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REVIEW ARTICLE

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Risk factors and preventive strategies for post-operative pancreatic fistula after pancreatic surgery: a comprehensive review

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ABSTRACT

Background: Pancreas surgery has developed into a fairly safe procedure in terms of mortality, but is still hampered by considerable morbidity. Among the most frequent and dreaded complications are the development of a post-operative pancreatic fistula (POPF). The prediction and prevention of POPF remains an area of debate with several questions yet to be firmly addressed with solid answers.

Methods: A systematic review of systematic reviews/meta-analyses and randomized trials in the English literature (PubMed/MEDLINE, Cochrane library, EMBASE) covering January 2005 to December 2015 on risk factors and preventive strategies for POPF.

Results: A total of 49 systematic reviews and meta-analyses over the past decade discussed patient, surgeon, pancreatic disease and intraoperative related factors of POPF. Non-modifiable factors (age, BMI, comorbidity) and pathology (histotype, gland texture, duct size) that indicates surgery are associated with POPF risk. Consideration of anastomotic technique and use of somatostatin-analogs may slightly modify the risk of fistula. Sealant products appear to have no effect. Perioperative bleeding and transfusion enhance risk, but is modifiable by focus on technique and training. Drains may not prevent fistulae, but may help in early detection. Early drain-amylase may aid in detection. Predictive scores lack uniform validation, but may have a role in patient information if reliable pre-operative risk factors can be obtained.

Conclusions: Development of POPF occurs through several demonstrated risk factors. Anastomotic technique and use of somatostatin-analogs may slightly decrease risk. Drains may aid in early detection of leaks, but do not prevent POPF.

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Introduction

Pancreatic surgery is now performed with better safety and lower mortality compared to the past.[1,2] Still, post-operative morbidity remains a challenge and occurs in up to 40–50% of patient, even in modern series.[3–5] Although complication patterns after pancreas surgery differ with type and indication, the most frequent complications reported after a pancreatiocoduodenectomy are delayed gastric emptying, post-operative hemorrhage and post-operative pancreatic fistulas (POPF). Among these, the most frequent and feared complication is the development of a POPF.

An international, uniformally agreed-on definition for pancreatic fistulae was for a long time not present and thus hampered comparison of both study results as well as the reported rates from one institution to another.[6] A suggested common approach has been given by the International Study Group on Pancreatic Fistulae (ISGPF) in 2005,[7] although different definitions based on drain output of amylase-rich fluid during any given post-operative time period continue to be used.

POPF is believed to result from growth failure in the pancreatic anastomosis with a subsequent leakage of pancreatic juice and enzymes into the abdomen. A pancreatic leak leads to prolonged hospitalization, increased morbidity and is even reported with increased mortality in several series.[8,9] Thus, treatment and associated clinical course is much dependent on the severity of the fistula, suggested split into three severity grades (A–C, see Table 1).[7] Treatment of POPF can be difficult and management may range from a simple observation with or without percutaneous drainage, to the urgent need for reoperation for the management of abdominal sepsis with organ failure and prolonged intensive care.

Several studies have looked into predictive patterns of occurrence, risk features and associated measures to prevent fistulas. A few recent studies, including conducted meta-analyses, have accumulated updated data. The aim of this review was to present the current knowledge on risk factors and preventive strategies for POPF in a collective synopsis.

Methods

We conducted a PubMed/MEDLINE literature search using the search terms alone and in combination of 'Post-operative' AND 'pancreatic fistula' OR 'POPF' AND 'pancreas surgery' AND 'risk factors' AND 'risk scores'. Only studies published after 2005 were considered to allow for likely reporting

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Table 1. Consensus parameters for POPF grading (ISGPS criteria).

Grade	A	B	C
Clinical conditions	Well	Often well	Ill appearing/bad
Specific treatment[a]	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)[b]	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

ISGPS denotes International Study Group of Pancreatic Surgery; US: ultrasonography; CT: computed tomographic scan; POPF: post-operative pancreatic fistula. Reproduced from Bassi et al., Surgery 2005 [7].
[a]Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analog and/or minimal invasive drainage.
[b]With or without a drain *in situ*.

according to the International Study Group on Pancreatic Fistula Definition issued that year.[7] The search period ended as of 3 December 2015 to cover the emerging evidence over the last decade, since the presentation of the ISGPS definition in 2005. Specific searches were done for combined key words with 'randomized controlled trials', 'prospective trials' and 'systematic reviews', the latter as the topic of POPF has been investigated in several more specific research questions. The final inclusion of papers to cite and refer was made at the discretion of the authors. Where several reports exist, we prioritized the most recent or the one with highest evidence level. Case reports, single-center retrospective studies and editorials were excluded. Specific management of POPF is a long and controversial chapter to cover in itself, and as such studies solely dealing with this aspect of POPF were excluded.

