REVIEW

Postoperative pancreatic fistula: a review of traditional and emerging concepts

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Abstract: Postoperative pancreatic fistula (POPF) remains the major cause of morbidity after pancreatic resection, affecting up to 41% of cases. With the recent development of a consensus definition of POPF, there has been a large number of reports examining various risk factors, prediction models, and mitigation strategies for this costly complication. Despite these strategies, the rates of POPF have not significantly diminished. Here, we review the literature and evidence regarding both traditional and emerging concepts in POPF prediction, prevention, and management. In particular, we review the evidence for the association between postoperative pancreatitis and POPF, and present a novel proposed mechanism for the development of POPF.

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

Introduction

Postoperative pancreatic fistula (POPF) remains the main source of major morbidity and mortality after pancreatic resection, affecting between 13% and 41% of patients.[1,2] POPF is associated with morbid sequelae including intra-abdominal sepsis and hemorrhage, carrying a mortality risk of 1% for all patients with POPF and 25% for patients with grade C POPF.[3] The development of a POPF results in a complex and lengthy duration of inpatient care with a significant cost burden. Despite numerous reports and trials describing novel methods to curtail the risk of POPF formation, the reported rates of POPF have not significantly improved over the last three decades.[4] This is largely attributable to the fact that the underlying mechanism of POPF is poorly understood, with only recent work beginning to reveal the role of postoperative pancreatitis (POP) in the development of POPF, rather than a mere loss of mechanical integrity of the pancreatoenteric anastomosis.

Early literature describing POPF has been heterogeneous due to varied definitions of POPF. The development of consensus definitions by the International Study Group on Pancreatic Fistula (ISGPF)[5] has allowed for more uniformity in the reporting of this complication. These definitions have been further refined in 2016 to limit the reporting of POPF to only those that impact the postoperative clinical course of the patient.[6] This has been crucial in allowing valid comparisons to be made between various interventions for the prevention and management of this complication.

The aim of this review is to discuss both traditional and emerging concepts in the understanding of POPF pathophysiology and management, with a focus on potential future directions for research in this field.

Definition

Until 2005, there was no consensus in the definition and grading of POPF resulting in an inability to compare various interventions and preventive techniques for this complication. This led to great variability in the reported rate of POPF after pancreatic resection. An International Working Group of 37 pancreatic surgeons was formed in 2005 to establish for the first time a standardized all-inclusive definition of POPF to address this issue. This led to the first widely accepted definition of POPF: "drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity."[5] A grading system was also established which stratified patients from a relatively benign clinical course (grade A fistula), moderately unwell patients requiring medical or minimally invasive intervention (grade B), and critically ill patients, often with sepsis, requiring invasive intervention (grade C).

This consensus definition was revised in 2016 mainly to restrict the definition of POPF to only those that were "associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula" (ie, grade B and C).[6] Thus, a grade A POPF has now been redefined and assigned the term "biochemical leak", as it does not cause any change to the clinical condition of the patient. The criteria for defining grade B and C POPFs were also made more specific to clarify the distinction between the two categories (Table 1). Importantly, this grading system has been repeatedly validated in terms of its association with other non-POPF complications,[8] length of hospital and intensive care unit (ICU) stay, and the cost of hospital stay.[9]

Traditional concepts
Mechanism and risk factors

The pathophysiology of POPF has been seldom evaluated and long assumed to be due to a gradual loss of mechanical integrity of the pancreatoenteric anastomosis leading to "leakage" of pancreatic fluid. There is a paucity of studies examining the precise mechanisms of POPF evolution, although many surgical methods to ameliorate this problem have been described, revealing a widespread misunderstanding of POPF as a mere loss of mechanical anastomotic integrity. Such reported methods emphasize mechanical buttressing or reinforcement of the anastomosis or staple line, including the use of fibrin sealants,[10] autologous tissue patches,[11] bioabsorbable mesh,[12] varied suturing techniques,[13] stents,[14] and various methods of pancreatoenteric anastomosis.[15] Very few of these have been consistently demonstrated in multiple high-volume randomized controlled trials (RCTs) to be effective in significantly reducing the rate or severity of POPF.[16]

Many cohort studies have examined and identified risk factors for the development of POPF. The factors most consistently shown to be predictive of POPF after pancreaticoduodenectomy (PD) include soft gland texture, non-pancreatic cancer non-chronic pancreatitis pathology, small pancreatic duct diameter (<3 mm), and high intraoperative blood loss (>1000 mL). These features may be used to determine the Fistula Risk Score (FRS), which is a validated scoring system used to predict the risk of POPF formation after PD.[17] Other reported but less-validated risk factors include that of increased body mass index (BMI),[18] excess intraoperative fluid administration,[19] increased pancreatic parenchymal remnant volume,[20] poor preoperative nutrition,[21] and male gender.[22] The mechanisms by which such preoperative factors lead to POPF have not been studied in detail.

