ISSN 2471-142X

PANCREAS
OpenJournal

Openventio
PUBLISHERS

Systematic Review

Management of Refractory Pancreatic Fistula: A Review of Literature

Hassan Aziz, MD[1*]; Shahzaib Ahmad, MBBS[2]; Faisal S. Jehan, MD[3]; Muhammad W. Saif, MD, MBBS[4]; Syed Ahmad, MD[5]

[1]*University of Iowa Hospitals and Clinics, Iowa City, IA, USA*
[2]*King Edward Medical University, Lahore, Pakistan*
[3]*Westchester Medical Center, New York, NY, USA*
[4]*Orlando Health, Orlando, FL, USA*
[5]*University of Cincinnati Medical Center, Cincinnati, OH, USA*

[*]***Corresponding author***
Hassan Aziz, MD
Assistant Professor, Department of Transplant and Hepatobiliary Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA; Tel. (319) 356-1137;
E-mail: Hassan-aziz@uiowa.edu

Article information

Received: July 21st, 2022; **Revised:** August 17th, 2022; **Accepted:** August 18th, 2022; **Published:** August 25th, 2022

Cite this article

Aziz H, Ahmad S, Jehan FS, Saif MW, Ahmad S. Management of refractory pancreatic fistula: A review of literature. *Pancreas Open J.* 2022; 5(2): 23-27.
doi: 10.17140/POJ-5-117

ABSTRACT

Background

Chronic non-healing or refractory pancreatic fistulae are rare complications of pancreatic surgery (pancreaticoduodenectomy, distal pancreatectomy) or pancreatitis.

Materials and Methods

We conducted a thorough literature search of electronic databases such as PubMed, Google Scholar, BioMed Central, and Cochrane Library using the keywords and medical subject headings (MeSH) terms "*chronic pancreatic fistula*", "*post-operative fistula*", "*fistula management*" and "*refractory pancreatic fistula*". The purpose of this review is to evaluate the management options for refractory pancreatic fistula (PF).

Results

Literature reveals that refractory pancreatic fistulae have been managed by techniques like endoscopic ultrasound (EUS)-guided techniques like transmural puncture by clamping, puncture of the fistula tract, transmural placement of pigtail stent, and EUS-guided pancreaticogastrostomy. Other techniques are postoperative endoscopic pancreatic stent placement in Grade C pancreatic fistula, intestinal decompression catheter insertion into the jejunum, embedding fistulojejunostomy, and fistulojejunostomy.

Conclusion

In conclusion, embedding fistulojejunostomy, EUS-guided transmural puncture by clamping, and EUS-guided transmural placement of pigtail stent are effective techniques for the management of refractory pancreatic fistulae. Yet further studies in a larger population are recommended.

Keywords

Chronic pancreatic fistula; Pancreatectomy; Pancreaticoduodenectomy; Fistutolojejunostomy; Post-operative pancreatic fistula.

INTRODUCTION

In 2005, the International Study Group of Pancreatic Fistula (ISGPF) defined pancreatic fistula (PF) as an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid.[1] The diagnostic criteria is serum amylase levels greater than three times the normal values starting from the third post-operative day.[2] The modification in the ISGPF definition of PF in 2016 led to "clinically relevant" grading; Grade A was more appropriately grouped as an asymptomatic pancreatic leak. Grade B included those cases requiring interventional procedures for fistula management, usually with persistent drainage after three weeks and signs of infection.[3] Grade C is the most severe form, with an incidence of 15% of the total PF after pancreaticoduodenectomy and mortality of 35%, and is characterized by the need for reoperation, organ failure, and sepsis.[4,5]

Post-operative pancreatic fistula is seen frequently, causing morbidity in up to 41% of cases of pancreatic resection surgery.[6] Despite a constellation of management options, the persistence of the pancreatic fistula is encountered in some cases. Although refractory PF is rare, it is associated with a high morbidity. The recurrence rate is higher in PF caused to pancreatic duct

