

# The Role of Surgical Management in Chronic Pancreatitis in Children: A Position Paper From the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee

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## ABSTRACT

**Objectives:** Chronic pancreatitis (CP) is rare in childhood but impactful because of its high disease burden. There is limited literature regarding the management of CP in children, specifically about the various surgical approaches. Herein, we summarize the current pediatric and adult literature and provide recommendations for the surgical management of CP in children.

**Methods:** The literature review was performed to include the scope of the problem, indications for operation, conventional surgical options as well as total pancreatectomy with islet autotransplantation, and outcomes following operations for CP.

**Results:** Surgery is indicated for children with debilitating CP who have failed maximal medical and endoscopic interventions. Surgical management must be tailored to the patient's unique needs, considering the anatomy and morphology of their disease. A conventional surgical approach (eg, drainage operation, partial resection, combination drainage-resection) may be considered in the presence of significant and uniform pancreatic duct dilation or an inflammatory head mass. Total pancreatectomy with islet autotransplantation is the best surgical option in patients with small duct disease. The presence of genetic risk factors often portends a suboptimal outcome following a conventional operation.

**Conclusions:** The morphology of disease and the presence of genetic risk factors must be considered while determining the optimal surgical approach for children with CP. Surgical outcomes for CP are variable and depend on the type of intervention. A multidisciplinary team approach is needed to assure that the best possible operation is selected for each patient, their recovery is optimized, and their immediate and long-term postoperative needs are well-met.

**Key Words:** chronic pancreatitis, pancreatic surgery, pediatric

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## What Is Known

- Experience with surgical therapies in children with chronic pancreatitis is expanding.
- Recommendations for selection of an appropriate operation are needed.

## What Is New

- Success of a surgical intervention for children with chronic pancreatitis is optimized when surgical decision-making is guided by the anatomy and morphology of disease.
- Conventional operations and total pancreatectomy with islet autotransplantation have associated procedural risks. Their short-term and long-term outcomes should be comprehensively discussed with families ahead of the surgical intervention.

## INTRODUCTION

Although pancreatic disorders in children have been increasingly recognized in recent years, the literature on chronic pancreatitis (CP) in the pediatric population remains limited. CP is characterized by progressive irreversible inflammatory destruction of the gland, leading to parenchymal fibrosis and ductal changes

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with subsequent loss of pancreatic exocrine and endocrine function (1,2). The incidence of CP in children has been estimated at 2 cases per 100,000 persons, and the prevalence has been reported as 5.8 per 100,000 persons (3). Although the incidence is relatively low, the overall disease burden is considerably high, with numerous emergency department visits, hospitalizations, procedures, and interventions (4). There are multiple risk factors for CP in children with genetic causes accounting for the majority of cases followed by obstructive and anatomic causes (5). Other identified risk factors include autoimmune and metabolic risk factors, hypertriglyceridemia, smoking, medications, or alcohol-related (5). Abdominal pain is common in children with CP and correlates with frequent emergency room visits and hospitalizations, dependence on pain medications, absences from school, and significant compromise on quality of life (4,5). In the INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In search for a cuRE) study, approximately 80% of children with CP complained of abdominal pain; pain was constant and requiring opioids in approximately 33% (5). Endocrine and exocrine pancreatic dysfunction are potential sequelae of disease progression.

Varying imaging modalities may be utilized to detect parenchymal changes and ductal abnormalities in the diagnosis of CP (6). Transabdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS) are imaging studies incorporated in the CP work-up with varied sensitivities and specificities (7). Endoscopic retrograde cholangiopancreatography (ERCP) can detect the pancreatic ductal changes of CP and provide a therapeutic approach via dilation and stenting of ductal strictures and removal of obstructing stones. ERCP is being used with increased frequency in the pediatric population with reported complication rates similar to adults (0%–11%) (1,8,9).

The primary goals of management of CP are control of pancreas-associated pain, treatment of exocrine and endocrine pancreatic insufficiency, and treatment of CP-related complications. Adult studies have reported that approximately 50% of CP patients will eventually require an operation for management of pain, complications, or suspicion of associated malignancy (10–12). Although similar data are not available in the pediatric population, surgery does play a role in the management of children with CP who do not have other medical or endoscopic options available. The most common indication for operation in CP is debilitating pain that has failed medical and endoscopic management, with less common indications in children including duodenal or biliary obstruction, pseudocysts, or suspicion of malignancy (13–15). The various surgical options may be divided into 2 categories: conventional operations (ie, drainage procedures, partial resections, and procedures combining drainage and resection); and total pancreatectomy with islet autotransplantation (TPIAT) (13–16). Selection of an operation must take into account anatomic and morphologic features of the pancreas, such as main duct dilation and/or the presence of an inflammatory head mass. The presence of underlying genetic risk factors for pancreatitis may also impact operation. Because of the paucity of literature on operations for CP in children, pediatric management has largely been based on adult data. The goals of this document are to summarize the existing literature regarding the surgical management of CP in children, to provide recommendations for surgical management in children with

CP based on available pediatric and adult data, and to identify knowledge gaps for future studies. Medical and endoscopic management of CP have been covered in 2 separate documents prepared by the Pancreas committee of NASPGHAN (17,18).

## METHODS

The working group involved in the development of this NASPGHAN position article included members of the NASPGHAN Pancreas Committee in early 2019 (M.A.H., K.B., H.B., K.E., R.K., V.M., J.D.N., Z.M.S., A.U.), 1 additional surgeon (A.G.), and 2 additional gastroenterologists (J.A.Q., S.J.S.), under the leadership of the Pancreas Committee chair (S.H.). One pediatric surgeon (J.D.N.) and 1 pediatric gastroenterologist (M.A.H.) led the project, providing global oversight and structure. Subgroups were created to engage in thorough review of the literature regarding the scope of the problem of CP in children, indications for operation in CP, conventional surgical options, total pancreatectomy with islet autotransplantation, and outcomes following operation for CP. Relevant available pediatric and adult literature was reviewed after each subgroup conducted PubMed searches (English literature). Regular email correspondences and telephone calls were conducted between the subgroup members and writing group leaders. Sections were written by each of the subgroups, and assembled into a comprehensive draft by the first and senior authors. The complete draft was circulated to all authors for review and comments before submission for publication. The generation of formal statement recommendations based on the medical literature to guide management by health care providers was not possible because of the relative lack of available publications comparing different surgical approaches in children. In replacement, a management algorithm was designed by the authorship to help guide clinical care of children with CP.

## INDICATIONS AND CONSIDERATIONS FOR OPERATION IN CHRONIC PANCREATITIS

The most common indication for surgical intervention in CP is the persistent pain impacting quality of life that is not adequately relieved by medications or endoscopic approaches. The ultimate goal of operation is to provide pain relief and liberate the patient from opioids, while preserving endocrine and exocrine pancreatic function. There are only a few reports of surgical interventions in children with CP, derived from small cohorts of patients without long-term outcomes. Therefore, it is not known how frequently surgical interventions are utilized or whether certain surgical procedures are indicated over others in children with CP. Overall, it is estimated that up to 50% of patients with CP will require operation during their lifetime (11,12,14,19). In the INSPPIRE cohort, at least 1 pancreatic operation was performed in 39% of children, including longitudinal pancreaticojejunostomy in 14%, partial resection in 1%, and TPIAT in 28% (4). It must be recognized, however, that INSPPIRE is a research consortium, and these findings may not be representative of the overall distribution of clinical cases of CP in children.

