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Pancreatic fistula after pancreatectomy: Evolving definitions, preventive strategies and modern management

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Abstract

Pancreatic resection is the treatment of choice for pancreatic malignancy and certain benign pancreatic disorders. However, pancreatic resection is technically a demanding procedure and whereas mortality after a pancreaticoduodenectomy is currently < 3%-5% in experienced high-volume centers, post-operative morbidity is considerable, about 30%-50%. At present, the single most significant cause of morbidity and mortality after pancreatectomy is the development of pancreatic leakage and fistula (PF). The occurrence of a PF increases the length of hospital stay and the cost of treatment, requires additional investigations and procedures, and can result in life-threatening complications. There is no universally accepted definition of PF that would allow standardized reporting and proper comparison of outcomes between different centers. However, early recognition of a PF and prompt institution of appropriate treatment is critical to the prevention of potentially devastating consequences. The present article, reviews the evolution of post resection pancreatic fistula as a concept, and discusses evolving definitions, the current preventive strategies and the management of this problem.

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Key words: Pancreatic fistula; Pancreaticoduodenectomy; Pancreatic anastomosis; Pancreatic anastomotic failure; Complications

INTRODUCTION

Pancreatic resection is the standard treatment for pancreatic malignancy and certain benign pancreatic disorders. However, pancreatic resection is technically a demanding procedure. At diagnosis, more than 85% of pancreatic tumors are at an advanced stage. Thus, potentially curative resections are possible only in 10%-15% patients^[1,2]. The standard surgical procedure for a lesion in the pancreatic head is pancreaticoduodenectomy (PD), while distal pancreatectomy (DP) with or without splenectomy, is performed for tumors in the body and tail.

At experienced high-volume centers, mortality after PD is currently 3%-5%. However, there is considerable post-operative morbidity, around 30%-50%^[3,4]. At present, the single most significant cause of morbidity and mortality after PD is the development of pancreatic leak and fistula (PF), and rates of up to 20% are reported from centers specializing in pancreatic surgery^[4-6]. The development of PF increases the length of hospital stay and the cost of treatment, necessitates the use of additional investigations and procedures, and can cause life-threatening complications.

Various strategies have been employed to decrease the incidence of PF, including pharmacologic manipulation, and modifications and refinements in the surgical technique. These have resulted in varying degrees of success. However, it is clear that early recognition of PF and prompt institution of appropriate treatment is the cornerstone in the prevention of potentially devastating consequences. The present article reviews the evolution of post-resection pancreatic fistula, and discusses the evolving definitions, and current preventive strategies and management approaches.

Table 1 The different components of previously used definitions of pancreatic fistula and the new grading system used by the International Study Group for Pancreatic Fistula (ISGPF)

Commonly used definitions used prior to the ISGPF recommendations				
Output > 10 mL/d of amylase rich fluid on post-operative day 5 or for > 5 d.				
Output > 10 mL/d of amylase rich fluid on post-operative day 8 or for > 8 d.				
Output between 25 mL/d and 100 mL/d of amylase rich fluid after post-operative day 8 or for > 8 d.				
Output > 50 mL/d of amylase rich fluid after post-operative day 11 or for > 11 d.				
ISGPF Definition: "Output <i>via</i> an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after postoperative d 3, with an amylase content greater than 3 times the upper normal serum value"				
Grade A	"Transient fistula"	No clinical impact	No peri-pancreatic collections on CT scan; little/no change in management	Clinically well; no sepsis; no prolongation of hospital stay; slow removal of operatively placed drains
Grade B		Clinical impact	Peri-pancreatic drains in place or repositioned to drain collections; Change in management is required	Clinically fairly well; degree of infection requiring specific treatment; prolongation of hospital stay; patients often discharged with drains in situ and observed in outpatient setting
Grade C		Severe clinical impact	Worrisome peri-pancreatic collections that require percutaneous drains; major change in management usually in ICU setting; possible re-surgery to salvage a difficult situation (completion pancreatectomy <i>etc</i>)	Clinically unwell; associated sepsis requiring aggressive antibiotics, octreotide and other intensive care support; major prolongation of hospital stay; associated complications and possibility of mortality

