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Total Pancreatectomy with Islet Autotransplant

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> *The surgeon is a doctor who can operate and knows when he should not do it.*
>
> Emil Theodor Kocher (1841–1917)

Introduction

Chronic pancreatitis (CP) is a difficult disease with a common progression to pancreatic exocrine insufficiency, diabetes mellitus, and narcotic dependence due to chronic pain over years to decades. Typical medical therapies include pancreatic enzyme supplementation and other medical therapy, interruption of pancreatic toxins (especially alcohol), and endoscopic interventions. While this is successful in many patients, there remains a subset of patients without adequate responses to medical and endoscopic interventions.

Typical surgical interventions have relied on the ability to either extirpate the segment of pancreas most affected by the CP, or by a variation of pancreatic duct drainage. These interventions have been proven to be effective in appropriately selected patient populations [1,2]. However, there are several subgroups of patients that are not as amenable to classical surgical interventions, including those with so-called minimal change or small duct pancreatitis, and those with familial disease, including *SPINK1*, *PRSS1*, *CTRC*, *CFTR*, and other mutations predisposing to CP.

In 1977, the first total pancreatectomy with islet autotransplantation procedure was performed by D. Sutherland and colleagues at the University of Minnesota, in part to better understand isolated pancreatic islet function after transplantation into the portal venous system. Interestingly, this operation was successful both in resolving the chronic pain from CP, and in long-term preservation of islet cell function [3,4]. Since that time, an experimental procedure performed at one institution has become a frequently performed operation at more than two dozen centers across the world with more than 1000 cases reported [5].

This procedure is unique in several ways. In addition to having a surgeon skilled in performance of one of the more challenging cases in surgery today, the key component of a successful procedure requires the presence of an experienced islet cell isolation facility, and a team of caregivers experienced in selecting and caring for the patient's issues such as diabetes mellitus, malnutrition, pain management, and exocrine dysfunction through surgery and recovery. Unlike typical transplantation, patients receiving islet autotransplantation do not require immunosuppression as they are receiving their own tissue. Given these components, mortality from this operation is <1% in reported series, but with morbidity expected after a pancreatectomy (up to 60%) [6].

Evaluation of the Patient with Chronic Pancreatitis for Surgical Intervention

The primary goal of performing a total pancreatectomy and islet autotransplantion is to provide relief of pain. An appropriate evaluation of the patient provides information about how best to develop an individualized treatment plan for each patient. Components of a typical evaluation for patients with CP considering surgery involve historical review (looking for pancreatic interventions and histopathology), imaging, and focused laboratory testing to evaluate markers for and etiology of CP, pancreatic exocrine and endocrine function (Table 66.1). Tumor markers should be considered, especially in older patients, to evaluate the possibility of

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Table 66.1 Evaluation of patients for TPIAT: common components.

History:
Drugs and alcohol
Genetic testing
Imaging
Pancreatic interventions
Episodes of pancreatitis
Imaging:
Computed tomography
Magnetic cholangiopancreatography
Endoscopic ultrasound
Laboratory:
Fecal elastase
Ca19-9, CEA
Hemoglobin A_{1C}
Functional testing:
Pancreatic function tests
Mixed meal testing

TPIAT: total pancreatectomy with islet autotransplant; CEA: carcinoembryonic antigen.

cancer as an etiology of pancreatitis. Other causes of chronic abdominal pain should be considered in each patient and investigated as appropriate. Many younger patients without obvious etiology should receive genetic counselling and testing. Evaluation by a medical psychologist is frequently helpful as interventions are considered.

Decision-Making Process

Candidates for TPIAT at our institution are evaluated and discussed after evaluation by a multidisciplinary group including gastroenterology, surgery, endocrinology, nurse coordinators, health psychology, genetics, dietetics, social services, and pain management. Our approach to interventions follows Fig. 66.1, with therapy tailored to the individual patient. Many patients will benefit from a medical or endoscopic intervention. In those patients with calcifications and dilated duct, a drainage procedure such as a Frey or Beger procedure are often offered, as recovery is shorter and long-term outcomes in properly selected patients are good [2].

