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The natural course of pancreatic fistula and fluid collection after distal pancreatectomy: is drain insertion needed?

Ye Rim Chang[1,2], Mee Joo Kang[1], Hongbeom Kim[1], Jin-Young Jang[1], Sun-Whe Kim[1]

[1]Department of Surgery, Seoul National University College of Medicine, Seoul, [2]Department of Surgery, Dankook University Hospital, Cheonan, Korea

Purpose: Postoperative pancreatic fistula (POPF) is one of the most common and clinically relevant complications after distal pancreatectomy. Some aspects of POPF management remain controversial. Therefore, the aim of this study was to determine the natural course of POPF and fluid collection after distal pancreatectomy and to reappraise the necessity of intraoperative abdominal drainage insertion.
Methods: For recent 10 years, 264 distal pancreatectomies were performed at Seoul National University Hospital. Clinicopathologic data including POPF and postoperative fluid collection (POFC), and its treatment modality were reviewed retrospectively. During follow-up, the location, size, and clinical impact of the POFC were determined on the basis of CT images.
Results: Clinically relevant POPFs were identified in 72 patients (27.3%). Therapeutic interventions were performed in 40 patients (55.6%), and conservative management was successful in 32 patients (44.4%). POFC was detected in 191 cases (72.3%) on the first postoperative CT. During follow-up, spontaneous regressions were observed in 119 cases (93.0%). Only thick pancreatic stump increased the risk of clinically relevant POPF (≥17.3 mm, P = 0.002) and the occurrence of POFC (≥16.0 mm, P < 0.001) in multivariate analysis.
Conclusion: Intraoperative abdominal drainage insertion could be selectively indwelled in patients with a thickness of pancreas ≥17.3 mm. Since radiologically-proven POFC after distal pancreatecomy showed a 93.0 rate of spontaneous regression, POFC without signs of infection can be safely monitored.
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Key Words: Pancreas, Pancreatectomy, Drainage

INTRODUCTION

Postoperative pancreatic fistula (POPF) is one of the most common complications of pancreatic surgery [1]. Recent advances in operative techniques and perioperative care have resulted in lower morbidity and mortality rates; however, POPFs may still lead to intra-abdominal abscess, hemorrhage, and sepsis. Although the early diagnosis and prevention of POPF have been extensively discussed, the management of patients after distal pancreatectomy remains unclear [2].

Given that pancreatic juice is not activated after distal pancreatectomy, the severity and clinical course of the POPF is milder after distal pancreatectomy than after pancreatoduodenectomy [3]; thus, the postoperative management after distal pancreatectomy should be different from that after pancreatoduodenectomy. However, little is known about the optimal management of POPFs including the optimal drainage of the remnant pancreas, the optimal technique for closure

of the pancreatic stump, and the clinical impact and natural course of the fluid collection that is commonly observed in the postoperative CT scans.

Therefore, the aim of this study was to evaluate the natural course of the POPF after distal pancreatectomy and to reappraise the necessity of intraoperative abdominal drainage insertion.

METHODS

Data collection

A total of 264 distal pancreatectomies were performed by 2 experienced pancreatic surgeons at Seoul National University Hospital from May 2004 to April 2013. Patient characteristics were reviewed for age, sex, histologic diagnosis, operative method, type of stump closure, pancreatic texture, size of the main pancreatic duct, pancreatic thickness, presence of POPF, and treatment modality for POPF. Moreover, the postoperative fluid collection (POFC) including its location, size, and clinical impact was assessed during follow-up on the basis of CT images. Patients with no postoperative follow-up CT scans were excluded from the study.

Operative techniques

Pancreatic transection was performed with either 2 types of stapler or with a scalpel and a hand-sewn suture of the pancreatic remnant. The transection level was determined according to tumor location and size, which was classified into the following 4 types in this study: the left side of the gastroduodenal artery, superior mesenteric vein, left border of the aorta, and far distal side of the pancreas.

Reinforcement of closure of the pancreatic stump was performed in the cases with nonstapler closure of the pancreatic remnant, and a very thick pancreas, which are associated with an increased risk of POPF. Fibrin sealant was always applied to the pancreatic stump. TachoSil (Nycomed, Linz, Austria) or Neoveil (Gunze Ltd., Osaka, Japan) was selectively applied to decrease the occurrence of POPF. A surgical drain was always placed intraoperatively. A 10-mm silastic drain was intraoperatively placed and anchored onto the pancreatic stump via the left subphrenic space.

