Pancreatic Fistula After Distal Pancreatectomy

Predictive Risk Factors and Value of Conservative Treatment

Virginie Pannegeon, MD; Patrick Pessaux, MD; Alain Sauvanet, MD; Marie-Pierre Vullierme, MD; Reza Kianmanesh, MD; Jacques Belghiti, MD

Hypothesis: Predictive factors of pancreatic fistula (PF) and the value of conservative management of PF following distal pancreatectomy (DP) are poorly known.

Design: Case series.

Setting: A university hospital referral center.

Patients: From 1991 to 2003, 175 patients underwent DP with routine drainage of the pancreatic stump and postoperative repeated measures in drainage fluid. Pancreatic fistula was defined as an amylase level in surgical drainage fluid more than 5-fold the serum level after postoperative day 5, or amylase-rich fluid collection. Computed tomographic scan was only done for suspicion of abdominal collection. Conservative management of PF included percutaneous drainage of abdominal collection and total parenteral nutrition or maintaining oral feeding in some patients with low-volume PF.

Intervention: Conservative management of PF after DP.

Main Outcome Measures: Incidence of PF according to indication, concomitant splenectomy, additional procedure, texture of parenchyma, location of transection (neck vs body), and technique of stump suture (stapler vs hand sewn), including elective ligation of the main duct, transfusions, and prophylactic use of octreotide.

Results: There was no mortality. Forty patients (23%) developed PF, which was symptomatic in 25 patients (63%); computed tomographic scan identified an abdominal collection in 26 (65%). Multivariate analysis identified 2 predictive factors for PF: no elective ligation of the main pancreatic duct (odds ratio, 2.2 [95% confidence interval, 1.0-4.7]) and transection at the body (odds ratio, 2.1 [95% confidence interval, 1.1-5.5]). If none or both predictive factors were present, the observed rate of PF was 16% and 63%, respectively. Pancreatic fistula was managed conservatively in 38 patients (95%), including percutaneous drainage in 16, and by reoperation in 2.

Conclusions: Pancreatic fistula following DP is more frequent in cases of pancreatic division at the body level and no elective ligation of the main duct. Routine drainage of the pancreatic stump does not prevent postoperative abdominal collections. Conservative management of PF is successful in 95% of cases.

Arch Surg. 2006;141:1071-1076

DISTAL PANCREATECTOMY (DP) usually consists of the resection of pancreatic parenchyma left to the portal vein and can be performed with or without splenectomy in cases of benign lesion.1,2 Current indications of DP include mainly benign or malignant pancreatic tumors, chronic pancreatitis, and trauma.1,4 Postoperative mortality of DP is presently lower than 3% and the rate of postoperative morbidity ranges from 9% to 31%.3,7 Pancreatic fistula (PF) is the most frequent complication, occurring in 3% to 26% of cases after DP,3,6,8 and can lead to intra-abdominal abscess and bleeding. The variability of the PF rate is probably due to a nonstandardized definition in the literature. Thus, factors predisposing to PF still remain poorly recognized. Only a few studies have suggested that underlying disease (ie, malignancy or trauma), methods of pancreatic transection, technique of stump closure, and a concomitant splenectomy influence the rate of PF.1,0-12 Conservative treatment of PF, including total parenteral nutrition (TPN) and percutaneous drainage in cases of intra-abdominal abscess, is usually adopted but has not been evaluated in a large series.

The aim of this study was to determine clinicopathological and operative fac-

Author Affiliations:
Departments of Digestive Surgery (Drs Pannegeon, Pessaux, Sauvanet, Kianmanesh, and Belghiti) and Radiology (Dr Vullierme), Assistance Publique Hôpitaux de Paris, Hospital Beaujon, University of Paris VII, Clichy, France.

See Invited Critique at end of article
was done before oversewing the distal stump or, more rarely, the surgeon. Elective ligation of the main pancreatic duct plier; or both. The method of closure was at the discretion of the celiac trunk or more distally.

