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REVIEW ARTICLE

Anastomotic leakage in pancreatic surgery

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Introduction

Currently pancreaticoduodenectomy (PD) is the treatment of choice for tumours of the periampullary region. PD is a complex, high-risk surgical procedure, considered to be one of the most binding operations – or, maybe, *the* most binding – in abdominal surgery [1–4].

In 1979 Moossa defined PD as 'the Cadillac of abdominal surgery' [5]. In the same period the in-hospital mortality rate after PD was 20–30% with an extremely high morbidity; severe, life-threatening complications were judged to be a part of the procedure [6,7].

Nowadays PD is a routine procedure in specialized high-volume centres and mortality has decreased significantly in the last two decades. Many efforts have been made to gain better results; they must be identified in preoperative and postoperative management and appropriate selection of patients, improved surgical skills, and development of multidisciplinary teams dedicated to the care of pancreatic patients [8,9]. However, even if mortality is less than 3–5% in experienced hands, the overall morbidity rate is still high – from 30% to 50% – leading to prolonged in-hospital stay and increased costs [1–61].

Anastomotic leakage and the subsequent pancreatic fistula (PF) are the most important complications after PD. The pancreatic leakage is considered to be the underlying phenomenon of other major complications; the anastomotic dehiscence with autodigestion and destruction of surrounding tissue and vessels from leaking activated pancreatic juice can cause peripancreatic collections, intra-abdominal abscess, delayed gastric emptying and postoperative haemorrhage.

The reported rate of PF is highly variable, ranging from 2% to 50% [1–61]. This wide range is due to several factors and, among these, the lack of a universally accepted definition of PF [10–12].

The aim of this paper is to review the causes, risk factors, definitions, prevention and treatment of anastomotic leakage in pancreatic surgery, with particular regard to leakage of the pancreatico-enteric anastomosis after PD.

Pathophysiology and risk factors

The most important pathophysiological factor involved in the development of a pancreatic fistula is the pancreatic juice itself. In fact it is rich in proteases that, whenever activated, determine the digestion and the destruction of the tissue leading to partial or complete anastomotic dehiscence. In addition, pancreatic juice, through the fistulization of pancreatico-enteric anastomosis can cause inflammation and autodestruction of the peripancreatic and retroperitoneal tissues as well as the surrounding vessels and viscera, with possible dramatic vascular erosions. These phenomena can lead to haemorrhage, intra-abdominal abscess, peripancreatic and retroperitoneal collections and delayed gastric emptying which is, in most cases, an indirect sign of intra-abdominal complications. The presence of an intra-abdominal abscess is strongly associated with the presence of a leak from the pancreatic anastomosis: at least 50–60% of abscesses observed following PD are related to pancreatic leakage [13–18]. All these complications

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may be associated with sepsis, shock, single or multi-organ failure and death [1,3–8,16–18,62–64]

The two most important risk factors for PF formation are the presence of a soft texture within the pancreatic remnant and a small and 'deep' Wirsung duct, which complicates the achievement of a safe pancreatico-enteric anastomosis [10,13,15,19, 64–66]. This is a frequent event in cases of non-obstructive neoplasms such as tumours of the duodenum, common bile duct, endocrine neoplasms, papilla of Vater and small ductal cancers. On the other hand, the occurrence of a pancreatic leak among patients who underwent PD for chronic and/or obstructive pancreatitis is uncommon, due to fibrotic pancreatic parenchyma, Wirsung duct dilatation and reduced digestive secretions [19,20,65–69]. Some authors have reported an incidence of pancreatic fistula between 12% and 36% in patients with normal pancreatic texture compared with an incidence ranging from 0% to 9% in patients with fibrotic pancreas [16,70].

The presence of a high-tension anastomosis and poor blood supply are other 'surgical factors' associated with an increased risk of leakage [1–4,19,20,70–73]. Moreover reoperation, emergency surgery, jaundice, renal failure, cirrosis and preoperative undernutrition are known to be associated with higher risk of PF development [19,63,73–75].

