be approximately 40%, with a PPC forming in approximately 10% of these cases [2]. Studies show that PPCs less than 6 cm in diameter are likely to resolve spontaneously after about 6 weeks [12], and treatment is rarely indicated for PPCs that form after acute pancreatitis. However, PPCs that fit the "six or six rule," i.e. those that are greater than 6 cm in diameter or persist for more than 6 weeks, are less likely to resolve spontaneously [13]. Studies show that even when asymptomatic, such PPCs are associated with risks such as infection, bleeding, and intraperitoneal rupture, and often require drainage with endoscopic treatment or another method. Especially PPC, which is more than 10 cm or has the pancreatic duct anatomy assessed by magnetic resonance cholangiopancreatography (MRCP), EUS or endoscopic retrograde cholangiopancreatography (ERCP), has high risk of becoming symptomatic or occurring the complications [14]. In addition, it is believed that regardless of size or duration, treatment is indicated for infected PPCs and symptomatic PPCs presenting with symptoms such as abdominal pain when there is also bile duct stenosis or gastrointestinal obstruction.

Although no further consensus has been reached regarding the timing of treatment indicated for WON, findings from clinical experience indicate that drainage is not even necessary for some cases of large WON, even when there is a large amount of necrotic tissue, and that similarly to PPC, treatment is indicated for symptomatic and infected cases, but asymptomatic cases can be managed with observation. However, WON that includes a large amount of necrotic tissue is unlikely to resolve spontaneously and is prone to infection, and thus is more commonly treated than PPC.

Treatment at less than 4 weeks after acute pancreatitis poses a risk of intraperitoneal rupture at the APFC/ANC stage because necrotic tissue is not adequately liquefied and the perimeter is not fully encapsulated; thus, it is considered best to perform drainage electively [15, 16]. Clinically speaking, if imaging reveals that tissue is liquefying and becoming encapsulated, there is no need to wait exactly 4 weeks while an infection is developing, and it is also important to not miss the window for treatment. However, the diagnosis between sterile or infected is often difficult. Infected WON is clinically diagnosed on the basis of clinical signs, laboratory data, a high fever, evidence of systemic inflammatory response syndrome, and the presence of gas in the fluid collection on computed tomography (CT). Recently, it was reported that the aspiration of fluid from PFC under EUS and the microbiologic analysis played an important role of diagnosis and treatment [17].

EUS-guided drainage for PPC/WON

Endoscopic treatments for PPC/WON are broadly divided into transpapillary drainage of the cyst through the pancreatic duct and transgastrointestinal drainage of the cyst. To develop a treatment strategy, it is important to understand the pathology. Especially when performing transgastrointestinal treatments, it is important to determine whether fluid has accumulated in the omental bursa as a result of acute pancreatitis (i.e. the wall of the stomach is the wall of the cyst) or a cyst caused by pancreatic duct disruption associated with acute pancreatitis has become encapsulated outside of the omental bursa (if the wall of the cyst and the wall of the stomach are not attached, the fluid inside may leak into the peritoneal cavity when the cyst is punctured). The two types of cyst are clinically discriminated by assessing the pancreatic duct disruption with MRCP or ERCP. However, we often experienced cases that were difficult to discriminate. The majority of cases of WON are the former, which means that transgastrointestinal treatment can be performed relatively easily, but caution should be taken with massive WON because the puncture point is not always backed by the wall of the stomach. Most cases of PPC, however, are the latter, and require caution because perforation can occur; causing cystic fluid to leak into the peritoneal cavity, and free air can be observed on CT. In addition, as described above, PPC is often caused by pancreatic duct disruption, which means that it may not heal completely with drainage unless the disrupted site is restored to normal function, and may require transpapillary pancreatic duct intervention at a later date. Thus, in PPC cases where pancreatic duct disruption is suspected, transpapillary drainage should be performed from the start. However, in large size PPCs or infected PPC cases, transgastrointestinal drainage is recommended at the first step because the transgastrointestinal drainage is more effective, leading to more rapid improvement than the transpapillary drainage. After the complete resolution of a cyst, endoscopic retrograde pancreatography should be performed to assess the pancreatic duct disruption, and if necessary, pancreatic duct stent should be placed to restore the disrupted site.

After Rogers et al. first described a technique for cyst puncture with a direct-view endoscope [18], approaching pseudocysts via the gastrointestinal tract with a direct-view endoscope became mainstream in endoscopic treatment. After the advent of endoscopic ultrasound technology, Grimm et al. described the first EUS-guided drainage method in 1992 [19]. With this method, the puncture route with the shortest distance between the gastrointestinal tract and the wall of the cyst can be chosen under EUS guidance. In addition, PPC/WON can sometimes cause portal hypertension associated with obstruction of the portal vein or the splenic vein [20–22], which causes collateral vascular routes to develop around the stomach; it is safer to use EUS than a direct-viewing endoscope for these cases because the cyst can be punctured while checking for intersecting blood vessels. Two randomized controlled trials (RCTs) have also shown that EUS-guided drainage is superior to drainage with a direct-viewing endoscope in terms of its success rate and rate of complications [23, 24]. Furthermore, EUS-guided drainage for PPC has spread worldwide with the development of endoscopic treatment techniques and devices; it has been shown to be a very useful and safe treatment method, having a technical success rate of 95%, a clinical success rate of 90%, and a complication rate of 0–9% [6, 25, 26]. As with PPC, EUS-guided drainage has also been shown to be an effective endoscopic treatment for WON. However, WON contains necrotic tissue and thus drainage is often insufficient when a plastic stent with a small internal diameter is inserted. The response rate of infected WON to EUS-guided drainage alone is actually reported to be roughly 40–50% [27].

EUS-guided drainage procedures for treating PPC/WON

First, a convex ultrasound endoscope is inserted to visualize the lesion. PPCs are easy to visualize because the cyst only contains fluid and thus is recognized as an anechoic cystic lesion. WON, however, cannot be clearly visualized in some cases, such as when hyperechoic necrotic tissue is observed in the walled-off area but not much is liquefied or there is air inside the WON; the entire area becomes hyperechoic and it is not easy to distinguish WON from the gastrointestinal tract, which contains adipose tissue and air. The relative position of the gastrointestinal tract and WON on CT and the position of the scope in fluoroscopy are used to identify the lesion through careful observation. After confirming that there are no blood vessels crossing the puncture route, the cyst is punctured with a 19G fine needle aspiration (FNA) puncture needle under EUS guidance. Aspiration of cyst contents and/or demonstration of contrast injection into the cavity under fluoroscopic guidance before guidewire insertion is important to confirm cavity access especially in WON, which cannot be clearly visualized under EUS. Besides, aspirated material should be sent for microbiological analysis with bacterial culture and Gram stain. However, when the WON does not contain much fluid, the fluid frequently cannot be aspirated even when the cyst is punctured with a 19G needle. Next, a stiff 0.035-inch or 0.025-inch guidewire is inserted into the cyst, and the punctured area is dilated with an ERCP catheter or cautery dilator while advancing the guidewire. Then, the fistula is dilated with a 4–6 mm biliary dilatation balloon, and one or several 7Fr double-pigtail plastic stents are placed inside. To prevent stent migration, it is important to distinctly mark the area just in front of the pigtail on the gastrointestinal tract side with a marker. The stent is slowly advanced through the cyst away from the fistula, the location of the mark is confirmed with an endoscope, and the stent is placed. The basic method to ensure effective drainage during the initial drainage session is internal-external drainage by placing a 5Fr or 6Fr nasocystic catheter (Video S1).

