Invited Special Paper

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Updates in the management of postoperative pancreatic fistula

Martina Nebbia, MD[a,*], Giovanni Capretti, MD[a,b], Gennaro Nappo, MD[a,b], Alessandro Zerbi, MD[a,b]

Abstract

Postoperative pancreatic fistula (POPF) remains a common and dreaded complication after pancreatic resections and is associated with increased morbidity and mortality. Over the years, several different strategies have been investigated to prevent and mitigate POPF. However, when a POPF occurs, a consensus on the optimal management strategy of grade B and grade C POPF is still lacking, and the current management strategy is often based on local expertise and driven by patient's condition. Nevertheless, whereas the incidence of POPF after pancreatic surgery has remained stable, the overall mortality related to this complication has decreased over the years. This reflects an improvement in the management of this complication, which has become increasingly conservative. The aim of this review is to provide an updated evidence-based overview on the management strategies of POPF for surgeons and physicians in the clinical practice.

Keywords: distal pancreatectomy, pancreaticoduodenectomy, postoperative complications, postoperative pancreatic fistula

Introduction

Postoperative pancreatic fistula (POPF) remains one of the most frequent and dangerous complications after partial pancreatectomy and is associated with increased morbidity and mortality[1–3].

The benchmark from the International Study Group of Pancreatic Surgery (ISGPS) Evidence Map of Pancreatic Surgery shows a grade B and C POPF rate of 14% (99% CI: 12–17%) in 99 randomized controlled trials (RCTs) after PD and 23% (99% CI: 17–30%) after DP[4].

The highest rate of POPF follows central pancreatectomy, ranging from 20 to 60% depending on the series, because of the presence of two pancreatic remnants and thus of two potential sites for POPF development[5].

Whereas the incidence of POPF after pancreatic surgery has remained stable, the overall mortality related to this condition has decreased over the years. This reflects an improvement in POPF management, which has become increasingly conservative.

[a]Pancreatic Surgery Unit, IRCCS Humanitas Research Hospital, Via Manzoni, Rozzano and [b]Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, Pieve Emanuele, Milan, Italy

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Pancreatic Surgery Unit, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Tel.: +39 028 224 3675; fax: +39 028 224 4590. E-mail: martina.nebbia@humanitas.it (M. Nebbia).

International Journal of Surgery (2024) 110:6135–6144

Received 12 November 2023; Accepted 11 March 2024

Published online 21 March 2024

http://dx.doi.org/10.1097/JS9.0000000000001395

HIGHLIGHTS

- Postoperative pancreatic fistula (POPF) remains one of the most frequent and dangerous complications after partial pancreatectomy and is associated with increased morbidity and mortality.
- Management strategies of POPFs have long been poorly standardized and are often based on surgeon's expertise and driven by patient's status.
- This narrative review aims to provide an updated evidence-based overview on the current practice management strategies of POPF, including the optimal drainage of the remnant pancreas, nutritional support, use of somatostatin analogues, threshold for using antibiotic, and indications for reoperation.

The consensus definition of POPF, formulated in 2005 and updated in 2016 by the ISGPS, standardized for the first time the classification of POPFs grading the severity according to the clinical impact on the patient's postoperative course[6].

Several elements have been recognized as risk factors for POPF development, including pancreatic parenchymal texture, disease pathology, pancreatic duct size, and intraoperative blood loss[7].

Unlike its prevention and mitigations strategies, management strategies of POPFs have long been poorly standardized and are often based on surgeon's expertise and driven by patient's status[2,7–14].

A consensus on the optimal treatment strategy of POPF, which include the optimal drainage of the remnant pancreas, nutritional support, use of somatostatin analogues, threshold for using antibiotic and indications for reoperation, is still debated and varies from institutions[15].

This is particularly important because a poor management of this complications may not only negatively affect the quality of life in these patients, but also delay or limit the administration of adjuvant treatments, affecting the overall survival[16,17].

The aim of this narrative review is to provide an updated evidence-based overview on the current practice management strategies of POPF.

Definition, diagnosis, and grading

POPF develops as a consequence of pancreatic juice leakage from an impaired sealing of the pancreatic anastomosis (in the case of PD or middle pancreatectomy), at the site of the pancreatic stump (for distal pancreatectomy) or surgically exfoliated surface (e.g. enucleation).

From a clinical standpoint, it can be asymptomatic, but it can lead to the development of further sequelae as abdominal collections, bleeding, sepsis and, ultimately, postoperative mortality[18].

According to the 2005 ISGPF, the necessary criterion for the diagnosis of POPF is the detection on any measurable volume of drain (intraoperatively placed) fluid on or after postoperative day 3 with amylase level > 3 times the upper limit of normal amylase for each specific institution[19].

Based on the 2016 ISGPS update, three different grades of pancreatic juice leakage can be identified, with different clinical impact[6]:

Biochemical leak

It is an asymptomatic pancreatic leak, which does not affect the normal postoperative course (previous Grade A POPF, according to the 2005 classification) and does not require any treatment or invasive procedure. The drains can be left in place even after discharge for up to 3 weeks.

The macroscopic appearance of the drain material can vary from amaranth to greenish/yellowish infected fluid, to limpid pancreatic juice.

Grade B

Involves therapeutic intervention such as an endoscopic or radiological drainage of collections or angiographic procedures to enhance the fistula healing. The drains are left *in situ* over 3 weeks or, if needed, they might be replaced under radiologic guidance. Patients with grade B POPF can present with a variety of nonspecific symptoms including abdominal pain, fever, and increased inflammations index and requires only antibiotic therapy. Whenever a single or multiorgan failure occurs the fistula shifts to a grade C POPF.

Grade C

This grade is framed as a severe POPF. Patients with a grade C have developed single or multiple organ failure as a direct result of the POPF and might require surgical reoperation to manage the clinical status. This is a life-threatening condition and is associated with a mortality up to 39%[20].

If the 2016 updated ISGPS definition has the merit of replacing grade A POPF by introducing the concept of biochemical leak (BL), however, grade B definition still combines a heterogeneous group of clinical conditions.

For these reasons, a stricter distinction of grade B POPF in three different sub-categories has been proposed: *B1*, maintenance of abdominal drain more than 3 weeks; *B2*, use of antibiotics or other specific medical treatment for POPF; and *B3*, use of interventional procedures for the POPF treatment[21].

Nappo *et al.*[22], in a retrospective study including 716 patients, shows that this subclassification allows to better discriminate the severity of postoperative course, especially after PD, supporting its adoption in the new ISGPS classification.

Clinical presentation

From a clinical standpoint, patient with POPF can present asymptomatic or with wide range of nonspecific symptoms. The development of a POPF should be suspected any time that a patient who underwent pancreatic resection presents a deviation from the normal postoperative course.

Parallel to the transformation of the drainage material from serous to dark brown or corpuscular, patients can present with unspecific symptoms like abdominal pain, delayed gastric emptying (DGE), impaired bowel function. Fever and increased C-reactive protein (CRP) levels and white blood cells count may be suggestive of an undrained peripancreatic fluid collection related to POPF.