Pancreas Open J. 2022; 5(2): 23-27. doi: 10.17140/POJ-5-117

disruption (PD). The recurrence rate of pancreatic fistulae is up to 30% in patients with partial PD undergoing endoprosthesis. The incidence of recurrent PF ranges from 67-80% in patients with complete PD.[7] Refractory PF causes an abdominal abscess, hemorrhage, pancreatic pseudocyst, serum electrolyte imbalance, body fluid loss, malnutrition, and infection.[8]

The definition of refractory PF fistula is somewhat vague. PF usually spontaneously heals in most cases, but they persist or recur in a few cases. Studies show that 50-80% of all types of PF resolve within 4-6-weeks.[9] If medical or endoscopic interventions fail to correct PF beyond six-weeks, it is referred to as refractory PF.[10] The purpose of this review is to evaluate the management options for refractory PF.

MATERIALS AND METHODS

We conducted a thorough literature search of electronic databases such as PubMed, Google Scholar, BioMed Central, and Cochrane Library using the keywords and medical subject headings (MeSH) terms "*Chronic pancreatic fistula*", "*post-operative fistula*", "*fistula management*" and "*refractory pancreatic fistula*". The literature search yielded research studies related to refractory pancreatic fistulae, and we screened those encompassing management options for refractory pancreatic fistulae. No language compulsions were followed in study selection. The primary outcome in the included studies was the resolution of the persistent pancreatic fistula.

RESULTS

A total of 7 studies were retrieved from the above-mentioned search. The studies highlight the different management options for refractory PF. Operative choices depend on the ductal anatomy and history of previous resections. Endoscopic approaches may be attempted first as they carry less morbidity than surgical approaches (Table 1). The paragraphs below highlight the management options for such patients, starting from medical management to endoscopic options, and finally, surgical options.

Medical Management of Refractory Pancreatic Fistula

Although conservative and medical management plays a limited role in refractory PF cases, these measures are employed for symptomatic management while the surgeon plans the intervention. These measures include reduction of pancreatic stimulation by maintaining the patient's nil by mouth (NPO) and nasojejunal feeding to correct malnutrition. In addition, enteral nutrition is associated with a lower incidence of infection, higher 30-day fistula closure rates, and shorter time to closure of the post-operative pancreatic fistula than total parenteral nutrition.

Somatostatin analogs, such as octreotide (100 µg subcutaneously three times a day), can be used in patients with high-output PFs or those with electrolyte abnormalities or skin breakdown. Somatostatin preparations may effectively reduce fistula output, but not fistula closure rate. In a 2012 meta-analysis of seven randomized trials that included 297 patients, of which 102 had pancreatic fistulae, closure rates were not significantly higher in patients treated with somatostatin analogs than in controls.[6]

Endoscopic ultrasound-guided transmural puncture by clamping: Partial pancreatic duct disruption responds well to transpapillary endoprosthesis placement, facilitating the drainage of pancreatic secretions by reducing the transpapillary pressure gradient. However, this technique seldom exists in complete pancreatic duct disruption settings, where the pancreatic tissue proximal to the disruption continues to drain secretions, forming a PCD despite endoprosthesis placement. It forms a complicated fistulous tract that is refractory to conservative treatment. EUS-guided transmural puncture using a clamp has been reported to be an effective endoscopic correction technique in such cases. Rana et al[8] attempted to create a pancreatic fluid collection (PFC) by clamping the disrupted duct with a catheter for almost 48 hrs Subsequently. The PFC was drained using EUS-guided transmural drainage with a 19-gauge needle. The fistulous tract was dilated with a 4 mm balloon when the PFC was >4 cm, and 3 or 5 cm double pigtail stents were placed. For PFC≤4 cm, the transmural tract was kept, and a double-pigtail stent was positioned. When performed on five patients, it was successful in four patients, with a cure rate of 80%.

Endoscopic ultrasound-guided puncture of fistula tract: When abutting the pigtail catheter with the gastroduodenal lumen is impossible, direct drainage of the PFC must be performed. Sometimes, the pigtail catheter may not be adjacent to the enteric lumen, depending on the anatomy or site of pancreatic duct disruption.