Caring for children with CP requires a multidisciplinary approach with a team that consists of pancreatologists, endoscopists, surgeons, radiologists, pain specialists, psychologists, endocrinologists, and nutritionists. The specific operation must be tailored to the anatomy and morphology of pancreatic disease, and not 1 single

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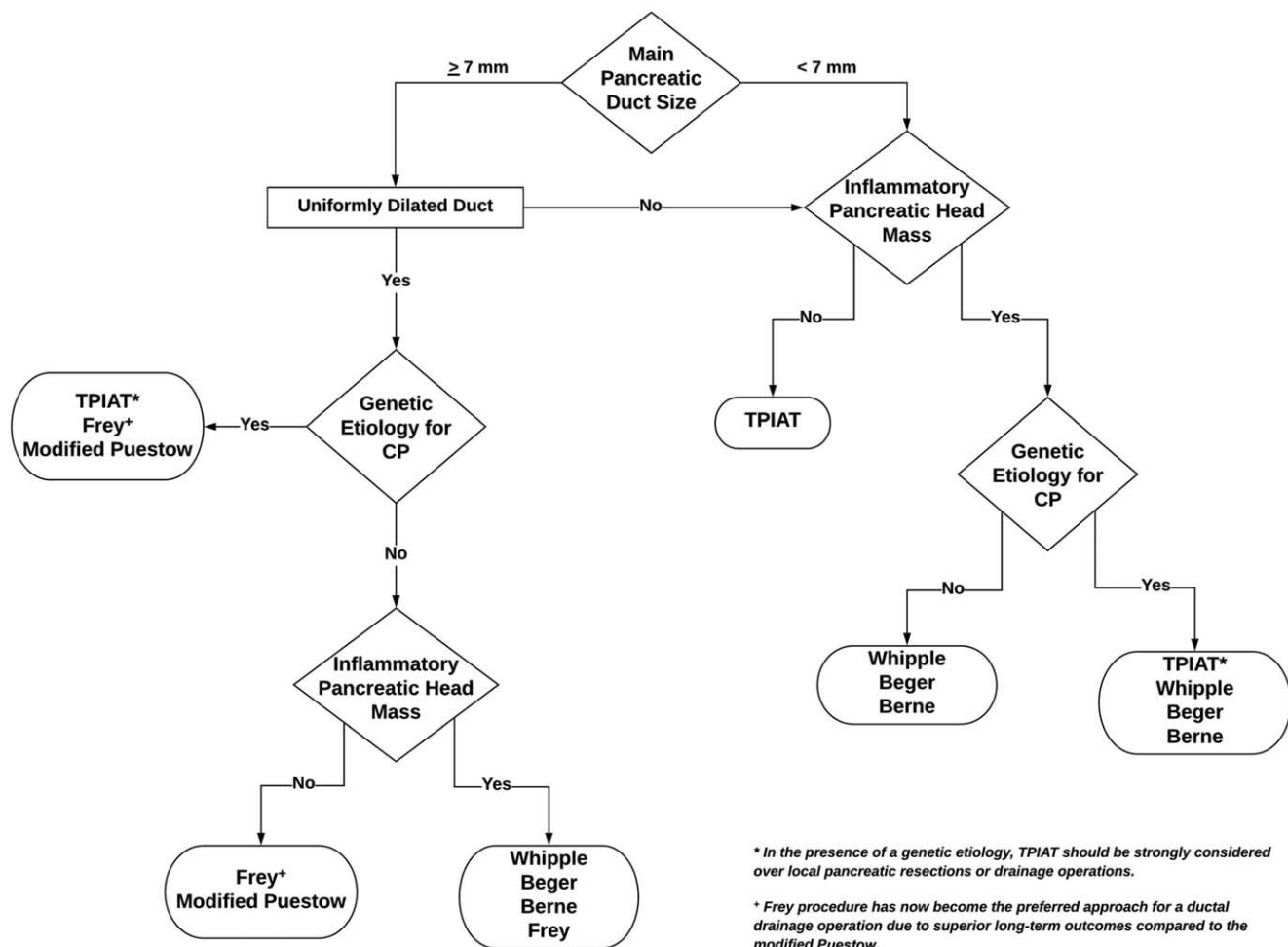
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surgical option can be recommended for every CP patient. Conventional surgical approaches are classified into the following groups: drainage operations to decompress a dilated ductal system, resections to remove a portion of the pancreas (most commonly, an inflammatory mass in the head of the pancreas), or a combination of drainage and resection (eg, duodenum-preserving pancreatic head resections, including Beger procedure, Berne procedure, and Frey procedure). Total pancreatectomy with islet autotransplantation is a surgical option in patients who do not have the anatomy or morphology of disease to consider a drainage operation or partial resection and in patients who have failed previous conventional surgical approaches, or when genetic predispositions are present. In the latter cohort, the total pancreatectomy definitively addresses the underlying “field defect” of a genetic risk factor. We have developed an algorithm to determine the optimal surgical approach for children with CP that has failed all medical or endoscopic approaches (Fig. 1).

## Rationale for Considering Conventional Operations

Although sphincterotomy, stone extraction, and stricture dilation are feasible in the pediatric age group through ERCP, they may not resolve the poor drainage throughout the entire pancreatic duct, thus the argument for surgical drainage operations. Drainage operations were developed with the premise that the pain in CP is because of pancreatic ductal hypertension, and adequate drainage of “large duct disease” would decompress the duct and relieve the pain (20). Historically, the most commonly performed drainage operation has been the Partington-Rochelle “modified Puestow procedure” (longitudinal pancreaticojejunostomy). A more recent modification to this operation, however, has been the Frey procedure, which adds additional limited coring out of the pancreatic head to improve decompression of the duct in the head of the

### Algorithm for Operative Decision Making for Chronic Pancreatitis



**FIGURE 1.** Algorithm for the selection of the most appropriate operation for debilitating chronic pancreatitis, based on anatomic and morphologic abnormalities of the pancreas. Underlying etiology of pancreatitis should be taken into consideration, as emerging evidence suggests that children with genetic risk factors are more likely to have suboptimal outcomes following conventional operation, compared with total pancreatectomy with islet autotransplantation (TPIAT).

pancreas and uncinate tributaries and to remove the portion of the gland at high risk of progressive inflammatory response (21–25). In many experienced pancreas centers, the Frey procedure has become the preferred approach for a ductal drainage operation because of potentially superior longer term outcomes (26).

Although more common in adult CP patients, a cohort of children with CP may present with inflammatory enlargement of the head of the pancreas, contributing to the obstruction of ductal drainage. Furthermore, studies have reported that the perineural infiltration that occurs within the inflammatory head mass significantly contributes to the pain in CP (27,28). Partial resections have been utilized in CP patients with this morphology of disease, in order to resect the “dominant head mass” (often termed, the “pace-maker” of disease) believed to trigger pain. The classic pancreatic head resection has been the pancreaticoduodenectomy (Whipple procedure); however, while providing excellent pain relief outcomes in adults (29), pancreaticoduodenectomy has not been widely applied in children because of the disadvantages of sacrifice of the duodenum and bile duct, as well as extensive loss of pancreatic parenchyma resulting in high risk of endocrine and exocrine insufficiency. More recently, duodenum-preserving pancreatic head resections (DPPHRs; eg, Beger procedure, Berne procedure) have been developed to preserve alimentary and biliary continuity while still allowing for resection of the pancreatic head mass (30).

Selection of the appropriate operation for the appropriate patient is key for a successful surgical outcome. In general, the impact of conventional surgeries on CP outcomes in children is not known. Most pediatric studies are limited by small sample size and short duration follow-up. Attempts to spare pancreatic tissue by ductal decompression alone, without resection, may produce mixed results (31). CP tends to be a diffuse glandular disorder, involving the entire pancreas, and pain in CP may be related to “wiring” rather than “plumbing” (ie, duct) issues. Therefore, ductal decompression alone may not provide long-lasting relief. The pain control from conventional surgeries may be transient and pain recurs in up to 50% of patients (32–37). In the INSPPIRE cohort of children with CP, surgery was perceived as helpful in 73% of patients undergoing longitudinal pancreaticojejunostomy and in 1 patient undergoing partial resection (4). As previously stated above, INSPPIRE is a research consortium, and as such, these outcomes may not be generalizable.