Although advanced age is associated with increased perioperative mortality, there seems not to be an increased risk of POPF. In a study comparing patients <75 (n=422) and ≥75 (n=102) years of age undergoing PD, the latter age category was associated with a higher rate of perioperative mortality (1.9% vs 5.9%, p=0.037), but not associated with increased risk of POPF (10% vs 7.8%, p=0.579).[23]

Table 1 2017 ISGPF definitions and grades of postoperative pancreatic fistula[6]

Event	Biochemical leak	Grade B POPF	Grade C POPF
Drain amylase concentration >3× upper limit of normal serum value	Yes	Yes	Yes
Persisting peripancreatic drainage >3 weeks	No	Yes	Yes
Clinically relevant change in the management of POPF	No	Yes	Yes
Percutaneous or endoscopic drainage of POPF-associated collections	No	Yes	Yes
Angiographic procedures for POPF-associated bleeding	No	Yes	Yes
Reoperation for POPF	No	No	Yes
Signs of infection related to POPF	No	Yes (without organ failure)	Yes (with organ failure)
POPF-related organ failure	No	No	Yes
POPF-related death	No	No	Yes

Abbreviations: ISGPF, International Study Group on Pancreatic Fistula; POPF, postoperative pancreatic fistula.

Sequelae of POPF

The sequelae of POPF can be broadly divided into two specific categories: hemorrhage and sepsis. Either of these may further lead to other systemic consequences including prolonged hospital stay, delayed gastric emptying (DGE), enteric fistulae, multiorgan failure, and/or death.

Hemorrhage

Hemorrhagic complications are highly feared sequela of POPF due to their ability to cause dramatic and rapid deterioration of the patient. Most commonly, this occurs due to a pseudoaneurysm of a large visceral artery that develops due to prolonged contact with pancreatic fluid which has a high proteolytic capacity.[24] Arteries that are commonly involved include the common hepatic, splenic, gastroduodenal, and superior mesenteric artery. Such pseudoaneurysms also may be discovered at the time of postoperative axial imaging performed for other reasons, and if left untreated, may increase in size leading to rupture, which is usually associated with severe hemorrhage and hemodynamic instability. Therefore, early treatment of these lesions is of paramount importance, and will be discussed in further detail below (see "Management" section).

Sepsis

Infective sequelae of pancreatic resection are more common after PD than after distal pancreatectomy (DP), presumably due to contamination of the operative field by biliary and enteric content during the anastomotic phase of the operation. The development of this complication is often insidious and manifests clinically as the development of fever, DGE, abdominal pain, and/or rising inflammatory markers. Turbidity of drain fluid may also herald intra-abdominal sepsis, and should be evaluated with Gram stain, microscopy, and culture. Contrast-enhanced CT imaging should be performed to evaluate such patients to determine whether there are any drainable fluid collections. On CT imaging, a walled-off peripancreatic fluid collection may be seen representing an abscess. Such collections are most commonly managed with minimally invasive radiologically guided percutaneous or endoscopic drainage and rarely require laparotomy.

Related major complications

Patients who develop POPF are also more likely to develop non-fistula postoperative complications including prolonged duration of hospital stay, wound infection, acute cardiac events, bile leak, and mortality.[25] Notably, POPF and POP have both been identified as predictors of the development of DGE after PD, which leads to poorer nutritional outcomes and increased length of hospital stay.[26]

Prediction of POPF

Early prediction of the development of a pancreatic fistula is important as it allows for identification of at risk patients who will need close monitoring, and equally the implementation of enhanced recovery protocols in patients who are deemed to be at low risk.[27] In addition, the early diagnosis of POPF allows prompt intervention to prevent the development of disastrous and potentially lethal sequelae.

Preoperative

The type of resection planned for the patient is known to influence the rate of POPF formation. POPF rates for PD, DP, and central pancreatectomy (CP) are 13%,[2] 29%,[28] and 41%,[1] respectively. Rates of POPF after enucleation of pancreatic tumors have been reported to be as high as 73%, with the risk particularly high when the tumor is located <3 mm from the main pancreatic duct.[29] The high rates of POPF after CP occur due to the existence of both a remnant pancreatic stump and a pancreatoenteric anastomosis. CP and enucleation are usually only justified in healthy and young individuals where the lesion is benign, where any other resection (eg, subtotal pancreatectomy) is likely to cause severe long-term morbidity (eg, pancreatic exocrine insufficiency, diabetes mellitus) in an otherwise fit patient.[30]

Rates of POPF are lowest for patients who have a histopathological diagnosis of either pancreatic ductal adenocarcinoma (PDAC) or chronic pancreatitis, as both are associated with atrophy of the remnant gland due to chronic ductal obstruction.[17] This results in a fibrotic pancreas with a widened pancreatic duct in which a pancreatoenteric anastomosis may be technically easier to achieve.

Some authors have reported the use of preoperative axial imaging studies to predict POPF formation by characterizing its enhancement patterns. Preoperative imaging can provide some insight into important factors such as the consistency of the future remnant pancreas and also the presence of pancreatic ductal dilatation. In a cohort of 29 patients undergoing pancreatic resection, magnetic resonance imaging findings of a higher pancreas-to-muscle signal intensity ratio on T1 images were associated with a higher risk of POPF. A signal intensity ratio cutoff value of 1.41 had a positive predictive value of 73% and a negative predictive value of 89% with regard to the development of POPF.[31] In another study of 146 patients undergoing PD using triple phase CT imaging, a slower rate of contrast enhancement of the remnant gland

was associated with a lower rate of POPF formation.[32] This likely relates to a more fibrotic and less vascular pancreatic remnant. Such reports have been observed in small observational cohorts with results yet to be validated in larger sample sizes.