Table 1. *Success Rates of Different Surgical Interventions Done in Refractory Pancreatic Fistula*

Study	Year	Country	Management Technique	Number of Participants	Success Rate
Rana et al[8]	2019	India	EUS-guided transmural puncture by clamping	5	80%
			EUS-guided puncture of fistula tract	1	100%
			EUS-guided transmural placement of Pigtail Stent	3	100%
			EUS-Guided Pancreaticogastrostomy	4	100%
Luo et al[9]	2018	Taiwan	Embedding Fistulojejunostomy	5	80%
Calu et al[11]	2012	Romania	Fistulojejunostomy	1	100%
Hama et al[10]	2011	Japan	Intestinal decompression catheter insertion into jejunum	1	100%
Grobmyer et al[9]	2009	USA	Postoperative endoscopic pancreatic stent placement in Grade C PF	8	62.5%
Nair et al[12]	2007	USA	Fistulojejunostomy	8	62.5%

USA- United States of America, PF: Pancreatic Fistula, EUS: Endoscopic Ultrasound

Pancreas Open J. 2022; 5(2): 23-27. doi: 10.17140/POJ-5-117

The disrupted duct was localized directly using a linear echoendoscope and drained using a 19-gauge needle. The transmural tract may be dilated, and a plastic stent may be placed. One patient with refractory PF was successfully treated with a direct puncture of the fistula tract.[13]

Endoscopic ultrasound-guided transmural placement of pigtail stent through gastric opening of trans-gastric post-percutaneous drainage: Disconnected pancreatic duct syndrome (DPDS) poses a considerable challenge in its management owing to the development of refractory PF that further complicates post-percutaneous drainage (PCD). The endoscopic transmural approach is a minimally invasive technique employed to resolve PCD in fistulae resulting from DPDS with draining secretions >50 ml/day. Transmural plastic stents successfully managed walled-off necrosis and DPDS, ensuring enteral drainage of secretions, thus preventing pancreatic fluid collection. The absence of pancreatic fluid collection is directly related to the minimal chance of developing recurrent fistulae. However, surgical management is required in cases of refractory PF. EUS-guided transmural pigtail stent placement is effective, even in refractory cases that require open surgery. Rana et al8 described the formation of the PFC by instilling 100-300 ml of water in PCD catheters. However, if this technique failed, the pigtail catheter was adjoined with the gastroduodenal lumen, and then upon dilatation of the fistulous tract, a 3 or 5 cm pigtail stent was placed. This method was successful in three patients, and all the patients were completely cured with no complications.

Endoscopic ultrasound-guided pancreaticogastrostomy: Conventional endoscopic transpapillary drainage catheters may be insufficient for some patients. EUS-guided pancreaticogastrostomy is an endoscopic technique often employed to correct refractory PF and dilated pancreatic duct drainage in symptomatic patients in whom drainage is impossible.

Fluoroscopy with contrast media is used to augment endoscopic findings of disrupted pancreatic duct anatomy. It involves transgastric endosonography to visualize the fistulous tract. A transgastric puncture of the pancreatic duct through the fibrous parenchyma was performed using a 19-gauge needle. A 0.035-inch guidewire was inserted through the needle into the duct in the tail direction. A high-frequency ring knife was pushed forward over the guidewire up to the gastric wall to perform gastropancreaticostomy with the help of a ring knife and concentric cauterization. A stent was placed 1.5 2 cm above the mucosa of the gastric wall within the gastric cavity. This allows the direct drainage of pancreatic secretions into the gastric lumen. Research suggests that EUS-guided pancreaticogastrostomy may be a safe procedure; however, further investigations must be performed to evaluate patient selection for the procedure. Rana et al[8] demonstrated that EUS-guided pancreaticogastrostomy might be utilized in treating refractory PF when other EUD-guided techniques such as clamping, transmural pigtail stent placement, and fistula puncture failed to resolve PF. They successfully treated 4 patients using this technique, and the success rate was 100% and the healing time ranged from 5-21-days.