Postoperative management

A regular diet was started on postoperative day 2 or 3. Abdominal CT scans were performed on postoperative days 4–7 to exclude postoperative complications such as POFC and to determine whether to remove the surgical drain. The removal of the surgical drain was delayed until the daily amount of fluid decreased below 10 mL in patients with POFC and well-functioning surgical drains or in those without POFC but high drain amylase levels. An interventional procedure such as surgical drain repositioning or insertion of a new percutaneous drainage (PCD) catheter was performed in patients with POFC who had an ineffective surgical drain and associated leukocytosis, symptoms, or fever. Endoscopic aspiration of pseudocyst or cystogastrostomy was performed only when a percutaneous approach was not feasible or had failed. The drain was removed immediately after CT scan in patients without POFC, and those with POFC who did not have any associated clinical impact.

After discharge, a follow-up abdominal CT scan was performed after 3, 6, and 12 months. Additional CT scans were selectively performed 1 month after discharge in patients with POPF, and those with POFC requiring specific treatment.

Definition of POPF

The diagnosis of pancreatic fistula was determined according to the criteria established by the International Study Group on Pancreatic Fistula (ISGPF) [4]. Pancreatic fistulas are classified by the ISGPF and the Clavien-Dindo classification [5]. In patients with peripancreatic fluid collection and an ineffective drain making the drain amylase levels unreliable, the ISGPF criteria were not applicable. Therefore, these patients were classified as having POFC without evidence of POPF, and their clinical course was investigated.

Measurement of the pancreatic thickness and POFC

Contrast-enhanced, dynamic multidetector CT studies with a 3-mm thickness interval were performed preoperatively and postoperatively. The size of the main pancreatic duct and the pancreatic thickness of the transection site were measured preoperatively on axial CT images during the late arterial phase. The transection line was estimated based on postoperative CT images. The size of POFC was defined as the longest diameter of the peripancreatic fluid collection based on the postoperative CT images at 7 days, and at 1, 3, 6, and 12 months, in order to determine the POFC changes.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA). The chi-square test was used to analyze differences between groups. Univariate and multivariate logistic regression analyses were used to identify predictive factors for the development of POPF and POFC. A P-value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Among the 264 patients with a mean age of 55.8 ± 13.7 years, cystic neoplasms were the most common (n = 130), followed by pancreatic cancer (n = 83), and neuroendocrine tumors (n

= 34). Laparoscopy was performed in 106 cases (Table 1). The following complications other than POPF were detected in 11 patients: pleural effusion (n = 3), wound complication (n = 2), pneumonia (n = 2), deep vein thrombosis (n = 2), acute pyelonephritis (n = 1), and immediate postoperative bleeding (n = 1).

POFC and pancreatic fistula

Clinically relevant POPFs were identified in 72 patients (27.3%). A surgical drain was placed and anchored in all patients intraoperatively; however, only 33 of the drains remained on the pancreatic stump to ensure effective drainage of the POPF or POFC. Antibiotics were used in 46 patients (17.4%). PCDs were performed in 36 cases (13.6%), as follows: repositioning of a previously inserted surgical drain (n = 8); and insertion of a new catheter (n = 28). Two of the seven cases of endoscopic internal drainage were performed after readmission in the conservatively treated patients, during the initial admission period.

Table 1. Patient characteristics (n = 264)