Intraoperative

The FRS is the most widely used predictive tool, utilizing several intraoperatively determined factors that have repeatedly been shown to predict the development of POPF during a PD. This scoring system (Tables 2 and 3) utilizes gland texture, histopathological diagnosis, pancreatic duct diameter, and intraoperative blood loss to assign a score out of 10, which is then used to determine whether the patient is at negligible (score 0), low (score 1–2), moderate (score 3–6), or high (score 7–10) risk of developing a POPF.[17] In a multi-institutional validation study of the FRS evaluating 594 patients who underwent PD, the incidence of grade B/C POPF was 6.6% for low risk, 12.9% for moderate risk, and 28.1% for high-risk patients.[33]

Table 2 Fistula Risk Scoring system for the prediction of postoperative pancreatic fistula[17]

Risk factor	Parameter	Points*
Gland texture	Firm	0
	Soft	2
Pathology	PDAC or chronic pancreatitis	0
	Ampullary, duodenal, cystic, islet cell, etc	1
Pancreatic duct diameter	≥5 mm	0
	4 mm	1
	3 mm	2
	2 mm	3
	≤1 mm	4
Intraoperative blood loss	≤400 mL	0
	401–700 mL	1
	701–1000 mL	2
	>1000 mL	3

Note: *Out of 10.
Abbreviation: PDAC, pancreatic ductal adenocarcinoma.

Table 3 FRS zones and probability of POPF after PD – results from a multi-institutional validation study of 594 PD patients[33]

FRS points (out of 10)	Risk zone	Risk of POPF* (%)
0	Negligible	**
1–2	Low	6.6
3–6	Moderate	12.9
7–10	High	28.1

Notes: *Clinically relevant. **No patients in this validation cohort were of negligible risk.
Abbreviations: FRS, Fistula Risk Score; PD, pancreaticoduodenectomy; POPF, postoperative pancreatic fistula.

Postoperative

Both macroscopic and biochemical analyses of drain effluent are significant predictors of POPF development. Macroscopically, drain fluid that is red-brown in colour in the first few postoperative days is thought to be associated with enzymatic breakdown of intra-abdominal proteins caused by a leakage of protease-rich pancreatic fluid.[5] Biochemically, amylase concentration in the drain fluid in the postoperative phase is a strong predictor of POPF development. In a prospective validation study of patients undergoing PD, a postoperative day 1 drain amylase level of <600 U/L was found to be a stronger predictor of the absence of POPF than a soft gland and duct diameter.[34]

Prevention of POPF

Nutrition

A number of studies have demonstrated both obesity and malnutrition as risk factors for the development of POPF. In a prospective cohort study of 87 patients undergoing PD, a higher BMI and lower prognostic nutritional index were significantly associated with a higher risk of POPF.[35] In addition, rates of POPF have been found to be higher in patients with sarcopenia.[36] Although preoperative nutritional optimization has not been evaluated in randomized trials for its capacity to prevent POPF, multimodal prehabilitation prior to major oncological surgery has been shown to decrease postoperative morbidity.[37] Units performing pancreatectomy should therefore consider the involvement of specialist dieticians in the preoperative phase to screen patients for malnutrition and for the purposes of prehabilitation.

In the postoperative phase, the optimal route of the administration of nutrition has yet to be definitively confirmed. A systematic review of seven RCTs and eight retrospective cohort studies comparing enteral and total parenteral nutrition after PD did not show a significant difference in rates of POPF with any particular feeding modality.[38] A number of RCTs exploring these two modalities also do not demonstrate a significant difference.[39–41] One retrospective cohort study demonstrated a 6% re-laparotomy rate for tube-related complications in patients who received a feeding jejunostomy at the time of operation.[42] The use of "immunonutrition" via arginine- and omega-3-enriched enteral feeds has been demonstrated to reduce postoperative complications and length of hospital stay in one RCT.[41]

One multicenter RCT comparing early enteral and total parental nutrition in patients undergoing PD demonstrated an increase in overall postoperative complications and rate and severity of POPF in patients receiving early enteral feeds

via the nasojejunal route.[43] Notably, the increase in rate of enteral feeds in this study was in 25 mL/hour increments per day, which is considerably faster than standard rates.[44] Whether such an increase in rates of complication persists at a slower rate of enteral feed infusion needs to be explored in further prospective studies.

Neoadjuvant chemotherapy (NAC)/radiotherapy

The role of NAC and/or radiotherapy is a contentious issue and its oncological benefit has yet to be demonstrated in the setting of large volume RCTs, but is becoming more widely utilized in the setting of pancreatic cancer.[45] This has led to a number of cohort studies evaluating the effect of NAC on postoperative morbidity, particularly with regard to the development of POPF. In a review of American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) data, postoperative outcomes from 3408 patients who underwent pancreatectomy were analyzed. In these data, neoadjuvant treatment was associated with lower rates of POPF (10.2% vs 13.2%, p=0.017) despite higher intra/postoperative blood transfusion requirements (27.4% vs 20.3%, p<0.0001). A retrospective analysis of 79 patients who underwent neoadjuvant chemoradiation prior to PD for periampullary malignancies demonstrated no difference in mortality, less POPF, and less intra-abdominal abscess compared with historical controls.[46] These findings were replicated in another retrospective cohort study of 58 patients with PDAC who underwent DP, where 28 patients had received neoadjuvant chemoradiation, and 30 patients had upfront resection. The patients who received neoadjuvant chemoradiation experienced significantly less POPF, and lower drain amylase levels on postoperative day 1 and 3.[47] Furthermore, NAC and radiotherapy alone have each been reported to be of benefit in reducing rates of POPF.[48,49] The mechanisms by which neoadjuvant therapy reduces POPF rates are uncertain; however, it may in part relate to a longer period of pancreatic ductal obstruction and atrophy of the remnant gland, particularly in head of pancreas tumors.