The standard procedure was DP with splenectomy. We recently began performing spleen-preserving pancreatectomy with preservation of the splenic vessels in cases of certainly benign pancreatic transection was performed with a conventional scalpel in all cases. The transection was considered as located at the neck when performed at the level of the portal vein and as located at the body when performed on the left side of the celiac trunk or more distally.

Closures of the pancreatic stump were made either manually, using nonabsorbable monofilament suture; with a stapler; or both. The method of closure was at the discretion of the surgeon. Elective ligation of the main pancreatic duct was done before oversewing the distal stump or, more rarely, after stapling by suturing just to the right side of the staple line.

In the latter case, after pancreatic transection, the Wirsung duct was visualized on the left side of the staple line and a U-shaped stitch was performed at the same level immediately on the right side of the staple line.

A multichannel open drain was placed near the pancreatic suture in all cases. Fibrin glue was never used. Prophylactic use of octreotide (Sandostatine; Novartis, Rueil Malmaison, France; 100 μg 3 times a day; begun intraoperatively and maintained for 7 days) was left at the discretion of the surgeon.

POSTOPERATIVE FOLLOW-UP

The drain was progressively withdrawn (2 cm per day) after postoperative day 5. Postoperative assessment included repeat measurement (day 1, 3, 5, 7, and 10) of the amylase concentration in serum and drainage fluid, as long as the drain was in place. Computed tomography (CT) was performed if the patient had any symptoms suggestive of abdominal collection (pain, fever, vomiting) or if a major hyperleukocytosis was present.

Oral feeding was allowed after the return of bowel function, usually before complete drain removal, except in cases of suspected or confirmed PF.

Conservative management of PF was attempted whenever possible as a first-intention treatment and included TPN, percutaneous drainage of an intra-abdominal collection, antibiotics, and octreotide administration. Recently, asymptomatic patients with low-output fistula (<30 mL per day) were treated only with octreotide without discontinuation of oral feeding.

STATISTICAL ANALYSIS

The statistical analysis was performed with SPSS software (version 10.0; SPSS Inc, Chicago, Ill). All means are expressed ± standard deviation. The univariate analysis was done using a χ² test for qualitative variables and a 2-tailed Fisher exact test in the case of small numbers. The multivariate analysis was done using a nonconditional logistic regression model expressed in odds ratios (ORs). To test the independence of the risk factors, the significant variables (P<.15) in the univariate analysis were entered into a multivariate logistic regression model with likelihood ratio forward selection with a criterion of P<.05.

RESULTS

INDICATIONS AND PROCEDURES

From January 1991 to December 2003, 175 patients (98 women and 77 men) underwent DP. Mean±SD age of the patients was 51±15 years (range, 17-81 years). Indications for DP are listed in Table 1. Most patients (114 [65%]) were operated on for benign lesions, including 36 with pseudocysts and 7 with chronic pancreatitis. In cases of pseudocysts, DP was indicated for complication (rupture, hemorrhage) or suspicion of mucinous cystadenoma. Patients with chronic pancreatitis were operated on for intractable pain. Of the latter, 3 had a dilated main pancreatic duct at the level of transection and underwent associated ductal drainage, with Roux-en-Y pancreaticojejunostomy in 2 and pancreaticogastrostomy in 1. Four patients underwent DP for pancreatic trauma. Of malignant diseases (61 patients [35%]), endocrine tumors were the most frequent indication.
Overall, the pancreas was divided at the neck in 138 patients (79%) and at the body in 37 (21%). There was no correlation between the level of pancreatic transection and the diagnosis (benign vs malignant, \( P = .10 \)), the indication (tumor vs other, \( P = .26 \)), and the parenchyma texture (soft vs hard, \( P = .60 \)).

Splenic preservation was performed in 15 patients (9%). An additional procedure was performed in 44 patients (25%) (Table 2), including contiguous organ resection (excluding the spleen) in an effort to achieve a negative resection margin (R0) in 27 patients. More than 1 additional procedure was performed in 14 patients. Right portal vein ligation was performed in 6 patients, with endocrine liver metastasis as preparation for major hepatectomy for a 2-step approach.\(^1\) Octreotide was used prophylactically in 77 patients (44%).