DEFINITIONS

There is no universally accepted definition of PF. While some workers have emphasized on the volume (and colour) of the drain output, and its duration, others have stressed more on the amylase content of the drainage fluid^[7-9]. In a study published in 2004, Bassi *et al*^[10] summarized 4 definitions of PF (Table 1) and applied each definition to 242 patients who had undergone pancreatic resection. The results revealed wide variations in the incidence of PF, from 10% to 29% depending upon the definition used. Therefore, it is essential to standardize the reporting of post-PD complications, especially PF. This led to the unified definition, now known as the International Study Group on Pancreatic Fistula (ISGPF) definition^[11]. The definition was intended to standardize the reporting of postoperative PF. The essential component of an anastomotic leak was the high amylase content (> 3 times the upper normal serum value), of the drain fluid (of any measurable volume), at any time on or after the 3rd postoperative day. The ISGPF definition also graded PF (Grades A, B and C) according to the clinical impact on the patient's hospital course and eventual outcome. The various components of the previously used definitions and the new grading of the ISGPF are shown in Table 1. More recently, Pratt *et al*^[12] sought to validate the ISGPF classification in 176 patients who underwent PD and concluded that with increasing fistula grades, there was a negative clinical and economic impact on patients and their healthcare resources.

However the applicability and utility of the ISGPF definition in allowing uniform comparisons of fistula rates has been questioned by some workers. In a recent publication, Strasberg *et al*^[13] proposed that intra-abdominal collections along with hemorrhage and peritonitis are also the result of a pancreatic anastomotic failure. These workers sought to redefine pancreatic fistulae as "pancreatic anastomotic failures (PAF)" which includes the entire spectrum of clinically relevant problems associated with

the loss of integrity of a pancreatico-enterostomy. They also sought to categorize fistulae that occur after DP or segmental resection and enucleation, situations which do not involve pancreatico-enterostomy, as an entity that is distinct from fistulae occurring after PD. These fistulae were termed as pancreatic occlusion failure (POF). POF commonly runs a more benign course (compared to PAF), since enzyme activation does not occur in the absence of a pancreaticoenteric anastomosis. Strasberg *et al* also noted that the definition of PAF should only include patients in whom there is a change in the management, whereas asymptomatic fistulae with merely high drain amylase and no change in the clinical course should not be considered as an operative complication, as proposed by the ISGPF definition. They thus defined PAF and graded its severity into 7 categories in 5 grades (Table 2). They proposed the adoption of the definition of PF used by the Johns Hopkins group^[14]. These workers considered any intra-abdominal fluid collection after pancreatic surgery as PAF, if it was not found to be caused by the failure of other anastomoses performed during a PD. In addition, any hemorrhage was considered as PAF unless the pancreatico-enterostomy was shown to be intact. With respect to intra-abdominal collections, a recent study concluded that post-operative intra-abdominal collections after PD were PF. In this study, it was observed that when the initial drain amylase levels were normal, repeat estimation of the amylase level helped uncover previously undiagnosed PF or newly developed PF, thus providing a more precise estimate of postoperative PF rate^[15]. From the preceding discussion it is evident that the definition of what constitutes a pancreatic fistula or anastomotic failure is still a matter of considerable debate. Clearly, more studies are needed before a common unifying definition of PF can be adopted.

PREVENTIVE STRATEGIES FOR PF

Considering the dismal outcome of a PF, much effort

Table 2 Pancreatic anastomotic failure (PAF) as described by Strasberg *et al*

Definition: "Drainage of greater than 50 mL amylase-rich fluid (> 3-fold elevation above upper limit of normal in serum) per day through the drains on or after postoperative d 10, or pancreatic anastomotic disruption shown radiographically"	
Grade 1	Deviation from normal postoperative course without pharmacologic, endoscopic, surgical or radiologic intervention (certain drugs allowed)
Grade 2	Pharmacologic treatment needed. Includes blood transfusions and total parenteral nutrition
Grade 3 (a/b)	Surgical, endoscopic or interventional radiologic treatment needed a: Not under general anesthesia b: Under general anesthesia
Grade 4 (a/b)	Life threatening complications and organ dysfunction a: Single organ b: Multi-organ
Grade 5	Death due to PAF

has gone into preventing its occurrence. These measures primarily include technical modifications of constructing a pancreatic anastomosis. The correct management of a pancreatic remnant after a PD is a matter of much debate and this is reflected in the variety of techniques that have evolved over the years for the construction of a safe pancreatic anastomosis. Furthermore, the outcome of a pancreatic anastomosis depends, among other factors, on the consistency of the pancreatic parenchyma and the diameter of the main pancreatic duct. Clearly, the outcome is better when the pancreas is hard and the duct is dilated (*e.g.* in chronic pancreatitis) as compared to a soft pancreas with a non dilated duct (*e.g.* in low common bile duct cancer).