Pharmacological

The use of somatostatin analogs remains a point of debate among many pancreatic surgeons, with significant heterogeneity in the literature with regard to its purported benefits and detriments despite the existence of >10 RCTs exploring this issue.[50–60] Octreotide has long been used in pancreatic surgery due to its mechanism of action, which is to bind to G-coupled somatostatin receptors, thus exerting an inhibitory action on both exocrine and endocrine functions of the pancreas.[61] Reduction in pancreatic exocrine secretions may encourage healing of pancreatoenteric anastomoses or staple lines. The benefit in reducing POPF and postoperative complications was demonstrated in a number of early randomized trials. In a multicenter trial of 246 patients undergoing elective pancreatic resection, the administration of octreotide was associated with a significantly lower rate of POPF, and also a lower rate of complications in those deemed to be at high fistula risk.[51] These findings were supported by another multicenter RCT of 218 patients, which demonstrated a significantly lower rate of POPF in patients who received octreotide; however, it was not clear as to what proportions of these were clinically relevant.[62]

These trials, however, have been criticized for an overall high rate of POPF, and investigators have sought to determine the role of octreotide in a more modern surgical context. Lowy et al performed a single-institution RCT in 120 patients undergoing PD for periampullary malignancy. They found that the administration of octreotide was not associated with any significant reduction in POPF rates.[63] These findings were supported by another RCT of 383 patients where no significant reduction in POPF rates was seen in the octreotide group.[60] More recently, pasireotide, a longer acting somatostatin analog, has been evaluated in an RCT of 300 patients undergoing pancreatic resection. Whilst this has demonstrated a reduction in POPF rates, this drug has not been approved for use by the Food and Drug Administration in pancreatic surgery.[64] Notably, in a recent large multinational retrospective cohort study with propensity score matched analysis, the use of octreotide was actually found to be associated with a greater risk of POPF development in patients with high-risk pancreata (p<0.001).[65] The use of octreotide, therefore, remains heterogeneous among pancreatic units across the globe.

Intravenous fluids

The role of goal-directed intravenous fluids in the perioperative phase is integral to care of the post-pancreatectomy patient. A number of cohort studies have shown an association with excess fluids and a higher risk of POPF formation.[19,66] A moderately restrictive fluid regimen using hypertonic saline has also been demonstrated in a prospective randomized trial to be of benefit in the prevention of POPF and reduction of return to theater, readmissions, length of stay, and mortality.[67] Whilst the benefit of hypertonic solutions requires validation in further prospective studies, a policy of goal-directed fluid administration appears to be a prudent measure.

Anastomosis

The operative management of the remnant pancreas after partial pancreatic resection remains the topic of significant debate, with no clear optimal surgical technique having been demonstrated to decrease the rates of POPF. Consequently, there is significant variation in operative technique among high-volume pancreatic surgeons.

A number of pancreatoenteric anastomotic techniques have been evaluated in prospective studies in regard to the rate of POPF. This includes the comparison of pancreatogastrostomy (PG) with the more traditional pancreato-jejunostomy (PJ). PG is theoretically thought to reduce the rate of POPF by deactivating pancreatic enzymes in an acidic environment and the lack of trypsin activating enterokinase in the gastric epithelium. In the largest multicenter RCT to date of PG versus PJ during PD (RECOPANC study), 440 patients were randomized to one of these two anastomoses, revealing no significant difference in the rate of POPF (20% vs 22%, p=0.617). However, PG was associated with an increased rate of grade A/B post-pancreatectomy hemorrhage, perioperative stroke, reduced need for long-term exocrine enzymatic replacement, and some improvement in quality of life measures. A nonsignificant trend toward increase in the rate of POPF was observed when the surgery was performed by surgeons with an annual caseload of <10 per year versus >25 per year (OR 2.801, 95% CI 1.155–6.794, p=0.064).[68] A meta-analysis of eight RCTs comparing 607 patients who underwent PG and 604 patients who underwent PJ revealed a significant reduction in POPF with the PG technique.[69] However, a recent retrospective cohort study of 58 patients undergoing CP has demonstrated a higher rate of POPF in patients receiving PG as opposed to PJ.[70] The authors hypothesize that this may be due to a greater amount of tension that exists in a PG anastomosis as opposed to PJ.