Notably, in most cases, POPF develops within few days after the surgery; however, in few cases patients present with a latent POPF, which initially lacks amylase-rich drain effluent but eventually shows the clinical and radiological findings indicative of POPF[23].

The early recognition of this complication is fundamental for its successful management. Latent POPFs represent a rare but treacherous presentation, a close observation in the early postoperative period is fundamental because a timely treatment of this condition is the key element to avoid life-threatening sequalae.

A standardized postoperative patient monitoring to early detect any deviation from the normal postoperative course is the first step in the management of a POPF and to improve patient's outcome. However, in the current clinical practice, guidelines on effective postoperative patient monitoring, are lacking.

Smits *et al.*[24] developed a best-practice algorithm based on national (Dutch) and international consensus on early detection and step-up management of pancreatic fistula to prevent further clinical deterioration. More recently, in the *PORSH-trial*, the Dutch group demonstrated that the application of a standardized detection and management algorithm for POPF in the postoperative period could nearly half the mortality at 90 days after PD[25].

Management

Nonoperative management

Antibiotic therapy

Microbial growth in POPF is strongly associated with poor outcome after pancreatic surgery and marks a turning point in the development of POPF into life-threatening intra-abdominal infection, sepsis, and erosive bleeding resulting in postpancreatectomy hemorrhage (PPH), increasing morbidity and mortality[26–28].

Manipulation of the bile duct and multiple enteric anastomoses, together with the physiologic alterations occurring during PD (fluid shifts, blood loss, and systemic vasodilation), play a role in this process, representing the source of microorganism's contamination.

Moreover, preoperative biliary procedures, which introduce bacteria into a normally sterile biliary tree and the resulting intraoperative biliary contamination are associated with and increased infection risk also for multidrug resistant (MDR) bacteria[17,29,30].

Several studies have shown the correlation between bacteriobilia found on intraoperative bile culture and not just postoperative surgical site infection (SSI) but also with organ space infection and sepsis[29,31,32].

In light of this, intraoperative bile sampling during PD allows the identification of potentially pathogenic microorganisms, enabling the clinician to target postoperative antibiotic treatment to cover also MDR bacteria.

This is especially important considering that frequently postoperative infectious complications after pancreatic surgery are sustained from a polymicrobial flora, with a median of three species of microorganisms isolated in the of POPF fluid[17,33].

A proper preoperative prophylaxis strategy has been proven effective in reducing CR-POPF and multiple resulting sequelae[3,33,34]. This strategy should include surveillance preoperative rectal swabs to check for the presence of resistant bacteria and an antimicrobial therapy with antienterococcal activity should be chosen in stent-bearing patients[32,35].

Some authors have postulated that prolonged antibiotic prophylaxis may reduce postoperative infectious complications after PD[36]. A recent metanalysis including 10 studies evaluating the effect of prolonged antibiotics after pancreatoduodenectomy showed that prolonged antibiotic prophylaxis is associated with fewer organ/space infection in patients who undergo preoperative biliary drainage[37]. However, the authors did not observe a difference in POPF rate between patients receiving perioperative versus prolonged prophylaxis (OR 1.35, 95% CI: 0.94–1.93)[37].

Conversely, Ocuin *et al.*[38], in a recent single-center study, observed that extended antibiotic therapy (10 days of broad-spectrum antibiotics) is associated with a lower rate of POPF after pancreatoduodenectomy in patients with a fistula risk score ≥ 3 .

Postoperatively, the threshold to start antibiotic treatment is still debated and mainly driven by patient's conditions. In the clinical practice antibiotic therapy should be started whenever the patient should manifest signs of infection and should be targeted on the basis of cultural isolation data available from both intraoperative bile culture and drain effluent.

However, since cultural data may not be immediately available in the early postoperative period, a step- up strategy, starting with a broad-spectrum antibiotic subsequently shifted to targeted therapy once the results and the antibiogram are available, should be adopted.

Drainages management

Intraoperative drains placement after pancreatic resections as well as the timing of their removal is still a matter of debate.

The rationale behind prophylactic drains placement is early recognition and mitigation of postoperative complications, such as postpancreatectomy hemorrhage, POPF, and biliary leaks.

Moreover, drains allow to measure amylase levels on the drain effluent, which, together with the macroscopic appearance, is the key element to guide the timing of removal[39,40].

However, concerns also have been raised that drains placement presents its own risks, including serving as a potential pathway for retrograde infection which may shift a self-limiting postoperative fluid collection into an abscess, and they may cause trauma from suction, potentially eroding into anastomoses leading to fistula or hematoma development, increasing morbidity and hospitalization[41].

Owing this and the implementation of POPF predictive scores, some authors have postulated that intra-abdominal drains can be avoided in selected cases after PD and DP in patient at low risk of developing POPF according to the fistula risk score (FRS)[7,39].

To date, drains placement is recommended, and postoperative drain management policy should be driven by the amylase levels on the effluent together with the macroscopic appearance and the volume output.

Regarding the type of drains, open passive (e.g. Penrose drains) and closed-suction drains system (e.g. Jackson-Pratt drain) seems to be comparable in terms of postoperative morbidity, mortality, and in preventing bacterial contamination[42].

Other than the 'diagnostic' purpose, intraoperatively placed drains may also have a 'therapeutic' function, due the possibility to progressively mobilize them in order to promote the spontaneous healing process of the fistula, supporting the success of nonoperative management.

In specific cases, drainage mobilization could also help evacuating any surrounding collection that was not captured in the initial position, potentially contributing reducing the rate of late POPF and intra- abdominal collections.

All the above-mentioned functions are supported by the assumption that once drains are placed intraoperatively, their position remains virtually stable until they are mobilized or removed.

Marchegiani *et al.*[43] showed that postoperative drain dislocation is a frequent event, usually occurring in the early postoperative period (POD 1), with no significant difference in terms of rate of dislocation between PD and DP (29 vs. 39%, respectively).

Interestingly, in this series, dislocation of surgical did not increase postoperative morbidity, including POPFs rate[43].

These results are in line with other studies in literature, reinforcing the knowledge that drainless policy might be adopted in selected patients at negligible risk of developing POPF[44–47].

As for the optimal timing of removal, an increasing body of literature underpins the adoption of protocols for early drain removal based on the activity of amylase in the drainage fluid in selected patients at low risk for developing POPF[40,48–50].

However, the definition of 'early removal' is heterogeneous among the series, as well as the eligible patients.

An early drain removal policy may be considered in selected patients at low risk of developing POPF based on fistula risk scores, intraoperative pancreas appearance and driven by amylase levels in the early postoperative days.

Indications on drainage placement, especially after DP, continues to be controversial and structured multicenter randomized trials on prophylactic drainage placement versus a no-drain strategy with stratification for fistula risk are needed.