Results

Of a total of 1998 hits in the PubMed literature, we included 49 systematic reviews and meta-analyses,[10–58] all of which were conducted within the last 5 years (2011–2015). Three of these were Cochrane reviews.[29,35,36] Further, randomized clinical trials and trial protocols (for unpublished/ongoing studies) were identified.[59–76] Additional citations, such as prospective clinical evaluation, collective reviews or seminal reports that are influential on the specific concepts were cited when applicable to the topic discussion.

Based on the identified and updated recent literature, we first present and discuss risk estimation of POPF based on surgery and surgical techniques including the type of anastomosis; second, we will discuss pancreas-specific factors including texture and the types of underlying pathology; third, we will discuss biomarkers of risk; further, we will present results from interventions, including use of drains, stents or products; finally, we will discuss the available clinical risk scores and their current role.

Pancreas surgery and POPF

A collective review of all reports using the standard POPF definitions found a POPF rate after pancreaticoduodenectomy in the range of 20–25%, while the fistula rate after distal pancreatectomy exceeded 30%.[26] However, there is considerable bias in this as procedure may be strongly related to the type of underlying pathology. For example, pancreatic neuroendocrine tumors (PNETs) had a higher risk of POPF,[77] but this was largely attributed to the fact that these types of tumors more frequently underwent atypical resections and enucleations,[77,78] thus posing a different risk for ductal injury. Similarly, distal pancreatectomies have higher fistula rates (25–40%)[79] than formal pancreas resections, such as pancreaticoduodenectomy. In distal resections, tail resections appear to have higher risk than more central resections,[80] and a systematic review demonstrated superiority of stapler closure over suture closure in distal pancreatectomies.[10] However, the largest RCT on stapler versus hand-sewn closure of the pancreatic remnant (the DISPACT trial) found no difference between the two methods.[61] 'Wrapping' techniques using the omentum or falciform ligament to wrap the pancreaticojejunal anastomosis or the pancreatic section of distal pancreatectomy have not been associated with reduction of fistulas.[23] Currently, no differences between laparoscopic and open surgery in the incidence of POPF have been demonstrated in distal resections or pancreaticoduodenectomy for either benign or malignant disease, but data on oncological outcomes are insufficient.[16,81,82] A recent small RCT failed to demonstrate a difference between pancreaticojejunostomy and stapled closure in distal pancreatectomy.[76]

Anastomotic technique after pancreaticoduodenectomy

The best anastomotic technique in pancreas surgery has been an area of controversy for a long time and raised considerable debate among experts and investigators.[83] Several recent studies and meta-analyses have reported POPF results from various variations of surgical anastomotic techniques.[43,47,48,50,65,84,85]. Six meta-analyses [43,45–48,50] have investigated the effect of the two most commonly performed anastomotic techniques for creating continuity between the pancreas remnant and the gastrointestinal tract – pancreaticogastrostomy and pancreaticojejunostomy – and their effect on fistula rates, and found significantly different rates of POPF in all six meta-analyses. The difference in the POPF rates is likely due to the variation in studies included, yet the risk reduction remains similar across studies (odds ratio at about 0.51 in favor of pancreaticogastrostomy). The meta-analyses, although conducted and published within the same time-frame (five published in 2015, one in 2014) include different number of trials and patients (ranging from 4 to 8 randomized trials; and from 676 to 1211 patients included), and also arrive at different conclusions concerning the additional effect on other outcomes, such as biliary fistula rates and intra-abdominal fluid collections. Despite the slight difference in included material, the superiority of pancreaticogastrostomy appears consistent in all the meta-analyses, as all six studies conclude with an overall reduced risk for POPF. Notably, a recent small Canadian RCT found no difference between the two techniques, and the trial was stopped early.[85]

Anastomosis between the pancreatic stump and the jejunum includes various forms ranging from end-to-side

duct-to-mucosa anastomosis, end-to-side or end-to-end invagination techniques (dunking). The most frequently used technique for pancreaticojejunostomy is the end-to-side, duct-to-mucosa anastomosis.

A Chinese RCT [75] showed that an invagination technique ('binding pancreaticojejunostomy') significantly decreased post-operative complication and pancreaticojejunostomy leakage rates (with fistula rates approaching zero) and shortened hospital stay when compared with conventional pancreaticojejunostomy. However, these results were not confirmed in two French prospective case–control studies.[86,87] Thus, the role of this technique is not yet confirmed or validated externally.

The neck of the pancreas is a vascular watershed between the celiac and superior mesenteric arterial systems. In a prospective, non-randomized study,[88] the blood supply at the cut surface of the pancreas was evaluated, and if found inadequate, the pancreas was cut back 1.5–2.0 cm to improve the blood supply. The technique resulted in a very low POPF rate.