Variations in PJ technique have also been explored, with the two most common being duct-to-mucosa and the invagination technique. Two recent RCTs comparing duct-to-mucosa versus invagination pancreaticojejunostomy reveal no significant difference in the rate of POPF between the two techniques.[71,72] However, one of the RCTs demonstrated a significantly lower POPF rate with the invagination technique in a subgroup analysis of patients with a soft pancreas (10% vs 42%, p=0.010).[71] A number of meta-analyses examining RCTs comparing these two techniques have been conducted, each showing no difference in the incidence of POPF. However, a significant degree of heterogeneity in the reported definition of POPF complicates the comparison between duct-to-mucosa and the invagination PJ technique.[73–76]

One retrospective study of 44 patients undergoing stapled closure of the pancreatic stump after PD reported a surprisingly low POPF rate of 13.6%. This led the authors to suggest that avoidance of a pancreatoenteric anastomosis circumvents enterokinase-mediated activation of pancreatic enzymes, which in turn may explain the low POPF rate.[77] Indications for stump closure in this series included a small main pancreatic duct diameter, soft texture of the pancreatic remnant, and personal experience of the surgeon. Evaluation of this technique in a randomized controlled trial setting has yet to be performed.

Glues

The use of fibrin sealants and acrylic glues to decrease the risk of POPF has also been investigated, but none have definitively demonstrated a clinical benefit. A prospective cohort study evaluating pancreatic ductal occlusion with acrylic glue (without pancreatoenteric anastomosis) versus conventional pancreaticojejunostomy after PD revealed no significant difference in clinically relevant POPF rates (OR 1.45, 95% CI 0.012–1.096, p=1.004).[78] A RCT comparing pancreatoenteric anastomosis with and without occlusion of the main pancreatic duct with fibrin glue similarly revealed no statistically significant difference in the rates of POPF (15% vs 17%, respectively), deep collections, or intra-abdominal collections.[79] A meta-analysis of seven RCTs evaluating the use of fibrin sealants after partial pancreatectomy also revealed no significant difference in the rates of POPF (OR 0.83, 95% CI 0.6–1.14, p=0.245), although a trend toward less postoperative hemorrhage was seen with fibrin sealants (OR 0.43, 95% CI 0.18–1.0, p=0.05).[80]

Stents

The use of pancreatic stents has also been evaluated in the literature. In the context of PD, stents may be categorized as either internal or external. Internal stents are introduced into the main pancreatic duct, over which the pancreatoenteric anastomosis is fashioned. Conceptually, this is designed to divert pancreatic juice further downstream, away from the pancreatic anastomosis, and also to avoid inadvertent sutured closure of the pancreatic duct. Such stents have proven problematic, mainly with the issue of distal migration of the stent. Internal stents also seem not to significantly reduce the rates of POPF, with some studies demonstrating an increase in the rate of this complication especially in high-risk pancreata.[65,81,82]

Stents may also be externalized through the abdominal wall to drain extracorporeally. Several RCTs and one retrospective cohort study with propensity score matched

analysis have reported a reduction in POPF rates with the use of external stents.[65,81,83–85] However, a Cochrane review evaluating three RCTs comparing internal versus external stents failed to show superiority of one form of stent over the other in terms of POPF reduction.[86] External stents have been associated with a significantly longer length of hospital stay than internal stents, likely due to complications of the outpatient management of such a prosthesis.[87] A recent propensity score matched retrospective cohort analysis by Ecker et al of 522 patients with high-risk pancreata (FRS criteria) demonstrated a reduction in POPF rates with the use of externalized stents, and an increase in POPF rates with internal stents compared with no stents (external 15.2% vs internal 43.8% vs no stent 33.8%, *p*<0.001).[65]

Transpapillary stents inserted by endoscopic retrograde cholangiopancreatography (ERCP) have been explored as a measure to prevent POPF after DP. A meta-analysis of one RCT and three cohort studies encompassing 200 patients demonstrated a significantly lower rate of POPF in patients who underwent preoperative transpapillary stenting. However, the results of the single RCT (showing an increase in the rate of POPF) rather demonstrated an increase in POPF rates. Given the risk of ERCP-induced pancreatitis in the setting and the lack of convincing evidence to support its routine use, it seems prudent to avoid transpapillary intervention where possible.

DP stump

The management of the remnant pancreatic stump after DP remains a significant challenge despite numerous methods described in an attempt to reduce the risk of POPF. Such methods include comparisons between stapled closure and the role of oversewing the pancreatic stump. A multicenter RCT in 450 patients comparing hand sewn versus stapled closure of the DP stump demonstrated no difference in POPF rates between the two techniques.[88]

One retrospective cohort study has shown that dedicated oversewing of the main pancreatic duct reduces the rates of POPF (9.6% vs 34.0%, *p*<0.001).[89] It is possible, however, that such a result was attained due to more accurate identification of the pancreatic duct in harder and more fibrotic pancreata, which is associated with a lower risk of POPF.

