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Consensus guidelines on the diagnosis and treatment of pancreatic pseudocyst and walled-off necrosis from a Chinese multiple disciplinary team expert panel

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ABSTRACT

Objective: To prepare a set of practice guidelines to standardize the entire process, from diagnosis to treatment and follow-up, for pancreatic pseudocysts and walled-off necrosis.

Methods: Thirty-six experts in the fields of digestive endoscopy, pancreatic surgery, interventional radiology, and others presented their opinions via discussions in online conferences by referring to the patient, intervention, comparison, and outcomes principles and then reviewed the evidence and statements using the Delphi method to reach a consensus. The consensus of >80% was finally achieved for the items.

Results: The experts discussed and reached a consensus on 29 statements including 10 categories: (1) definition and classification, (2) imaging and endoscopic diagnosis, (3) therapeutic implications, (4) surgical therapy, (5) percutaneous catheter drainage, (6) endoscopic retrograde cholangiopancreatography, (7) EUS-guided drainage, (8) stent selection for EUS-guided drainage, (9) complication related to stents for cyst drainage, and (10) drug treatment and follow-up.

Conclusion: This consensus based on the clinical experience of experts in various fields and international evidence-based medicine further standardizes the multidisciplinary diagnosis and treatment processes for pancreatic pseudocysts and walled-off necrosis.

Keywords: Pancreatic pseudocyst; Walled-off necrosis; Consensus; Diagnosis and treatment

INTRODUCTION

Pancreatic fluid collection (PFC), a common complication of acute and chronic pancreatitis (AP and CP, respectively), manifests as pancreatic pseudocysts (PPCs) and walled-off pancreatic necrosis (WON), a type of pancreatic cystic disease.[1] Improper handling of PFCs may result in infected pancreatic necrosis (IPN); intracyst, intraperitoneal, or gastrointestinal bleeding; pancreatic fistula; intestinal fistula; and other pressing complications. Therefore, international guidelines and consensus on the diagnosis and treatment of AP emphasize the diagnosis and treatment principles of PFC.[1–4]

Rapid advances in digestive endoscopy, pancreatic surgery, imaging technology, and other diagnostic and therapeutic technologies in recent years, particularly increased developments in EUS technology, and the clinical application of new types of stents for cyst drainage have resulted in the establishment of additional treatment strategies for PPC and WON.

The treatment strategy for PPC and WON is comprehensive and warrants multidisciplinary participation. However, at present, the treatment concepts for PPC and WON are inconsistent; further, the timing of interventional therapy is unclear, and complication management is insufficient. Therefore, the development of a multidisciplinary expert consensus on PPC and WON is warranted. In August 2022, led by the National Clinical Research Center for Digestive Diseases (Shanghai), the Ultrasound Endoscopy Group of the Chinese Society of Digestive Endoscopology, and Pancreatology Committee of the Chinese Medical Doctor Association combined the latest international data on evidence-based medicine and formed a group of experts in the fields of digestive endoscopy, pancreatic surgery, and imaging technology to prepare the first international consensus on the diagnosis and treatment of PPC and WON. The major aim was to further standardize the clinical diagnosis and treatment of PPC and WON and promote the development of new comprehensive treatment technologies based on interventional endoscopy.

METHODS

The statements of this consensus are proposed with reference to the PICO (participants, interactions, comparisons, and outcomes) principle.[5] In accordance with the grading of GRADE (Recommendations Assessment, Development, and Evaluation) system,[6] the quality of evidence was classified into high, medium, low, and very low categories, and the level of recommendation was

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Table 1

Summary of the 29 statements.

Statements		Evidence quality/ recommendation strength	Consensus level, %
Section 1: Definition and classification	1. PPC is a delayed complication of AP and mainly comprises liquid with minimal or no necrosis, different from WON.	A/1	100
	2. Both PPC and WON can be associated with a bacterial or fungal infection, leading to IPN, and WON probably causes IPN.	A/1	100
	3. PPC can also occur due to CP, pancreatic tumors, or other pancreatic diseases. The mechanism may be related to retention cysts caused by pancreatic duct obstruction.	C/2	96.3
Section 2: Imaging and endoscopic diagnosis	4. CT or MRI is the first choice for PPC and WON diagnosis. MRI is more helpful to determine the contents of cyst fluid and solid debris.	B/2	92.6
	5. EUS is superior to CT or MRI in judging the nature of PPC. It can accurately determine the proportion of necrosis in the cyst, helpful in distinguishing between PPC and WON.	A/1	100
	6. EUS-guided FNA is of some value in judging whether PPC/WON is associated with infection (IPN), but EUS-FNA for diagnosis alone is not recommended, and it is usually implemented when endoscopic drainage is planned.	B/2	100
Section 3: Therapeutic implications	7. PPC/WON lasts for ≥4 wk, and there are indications for intervention when the cyst diameter is ≥6 cm and/or secondary compression symptoms of the cyst and/or progressive enlargement of the cyst and/or cyst infection and/or pancreatic portal hypertension.	A/1	100
	8. If the diameter of PPC/WON is <6 cm and there are no obvious symptoms or serious complications, PPC/WON can be conservatively treated and observed for a period to ensure self-absorption.	B/2	100
	9. It is difficult for PPC caused by CP to self-resolve, and positive drainage is recommended. If there is a tendency for malignant transformation, early surgical treatment is recommended.	C/2	81.5
Section 4: Surgical therapy	10. When PPC/WON is at a distant location from the stomach and duodenum wall and percutaneous drainage cannot be performed, Roux-en-Y cystojejunostomy is recommended.	B/2	82.1
	11. If the endoscopic and conservative treatment of PPC/WON is ineffective, laparoscopic internal drainage is preferred when surgical treatment was needed.	B/1	88.9
Section 5: Percutaneous catheter drainage	12. When PPC/WON is at a distant location from the stomach wall and has a percutaneous puncture path, PCD is recommended.	B/1	96.3
	13. After PCD, there is a certain incidence of bleeding, infection, pancreatic fistula, or intestinal fistula, requiring close observation and timely intervention.	C/2	96.3
Section 6: Endoscopic retrograde cholangiopancreatography	14. If PPC/WON is connected with the pancreatic duct and secondary to CP, ERCP can be performed to place a pancreatic duct stent for drainage.	B/1	100
	15. There is a risk of infection or AP after ERCP-guided drainage. For PPC/WON with partial interruption of the pancreatic duct, EUS-guided drainage is required when necessary.	C/2	100
Section 7: EUS-guided drainage	16. EUS-guided puncture and drainage are recommended as the first-line treatment for PPC/WON. It has a high success rate, low complication, and recurrence rates and can considerably reduce the length of hospital stay and cost.	A/1	100
	17. Puncture and drainage of PPC/WON by direct visualization using an ordinary endoscope is not recommended; it has high operation failure and complication rates.	B/1	100
	18. EUS puncture and drainage should be performed at the place where the cyst is closest to the digestive tract wall. Further, the puncture path should avoid blood vessels. The steps involved are guided wire insertion, electrotomy, sinus expansion, and then stent insertion. If necessary, FNA should be performed first to determine the nature of the cyst fluid.	A/1	96.3

(*continued*)

Table 1
(continued).