Surgeons and hospitals: new risk factors?

Today many authors support the concept that among the most important factors affecting the rate of pancreatic anastomotic leak are the surgeon's and centre's experience [1,3,8–13,15,76]. The preoperative selection, the intraoperative skill and, above all, the postoperative care of patients undergoing pancreatic resection, are best achieved by a multidisciplinary team including surgeons, radiologists, anaesthesiologists, gastroenterologists and a specialized nursing team. A reduction and a better management of complications should be expected if operations are concentrated in few high-volume centres where a restricted number of well-trained surgeons can achieve large experience standardizing the surgical technique [21,22,76–82]. Many authors demonstrated a progressive reduction in mortality and morbidity rates after PD in experienced centres. The first one was J.M. Howard who reported (in 1968!) a series of 41 PD without mortality [83]. More recently Trede et al. and Cameron et al. reported large series of PD without mortality [1,23]; nowadays in specialized hospitals the mortality rate after major pancreatic resection is $<5\%$. Cameron et al. defined high-volume hospitals as those performing at least 20 PD per year for 6 consecutive years [24]. Many elegant studies have shown that centralization to high-volume specialized hospitals has led to a significant lower mortality for PD compared with the low-volume centres [1,3,8,12–15,21–24,76–83]. Many surgeons can perform PD from a technical point of view but only a few can achieve the optimal experience to manage safely – in a multidisciplinary setting – the major complications related to pancreatic resection.

Management of the pancreatic remnant

As mortality and morbidity following PD are strictly related to the breakdown of the pancreatic anastomosis, great concern has always been given to the management of the pancreatic remnant and different surgical techniques have been proposed for gastrointestinal continuity reconstruction, up to total pancreatectomy to avoid the anastomosis [25–50,84–88].

Two general rules seem to be popular (not evidenced-based!) among pancreatic surgeons: (1) it is important to mobilize the pancreatic remnant from the surrounding retroperitoneum to reduce the anastomotic tension; (2) blood supply at the cut surface of the pancreas should be evaluated, and if deemed inadequate, the pancreas can be cut back 1–2 cm more.

After the original description of PD the pancreatic stump was mainly managed by pancreatico-jejunal anastomosis [25–28,30]. Many alternatives have been introduced to improve the results: invaginating end-to-end or end-to-side pancreaticojejunostomy with a one- or two-layer suture, duct-to-mucosa anastomosis (with or without internal or external stenting of the duct), simple suture legation of the pancreatic duct without enteric anastomosis and 'glue occlusion' of the duct [31–45]. The simple suture ligation of the duct without enteric anastomosis proved to be a high-risk procedure, with anastomotic fistulas occurring in 50–100% of the patients [30,43]. Also regarding the occlusion of the main pancreatic duct with fibrin glue, its use has now been abandoned on the basis of different randomized controlled trials [38–40,45].

In conclusion, even if few randomized controlled trials are available, none of the different surgical techniques used to perform a pancreaticojejunostomy showed better results when compared with each other.

Another option is represented by the pancreaticogastrostomy [84,85]. Table I shows the different

Table I. Technical advantages of the pancreogastric anastomosis after PD.

- The stomach and the pancreas are closed, facilitating a tension-free anastomosis.
- The stomach wall has a good blood supply, enhancing anastomotic healing.
- In the absence of enterokinase activity and thanks to the gastric acid pH, pancreatic enzymes are not activated, thus reducing the risk of leakage.
- The pancreatic anastomosis can be controlled in the postoperative course through endoscopy, possible anastomotic bleeding can be treated easily.

theoretical advantages of pancreaticogastric anastomosis [46–50,85,86].

Yeo et al., in the first prospective randomized trial comparing pancreaticogastrostomy and pancreaticojejunostomy after PD, demonstrated a similar pancreatic leak rates in the two groups [46]. Recently, at our institution we carried out a prospective randomized study comparing these two reconstructive techniques in a homogenous population of patients and we found a lower rate of biliary fistula, abdominal collections and delayed gastric emptying in the pancreaticogastrostomy group, but not a significant difference in the incidence of pancreatic leak [48].