The application of a jejunal seromuscular patch to the DP staple line has also been investigated, with no change in the rates of POPF.[90] Drainage of the remnant stump with a pancreatoenteric anastomosis has also been evaluated, with no significant difference in POPF rates demonstrated.[91]

A variety of ancillary methods have been described to reinforce stump closure of the remnant pancreas after DP. This includes the use of staple line reinforcement with an absorbable mesh. A number of small sample size prospective trials and retrospective cohort studies have demonstrated some reduction in POPF with its use.[12,92,93] However, a multicenter RCT of 275 patients evaluating the use of an absorbable fibrin sealant patch (TachoSil) revealed no significant reduction in grade B or C POPF with its use patients undergoing DP (TachoSil 8% vs no TachoSil 14%, *p*=0.139).[94] Various glues have also been evaluated, with most studies showing no reduction in the rates of POPF. Such glues include cyanoacrylate formulations[95] and fibrin glues.[10]

Drains

Whether use of surgical intra-abdominal drains influences the risk of POPF and postoperative complications remains uncertain and a point of some contention. Conlon et al[96] conducted an RCT of 179 patients who underwent pancreatic resection, randomized to having a drain or no drain placed at the time of surgery. In this study, patients with a drain had a higher incidence of POPF, intra-abdominal abscess and/or collection. However, another RCT by Van Buren et al[97] of 137 patients undergoing PD demonstrated an increase in POPF, gastroparesis, intra-abdominal collection/abscess, need for a percutaneous drain, and length of hospital stay. Most recently, the 2016 PANDRA trial[98] evaluated 395 patients undergoing PD randomized to either receiving an intra-abdominal drain or not at the time of surgery. This demonstrated a significant reduction in POPF rate (5.9% vs 11.9%, *p*=0.030) and fistula-associated complications (13.0% vs 26.4%, *p*=0.0008) in patients who did not receive a surgical drain. The results unfortunately were not stratified by FRS in this cohort. Interestingly, there was a significantly larger proportion of patients who had undergone neoadjuvant therapy and received somatostatin analogs in the "no drain" group. Moreover, the use of drains was not seen to be independently associated with the need for reintervention on multivariable analysis. It currently seems appropriate to undertake a selective approach to drain placement, where avoidance of a drain may be suitable in those patients deemed to be at low risk of POPF (large pancreatic duct diameter and hard glandular consistency).

Patients who do receive an intra-abdominal drain may benefit from its early removal by reducing the risk of secondary infection. In a prospective study of 114 patients randomized to early (day 3) or late (day 5+) drain removal, the early removal group experienced reduced rates of abdominal

complications and reduced pulmonary complications. However, patients with a drain amylase concentration of >5000 on postoperative day 1 were excluded from randomization.[99] Moreover, there was a greater number of patients with smaller duct diameter in the late drain removal group, which may confound these results. Importantly, Penrose drains were used in this study, as opposed to the more popular closed drainage systems. The open nature of the former would theoretically make them more likely to be associated with infection. Thus, these data should be interpreted with caution. It may be appropriate to remove drains early in patients who are at a low risk of development of fistula (eg, with a low FRS).

Minimally invasive pancreatectomy
DP
The use of a minimally invasive approach seems not to affect the rate of POPF in DP. In a propensity score matched analysis of laparoscopic (n=51) versus open (n=51) DP for pancreatic cancer, there was no significant difference in the rate of POPF (10% vs 19%, respectively, *p*>0.05).[100] This is consistent with findings from another retrospective analysis of laparoscopic (n=33) versus open (n=46) DP for pancreatic cancer (POPF rates 9% vs 15%, respectively, *p*=0.42).[101] In an analysis of ACS-NSQIP data for 1815 patients who underwent open (n=921), laparoscopic (n=694), or robotic (n=200) DP, no difference was seen in the rates of POPF (17% vs 18% vs 21%, respectively, *p*=0.6484).[102]

PD
In a multi-institutional study with propensity score matched analysis of patients undergoing open (n=152) versus robotic (n=152) PD, there was no significant difference seen in the rate of POPF (6.6% vs 11.2%, respectively, *p*=0.23).[103] Moreover, in a matched case-control study comparing postoperative outcomes of open (n=93) versus laparoscopic (n=93) PD, there was no difference in the rates of POPF between these groups (6.5% vs 6.5%, *p*=1.00).[104] It must be emphasized that both these studies involved institutions performing a high volume of minimally invasive pancreatic resections.

Management
The key to management of POPF includes early recognition of this problem and also prevention of further life threatening sequelae such as bleeding and sepsis.

Biochemical leak
Patients with a biochemical leak of asymptomatic amylase-rich drain effluent may be safely managed conservatively,

but require multidisciplinary involvement to prevent its progression to a clinically relevant POPF.

Observation
Vigilant observation in this context involves close monitoring for signs of sepsis including fevers and/or rising inflammatory markers. These findings may herald the development of an infected intra-abdominal fluid collection. A contrast-enhanced CT of the abdomen is usually required to assess for drainable collections and the commencement of broad spectrum antibiotic therapy.

Nutrition
From the perspective of nutrition, enteral rather than parenteral nutrition has been demonstrated in an RCT of 78 patients with POPF to be superior in spontaneous fistula closure rates.[105] Somatostatin analogs were not administered in this particular trial. In situations where the pancreatoenteric anastomosis is isolated from the alimentary tract, it would be appropriate to recommence an oral diet as usual. In situations where such isolation does not exist (eg, PG), it may be advisable to perform an oral contrast study to ensure the absence of a mechanical anastomotic leak prior to resuming an oral diet.