Would a 7Fr or 10Fr plastic stent be better? Is one stent sufficient or would it be better to place multiple stents? In 2013, Bang et al. conducted a multivariate analysis of 117 cases of PPC treated with EUS-guided drainage comparing a 7Fr stent group with a 10Fr group and a single stent group with a multiple stent group, but found that the outcome of treatment did not vary in either comparison [28]. Based on our experience, we also believe that a single 7Fr plastic stent is sufficient to treat PPC. WON, however, contains necrotic tissue and thus it is best to use one 5Fr or 6Fr nasocystic catheter and at least two 7Fr plastic stents to safely dilate the fistula a second time during initial drainage and to ensure good drainage. This is particularly true for cases in which imaging findings indicate a high likelihood of requiring repeated necrosectomy. Then, would a straight plastic stent or a double-pigtail plastic stent be better? There is no RCT, but the previous report suggested that complications could be increased by using the straight plastic stent instead of the double-pigtail plastic stent as they may induce pressure necrosis of the cyst wall, causing cyst rupture or severe bleeding [29]. In these results, the double-pigtail plastic stent is recommended rather than the straight plastic stent.

There are various methods of treating WON that contain a large amount of internal necrotic tissue, and many previous studies have used physiological saline through a nasocystic catheter to lavage the internal cavity of the cyst [30, 31]. One study, albeit a retrospective one, in which a group that had a nasocystic catheter placed and lavaged with physiological saline after 48–72 h to treat WON was compared to a group that had only a plastic stent placed and not a nasocystic catheter, found that the former yielded a significantly higher rate of WON reduction after one month of treatment and was effective at preventing plastic stent obstruction [32]. Although there is no hard evidence to support this, no procedural accidents have been observed with lavage and thus it is probably appropriate to perform lavage through a nasocystic catheter.

The double-guidewire technique is useful when placing a nasocystic catheter or multiple plastic stents [33]. In this method, after puncturing the cyst under EUS guidance and placing one guidewire in the cyst, the other guidewire is inserted into the cyst using a double-lumen catheter or 10Fr Soehendra dilatation catheter before the stent is placed, allowing the procedure to be performed efficiently.

A forward-view convex endoscope was recently developed specifically for this treatment. The endoscope, puncturing, and ultrasound scanning functions on this ultrasound endoscope are integrated, which gives it greater puncturing force compared to conventional oblique-view convex ultrasound endoscopes and should make it useful in EUS treatment procedures. A multi-center prospective trial published in 2011 that examined the use of this endoscope in EUS-guided drainage found that the treatment outcome and the procedure time were almost equivalent between the group in which a forward-view convex type was used and the group in which a conventional anterior oblique-view convex type was used [34]. In addition, another puncture method uses a cautery needle instead of a 19G FNA needle. The perimeter is cauterized at the same time that the area is punctured, which makes it easier to subsequently dilate the fistula, but could potentially cause bleeding during puncturing. However, studies have shown that there is no significant difference between using a cautery needle and using a non-cautery needle [35]. The ultrasound endoscope and the puncture needle used for treatment can be chosen based on whatever method is easiest for the operator.

To prevent recurrence, it is best not to remove the internal drainage stent after treatment. A RCT followed a group in which the internal drainage stent was removed and a group in which it was not removed for an average of 14 months and compared the rates of recurrence; the rate of recurrence was 36% (5/14) in the removal group and 0% (0/13) in the non-removal group, and no issues related to long-term stent placement were observed [36].

Endoscopic necrosectomy for WON

As described above, WON that includes a large amount of necrotic tissue does not drain well with EUS-guided drainage alone, and it is often difficult to control infection in such cases. Such cases were traditionally treated with surgical necrosectomy. However, it is very risky to perform surgery when a patient has an infection and their general condition is poor, as the rate of complications (55%) and the mortality rate (14%) are both very high [37]. Therefore, endoscopic necrosectomy, first described by Seifert in 2000, was developed as a minimally invasive treatment alternative to surgical necrosectomy [27]. After that point, many facilities began to publish studies of this technique, and three multi-center studies involving many cases have recently been published from Germany, the United States, and Japan [38–40] (Table 1). In these studies, the success rates of treatment were 75–91%, the rates of complications were 26–33%, and the mortality rates were 5.8–11.0%, which was better than the treatment outcome with EUS-guided drainage alone, suggesting that this method of treatment is safer than surgical necrosectomy. A 2010 RCT from the Netherlands compared a group receiving a “step-up approach” of first performing percutaneous or endoscopic drainage and later adding necrosectomy with a retroperitoneal approach as necessary with a group in which surgical necrosectomy was performed first ($n = 45$ in each group); there was no significant difference in mortality, but the incidence of multiple organ failure was significantly lower in the step-up approach group, and 35% of patients in that group were able to be

Table 1 Treatment outcomes of direct endoscopic necrosectomy in three multi-center studies

	Seifert H [38] (Gut 2009)	Gardner TB [39] (GIE 2011)	Yasuda I [40] (Endoscopy 2013)
No. patients	93	104	57
No. institutions	6 (Germany)	6 (USA)	16 (Japan)
Clinical success rate	75 (81%)	95 (91%)	43 (75%)
Complication rate	24 (26%) • Bleeding: 13 • Perforation: 5 • Fistula formation: 2 • Air embolism: 2 • Others: 2	14 (14%) • Bleeding: 3 • Retrogastric perforation: 3 • Pneumoperitoneum: 3 • Infections: 4 • Air embolism: 1	19 (33%) • Bleeding: 9 • Perforation: 3 • Air embolism: 1 • Splenic aneurysm: 1 • Mallory-Weiss tear: 1 • Ileus: 1 • Cardiorespiratory arrest: 1
Mortality rate	7 (7.5%) • Bleeding: 1 • Sepsis: 4 • Air embolism: 1 • Multiple organ failure: 1	2 (1.9%) • Air embolism: 1 • Bleeding: 1	6 (11%) • Multiple organ failure: 2 • Air embolism: 1 • Splenic aneurysm: 1 • Bleeding: 1 • Cardiorespiratory arrest: 1