Post-operative endoscopic pancreatic stent placement: A refractory grade C pancreatic fistula is managed with post-operative endoscopic pancreatic stent placement. Grobmyer et al[9] confirmed extravasation of contrast from the distal end of the pancreatic duct using endoscopic retrograde cholangiopancreatography (ERCP). Pancreatic stents were placed in eight patients at a median of 48-days post-operatively and left for 47-days. Before stent removal, ERCP demonstrated closure of the pancreatic fistula. The median time to complete resolution of the fistula was 41-days after stent placement. This technique was successful in 62.5% of the cases after the first intervention, and the rest underwent transgastric and computed tomography (CT) drainage, after which the cure rate was 100%. Thus, refractory grade C pancreatic fistulae can be secured using this technique.

Intestinal decompression catheter insertion to jejunum: Refractory PF can also be managed by placing an intestinal decompression catheter (IDC). An anastomosis is made between the fistulous tract and jejunum using an IDC. This procedure can be performed under local anesthesia. Hama et al[10] successfully placed an IDC as an alternative, uneventful, and safe technique for refractory fistula management.

Embedding fistulojejunostomy: Embedding fistulojejunostomy (EFJ) is an innovation in contemporary fistulojejunostomy procedures. In contrast to fistulojejunostomy, EFJ involves detachment of the fistula tract from the external site and its insertion into the jejunal lumen. It does not require direct suturing of the fistula tract into the Roux-n-Y jejunal lumen, as observed in Fistulojejunostomy. Luo et al[14] evaluated EFJ in five patients with refractory PF for ≥30-days. They demonstrated that 80% of patients underwent complete recovery after EFJ when the follow-up from 12-124-months. One patient required surgical correction due to wound infection. EFJ is preferable to Fistulojejunostomy in terms of mean operating time <15 min, minimal blood loss, and shorter hospital stay ≤10-days. The indication for EFJ in refractory PF is a fistula wall thickness of ≥3 mm for more than 3-months.

Fistulojejunostomy: Fistulojejunostomy is one of the most common procedures used for managing refractory external pancreatic fistulae. It involves incision of the fistulous tract from the skin reaching the abdomen and removal of a substantial part of the fistulous tract up to the root of the mesocolon. Fistulojejunostomy was then performed in an end-to-side manner. A single layer of absorbable suture is typically required in this procedure. Calu et al[11] document Fistulojejunostomy as an effective, safe, and fast procedure for intractable external PF with minimal complications, recurrence, or pseudocyst formation. The effectiveness of Fistulojejunostomy is well-pronounced in the surgical management of pancreatic duct disruption that occurs as a complication of necrosectomy done in acute pancreatitis.

Furthermore, when the inflammatory reaction or adhesions hamper the dimensions of the pancreatic remnant, Fistulojejunostomy remains a viable option for surgical correction of refractory that failed non-interventional treatment EUS-guided stunt placement. Nair et al[12] studied the outcomes of fistulojejunostomy in refractory PF in 8 patients from 2003 to 2006. The outcomes were uneventful in 62.5% of the cases.

Pancreas Open J. 2022; 5(2): 23-27. doi: 10.17140/POJ-5-117

Furthermore, the mean hospital stay was 8-days. The average blood loss was 280 ml, but the operating time was 2.5 hrs longer than most endoscopic techniques.

Total pancreatectomy: Research shows that 15% of all pancreatic fistula cases have complications, such as sepsis and life-threatening hemorrhage. In such cases, elective total pancreatectomy is preferable and should be considered. Elective total pancreatectomy is indicated when all other surgical measures fail. It avoids emergency completion of pancreatectomy and is associated with a high mortality rate. It is a non-conservative method that may be seen as a last resort and a desperate measure to eliminate PF.