Other innovations include the use of biological adhesives designed to seal the anastomosis, ligation or occlusion of the main pancreatic duct, optimization of the blood supply to the pancreatic remnant, use of somatostatin and its analogues to inhibit pancreatic secretion, and even total pancreatectomy^[16].

Pancreatic duct occlusion

Occlusion of the pancreatic duct can be achieved by simple suture ligation of the duct or injection of the duct with non-reabsorbable or reabsorbable glues. Simple duct ligation, advocated in the past, has been largely abandoned due to high PF rates, nearing 50%^[17,18]. However in a recent prospective randomized controlled trial (RCT) by Tran *et al*^[19] which compared pancreaticojejunostomy with duct occlusion alone, there were no significant differences in the morbidity or mortality, but the incidence of diabetes mellitus was higher in patients with duct occlusion.

In a study on 51 patients, Di Carlo *et al*^[20] used a nonreabsorbable glue (neoprene) to occlude the pancreatic duct after PD. The authors concluded that intra-ductal injection of Neoprene after pancreaticoduodenectomy was a safer procedure compared to pancreaticojejunal anastomosis and was not associated with post surgical diabetes. In a prospective, multi-center RCT of 182 patients undergoing either PD or DP, 102 patients received pancreatic ductal occlusion with fibrin glue. Analysis showed that duct occlusion had no effect on the rate or severity of intra-abdominal complications after pancreatic resection^[21].

Type of pancreatic anastomosis: Pancreaticojejunostomy (PJ) versus pancreaticogastrostomy (PG)

The safe reconstruction of pancreatocenteric continuity is the key to preventing a PF. The risk of fistula formation depends on the consistency of the remnant pancreas, caliber of the main pancreatic duct, pancreatic vascularity and the technique of construction of the pancreatic anastomosis^[22,23]. PJ and PG are the two most commonly employed techniques for the reconstruction of pancreatocenteric continuity. PJ can be performed by the dunking method or the duct-to-mucosal anastomosis. Surgical techniques such as PG and PJ which are employed for the management of the pancreatic remnant after PD have been evaluated in only a few randomized controlled studies^[14,24,25]. Earlier uncontrolled studies were in favor of PG^[26,27]. Due to the close proximity of the stomach, a PG was believed to be easier to perform and less prone to ischemia as a result of the rich blood supply of the stomach. However, all the RCTs have failed to show any difference in the overall post-operative complication rate or incidence of PF. Two recent meta-analyses have shown that while non randomized observational studies showed a superiority of PG over PJ, RCTs failed to show superiority of any one technique, thereby concluding that both PJ and PG provided equivalent results^[28,29]. Thus, it can be concluded that as long as a tension-free anastomosis between well perfused tissues is performed, employing fine sutures and using the same technique, any type of pancreatic anastomosis should result in a good outcome^[3,30].

Stenting of the main pancreatic duct

Stenting of the pancreatic duct during pancreatocenteric anastomosis facilitates the precise placement of mucosal sutures, diverts pancreatic juice away from the anastomotic site and decreases the risk of inadvertent pancreatic duct occlusion. In doing so, it is believed that the anastomotic integrity improves, thereby reducing the PF rate. The results of this strategy have been encouraging^[31,32]. In a prospective but non-randomized trial in 85 patients, Roder *et al*^[31] demonstrated that stenting the pancreatic duct reduced the PF rate from 68% to 29.3%, and the median hospital stay from 29 d to 13 d. Poon *et al*^[33] reported that external drainage of the pancreatic duct with a stent reduced the leakage of PJ after PD. On

the other hand, some well designed studies have shown no benefit of internal stenting in preventing PF^[34,35]. Thus, the available evidence is conflicting and the use of stents depends on personal choice and experience of the pancreatic surgeon.