**POSTOPERATIVE COURSE**

There was no postoperative mortality. The overall morbidity rate was 42% (73 patients). Pancreatic fistula was the most common complication, occurring in 40 patients (23%) (Table 3). Twenty-five patients (25 [63%] of 40) had symptomatic PF (fever, abdominal pain, vomiting). In the 15 other patients, FP was asymptomatic and diagnosed by routine assay of amylase concentration in the drainage fluid. Pancreatic fistula was identified on average 10 days after surgery (range, 5 to 21 days), including after return of oral feeding in 25 cases (63%). At the time of PF diagnosis, a surgical drain not producing amylase (“negative” surgical drain) had been removed in 20 patients (50%).

Thirty-six patients had a postoperative CT scan and 26 (26 [65%] of 40) patients had an intra-abdominal collection (mean ± SD diameter, 7 ± 3 cm; range, 3-13 cm). These collections were treated by percutaneous drainage in 16 cases (62%), percutaneous puncture in 5 (19%), no intervention in 4 (15%), and reoperation in 1 at postoperative day 15 for the drainage of an infected collection not accessible percutaneously. Of the 16 patients who had percutaneous drainage, 4 (25%) had the surgical drain still in place. Bacteriological analysis revealed infection in surgically or percutaneously collected fluid in 22 patients. There was no morbidity related to percutaneous drainage. Mean ± SD maximal daily output of PF was 85 ± 23 mL (range, 10-230 mL).

Conservative management of PF was instituted in 39 patients (98%) and was successful in 38 patients (97%). Twenty-eight patients (70%) received TPN for a mean ± SD duration of 20±14 days (range, 5-65 days). No patients experienced complications of TPN. Octreotide was administered as curative treatment in 35 patients (88%) and antibiotics were given in 24 (60%). In the patients with a high amylase level in surgical drainage, drains were withdrawn after mean ± SD 19±16 days (range, 4-90 days). In the 16 patients who required percutaneous drainage, drains were inserted on average on postoperative day 9±4 (mean ± SD) (range, 5-21 days) for a mean ± SD duration of 17±14 days (range, 2-58 days). No patients treated percutaneously required further surgery. The overall mean ± SD time to PF closure was 21±11 days (range, 4-65 days) after diagnosis: 23±13 days in the 28 patients treated with TPN and 13±12 days in the 12 who received oral feeding (\( P = .03 \)).

Three patients with PF developed hemorrhage, including 2 who had bleeding through the drainage tract at postoperative days 14 and 23. In 1 patient, hemorrhage stopped spontaneously but transfusion was needed; the other patient needed surgical hemostasis. The third patient developed pseudoaneurysm of the gastroduodenal artery, revealed by hemosuccus pancreaticus 1 month after hospital discharge, and was treated by transcatheter embolization. Altogether, 2 patients with PF (2 [5%] of 40) underwent reoperation (1 with an abdominal collection not accessible by percutaneous drainage and 1 who developed hemorrhage).

Mean ± SD hospital stay was 36±17 days (range, 16-88 days) for patients who developed PF vs 15±13 days (range, 7-35 days) for those without PF.

**RISK FACTORS OF PF**

Subgroup analysis of the following factors did not reveal a statistically significant difference in the incidence of PF: indication for DP, splenic preservation, additional procedure, texture of parenchyma at the transection margin, technique of closure of the pancreatic stump, blood transfusion, and preventive use of octreotide (Table 4). Conversely, the rate of PF was 35% (13/37) when the pancreas was transected at the body vs 20% (27/
The present study analyzed both mortality and morbidity associated with DP, with specific attention to PF. Our data support the assumption that DP can now be performed without mortality. However, the morbidity is still high, close to 40%. Specifically, PF was the most frequent complication, occurring in 23% of our patients. By multivariate analysis, PF occurred significantly more often when the pancreas was transected at the body (vs the neck) and when elective ligation of the main pancreatic duct was not performed. No other clinicopathological or operative factor was found to be associated with an increased risk for PF.