The presence of duct dilation has long been an indication and potential predictor of response to drainage operations in some groups, including in hereditary pancreatitis (38). In a small study, children with CP and main duct dilatation (5–10 mm) underwent a longitudinal pancreaticojejunostomy. At a median follow-up of 4.5 years, children with hereditary pancreatitis were less likely to have sustained response and pursued TPIAT (39). Thus, the underlying etiology of CP should be considered when planning for operation, as longitudinal pancreaticojejunostomy may fail to relieve pain even with adequate preoperative main duct dilation; therefore, these patients should be very carefully selected for the appropriate operation.

### Rationale for Considering Total Pancreatectomy With Islet Autotransplantation

A large proportion of children with debilitating refractory CP do neither have the morphology of an inflammatory head mass nor do they present with main pancreatic duct dilation; rather, many children with CP present with “small-duct disease,” and as such, drainage or partial resection operations should not be offered to this cohort. TPIAT is the optimal surgical option for debilitated patients

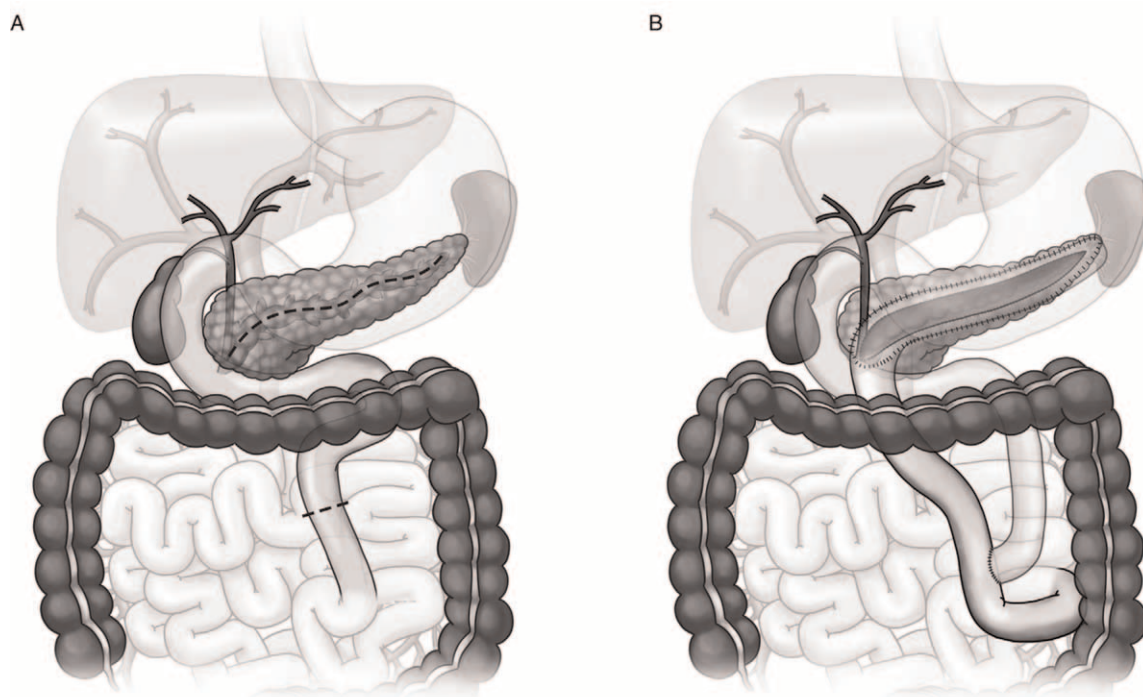
who lack both an inflammatory head mass and substantial uniform ductal dilation. In patients who have undergone prior drainage operation or resection, and have either failed to respond optimally or have had a recurrence of their debilitation, TPIAT is the most effective next intervention (40).

As discussed above, overall, children with genetic etiologies have an unpredictable, and more commonly suboptimal, response to conventional operations in terms of pain and progression of disease, and as such, families should be carefully counseled regarding the pros and cons of conventional operations versus TPIAT (31). Children with genetic etiologies for CP have excellent pain resolution after TPIAT but may face a higher risk of diabetes if a previous drainage operation was performed (41–44). Duct drainage operations dissect and open the pancreatic duct, which then compromises the intraductal perfusion of enzymes needed to optimally isolate islets (41,45). TPIAT has been increasingly recommended over the last several years for children with CP, specifically if secondary to genetic/hereditary causes. As the operation removes endocrine tissue as well and relies on engraftment and function of the isolated islets, however, insulin independence may not be achieved in over half of the patients. Recent studies show improved pain relief and insulin independence if TPIAT is performed at a younger age (3–8 years of age) (46).