In general, a drain is placed near the pancreatic anastomosis. The drain must not directly touch the anastomosis, as theoretically this can make it easier for an anastomotic leakage to develop. For the same reason the drain should not left inside for a longer time than needed but should be removed, whenever possible, in a few days. At the same time, when the complication develops, thanks to the 'well left' drain the fistula can be completely drained and an operative reintervention avoided ... The problem of the 'drain management' is still open. It is interesting to underline that Conlon et al. in a prospective randomized trial did not find differences in terms of morbidity when comparing patients with versus patients without drains [87,88].

At the moment there is no definite evidence that any particular reconstructive surgical technique is safer and associated with better results than any of the others. Moreover, there have been few prospective trials and the lack of a universally accepted definition of PF makes it difficult to evaluate the different results achieved objectively.

Octreotide in the prevention of pancreatic leakage

As postoperative complications after PD are mainly caused by the action of enzymes, the pharmacological inhibition of pancreatic exocrine secretion in the perioperative period can be of help in the prevention of pancreatic leakage. Octreotide is a long-acting somatostatin analogue which can significantly reduce pancreatic and gastric as well as enteric secretions [89,90]. For this reason octreotide has been used as prophylactic agent for anastomotic leak after elective pancreatic head resection [91]. One experimental study demonstrated that somatostatin treatment in patients who undergo PD results in a significant reduction of postoperative drainage volume as well as serum levels of amylase and lipase [92].

In different studies octreotide has been administered preoperatively, intraoperatively and postoperatively and its potential benefit has been evaluated in several randomized controlled trials with controversial results. Recently Connor et al. [51], in a meta-analysis of 10 well-selected randomized clinical trials [52–61] with a total of 1918 patients (Table II), demonstrated that somatostatin and its analogues (octreotide) did not reduce the mortality rate after pancreatic surgery but did reduce both the total morbidity ($p = 0.002$) and pancreas-specific complications ($p = 0.003$). Moreover somatostatin and octreotide can reduce the rate of biochemical fistula formation but not the incidence of clinical anastomotic disruption. The absolute difference in the number of complications suggestive of an anastomotic leak for all the included trials between patients treated with octreotide/somatostatin and those in the control group was 11% (37% versus 26%, respectively). Thus nine patients required to be treated with these drugs to prevent one pancreas-specific complication.

However, while octreotide is widely used in Europe, many American surgeons remain unconvinced regarding a real advantage from using octreotide, believing that a reduction in postoperative pancreatic leakage depends mainly on other factors, such as the centralization of pancreatic patients in high-volume centres [56,57,59].

Rosenburg et al. showed that the use of octreotide is a cost-effective strategy in patients undergoing elective pancreatic surgery, able to reduce the hospitalization of these patients and its related costs. This economic evaluation estimated that the routine use of octreotide would prevent 16 patients from developing complications per 100 patients treated and would save $1642 per patient [93].

Multicentre prospective randomized controlled trials are needed in this area, with clearly defined criteria on indications, dose and timing of administration to assess the potential advantage of octreotide use. Moreover any future attempt to identify subgroups of patients who are most likely to benefit from these drugs will require standardization of definitions, surgical techniques and risk stratification.

The problem of the definition

The lack of a single, objective, universally accepted definition of PF makes it difficult to compare different surgical techniques and the usefulness of prophylactic drugs in pancreatic surgery [11–13].

In particular, many studies involving pancreatic surgery defined a leak by the volume of drain output and/or drain fluid amylase concentration. However, there is a considerable variation in fluid volume, amylase content, values and timing of test administration between different studies. In general, the studies in the American literature use a definition of PF as drainage of >50 ml/24 h of fluid with drain amylase level of more than three times the serum amylase level for at least 10 days after surgery [1,3,20,21,46]. German and Italian papers report a definition as drain fluid with >10 ml/24 h with drain amylase level of more than three times the serum amylase level for 3–4 days in the postoperative period,

Table II. Randomized clinical trials comparing the effect of somatostatin and its analogues with placebo and controls on complication rate after pancreatic surgery.