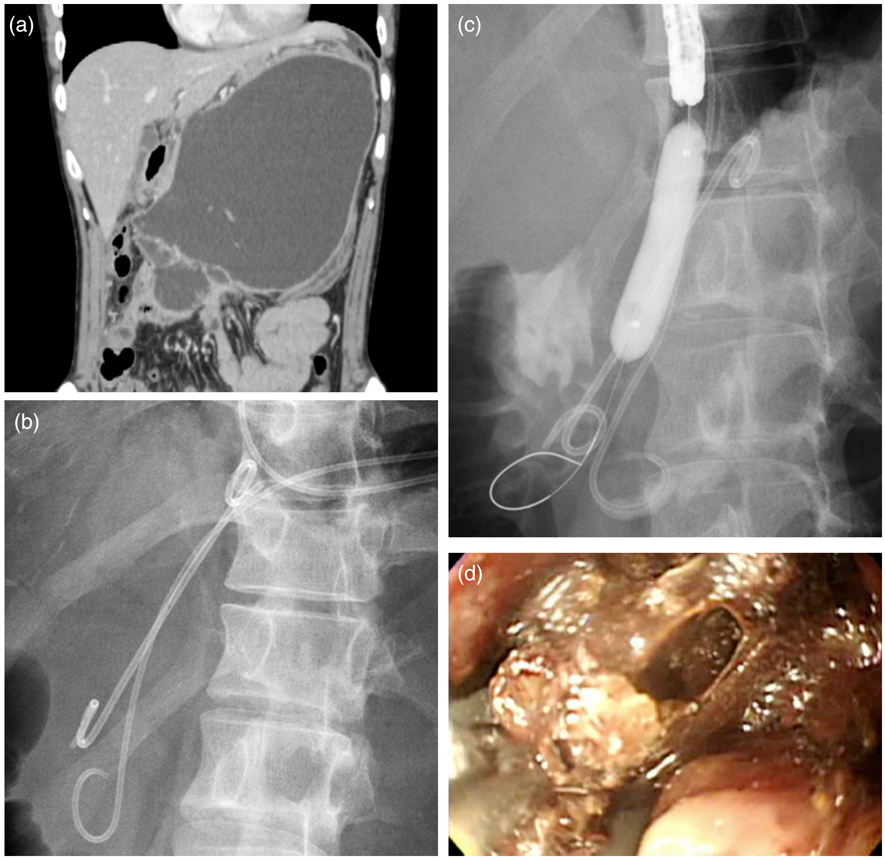

Fig. 1 Endoscopic ultrasound (EUS)-guided drainage and endoscopic necrosectomy. (**a**) Computed tomography (CT) revealed the encapsulated multilocular walled-off necrosis (WON) around pancreas. (**b**) After WON was punctured under EUS guidance, the drainage using one 7Fr pigtail plastic stent and a nasocystic catheter was performed. (**c**) A few days after drainage, the fistula was dilated with a large balloon and a normal upper gastrointestinal scope was slowly advanced into the WON while deflating the balloon. (**d**) Necrotic tissue was gradually removed using a snare or forceps

treated with minimally invasive drainage alone [41]. With regard to the postoperative outcome, the study also notes that the percentage of patients that developed diabetes and the percentage that were taking a digestive aid was significantly lower in the step-up approach group. In addition, the first RCT (the PENGUIN trial) [42] of endoscopic necrosectomy and surgical necrosectomy, which was published by a German team in 2012, only examined a small number of cases (10 in each group) but found that procedural accidents and postoperative complications were significantly less common in the endoscopic necrosectomy group, as well as the incidence of new organ dysfunction and pancreatic fistula. The results of such studies indicate that performing minimally invasive endoscopic drainage followed by endoscopic necrosectomy as needed is gaining consensus as the treatment strategy for infected WON. In addition, in cases where the lesion extends far from the gastrointestinal tract toward the pelvic cavity, it is necessary to consider a hybrid approach where a percutaneous approach is added at an early stage [43].

Endoscopic necrosectomy procedures for WON

Endoscopic necrosectomy should be performed a few days after drainage. The reasons for this are as follows: (1) when the wall of the cyst is not sufficiently adhered to the wall of the stomach, trying to perform necrosectomy right after drainage increases the risk that the scope migrates into the peritoneal cavity and perforation occurs; (2) if clinical findings improve with drainage alone, there is no need to perform necrosectomy, which has a high complication rate; and (3) the most common complication of endoscopic necrosectomy is bleeding, which is sometimes associated with balloon dilatation of the fistula (delayed dilatation lowers the risk of bleeding). In the method we use, we place the guidewire into the WON through the fistula with an ERCP catheter using a normal upper gastrointestinal scope, dilate the fistula with an 18–20 mm gastrointestinal dilatation balloon, and slowly advance the scope into the WON while deflating the balloon. We then thoroughly lavage the inside of the WON with physiological saline, and once we are able to get a good field of vision, we remove necrotic tissue gradually using a snare or forceps (Fig. 1) (Video S2). We prefer to use a 10 mm polypectomy snare because it allows us to remove a reasonably large amount of necrotic tissue and is highly efficient. Then, recently the method of hydrogen peroxide (H_2O_2)-assisted DEN was reported [44]. H_2O_2 irrigation facilitates necrotic tissue dislodgement, debridement, and debris extraction during treatment of WON, leading to reduction in the need of mechanical debridement using standard endoscope. We continue removing tissue while taking care not to damage blood vessels or make a perforation, and thoroughly lavage the area as needed. The visualization of pink granulation tissue indicates that the area has been sufficiently cleaned. For economic reasons as well as medical reasons, we try to avoid removing the stent before necrosectomy, but we remove it as needed if it will interfere with necrosectomy. In addition, it is important to always use CO_2 for insufflation when performing necrosectomy to prevent air embolism from occurring as a procedural accident. Although clinically significant CO_2 embolism is rare, the incidence of CO_2 embolism during laparoscopic surgery was reported [45]. At the moment, we do not know the whether CO_2 embolism has occurred during DEN. CO_2 embolism is a potentially fatal complication of DEN because it is caused by entrapment of CO_2 in an injured vein, artery, or solid organ. Excessive CO_2 insufflation can cause CO_2 embolism or the cyst to rupture, so it must be used in moderation. Our target duration for one procedure is roughly one hour or less, and we try to perform them twice a week. Complete removal of necrotic tissue and good exposure of granulation tissue are considered to be desirable endpoints for necrosectomy once the fever and the inflammatory response subsides. Conversely, in cases where it is difficult to control the infection even with necrosectomy, it is highly likely that drainage from another cavity is insufficient. In such cases, the additional drainage method described below should be considered and needless multiple necrosectomies should be avoided to minimize the risk of complications.