Parameter	Value
Age (yr)	55.8 ± 13.7
Sex, male:female	116:148
Diagnosis	
Pancreatic cancer	83 (31.4)
Intraductal papillary mucinous neoplasm	48 (18.2)
Neuroendocrine tumor	34 (12.9)
Mucinous cystic neoplasm	33 (12.5)
Solid pseudopapillary neoplasm	31 (11.7)
Serous cystic neoplasm	18 (6.8)
Others[a)]	17 (6.4)
Tumor size (cm)	3.7 ± 2.4
Soft pancreatic texture	179 (67.8)
Pancreatic stump thickness (mm)	17.4 ± 4.9
Main pancreatic duct diameter (mm)	2.1 ± 2.0
Operation method	
Distal pancreatectomy (DP)	105 (39.8)
Laparoscopic DP	83 (31.4)
Subtotal pancreatectomy	40 (15.2)
Spleen preserving DP (SPDP)	13 (4.9)
Laparoscopic SPDP	23 (8.7)
Stapler closure	173 (65.5)
Level of transection	
Gastroduodenal artery	40 (15.2)
Superior mesenteric vein	104 (39.4)
Left border of aorta	64 (24.2)
Far distal side	56 (21.2)
Estimated blood loss (mL)	274.4 ± 268.8
Operative time (min)	163.5 ± 60.6

Values are presented as mean ± standard deviation or number (%).
[a)]Pseudocyst, abdominal fibromatosis, metastatic renal cell carcinoma, metastatic lung cancer, pancreatic intraepithelial neoplasm.

The mean hospital stay for all patients was 11.2 ± 7.2 days, and the rate of readmission was 3.8 (Table 2).

Outcomes of interventional procedures

There were 4 cases of failure of the percutaneous procedure, representing a failure rate of 10.0. Spontaneous regressions were observed in 2 cases; however, 1 patient underwent endoscopic cystogastrostomy, and the other patient was readmitted for endoscopic insertion of a retrograde pancreatic duct stent, after the initial discharge.

Natural course of POPF and POFC

Postoperative CT scans were performed in all patients after 7 days. The follow-up CT scans performed after 1 month (n = 55), 3 months (n = 262), 6 months (n = 245), and 12 months (n = 230) were reviewed. The natural course after distal pancreatectomy is summarized in Fig. 1. The cases of POPF were classified as POPF without POFC (n = 15) and POPF with POFC (n = 74). Ten of the 15 cases of POPF without POFC, prolonged drainage defined as drain placement for ≥10 days were required. A nonsymptomatic, small pseudocyst newly appeared on the pancreatic stump in 10 of these 15 patients during 1-year follow-up; however, none of these patients required additional treatment.

Table 2. Postoperative outcomes (n = 264)

Parameter	Value
Pancreatic fistula	
ISGPF classification	
Grade A	17 (6.4)
Grade B	72 (27.3)
Grade C	0 (0)
Clavien-Dindo classification	
Grade I	17 (6.4)
Grade II	32 (12.1)
Grade IIIa	40 (15.1)
Grade IIIb–V	0 (0)
Surgical drain on pancreatic stump	87 (33.0)
Prolonged drainage	18 (20.7)
Replacement to PCD	8 (9.2)
Duration of drainage (day)	13.4 ± 14.2
Intravenous antibiotics	46 (17.4)
Intervention	40 (15.1)
External drainage (PCD)	36 (13.6)
Internal drainage (endoscopic cystogastrostomy, aspiration)	7 (2.7)
Both	3 (1.1)
Size of POFC which required intervention (mm)	57.7 ± 23.6
Length of hospital stay (day)	11.2 ± 7.2
Readmission	10 (3.8)

Values are presented as number (%) or mean ± standard deviation.
ISGPF, International Study Group of Pancreatic Fistula; PCD, percutaneous drainage; POFC, postoperative fluid collection.

Classification	Initial Treatment	n = 264
POPF without POFC (n = 15)	None	5 (33.3%)
	Prolonged use of surgical drain	10 (66.7%)
POPF with POFC (n = 74)	None	14 (18.9%)
	Antibiotics	43 (58.1%)
	Prolonged use of surgical drain	19 (25.7%)
	PCD	36 (48.6%)
	Cystogastrostomy	4 (5.4%)
	EUS-guided aspiration	1 (0.5%)
POFC without evidence of POPF (n =117)	None	114 (97.4%)
	Antibiotics	2 (1.7%)
	PCD[a]	1 (0.8%)

POPF without POFC	n = 15
Newly appeared silent pseudocyst[d]	10 (66.7%)

POFC without management[b]	n = 128
Spontaneous complete regression	119 (93.0%)
Remnant silent pseudocyst[c]	7 (5.5%)
Endoscopic cystogastrostomy due to symptom	2 (1.6%)