Statements		Evidence quality/ recommendation strength	Consensus level, %
Section 8: Stent selection for EUS-guided drainage	19. A plastic stent can be used for PPC drainage, but it is not effective for WON drainage.	B/1	100
	20. LAMSs can be used for PPC or WON drainage, particularly for drainage of WON with a high amount of solid debris.	A/1	100
	21. Other types of metal stents are not recommended for PPC/WON drainage.	A/1	85.7
	22. At present, there is still controversy that a LAMS needs to be combined with a plastic stent for PPC/WON drainage.	B/1	96.6
	23. If LAMS is used in PPC/WON with DPDS, it should be replaced with a plastic stent after removal to maintain the continuous drainage of the damaged pancreatic duct and prevent cyst recurrence.	B/1	89.7
Section 9: Complication related to stents for cyst drainage	24. Plastic stent drainage of PPC has the risks of stent blockage, displacement, concurrent infection, and bleeding.	B/1	96.6
	25. LAMS has a certain degree of bleeding risk; therefore, close monitoring of the condition is necessary. In case of bleeding, the stent should be removed immediately, and if necessary, DSA hemostasis or surgery must be performed.	B/2	96.6
	26. DEN is required in case of infection or fever after the placement of the LAMS.	B/2	93.1
	27. The best time to remove the LAMS is 3 wk to 2 mo after it is implanted, and a long retention time will lead to stent embedding.	A/1	100
Section 10: Drug treatment and follow-up	28. Acid suppressants and pancreatin preparations can be used to maintain the treatment of PPC/WON without symptoms and intervention indications.	C/2	82.8
	29. PPC/WON requires close follow-up after endoscopic or other methods of treatment. Imaging should be conducted every 3–6 mo, and if necessary, intervention should be performed again.	B/2	100

A: high; B: medium; C: low; D: very low.

AP: acute pancreatitis; CP: chronic pancreatitis; CT: computed tomography; DEN: direct endoscopic necrosectomy; DSA: digital subtraction angiography; ERCP: endoscopic retrograde cholangiopancreatography; FNA: fine-needle aspiration; IPN: infectious pancreatic necrosis; LAMS: lumen-apposing metal stent; MRI, magnetic resonance imaging; PCD: percutaneous catheter drainage; PPC, pancreatic pseudocyst; WON: walled-off pancreatic necrosis.

considered either strong or weak. Finally, an improved Delphi method was applied to reach a consensus through experts' voting. A consensus was reached when the proportion of ① + ② in the voting opinions was >80%, and the consensus level was expressed by the proportion (%) of ① + ② in the voting opinions.

With due consideration to the COVID-19 pandemic, the MDT expert panel held 3 online seminars. The consensus of 2 versions was finally reached, and the Chinese version was published in the *Chinese Journal of Digestive Endoscopy* and the *Chinese Journal of Pancreatic Diseases* in November 2022. The English version of the manuscript is for the reference of international communities.

RESULTS

There were 29 recommendations in 10 categories with a consensus level of >80% (Table 1).

Section 1: Definition and classification

Statement 1: PPC is a delayed complication of AP and mainly comprises liquid with minimal or no necrosis, different from WON.

Evidence quality: A strength of recommendation: Strong consensus level: 100%

PPC is a common complication of AP and CP. Approximately 70% of PPC cases occur in patients with alcoholic pancreatitis; 15% of cases are idiopathic, and some cases are caused by surgery- or trauma-induced pancreatic injury.[7] PPC usually occurs 4 weeks after AP onset, with a complete accumulation of nonepithelial fluid within the capsule, including pancreatic secretions, granulation tissue, and fibrous tissue. International guidelines[1–4] state that peripancreatic fluid accumulation associated with AP can be divided into 4 categories based on the onset time and composition of the accumulated fluid: acute peripancreatic fluid collection (APFC), acute necrotic collection, PPC, and WON. This consensus primarily focuses on PPC and WON and the diagnosis and treatment of APFC; acute necrotic collection in the acute phase and IPN in the later phase have not been discussed.

Statement 2: Both PPC and WON can be associated with a bacterial or fungal infection, and WON probably causes IPN

Evidence quality: A strength of recommendation: Strong consensus level: 100%

PPC and WON can easily cause spontaneous or exogenous infections owing to puncture and drainage because their cysts are rich in nutrients and contain a high proportion of proteins. The spontaneous infection may be mainly caused by low immunity, damaged intestinal mucosal barrier, ectopic intestinal flora, and other factors.[7] Infection caused by PPC can result in fever, abdominal pain, increased white blood cell count, elevated serum procalcitonin levels, and the "bubble sign" in the cyst upon computed tomography

(CT).[8] Sometimes, after a PPC infection, the "bubble sign" might not appear on CT; in such cases, the infection can be confirmed after drainage and cyst fluid culture. The infection rate of PPC is approximately 20%–40%.[7] Compared with patients with PPC with clear cyst fluid, those with WON are more prone to infection owing to the presence of more solid components and organic substances.

Statement 3: PPC can also occur due to CP, pancreatic tumors, or other pancreatic diseases. The mechanism may be related to retention cysts caused by pancreatic duct obstruction.

Evidence quality: C strength of recommendation: Weak consensus level: 96.3%

Pseudocysts formed in individuals with CP are usually owing to acute exacerbation of basic diseases, mostly retention cysts, which are related to pancreatic duct obstruction. Nealon and Walser[9] classified PPC into 7 types based on the relationship between the cysts and the anatomical position of the main pancreatic duct. The 7 types are as follows: type I, normal pancreatic duct, and the pancreatic duct are not connected with the cyst; type II, normal pancreatic duct, but the pancreatic duct is connected with the cyst; type III, pancreatic duct stenosis, but the pancreatic duct is not connected with the cyst; type IV, pancreatic duct stenosis, and the pancreatic duct are connected with the cyst; type V, a part of the pancreatic duct is normal with complete pancreatic duct disruption; type VI, CP, but the pancreatic duct is not connected with the cyst; and type VII, CP, and the pancreatic duct is connected with the cyst. However, imaging results alone are insufficient to judge the relationship between the pancreatic duct and cyst; therefore, it is difficult to classify PPC before treatment.