Endoscopic drainage and necrosectomy with a large-diameter metal stent

In recent years, a number of studies have used large-diameter metal stents instead of plastic stents for PFC drainage because they offer good drainage and promote quick fistula formation [46–49] (Video S3). Most of these studies used conventional fully covered biliary metal stents. Although it is difficult to evaluate results because some studies did not clearly differentiate between PPC and WON, the technical success rate was 94–100% and the clinical success rate was 78–95%. A metal stent is easier to place than multiple plastic stents and the large diameter of the metal stent enables highly effective drainage, but somewhat longer stents need to be used to prevent displacement and migration. Endoscopic necrosectomy for WON would ideally be performed with the stent still in place, but the stent would probably be removed beforehand because it is long and may migrate when the scope is inserted. Furthermore, treatment can cause the stent to become displaced when the size of the cyst shrinks, which can cause the end of the metal stent to touch the wall of the cyst and lead to bleeding inside of the cyst. Conventional biliary metal stents have few advantages despite costing much more than plastic stents.

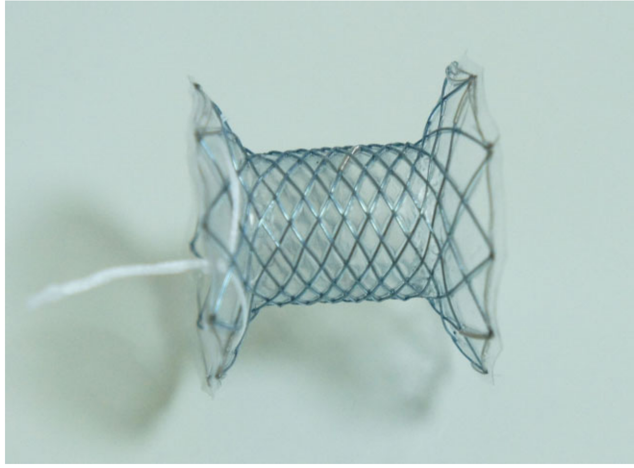

Fig. 2 A novel biflanged metal stent that was designed for endoscopic ultrasound (EUS)-guided Drainage (Nagi stent, Taewoong Company, Seoul, Korea)

Novel biflanged metal stents (Fig. 2) that are designed specifically for cyst drainage have been developed in recent years, allowing a scope to be passed through repeatedly once the stent is in place and thus making it easy to perform necrosectomy [50–53]. Clinical research on these stents is ongoing, but they are being used in treatments. There are currently three types of stent, namely, the AXIOS stent by Xlumena (internal diameter: 10 mm or 15 mm; length: 10 mm), the Nagi stent by Taewoong (internal diameter: 16 mm; length: 30 mm or 20 mm), and the Hanaro stent by MI Tech (internal diameter: 12 mm; length: 40 mm). All of these are braided fully covered metal stents. The method of placement is similar to that of a plastic stent until the point where the fistula is dilated with a 6 mm biliary dilatation balloon. After that, the sheath is advanced into the cyst with a guidewire and the side of the stent facing the cyst is expanded. Stent expansion can be confirmed on the ultrasound endoscope view. Next, after slowly pulling the stent through to the point where the stent is aligned with the internal cavity of the cyst, the fistula is identified on the endoscope view while slowly pulling on the ultrasound endoscope. After confirming the mark on the gastrointestinal side, the stent is expanded on the gastrointestinal side. The fluid inside the cyst will drain all at once, demonstrating just how effective a large-diameter stent is for drainage (Fig. 3) (Video S4). If endoscopic necrosectomy is to be performed at a later date, this process will allow a normal upper gastrointestinal endoscope to be repeatedly passed through the stent into the cyst, and the stent will not be displaced during the procedure because the biflanged part of

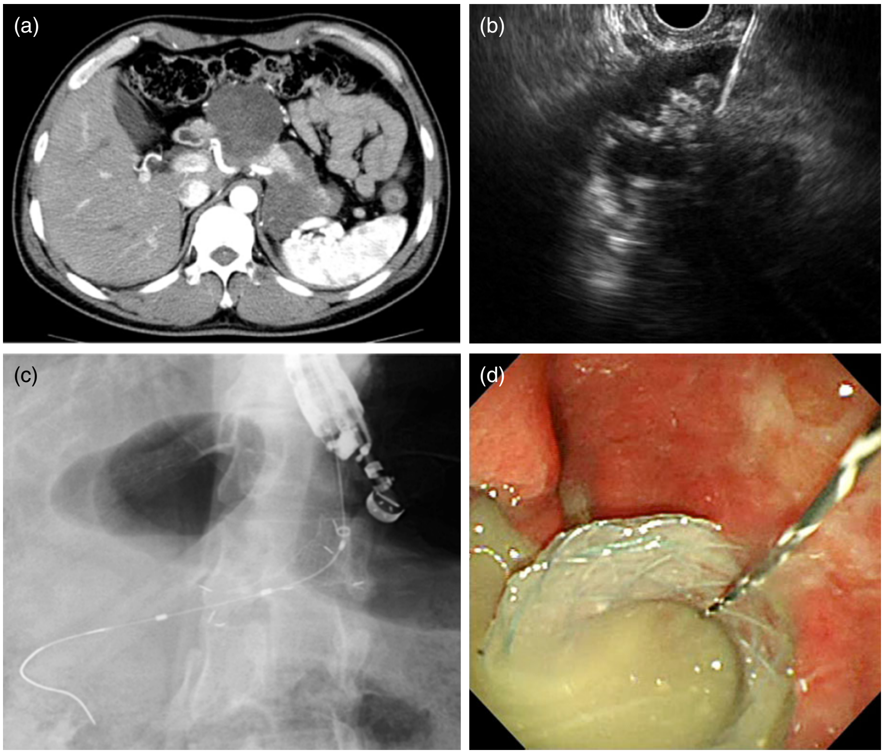

Fig. 3 Endoscopic ultrasound (EUS)-guided drainage for walled-off necrosis (WON) with a large-diameter biflanged metal stent. (**a**) WON occurred after severe necrotizing pancreatitis due to bile duct stones. The patient was admitted with high fever and abdominal pain due to infected WON. (**b**) The WON was visualized by a convex ultrasound endoscope and punctured with a 19G aspiration needle. (**c**) A large-diameter biflanged metal stent was placed after the fistula was dilated with a cautery dilator and a dilatation balloon. (**d**) After the placement of the metal stent, a large amount of pus was discharged