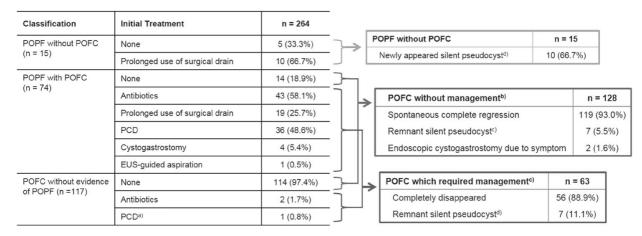| POFC which required management[c]	n = 63
Completely disappeared	56 (88.9%)
Remnant silent pseudocyst[d]	7 (11.1%)

Fig. 1. The natural course of the postoperative pancreatic fistula (POPF) and postoperative fluid collection (POFC) after distal pancreatectomy. PCD, percutaneous drainage; EUS, endoscopic ultrasonography. [a]PCD was performed in patients who developed hematomas. [b]Clavien-Dindo classification 0 and I. [c]Clavien-Dindo classification II–V. [d]A "Silent pseudocyst" is defined as a small nonsymptomatic pseudocsyt, which was present at the pancreas resection margin until the end of follow-up.
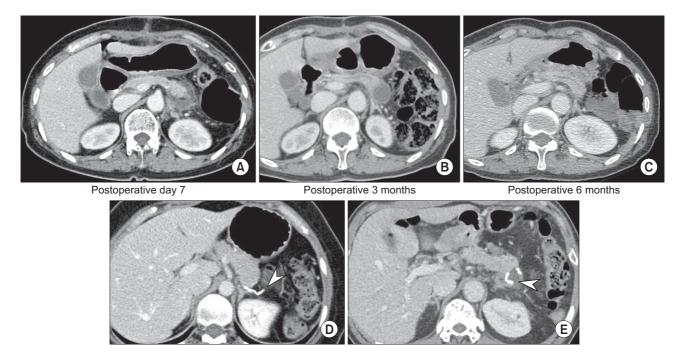

Postoperative day 7 Postoperative 3 months Postoperative 6 months

Fig. 2. Postoperative CT findings after distal pancreatectomy. (A-C) Pseudocyst formation. (A) Postoperative fluid collection (POFC) is initially dispersed around the pancreatic stump. (B, C) The fluid collection typically became a round-shaped pseudocyst during follow-up. (D-E) Stapler dislocation. Stapler dislocation (arrows) was observed in 23 (12.0%) of 191 patients with POFC.

POFC was detected in 191 cases (72.3%). POPF-related POFC and POFC without evidence of POPF were detected in 74 cases (38.7%) and 117 cases (61.3%), respectively. Among the 128 patients (67.0%) who were simply monitored, spontaneous complete regression of the POFC was observed in 119 patients (93.0%). A remnant and silent pseudocyst was found in 7 patients (5.5%).

Seven (11.1%) of the 63 patients who required POFC manage-ment including antibiotics, prolonged use of the surgical drain, PCD, and an endoscopic procedure had a remnant silent pseudocsyt and did not undergo an additional procedure during the follow-up period.

Of the 206 patients with POPF or POFC, only 2 patients underwent endoscopic cystogastrostomy during follow-up because of postprandial discomfort, while the other 204 patients showed spontaneous regression or a remnant, small,

nonsymptomatic pseudocyst at the resection margin (Fig. 1).

As shown in Fig. 2A-C, fluid collections are initially dispersed around the pancreatic stump. During follow-up, the fluid collection typically became a round-shaped pseudocyst. Among the 63 patients with POFC who required treatment (ISGPF grade B), remnant pseudocysts at the pancreatic stump without any clinical impact were observed in seven cases (Fig. 1). Stapler dislocation (Fig. 2D, E) was observed in 23 (12.0) of 191 patients with POFC.