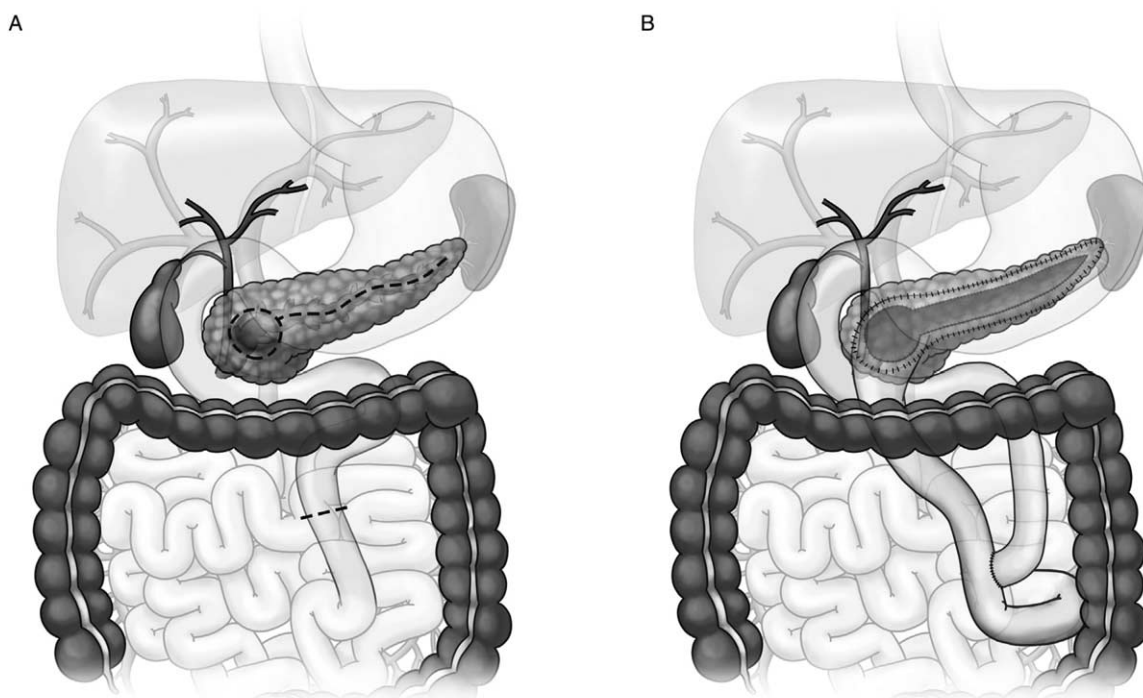
### CONVENTIONAL SURGICAL OPTIONS FOR CHRONIC PANCREATITIS

The conventional surgical options available to treat debilitating CP can be divided into drainage procedures, resection procedures, and DPPHRs. As indicated above, consideration of the specific anatomic and morphologic changes in the pancreas is critical to determining the most appropriate operation for each patient (47). In patients with main pancreatic duct dilation without a coinciding inflammatory pancreatic head mass, a longitudinal pancreaticojejunostomy, or “modified Puestow” procedure, (Fig. 2) may be an effective drainage operation (16). This technique may be considered when the main pancreatic duct is substantially dilated to at least 7 mm in size, with relatively uniform dilation from the head to the tail of the pancreas. Although a surgical drainage procedure is technically possible in ducts with less dilation (eg, 5–6 mm), there remains an increased likelihood of the anastomosis between the jejunum and pancreatic duct losing patency with smaller duct diameter and thereby failing to definitively improve symptoms. In the adult CP population, a uniformly dilated duct of at least 7 mm is only found in approximately 25% of patients, and the percentage is even lower in children (47). The operative technique includes exposure of the anterior surface of the pancreas, identification of the pancreatic duct by needle aspiration, incision of the duct longitudinally from the head to the tail of the pancreas, and anastomosis of a Roux-en-Y jejunal limb to the opened pancreatic duct along its entire length (Fig. 2) (16). Although the longitudinal pancreaticojejunostomy can provide early postoperative pain relief (48), up to 50% of patients experience recurrent symptoms at 5 years following the operation (49). Unfortunately, the long-term outcome of longitudinal pancreaticojejunostomy is poor, and pure drainage procedures have been replaced with techniques that combine both drainage and resection (16). Importantly, pure drainage procedures do not ensure sufficient pain relief in those with enlargement of the pancreatic head (50). Even in the absence of an inflammatory head mass, the modified Puestow procedure has, however, fallen out of favor as a drainage procedure in many experienced pancreas centers, having been replaced by the Frey procedure (Fig. 3), which adds a limited coring out of the pancreatic head in continuity with a longitudinal pancreaticojejunostomy to ensure optimal drainage of the head of the pancreas all the way through the tail (25,26).





**FIGURE 2.** Longitudinal pancreaticojejunostomy (modified Puestow procedure). (A) In patients with uniform substantial dilation of the pancreatic duct ( $\geq 7$  mm), the duct is longitudinally opened from the head to the tail of the pancreas (along dashed line). (B) A Roux-en-Y jejunal limb is created approximately 30 to 40 cm distal to the ligament of Treitz and anastomosed to the opened main pancreatic duct along the length of the pancreas.



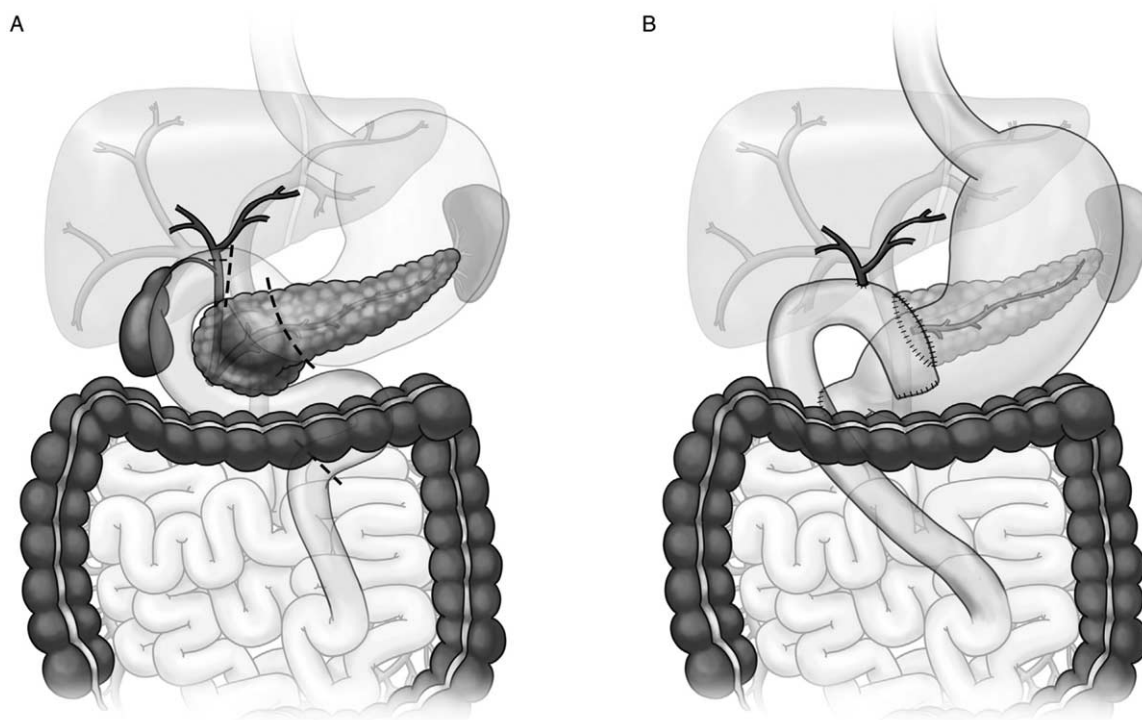
**FIGURE 3.** Frey procedure. (A) Small limited resection of the head of the pancreas is added to longitudinal opening of the main pancreatic duct toward the tail of the pancreas (dashed line). (B) Roux-en-Y jejunal limb is anastomosed to the excavated head of the pancreas and the opened main pancreatic duct along the length of the pancreas.

Resection procedures are indicated in patients who have an inflammatory pancreatic head mass, with or without ductal obstruction. A large proportion of adult patients with CP present with inflammatory changes in the pancreatic head; however, in patients with segmental CP in the pancreatic body or tail, a central pancreatectomy or a distal pancreatectomy may be considered (16). More specifically, in children who have developed pain and debilitation in the setting of a disconnected main pancreatic duct (eg, following either necrotizing pancreatitis or traumatic disruption) with CP affecting only the pancreatic tail, a distal pancreatectomy may be considered. Postoperative pancreatic fistula, pancreatogenic diabetes mellitus, and exocrine pancreatic insufficiency (EPI) are the leading causes of morbidity after distal pancreatectomy (51).

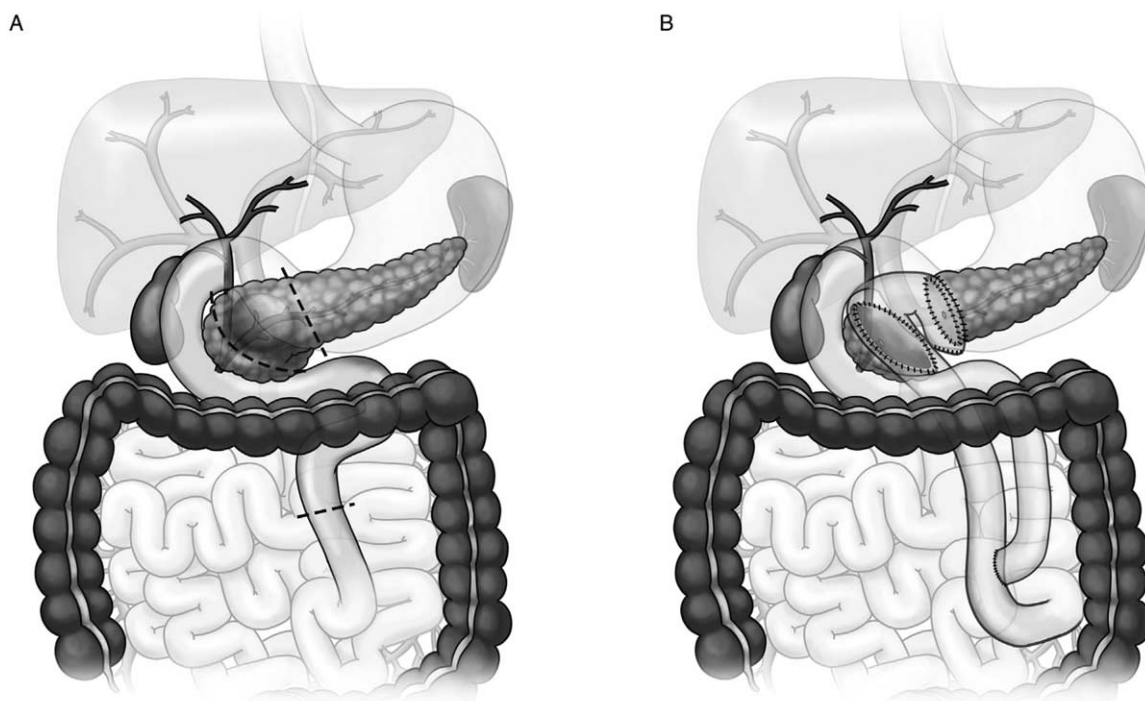
When the head of the pancreas is compromised by an inflammatory head mass, the available operations can be divided based on the preservation or not of the duodenum. The Whipple pancreaticoduodenectomy is primarily indicated for malignant processes involving the head of the pancreas (52,53), but it has also gained applicability in patients with CP (16). The operation entails resection of the head of the pancreas and the C-loop of the duodenum (preferably preserving the pylorus) with reconstruction involving pancreatic, biliary, and enteric anastomoses (Fig. 4) (54). When carried out by experienced pancreatic surgeons, this operation has been found to be well tolerated and effective with good short-term and long-term outcomes (16). Common postoperative complications include anastomotic leak (pancreatic, biliary, enteric), adhesive small bowel obstruction, pancreatic fistulae, anastomotic strictures, and delayed gastric emptying (52). Furthermore, a major disadvantage of the pancreaticoduodenectomy is the impact on the surrounding, nondiseased organs, as the duodenum and common bile duct are sacrificed (50). Varshney et al evaluated

