Current Definition of and Controversial Issues Regarding Postoperative Pancreatic Fistulas

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The International Study Group for Pancreatic Fistula (ISGPF) made the first attempt to standardize the outcome measure of fistulas in the field of pancreatic surgery by publishing the definition and classification of postoperative pancreatic fistulas (POPFs) in 2005. POPFs were determined by any measurable volume of fluid output via an operatively placed drain with amylase activity greater than three times the upper normal serum value. Taking into account more than 10 years of reported experience worldwide, the updated definition published in 2016 by the reconvened International Study Group for Pancreatic Surgery (ISGPS) attempted to overcome the limits of the previous classification. The crucial concept of POPF clinical significance was introduced by eliminating grade A from the fistula scenario. The wider use of interventional procedures has also made it necessary to recode grade C POPFs, which now have clearer boundaries, toward the worst end of the severity scale. Grade B still represents the most prevalent and heterogeneous category of POPFs, both in terms of clinical burden and management. In the near future, further efforts will be required to better stratify grade B POPFs to standardize treatment strategies and compare outcomes among institutions. (*Gut Liver* 2019;13:149–153)

Key Words: Pancreatic fistula; Pancreaticoduodenectomy; Pancreatectomy; Pancreaticojejunostomy; Outcome

INTRODUCTION

The scientific literature extensively describes the rapid and accelerating changes affecting healthcare. Particularly in the field of surgical specialties, common needs are represented by the pressure to improve quality, enhance assistance, expand the access to cure, and to reduce costs. This is the reason why the

ability to measure, monitor and report the system's performance become essential to compare results obtained at different institutions acting in similar clinical scenarios. Measure of outcome are particularly suitable for the assessment of quality of results of surgical care as surgery involves an intervention with an expected outcome. Moreover, the reproducibility of results and the use of a common language are the fundamental prerequisites for the progress of surgical practice through clinical research.

Complex procedures, such as major pancreatic surgery, have been lately centralized within high-volume centers around the World with the result of improving the healthcare quality. However, this represents the point of arrival of a process that began almost 30 years ago when the clinical research in the field of pancreatic surgery was not yet a global concept, when postoperative pancreatic fistula (POPF) represented the main determinant of morbidity and mortality after a major pancreatic resection becoming legitimately the main outcome measure.

At that time, the major issue was the lack of an unequivocal definition of POPF.

THE 2005 INTERNATIONAL STUDY GROUP FOR PANCREATIC FISTULA DEFINITION AND GRADING

Before 2005, at least 26 different definitions of POPF existed. As a matter of fact, applying different definitions of POPF to the same cohort of patients resulted in an incidence varying from 10% to 29%.¹ Any critical comparison between outcomes among surgeons and centers was impossible. In 2005, an International group of 37 pancreatic surgeons, the International Study Group for Pancreatic Fistula (ISGPF), was convened to reach a universally accepted definition of POPF:² a fluid output of any measurable volume via an operatively placed drain with amylase activity greater than 3 times the upper normal serum value. Moreover, a clinical system of three discrete grades of

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POPF (grades A, B, and C) was proposed based on the complication-specific severity (Table 1). Since its publication in May 2005, the original paper by the ISGPF² has been cited 3,631 times (until April 2018, source Google Scholar) making it the third most cited paper in the general surgery literature,³ and its acceptance by the surgical community resulted in the application of such definition of POPF to more than 320,000 patients in original studies.

VALIDATION AND ISSUES RELATED TO 2005 DEFINITION AND GRADING OF POPF

From a methodological point of view, the 2005 classification was not derived and then validated on an actual population of patients. Rather, it was only the result of the consensus obtained by expert pancreatic surgeons. It represents a milestone because from that experience the clinical research in the pancreatic field has exploded and became global thanks to a “common

language:” the standardization of outcome measure. After its publication, several studies provided a clinical and economic validation from different points of view.⁴⁻⁷ In contrast, the first significant issue raised against the 2005 POPF grading system was that patients not developing POPF and those developing grade A POPF basically have an identical clinical course. For instance, a certain patient suffering from a grade A POPF could either present with an amylase-rich fluid from a surgical drain that is removed before discharge as well as a patient with a completely uneventful postoperative course. Moreover, the introduction of selective use of surgical drains policies on the basis of POPF risk resulted in a virtual elimination of all grade A POPF.⁸⁻¹⁰ Finally, although in the absence of an official definition, most papers began to refer to a new entity called “clinically relevant POPF (CR-POPF),” taking into account only grade B and C POPF.¹⁰⁻¹⁵ At that point there was no more a common language and papers including grade A in reporting the incidence of POPF regularly demonstrated higher rates of POPF if