Benign and malignant pancreatic tumors can also result in pancreatic duct obstruction, leading to PPC or secondary AP forming PPC or WON. Pancreatic cancer is characterized by the presence of solid spaces mostly, which can be identified via patient symptoms, imaging examination, blood tumor marker detection, and so on.[7] For patients with a suspected tumor and PPC, cyst drainage should be carefully performed to avoid metastasis of the implanted tumor. Although imaging manifestations of pancreatic cystic tumors can be similar to those of PPC, the cystic wall of pancreatic cystic tumors mostly contains epithelial tissues. Pathological examination, tumor marker detection, amylase detection, or molecular biology techniques can be performed using aspirated cyst fluid. Further, imaging can be performed to closely follow up asymptomatic patients.

Section 2: Imaging and endoscopic diagnosis

Statement 4: CT or magnetic resonance imaging (MRI) is the first choice for PPC and WON diagnosis. MRI is more helpful to determine the contents of cyst fluid and solid debris.

Evidence quality: B strength of recommendation: Weak consensus level: 92.6%

On abdominal CT, PPC appears as a cyst with a relatively uniform density and few solid components. Enhanced CT helped in accurately evaluating the size, diameter, and peripheral blood vessels of the cyst[10] (Figure 1). The CT characteristics of WON are as follows: the cystic cavity contains necrotic tissue in addition to fluid volume accumulation; the content of necrotic matter can be determined using CT density value. MRI can be performed to determine the nature and fluid and necrotic contents of the cyst more accurately. Magnetic resonance cholangiopancreatography (MRCP) can help preliminarily determine the relationship between the cyst and pancreatic duct.[1,11] Further, MRCP and EUS can be performed to determine the necrotic matter content in the cyst to differentiate between WON and PPC. Finally, abdominal B-ultrasonography can be performed as an optional imaging method, and peripancreatic fluid dark areas without echo can be observed using this technique.

Statement 5: EUS is superior to CT or MRI in judging the nature of PPC. It can accurately determine the proportion of necrosis in the cyst, helpful in distinguishing between PPC and WON.

Evidence quality: A strength of recommendation: Strong consensus level: 100%

EUS is closer to PPC or WON when scanning; therefore, it can accurately observe the changes in the cyst wall structure, including the presence of mural nodules, flocs, or solid debris in the cyst as well as partitions (Figure 1). As a result, EUS can more accurately

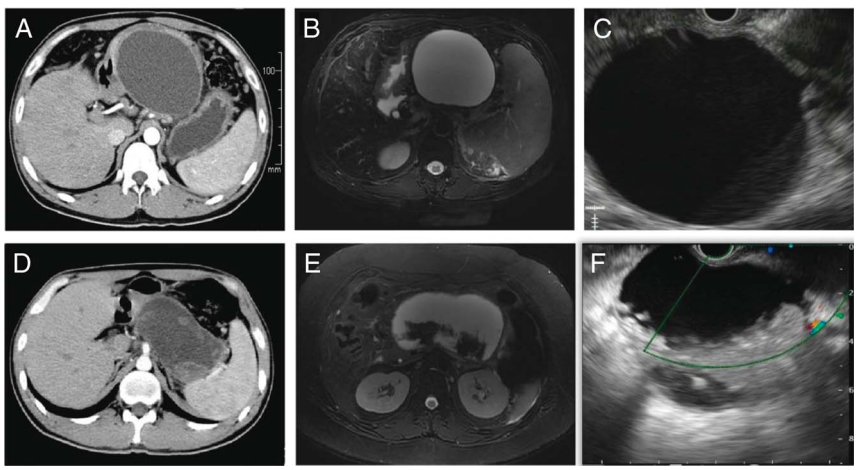

Figure 1. CT, MRI, and EUS images of typical PPC (A–C) and WON (D–F). CT: computed tomography; MRI, magnetic resonance imaging; PPC, pancreatic pseudocyst; WON: walled-off pancreatic necrosis.

judge the proportion of cyst necrosis, particularly for distinguishing between PPC and WON.[12] Previous guidelines defined PPC as no solid debris in the cyst upon enhanced CT.[1] Partial WON exhibits good homogeneity on CT; however, EUS can more accurately diagnose WON. In general, for pseudocysts with less amount of solid debris, necrotic tissues can only be found during drainage.[13] Further, there is no standard value of the proportion of solid debris in PPC and WON under EUS. Nevertheless, some studies hypothesize that solid debris content of >20% in cysts may be the boundary value for distinguishing between WON and PPC.[14]

Statement 6: EUS-FNA is of some value in judging whether PPC/WON is associated with infection (IPN), but EUS-FNA for diagnosis alone is not recommended, and it is usually implemented when endoscopic drainage is planned.

Evidence quality: B strength of recommendation: Weak consensus level: 100%

Imaging plays an essential role in judging the range of IPN infection, evaluating its severity, and selecting follow-up treatment measures. In CT, the "bubble sign" is direct evidence for IPN diagnosis. In case a definite diagnosis cannot be achieved, EUS-FNA may be performed as appropriate, and a puncture liquid smear or culture may help identify the infected bacteria.[15] However, FNA poses the risk of PPC or WON infection; therefore, EUS-FNA should not be performed solely for diagnosis.[16]

Section 3: Therapeutic implications

Statement 7: PPC or WON lasts for ≥4 weeks, and there are indications for intervention when the cyst diameter is ≥6 cm and/or secondary compression symptoms of the cyst and/or progressive enlargement of the cyst and/or cyst infection and/or pancreatic portal hypertension.

Evidence quality: A strength of recommendation: Strong consensus level: 100%

No intervention is needed in 40%–70% of PPC cases with no or mild symptoms, and the cyst can be absorbed on its own.[7,12] Nearly 50% of cases of asymptomatic WON can spontaneously disappear after conservative treatment.[17] The 1992 Atlanta Pancreatitis Treatment Guidelines recommend drainage of PPCs ≥6 cm and/or that are symptomatic and with a duration of ≥6 weeks.[18] Pseudocysts in CP, with a thick cyst wall and pancreatic duct interruption, cannot be automatically absorbed after appearance and can only be resolved with the clinical intervention.[19] Further, PPC/WON is not easily resolved when (1) cyst diameter is ≥6 cm; (2) cysts persist for ≥6 weeks; and (3) there are complications such as intracystic infection, hemorrhage, and compression of adjacent organs.[12]