their experience performing a pancreaticoduodenectomy in 4 pediatric patients with pathology involving the head of the pancreas requiring surgical intervention. No anastomotic leak or pancreatic or jejunal fistulae were observed in their cohort, demonstrating that the pancreaticoduodenectomy can be safely performed in children (52).

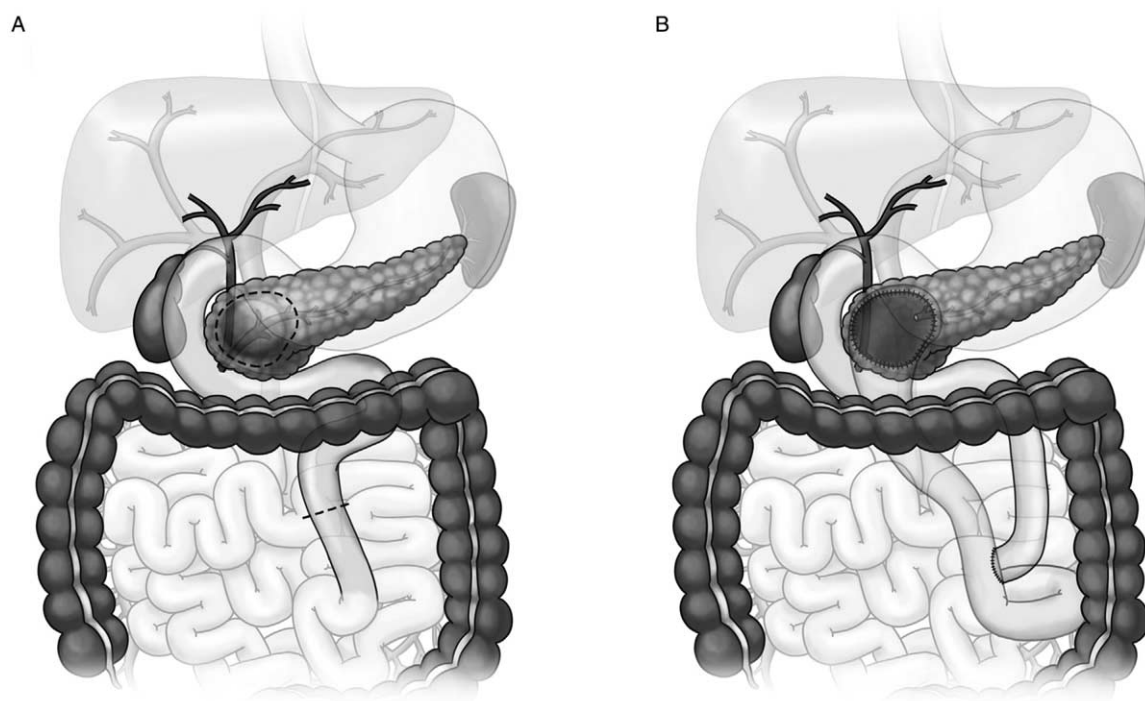
There are 3 types of DPPHR: the Beger, the Berne, and the Frey procedures. These procedures are less radical compared with the previously mentioned Whipple pancreaticoduodenectomy, as they all preserve alimentary tract continuity with preservation of the duodenum and common bile duct, and all may be considered in debilitating pancreatitis with an inflammatory pancreatic head mass. The Beger procedure is similar to the pancreaticoduodenectomy in that the neck of the pancreas is divided over top of the portal vein but the pancreatic head is resected with preservation of the duodenum and a thin layer of pancreatic tissue surrounding the bile duct (Fig. 5A) (16). A Roux-en-Y jejunal limb is anastomosed to the pancreatic head and to the pancreatic body/tail remnant with 2 separate anastomoses (Fig. 5B). The Berne modification (Fig. 6A) involves a pancreatic head resection identical to the Beger technique but it offers a technical simplification of the Beger operation in that it does not require division of the pancreatic neck overlying the portal vein, a maneuver that can be hazardous in the setting of inflammation and portal hypertension (16). In addition, the reconstruction requires only a single Roux-en-Y jejunal anastomosis to the pancreatic rim at the site of the head excavation (Fig. 6B). As described previously, the Frey procedure (Fig. 3) entails a smaller, more limited, pancreatic head resection than the Beger and Berne procedures, and it is combined with a longitudinal opening of a diffusely large and dilated main pancreatic duct toward the pancreatic tail with a Roux-en-Y jejunal anastomosis. Similar to



**FIGURE 4.** Whipple pancreaticoduodenectomy. (A) The head of the pancreas and the C-loop of the duodenum are resected (demarcated by the dashed lines) with or without preservation of the pylorus. (B) The jejunum is used for creation of a pancreaticojejunostomy anastomosis to the remnant pancreatic stump, a hepaticojejunostomy/choledochojejunostomy anastomosis, and a gastrojejunostomy or duodenojejunostomy (in the case of pylorus preservation).



**FIGURE 5.** Beger procedure. (A) The head of the pancreas is resected (between the dashed lines) with division of the pancreatic neck overlying the portal vein. (B) A Roux-en-Y jejunal limb is anastomosed to the excavated pancreatic head remnant and to the pancreatic body/tail remnant using 2 separate anastomoses.



**FIGURE 6.** Berne procedure. (A) The Berne procedure is a technical simplification of the Beger operation, in that the same extent of pancreatic head resection (encircled by dashed lines) is performed but without division of the pancreatic neck. (B) A single anastomosis is created between the excavated cavity in the pancreatic head and the Roux-en-Y jejunal limb.

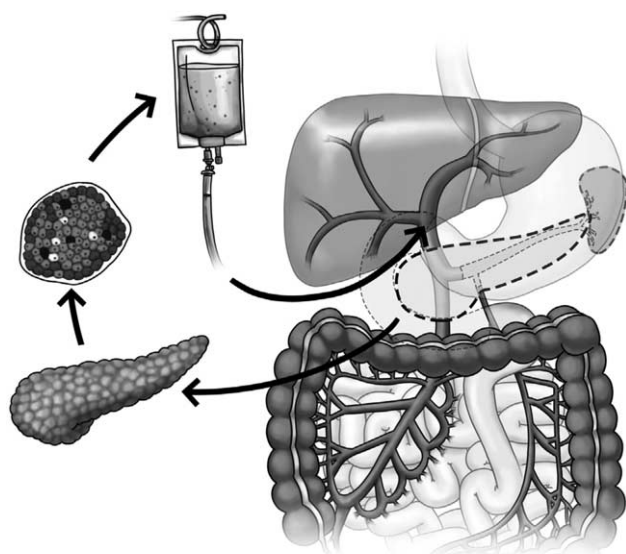


the Whipple pancreaticoduodenectomy, DPPHR operations also carry a risk of postoperative anastomotic leak. A significant advantage of the DPPHR techniques over the Whipple pancreaticoduodenectomy is that the alimentary tract and bile duct remain intact in comparison.

