Postoperative pancreatic fistula: An international study group (ISGPF) definition

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Definition,* Verona, Italy; Athens, Greece; Poissy, France; Baltimore, Md; Liverpool, United Kingdom; Hamburg, Germany; Rochester, NY; Seattle, Wash; and Heidelberg, Germany

Background. Postoperative pancreatic fistula (POPF) is still regarded as a major complication. The incidence of POPF varies greatly in different reports, depending on the definition applied at each surgical center. Our aim was to agree upon an objective and internationally accepted definition to allow comparison of different surgical experiences.

Methods. An international panel of pancreatic surgeons, working in well-known, high-volume centers, reviewed the literature on the topic and worked together to develop a simple, objective, reliable, and easy-to-apply definition of POPF, graded primarily on clinical impact.

Results. A POPF represents a failure of healing/sealing of a pancreatic-enteric anastomosis or a parenchymal leak not directly related to an anastomosis. An all-inclusive definition is a 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. Three different grades of POPF (grades A, B, C) are defined according to the clinical impact on the patient’s hospital course.

Conclusions. The present definition and clinical grading of POPF should allow realistic comparisons of surgical experiences in the future when new techniques, new operations, or new pharmacologic agents that may impact surgical treatment of pancreatic disorders are addressed. (Surgery 2005;138:8-13.)

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Accepted for publication May 9, 2005.

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0039-6060/$ - see front matter © 2005 Mosby, Inc. All rights reserved.
doi:10.1016/j.surg.2005.05.001
A universally accepted, objective definition of a pancreatic anastomotic leak is absent in the gastrointestinal surgical literature, leading to an inability to compare objectively the surgical experiences with different operations, techniques, or pharmacologic adjuvants in pancreatic surgery.1-5,11 Currently among high-volume centers, the mortality rate after pancreatic resection has decreased to less than 5%, but the morbidity remains high, ranging from 30% to 50%.3-5,11 Postoperative pancreatic fistula (POPF) has been regarded traditionally as the most frequent major complication and is a potentially serious, life-threatening event that may prolong hospital stay and increase costs.

With the advent of innovative techniques in many different aspects of pancreatic surgery, an objective and uniform definition of POPF should be developed to allow accurate comparison of different surgical experiences.1,3,35 After pancreaticoduodenectomy, the reported rate of POPF is highly variable, ranging from 2%4 to more than 20%.5,22,29,30,39,40-43,47-51 These differences might be related to the variability of the definitions used. In a recent study,3 a Medline search of the last 10 years for definitions of POPF was performed. A score was assigned to the definitions used for POPF on the basis of 2 basic parameters: daily output (milliliters) and duration of the fistula. Among the 26 different definitions of POPF used, only 14 were found suitable to apply a score on the basis of these 2 basic parameters. Four final definitions summarizing the various aspects of POPF were formulated (Table I) and then applied to a group of 242 patients in a single center who underwent proximal or central pancreatectomy with a pancreatic-enteric anastomosis. The incidence of POPF ranged from 10% to 29% according to the different definitions applied. Interestingly, there were marked differences in the “incidence” of POPF, depending on the definition used.3 On the basis of this study, an international consensus was reached that a common, objective definition of POPF was necessary. Our aim was to formulate an acceptable and objective definition of POPF that decreases interobserver variability.

**METHODS**

An international working group of 37 pancreatic surgeons from Europe, Japan, Australia, North America, and South America was convened. All the involved surgeons work in well-known international, high-volume centers, and their clinical experiences are well documented in scientific papers. They reviewed both the literature and their institutional experience. Draft definitions and severity grades of fistula were circulated to all participants for comment. Revised definitions were circulated for approval or further comment. After more than 1 year of electronic mail or, on occasion, face-to-face discussions, the final version of the POPF definition reported here was discussed during the International Postgraduate Course “HPB Marathon” held in Athens, Greece, on March 2004 and then updated during the “Pancreas Cancer Conference” held in Tirrenia, Italy, on April 2004, the 6th World Congress of the International Hepato Pancreatic Biliary Association held in Washington DC, USA, on June 2004, and during the European Pancreatic Club held in Padova, Italy, in the same month.