As for the timing of cyst drainage, although a study[20] suggests the safety and feasibility of EUS-guided puncture and drainage at the early phase (<4 weeks) of peripancreatic fluid volume accumulation after AP, early intervention is still not recommended. Early interventional treatment of cysts without an intact cyst wall increases the risk of complications. Recently, in a study[21] involving 170 patients with AP within 4 weeks (early group) and ≥4 weeks (delayed group) and EUS-guided puncture and drainage with peripancreatic effusion, the cyst diameter in the early group (12.3 ± 2.1 cm) was significantly larger than that in the delayed group (10.5 ± 2.7 cm); further, the proportion of solid components in the cyst (47.7% ±8.9%) and direct endoscopic necrosectomy (DEN) (50.0%) was significantly higher than those in the delayed group (28.3% ±11.7% and 7.4%, respectively). The low rate of reinterventional therapy in the delayed group may be related to the liquefaction of necrotic products over time. Further, the study revealed that the larger the cyst diameter, the more the necrotic matter content, and a greater number of follow-up interventions are required. Cyst diameter of ≥10 cm and necrotic content of ≥30% are risk factors for reintervention.[22]

The timing of PPC or WON treatment can be summarized as follows: (1) the cyst is present for ≥4 weeks; (2) its diameter is ≥6 cm; (3) there are secondary compression symptoms; (4) there is a progressive enlargement of the cyst; and (5) there are complications such as intracapsular infection and pancreatic portal hypertension. If the criterion (1) + (2)/(3)/(4)/(5) is met, interventional treatment is recommended. Cysts complicated with acute hemorrhage do not require intervention. However, intervention can be considered for stale hemorrhages complicated with infection, and short-term hemorrhages should be carefully treated.

Statement 8: If the diameter of PPC/WON is <6 cm and there are no obvious symptoms or serious complications, PPC/WON can be conservatively treated and observed for a period to ensure self-absorption.

Evidence quality: B strength of recommendation: Weak consensus level: 100%

Conservative treatment means medical support treatment using non-surgical interventions. PPC/WON can be absorbed on its own via intravenous infusion, acid inhibition, enzyme inhibition, anti-infection, and nutritional support.[17] In general, individuals who meet the following criteria can undergo conservative treatment: (1) their general condition is good; (2) the etiology is not a chronic pancreatic disease; (3) there is a single small cyst (diameter <6 cm) without a progressive enlargement trend, and its existence time is <4 weeks; and (4) the cyst wall is thin, the cyst cavity is not connected with the main pancreatic duct, and the nature of the cyst fluid is stable, except for bleeding, infection, and other complications. Such patients can be followed up via abdominal B-ultrasonography or CT or MRI every 6–8 weeks, and those without symptoms or progressive enlargement of the cysts can be continuously observed without intervention.

Statement 9: It is difficult for PPC caused by CP to self-resolve, and positive drainage is recommended. If there is a tendency for malignant transformation, early surgical treatment is recommended.

Evidence quality: C strength of recommendation: Weak consensus level: 81.5%

Approximately 20%–40% of cases of CPs complicated with PPC are mostly caused by obstruction of the main or branched pancreatic duct. In such cases, PPC cannot be resolved without removing relevant factors; therefore, positive drainage is recommended. In patients with CP, a PPC with a diameter of <5 cm but connected with the pancreatic duct can be positively drained through the papilla under an endoscope.[23] PPC caused by CP has a certain risk of malignancy. Therefore, for such cases, immediate surgical treatment is recommended. Surgical intervention is also recommended for partial patients with a ruptured pseudocyst.

Section 4: Surgical therapy

Statement 10: When PPC/WON is at a distant location from the stomach and duodenum wall and percutaneous drainage cannot be performed, Roux-en-Y cystojejunostomy is recommended.

Evidence quality: B strength of recommendation: Weak consensus level: 82.1%

Surgical treatment of PPC mainly includes internal and external drainage[12]; internal drainage includes cystogastric drainage and cystojejunostomy. Cystojejunostomy is the most widely used surgical internal drainage in clinical settings. Roux-en-Y cystojejunostomy has an ideal effect and is mainly applicable to individuals with a low cyst position. Internal drainage should be performed after the cyst wall matures; however, with the development of endoscopic cyst drainage, surgical cystogastric drainage has gradually been replaced. Nevertheless, the effect of surgical internal drainage is better than that of external drainage, which refers to the external drainage of the cyst; this is applicable only to individuals with a short cyst formation time (<4 weeks), a thin cyst wall, and secondary bacterial infections. At present, it is rarely used in clinical settings.

Statement 11: If the endoscopic and conservative treatment of PPC/WON is ineffective, laparoscopic internal drainage is preferred when surgical treatment was needed.

Evidence quality: B strength of recommendation: Strong consensus level: 88.9%

The surgical indications for PPC are similar to those for treatment. For patients who cannot undergo endoscopic drainage or percutaneous puncture drainage, surgical treatment is recommended after excluding surgical contraindications. However, the incidence of postoperative complications is as high as 25%, and the mortality rate is 5% in the surgical treatment of PPC.[24] There have been rapid developments in laparoscopic surgery, and its operation is similar to traditional surgery, with obvious advantages, such as less trauma and fast recovery; however, the operational requirements of this technique are high. Laparoscopic intracavitary drainage of pseudocysts is significantly superior to conventional open surgery in reducing postoperative complications, incidence rate, and postoperative pain and ensuring early recovery.[25]

Section 5: Percutaneous catheter drainage

Statement 12: When PPC/WON is at a distant location from the stomach wall and has a percutaneous puncture path, percutaneous catheter drainage (PCD) is recommended.

Evidence quality: B strength of recommendation: Strong consensus level: 96.3%

PCD is a minimally invasive procedure that was earlier used to treat PPC. Most PCDs are performed under the guidance of an abdominal ultrasound or CT, without waiting for the cyst wall to mature. This drainage technique is mostly used to treat APFC in AP with acute exudation (<4 weeks). However, this technique has high technical requirements, and in some patients, the condition might relapse. At present, PCD is also used to drain a part of the PPC or WON, with the advantages of simple operation and real-time observation of the properties of the drainage fluid.

In general, PCD is suitable for PPC with normal pancreatic duct anatomy and when the cyst is located far away from the stomach wall. Further, it can be used as an emergency treatment option for patients with critical illnesses and high surgical risk. If PPC causes recurrent symptoms, severe infection, intracystic hemorrhage, cyst rupture, and other life-threatening complications, PCD is recommended for those who are unconditionally treated using endoscopy in a timely manner. However, if the treatment effect is not satisfactory, surgical treatment should be reconsidered. A study revealed that the total effective rate of PCD for PPC treatment is 62%, with no cases of death.[26] Another study revealed that the failure rate of PCD is approximately 16%, the recurrence rate is 7%, and the complication rate is 18%.[27] Most patients with CP have an abnormal pancreatic duct structure and the cyst is connected with the main pancreatic duct; therefore, the failure rate of PCD is high.