Table 1. Evolution of the Classification of POPFs

ISGPF (2005) ²	Definition	A fluid output of any measurable volume via an operatively placed drain with amylase activity greater than 3 times the upper normal serum value		
	Grade	A	B	C
	Clinical condition	Well	Often well	Ill appearing/bad
	Specific treatment*	No	Yes/no	Yes
	US/CT	Negative	Negative/positive	Positive
	Persistent drainage (after 3 wk)	No	Usually yes	Yes
	Reoperation	No	No	Yes
	Death related to POPF	No	No	Possibly yes
	Signs of infection	No	Yes	Yes
	Sepsis	No	No	Yes
	Readmission	No	Yes/no	Yes/no
ISGPS (2016) ¹⁷	Definition	Any measurable volume of drain fluid on or after postoperative day 3 with amylase level >3 times the upper limit of normal amylase value for each specific institution. The condition needs to be clinically relevant		
	Grade	-	B	C
	Persistent drainage (after 3 wk) [†]		Yes	
	Clinically relevant change in management of POPF		Yes	
	Percutaneous or endoscopic drain [†]		Yes	
	Angiographic procedures for bleeding [†]		Yes	
	Signs of infection without organ failure [†]		Yes	
	Reoperation [†]			Yes
	Organ failure ^{†,‡}			Yes
	Death [†]			Yes

POPFs, postoperative pancreatic fistulas; ISGPF, International Study Group for Pancreatic Fistula; US/CT, ultrasounds/computed tomography; ISGPS, International Study Group for Pancreatic Surgery.

*Total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or percutaneous drainage; [†]Treatment/event related to POPF;

[‡]Organ failure is defined as a need for reintubation, hemodialysis, and/or inotropic agent use for >24 hours because of respiratory, renal, or cardiac insufficiency, respectively.

compared to those considering only grades B and C together as CR-POPF.

The second raised issue dealt with the opportunity to discharge a patient leaving a drain in place and managing it in the outpatient clinic setting. According to the 2005 classification,² leaving the drain in place for more than three weeks should upgrade from grade A to grade B POPF. Although more than 10 years ago it could have been justified, this definition lastly became anachronistic since, thanks to minimally invasive surgery and to the enhanced recovery after surgery programs, many patients are discharged with a drainage in place and without a significant clinical impact.

Eventually, a possible divergent interpretation of grade B and C POPF¹⁶ has also been shown in recent years. An extensive use of interventional drains (ID), either percutaneous or endoscopic, was not foreseen at the time of the first definition and this issue was left unsolved or at least not clear. In the original paper,² the use of ID was reported both for grade B and C POPF in the table, but defined as grade C POPF in the text. This meant that, whereas a clinically relevant POPF treated with antibiotic therapy and artificial nutrition was invariably classified as grade B and a POPF requiring relaparotomy as grade C, the frequent clinical pictures of POPFs requiring multiple interventional procedures were inconsistently classified either as grade B or C through the papers. Again, the fact that POPFs requiring ID were alternately classified as grade B or C disallowed the comparison between results coming from different institutions. After demonstrating a clear difference in patients' outcome comparing the use of ID to the need of relaparotomy due to POPF, a paper from the Heidelberg's group¹⁶ triggered the need for an updated definition and classification of POPF.

THE 2016 INTERNATIONAL STUDY GROUP FOR PANCREATIC SURGERY DEFINITION AND GRADING UPDATE

After extensive consultations between experts, the updated definition of POPF has been published in 2016¹⁷ as any measurable volume of drain fluid on or after postoperative day 3 with amylase level >3 times the upper limit of normal amylase value for each specific institution. However, to be defined as a POPF, this condition needs to be clinically relevant. The grading system has been revised as well (Table 1) and, like the previous classification, it can only be applied *a posteriori*, once the entire clinical course has ended. In the new grading system grade A POPF does no longer exist and is replaced by the term biochemical leak (BL). BL does not represent the first grade of severity of POPF, but rather it should only be used for that condition characterized by the presence of fluids rich in amylase from drains without any clinical impact for the patient. The further merit of this update is that of having drawn precise boundaries in the definition and in the grading system of POPF, in the attempt of not leave room for biased interpretations. For instance, the use

of ID now invariably classifies POPF as grade B. Moreover, all possible clinical evolutions that could lead to an upgrading of POPF have to be strictly related to the POPF itself. This is the reason why respiratory failure with subsequent reintubation due to pneumonia in a patient with a percutaneous drain placed due to POPF does not involve an upgrade from grade B to grade C. Table 2 shows how usual clinical pictures are graded in a different way according to the two classifications of POPF.