The co-called 'Blumgart anastomosis' using transpancreatic U-sutures has also been proposed to decrease the leak rate, and modifications of this technique have achieved a favorable outcome in some non-randomized trials. Others have investigated the effect of separating the pancreaticojejunostomy from the biliary anastomosis, but found no significant difference in fistula rates with single-loop over double-loop (Roux-en-Y) anastomosis.[17]

Some expert centers perform total pancreatectomy in highly selected cases to prevent a POPF from a high-risk pancreatic anastomosis in patients unlikely to tolerate a severe leak. In a recent study from Heidelberg in Germany,[89] around 20% of 434 total pancreatectomies were performed because of the morphology of the otherwise remaining pancreas; athrophic with pre-existing diabetes mellitus, extremely soft or lipomatous pancreas or a pancreas with inherent pancreatitis that would be associated with a presumably unacceptable high risk of anastomosis-related complications; or because of high risks of combined arterial resections and potential POPF. Notably, these are highly selected patients and represent a situation where the pros and cons of total pancreatectomy must be carefully discussed with the patient prior to surgery. While the pertinent information is not easily obtained pre-operatively, the patient's frailty (presence of comorbidity), the impression of the pancreatic gland on imaging studies (atrophic, small duct), the underlying pathology (benign vs. malign) and the type of procedure planned (respective procedure) may give some advice to the likelihood that a total pancreatectomy may be considered as an alternative to a high-risk pancreatic anastomosis.

Pancreatic gland and duct characteristics

Small pancreatic duct (such as $\leq$3 mm) has been reported to be an independent risk factor for POPF.[90,91] Gland texture also represents a potential contributing factor in anastomotic failures.[92] A 'soft gland' is usually associated with higher risk of POPF, but there is a lack of consensus in how to objectively score this feature. The combination of a soft gland and a small duct increases the risk for fistulae with several magnitudes.[93] One study performed ultrasound elastography intraoperatively in order to quantify the texture of the gland.[94] Others have suggested pre-operative computed tomography (CT) calculated pancreatic remnant volume and duct width to offer useful information about the risk of POPF.[95] Evaluation of the 'elastic modulus' by a mechanical method *ex vivo* has been attempted to correlate with the tactile impression of the operating surgeon.[96] While the measurements correlated well (but not perfect) with the surgeons' tactile impression of a hard or soft gland, the method is limited by the *ex vivo* approach. Currently, the surgeon's tactile impression is what determines gland texture. Whether alternative techniques are warranted to specifically reduce POPF rates in soft glands with small ducts have yet to be demonstrated.

Biomarker and alternative detection techniques

Metabolic profiling of predictive biomarkers has also been attempted.[97] A fluorescent-based chymotrypsin detection probe was able to detect increased enzyme in pancreatic fluid, which correlated with development of fistulae.[98] Validation and generalized availability hampers the daily use of these promising techniques.

Currently, the use of a low albumin level may be the most consistent, widespread available and low cost alternative for prediction of fistula risk.[90,99–101] A study using intraperitoneal microdialysis [97] to monitor intraperitoneal metabolites (glycerol, lactate, pyruvate and glucose) close to the pancreaticojejunostomy showed that patients who later developed clinically significant POPF had higher intraperitoneal glycerol concentrations and lactate/pyruvate ratios, and lower glucose concentrations in combination with an increase in trypsinogen activation peptide. Also, several different measures of amylase in either serum or drain fluids have been proposed to correlate with fistula risk.[102–104]

Stents in pancreatic surgery

Stents to drain the pancreatic duct can be placed externally or internally after pancreatic surgery. Stents represent another controversial area for which evidence is conflicting. One single-institution series found no protective effect of either internal or external stent use, and suggested even some adverse effects to be associated with the placement of stents.[105] A Cochrane systematic review [36] suggested the use of stents to be potentially beneficial, but based on few patients ($n = 656$) and low-level evidence. In another meta-analysis of four trials comprising 416 patients,[24] the use of external pancreatic duct stenting was found to reduce the incidence of both any grade POPF formation [OR 0.37, 95% confidence interval (CI) 0.23–0.58, $p < 0.001$] and clinically significant (grade B or C) POPF formation (OR 0.50, 95% CI 0.30–0.84, $p < 0.001$) following pancreaticoduodenectomy. The use of internal stents in pancreatic ducts anastomosis did not appear to reduce the rate of POPF in a second meta-analysis,[52] but the evidence is weak and based on limited

level 1 evidence. Currently, the jury is still out on this question, and the decision to place a stent or not is left to the surgeon's discretion.