New evidence may emerge from the ongoing *PANDORINA trial*, a binational multicenter randomized controlled (noninferiority) trial evaluating whether the omission routine intra-abdominal drainage after DP increases postoperative complications[51].

Nutritional support

Nutritional support has been regarded as a key element of conservative therapy of POPF.

Historically, attempts to accelerate POPF closure were made by prolonged fasting, since oral feeding was believed to increase the production of pancreatic juice and trigger the activation of trypsinogen, eventually exacerbating the fistula.

However, patients with grade B and C POPF, are in a catabolic process with a higher basal energy expenditure and an insufficient nutrient intake can worse the clinical course and lead to further complications.

Moreover, patients with high-output POPF (> 200 ml in the 24 h) are at risk of fluids and electrolytes imbalance, since the loss of pancreatic juice, which is bicarbonate rich, can lead to metabolic acidosis.

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines suggest for patients with a clinically relevant POPF, an energy supply not exceeding 20–25 kcal/kg body weight/day that might be increased up to 25–30 total kcal/kg body weight/day in the case of severe malnutrition. If these target values are not reached, supplementary parenteral nutrition may be given[52].

The position paper of the ISGPS recommends either enteral nutrition (EN) or fasting with total parenteral nutrition (TPN) for patients with B and C grade POPF, and oral feeding for those with a BL[53].

However, the superiority of EN or TPN for fistula healing and the benefit of avoiding oral feeding is still debated and mostly arbitrary, since strong evidence and standardized protocols of nutrition routes are lacking (Table 1A).

TPN has the advantage of blocking the food-induced pancreatic secretion, however, long-term use of TPN can cause morphological changes in the intestinal mucosa and in the pancreas itself, other than lead to wound infection, sepsis, fluid overload, and metabolic complications[54].

On the other hand, EN generally not only avoids pancreatic stimulation but also may stimulate the release of specific gut peptides forming a negative feedback control system, and thus inhibiting pancreatic secretion[54].

In the setting of grade B and C POPF, EN therapy seems to be superior to TPN.

In fact, as shown by Keck *et al.* in a randomized controlled trial, EN seems to increase by more than twofold the probability of fistula closure (OR 2.571, 95% CI: 1.031–6.41), shorten the time to closure, and is associated with significantly faster recovery, lower rates of nutrition-related complications, and lower cost than TPN[55] .

More recently, Wu *et al.*[56] in a noninferiority randomized trial comparing oral versus enteral feeding for patients with POPF after pancreatoduodenectomy, shows that oral feeding did not increase the duration or grade of POPF (88 vs. 89% respectively; difference −1.8%, lower limit of 95% CI −14.4%; $P = 0.020$ for noninferiority), and was associated with reduced duration of stay and hospital costs. These findings support the idea that oral feeding does not exacerbate POPF.

Somatostatin analogs

Somatostatin is a naturally occurring hormone, which has the effect of reducing exocrine pancreatic secretion and increasing the net absorption of water and electrolytes[57].

Because of these properties, somatostatin has been postulated to be useful in the conservative management of fistula by reducing output and enhancing the closure.

The major disadvantage of somatostatin is the short half-life (1–2 mins) hence, over years, somatostatin synthetic analogues with longer half-life, like octreotide and lanreotide, have been developed.

Several studies and RCTs investigated the impact of preoperative and postoperative somatostatin and somatostatin analogs administration to prevent the occurrence of POPF[58–61].

Bootsma *et al.*[62] in a recent Dutch nationwide analysis suggests that administration of lanreotide in patients undergoing open pancreatoduodenectomy is associated with a reduced rate of POPF (OR 0.387; 95% CI: 0.180–0.834, $P = 0.015$) compared to other protocols.

More recently the efficacy of pasireotide, which displays a broader affinity to somatostatin receptor subtypes than octreotide, was noted.

Allen *et al.*[63], in a large RCT, investigated whether pasireotide can be used to prevent POPFs in both PD and DP, demonstrating a significant reduction of POPF after PD and DP in patients receiving preoperative subcutaneous pasireotide.

However, the therapeutic benefit of these drugs in enhancing fistula closure and reduction in time to fistula closure remains unclear.

Gans *et al.* in a systematic review of somatostatin and somatostatin analogs for the treatment of pancreatic fistula analyzed seven RCTs. According to the studies included in this review, there is no solid evidence that somatostatin analogues result in a higher closure rate of pancreatic fistula compared with other treatments (OR for fistula closure = 1.52, 95% CI: 0.88–2.61)[64].

To date, there is no strong evidence showing the advantage of postoperative administration of somatostatin/somatostatin analogs to enhance fistula closure and reduction in time to fistula (Table 1A).

Further evidence arising from controlled trials is needed to clear whether new somatostatin analogs may have a therapeutic role in the management of POPF.

Interventional management

Percutaneous or endoscopic drainage

Drainage of the collected pancreatic fluid is mandatory when the patient shows clinical signs of infection not only to mitigate the associated symptoms such as abdominal pain, gastric outlet obstruction and, most importantly, to prevent postoperative hemorrhage (e.g. formation of arterial pseudo-aneurysms secondary to POPF) and septic shock that can lead to life-threatening consequences[65].

A step-up approach, consisting of percutaneous catheter drainage followed, only in case of failure, by surgical necrosectomy, has replaced surgical debridement as the standard treatment, reducing the risk of further morbidities and subsequent complications[66].

A percutaneous approach is a viable and safe option as long as the patient is hemodynamically stable and there is a safe access route to the collection.

Drainage placement is performed under ultrasound (US) or CT-scan guidance using the Seldinger technique, which is usually preferable over the trocar technique since allows a highly accurate and safe image-guided needle placement[67].

Table 1

Recommendations based on recent literature.

Nonoperative management	
A). Nonoperative management	
Antibiotic therapy	
Preoperative prophylaxis	Preoperative prophylaxis strategy should include surveillance swabs to check for the presence of resistant bacteria and an antimicrobial agent with antienterococcal activity should be chosen in bearing-stent patients
Postoperative treatment	Should be started whenever the patient manifest signs of infection and should be targeted on the basis of cultural isolation data available from both intraoperative bile culture and drain effluent.
	A step-up strategy (broad- spectrum antibiotic subsequently shifted to targeted therapy once the results and the antibiogram are available) should be adopted
Drainages management	
Drainages placement	To date, drains placement is recommended, and postoperative drain management policy should be driven by the amylase levels on the effluent together with the macroscopic appearance and the volume output
Timing for drainages removal	An early drain removal policy may be considered in selected patients at low risk of developing POPF based on fistula risk scores, intraoperative pancreas appearance and driven by amylase levels in the early postoperative days
Nutritional support	
Artificial nutrition	The position paper of the ISGPS recommends either EN or fasting with TPN for patients with B and C grade POPF
Nutrition route	To date, there are no evidence supporting the superiority of EN or TPN for fistula healing, as well as the benefit of avoiding oral feeding is still debated and mostly arbitrary, since strong evidence and standardized protocols of nutrition routes are lacking
Somatostatin analogs	
	To date, there is no strong evidence supporting postoperative administration of somatostatin/somatostatin analogs to enhance fistula closure and reduction in time to fistula
B). Interventional management	
Interventional management	
Percutaneous or endoscopic drainage	Endoscopic and percutaneous drainage appear to be equally effective and complementary interventions for POPF-associated collections.
	A step-up approach should be considered, especially in the setting of refractory POPF
Angiographic embolization	Angiography with embolization should be the initial approach for delayed bleeding if the patients is hemodynamically stable.
	Different techniques may be used including proximal embolization and vessel occlusion at the site of the bleeding with nonabsorbable materials include PVA particles and metallic coils. If the bleeding site is in a major artery, stent grafting is usually the treatment of choice
Surgical reintervention	Surgical exploration should be considered only in the case of unstable patients with active bleeding or failed control of bleeding after interventional angiography or endoscopy.
	The choice between pancreas- preserving procedures vs completion pancreatectomy relies on intraoperative findings and patient's clinical stability