Predictive factor of POPF and POFC

Clinically relevant POPFs occurred more frequently in patients who underwent procedures with a thicker pancreas transection plane (16.8 mm *vs.* 19.3 mm, P < 0.001). POFC also occurred more frequently in patients with increased pancreas stump thickness (14.6 mm *vs.* 18.6 mm P < 0.001), and in those who underwent procedures where the pancreatic transection

plane was more distal than the superior mesenteric vein (P = 0.006). There was no difference in the rate of POPF formation or POFC according to the original disease (Tables 3, 4). The receiver operating characteristics (ROC) curve for POPF showed that the area under the ROC curve was greatest at a cutoff value of 17.3 mm. In total, 49.6 had a stump thickness ≥17.3 mm. For POFC, the cutoff value of stump thickness by ROC curve analysis was 16.0 mm, and 161 patients (61.0%) had a stump thickness ≥16.0 mm. Only thick pancreatic stumps increased the risk of clinically relevant POPF (≥17.3 mm; odds ratio [OR], 3.979; P = 0.002) and the occurrence of POFC (≥ 16.0 mm; OR, 7.574; P < 0.001) in multivariate analysis (Table 5).

DISCUSSION

POPF is one of the most common and clinically relevant complications after pancreatectomy, occurring in 3–34 of cases

Table 3. Predictive factors of clinically relevant POPF

Variable	No, grade A (n = 192)	Grades B, C (n = 72)	P-value
Age (yr)	56.4 ± 14.4	54.3 ± 11.5	0.273
Sex, male:female	78:114	38:34	0.095
Diagnosis			0.195
Cystic tumor	90 (46.9)	40 (55.6)	
Pancreatic cancer	67 (34.9)	16 (22.2)	
Neuroendocrine tumor	22 (11.5)	12 (16.7)	
Others	13 (6.8)	4 (5.6)	
Malignant pathology	73 (38.0)	19 (26.4)	0.083
Soft pancreatic texture	131 (74.0)	48 (73.8)	0.977
Pancreatic stump thickness (mm)	16.8 ± 4.8	19.3 ± 4.9	<0.001
Pancreatic stump thickness (mm)			
<17.3	51 (26.6)	6 (8.3)	0.001
≥17.3	141 (73.4)	66 (91.7)	
Pancreatic duct diameter (mm)	2.3 ± 2.3	1.6 ± 0.8	0.064
Level of transection (GDA–SMV:aorta–far distal)	110:82	34:38	0.166
Laparoscopic operation	108 (56.3)	38 (52.8)	0.677
Stapler closure	125 (65.1)	48 (66.7)	0.885

Values are presented as mean ± standard deviation or number (%). POPF, postoperative pancreatic fistula; GDA, gastroduodenal artery; SMV, superior mesenteric vein.

Table 4. Predictive factors of POFC

Variable	No POFC (n = 73)	POFC (n = 191)	P-value
Age (yr)	57.1 ± 13.9	55.3 ± 13.6	0.339
Sex, male:female	30:43	86:105	0.582
Diagnosis			0.418
Cystic tumor	36 (49.3)	94 (49.2)	
Pancreatic cancer	27 (37.0)	56 (29.3)	
Neuroendocrine tumor	6 (8.2)	28 (14.7)	
Others	4 (5.5)	13 (6.8)	
Malignant pathology	31 (42.5)	61 (31.9)	0.114
Soft pancreatic texture	41 (65.1)	138 (77.1)	0.068
Pancreatic stump thickness (mm)	14.6 ± 4.3	18.6 ± 4.7	<0.001
Pancreatic stump thickness (mm)			
<16.0	26 (35.6)	13 (6.8)	< 0.001
≥16.0	47 (64.4)	178 (93.2)	
Pancreatic duct diameter (mm)	2.2 ± 1.7	2.1 ± 2.1	0.779
Level of transection (GDA–SMV:aorta–far distal)	50:23	94:97	0.006
Laparoscopic operation	46 (63.0)	100 (52.4)	0.130
Stapler closure	41 (56.2)	132 (69.1)	0.060

Values are presented as mean ± standard deviation or number (%). POPF, postoperative pancreatic fistula; GDA, gastroduodenal artery; SMV, superior mesenteric vein.

Table 5. Multivariate analysis of risk factors for clinically relevant POPF and POFC

	Clinically relevant POPF			POFC		
	Odds ratio	95 CI	P-value	Odds ratio	95 CI	P-value
Pancreatic stump thickness[a]	3.979	1.626–9.937	0.002	7.574	3.616–15.864	<0.001

POPF, postoperative pancreatic fistula; POFC, postoperative fluid collection; CI, confidence interval.
[a]Cutoff value for clinically relevant POPF and POFC were 17.3 mm and 16.0 mm, respectively.