Post-operative drains

Use of drains to prevent or to assess risk of fistula continues to be debated.[106–109] A recent RCT was stopped prematurely as the no-drain group had an excess mortality compared to the drain group (12% in no-drain compared to 3% for drains), and has argued that routine non-use of drains should be avoided.[64] A subsequent meta-analyses [11] found one RCT and four non-randomized comparative studies recruiting 1728 patients. Patients without prophylactic drainage after pancreaticoduodenectomy had significantly higher mortality (OR =2.32, 95%CI: 1.11–4.85; $p = 0.02$), despite the fact that they were associated with fewer overall complications (OR =0.62, 95%CI: 0.48–0.82; $p = 0.00$), major complications (OR =0.75, 95%CI: 0.60–0.93; $p = 0.01$) and readmissions (OR =0.77, 95%CI: 0.60–0.98; $p = 0.04$). There were no significant differences in the rates of pancreatic fistula, intra-abdominal abscesses, post-pancreatectomy hemorrhage, biliary fistula, delayed gastric emptying, reoperation or radiologic-guided drains between the two groups. Notably, this meta-analyses is highly skewed toward the trial results from the van Buren study,[64] questioning the validity of performing meta-analytic techniques to this question in the first place. Results from the DRAPA trial may give new clues to the role and use of drains in pancreatic surgery.[63]

Somatostatin analogs

Use of octreotide after pancreatic surgery remains a controversial topic.[35,110–112] In a Cochrane review [35] covering 21 trials with a total of 2348 patients, there was a reduction in overall fistula rates with the use of somatostatin-analogs after pancreas surgery (RR 0.66; 95% CI 0.55–0.79; $n = 2206$). However, when investigating those trials that specifically reported clinically relevant fistulae, no difference was found (RR 0.69; 95% CI 0.38–1.28; $n = 292$). Intra-arterial injection of octreotide did not affect gland texture in a small RCT.[70]

Pasireotide is a new somatostatin analog used in the treatment of Cushing syndrome, and with a 40-times higher affinity to the somatostatin-5 receptor compared to other somatostatin-analogs. A recent RCT on pasireotide [113] demonstrated a significant reduction in clinically relevant fistulas, leaks and abscesses (relative risk, 0.44; 95% CI, 0.24 to 0.78; $p = 0.006$). The effect remained significant in favor of pasireotide when looking specifically at type of surgery (pancreaticoduodenectomy vs. distal resections) and duct size (dilated vs. normal). This drug is currently more costly than other somatostatin-analogs, for which cost-effectiveness have not been demonstrated.[114]

Fibrin sealants and duct occlusion techniques

Covering of the anastomosis with a sealant to protect from leakage is an intuitively attractive approach. However, evidence is weak and most studies report no beneficial effect of this approach.[25,115] No effect of Tachosil™ was reported in a randomized trial.[71] Occlusion of the pancreatic duct with a chemical substance to avoid a pancreatic anastomosis during pancreaticoduodenectomy has been tried in some centers. A Dutch/Italian RCT [116] showed that duct occlusion (Ethibloc, Neoprene or Trasylol) without pancreaticojejunostomy significantly increased the risk of endocrine pancreatic insufficiency. However, the technique did not reduce post-operative complications or mortality, and there has been no widespread use of this method.

Clinical risk scores

Independent risk factors associated with POPF have been proposed in multivariable risk scores for pre-operative risk prediction.[117–121] Common to several scores is that BMI and pancreatic duct size together are strong predictors of the risk of POPF. The Fistula Risk Score proposes four variables on a 10-point scale; however, the score can only be evaluated intraoperatively as it considers the amount of blood loss as one of the risk factors. In addition gland texture, duct size and type of pathology (pancreas mass vs. others) are included.[120] Indeed, intraoperative blood loss appears to be the strongest factor in this construct.[121] Also, the validation effort of a multicenter study was weak at best as it essentially compared results among four surgeons, and thus generalizability has yet to be proven. An alternative score relied on pathologist assessment of pancreatic fibrosis and fatty infiltration, thus hampering the pre-operative assessment of risk.[119] Consequently, only one proposed pre-operative risk score has yet to be externally validated. This appears simple and easy to use and essentially relies on BMI and duct size alone.[118]

Conclusions

The prediction and prevention of POPF remains an area of debate. Patient, surgeon and intraoperative factors are all important in addressing the POPF risk. Non-modifiable factors such as patients' age, BMI, comorbidity and the underlying pathology that indicate surgery may be inherently associated with risk. Gland texture and duct size are similarly non-modifiable, while choice of anastomotic technique and use of somatostatin-analogs may reduce the POPF risk. Sealant products are not effective. Perioperative bleeding and transfusion increase risk and is object to the surgeons' meticulous focus on technique. Drains do not prevent fistulae, but may help in early detection and appropriate timely intervention.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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