EN, enteral nutrition; ISGPS, International Study Group for Pancreatic Surgery; POPF, postoperative pancreatic fistula; TPN, total parenteral nutrition; PVA, polyvinylic alcohol.

The collection is punctured with a small caliber needle, guidewires are inserted, and the drainage catheter is then advanced over the guidewire and placed into the fluid collection (Figure 1).

Several studies have shown that percutaneous drainage is technically safe, with a reported success rate ranging between 85 and 97.6% cases depending on the series and without the need for reoperation[68,69].

However, percutaneous catheters have some downsides, given the need for frequent output monitoring, daily catheter flushing, subsequent catheter exchange due to malfunction or dislodgement and upsize which may lead to local skin irritation and drain track infection[70].

The use of endoscopic-ultrasound (EUS) guided transmural drainage of POPF-related collections, has increased in frequency due to the favorable outcome in the setting of pseudocysts secondary to acute pancreatitis or infected necrotizing pancreatitis[71–73].

EUS-guided transmural drainage is especially useful to treat refractory POPF after percutaneous drainage and difficult-to-reach collections after DP where the location of the collection within the resection bed may be better accessed from the stomach (i.e. cyst-gastrostomy)[74,75].

In this case, an FNA needle is used to puncture through the gastric wall and access the collection. A guidewire is advanced into the collection cavity under fluoroscopic guidance and the cyst-gastrostomy tract can be dilated using a biliary or esophageal balloon dilator. One or multiple pigtail biliary stents (usually 7F or 10F) are then placed, and debridement may be performed if needed (Figure 2).

Compared to percutaneous drainage, endoscopic drainage offers several potential benefits.

The real-time high-resolution viewing of the collection, and any associated vasculature, allows for safe access and allow and to debride the necrotic tissue resulting from pancreatic enzymatic digestion.

Furthermore, the lack of an external catheter, lower fluid and electrolyte losses obviates the need for catheter care and is more convenient for patients and caregivers[76].

On the other hand, endoscopic drainage requires more advanced expertise, compared to percutaneous drainage, and is usually available only in referral centers with advanced interventional endoscopists and require subsequent removal of the stents and could be performed usually at least after 4 weeks from the collection development[77,78].

Several studies have compared the drainage of collections associated with POPF using endoscopic and percutaneous technique.

A recent retrospective study by Efishat *et al.*[79] shows that technical success was achieved in almost all patients in both endoscopic and percutaneous groups (100 and 97%) and clinical success was achieved in 67 and 59%, respectively ($P = 0.63$), with no differences in term of recurrence between the two groups.

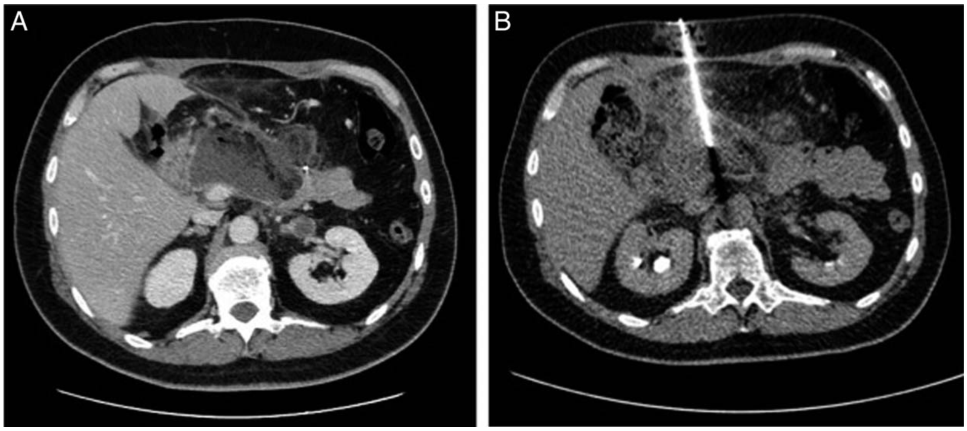

Figure 1. (A) CT-scan shows postpancreaticoduodenectomy fluid collection. (B) A percutaneous. drainage is inserted into the collection using the Seldinger technique under CT-scan.

Endoscopic and percutaneous drainage appear to be equally effective and complementary interventions for POPF-associated collections. The choice between the two routes of drainage should take into account the location of the collection, timing, and the expertise of the interventional endoscopists and a multidisciplinary step-up approach should be considered, especially in the setting of refractory POPF (Table 1B).

Angiographic embolization

Leakage of amylase-rich pancreatic juice can cause vessel erosion resulting in PPH. This a relatively rare complication but it is responsible for up to 38% of deaths[80].

According to the ISGPS, in contrast with early PPH which develops within 24 h from surgery and is usually due technical failure in achieving adequate hemostasis, late PPH occurs later with a median onset between 13 and 27 days postoperatively and is likely due to vascular erosion caused by intra-abdominal abscesses and POPF, often leading to the formation of a pseudoaneurysm[81].

Delayed hemorrhage, especially from a ruptured pseudoaneurysm, is a rare but rapidly progressing and potentially life-threatening complication following pancreaticoduodenectomies[82].

Following pancreatic head resections, common sites of bleeding include the peripancreatic vasculature (gastroduodenal artery - GDA stump, common hepatic artery- CHA and its branches, portal vein- PV, superior mesenteric artery- SMA and its branches, splenic artery), resection surfaces, and anastomotic sites (pancreatico-enteric anastomosis, entero-enteric anastomosis, and marginal ulcer)[80,81].

Symptoms and presentation depend on the site of bleeding, varying from signs of upper gastrointestinal bleeding (hematemesis, melena, or blood per nasogastric tube), followed by blood in drainage fluid, drop in hemoglobin and lower gastrointestinal bleeding (e.g. hematochezia). Delayed hemorrhage, especially from a ruptured pseudoaneurysm, is a rare but rapidly progressing and potentially life-threatening complication following pancreaticoduodenectomies.