### TOTAL PANCREATECTOMY WITH ISLET AUTOTRANSPLANTATION FOR CHRONIC PANCREATITIS

TPIAT is a complex surgical intervention for the treatment of debilitating CP. The primary goal of the operation is to relieve pain, liberate from opioid use, and improve quality of life by removing the pancreas, with the secondary goal being to mitigate (or even prevent) postoperative diabetes by transplanting the patient's own islets isolated from the pancreas (Fig. 7). Although it has been shown to be of benefit in the management of children who have failed medical and endoscopic therapy (55,56), the decision to pursue TPIAT should not be made lightly. Multidisciplinary evaluation is necessary to establish whether TPIAT is appropriate for the candidate's medical and psychosocial circumstances. Specialized providers in pediatric pancreatology, pediatric surgery, endocrinology, pain management, psychology, and social work are all necessary to determine the appropriateness of a candidate for TPIAT. If splenectomy will be performed during the operation, infectious disease consultation for appropriate preoperative vaccinations may be necessary. Similar to other transplant services, individualized and group evaluations should be discussed as a committee with all medical, surgical, and psychosocial factors being considered.

As a significant number of patients referred for TPIAT are sent to tertiary pediatric academic centers that are not the home institution for the patient, careful review of prior laboratory and imaging tests are necessary to determine what additional testing may be required. Pancreatic anatomic imaging can help in the consideration of TPIAT versus another surgical procedure, and as already discussed above, etiology of CP (eg, genetic risk factors)



**FIGURE 7.** Total pancreatectomy with islet autotransplantation. The primary goal of operation is to relieve pain and improve quality of life by removal of the pancreas (heavy dotted lines). Islets are then isolated from the pancreas and autotransplanted into the liver via the portal vein in order to mitigate (or even prevent) postoperative diabetes.

**TABLE 1.** General criteria for consideration of total pancreatectomy with islet autotransplantation

1. Objective criteria meeting diagnosis of CP or ARP, lasting 6 months or longer
2. Criteria consistent with debilitation, by virtue of opioid dependence or significantly impaired quality of life
3. Absence of reversible cause of pancreatitis
4. Failure to respond to maximal medical and endoscopic therapy
5. Adequate islet function (nondiabetic or C-peptide positive)
6. Absence of physiologic or psychosocial contraindications to operation

ARP = acute recurrent pancreatitis; CP = chronic pancreatitis; TPIAT = total pancreatectomy with islet autotransplantation.

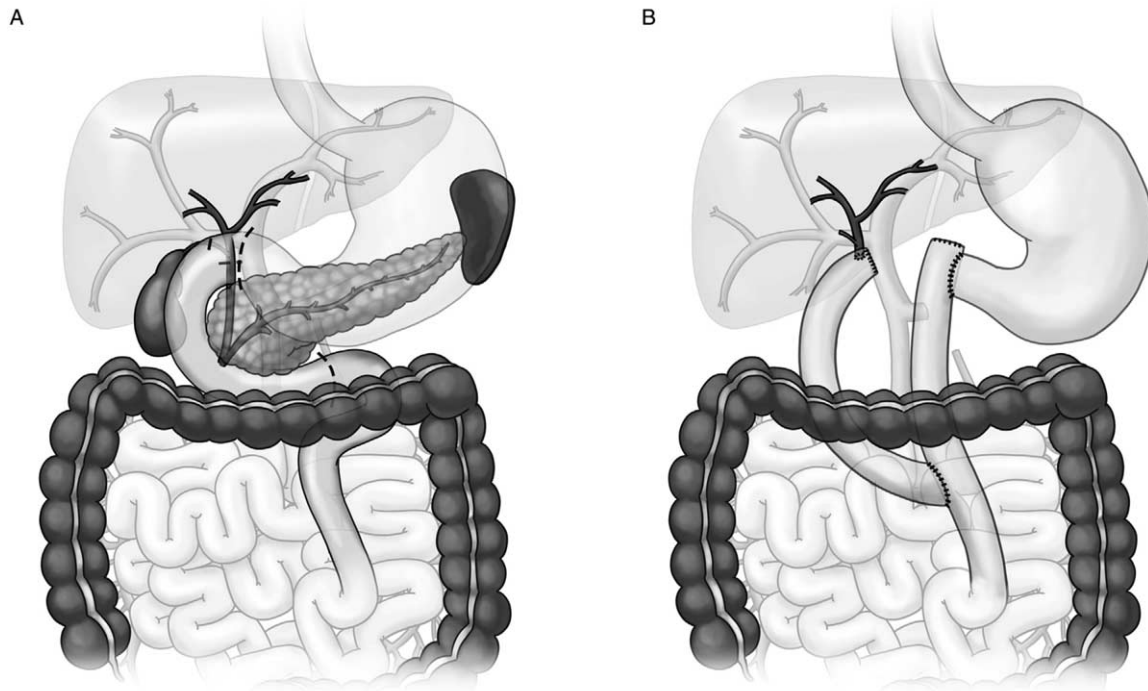
plays an important role in decision-making. Establishing preoperative endocrine function and estimating islet cell mass are critical in family counseling when considering TPIAT. Magnetic resonance (MR) or computed tomography (CT) imaging is performed to detail the abdominal vasculature landscape and organ anatomy.

Pediatric TPIAT centers may have individualized criteria for the selection of appropriate candidates, which take into account patient complexity, timing, and location. A summary of general criteria for consideration of TPIAT is presented in table 1T, taken as a compilation of the currently available literature (44,57,58). In addition to these factors, important considerations include timing, pain status, and social circumstances. Given TPIAT outcomes are influenced by preoperative islet mass and chronic pain (narcotic bowel syndrome and central pain sensitization), careful consideration of timing is necessary. Optimal timing of TPIAT in children remains an area of investigation, especially given the limited longterm data available. As such, open and transparent discussions with patients and families regarding potential short-term and long-term outcomes and complications is critical.

TPIAT is a major abdominal operation, consisting of pancreatectomy, cholecystectomy,  $\pm$  splenectomy, Roux-en-Y hepaticojejunostomy/choledochojejunostomy, and Roux-en-Y duodenojejunostomy. The pancreas is removed together with the majority of the duodenum (and often spleen) (Fig. 8A). The pancreas is taken to an islet isolation facility for enzymatic and mechanical digestion and isolation of islets. Meanwhile, surgical attention is turned to the biliary and alimentary reconstruction, as depicted in Figure 8B. A gastrojejunal (GJ) tube is placed for postoperative feeding because of a high incidence of delayed gastric emptying over the first several weeks after operation. The final phase of the operation involves infusing the isolated islets back into the patient, with the most common primary site being the liver via portal vein infusion. Ongoing research is, however, being performed regarding alternative sites, as discussed below.

A variety of pre-, intra-, and postoperative factors may influence the ultimate number of functional islets, and thereby reduce the chances of achieving insulin independence. Preoperatively, prior pancreatic surgery may adversely affect islet yield, with the modified Puestow procedure having the most negative impact on subsequent islet yield during TPIAT than other traditional pancreatic operations (59,60). The presence of diabetes before TPIAT may adversely affect functional islet yield (61). Historically, diabetes has been considered a late complication of CP; however, a recent study of the INSPPIRE cohort suggests that only one-third of ARP/CP patients with diabetes were diagnosed after their pancreatitis diagnosis (62). Intraoperatively, 2 main factors influence islet yield: degree of pancreatic warm ischemia and effectiveness of islet isolation. The process of islet isolation involves enzymatic and mechanical digestion of the tissue with collagenase and neutral proteases to separate the islets from acinar tissue using density





**FIGURE 8.** Total pancreatectomy with islet autotransplantation. (A) The entire pancreas is removed, along with the majority of the duodenum (segment between dashed lines) with preservation of the pylorus and D1, and the bile duct is divided. The spleen is most commonly removed as well, because of the risk of added ischemia in cases in which splenic preservation is attempted with preservation of the splenic vessels. (B) Biliary and alimentary tract reconstruction is achieved with a Roux-en-Y hepaticojejunostomy or choledochojejunostomy and a Roux-en-Y duodenojejunostomy.

gradient centrifugation. Advanced pancreatic ductal abnormalities, significant fibrosis, and calcifications can hinder enzyme perfusion, and hence diminish islet yield (59). Postoperatively, beta cell apoptosis is exacerbated by hyperglycemia (63,64). Thus, it is critical that exogenous insulin be given post-TPIAT to maintain euglycemia and protect the islets during engraftment until neovascularization occurs, up to 12 weeks post-implantation.