Pancreatic fistula complicates 3% to 26% of DP. This wide variability of the PF rate following DP is probably explained by the variability of the definition of PF in the literature. Definitions of PF usually rely on 3 criteria: amylase concentration in drainage fluid, number of days of drainage, and output of drainage. Some definitions are either imprecise (including patients with “amylase-rich” fluid drainage) or too restrictive (>30 mL daily of drainage fluid containing at least 5000 U of amylase for more than 10 days). Also, these definitions do not include “occult” PF, diagnosed only by assay of the amylase level in drainage fluid (5-fold greater than the serum amylase level after postoperative day 5) in an otherwise asymptomatic patient. In our study, we also considered that symptomatic patients with amylase-rich fluid collections had PF. In contrast, some studies distinguish PF from intra-abdominal abscess without indicating the amylase level in the abscess fluid. The 23% rate of PF that we observed is close to the highest reported rates in the literature but could be explained by the nonrestrictive definition of this complication that we used in our study.

By multivariate analysis, we identified 2 factors that significantly increased the risk of PF: pancreatic transection at the body level (vs at the neck) and absence of elective ligation of the main pancreatic duct. To our knowledge, the former risk factor was identified in only 1 comparative study, which reported a 17% rate of PF after 40% to 80% DP vs 8% after 80% to 95% DP in patients with chronic pancreatitis. We suggest 2 possible explanations for these findings: (1) the triangular shape of the pancreatic body impedes completion of both atraumatic and tight suture of the stump, whereas the oblong neck is easier to close and (2) in cases of chronic pancreatitis, pancreatic division at the body increases the risk of persisting main duct stenosis downstream of the stump closure. Our study confirms the importance of specific ligation of the main pancreatic duct, previously identified as the only independent risk factor by Bilimoria et al. who performed a multivariate analysis on 126 patients. Other authors have pointed out that inability to find the main pancreatic duct for ligation was a major factor of postoperative fistula. In fact, the main pancreatic duct rarely eludes detection if sharp and careful transection of the pancreas is carried out. Interestingly, we did not observe a different risk of PF according to the pancreatic texture, as previously reported. We did not evaluate the influence of body mass index, which was also identified as a risk factor of PF.

Since PF still occurred in 16% of patients who underwent DP with neck transection and elective ligation of the main pancreatic duct, some other mechanisms must

### Table 4. Factors Associated With Postoperative Pancreatic Fistula: Univariate Analysis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Fistula (n = 40)</th>
<th>No Fistula (n = 135)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign (n = 114)</td>
<td>30 (75)</td>
<td>84 (62)</td>
<td>.13</td>
</tr>
<tr>
<td>Malignant (n = 61)</td>
<td>10 (25)</td>
<td>51 (38)</td>
<td></td>
</tr>
<tr>
<td>Tumor (n = 119)</td>
<td>24 (60)</td>
<td>95 (70)</td>
<td>.21</td>
</tr>
<tr>
<td>Pancreatitis and trauma (n = 56)</td>
<td>16 (40)</td>
<td>40 (30)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Observed Rates of Pancreatic Fistula According to Risk Factors Identified by Multivariate Analysis

<table>
<thead>
<tr>
<th>Body Traversal</th>
<th>Ligation of Main Pancreatic Duct</th>
<th>No. of Patients</th>
<th>No. (%) of Patients With Pancreatic Fistula</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Yes</td>
<td>85</td>
<td>14 (16)</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>53</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>29</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>8</td>
<td>5 (63)</td>
</tr>
</tbody>
</table>

138) after transection at the neck (P<.04). Multivariate analysis identified 2 independent risk factors for PF: absence of elective ligation of the main pancreatic duct (OR, 2.2 [95% confidence interval, 1.0-4.7]) and transection at the body (OR, 2.1 [95% confidence interval, 1.1-5.5]). According to these 2 predictive factors, the observed rates of PF ranged from 16% to 63% (Table 5).