DISCUSSION

Pancreatic duct disruption may occur because of complications in the surgical management of acute or chronic pancreatitis, trauma, pancreatic neoplasms, and pancreatic resection. A constellation of systemic signs and symptoms are usually observed in external or internal pancreatic fistulae. The most common symptoms are abdominal abscess, hemorrhage, pancreatic pseudocyst, skin erosion, serum electrolyte imbalance, body fluid loss, malnutrition, and infection. Iatrogenic causes remain the most common causes of pancreatic fistula.[12] Post-operative pancreatic fistula (POPF) is frequently observed, causing morbidity in up to 41% of cases of pancreatic resection surgery. Post-operative pancreatitis is a risk factor for fistula development. In addition, a fistula or abscess may serve as a gateway for infection that may extend to the abdominal viscera, which warrants prompt fistula management. Otherwise, pancreatic fistula entails the risk of sepsis, contributing to 1% mortality associated with it.[1] Pancreatic fistula is further stratified into internal pancreatic fistula and external pancreatic fistula. The former is characterized by pancreatic-enteric anastomosis, in which the pancreatic duct system or parenchyma communicates with the abdominal cavity, leading to the spilling of pancreatic secretions.[15]

An external pancreatic fistula is a communication between the pancreas and skin. This first to last usually causes excoriation of the skin. A higher-output external pancreatic fistula drains secretion >200 ml/day while a low-output external pancreatic fistula drains secretions <200 ml/day. Most cases of pancreatic fistulae are self-limiting and negotiated with conservative or supportive management. Biological glue application for external pancreatic fistula, a somatostatin analog, and minimal pancreatic stimulation by total parenteral nutrition, keeping the patient nil per oral (NPO), is an important cornerstone of nonsurgical management. Surgical debridement or open surgery for correcting pancreatic fistula is indicated when signs of infected or sterile pancreatic necrosis, visceral damage, or sepsis are present. Minimally invasive approaches to curtail pancreatic fistula include endoscopic debridement, laparoscopic pancreaticoduodenectomy, and percutaneous CT-guided catheter drainage.[8] Despite the plethora of management options, recurrence of pancreatic fistula is encountered in many cases. The recurrence rate of pancreatic fistula is up to 30% in patients with partial pancreatic duct disruption undergoing an endoprosthesis. At the same time, the incidence of refractory fistula is from 67-80% in patients with complete pancreatic duct disruption.

When patients fail to respond to percutaneous drainage, endoscopic interventions, or other novel techniques, operative intervention is the most viable strategy to eradicate the fistula. It should be emphasized that sufficient time must be allowed for spontaneous closure of the fistula; as stated, spontaneous closure of fistulae can occur at an average of 70-days.[16] Many different operative approaches have been employed. Operative choices depend on the ductal anatomy and history of previous resections.[17] If a patient has had a prior pancreatoduodenectomy, then either a completion pancreatectomy or a revision of the anastomosis can be performed. Many authors have demonstrated substantial morbidity and mortality associated with performing a completion pancreatectomy.[18] This operation is associated with substantive perioperative complications related to the technical challenges associated with reoperation and incurs significant life-long morbidity in the apancreatic state. Distal pancreatectomy can be performed in patients with duct disruption in the body or tail regions. Other novel operative approaches to treat refractory pancreatic fistulae are described in detail in this review article. One of the limitations of the studies available in the review is small sample size. Further studies in a larger population are recommended.

CONCLUSION

Embedding Fistulojejunostomy is a safe technique for managing refractory external pancreatic fistula and is indicated when pancreatic fistula persists for more than 90-days with a wall thickness ≥ 3 mm. EUS-guided pancreaticogastrostomy, and EUS-guided puncture of the fistula tract are alternative techniques for managing refractory PF with variable success rates. Yet further studies in a larger population are recommended.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Bassi C, Dervenis C, Butturini G, International study Group on Pancreatic Fistula Definition, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery.* 2005; 138(1): 8-13. doi: 10.1016/j.surg.2005.05.001

2. Chen BP, Bennett S, Bertens KA, Balaa FK, Martel G. Use and acceptance of the International Study Group for Pancreatic Fistula (ISGPF) definition and criteria in the surgical literature. *HPB (Oxford).* 2018; 20(1): 69-75. doi: 10.1016/j.hpb.2017.08.022

3. Alexakis N, Sutton R, Neoptolemos JP. Surgical treatment of pancreatic fistula. *Dig Surg.* 2004; 21(4): 262-274. doi: 10.1159/000080199