Somatostatin analogs
There has been no clear benefit demonstrated in the use of somatostatin analogs to treat established POPF. Despite this, the use of this drug remains popular, possibly as a result of a number of early single armed case series reporting a high rate of spontaneous pancreatic fistula closure.[106,107] A meta-analysis of seven RCTs evaluating a variety of somatostatin analogs (somatostatin, lanreotide, and octreotide) in 102 patients with established POPF showed that rates of POPF resolution were not increased with the use of these drugs. Due to significant inter-study heterogeneity, a comparison of POPF severity could not be performed.[108]

Grade B/C pancreatic fistula
Where the patient remains clinically stable, a "step-up" approach to POPF management is usually suitable.[109]

Minimally invasive drainage techniques
The evolution of interventional radiology has dramatically reduced the need for unplanned re-laparotomy after pancreatic resection in patients with POPF. Where a CT scan has detected an intra-abdominal peripancreatic collection that is safely accessible by percutaneous route, radiologically

guided drainage of such collections has been demonstrated to be both effective and safe.[110,111] In patients where the fluid collection is positioned in the lesser sac and cannot be reached by percutaneous route, endoscopic ultrasound may be utilized to drain these collections through the posterior wall of the stomach.[112]

Peripancreatic collections after DP are more likely to be sterile than after PD as there has been no breach of the bowel wall. Thus, a more conservative approach may be undertaken with these fluid collections occurring after DP, particularly where there is a low-risk pancreatic remnant. One observational study demonstrated that such collections occur in 43% of patients after DP, with over 90% spontaneously decreasing in size without further intervention.[113]

Angiographic intervention

In the setting of a patient with a grade B/C POPF, a significant drop in hemoglobin coupled with the development of hemodynamic instability should raise suspicion of an intra-abdominal bleed. Such patients should be urgently evaluated with a CT angiogram to identify any arterial pseudoaneurysms and/or points of arterial hemorrhage, which may subsequently be managed with angiographic stenting and/or embolization.[114,115] This minimally invasive approach to the management of such vascular complications is valuable as it often avoids the need for re-laparotomy and its associated risks and morbidity. Moreover, in a post-pancreatectomy patient, the development of postoperative adhesions can make difficult the task of rapidly identifying bleeding retroperitoneal vessels and achieving effective hemostasis.

Emergency laparotomy

Advances in interventional radiology and angiographic techniques have fortunately led to a decrease in the need for re-laparotomy for POPF.[116] However, there are still circumstances in which open surgery is a more favorable option. These include situations in which there is catastrophic hemorrhage that requires evacuation of a large amount of blood and hematoma and rapid attainment of hemostasis. Other surgical options in this setting include intra-abdominal lavage and wide drainage for infected collections that are refractory to minimally invasive treatments either due to their size or the inspissated nature of their contents. Breakdown of a pancreaticojejunostomy may be salvaged in some situations by performing a pancreaticogastrostomy.[117] In situations where there is complete dehiscence of the pancreaticoenterostomy and/or necrotizing pancreatitis, completion pancreatectomy may present the most appropriate and safe option for the

patient, although this carries the very morbid sequela of brittle diabetes.[118] Thus, surgical treatments are reserved for patients where minimally invasive methods are either inappropriate or have failed.[119]

Supportive care

The patient who has developed sepsis and/or hemorrhage as a result of POPF will also require supportive care. This includes management of the patient in the ICU, where appropriate inotropic and ventilatory support can be provided if necessary. The bleeding patient will also require judicious blood transfusion often with concomitant correction of coagulopathy especially in the setting of massive transfusion.

Emerging concepts
Pathophysiology/risk factors

Challenging the notion that POPF is a factor that develops over time, work by de Reuver et al[120] and Nahm et al[121] demonstrates that high amylase concentration in immediate intraoperatively derived fluid from the peripancreatic environment (intraoperative amylase concentration, IOAC) is highly predictive of the development of POPF after PD and DP, respectively. IOAC was demonstrated to be an excellent predictor of POPF in both situations with an area under the receiver operator characteristic (AUROC) curve of 0.93 (95% CI 0.87–0.99) for PD and 0.92 (95% CI 0.81–0.99) in DP. These data suggested for the first time that the underlying pathophysiological events that lead to the eventual recognition of a POPF as per the ISGPF definition occur at the time of pancreatic resection.

The density of acinar cells at the pancreatic neck margin has also been demonstrated to correlate highly with the IOAC and the development of POP (as measured by urinary trypsinogen-2 and serum amylase/lipase on postoperative day 1). The IOAC and the development of POP are, in turn, strongly associated with the development of POPF and a composite endpoint of systemic postoperative complications. This is supported by a growing body of biochemical evidence supporting the association between POP and POPF.[122–124]

The interaction between IOAC, acinar cell density, POP, and POPF has yet to be definitively elucidated; however, the authors have hypothesized a potential mechanism (Figure 1) whereby high-risk pancreata with a high acinar cell density are prone to both immediate leakage of protease-rich pancreatic fluid (IOAC) and the development of pancreatitis in the remnant gland as a result of ischemia and/or glandular manipulation.