**RESULTS**

**Terminology.** The most commonly used terms to identify the complication are as follows: fistula, leak, leakage, focal postoperative pancreatitis, and anastomotic failure or anastomotic insufficiency.1-5,11 The Heidelberg and Johns Hopkins groups used a similar definition of POPF: drainage of more than 50 mL of fluid in 24 hours, with an amylase content of more than 3 times the serum amylase activity for more than 10 days after operation.4,13 German and Italian studies8,10 used a definition of POPF as drainage fluid of more than 10 mL in 24 hours with the amylase at least 3 times the normal serum activity 3 or 4 days postoperatively. A less-strict definition was used by a Japanese group45: fluid drainage for more than 7 days postoperatively containing amylase activity of more than 3 times the serum activity. Others suggested that radiologic imaging is necessary for a definitive diagnosis.5,11,21,23,29,30 In 1997, Lowy et al19 introduced the concept of a “clinically significant leak” defined as fever (>38°C), leukocyte count of greater than 10,000 cells/mm³, sepsis, and/or the need for drainage.

**Table I.** Four final definitions summarizing the current pancreatic fistula concept according to the literature*

<table>
<thead>
<tr>
<th>Definition</th>
<th>Duration (days)</th>
<th>Amylase Content</th>
</tr>
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<tbody>
<tr>
<td>1. Output &gt; 10 mL/d of amylase-rich fluid postoperative (postop) day 5 or for &gt; 5 days.</td>
<td>&gt; 10</td>
<td>&gt; 3 times normal</td>
</tr>
<tr>
<td>2. Output &gt; 10 mL/d of amylase-rich fluid after postop day 8 or for &gt; 8 days.</td>
<td>&gt; 10</td>
<td>&gt; 3 times normal</td>
</tr>
<tr>
<td>3. Output between 25 mL/d and 100 mL/d of amylase-rich fluid after postop day 8 or for &gt; 8 days.</td>
<td>&gt; 25</td>
<td>&gt; 3 times normal</td>
</tr>
<tr>
<td>4. Output &gt; than 50 mL/d of amylase-rich fluid after postop day 11 or for &gt; 11 days.</td>
<td>&gt; 50</td>
<td>&gt; 3 times normal</td>
</tr>
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*Source: Bassi C et al3.
It is clear from these and other definitions used and from a general review of the related literature,1-5,11 that there is considerable overlap of the terms fistula and leak; they appear to be contingent definitions, and the terms fistula, leak, leakage, and anastomotic insufficiency should be considered interchangeable. The vast majority of the surgeons involved in the ISGPF currently prefer to use the term fistula.

**Definition of POPF.** A general definition of pancreatic fistula is an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid. However, a POPF represents failure of healing/sealing of a pancreatic-enteric anastomosis, or it may represent a parenchymal leak not directly related to an anastomosis such as one originating from the raw pancreatic surface (eg, left or central pancreatectomy, enucleation, and/or trauma). In this case, there is a leak from the pancreatic ductal system into and around the pancreas and not necessarily to another epithelialized surface (eg, via a surgical drain).

**Suspicion and diagnosis.** The diagnosis of POPF may be suspected on the basis of the many clinical or biochemical findings. A broad definition begins with the following criteria: Output via an operatively placed drain (or a subsequently placed, percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than 3 times the upper normal serum value.

Drain fluid could have a “sinister appearance” that may vary from a dark brown to greenish bilious fluid (provided the anastomosis is near or aboral to a bilioenteric anastomosis) to milky water to “clear spring water” that looks like pancreatic juice. Associated clinical findings may include abdominal pain and distention with impaired bowel function, delayed gastric emptying; fever (>38°C), serum leukocyte count greater than 10,000 cells/mm3, and increased C-reactive protein may also be present.

Radiologic documentation is neither mandatory nor necessarily recommended for diagnosis.38 However, imaging may be useful by identifying erosion or migration of the drain into an enteric viscus and thus the need for drain withdrawal to allow healing of the site of erosion.