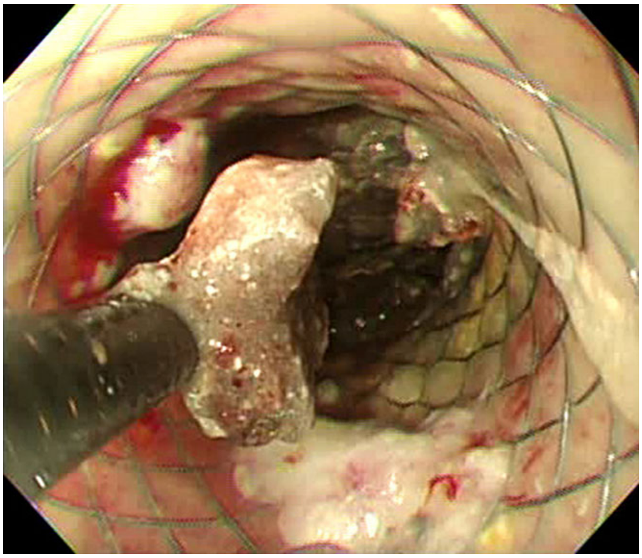

Fig. 4 Endoscopic necrosectomy through a large-diameter biflanged metal stent. A few days after drainage, an upper gastrointestinal endoscope was inserted into walled-off necrosis (WON) through the metal stent directory and DEN was performed. Necrotic tissue was gradually removed with a snare

the stent is secured (Fig. 4) (Video S5). Balloon dilatation is typically not necessary, which shortens treatment time and lowers the risk of bleeding associated with balloon dilatation. These stents allow necrosectomy to be performed effectively, which makes early treatment possible and helps to reduce the incidence of complications [54]. The metal stent is removed with a snare at approximately one month after the conclusion of treatment, and if there is excess space, a 7Fr double-pigtail plastic stent is inserted to prevent recurrence. In our experience, we have not had any major problems with these novel biflanged metal stents and consider that safety is not an issue, but future studies will need to compare the actual treatment outcome of novel biflanged metal stents to the outcome of conventional plastic stents. As metal stents are more expensive than plastic stents, a RCT that also includes cost analysis will be necessary.

Additional endoscopic drainage techniques for complicated WON

With the development of endoscopic necrosectomy, the clinical success rate of endoscopic treatment for WON has improved to over 80%. However, this also means that 20% of cases are difficult to treat with endoscopic treatments alone and may require additional percutaneous drainage and eventually surgical therapy. Although WON is encapsulated, it is rare for it to have a simple spherical shape; it often has a complex shape and is multilocular. Cysts that form originally as unilocular divide into multilocular cysts as they develop; each of these cavities typically has interconnecting routes. However, when these routes are narrow, draining the main cavity alone will not drain the sub-cavities sufficiently, and it is difficult to control infection even with necrosectomy of the main cavity. Based on our experience,

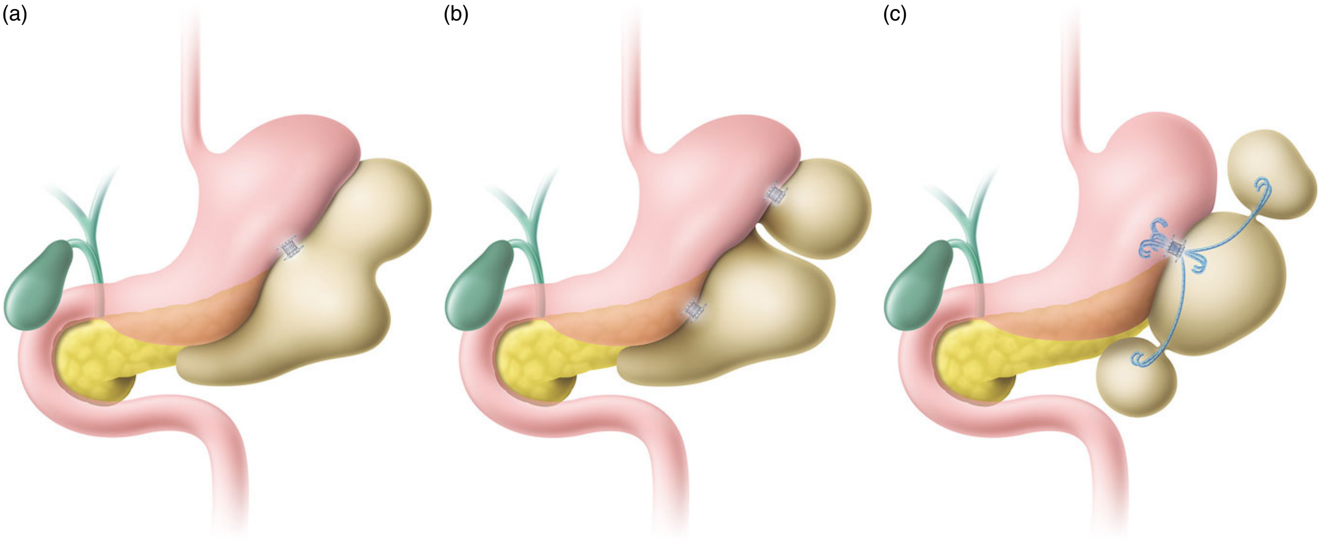

Fig. 5 Schema of additional endoscopic drainage technique. (**a**) SGT (single transluminal gateway technique). (**b**) MTGT (multiple transluminal gateway technique). (**c**) SGTMD (single transluminal gateway transcystic multiple drainages)

small sub-cavities will shrink if treatment with antibiotics is continued after draining the main cavity, but sub-cavities of a certain size still require invasive drainage. Percutaneous drainage is associated with problems such as formation of a pancreaticocutaneous fistula after treatment, decreased ADL (activities of daily living), and prolonged hospitalization, and thus it is desirable to perform endoscopic treatment alone if possible. To this end, recent studies have described the multiple transluminal gateway technique (MTGT) [55] and single transluminal gateway transcystic multiple drainages technique (SGTMD) [56] as techniques for additional endoscopic drainage (Fig. 5). MTGT, which was described by Varadarajulu et al. in 2011, is a method where EUS-guided drainage of large multilocular WON is performed in several (typically two) separate locations. Multiple fistulae form for drainage and endoscopic necrosectomy is performed through those fistulae if necessary. MTGT was found to yield a significantly better treatment outcome than the conventional method of draining only the main cavity (91.7% vs 52.1%, $P = 0.018$). A recent study has also noted that WON usually requires additional treatment with endoscopic necrosectomy an average of six times [38], but can be cured after an average of 1.5 times if MTGT is used in necrosectomy. They recommend that MTGT be performed early on for large multilocular WON (over 12 cm) [28]. However, this method is only effective when sub-cavities are close to the gastrointestinal tract and can be punctured safely. To solve this problem, we described a method called SGTMD in 2014 as an effective method for cases where sub-cavities are located far from the gastrointestinal tract, for example, around the spleen. As noted previously, the main cavity and sub-cavities typically have narrow routes between them in almost all cases. Therefore, an ERCP catheter and a soft guidewire are used to seek these routes within the main cavity. If a guidewire can be inserted into a sub-cavity, a 7Fr double-pigtail plastic stent or a transnasal drainage tube can be placed in the sub-cavity through that route to drain the sub-cavity. Use of the MTGT and SGTMD methods should further improve the outcome when endoscopic treatment of WON is performed alone [8].