Role of magnification in pancreatic anastomosis

Since a duct to mucosa anastomosis is crucial for good outcome, a meticulous approximation assumes great importance. Operating loupes have been used by many experts to allow precise construction of a pancreatic anastomosis. Wada *et al*^[36] in a retrospective analysis highlighted the role of the operating microscope in constructing a pancreatic anastomosis. Technical errors which may occur during anastomosis include crossing of the sutures, including both sides of the pancreatic duct while passing the suture, taking unequal and inadequate amounts of pancreatic duct and jejunal mucosa, and incorrect knot placement resulting in air knots. All these events can be avoided by using magnification. The study by Traverso, reported a markedly reduced incidence of PF with the operating microscope compared to operating loupes.

OTHER SURGICAL TECHNICAL MODIFICATIONS/APPROACHES

Blood supply based technique of PJ

One of the few modifications which have demonstrated a substantial reduction in the rate of PF after PD was proposed by Strasberg *et al*^[37]. These workers put forward the concept of vascular watershed in the pancreatic neck and its role in ischemia of the cut surface of the pancreatic remnant. In their technique, the blood supply at the cut surface of the pancreas was evaluated, and if necessary, the pancreas was cut back 1.5 cm to 2.0 cm to improve the blood supply ($n = 47$; 38% patients). Thereafter, the anastomosis was performed meticulously under magnification. The authors concluded that a combination of optimization of blood supply to the pancreatic remnant, and a meticulous technique resulted in reduced PF rate, from previous reports of 10% to 1.6% in their series of 123 resections.

Duct-to-mucosa versus invagination anastomosis

A number of studies have demonstrated a lower rate of PF using the duct-to-mucosa technique for pancreatic anastomosis^[38-40]. However a prospective RCT by Bassi *et al*^[41] revealed no significant difference in the morbidity and PF rate between duct-to-mucosa anastomosis and single layer end-to-side pancreatico-jejunoanastomosis.

Total pancreatectomy

The rationale for total pancreatectomy is that it allows a more extensive lymphadenectomy, obviates the risk of leak from the pancreatic anastomosis and decreases the chances of a positive resection margin. However, total pancreatectomy is associated with obligatory diabetes mellitus, decreased immunity because of splenectomy, and loss of pancreatic exocrine function. Most studies have

reported either worse survival or no survival difference between total pancreatectomy and standard PD^[42-44]. Total pancreatectomy should not be performed in most cases of carcinoma of the pancreatic head, unless serial positive resection margins are obtained on frozen section examination, or the pancreas is deemed to be very soft with a very high risk of pancreatic leak, and in patients with documented family history of multi-centric disease^[45].

Stapled or hand-sewn closure of the pancreatic remnant after DP

PF remains a major cause of morbidity after DP. A number of techniques have been used to reduce the incidence of PF after DP, including hand-sewn closure, staple closure, combined staple and suture closure, fibrin glue application, serosal jejunal patch and prolamine injection^[46]. While hand-sewn closure has stood the test of time, the use of staplers is gaining increasing acceptance, especially with the advent of laparoscopic DP. Knaebel *et al*^[47] performed a meta-analysis that included six studies comparing stapler versus hand-sutured closure, which showed a non-significant combined odds ratio for pancreatic fistula of 0.66 (95% confidence interval 0.35 to 1.26, $P = 0.21$) in favor of staple closure. However, a large retrospective study of 302 DP's, showed that stapler closure was associated with a higher rate of pancreatic fistula^[48]. Thus, the jury is still out and surgeons must follow their own individual experience when dealing with pancreatic remnant after DP. In hand sewn closure, the guiding principle is to make every effort to identify the pancreatic duct, close it with fine sutures and then close the entire stump with sutures.