**Grading.** Since the broad definition may be so inclusive that many asymptomatic patients that fit the definition of POPF may not be clinically ill, we also propose a clinical grading system for POPF (grades A, B, C). Table II is an attempt to summarize the main features of each POPF grade. The grade of severity may only be decided after complete follow-up, including discharge from the hospital or death, when the ultimate effect of the POPF on outcome can be determined.

**POPF grade A:** This grade of POPF is the most common; called “transient fistula,” it has no clinical impact. Grade A POPF requires little change in management or deviation from the normal clinical pathway. The patient is fed orally and remains clinically well, and the use of total parenteral nutrition, antibiotics, or somatostatin analogues are not indicated. A computed tomographic (CT) scan typically shows no peripancreatic fluid collections. Grade A POPF requires delayed a delay in hospital discharge and is managed frequently by slow removal of the operatively placed drains.

**POPF grade B:** This POPF grade requires a change in management or adjustment in the clinical pathway. Often the patient is kept with nothing by mouth (NPO) and is supported with partial or total parenteral nutrition. The peripancreatic drains are usually maintained in place, but if the drains are not functioning to fully drain the fistula, a CT scan may show peripancreatic collection(s) requiring repositioning of the drains. When associated with abdominal pain, fever, and/or leukocytosis, antibiotics are usually required; somatostatin analogues may also be used. Grade B POPF usually leads to a delay in discharge, or readmission after a previous discharge may be required. Many patients with grade B POPF can be discharged with drains in situ and observed in the outpatient setting. If an invasive

<table>
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<th>Table II. Main parameters for POPF grading</th>
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<tr>
<td><strong>Grade</strong></td>
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<tr>
<td>Clinical conditions</td>
</tr>
<tr>
<td>Specific treatment*</td>
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<tr>
<td>US/CT (if obtained)</td>
</tr>
<tr>
<td>Persistent drainage (after 3 weeks)†</td>
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<td>Reoperation</td>
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<td>Death related to POPF</td>
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<td>Signs of infections</td>
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<td>Sepsis</td>
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<tr>
<td>Readmission</td>
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US, Ultrasonography; CT, computed tomographic scan; POPF, postoperative pancreatic fistula.

*Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.
†With or without a drain in situ.
procedure is needed, the POPF shifts into grade C (see below).

**POPF grade C:** In a grade C POPF, a major change in clinical management or deviation from the normal clinical pathway occurs. Clinical stability may be border line. Clinical intervention is aggressive with the patient kept NPO and total parenteral nutrition or enteral nutrition, intravenous antibiotics, and somatostatin analogues instituted, often in an intensive care unit setting. A CT scan usually shows worrisome, peripancreatic fluid collection(s) that require percutaneous drainage. The patient typically requires an extended hospital stay with a major delay in hospital discharge.

A deteriorating clinical status with a grade C POPF, together with sepsis and organ dysfunction, may require re-exploration for 1 of 3 options: (1) an attempt to repair the site of leakage with wide peripancreatic drainage, (2) conversion to alternative means of pancreatic-enteric anastomosis (eg, conversion of pancreaticojejunostomy to pancreaticocystogastrostomy), or (3) completion pancreatectomy. In patients with grade C POPF, there are often associated complications and the possibility of postoperative mortality.

**DISCUSSION**

The word *fistula* (according to Stedman’s Concise Dictionary) is “an abnormal passage from one epithelialized surface to another, congenital or created surgically.” *Leak* and *leakage* are more common words that relate to the escape of fluid: *leak* means “to let out” or “to escape through a hole, crevice or other opening,” while *leakage* is the “act, process, or instance of leaking of fluid”; indeed, *fistula* seems to be the more appropriate term for the common complication after pancreatic surgery.