Statement 13: After PCD, there is a certain incidence of bleeding, infection, pancreatic fistula, or intestinal fistula, requiring close observation and timely intervention.

Evidence quality: C strength of recommendation: Weak consensus level: 96.3%

The main common complications of PCD include hemorrhage, infection, sepsis, pancreatic fistula, and intestinal fistula. The rare complications include spleen injury, pneumonia, pneumothorax, empyema, myocardial infarction, and intestinal obstruction. A study reported that PCD was associated with an increased risk of pancreatic fistula, and the incidence of pancreatic fistula after PCD was as high as 14%.[28] In PCD, the drainage fluid may suddenly become bloody; therefore, the possibility of celiac blood vessel rupture should be considered. If needed, emergency digital subtraction angiography (DSA) or surgery can be performed to stop the bleeding. Cavity organ and blood vessel injuries are also important complications of PCD for PPC. Most PCD-related bleeding events require surgical intervention; however, the overall postoperative mortality is similar to that of patients without bleeding complications.[29] Moreover, a retrograde infection caused by PCD is common; however, its origin remains controversial and can also be caused by ectopic intestinal flora.

Strictly speaking, pancreatic fistula is not a direct complication of PCD. Because PPC or WON is connected to the main or branched pancreatic duct, the drainage fluid will contain translucent clear pancreatic juice in the later phase, accompanied by elevated amylase levels in the drainage fluid (usually >1000 U/mL), which is of diagnostic value for determining the origin of the pseudocyst. Most intestinal fistulas are not caused by direct damage to the intestinal wall by the drainage tube but are related to the abdominal environment in which the intestine is located (pancreatic juice erosion or infection); some IPNs directly cause intestinal fistulas after drainage.

Section 6: Endoscopic retrograde cholangiopancreatography

Statement 14: If PPC/WON is connected with the pancreatic duct and secondary to CP, endoscopic retrograde cholangiopancreatography (ERCP) can be performed to place a pancreatic duct stent for drainage.

Evidence quality: B strength of recommendation: Strong consensus level: 100%

ERCP is the earliest available endoscopic technique for PPC treatment. Endoscopic drainage of PPC refers to the drainage of cyst fluid into the digestive tract under the guidance of an endoscope to relieve symptoms and resolve cysts. ERCP-guided internal drainage is also called transpapillary cyst drainage. In this, stents are inserted into the pancreatic duct to relieve duct stenosis and restore duct continuity. This method is mainly applicable to PPCs connected with the main pancreatic duct, such as PPCs related to CP.[23] A study[30] reported that ERCP is safe and effective for PPC treatment. In general, pancreatic duct stents need to be

retained for a long time (>4 months). If needed, stents can be replaced midway. The most common complication of ERCP is postoperative AP, followed by cyst infection. Most pseudocysts in the head of the pancreas are connected to the main pancreatic duct. In a few cases where ERCP cannot be performed owing to cyst compression, the cyst can be drained via the digestive tract before performing ERCP.

Statement 15: There is a risk of infection or AP after ERCP-guided drainage. For PPC/WON with partial interruption of the pancreatic duct, EUS-guided drainage is required when necessary.

Evidence quality: C strength of recommendation: Weak consensus level: 100%

A single-center randomized controlled trial[31] analyzed and compared the application of surgery and endoscopy (ERCP combined with EUS) and 2 different treatment methods for PPC treatment. The effect of endoscopic drainage for PPC was no less than that of surgical drainage. Further, no significant difference was observed in the recurrence rate between the 2 groups after surgery; however, the endoscopic drainage group was superior to the surgical drainage group in terms of hospitalization time and cost. Moreover, endoscopic treatment of peripancreatic fluid accumulation (PPC or WON) has a higher initial treatment success rate, lower reintervention and adverse event rates, and shorter length of hospital stay than those of PCD.[32,33]

Whether ERCP-guided pancreatic stent implantation combined with EUS cyst drainage can reduce the recurrence rate of cysts remains controversial. A multicenter study hypothesized that the effect of ERCP combined with EUS for PPC drainage was equivalent to EUS drainage alone. The combined use of gastrointestinal drainage and duodenal papillary drainage could not improve the drainage effect of cysts and could not prevent cyst recurrence.[34] Pancreatic trauma often results in pancreatic duct interruption. In 84% of patients with peripancreatic effusion after pancreatic trauma, cyst recurrence caused by disconnected pancreatic duct syndrome (DPDS) can be reduced via long-term transpapillary drainage through a stent after main pancreatic duct interruption.[35] A study confirmed that ERCP combined with EUS can reduce the occurrence of pancreatic fistula in PPC or WON with partial pancreatic duct interruption.[36]

Section 7: EUS-guided drainage

Statement 16: EUS-guided puncture and drainage are recommended as the first-line treatment for PPC/WON. It has a high success rate, low complication, and recurrence rates and can considerably reduce the length of hospital stay and cost.

Evidence quality: A strength of recommendation: Strong consensus level: 100%

Compared with surgery, endoscopic drainage is minimally invasive, has lesser complications, and has a lower recurrence rate. Further, endoscopic drainage is less invasive than surgery, can avoid the occurrence of pancreatic fistula, and has a high long-term cure rate. At present, it is an important technique for the clinical treatment of PPC.[1] EUS-guided puncture and drainage of pseudocysts have a high success rate, low complication rate, and good long-term effects. It is considered the first choice of endoscopic treatment technology for PPC or WON.[7] EUS can differentiate solid debris in the cyst fluid and detect the distribution of blood vessels inside and outside the cysts using the Doppler effect; as a result, it can avoid blood vessels and select the best puncture point.[37] Chinese scholars performed EUS-guided puncture and drainage as early as 2006,[38] which is a safe and effective new procedure to treat PPC. The EUS treatment principles are as follows: (1) puncture should be performed at the most swollen part of the cyst on the premise of avoiding large vessels; (2) the cyst reaches the treatment indication; and (3) if necessary, EUS-FNA is performed to exclude intracapsular tumors.

Statement 17: Puncture and drainage of PPC/WON by direct visualization using an ordinary endoscope are not recommended; they have high operation failure and complication rates.