Hybrid approach (percutaneous endoscopic necrosectomy)

Cases of huge WON that extend from the retroperitoneum to the left or right pelvis are frequently observed. There is open space in the pelvis, which makes it easy for a large sub-cavity to form in the pelvic cavity when liquefied WON expands to the pelvis. Because there is a route from the border of the pancreas to the sub-cavity inside the pelvic cavity, transgastrointestinal drainage can be performed by placing a long plastic stent and transnasal tube into the pelvic cavity using the SGTMD method described above. However, when a large sub-cavity (≥5 cm) has formed, the large amount of necrotic tissue causes poor drainage, and the infection cannot be controlled without necrosectomy. In such cases, it is very risky to perform necrosectomy by inserting the endoscope transgastrointestinally through the narrow route from the border of the pancreas to the pelvic cavity. There are limitations to transgastrointestinal endoscopic treatment for huge WON that extends to the pelvic cavity, and a percutaneous approach should be considered at an early stage in such cases. As one minimally invasive therapy, a hybrid approach of endoscopic treatment that uses video-assisted retroperitoneal debridement (VARD) [57] has been reported for WON [58–60]. First, the sub-cavity

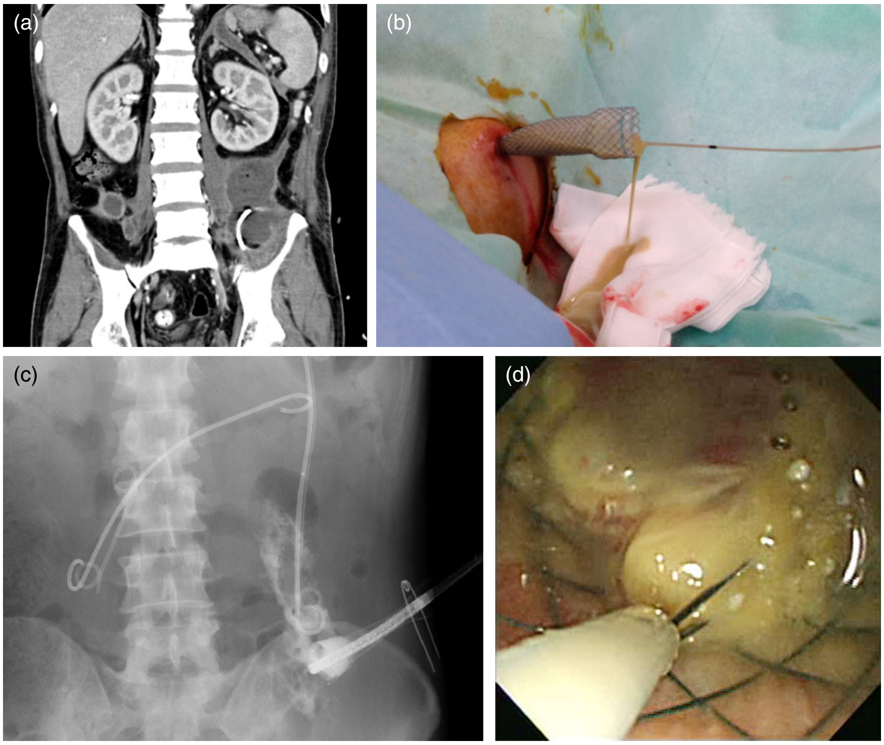

Fig. 6 Hybrid approach (percutaneous endoscopic necrosectomy). (**a**) Computed tomography (CT) revealed the huge walled-off necrosis (WON) extending from the retroperitoneum to the left pelvis. After some sessions of endoscopic necrosectomy around the pancreas, the cavity including necrotic tissue remained in the left pelvis, and so high fever had persisted. (**b**) One week after the placement of percutaneous drainage catheter, percutaneous placement of a large-diameter metal stent was performed. A large amount of pus was drained. (**c**) An ultra slim scope was inserted into WON through the metal stent. (**d**) Percutaneous endoscopic necrosectomy was performed. Decline of fever and improvement of inflammatory response was carried

within the pelvic cavity is approached by percutaneously puncturing the WON under ultrasound or CT guidance, and a drainage tube is placed inside. A fistula will form approximately one week after the drainage tube is placed. That fistula is dilated with a large balloon, and a large-diameter metal stent is placed inside (Video S6). Then, the metal stent is firmly secured to the skin to avoid displacement. At a later date, endoscopic necrosectomy is performed by inserting an endoscope through the metal stent into the WON in the pelvic cavity (Fig. 6). There are no comprehensive studies on this method and further investigation of its safety and effectiveness are necessary. However, it is very useful because the procedure can be performed with normal intravenous anesthesia and it is minimally invasive compared to surgical necrosectomy.

Limitations of transgastrointestinal endoscopic treatments

Endoscopic treatments are excellent minimally invasive treatments because they do not impact the patient's ADL. As outlined above, advances in endoscopic medical devices and the development of various treatment methods have led to dramatic improvement in the mortality rate from WON. Not only has the mortality rate improved, it is now becoming possible to treat WON with less invasive methods in a shorter treatment period. However, it is dangerous to think that all cases of WON should be treated with endoscopic methods alone. The amount of necrotic tissue that can be removed by surgical necrosectomy is vastly greater than the amount that can be removed by the small forceps and snares used in endoscopic necrosectomy. Even in the surgical field, traditional laparotomic drainage and necrosectomy methods have recently been evolving into laparoscopic necrosectomy, and surgical necrosectomy may still come to have an important place in treating WON in the future if combined with recent advances in robotic surgery. In any case, endoscopic treatments should not be considered to be the only treatment for WON, and adopting a comprehensive strategy that includes percutaneous and surgical approaches will lead to better treatments. A WON treatment flowchart presented by Schmidt at the SSAT/AGA/ASGE State-of-the-Art conference reflects similar thinking [61].

Conclusion

This paper reviewed advances in endoscopic treatments for PPC/WON as well as the methodology underlying those treatments. Although considerable advances have now made it possible to treat most cases of WON with endoscopic treatment alone, treatments for WON should be considered from a wide range of options including surgical therapy without being restricted to endoscopic treatments.