Hepatic implantation is the most common site of implantation for pediatric TPIAT, despite it not being an ideal site because of low oxygen tension and exposure to drugs/toxins that are processed by the liver. The surgical ease of implantation and developments that have minimized portal vein thrombosis and bleeding complications have, however, resulted in hepatic implantation being most widely used. Additional sites for implantation are being evaluated, principally the peritoneum and omentum (65). The presence of good arterial blood flow, numerous lymphatic vessels, and portal drainage provides a good environment for neovascularization. Additional sites of transplantation in humans have included the renal capsule and bone marrow (66), with others (eg, gastrointestinal wall, testis, thymus, anterior chamber of the eye, cerebral ventricles) being investigated in experimental animal models (67).

In the immediate postoperative period, an intravenous insulin infusion is necessary in order to minimize insulin secretory demand from the freshly transplanted islets. Transition to subcutaneous insulin, often via insulin pump, is undertaken upon return to enteral feeding. As stated above, maintaining euglycemia is critical in the postoperative period, and the use of continuous glucose monitoring can facilitate this. Weaning of insulin should not be attempted until approximately 3 months after TPIAT in order to allow time for sufficient islet neovascularization. Similar to other diabetic patients, euglycemia is the goal. Most TPIAT patients have partial islet graft function and are insulin-dependent but benefit from better

glycemic control than if they had undergone total pancreatectomy alone. Data thus far, demonstrate that children are more likely to wean completely off insulin after TPIAT than adults (46,68). With limited long-term post-TPIAT data in children at this time, all patients and families going into a TPIAT should, however, assume some level of insulin need and be prepared for lifelong diabetes management.

Gastrointestinal dysmotility, EPI, and malnutrition are common complications of CP before TPIAT. Even in the absence of these pre-operatively, they may all occur postoperatively (69–71). Regardless of the presence or absence of EPI pre-TPIAT, all TPIAT patients will have EPI after the operation, and thus will require lifelong pancreatic enzyme replacement therapy (PERT). Close management by a pediatric gastroenterologist and nutritionist with expertise in managing EPI and PERT dosing is integral to maintaining appropriate nutrition and fat-soluble vitamin levels. Vitamin A/D/E/K supplementation is empirically performed. Iron profiles and vitamin B12 status should also be monitored and replaced as indicated. If iron supplementation is required, enteral iron is often sufficient. In order to minimize the risk of overwhelming post-splenectomy infection (OPSI), patients should receive full vaccinations against encapsulated bacteria and undergo daily antibiotic prophylaxis (oral penicillin VK) until at least 5 years of age and for 1 year after surgical splenectomy.

## OUTCOMES FOLLOWING OPERATIONS FOR CHRONIC PANCREATITIS

### Outcomes Following Conventional Operations

Whenever performed by experienced hands, conventional operations involving drainage, partial resection, or a combination of

TABLE 2. Overall outcomes associated with operations for chronic pancreatitis

	Modified Puestow	Pancreaticoduodenectomy	DPPHR	TPIAT
Pain reduction	<60%*	80%	85%	90%*
Exocrine pancreatic insufficiency	33%*	74%	62%	100%*
Endocrine pancreatic insufficiency	33%*	27% to 48%	10% to 18%	50% to 60%*
Postoperative mortality	0% to 1%*	2% to 5%	0% to 5%	0% to 1%*

Only outcomes related to procedures for acute recurrent or chronic pancreatitis are included. DPPHR = duodenum-preserving pancreatic head resection; TPIAT = total pancreatectomy with islet autotransplantation. \*. Highlights pediatric data whenever available.

both, are welled and effective in terms of long-term pain relief and quality of life (able 2T) (72). Exocrine and endocrine functions can, however, continue to deteriorate over time, possibly secondary to continued cellular damage and parenchymal loss (16).

Generally speaking, the longitudinal pancreaticojejunostomy (modified Puestow) has been reported to have good immediate and short-term success rates (21); however, pure surgical drainage procedures have been reported to have poor long-term outcomes (47). Limited data in children with CP report about 50% of children had persistent symptoms or required hospital admissions for episodes of pancreatitis 15 years after operation (21,38). Laje and Adzick (39) reported outcomes on 6 pediatric patients with CP who underwent longitudinal pancreaticojejunostomy at their institution. Two patients were pain-free short-term (<1 year) after the operation; however, another 2 developed recurrent pain within 2 years of operation and another 2 went on to require TPIAT to treat intractable pain after only short-term improvement. Two of the patients developed insulin-dependent diabetes mellitus within 1 year of undergoing longitudinal pancreaticojejunostomy. More recently, Hodgman et al (31) reported an improvement or resolution of abdominal pain in less than 60% of children undergoing longitudinal pancreaticojejunostomy. The longitudinal pancreaticojejunostomy may be promising only if the duct is substantially ( $\geq 7$  mm) and uniformly dilated (47). In many experienced pancreas centers, the Frey procedure has now replaced the longitudinal pancreaticojejunostomy as the surgical drainage procedure of choice for large duct disease, on the basis of evidence that failures following modified Puestow have most commonly been related to inadequate decompression of the head of the pancreas and the continued presence of the portion of the gland at highest risk for progressive inflammation (26,73).

The Whipple pancreaticoduodenectomy, a resection-only operation, was originally designed for pancreatic head malignancies. In addition to being more invasive than other techniques (eg, includes duodenal resection), pancreaticoduodenectomy has demonstrated higher morbidity, predominantly related to the risk of pancreatic leak (74). Although pancreaticoduodenectomy may be indicated in children with tumors (eg, pancreatoblastoma and solid pseudopapillary neoplasms) (75,76), it is rarely considered as a management option in children with CP. In adults, perioperative mortality in experienced centers ranges from 2% to 5%; however, a major factor contributing to this mortality rate is the comorbidity profile of the adult population (47). Complications that may be encountered following pancreaticoduodenectomy include pancreatic fistula (9%), bile leak (2%), postoperative bleeding (5%–7%), wound infections (8%–10%), delayed gastric emptying (23%–31%), and anastomotic ulcers (77). Nevertheless, Whipple pancreaticoduodenectomy has been shown to provide long-lasting pain relief in approximately 80% of adults with CP (78). In some adult studies, 50% to 100% of patients developed EPI requiring PERT, and up to 48% to 74% of patients developed insulin requirements after undergoing pancreaticoduodenectomy (78,79). Long-term quality-of-life parameters improved over time following

pancreaticoduodenectomy but did not approach those of a generally healthy population, and furthermore, a high percentage of pancreaticoduodenectomy patients had progressive worsening of gastrointestinal functioning after the operation (80). The outcome data for pancreaticoduodenectomy in the pediatric population is scarce, in large part, because of infrequent indications to perform this operation in childhood.