Evidence quality: B strength of recommendation: Strong consensus level: 100%

The success rate of EUS-guided cyst puncture and drainage was noted to be 80%–100%; its technical success rate was significantly higher than that of traditional endoscopic puncture and drainage (33.3%–72.4%).[39] In 1989, Cremer et al.[40] reported for the first time that drainage under the guidance of an ordinary gastroscope includes endoscopic cystogastrostomy and endoscopic cystoduodenostomy. Double-pigtail plastic stents were placed between the PPC and stomach or duodenum to drain cyst fluid. However, the application scope of endoscopic puncture and drainage under direct vision is limited:[12] (1) on imaging, the distance between the cyst and the digestive tract wall is small, and endoscopic examination revealed that the digestive tract wall is considerably compressed, and (2) there was no varicose vein in the digestive tract wall, and pseudoaneurysm and malignant lesions were excluded. Although drainage under direct vision is characterized by less trauma,[41] it cannot avoid blood vessels, its success rate is lower than that of EUS-guided technology,[39] and the risk of bleeding and infection is high; therefore, it has been replaced by EUS.

Studies have reported the use of natural orifice transluminal endoscopic surgery for treating PPC or WON. Its effect is equivalent to that of laparoscopy and open surgery, with the advantage of less trauma. However, it has high technical requirements and warrants the participation of multidisciplinary teams.[42,43]

Statement 18: EUS puncture and drainage should be performed at the place where the cyst is closest to the digestive tract wall. Further, the puncture path should avoid blood vessels. The steps involved are guided wire insertion, electrotomy, sinus expansion, and then stent insertion. If necessary, FNA should be performed first to determine the nature of the cyst fluid.

Evidence quality: A strength of recommendation: Strong consensus level: 96.3%

The specific steps involved in EUS-guided cyst puncture and drainage are as follows[44]: (1) first, the location and size of the pseudocyst should be determined under EUS and the appropriate puncture point should be selected; (2) a 19-gauge puncture needle should be inserted into the PPC through the endoscopic duct, and a guide wire should be inserted into the PPC under the guidance of X-rays to ensure the guide wire hovers in the cyst; (3) an electric knife should be placed along the guide wire to create a channel between the stomach and capsule wall, and the balloon should be expanded; and then (4) the drainage stent (plastic or metal stent) should be placed. Recently, the clinical applications of an "integrated" stent were highlighted, improving the convenience of

surgery. If EUS is unable to determine the nature of the cyst, FNA can be performed first to achieve a clear diagnosis.

Section 8: Stent selection for EUS-guided drainage

Statement 19: A plastic stent can be used for PPC drainage, but it is not effective for WON drainage.

Evidence quality: B strength of recommendation: Strong consensus level: 100%

The most used stent for cyst drainage is a double-pigtail plastic stent with a diameter of 7F–10F (2–3 mm). A study comparing the effects of drainage stents with different diameters reported that[45] a 10F double-pigtail plastic stent can quickly drain cysts and shorten the length of hospital stay and that its infection and cyst recurrence rates are similar to those of 7F stents; long-term follow-up (10–103 months) using a single 7F plastic stent for PPC drainage revealed that the treatment success rate (cyst reduced by >50% in 2 weeks) was 100%. The successful rate of drainage of noncomplex PPC plastic stents with a single component was independent of the diameter and number of stents used.[13] However, plastic stents are prone to blockage and displacement; therefore, it is recommended to place several pigtail tubes for drainage whenever possible to reduce the incidence of complications. Further, plastic stents have a better economic benefit ratio for treating PPC.[46] It is worth noting that, for treating large WON (>15 cm), lumen-apposing metal stent (LAMS) is not superior to plastic stent. Further research is needed to clarify this in the future.[47]

Statement 20: LAMSs can be used for PPC or WON drainage, particularly for drainage of WON with a high amount of solid debris.

Evidence quality: A strength of recommendation: Strong consensus level: 100%

LAMS is a drainage stent based on the structure of a biliary metal stent. It has 2 wings to prevent displacement (Figure 2). The end of the biliary metal stent is deburred, and the surface is covered with biofilm. The 2 ends of the stent can cling to the stomach wall and inner wall of the cyst, respectively. The stent is 10 mm long, and its inner diameter can reach 10–20 mm. Further, its cyst drainage effect is better than plastic stents and biliary metal stent. Moreover, LAMS placement technology is not complicated, its operation time is short, and the placement success rate is high.

Figure 2. Schematic illustration of dual chamber-fixed metal support (LAMS). LAMS: lumen-apposing metal stent.

A recent study[48] reported that LAMSs had a higher success rate than plastic stents (95.6% *vs.* 89.4%) in treating PPC. Another study[49] on the registration of imported LAMS (AXIOS) reported that the technical success rate of LAMSs was 100%; the clinical success rate was 93.3%; and infection, stent blockage, and displacement rates were 13.3%, 10.0%, and 6.7%, respectively. Nevertheless, additional studies on LAMSs are underway.[50] Multiple meta-analyses have confirmed that metal stents are superior to plastic stents for treating PFC, particularly WON.[51,52] Another unique advantage of LAMSs is that for patients with cyst infection during the treatment process, ensuring that the stent does not shift, it is feasible to perform DEN, thereby creating minimally invasive treatment conditions for patients with concurrent PPC infection.[53] Compared with PPC, the low success rate of endoscopic treatment of WON is directly related to the necrotic content in WON.[14]

Statement 21: Other types of metal stents are not recommended for PPC/WON drainage.

Evidence quality: A strength of recommendation: Strong consensus level: 85.7%

In 2010, the first international report to use a biliary membrane–covered metal stent to drain PPC was released, and it reported that the fully covered metal stent was safe and effective for PPC drainage.[54] The position of the metal stent can be postoperatively adjusted to prevent stent displacement. Furthermore, according to the size of the cyst and the nature of the cyst fluid, it can be considered whether a nasal cyst tube or a plastic stent should be placed in the metal stent to assist with drainage and flushing. The metal stent exhibits higher flexibility and tension, has a thicker diameter, facilitates sufficient and effective drainage, and exhibits a longer patency time than the plastic stent.[55] However, because of its cylinder shape that is easy to shift, the clinical application of biliary membrane–covered metal stents in PPC or WON treatment has gradually reduced. A study that compared the drainage safety of 2 different metal stents revealed that the biliary membrane–covered metal stent was less safe than the new stent LAMS, and the incidence of complications with the latter was significantly lower than those with the biliary membrane–covered metal stent.[56]

Statement 22: At present, there is still controversy that a LAMS needs to be combined with a plastic stent for PPC/WON drainage.