Role of Octreotide and Somatostatin analogues in decreasing the rate of PF after pancreatic surgery

Octreotide is a synthetic analogue of somatostatin, and like somatostatin inhibits pancreatic exocrine secretion. Several prospective RCTs conducted in Europe evaluated the use of subcutaneous octreotide/somatostatin in patients undergoing elective pancreatic resection for different indications^[8,49-52]. The results show that octreotide reduced the development of pancreatic fistula and other complications. However RCTs by Sarr *et al*^[9], Yeo *et al*^[53] and Lowy *et al*^[54], failed to show a similar benefit in the peri-operative use of somatostatin analogues in patients undergoing pancreatic resection. Meta-analysis and systematic reviews of octreotide use have also yielded conflicting results^[55,56]. These findings notwithstanding, many surgeons continue to use octreotide in patients undergoing pancreatic surgery. Selective administration of octreotide in patients considered to have high risk pancreas (soft texture, small duct size, and presence of ampullary, duodenal, cystic or islet cell pathology) may be associated with a decreased incidence of PF^[57].

MANAGEMENT OF PF (FIGURE 1)

Despite numerous novel strategies designed to prevent the development of postoperative PF, it is clear that in order to minimize the potentially devastating effect of PF,

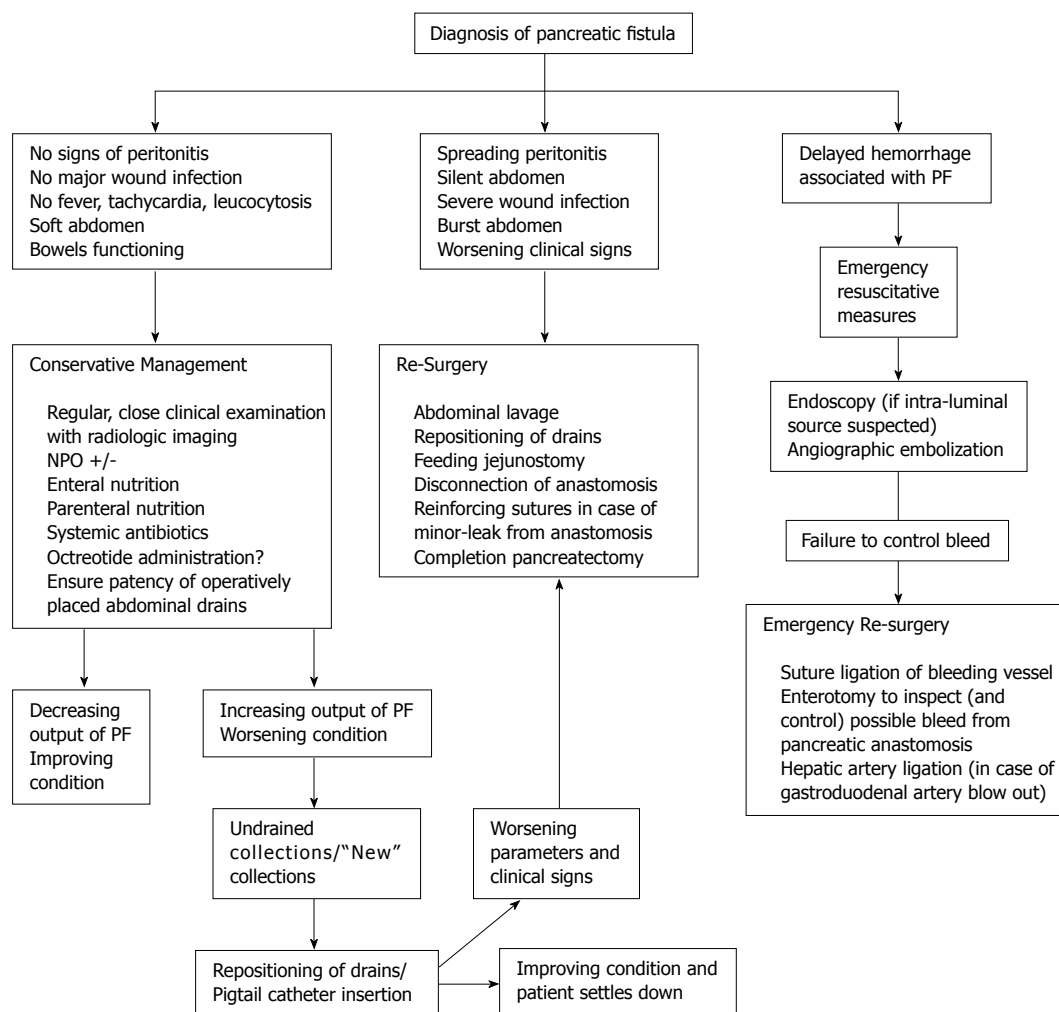


Figure 1 Approach to management of post pancreatectomy PF. Other procedures to manage complex PF may have to be added.