Reference	Type of trial	Number of patients	Patients (%) with chronic pancreatitis	Drug, dose and type of administration	Pancreatic complications (%)	Treatment provides benefit
Buchler et al. [52]	M, DB, PC	246	112 (46%)	O, Pr, 100 μg per 3/day, 7 days	O: 44 (35%) P: 74 (61%)	Yes
Pederzoli et al. [53]	M, DB, PC	252	95 (38%)	O, Pr, 100 μg per 3/day, 7 days	O: 26 (21%) P: 48 (37%)	Yes
Montorsi et al. [54]	M, DB, PC	218	18 (8%)	O, Pr, 100 μg per 3/day, 7 days	O: 18 (16%) P: 43 (40%)	Yes
Friess et al. [55]	M, DB, PC	247	247 (100%)	O, Pr, 100 μg per 3/day, 7 days	O: 22 (18%) P: 43 (34%)	Yes
Lowy et al. [56]	S	110	5 (5%)	O, I, 100 μg per 3/day, 10 days	O: 19 (33%) C: 13 (25%)	No
Yeo et al. [57]	S, DB, PC	211	22 (10%)	O, Pr, 250 μg per 3/day, 7 days	O: 23 (22%) P: 18 (17%)	No
Gouillat et al. [58]	M, DB, PC	75	4 (5%)	S, Po, 6 mg/day infusion, 7 days	S: 6 (16%) P: 14 (38%)	Yes
Shan et al. [59]	S	54	0 (0%)	S, Po, 250 μg/day infusion, 7 days	S: 6 (22%) P: 13 (48%)	Yes
Sarr et al. [60]	M, DB, PC	275	17 (6%)	V, P, 0.6 mg per 2/day, 7 days	V: 37 (26%) P: 41 (30%)	No
Suc et al. [61]	S	230	30 (13%)	O, I, 100 μg per 3/day, 10 days	O: 44 (36%) C: 48 (44%)	Yes
Total		1918	550 (29%)		O/S/V: 249 (26%) C/P: 351 (37%)	

M, multicentre; DB, double-blind; PC, placebo-controlled; O, octreotide; S, somatostatin; V, vapreotide; Pr, preoperative administration; I, intraoperative administration; Po, postoperative administration; P, placebo; C, control.

but many other definitions are present in the surgical literature [8–10,18,47]. Moreover, a distinction between 'clinical' and 'biochemical' pancreatic leak should be made, and a 'clinically relevant fistula' has been defined as an anastomotic leak associated with symptoms [51,56]. Last, but not least, the role of radiological imaging is debated in defining the presence of a definite anastomotic leak.

After a Medline search of the last 10 years our group found 26 different definitions for PF. We observed that the incidence of anastomotic leakage ranged from 10% to 28.5% in a group of 242 patients who underwent pancreatic resection and pancreaticoenteric anastomosis by our team depending on the PF definition applied [11].

To try to solve the problem, an international working group of 37 pancreatic surgeons from high-volume centres (International Study Group on Pancreatic Fistula Definition, ISGPF) reviewed the literature and their own experience with pancreatic leakage and determined a common definition of pancreatic fistula [12].

Definition of pancreatic fistula

The ISGPF defined pancreatic fistula as: 'an abnormal communication between the pancreatic duct epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid' [12].

Diagnosis and grading

The diagnosis of a PF should be based on different parameters – clinical and biochemical. According to the ISGPF a pancreatic fistula must be suspected when 'the output through an operatively-placed – or subsequently placed percutaneous drain – of any measurable volume of drain fluid on or after post-operative day three with amylase content greater than three times the upper normal serum value' [12].