Many patients who have failed medical or endoscopic interventions have small-duct or minimal-change chronic pancreatitis (MCCP). This disease is characterized by chronic inflammatory destruction of the gland with subsequent exocrine/endocrine dysfunction and persistent abdominal pain without main duct dilation [7]. In the setting of small duct/minimal change disease total pancreatectomy represents the only valid surgical option for the treatment of pain [8,9]. Additionally, patients with genetic/familial disease are more likely to develop recurrent or progressive disease [10].

Patients who are being considered for a TPIAT meet the criteria in Table 66.2 [11], with proven pancreatitis, a significant effect on lifestyle, no reversible cause of pancreatitis, failure to respond to appropriate medical and endoscopic management, and adequate islet cell function.

There are a number of contraindications to this procedure, which include active drug abuse or alcoholism (we require 6 months of sobriety), active cardiac and respiratory disease with high perioperative risk, poorly controlled psychiatric disease, and inability to comply with postoperative care [16]. Additionally, pancreatic cancer or diffuse neoplasm and preexisting liver disease, including cirrhosis, portal hypertension or portal vein thrombosis are contraindications for major pancreatic resection or intraportal islet transplant [12,13]. Finally, patients with diabetes mellitus without C-peptide response will receive poor islet cell yields and poor postoperative graft function so TP alone is offered without the IAT [14].

A total pancreatectomy with islet autotransplantation is performed for management of a patient's pain. Previous learning has suggested that the pain from CP may "burn out" or resolve over 1–2 decades, although recent evidence suggests that this may not be the case [15]. A thorny issue is the question of when to intervene with surgery for patients suffering from chronic pain due to pancreatitis. A number of groups have investigated this

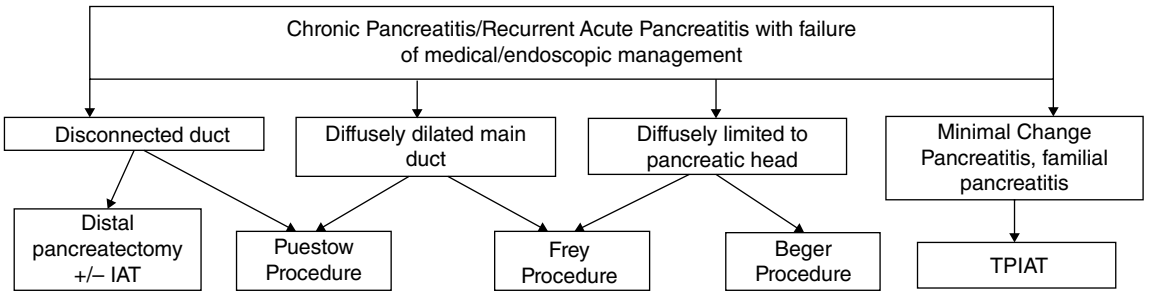

Figure 66.1 Decision tree for patients who have failed nonsurgical treatment for acute recurrent or chronic pancreatitis. TPIAT: total pancreatectomy with islet autotransplant.

Table 66.2 University of Minnesota criteria for total pancreatectomy and islet autotransplantation (must fulfill 1–5).

1) Diagnosis of chronic pancreatitis, based on chronic abdominal pain of ≥6 months duration and at least one of the following:
   - Pancreatic calcifications on computerized tomography scan.
   - At least two of the following: ≥4/9 criteria on EUS, compatible ductal or parenchymal abnormalities on secretin MCRP; abnormal endoscopic pancreatic function tests (peak HCO_2 ≤ 80 mmol/L).
   - Histopathology confirmed diagnosis of chronic pancreatitis.
   - Compatible clinical history and documented hereditary pancreatitis (e.g., *PRSS1* gene mutation).
   - History of recurrent acute pancreatitis (more than one episode of characteristic pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase greater than three times upper limit of normal).
2) At least one of the following:
   - Daily narcotic dependence
   - Pain resulting in impaired quality of life, which may include: inability to attend school, recurrent hospitalizations, or inability to participate in usual, age-appropriate activities
3) Complete evaluation with no reversible cause of pancreatitis present or untreated
4) Failure to respond to maximal medical and endoscopic therapy
5) Adequate islet cell function (nondiabetic or C-peptide positive)