In the pancreatic surgery literature, it is almost impossible to find the same definition of POPF in any 2 papers. Even surgeons highly specialized in pancreatic surgery do not provide a simple and reliable definition but still report surprisingly high rates of “collections,” “abscesses,” “re-operation,” and “mortality rates,” in many cases related to anastomotic failure. Yet, they report a simultaneous low incidence of POPF. Since these different definitions could lead to misleading discrepancies on the basis of only differences in terminology, and since intra-abdominal collections and abscesses may be a manifestation of pancreatic anastomotic failure, we suggest the need to propose a unifying definition of POPF.

Clinically, POPF may be suspected early (after postoperative day 3) on the basis of the quality rather than the amount of drain output, but only a long-standing observation will confirm the diagnosis because many patients will have an inflammatory serous output not related to anastomotic leak. Indeed, only after clinical recovery is complete, is it possible to ultimately distinguish and to grade the POPF as grades A, B, and C with respect to the clinical impact.

The volume of fluid output on any one day is relative, as demonstrated by the wide range reported in the literature. Also, one must consider the duration of the complication. In some cases, as in left resections, POPF may be characterized by an output of a few drops of “sinister fluid,” frequently appearing as pus, leading to hesitation in removing the drain. With the present definition, these situations are graded as group A as long as the patient is asymptomatic or as grade B if there are related symptoms or an in situ drain with management in the outpatient setting for more than 3 weeks postoperatively.

As further emphasis of the confusing definitions that are based strictly on the quantitative drain output, it is interesting to note that some authors have modified their definition of *fistula* during the last few years, increasing the daily output value from 10 to 50 mL. Also, one must consider that currently the clinical impact of complications in pancreatic surgery is less than that in the past.

The amylase content is well recognized as an integral and unavoidable biochemical definition of POPF, but the amylase activity can range from hundreds to thousands of International Units depending on pancreatic glandular function and dilution by inflammatory serous fluid: There do not seem to be any data suggesting a reliable cutoff value for absolute amylase activity. The surgeons participating in our consensus agreed to a broadly inclusive value of more than 3 times the normal serum value to denote when the POPF is first “suspected.” Only later can the POPF be graded.

The routine use of imaging for staging POPF was reported in only 7 of the 26 definitions collected. As already stressed, sinography should not be considered mandatory or recommended for diagnosis, but, in selected patients, it may be useful for management. For example, the retrospective analysis of the postoperative complications occurring in the Verona patients showed that several of the recorded POPFs were, in fact, enterocutaneous fistulas caused by the drainage tube having eroded into
the jejunum. These enteric fistulas closed quickly on withdrawal of the drain.

Finally, among the clinical parameters to be considered, the duration (and delay) of hospital stay should be addressed. After collecting and analyzing these data among different centers in different countries, it seems reasonable to limit the definition of duration of hospital stay to 1 standard deviation beyond the mean length of stay for all personal cases, as suggested recently by Traverso et al.37 We decided not to use this parameter in the suggested grading because other, more simple parameters appear to be able to distinguish between grades A, B, and C. Moreover, because delay in hospital stay is variable between countries, it would require an institution to calculate its own average duration of stay, which places an extra constraint on defining and grading POPF. Should the term POPF itself be reviewed in some way? For example, do we need to add to our definition the concept of perianastomotic collections or abscess that, when percutaneously drained, do not prolong the hospital discharge? Should percutaneous drainage place the patient into a lesser category than those of patients who require reoperation for complication of an anastomotic leak? Using our criteria, we capture these conditions into POPF grade C.

The usefulness of the clinical grading system becomes apparent with the following 2 examples. The all-inclusive broad definition using drain volume or amylase concentration cannot be used by those surgeons who do not place drains intraoperatively.26,42 Also, even if drains are used, they may not be located near the collection from the leaking anastomosis, and the drain would not indicate a leak. These 2 examples would escape our broad definition until an invasive procedure was required but then would be included in the POPF clinical grading (grade C).

Moreover, one also could include in grade B a patient who had no drains but had postoperative mild fever, leukocytosis, and ileus, and a small amount of peripancreatic fluid collection detected on ultrasonography or CT scan, and who was treated with a course of antibiotics and recovered without invasive procedures.

We suggest that use of our proposed definition of POPF will confirm its clinical value and allow accurate comparison of different surgical experiences.

REFERENCES