[6-9]. Some aspects of POPF management including the optimal drainage of the remnant pancreas and the technique for closure of the pancreatic stump after distal pancreatectomy remain controversial [2].

With regard to the use of abdominal drains after pancreato-duodenectomy, the use of selective drainage and early drain removal is currently recommended in low-risk patients [10,11]. Although a retrospective study reported that drainage did not reduce morbidity or the need for therapeutic intervention [12], and a meta-analysis reported that the routine use of abdominal drains increases the risk of major complications after distal pancreatectomy [13-15], there are currently limited data regarding distal pancreatectomy. Moreover, no studies have investigated the long-term radiological changes and clinical impact associated with POPF or POFC after distal pancreatectomy to assist in determining the optimal manage-ment of patients after distal pancreatectomy regardless of widely performed postoperative surveillance using imaging modalities. Therefore, serial CT scans were analyzed to eval-uate the natural course of the POPF and POFC after distal pan-createctomy in the present study.

The review of the CT images showed that only 33 of the intraoperatively placed abdominal drains remained on the stump of the remnant pancreas despite the efforts to prevent its displacement. Among those, adequate drainage was obtained by prolonged use of surgical drain in 20.7, which is comparable to the previously reported rate of 18 [16]. Among 72 cases of clinically relevant POPF, therapeutic interventions were per-formed in 40 patients (55.6%) and conservative management was successful in 32 (44.4%).

Several aggressive strategies have been previously reported in terms of the technique used for the closure of the pancreatic stump after distal pancreatectomy to reduce POPF. Preoperative endoscopic sphincterotomy and stenting from a German study [17] were reported as feasible and safe, however, these results were not reproducible in a subsequent randomized controlled trial [18]. Isolated Roux-en-Y anastomosis of the pancreatic stump after distal pancreatectomy [19,20], another aggressive strategies adopted in several centers. However, clinical impact of pancreatic occlusion failure after distal pan-createctomy is a milder than that of pancreatic anastomotic failure after pancreatoduodenectomy, because the pancreatic juice is not activated [3]. A previous study reported that cultures were positive in 74 and 31 of fluid collections after pancreatoduodenectomy and distal pancreatectomy, respec-tively [16]. In this context, several studies report that POPF can be managed conservatively after conventional distal pan-createctomy [9,21]. The reported success rate of nonoperative management including antibiotics, supplemental nutrition, somatostatin analogues, and adequate drainage ranges from 92 [22] to 95 [21].

Similarly, the most severe complication observed in this study was classified as grade 3A. Of the 128 patients with POFC without management, only 2 patients (1.6%) required therapeutic intervention, while the other 119 patients (93.0%) showed spontaneous regression or a remnant, small, nonsymp-tomatic pseudocyst at the resection margin which could raise question regarding the necessity of the routine placement of intraoperative abdominal drain.

The only predictive factor of POPF and POFC in this study was a thickness of the pancreatic stump. In patients with a thickness less than 17.3 mm, clinically relevant POPF occurred only in 6 patients (2.3%) among 264 patients. Among the 18 patients with prolonged use of surgical drain, 16 patients had thickness more than 17.3 mm. POFC occurred in 13 cases (4.5%) when thickness was less than 16.0 mm. Therefore, surgical drain could be selectively indwelled in patients with a thick pancreas, however, definitive evidence regarding the necessity and indication usage of surgical drain in the distal pancreatectomy is needed.

This study provides unique information regarding the natural course after distal pancreatectomy based on regular follow-up imaging and clinical data. However, this study is limited in that several types of surgery, transection methods, reinforcement methods of the pancreatic stump were included. Comparison of outcomes between patients with and without a drain, according to POPF risk, was not shown because of the retrospective design of the study and definitive evidence regarding the necessity of surgical drain after distal pancreatectomy is needed. In conclusion, intraoperative abdominal drainage insertion could be selectively indwelled in patients with a thickness of pancreas ≥17.3 mm. Since radiologically-proven POFC after distal pancreatecomy showed a 93.0 rate of spontaneous regression, POFC without signs of infection can be safely monitored.

CONFLICTS OF INTEREST

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

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