The mechanism by which POP eventuates has yet to be explored in detail, although preliminary work by Ansorge et al
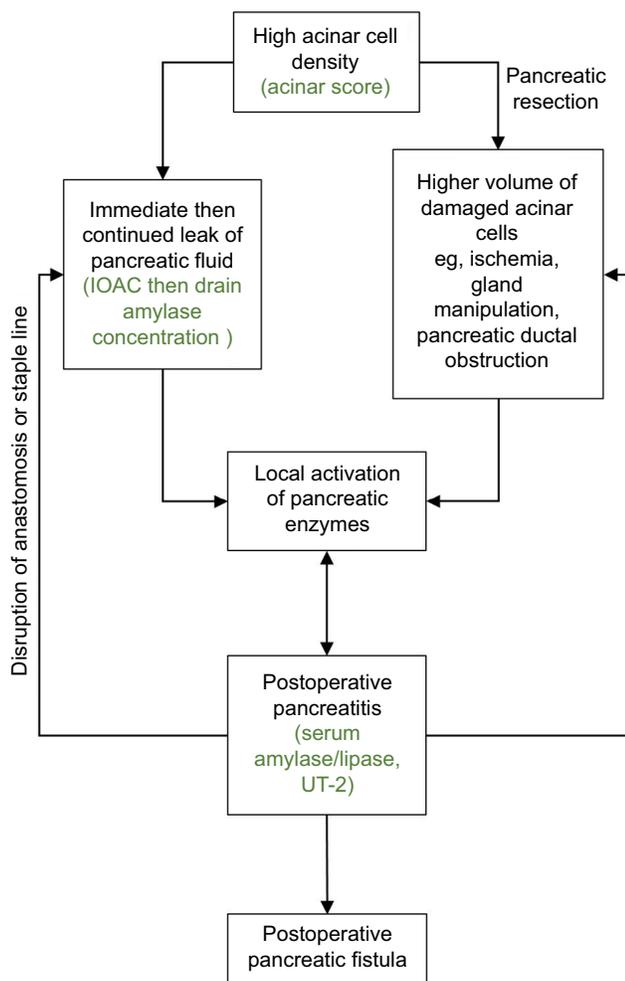
Figure I Hypothesized mechanism for the development of postoperative pancreatitis and POPF.
Abbreviations: IOAC, intraoperative amylase concentration; UT-2, urinary trypsinogen-2; POPF, postoperative pancreatic fistula.

suggests that focal ischemic pancreatitis may be involved. An observational cohort study of 48 patients undergoing PD was performed with measurement of plasma amylase concentration and intraperitoneal levels of lactate, pyruvate, and trypsinogen activation peptide (TAP) near the pancreatic anastomosis using microdialysis techniques.[125] This revealed that there was a higher perianastomotic lactate/pyruvate ratio indicating local ischemia, and also significantly higher levels of perianastomotic TAP and plasma amylase, indicating that pancreatitis was associated with the development of POPF. This implicates pancreatitis as an important factor in the development of POPF, rather than a mere disruption of mechanical anastomotic integrity.

Further evidence of ischemia as a mechanism for POP includes the observations of altered blood flow following sharp division of the pancreatic neck during pancreatic resection. This has been observed directly by a lack of brisk

bleeding, by Doppler assessment (lack of Doppler signal),[126] and also using indocyanine green dye which demonstrates ischemia at the level of the pancreatic neck.[127]

The finding of POP as an integral step in the development of POPF brings significant implications for the prediction, prevention, and management of POPF.

Prediction

Biochemical markers of POP after pancreatic resection are evident from the first postoperative day. These include serum amylase and lipase, and urinary trypsinogen-2. In an observational study of 61 patients undergoing pancreatic resection, the presence of POP on the first postoperative day as determined by these markers was found to be a strong predictor of the development of POPF (OR 17.81, 95% CI 2.17–145.9).[128]

Histological assessment of the pancreatic neck margin to determine the acinar cell density has also been shown to strongly predict the development of POPF (AUROC 0.744, p=0.003).[128] This may be determined in the intraoperative phase at the time of frozen section. Future studies in larger cohorts are required to validate this finding, and to assess whether the acinar cell density may be a more accurate and quantitative way to characterize the remnant gland than simply assessing glandular "texture."

Prevention and management

Studies investigating methods to mitigate the risk and severity of POPF should now not only include physical methods to reinforce or buttress the pancreatic anastomosis or staple line, but also include strategies to ameliorate POP. This may involve the prevention of pancreatic ischemia, reducing pancreatic inflammation, and agents to inhibit the activation of proteolytic enzymes. To date, the use of such strategies has not been evaluated in large-scale RCTs, and therefore cannot be recommended for routine clinical use. This includes the use of trypsin inhibitors, such as ulinastatin, which have been shown to decrease rates of both POP and POPF in two moderately sized RCTs.[129,130] Moreover, a recent RCT evaluating intravenous hydrocortisone in 155 patients undergoing PD demonstrated a significant reduction in overall postoperative complications and a nonsignificant trend toward reduction in POPF.[131]

Conclusion

Despite decades of research, rates of POPF have remained largely unchanged after pancreatic resection. This largely relates to a poor understanding of the pathophysiology of

this complication. POP is now emerging as a possible critical factor in the underlying pathophysiology of POPF. Further research is required to investigate strategies to mitigate the effects of POP. Meanwhile, POPF remains a complex problem requiring a multidisciplinary approach to achieve effective prediction, prevention, and management.

Disclosure

The authors report no conflicts of interest in this work.

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