Evidence quality: B strength of recommendation: Strong consensus level: 96.6%

In 2018, for the first time, some scholars reported that the LAMS combined with the plastic stent was used to treat PPC.[57] A retrospective analysis of the efficacy of 47 patients with PPC treated with LAMS + plastic stent drainage was performed, and the rate of reintervention in the LAMS group was 17%, whereas the LAMS + plastic stent group did not require reintervention. Other studies revealed that with the use of the LAMS + plastic stent, the incidence of adverse events was significantly lower than that with LAMS alone (10% *vs.* 42.9%).[58] However, recent studies suggest that the success and complication rates of PFC drainage with LAMS combined with plastic stents do not significantly differ from those with LAMS alone.[59] One study included 68 patients with PPC and revealed that LAMS combined with plastic stent did not

affect the success rate of cyst drainage, complication rate, and secondary intervention rate.[60]. Furthermore, subgroup analyses revealed that LAMS combined with plastic stent was not necessary for PPC or WON. Another retrospective analysis of 236 patients with PPC and 34 patients with WON showed that placement of the plastic stents after that of the LAMS did not increase the treatment success rate or reduce the incidence of adverse events.[61] Recently, a research found that the addition of a plastic stent within a LAMS was associated with a significantly lower global rate of adverse events (20.7% *vs*. 51.5%, $P = 0.008$) and stent occlusion rate (14.7% *vs*. 36.3%, $P = 0.042$) in EUS-guided drainage of WON.[62] Therefore, there is still controversy that LAMSs require to be combined with plastic stents for PPC drainage, and larger prospective clinical studies are required.

Statement 23: If LAMS is used in PPC/WON with DPDS, it should be replaced with a plastic stent after removal to maintain the continuous drainage of the damaged pancreatic duct and prevent cyst recurrence.

Evidence quality: B strength of recommendation: Strong consensus level: 89.7%

DPDS is an important but easily neglected complication in patients with PPC. DPDS is clinically manifested by the compression of a persistently enlarged pseudocyst, and its incidence in patients with necrotizing pancreatitis is as high as 50%.[63] DPDS is characterized by the destruction of the main pancreatic duct, leading to the separation of the pancreatic duct of the upstream pancreas from the downstream main pancreatic duct, which can be diagnosed using MRCP. The isolated pancreas remains functional. It can lead to a persistent peripancreatic fluid that cannot be absorbed by itself in the absence of acinar atrophy. The overall recurrence rate after PFC treatment is approximately 10%–30%, which primarily occurs in patients with DPDS.[61] A study revealed that among patients with PPC who underwent endoscopic drainage, none of them with a complete main pancreatic duct experienced recurrence, whereas 7 of the 94 patients with DPDS experienced recurrence.[64] DPDS treatment with ERCP via papillary drainage also has a good effect.[65] EUS-guided transmural cyst drainage has a low incidence of complications.[66] Therefore, for patients with PPC and DPDS treated with LAMS, the metal stent should be replaced with a plastic stent during a later stage to promote the continuous drainage of pancreatic duct disconnection and prevent cyst recurrence.

Section 9: Complication related to stents for cyst drainage

Statement 24: Plastic stent drainage of PPC has the risks of stent blockage, displacement, concurrent infection, and bleeding.

Evidence quality: B strength of recommendation: Strong consensus level: 96.6%

The complication rate of PPC plastic stent drainage has been reported to be approximately 13%.[51] It primarily includes displacement or detachment, occlusion, and infection.[67] A few studies have reported operation-related bleeding complications during PPC drainage with a plastic stent, which was not attributed to the use of the stent itself.[68] The long-term retention of plastic stents has a risk of intestinal perforation. When treating PPC, long-term stent placement should be avoided.[69] In case of complications such as plastic stent-related infection, the stent should be removed or replaced.

Displacement means that the stent completely enters the capsule or moves out of the stomach completely, resulting in ineffective drainage of the cyst. Whether the stent ultimately should be endoscopically removed depends on whether the displaced stent can be automatically discharged. Displacement is commonly observed with the use of plastic and biliary metallic stents. LAMSs have antidisplacement wings that effectively prevent displacement.

Statement 25: LAMS has a certain degree of bleeding risk; therefore, close monitoring of the condition is necessary. In case of bleeding, the stent should be removed immediately, and if necessary, DSA hemostasis or surgery must be performed.

Evidence quality: B strength of recommendation: Weak consensus level: 96.6%

Hemorrhage is the most reported LAMS complication and has received the most clinical attention.[70] Any bleeding event that requires intervention, blood transfusion, and hospital observation after endoscopic drainage can be considered a bleeding complication. Most bleeding complications are caused by pseudoaneurysms. In the early stages of LAMS application, the incidence of bleeding complications is high, which is attributed to the insufficient judgment of preoperative vascular risk, the difference in puncture path selection, and long-term stent retention. The midterm analysis results of a randomized controlled trial revealed that[71] the DPS group had no adverse events, whereas the incidence of adverse events in the LAMS group was 50%, which primarily included delayed bleeding, embedding syndrome, and obstructive jaundice after stent-induced biliary stricture. Subsequent studies confirmed that the incidence of bleeding after drainage in LAMS was higher than that in DPS (21% *vs*. 1%).[72] The delayed bleeding rate of LAMS is reported to be 17%, and the average time from stent implantation to bleeding is 9.5 days.[55]

The possible causes of bleeding complications in LAMS are as follows: (1) after LAMS placement, the cyst rapidly collapses, and the distal end of the stent stimulates the posterior wall of the cyst to promote pseudoaneurysm occurrence, which is bleeding[73]; (2) some cysts have a large diameter. Although before drainage, imaging examination and evaluation have been completed, blood vessels may be omitted because of the tension of the cyst.[70] Most of the bleeding can be effectively controlled using conservative treatment; however, some patients require DSA to stop bleeding and, if necessary, surgical operation.[73] The LAMS should be placed for approximately 3 weeks to complete a CT examination, judge the effectiveness of cyst drainage, and evaluate the risk of bleeding. The stent should be removed as soon as possible if drainage is successful.[74] Bleeding can be located by observing clinical manifestations combined with imaging examination. In case of bleeding, the stent should be removed immediately, the bleeding point and its cause should be judged, and treatment should be provided based on the symptoms. When the bleeding volume is >400 mL, endoscopic imaging, intervention, and surgery are recommended.

There is no effective way to prevent bleeding caused by LAMS. The evaluation of blood supply using EUS or enhanced CT can be used to assess the bleeding risk. The placement of a plastic stent in the LAMS may reduce the direct contact between the end of the LAMS and the capsule wall or blood vessel, thus reducing the incidence of bleeding. Moreover, replacing the LAMS with DPS before patient discharge may be a feasible way to reduce the risk of delayed bleeding.[75]

Statement 26: DEN is required in case of infection or fever after the placement of the LAMS.