**COMMENT**

The present study analyzed both mortality and morbidity associated with DP, with specific attention to PF. Our...
be considered, such as the opening of small branch ducts and ischemia or limited necrosis on the transaction margin. These technical factors explain the several attempts to decrease the incidence of PF following DP by division of the pancreas with an electrocautery or ultrasonic dissector, occlusion of the pancreatic duct with prolamine or fibrin glue sealing, and suture of the pancreatic remnant with a stapler or using a gastric or jejunal seromuscular flap. Our retrospective and nonrandomized study showed that 21 (27%) of the 77 patients who prophylactically received octreotide experienced PF, compared with 19 (19%) of the 98 who did not (not significant). Of the 12 randomized trials that evaluated use of somatostatin or its analogs to prevent PF after elective pancreatectomy, only 3-7,9,10,13 gave specifically the results after DP and none of them demonstrated a significant advantage. As a consequence, the role of somatostatin analogs to prevent PF after DP still remains unclear.

The diagnosis of PF following DP can be late, as demonstrated by the fact that 63% of the patients with PF developed this complication after the return of oral feeding. Another clinically significant finding is the 72% rate of intra-abdominal collection in the patients who underwent postoperative CT scan. Late PF and PF with intra-abdominal collections occurred despite the routine use of a multichannel open drain placed close to the pancreatic suture, and at the time of diagnosis of PF, a “negative” drain had been already removed in 20 patients. Inability of surgical drainage to prevent postoperative collections, which were observed in 65% of patients with PF. Conservative management of PF, including percutaneous drainage for symptomatic abdominal collections, is successful in 95% of cases.

Accepted for Publication: August 30, 2005.

Correspondence: Alain Sauvanet, MD, Department of Digestive Surgery, Hôpital Beaujon, AP-HP, 100 Boulevard du Général Leclerc, 92118 Clichy-CEDEX, France (alain.sauvanet@bjn.ap-hop-paris.fr).

Author Contributions: Study concept and design: Pannegeon, Sauvanet, and Belghiti. Acquisition of data: Pannegeon, Vullierme, and Kianmanesh. Analysis and interpretation of data: Pessaux, Sauvanet, Kianmanesh, and Belghiti. Drafting of the manuscript: Pannegeon, Pessaux, Sauvanet, and Kianmanesh. Critical revision of the manuscript for important intellectual content: Sauvanet, Vullierme, and Belghiti. Statistical analysis: Pannegeon and Pessaux. Study supervision: Pessaux, Sauvanet, and Belghiti.

Financial Disclosure: None reported.

REFERENCES

Although fistula after pancreatic resection has become less life threatening, it remains a challenge to prevent and treat. This complication is at least as common after DP as after Whipple resection. This 13-year audit by Pannegeon et al of 175 patients who underwent DP, despite its suboptimal retrospective, uncontrolled study design, is sufficiently large to address possible risk factors. Pannegeon et al confirm published findings that direct pancreatic duct suture and transection at the pancreatic neck are associated with lower rates of fistula. As with Whipple resection, somatostatin analog administration after DP did not decrease the rate of fistula and was of limited value in its treatment. An underemphasized observation in this study (but one that is well known to experienced surgeons) is that fistula after DP tends to present late, typically days after resumption of an oral diet. This has important implications for American practice, which encourages ever-shorter lengths of stay. Presentation of fistula after DP may be subtle and not evident until outpatient convalescence; thus, the surgeon (and the office staff who may field initial calls) must still remain vigilant after hospital discharge. Total parenteral nutrition was used primarily in this series to manage PF; however, oral nutrition is often simpler, safer, and cheaper. This study also illustrates the dubious value of closed-suction drainage in early diagnosis or treatment of fistula. Half of the fistulae presented after removal of an “amylase-negative” drain, and 25% of percutaneous interventions were required with drains still in place, drains that failed to drain the very fluid for which they were prophylactically placed. Moreover, the rate of infected aspirate was strikingly high, given that leaks after DP initially consist of uncontaminated, inactivated pancreatic fluid because there is no enteric anastomosis. Despite accumulating evidence against the practice, it is difficult to dispel the continuing surgical myth of routine drainage after pancreatic resection.

Jeffrey B. Matthews, MD

Correspondence: Dr Matthews, Department of Surgery, University of Cincinnati College of Medicine, 231 Albert B. Sabin Way, ML-0558, Cincinnati, OH 45267-0558 (jeffrey.matthews@uc.edu).

Financial Disclosure: None reported.