If the patient is hemodynamically stable, angiography with embolization should be the initial approach for delayed bleeding.

A tri-phasic CT-scan to localize the bleeding may also be performed is the patient is stable; however, vascular spasm may be present and being responsible of false negatives. Failure to identify the bleeding site precludes targeted embolization (TE). In this setting, empiric embolization (EE) should be considered since it has been proven to be a safe and effective option in preventing rebleeding and mortality in patients with angiographically negative delayed PPH[83].

Different techniques may be used to stop bleeding, including proximal embolization and vessel occlusion at the site of the bleeding with nonabsorbable materials include polyvinylic alcohol (PVA) particles and metallic coils[84,85].

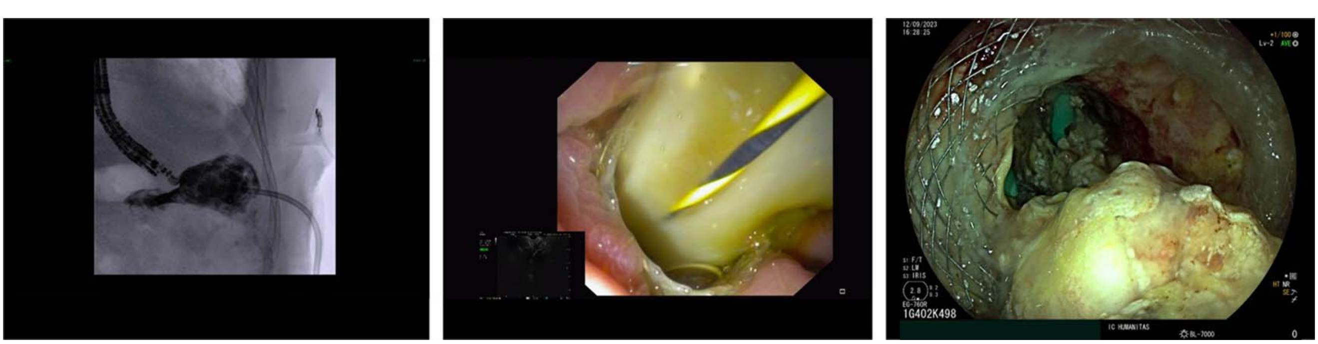

Figure 2. EUS-guided pancreatic fluid collection drainage.

If the bleeding site is located in a major artery, for example, the superior mesenteric or the hepatic artery, stent grafting is usually the treatment of choice[86].

Surgical exploration should be considered only in the case of unstable patients with active bleeding or failed control of bleeding after interventional angiography or endoscopy (Table 1B).

Surgical reintervention

Surgical reintervention is considered the last-resort treatment when conservative management fails and is associated with a mortality rate up to 56%[87].

Clear evidence on indications and proper timing for relaparotomy are still lacking and mostly rely on center and surgeon's expertise.

Surgical intervention should be considered when the patient deteriorates despite maximal supporting care, for septic intra-abdominal collections inaccessible to percutaneous or endoscopic drainage or for suspected peritonitis by visceral perforation.

Emergency relaparotomy is mandatory in presence of ongoing bleeding after failure or contraindication of radiologic endovascular procedures[80] (Table 1B).

In this scenario, the key decision is whether preserving the pancreatic remnant or proceed with the completion pancreatectomy (CPLP).

Pancreas-preserving procedures, based on the type on pancreatic resection, comprise drainage of the anastomotic region, repair or redo of the pancreatic anastomosis, oversewing of the stump or duct occlusion with fibrin sealant, salvage pancreatogastrostomy, and the bridge stent technique[88–90].

Although wide external drainage seems to be initially safer and more efficient, it might be an incomplete solution that requires additional re-explorations and prolonged length of stay, eventually leading to a higher mortality[91].

Salvage pancreatogastrostomy has also been proposed as an alternative safe and efficient option to completion pancreatectomy for the treatment of grade C POPF after PD with PJ[89]. However, the feasibility of this approach depends on the adequacy of the pancreatic remnant and requires additional dissection on severely compromised tissues. The bridge stent technique has been described as an alternative approach in the setting of a disrupted PJ anastomosis where a feeding tube stent is placed across a gap between the jejunal enterotomy and the pancreatic duct, and it can be secured at both ends or externalized, depending on the surgical site inflammation[90].

The choice of the technique mostly relies on intraoperative findings and patient's clinical stability, since access to the complication site can be problematic due to the significant inflammation from local sepsis and tissue degradation[20].

Indications for CPLP are excessive disruption of the anastomosis (more than half the circumference of the suture line), extended necrosis of the pancreatic stump, impossibility to intraoperatively recognize the Wirsung's duct and splenic artery lesions necessitating its ligation[92].

Compared with a CPLP, preserving the pancreas is a relatively easier technique, with less blood loss and shorter operative time and avoids the insulin-dependent diabetes that inevitably follows a CPLP[93].

On the other hand, pancreas-preserving procedures might not be sufficient and lead to further reinterventions, while CPLP has the advantage of eliminating the source of the leakage and associated inflammation.

Balzano *et al.*[94] in a retrospective study compared CPLP and pancreas-preserving procedures in patients undergoing relaparotomy for POPF, showing that mortality rate, blood loss, and transfusion requirement were similar for all techniques but patients undergoing a CPLP required a further relaparotomy less frequently than patients with pancreas preservation (7 vs. 59%, $P<0.01$), and the ICU stay was reduced after CPLP ($P=0.058$).

Furthermore, in patients treated with CPLP, the impact of the metabolic consequences related to this procedure can be mitigated by the association of islet autotransplantation (IAT) and, more recently, by the artificial bi-hormonal pump, as shown in the APPEL5 + study[95].

Considering this and the reassuring results on long-term quality of life (QoL), which have been shown to be comparable in patients undergoing TP and patients at high-risk for POPF (FRS 7– 10) undergoing PD, and the improved perioperative outcomes on short-term mortality and major morbidity, TP with IAT could be considered as an alternative initial approach to a very high-risk PD to avoid POPF-related sequelae[96–100].

Conclusions

POPF is a complex, multivariable phenomenon that continues to challenge pancreatic surgeons starting with its definition, prediction, and detection.

A standardized postoperative patient monitoring protocol early detect any deviation from the normal postoperative course is the first step in the management of a POPF and to improve patient's outcome.

When a patient develops a POPF, clinicians are faced with multiple, specific, and critical management decisions, particularly in respect to reducing the incidence and burden of B and C grade POPF.

A strong consensus on the optimal management strategy of clinically relevant pancreatic fistula is still lacking and the current management strategy still relies on local expertise and driven by patient's condition.

Current clinical practice relies mainly on mitigation strategy, proper caloric intake via artificial nutrition, drainage of symptomatic collected pancreatic fluid and surgical reintervention when conservative management fails.

The continuous implementation of centralized, high-volume pancreatic units with appropriate facilities and multidisciplinary experience to treat this complication may significantly contribute to standardize the management and improve the outcomes.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

Not applicable.