Acknowledgments The authors are indebted to the medical editors and Associate Professor Edward Barroga of the Department of International Medical Communications of Tokyo Medical University for the editorial review of the English manuscript. This work was supported in part by the Research Committee of Intractable Pancreatic

Diseases (Principal investigator: Tooru Shimosegawa) provided by the Ministry of Health, Labour, and Welfare of Japan.

Conflict of interest None declared.

References

1. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the lnternational Symposium on Acute Pancreatitis, Atlanta, Ga September 11 through 13, 1992. Arch Surg. 1993;128:586–90.
2. Klöppel G. Pseudocyst and other non-neoplastic cyst of the pancreas. Semin Diagn Pathol. 2000;17:7–15.
3. Baron TH, Thaggard WG, Morgan DE, Stanley RJ. Endoscopic therapy of organized pancreatic necrosis. Gastroenterology. 1996; 111:755–64.
4. Bollen TL, van Santvoort HC, Besselink MG, van Leeuwen MS, Horvath KD, Freeny PC, et al. The Atlanta classification of acute pancreatitis revisited. Br J Surg. 2008;95:6–21.
5. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–11.
6. Itoi T, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Moriyasu F. EUS-guided simultaneous internal and external drainage of pancreatic infected pseudocysts. Dig Endosc. 2006;18:71–4.
7. Inui K, Yoshino J, Okushima K, Miyoshi H, Nakamura Y, Watanabe S, et al. EUS-guided one-step drainage of pancreatic pseudocysts: experience in 3 patients. Gastrointest Endosc. 2001;54:87–9.
8. Mukai S, Itoi T, Sofuni A, Itokawa F, Tsuchiya T, Ishii K, et al. Expanding endoscopic interventions for pancreatic pseudocyst and walled-off necrosis. J Gatroenterol. 2014; doi: 10.1007/s00535-014-0957-8.
9. Binmoeller KF, Seifert H, Walter A, Soehendra N. Transpapillary and transmural drainage of pancreatic pseudocysts. Gastrointest Endosc. 1995;42:219–24.
10. Giovannini M, Bernardini D, Seitz JF. Cystogastrostomy entirely performed under endosonography guidance for pancreatic pseudocyst: results in six patients. Gastrointest Endosc. 1998; 48:200–3.
11. Baron TH, Harewood GC, Morgan DE, Yates MR. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. Gastrointest Endosc. 2002;56:7–17.
12. Bradley EL, Clements JL Jr, Gonzalez AC. The natural history of pancreatic pseudocysts: a unified concept of management. Am J Surg. 1979;137:135–41.
13. O'Malley VP, Cannon JP, Postier RG. Pancreatic pseudocysts: cause, therapy, and results. Am J Surg. 1985;150:680–82.
14. Chen J, Fukami N, Li Z. Endoscopic approach to pancreatic pseudocyst, abscess and necrosis: review on recent progress. Dig Endosc. 2012;24:299–308.
15. Van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology. 2011;141:1254–63.
16. Besselink MG, Verwer TJ, Schoenmaeckers EJ, Buskens E, Ridwan BU, Visser MR, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg. 2007;142:1194–201.
17. Negm AA, Poos H, Kruck E, Vonberg RP, Domagk D, et al. Microbiologic analysis of peri-pancreatic fluid collected during EUS in patients with pancreatitis: impact on antibiotic therapy. Gastrointest Endosc. 2013;78:303–11.
18. Rogers BHG, Cicurel NJ, Seed RW. Transgastric needle aspiration of pancreatic pseudocysts through an endoscope. Gastrointest Endosc. 1975;21:133–4.
19. Grimm H, Binmoeller K, Soehendra N. Endosonography-guided drainage of a pancreas pseudocyst. Gastrointest Endosc. 1992; 38:170–1.
20. Baron TH, Wiersema MJ. EUS-guided transesophageal pancreatic pseudocyst drainage. Gastrointest Endosc. 2000;52:545–9.
21. Sriram PV, Kaffes AJ, Rao GV, Reddy DN. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts complicated by portal hypertension or by intervening vessels. Endoscopy. 2005;37:231–5.
22. Kahaleh M, Shami VM, Conaway MR, Tokar J, Rockoff T, et al. Endoscopic ultrasound drainage of pancreatic pseudocyst: a prospective comparison with conventional endoscopic drainage. Endoscopy. 2006;38:355–9.
23. Varadarajulu S, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). Gastrointest Endosc. 2008;68:1102–11.
24. Park DH, Lee SS, Moon SH, Choi SY, Jung SW, Seo DW, et al. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. Endoscopy. 2009;41:842–8.
25. Seewald S, Ang TL, Kida M, Teng KY, Soehendra N. EUS 2008 Working Group document: evaluation of EUS-guided drainage of pancreatic-fluid collections (with video). Gastrointest Endosc. 2009;69(Suppl):S13–S21.
26. Will U, Wanzar C, Gerlach R, Meyer F. Interventional ultrasound-guided procedures in pancreatic pseudocysts, abscesses and infected necrosis—treatment algorithm in a large single-center study. Ultraschall Med. 2011;32:176–83.
27. Seifert H, Werhmann T, Schmit T, Zeuzem S, Caspary WF. Retroperitoneal endoscopic debridement for infected pancreatic necrosis. Lancet. 2000;356:653–5.
28. Bang JY, Wilcox CM, Trevino JM, Ramesh J, Hasan M, Hawes RH, et al. Relation- ship between stent characteristics and treatment outcomes in endoscopic transmural drainage of pancreatic pseudocysts. Gastrointest Endosc. 2013;77(5 Suppl): AB382.
29. Cahen D, Rauws E, Fockens P, Weverling G, Huibregtse K, et al. Endoscopic drainage of pancreatic pseudocysts: long-term outcome and procedural factors associated with safe and successful treatment. Endoscopy. 2005;10:977–83.
30. Seewald S, Groth S, Omar S, Imazu H, Seitz U, de Weerth A, et al. Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective treatment algorithm (videos). Gastrointest Endosc. 2005;62:92–100.
31. Raczynski S, Teich N, Borte G, Wittenburg H, Mossner J, Caca K. Percutaneous transgastric irrigation drainage in combination with endoscopic necrosectomy in necrotizing pancreatitis (with videos). Gastrointest Endosc. 2006;64:420–4.
32. Siddiqui AA, Dewitt JM, Strongin A, Singh H, Jordan S, Loren DE, et al. Outcomes of EUS-guided drainage of debris-containing pancreatic pseudocysts by using combined endoprosthesis and a nasocystic drain. Gastrointest Endosc. 2013;78: 589–95.
33. Itoi T, Itokawa F, Tsuchiya T, Kawai T, Moriyasu F. EUS-guided pancreatic pseudocyst drainage: simultaneous placement of stents and nasocystic catheter using double-guidewire technique. Dig Endosc. 2009;21(Suppl 1):S53–S56.
34. Voermans RP, Ponchon T, Schumacher B, Fumex F, Bergman JJ, Larghi A, et al. Forward-viewing versus oblique-viewing echoendoscopes in transluminal drainage of pancreatic fluid collections: a multicenter, randomized, controlled trial. Gastrointest Endosc. 2011;74:1285–93.