Evidence quality: B strength of recommendation: Weak consensus level: 93.1%

The inhibition of gastric acid production using proton pump inhibitors (PPIs) can reduce adverse events such as gastrointestinal ulcers, bleeding, or perforation at the cyst drainage site.[7] However, a retrospective study revealed that patients with endoscopic drainage WON receiving PPI may need to undergo further endoscopic necrotic resection before they can be successfully treated, which may be related to the reduced gastric acid entering the capsule cavity and the dissolved solid necrotic fragments in the capsule cavity by PPI.[76]

In general, the LAMS is relatively safe, and the incidence of complications is approximately 6%.[77] An increase in fever and inflammatory index values (temperature >38.0°C, white blood cells >10.0 × 10^9/L, C-reactive protein >10 mg/L, procalcitonin >0.5 ng/mL) after the operation, blood culture, or cyst fluid culture should be considered as cyst infection. Antibiotics should be used to prevent infection during the perioperative period and strengthened; the use of antibiotics is recommended for patients with infection. Transgastric DEN is required if PPC evolves into IPN. The infection may be caused by stent blockage or poor drainage. The previously reported plastic stent occlusion rate was as high as 18%.[78] A study found that the transient occlusion rate of LAMS in PPC drainage was 23.7% (28/118). The incidence of stent occlusion was 17.5% even for PPC without solid debris before the operation, which may be related to stent blockage by solid food residue.[79] For WON with a necrosis extent of at least 33%, an approach incorporating upfront necrosectomy at the index intervention rather than as a step-up measure could safely reduce the number of reinterventions required to achieve treatment success.[80] Therefore, it is important to necrosectomy after LAMS implantation to prevent and treat cyst infection.

Statement 27: The best time to remove the LAMS is 3 weeks to 2 months after it is implanted, and a long retention time will lead to stent embedding.

Evidence quality: A strength of recommendation: Strong consensus level: 100%

The difficult removal of the LAMS is generally related to its retention time. The "embedding syndrome" refers to tissue insertion and difficulty of removal under an endoscope, which is related to long-term stent placement. Some stents can be removed under an endoscope, and some require surgical intervention. Rare complications include cardia obstruction.[81] A case report[82] revealed that after 5 months of stent placement, the stent of a patient with "embedding" was finally removed with biopsy forceps under an endoscope, but this method did not apply to various types of LAMS because of the change in the weaving mode of the stent. The study revealed that a PPC cyst diameter of ≤7 cm and a stent retention time of ≥4 weeks were risk factors for LAMS complications.[77] Currently, there is no consensus on the time of stent removal. A recent study suggested that LAMS should be removed within 3–4 weeks after PPC elimination.[75] Furthermore, considering the long-term bleeding risk, LAMS placement should not exceed 2 months.[83] When compared with PPC, when LAMSs are used for WON drainage, the retention time can be appropriately extended.

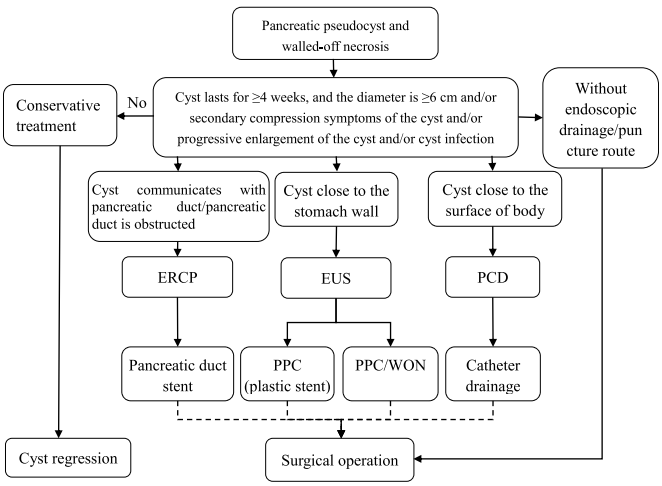

Figure 3. A flow diagram illustrating the treatment procedures for pancreatic pseudocyst and walled-off necrosis. PPC: pancreatic pseudocysts; WON: walled-off pancreatic necrosis; PCD: percutaneous catheter drainage.

Section 10: Drug treatment and follow-up

Statement 28: Acid suppressants and pancreatin preparations can be used to maintain the treatment of PPC/WON without symptoms and intervention indications.

Evidence quality: C strength of recommendation: Weak consensus level: 82.8%

PPC or WON with no symptoms and no requirement for intervention can be conservatively treated with drugs to help cyst absorption by itself.[7] A multicenter cohort study revealed that PPIs were associated with a lower incidence of pseudocysts in patients with AP.[84]

In cases of extensive necrotizing pancreatitis with exocrine pancreatic insufficiency and PPC or WON, pancreatin preparation should be used in combination.[85] Somatostatin analogs are commonly used conservative therapeutic drugs, which can inhibit pancreatic secretion and promote the absorption of PPC; however, there is no strong clinical evidence to confirm this.

A high dose of pancreatin (40,000 IU 3 times a day) has been reported to replace the successful treatment of refractory multiple PPCs, which may be correlated to the negative feedback regulation of endogenous pancreatic secretion by exogenous pancreatin supplementation, thereby reducing the accumulation of cyst fluid.[86] Little evidence exists on the application of large-dose pancreatin preparations in the treatment of PPC or WON, and the specific underlying mechanism of action and clinical promotion require to be studied further.

Statement 29: PPC/WON requires close follow-up after endoscopic or other methods of treatment. Imaging should be conducted every 3–6 months, and if necessary, intervention should be performed again.

Evidence quality: B strength of recommendation: Weak consensus level: 100%

After endoscopic stent drainage of PPC or WON, a long-term recurrence rate of approximately 10%–30% exists, primarily occurring in patients with DPDS.[63,67] Therefore, after PPC or WON treatment, abdominal CT or B-ultrasound examination should be performed every 3–6 months. In case of progressive cyst enlargement or accompanying symptoms during follow-up, imaging examination should be further improved for a comprehensive evaluation, and if necessary, further intervention should be conducted.[87]

In conclusion, PPC and WON require individualized treatment plans based on the origin, location, diameter, and other cyst-related factors. The application of EUS, especially LAMS, brings new options for treating

PPCs (Figure 3). The treatment plans differ at different stages. The entire treatment process requires the cooperation of multidisciplinary doctors from the fields of digestive endoscopy, pancreatic surgery, imaging medicine, and interventional radiology to achieve optimal treatment effects.

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Conflicts of interest

Zhaoshen Li is an Honorary Editor-in-Chief of the journal, and Zhendong Jin is an Associate Editor-in-Chief. The article was subjected to the standard procedures of the journal, with a review process independent of the editors and their research group.

Author Contributions

Zhu Huiyun, Du Yiqi, and Wang Kaixuan: methodology, writing—original draft. Jin Zhendong and Li Zhaoshen: conceptualization, resources, supervision, writing—review and editing.

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