Author contribution

M.N.: conceptualization, writing – original draft, and writing – review and editing; G.C. and G.N.: supervision and writing – review and editing; A.Z.: conceptualization, supervision, writing – review and editing.

Conflicts of interest disclosure

The authors declare that they have no financial conflicts of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Martina Nebbia.

Data availability statement

Not applicable.

Provenance and peer review

Invited paper.

References

[1] McMillan MT, Vollmer CM, Asbun HJ, *et al.* The characterization and prediction of ISGPF grade C fistulas following pancreatoduodenectomy. J Gastrointest Surg 2016;20:262–76.
[2] Fuks D, Piessen G, Huet E, *et al.* Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. Am J Surg 2009;197:702–9.
[3] Loos M, Strobel O, Legominski M, *et al.* Postoperative pancreatic fistula: microbial growth determines outcome. Surgery (United States) 2018;164:1185–90.
[4] Probst P, Hüttner FJ, Meydan Ö, *et al.* Evidence map of pancreatic surgery–a living systematic review with meta-analyses by the international study group of pancreatic surgery (ISGPS). Surgery 2021;170: 1517–24.
[5] Goudard Y, Gaujoux S, Dokmak S, *et al.* Reappraisal of central pancreatectomy a 12-year single-center experience. JAMA Surg 2014;149: 356–63.
[6] Bassi C, Marchegiani G, Dervenis C, *et al.* The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery (United States) 2017; 161:584–91.
[7] Callery MP, Pratt WB, Kent TS, *et al.* A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg 2013;216:1–14.
[8] Ferrone CR, Warshaw AL, Rattner DW, *et al.* Pancreatic fistula rates after 462 distal pancreatectomies: staplers do not decrease fistula rates. J Gastrointest Surg 2008;12:1691–8.
[9] Han IW, Cho K, Ryu Y, *et al.* Risk prediction platform for pancreatic fistula after pancreatoduodenectomy using artificial intelligence. World J Gastroenterol 2020;26:4453–64.
[10] Liu QY, Zhang WZ, Xia HT, *et al.* Analysis of risk factors for postoperative pancreatic fistula following pancreaticoduodenectomy. World J Gastroenterol 2014;20:17491–7.
[11] Pratt WB, Callery MP, Vollmer CM. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. World J Surg 2008;32:419–28.
[12] Wellner UF, Kayser G, Lapshyn H, *et al.* A simple scoring system based on clinical factors related to pancreatic texture predicts postoperative pancreatic fistula preoperatively. HPB 2010;12:696–702.
[13] Søreide K, Healey AJ, Mole DJ, *et al.* Pre-, peri- and post-operative factors for the development of pancreatic fistula after pancreatic surgery. HPB 2019;21:1621–31.
[14] Capretti G, Bonifacio C, De Palma C, *et al.* A machine learning risk model based on preoperative computed tomography scan to predict postoperative outcomes after pancreatoduodenectomy. Updates Surg 2022;74:235–43.
[15] Melloul E, Raptis DA, Clavien PA, *et al.* Poor level of agreement on the management of postoperative pancreatic fistula: results of an international survey. Hpb J 2012;15:307–14.
[16] Merkow RP, Bilimoria KY, Tomlinson JS, *et al.* Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Ann Surg 2014;260:372–7.
[17] Fong ZV, McMillan MT, Marchegiani G, *et al.* Discordance between perioperative antibiotic prophylaxis and wound infection cultures in patients undergoing pancreaticoduodenectomy. JAMA Surg 2016;151: 432–9.
[18] Pulvirenti A, Marchegiani G, Pea A, *et al.* Clinical implications of the 2016 international study group on pancreatic surgery definition and grading of postoperative pancreatic fistula on 775 consecutive pancreatic resections. Ann Surg 2017.
[19] Bassi C, Dervenis C, Butturini G, *et al.* Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138: 8–13.
[20] Standop J, Glowka T, Schmitz V, *et al.* Operative re-intervention following pancreatic head resection: indications and outcome. J Gastrointest Surg 2009;13:1503–9.
[21] Maggino L, Malleo G, Bassi C, *et al.* Decoding grade B pancreatic fistula: a clinical and economical analysis and subclassification proposal. Ann Surg 2019;269:1146–53.
[22] Nappo G, Capretti GL, Petitti T, *et al.* The evolution of post-operative pancreatic fistula (POPF) classification: a single-center experience. Pancreatology 2019;19:449–55.
[23] Pratt WB, Callery MP, Vollmer CM. The latent presentation of pancreatic fistulas. Br J Surg 2009;96:641–9.
[24] Smits FJ, Henry AC, Van Eijck CH, *et al.* Care after pancreatic resection according to an algorithm for early detection and minimally invasive management of pancreatic fistula versus current practice (PORSCH-trial): Design and rationale of a nationwide stepped-wedge cluster-randomized trial. Trials 2020;21:1–16.
[25] Smits FJ, Henry AC, Besselink MG, *et al.* Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in the Netherlands: an open-label, nationwide, stepped-wedge cluster-randomised trial. Lancet 2022;399:1867–75.
[26] Okano K, Hirao T, Unno M, *et al.* Postoperative infectious complications after pancreatic resection. Br J Surg 2015;102:1551–60.
[27] Correa-Gallego C, Brennan MF, D'Angelica MI, *et al.* Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. J Am Coll Surg 2012;215:616–21.
[28] Behrman SW, Zarzaur BL. Intra-abdominal sepsis following pancreatic resection: incidence, risk factors, diagnosis, microbiology, management, and outcome. Am Surg 2008;74:572–8.
[29] Povoski SP, Karpeh MS, Conlon KC, *et al.* Preoperative biliary drainage: impact on intraoperative bile cultures and infectious morbidity and mortality after pancreaticoduodenectomy. J Gastrointest Surg 1999;3:496–505.
[30] Howard TJ, Yu J, Greene RB, *et al.* Influence of bactibilia after preoperative biliary stenting on postoperative infectious complications. J Gastrointest Surg 2006;10:523–31.
[31] Cortes A, Sauvanet A, Bert F, *et al.* Effect of bile contamination on immediate outcomes after pancreaticoduodenectomy for tumor. J Am Coll Surg 2006;202:93–9.
[32] Gavazzi F, Ridolfi C, Capretti G, *et al.* Role of preoperative biliary stents, bile contamination and antibiotic prophylaxis in surgical site infections after pancreaticoduodenectomy. BMC Gastroenterol 2016;16:43.
[33] Yamashita K, Kato D, Sasaki T, *et al.* Contaminated drainage fluid and pancreatic fistula after pancreatoduodenectomy: a retrospective study. Int J Surg 2018;52:314–9.