it is essential that this complication is recognized as soon as it develops, and appropriate treatment measures are instituted promptly. The suspicion of PF begins whenever there is a deviation in the normal clinical course of a patient who has just undergone a major pancreatic surgery. This may mean a patient who develops unexpected upper abdominal discomfort (often associated with fever), leucocytosis, increasing tachycardia, or just feels unwell after an apparently “normal” initial post-operative recovery. Furthermore, there may be high amylase content of a drain, a persistently high drain output, altered drain colour and quality, and other complications such as severe wound infection and hemorrhage. Routine radiologic evaluation is neither necessary nor recommended for establishing a diagnosis of PF^[37]. What constitutes a PF is a matter of which definition is used, and varies from center to center. Regardless, once a diagnosis of PF is established, aggressive and appropriate conservative management is the key to successful outcome.

The management in the majority of patients is based on conservative measures. However, interventional radiological assistance is sometimes required, but repeat surgery is rarely indicated^[16,58].

CONSERVATIVE MANAGEMENT

A conservative approach to the management of PF is

successful in over 90% patients^[59,60]. This involves clinical evaluation of the patient at short intervals. If the patient does not have any fever, tachycardia, leucocytosis, severe wound infection, and the abdomen is soft (with functioning bowel), and no signs of peritonitis, it is safe to continue with conservative measures. These measures include maintenance of enteral nutrition (through an operatively placed nasojejun tube or a feeding jejunostomy), nasogastric suction (in the presence of delayed gastric emptying secondary to PF), and appropriate antibiotic coverage. In situations where the abdomen has not “really settled”, the option of total parenteral nutrition should be considered. All along, the abdominal drains and the main wound require close attention. The effectiveness of octreotide in aiding the closure of a PF has not provided encouraging results^[61]. The interventional radiologist may play a crucial role by image-guided repositioning of operatively placed drains and insertion of percutaneous catheters to drain collections seen on CT scan^[60,62]. Delayed hemorrhage following PF is perhaps best managed by angiography and embolization of the bleeding vessel. This treatment is successful in stopping the bleeding in 80% patients^[63]. The prognosis of patients with post-pancreatectomy hemorrhage depends on whether or not PF is present. The decision-making should be guided by factors such as the time of onset of the bleeding, presence of PF, vascular pathology, and the

underlying disease process^[63]. The failure to successfully control hemorrhage by conservative measures like angiographic embolization may necessitate repeat surgery^[63-66]. Obviously, the management of complications associated with PF requires a multidisciplinary approach, involving the pancreatic surgeon, intensive care team, and interventional radiologists. Kazanjian *et al*^[59] evaluated 437 patients who underwent PD. A total of 55 (12.6%) developed PF; 52 patients (94.5%) had successful conservative management with prolonged tube drainage, 4 required percutaneous drainage and only 3 patients (5.5%) had repeat surgery.

OPERATIVE MANAGEMENT

Pancreatic resection is now considered a safe procedure when performed in high volume centers. PF can be successfully managed by conservative measures, as described earlier. The indications for surgical intervention in PF include worsening clinical parameters, signs of spreading peritonitis, severe wound infection, wound dehiscence, and delayed hemorrhage. When a decision is made to reoperate a patient with PF, the following measures should be considered: abdominal lavage with repositioning of drains, control of hemorrhage, use of sutures to control a small dehiscence, disconnection of the pancreatic anastomosis, a feeding jejunostomy (if not already in place) and occasionally completion pancreatectomy^[61,67]. In patients with delayed hemorrhage who require repeat surgery, a thorough exploration of the resection site is required and if necessary, ligation of the arterial stumps (including occasionally the common hepatic artery) and inspection of the anastomosis by enterotomy^[64]. It is worth noting that with improvements in the results of pancreatic surgery and the success of interventional radiology in managing complications, completion pancreatectomy is seldom required, and it has even been suggested that it should no longer be considered in patients with a PF^[58].

The approach to the management of a patient with PF is summarized in Figure 1.

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