4. Klek S, Sierzega M, Turczynowski L, et al. Enteral and parenteral nutrition in the conservative treatment of pancreatic fistula: A randomized clinical trial. *Gastroenterology.* 2011; 141: 157-163, 163. e1. doi: 10.1053/j.gastro.2011.03.040

5. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of

the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery*. 2017; 161(3): 584-591. doi: 10.1016/j.surg.2016.11.014

6. Gans SL, van Westreenen HL, Kiewiet JJ, et al. Systematic review and meta-analysis of somatostatin analogues for the treatment of pancreatic fistula. *Br J Surg*. 2012; 99: 754-760. doi: 10.1002/bjs.8709

7. Will U. Endoscopic ultrasound-guided pancreaticogastrostomy. *Video Journal and Encyclopedia of GI Endoscopy*. 2013; 1(2): 563-566. doi: 10.1016/S2212-0971(13)70243-7

8. Rana SS, Sharma R, Gupta R. Endoscopic treatment of refractory external pancreatic fistulae with disconnected pancreatic duct syndrome. *Pancreatology*. 2019; 19(4): 608-613. doi: 10.1016/j.pan.2019.05.454

9. Grobmyer SR, Hunt DL, Forsmark CE, Draganov PV, Behrns KE, Hochwald SN. Pancreatic stent placement is associated with resolution of refractory grade C pancreatic fistula after left-sided pancreatectomy. *Am Surg*. 2009; 75(8): 654-657; discussion 657-8. doi: 10.1177/000313480907500804

10. Hama N, Kashiwazaki M, Asukai K, et al. [A case of refractory pancreatic fistula following pancreaticoduodenectomy treated successfully by intestinal decompression catheter insertion to jejunum under local anesthesia]. *Gan To Kagaku Ryoho*. 2011; 38(12): 2027-2029.

11. Calu V, Duţu M, Pârvuleţu R, Miron A. Persistent pancreatic fistula after surgical necrosectomy for severe pancreatitis. *Chirurgia (Bucur)*. 2012; 107(6): 796-801.

12. Nair RR, Lowy AM, McIntyre B, Sussman JJ, Matthews JB, Ahmad SA. Fistulojejunostomy for the management of refractory pancreatic fistula. *Surgery*. 2007; 142(4): 636-642; discussion 642.e1. doi: 10.1016/j.surg.2007.07.019

13. Minami K, Iwasaki E, Itoi T, Hibi T, Kanai T. Successful EUS-guided nondilated pancreatic duct stent placement in patient with refractory pancreatic fistula after pancreaticoduodenectomy. *VideoGIE*. 2017; 2(11): 315-316. doi: 10.1016/j.vgie.2017.07.012

14. Luo SC, Cheng SB, Wu CC, Huang CC, Lin YL, P'eng FK. Embedding fistulojejunostomy: An easy and secure technique for refractory external pancreatic fistula. *Asian J Surg*. 2018; 41(2): 143-147. doi: 10.1016/j.asjsur.2016.09.005

15. Coco D, Leanza S, Guerra F. Total pancreatectomy: Indications, advantages and disadvantages - A Review. *Maedica (Bucur)*. 2019; 14(4): 391-396. doi: 10.26574/maedica.2019.14.4.391

16. Sikora SS, Khare R, Srikanth G, Kumar A, Saxena R, Kapoor VK. External pancreatic fistula as a sequel to management of acute severe necrotizing pancreatitis. *Dig Surg*. 2005; 22: 446-451 ; discussion 452. doi: 10.1159/000091448

17. Cullen J, Sarr M, Ilstrup D. Pancreatic anastomotic leak after pancreaticoduodenectomy: Incidence, significance and management. *Am J Surg*. 1994; 168 (4): 295-298. doi: 10.1016/s0002-9610(05)80151-5

18. Ishikawa O, Ohigashi H, Imaoka S, et al. Concomitant benefit of preoperiative irradiation in preventing pancreas fistula formation after pancreaticoduodenectomy. *Arch Surg*. 1991; 126(7): 885-889. doi: 10.1001/archsurg.1991.01410310095014