[34] D'Angelica MI, Ellis RJ, Liu JB, *et al*. Piperacillin-tazobactam compared with cefoxitin as antimicrobial prophylaxis for pancreatoduodenectomy: a randomized clinical trial. JAMA 2023;329:1579–88.
[35] De Pastena M, Paiella S, Azzini AM, *et al*. Preoperative surveillance rectal swab is associated with an increased risk of infectious complications in pancreaticoduodenectomy and directs antimicrobial prophylaxis: an antibiotic stewardship strategy? HPB 2018;20:555–62.
[36] Sourrouille I, Gaujoux S, Lacave G, *et al*. Five days of postoperative antimicrobial therapy decreases infectious complications following pancreaticoduodenectomy in patients at risk for bile contamination. HPB 2013;15:473–80.
[37] Droogh DHM, Groen JV, de Boer MGJ, *et al*. Prolonged antibiotic prophylaxis after pancreatoduodenectomy: systematic review and meta-analysis. Br J Surg 2023;110:1458–66.
[38] Ocuin LM, Loftus A, Elshami M, *et al*. Extended antibiotic therapy is associated with a lower rate of clinically relevant postoperative pancreatic fistula after pancreatoduodenectomy in intermediate- and high-risk patients: a single-institution analysis. Surgery 2024;175:477–83.
[39] McMillan MT, Fisher WE, Van Buren G, *et al*. The value of drains as a fistula mitigation strategy for pancreatoduodenectomy: something for everyone? Results of a randomized prospective multi-institutional study. J Gastrointest Surg 2015;19:21–31.
[40] Molinari E, Bassi C, Salvia R, *et al*. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. Ann Surg 2007;246:281–7.
[41] Wang Q, Jiang YJ, Li J, *et al*. Is routine drainage necessary after pancreaticoduodenectomy. World J Gastroenterol 2014;20:8110–8.
[42] Marchegiani G, Perri G, Pulvirenti A, *et al*. Non-inferiority of open passive drains compared with closed suction drains in pancreatic surgery outcomes: A prospective observational study. Surgery 2018;164:443–9.
[43] Marchegiani G, Ramera M, Viviani E, *et al*. Dislocation of intra-abdominal drains after pancreatic surgery: results of a prospective observational study. Langenbecks Arch Surg 2019;404:213–22.
[44] Correa-Gallego C, Brennan MF, D'Angelica M, *et al*. Operative drainage following pancreatic resection: Analysis of 1122 patients resected over 5 Years at a single institution. Ann Surg 2013;258:1051–8.
[45] Zanini N, Lombardi R, Masetti M, *et al*. Operative drainage following pancreatic resections: we need more evidence. Ann Surg 2015;261:e160.
[46] Mehta VV, Fisher SB, Maithel SK, *et al*. Is it time to abandon routine operative drain use? A single institution assessment of 709 consecutive pancreaticoduodenectomies. J Am Coll Surg 2013;216:635–42.
[47] Fisher WE, Hodges SE, Silberfein EJ, *et al*. Pancreatic resection without routine intraperitoneal drainage. HPB (Oxford) 2011;13:503–10.
[48] Kawai M, Tani M, Terasawa H, *et al*. Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients. Ann Surg 2006;244:1–7.
[49] Dai M, Liu Q, Xing C, *et al*. Early drain removal is safe in patients with low or intermediate risk of pancreatic fistula after pancreaticoduodenectomy: a multicenter, randomized controlled trial. Ann Surg 2022; 275:E307–14.
[50] Bassi C, Molinari E, Malleo G, *et al*. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg 2010;252:207–14.
[51] Vissers FL, Balduzzi A, van Bodegraven EA, *et al*. Prophylactic abdominal drainage or no drainage after distal pancreatectomy (PANDORINA): a binational multicenter randomized controlled trial. Trials 2022;23:809.
[52] Meier R, Ockenga J, Pertkiewicz M, *et al*. ESPEN guidelines on enteral nutrition: pancreas. Clin Nutr 2006;25:275–84.
[53] Gianotti L, Besselink MG, Sandini M, *et al*. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery (United States) 2018;164:1035–48.
[54] O'Keefe SJD. Physiological response of the human pancreas to enteral and parenteral feeding. Curr Opin Clin Nutr Metab Care 2006;9:622–8.
[55] Klek S, Sierzega M, Turczynowski L, *et al*. Enteral and parenteral nutrition in the conservative treatment of pancreatic fistula: a randomized clinical trial. Gastroenterology 2011;141:157–163.e1.
[56] Wu JM, Kuo TC, Chen HA, *et al*. Randomized trial of oral versus enteral feeding for patients with postoperative pancreatic fistula after pancreatoduodenectomy. Br J Surg 2019;106:190–8.
[57] Gyr KE, Meier R. Pharmacodynamic effects of sandostatin® in the gastrointestinal tract. Digestion 1993;54(Suppl. 1):14–9.
[58] Shan YS, Sy ED, Lin PW. Role of somatostatin in the prevention of pancreatic stump-related morbidity following elective pancreaticoduodenectomy in high-risk patients and elimination of surgeon-related factors: prospective, randomized, controlled trial. World J Surg 2003; 27:709–14.
[59] Gouillat C, Chipponi J, Baulieux J, *et al*. Randomized controlled multicentre trial of somatostatin infusion after pancreaticoduodenectomy. Br J Surg 2001;88:1456–62.
[60] Suc B, Msika S, Piccinini M, *et al*. Octreotide in the prevention of intra-abdominal complications following elective pancreatic resection: a prospective, multicenter randomized controlled trial. Arch Surg 2004; 139:288–94.
[61] Sarr MGL, Woltering EA. The potent somatostatin analogue vapreotide does not decrease pancreas-specific complications after elective pancreatectomy: a prospective, multicenter, double-blinded, randomized, placebo-controlled trial. J Am Coll Surg 2003;196:556–64.
[62] Bootsma BT, Plat VD, van de Brug T, *et al*. Somatostatin analogues for the prevention of pancreatic fistula after open pancreatoduodenectomy: a nationwide analysis. Pancreatology 2022;22:421–6.
[63] Allen PJ, Gönen M, Brennan MF, *et al*. Pasireotide for postoperative pancreatic fistula. N Engl J Med 2014;370:2014–22.
[64] Gans SL, Van Westreenen HL, Kiewiet JJS, *et al*. Systematic review and meta-analysis of somatostatin analogues for the treatment of pancreatic fistula. Br J Surg 2012;99:754–60.
[65] Larsen M, Kozarek R. Management of pancreatic ductal leaks and fistulae. J Gastroenterol Hepatol 2014;29:1360–70.
[66] Baudin G, Chassang M, Gelsi E, *et al*. CT-guided percutaneous catheter drainage of acute infectious necrotizing pancreatitis: assessment of effectiveness and safety. AJR Am J Roentgenol 2012;199:192–9.
[67] Cronin CG, Gervais DA, Fernandez-Del Castillo C, *et al*. Interventional radiology in the management of abdominal collections after distal pancreatectomy: a retrospective review. AJR Am J Roentgenol 2011; 197:241–6.
[68] Zink SI, Soloff EV, White RR, *et al*. Pancreaticoduodenectomy: frequency and outcome of post-operative imaging-guided percutaneous drainage. Abdom Imaging 2009;34:767–71.
[69] Sanjay P, Kellner M, Tait IS. The role of interventional radiology in the management of surgical complications after pancreatoduodenectomy. HPB (Oxford) 2012;14:812–7.
[70] Kwon YM, Gerdes H, Schattner MA, *et al*. Management of peripancreatic fluid collections following partial pancreatectomy: a comparison of percutaneous versus EUS-guided drainage. Surg Endosc 2013;27:2422–7.
[71] Keane MG, Sze SF, Cieplik N, *et al*. Endoscopic versus percutaneous drainage of symptomatic pancreatic fluid collections: a 14-year experience from a tertiary hepatobiliary centre. Surg Endosc 2016;30: 3730–40.
[72] Baron TH, DiMaio CJ, Wang AY, *et al*. American Gastroenterological Association Clinical Practice Update: management of pancreatic necrosis. Gastroenterology 2020;158:67–75.e1.
[73] van Brunschot S, van Grinsven J, van Santvoort HC, *et al*. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. The Lancet 2018;391:51–8.
[74] Meierhofer C, Fuegger R, Spaun GO, *et al*. Endoscopic transmural therapy of pancreatic fistulas in an interdisciplinary setting—a retrospective data analysis. J Clin Med 2023;12:4531.
[75] Felsenstein M, Amini AC, Dorfer S, *et al*. Internal drainage for interdisciplinary management of anastomotic leakage after pancreaticogastrostomy. Surg Endosc 2023;37:5065–76.
[76] Rana SS, Bhasin DK, Rao C, *et al*. Consequences of long term indwelling transmural stents in patients with walled off pancreatic necrosis & disconnected pancreatic duct syndrome. Pancreatology 2013;13:486–90.
[77] Gardner TB, Coelho-Prabhu N, Gordon SR, *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.
[78] Siddiqui AA, Adler DG, Nieto J, *et al*. EUS-guided drainage of peripancreatic fluid collections and necrosis by using a novel lumen-apposing stent: a large retrospective, multicenter U.S. experience (with videos). Gastrointest Endosc 2016;83:699–707.
[79] Al Efishat M, Attiyeh MA, Eaton AA, *et al*. Endoscopic versus percutaneous drainage of post-operative peripancreatic fluid collections following pancreatic resection. HPB (Oxford) 2019;21:434–43.
[80] Wente MN, Veit JA, Bassi C, *et al*. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic. Surgery (ISGPS) definition Surgery 2007;142:20–5.