Thus, an accurate evaluation of the daily output and of the appearance (colour) of each drain, the measurement of amylase concentration in the drain fluid, laboratory serum test and monitoring of the clinical condition of the patient are necessary to diagnose the development of a PF as early as possible. In fact, drain fluids could have a colour that ranges from dark brown (infected fistula) to greenish bilious fluid to clear 'spring water' which seems to be pancreatic juice; laboratory tests can show an increased C-reactive protein associated with leucocytosis; patients may complain of abdominal pain, delayed gastric emptying, abdominal distension with altered bowel function, fever $>38^{\circ}$C and the evidence of a sepsis.

Radiological imaging is not necessary in the diagnosis of a PF. However, imaging techniques can be of help as they can show extended intra-abdominal and/

or infected collections or the site of the migration of the drain into an enteric viscus.

Different are criteria used to classify pancreatic fistulas. Based on the type of secretions they can be divided into 'pure', constituted exclusively of pancreatic juice, or 'mixed' fistulas in which pancreatic juice is combined with bile or enteric juice. Moreover, considering the daily output, pancreatic fistulas can be classified as low- or high-output fistulas and the cut-off value of the daily output considered is 200 ml/day.

The ISGPF introduced a grading system for PF (grades A, B and C) to evaluate the grade of clinical severity of the PF [12]. Grade A fistula is a 'transient fistula' without any clinical impact. In this case the patient is well and the use of antibiotics, octreotide or parenteral nutrition is not necessary. Moreover, a grade A fistula does not influence the postoperative course of the patient, who is discharged without delay.

Grade B fistula is a clinically significant PF. It can be associated with abdominal pain, fever or leucocytosis. Specific treatment is usually used and the patient is supported by parenteral or enteral nutrition. The drain should left in place. If abdominal computed tomography (CT) scan or ultrasound (US) shows intra-abdominal collections, the re-positioning of drains must be considered. Grade B fistula usually leads to prolonged in-hospital stay with increased costs. Many patients are discharged with drains *in situ*, which will be removed in the clinic.

Grade C fistula requires major changes in the postoperative management of the patient and it is a life-threatening event. Parenteral or enteral nutrition, intravenous antibiotics, octreotide administration and/or intensive care are needed. CT scan can show the presence of worrisome peripancreatic collections. Invasive management (open or RX-guided) can be required. Sepsis can be present and it can lead to multi-organ failure. A major delay in discharging the patient is usually required.

Treatment

The treatment of a patient with PF is strictly related to the clinical conditions. It is primarily conservative and effective in 85–90% of the cases [94–103]. In the remaining cases invasive re-intervention is necessary. Surgical exploration should be considered for a grade C fistula, especially when an abdominal abscess or sepsis – with or without organ dysfunction – is diagnosed [4,9,63,96,99].

The optimal surgical management in case of re-operation is based on different options: 'simple' wide peripancreatic drainage; a definitive demolition of the pancreatic anastomosis without a new enteric anastomosis; a conversion of a type of pancreatico-enteric anastomosis in another one; a completion pancreatectomy. However, resecting a few centimetres of the pancreatic remnant and performing a new pancreatico-enteric anastomosis is a high-risk procedure with the possibility of new anastomotic failure with continuing leakage, sepsis and abscess. Some papers reported a high survival in patients with peripancreatic abscess after completion pancreatectomy. If the general conditions of the patient are poor, an open drainage procedure should be performed, delaying the definitive operation [1,3,5,8,9,20–22,63,72,96–100].

In patients with a clinically relevant fistula, in the absence of a sepsis or abdominal abscess, a conservative management approach is appropriate. It is important to evaluate intra-abdominal collections: they must be well drained and a postoperative replacement of drains can be considered in some cases [98,99].

Conservative management includes fluid/electrolyte replacement, suspension of oral intake, nutritional support by parenteral or enteral nutrition and antibiotic administration [4,9,98,99]. In 1979 Klempa et al. introduced somatostatin and octreotide in the non-operative management of pancreatic fistula [92]. Octreotide was reported to significantly reduce the fistula output and to accelerate the healing time even if other trials did not demonstrate its usefulness. Thus, the benefit of octreotide administration on the fistula resolution is unclear and additional studies are needed.

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