35. Seewald S, Ang TL, Kida M, Teng KY, Soehendra N. EUS 2008 Working group document: evaluation of EUS-guided drainage of pancreatic-fluid collection (with video). Gastrointest Endosc. 2009;69:S13–21.
36. Arvanitakis M, Delhaye M, Bail MA, Matos C, De Maertelaer V, Le Moine O, et al. Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. Gastrointest Endosc. 2007;65:609–19.
37. Harrison S, Kakade M, Varadarajulu S, Parden J, Morgan D, Christein J. Characteristics and outcomes of patients undergoing debridement of pancreatic necrosis. J Gastrointest Surg. 2010; 14:245–51.
38. Seifert H, Biermer M, Schmitt W, Jurgensen C, Will U, Gerlach R, et al. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicenter study with long term follow-up (the GEPARD study). Gut. 2009;58:1260–6.
39. Gardner TB, Coelho-Prabhu N, Gordon SR, Gelrud A, Maple JT, Papachristou GI, et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. Gastrointest Endosc. 2011;73:718–26.
40. Yasuda I, Nakashima M, Iwai T, Isayama H, Itoi T, Hisai H, et al. Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis: the JENIPaN study. Endoscopy. 2013;45:627–34.
41. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362:1491–502.
42. Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis a randomized trial. JAMA. 2012;10:1053–61.
43. Baron TH, Kozarek RA. Endotherapy for organized pancreatic necrosis: perspectives after 20 years. Clin Gastroenterol Hepatol. 2012;10:1202–7.
44. Siddiqui AA, Easler J, Strongin A, Slivka A, Kowaiski TE, et al. Hydrogen peroxide-assisted endoscopic necrosectomy for walled-off pancreatic necrosis: a dual center pilot experience. Dig Dis Sci. 2014;59:687–90.
45. Park EY, Kwon JY, Kim KJ. Carbon dioxide embolism during laparoscopic surgery. Yonsei Med J. 2012;53:459–66.
46. Talreja JP, Shami VM, Ku J, Morris TD, Ellen K, Kahaleh M. Transenteric drainage of pancreatic-fluid collections with fully covered self-expanding metallic stents. Gastrointest Endosc. 2008;68:1199–203.
47. Fabbri C, Luigiano C, Cennamo V, Polifemo AM, Barresi L, Jovine E, et al. Endoscopic ultrasound-guided transmural drainage of infected pancreatic fluid collections with placement of covered self-expanding metal stents: a case series. Endoscopy. 2012; 44:429–33.
48. Penn DE, Draganov PV, Wagh MS, Forsmark CE, Gupte AR, Chauhan SS. Prospective evaluation of the use of fully covered self-expanding metal stents for EUS-guided transmural drainage of pancreatic pseudocysts. Gastrointest Endosc. 2012;76:679–84.
49. Weilert F, Binmoeller KF, Shah JN, Bhat YM, Kane S. Endoscopic ultrasound-guided drainage of pancreatic fluid collections with indeterminate adherence using temporary covered metal stents. Endoscopy. 2012;44:780–83.
50. Itoi T, Binmoeller KF, Shah J, Sofuni A, Itokawa F, Kurihara T, et al. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with video). Gastrointest Endosc. 2012;75:870–76.
51. Itoi T, Reddy DN, Yasuda I. New fully-covered self-expandable metal stent for EUS-guided intervention in infectious walled-off pancreatic necrosis (with video). J Hepatobiliary Pancreat Sci. 2013;20:403–6.
52. Yamamoto N, Isayama H, Kawakami H, Sasahira N, Hamada T, Ito Y, et al. Preliminary report on a new, fully covered, metal stent designed for the treatment of pancreatic fluid collections. Gastrointest Endosc. 2013;77:809–14.
53. Kawakami H, Itoi T, Sakamoto N. Endoscopic ultrasound-guided transluminal drainage for peripancreatic fluid collections: where are we now? Gut Liver. 2014;8:341–55.
54. Mukai S, Itoi T, Baron TH, Sofuni A, Itokawa F, et al. EUS guided placement of plastic vs biflanged metal stents for therapy of walled-off necrosis: a retrospective single-centre series. Endoscopy. 2014; (in press).
55. Varadarajulu S, Phadnis MA, Christein JD, Wilcox CM. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic wall-off pancreatic necrosis. Gastrointest Endosc. 2011;74:74–80.
56. Mukai S, Itoi T, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, et al. Novel single transluminal gateway transcystic multiple drainages after EUS-guided drainage for complicated multilocular walled-off necrosis (with videos). Gastrointest Endosc. 2014; 79:531–5.
57. Horvath K, Freeny P, Escallon J, Heagerty P, Comstock B, Glickerman DJ, et al. Safety and efficacy of video-assisted retroperitoneal debridement for infected pancreatic collections: a multicenter, prospective, single-arm phase 2 study. Arch Surg. 2010;145:817–25.
58. Navarrete C, Castillo C, Caracci M, Vargas P, Gobelet J, Robles I. Wide percutaneous access to pancreatic necrosis with self-expandable stent: new application (video). Gastrointest Endosc. 2011;73:609–10.
59. Bakken JC, Baron TH. Pancreatic necrosectomy via percutaneous self-expandable metal stent placement. Gastrointest Endosc. 2011;73(Suppl):AB103.
60. Bakken JC, Baron TH. Use of partially covered and fully covered self expandable metal stents to establish percutaneous access for endoscopic necrosectomy. Endoscopy. 2011;43(Suppl 1):A69.
61. Schmidt CM. Introduction: SSAT/AGA/ASGE state-of-the-art conference: necrotizing pancreatitis: novel minimally invasive strategies. J Gastrointest Surg. 2011;15:1086–8.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Video S1 EUS-guided drainage using plastic stents for infected pancreatic pseudocyst.

Video S2 Conventional direct endoscopic necrosectomy for walled-off necrosis.

Video S3 EUS-guided drainage using tubular metal stent for infected pancreatic pseudocyst.

Video S4 EUS-guided drainage using the lumen apposing metal stent for walled-off necrosis.

Video S5 Direct endoscopic necrosectomy through the lumen apposing metal stent.

Video S6 Hybrid approach for complicated walled-off necrosis extending to the left pelvis.