[81] Roulin D, Cerantola Y, Demartines N, *et al*. Systematic review of delayed postoperative hemorrhage after pancreatic resection. J Gastrointest Surg 2011;15:1055–62.
[82] Lee HG, Heo JS, Choi SH, *et al*. Management of bleeding from pseudoaneurysms following pancreaticoduodenectomy. World J Gastroenterol 2010;16:1239–44.
[83] Tan W, Yuan K, Ji K, *et al*. Targeted versus empiric embolization for delayed postpancreatectomy hemorrhage: a retrospective study of 312 patients. J Vasc Interv Radiol 2024;35:241–250.e1.
[84] Hur S, Yoon CJ, Kang SG, *et al*. Transcatheter arterial embolization of gastroduodenal artery stump pseudoaneurysms after pancreaticoduodenectomy: safety and efficacy of two embolization techniques. J Vasc Interv Radiol 2011;22:294–301.
[85] Bruder L, Schawe L, Gebauer B, *et al*. Evaluation of open surgical and endovascular treatment options for visceral artery erosions after pancreatitis and pancreatic surgery. Curr Oncol 2022;29:2472–82.
[86] Habib JR, Gao S, Young AJ, *et al*. Incidence and contemporary management of delayed bleeding following pancreaticoduodenectomy. World J Surg 2022;46:1161–71.
[87] Groen JV, Smits FJ, Koole D, *et al*. Completion pancreatectomy or a pancreas-preserving procedure during relaparotomy for pancreatic fistula after pancreatoduodenectomy: a multicentre cohort study and meta-analysis. Br J Surg 2021;108:1371–9.
[88] De Castro SMM, Busch ORC, Van Gulik TM, *et al*. Incidence and management of pancreatic leakage after pancreatoduodenectomy. Br J Surg 2005;92:1117–23.
[89] Bachellier P, Oussoultzoglou E, Rosso E, *et al*. Pancreatogastrostomy as a salvage procedure to treat severe postoperative pancreatic fistula after pancreatoduodenectomy. Arch Surg 2008;143:966–70.
[90] Kent TS, Callery MP, Vollmer CM. The bridge stent technique for salvage of pancreaticojejunal anastomotic dehiscence. HPB (Oxford) 2010;12:577–82.
[91] Van Berge Henegouwen MI, De Wit LT, Van Gulik TM, *et al*. Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy: drainage versus resection of the pancreatic remnant. J Am Coll Surg 1997; 185:18–24.
[92] Paye F, Lupinacci RM, Kraemer A, *et al*. Surgical treatment of severe pancreatic fistula after pancreaticoduodenectomy by wirsungostomy and repeat pancreatico-jejunal anastomosis. Am J Surg 2013;206: 194–201.
[93] Maeda H, Hanazaki K. Pancreatogenic diabetes after pancreatic resection. Pancreatology 2011;11:268–76.
[94] Balzano G, Pecorelli N, Piemonti L, *et al*. Relaparotomy for a pancreatic fistula after a pancreaticoduodenectomy: a comparison of different surgical strategies. HPB (Oxford) 2014;16:40–5.
[95] Van Veldhuisen CL, Latenstein AEJ, Blauw H, *et al*. Bihormonal artificial pancreas with closed-loop glucose control vs current diabetes care after total pancreatectomy: a randomized clinical trial. JAMA Surg 2022;157:950–7.
[96] Stoop TF, Ghorbani P, Scholten L, *et al*. Total pancreatectomy as an alternative to high-risk pancreatojejunostomy after pancreatoduodenectomy: a propensity score analysis on surgical outcome and quality of life. HPB 2022;24:1261–70.
[97] Scholten L, Stoop TF, Del Chiaro M, *et al*. Systematic review of functional outcome and quality of life after total pancreatectomy. Br J Surg 2019;106:1735–46.
[98] Stoop TF, Ateeb Z, Ghorbani P, *et al*. Surgical Outcomes After Total Pancreatectomy: a High-Volume Center Experience. Ann Surg Oncol 2021;28:1543–51.
[99] Stoop TF, Bergquist E, Theijse RT, *et al*. Systematic review and meta-analysis of the role of total pancreatectomy as an alternative to pancreatoduodenectomy in patients at high risk for postoperative pancreatic fistula: is it a justifiable indication? Ann Surg 2023;278: E702–11.
[100] Balzano G, Zerbi A, Aleotti F, *et al*. Total pancreatectomy with islet autotransplantation as an alternative to high-risk pancreatojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg. 2023;277:894–903.