DPPHRs (ie, Beger, Berne, Frey procedures) have gained significant popularity as alternatives to pancreaticoduodenectomy in CP patients with an inflammatory head mass as they offer the benefits of preserving the duodenum and the bile duct, limiting the extent of pancreatic parenchymal resection, and significantly lowering overall morbidity and gastrointestinal complications compared with pancreaticoduodenectomy (81). DPPHRs are most effective when performed by experienced pancreatic surgeons in patients with CP and an inflammatory pancreatic head mass. They provide long-term pain relief in 85% of patients and better early preservation of pancreatic function compared with pancreaticoduodenectomy (78). In a systematic review and meta-analysis done in 2008, DPPHRs were found to be superior to pancreaticoduodenectomy with shorter postoperative hospital stay, greater weight gain, and better quality of life (82). In a more recent meta-analysis of randomized controlled trials, DPPHRs were reported to have better outcomes compared with pancreaticoduodenectomy, including shorter operative time, fewer blood transfusions, lower postoperative morbidity, and better occupational rehabilitation (72). Moreover, in medium-term follow-up, compared with pancreaticoduodenectomy, patients who underwent DPPHRs were less likely to have EPI (82), endocrine insufficiency (83), and delayed gastric emptying (83). In long-term follow-up, however, the metabolic advantages of DPPHRs were lost, with equivalent endocrine and exocrine functional outcomes compared with pancreaticoduodenectomy (84,85). It is likely that DPPHR does not completely halt the parenchymal damage and atrophy over time, such that endocrine and exocrine insufficiency may continue to progress (16).

Reports of DPPHRs in the pediatric population with CP are scarce, predominantly because of the fact that most children with debilitating CP do not harbor an inflammatory pancreatic head mass that would need to be addressed at operation. In addition, it is important to consider that DPPHRs have been most popular at European centers, and overall experience has remained limited in the United States. The literature on DPPHRs for CP in children has been limited to outcomes following the Frey procedure. In a series of 9 children who underwent the Frey procedure, 78% experienced symptomatic relief and an improvement in quality of life over a mean of 4.6 years following the operation (22). In a more recent and larger series of 24 children, 91% of patients were pain-free at median follow-up of 29 months after the Frey procedure, with well-preserved pancreatic endocrine and exocrine function (19). Several studies have been published in adult patients with CP, in an effort to compare the outcomes of different techniques of DPPHR to each other. These studies have indicated that the Beger, Berne, and Frey

procedures have comparable long-term outcomes, in terms of pain control, quality of life, endocrine insufficiency, and EPI (16,50,86,87). These studies suggest that the choice of DPPHR technique may be left to the experience and comfort of the individual surgeon.

## Outcomes Following Total Pancreatectomy With Islet Autotransplantation

In recent years, TPIAT has proven to be extremely promising in the surgical management of CP in children, as defined by 3 outcomes: improvement in pain and health-related quality of life, liberation from opioids, and independence from exogenous insulin. As with any highly complex operation, TPIAT has its own set of possible complications including intra-abdominal bleeding (5%), portal vein thrombosis (3%), wound infections and intra-abdominal abscesses (5%), anastomotic leaks (4%), intestinal obstruction (5%), and a small long-term risk of anastomotic ulcer and/or gastritis leading to bleeding or pain (88–91). The prevalence of gastrointestinal dysmotility after TPIAT has been reported in adults to be nearly 45% (70).

Several studies have demonstrated the substantial benefit of TPIAT in managing children with debilitating CP (88–90). In a large study of 75 children, pancreatitis pain improved in 90% of patients, approximately 90% of children were free of opioids by 2 years following operation, and nearly all children no longer suffered missed school days because of their condition by 2 years (88). Regarding quality-of-life outcomes, both mental and physical components improved dramatically, with significant improvement in all domains of the SF-36 Quality of Life Health Survey (88). Overall, the insulin independence rate was 41%, insulin independence was durable lasting as long as 10 years after operation, and total islet equivalents (IEQ) was the strongest predictor of insulin independence (88). In another study, early postoperative outcomes of TPIAT in children were reported (90). By 90 days postoperatively, children achieved significant improvements in opioid dependence and in parenteral nutrition dependence, with SF-36 physical component and total scores and SF-10 physical component scores significantly improved as well (90). In a study reporting outcomes in children ages 3 to 8 years, all patients experienced pain relief and were weaned off opioids by 6 months after operation (46). Over 80% of this young cohort was able to achieve a period of insulin independence, with 64% of patients remaining insulin independent at most recent follow-up. Although this report highlighted that the youngest children seemed to experience the best pain relief and glycemic outcomes, additional studies are needed to determine the optimal timing for TPIAT.

Although positive outcomes of TPIAT in children exceed those in adults, the characteristics that are predictive of optimal pain and quality of life outcomes and insulin independence after TPIAT require further elucidation. In a study of over 500 patients undergoing TPIAT (490 adults, 91 children), prolonged preoperative opioid use and repetitive pancreatic duct stenting were factors associated with pain persistence and prolonged opioid use after TPIAT (92). The clinical implications of these findings are important to consider in the context of timing of TPIAT, as the development of central sensitization because of the neuroplastic changes from chronic pain can result in detrimental pain relief and quality of life outcomes after TPIAT. Islet mass transplanted has been the best predictor of insulin independence post-TPIAT, with lower body surface area and male sex identified as additional factors associated with insulin independence in children (88). Factors that have been associated with lower islet yield include more advanced imaging findings of parenchymal destruction (including atrophy and calcifications) (93), increased fibrosis (59), longer duration of disease

(94), and prior drainage or resection operations (60,95). A recent study has reported that preoperative ERCP does not adversely impact islet yield at the time of TPIAT (96). A greater understanding of these factors will be important in patient selection, determination of optimal TPIAT timing, and patient/family counseling regarding expectations for insulin independence post-TPIAT. The Prospective Observational Study of TPIAT (POST) is a multicenter NIDDK-funded study that is currently enrolling TPIAT patients with the goal of studying patient characteristics and timing of operation in order to optimize pain relief, quality of life, and glycemic outcomes (97).

Long-term outcomes (>10 years) following TPIAT have recently been reported in a predominantly adult cohort of 215 patients (only 14% of patients underwent TPIAT during childhood) (98). Overall, pain relief was sustained post-TPIAT, with rates of 82% at 10 years and 90% at 15 years. In the subset of pediatric patients, at 10 years, pancreatic pain prevalence was 11.8%, and opioid use prevalence was 16.7%. In the full cohort, the insulin independence rate at 10 years was 20%, and the rate of partial graft function was 32%. Importantly, pediatric patients were more likely to have islet function than adults, as age <18 years at time of operation was a predictor of insulin independence. As this study was constituted of mostly adult patients, we currently await further data to assess the long-term durability of TPIAT in the pediatric population.

## CONCLUSIONS

Children with CP experience morbidity from their pancreatitis, and they are at risk for exocrine and endocrine insufficiency, as well as chronic pain that significantly impacts their quality of life. Caring for children with CP requires a multidisciplinary approach with a team that consists of pancreatologists, endoscopists, surgeons, radiologists, pain specialists, endocrinologists, and nutritionists. CP management requires medical and endoscopic therapies through an integrated approach, and surgical treatment of CP is reserved for patients in whom medical and endoscopic therapies have failed. To determine the optimal surgical approach for children with CP, the morphology of disease must be considered, as well as the presence of genetic risk factors. Outcomes of operations for CP are variable depending on the type of intervention, and a multidisciplinary team approach is needed to assure appropriate patient and operation selection, as well as to optimize recovery and to manage short-term and long-term needs.

## GAPS AND FUTURE DIRECTIONS

Although the currently available literature for the surgical management of CP highlights the importance of individualized selection of operation based on disease and morphologic characteristics, significant gaps in our current knowledge remain. Areas for future research include, but are not limited to:

1. Patient selection—the right operation for the right patient.
2. Further delineation of the impact and outcomes of conventional operations versus TPIAT in the setting of CP with genetic risk factors.
3. Optimal timing of operation for CP.
4. Optimization of glycemic outcomes following TPIAT.
5. Education of providers, including the community of pediatric surgeons with less experience in children with CP to avoid inappropriate operations.
6. Identification of pediatric pancreas centers of excellence that can offer the most comprehensive multidisciplinary care for children with debilitating CP.
7. Health care cost-effectiveness of operations for CP management.



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