VALIDATION AND ISSUES RELATED TO 2016 DEFINITION AND GRADING UPDATE

The brevity, objective simplicity and clinical applicability, representing points of strengths of the first POPF definition,² are maintained in the 2016 update.¹⁷ In addition, 10 years of experience with more than 320,000 patients classified with the 2005 ISGPF definition have allowed to improve the definition and resolve the remaining concerns. The effects of the new classification are already evident in the consequent validating series already published.¹⁸ Due to the criterion of "clinical relevance," POPF rate drops from 34% to 27% after applying the new classification to the same series of pancreatic resections. Due to the redefinition of the severity of the grade C, many cases of 2005 grade C POPF have been included into the 2016 grade B category with a subsequent increase in its rate of about 10%. This first validation series¹⁸ demonstrates the ability of the updated classification in stratifying patients in three discrete groups of patients in terms of clinical and economic outcomes, but also reveals how patients have been polarized at both ends, namely those without a POPF and those with the most severe POPF, producing a "middle" category that includes extremely heterogeneous cases. Within grade B POPF, in fact, patients with various clinical management are included: drains left in place, antibiotics, artificial nutrition, somatostatin analogues, percutaneous or endoscopic drains, angiography in case of bleeding. The 2016 grade B POPF has become the most frequent¹⁸ and it would represent the ideal target for outcome optimization, but the heterogeneity of the clinical pictures included within it does not allow to identify a specific management. Despite the treatment escalation, for instance, the same patient initially treated with simple antibiotics, then with artificial nutrition and eventually with several procedures of ID placement requiring several controls with cross-sectional imaging will always be included in the grade B POPF category. Another large series has retrospectively applied the new definition of POPF¹⁹ revealing how at least three different subcategories of patients coexist within grade B POPFs: those experiencing only a prolonged time (more than 3 weeks) with the drain kept in place; those that in addition need antibiotics, artificial nutrition or somatostatin analogues, and those that in addition need interventional procedures like ID or angiography to manage episodes of bleeding. Indeed, these subclassification of grade B POPF seems to be particularly relevant

Table 2. Typical Clinical Images Graded According to the Two Different POPF Classification Systems

Patient	Procedure	Postoperative course	ISGPF (2005) ²	ISGPS (2016) ¹⁷
76-Year-old man with PDAC	Whipple	Uneventful Discharged on POD7	-	-
65-Year-old woman with IPMN	Whipple	Amylase-rich fluid from drains on POD4 Drains removed on POD7 Discharged on POD8	A	-
34-Year-old woman with NET	Distal pancreatectomy	Amylase-rich fluid from drain in POD4 Drain removed on POD12 Discharged on POD14	A	-
61-Year-old man with ampullary carcinoma	Whipple	Abdominal collections ID placement with amylase-rich fluid Antibiotics Discharged on POD27	B/C	B
85-Year-old man with PDAC	Distal pancreatectomy	Abdominal collections Antibiotics Sepsis due to severe pneumonia requiring reintubation Postoperative mortality	C	B
45-Year-old woman with NET	Spleen preserving distal pancreatectomy	Amylase-rich fluid from drain on POD3 Drain removed on POD5 Splenic infarction on POD7 Reintervention for splenectomy on POD8 Discharged on POD13	C	-
75-Year-old woman with IPMN	Whipple	Amylase-rich fluid from drain on POD4 Abdominal collections Severe bleeding on POD12 Relaparotomy on POD12 Discharged on POD47	C	C

POPF, postoperative pancreatic fistula; ISGPF, International Study Group for Pancreatic Fistula; ISGPS, International Study Group for Pancreatic Surgery; PDAC, pancreatic ductal adenocarcinoma; POD, postoperative day; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; ID, interventional drainage.

as hospital costs related to the burden of treatment progressively increase by 36%, 146%, and 189% respectively compared to costs for the management of patients without POPF.¹⁹ This substantial heterogeneity of clinical pictures and management could ideally prevent the development of appropriate prevention and treatment strategies. Indeed, the International Study Group for Pancreatic Surgery (ISGPS) classification is operational as every case is classified in a specific grade on the basis of treatment strategies, and treatment strategies belong to the surgeon's clinical attitude. For instance, the threshold for using antibiotics may vary from institutions preventing an adequate comparison of data. The 2016 updated classification of POPF is still easy-to-use, simple and brief and has allowed to overcome some limits highlighted in its previous version, however, it still does not allow to completely standardize treatment strategies among institutions.

CONCLUSIONS

Beyond the specific merit of universally coding POPF, the 2005 ISGPF experience acted as a small seed that in 10 years only made clinical research in pancreatic surgery a global concept. Speaking the same language, it was possible to compare results and measure performances improving the level of each institution. The updated 2016 version demonstrates how sharing ideas and thoughts is now a proven mechanism able to ensure progress and guarantee high standards for patients' care.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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