MRCP: magnetic resonance cholangiopancreatography.
Source: Adapted from [11].

question, and repeated data suggests that outcomes after surgery for pancreatitis (including TPIAT and other operations) are improved with duration of chronic pain of 3 years or less [16,17].

Islet Cell Laboratory

The critical nature of an effective islet cell laboratory cannot be overstated. The presence of at least partial graft function is critical to maintain goal glycemic control and reduce glycemic variability, and insulin independence is associated with better quality of life after TPIAT [18]. Islet laboratories with significant annual experience have better islet yields on long-term graft function than those who do fewer isolations [19].

An important distinction in the setting of islet autotransplantation is that the US Food and Drug Administration does not consider these islets a manufactured biologic product. This requires processing of the islets under current Good Tissue Practice but not the more stringent current Good Manufacturing Practice regulations. In this setting, the goal of processing islets is to maximize islet yield, and not purity.

For the islet isolation step, after removal the whole pancreas is taken immediately to the islet facility, where it undergoes enzymatic and mechanical digestion to separate the pancreatic islets from acinar and pancreatic ductal tissue. Digestion is aided by use of the Ricordi Chamber, which enhances exposure of the pancreatic tissue to digestive enzymes [20]. The isolated islet tissue is returned to the operating room where islets are infused into the portal vein. Significant recent advances have been made in use of tailored enzyme preparations to enhance optimized islet isolation [21].

Unsurprisingly, there are far fewer facilities that have the manufacturing resources to perform islet isolation than there are that have skilled pancreatic surgeons. To address this issue, a number of centers have explored distant processing of the pancreas at a core facility with return of the isolated islets for infusion to the operative site. While time from removal of pancreas to infusion of islet is typically 8–10 hours longer, graft function results in these studies have been roughly comparable to those where pancreas was processed locally [22,23].

The Operation: Unique Features

The operation of total pancreatectomy with islet autotransplant is essentially a total pancreatectomy with duodenectomy (plus/minus distal gastrectomy) with a splenectomy. Although some institutions advocate a splenic-preserving procedure, because of the concern for affecting blood flow to the pancreas during surgery and the concern for postoperative sinistral portal hypertension with resultant gastric varices, we typically perform a splenectomy at the same setting. Patients should therefore be vaccinated preoperatively against *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Neisseria meningitidis* to minimize the likelihood of developing potentially lethal post-splenectomy sepsis. Appropriate vaccination strategies for these organisms change on a regular basis, with the most current guidelines typically available on the Centers for Disease Control and Prevention website [24]. Vaccination has been shown to significantly reduce the risk of post-splenectomy sepsis [25].

Another variation in patients undergoing pancreatectomy for islet cell isolation is the approach to preserve pancreatic blood supply to decrease warm ischemia time. In this case, the splenic artery and vein and gastroduodenal artery are identified, isolated, and preserved until the final dissection is complete. Typically these vessels are then ligated along with the common bile duct and uncinate process to complete the resection. The pancreas is immediately placed in a basin with iced saline where the duodenum is excised, excess peripancreatic

tissue is removed, and the gland is exsanguinated to facilitate enzymatic digestion. The gland is then sent to the islet cell laboratory for processing.

One controversy is whether to perform pylorus preserving or a standard distal gastrectomy during the resection. It is argued that delayed gastric emptying is shorter in those undergoing a classical resection, and that the risk of postoperative dumping syndrome is lower in those with pylorus-preserving resection. One of the outcomes awaited in the POST trial (a prospective, multicenter observation trial of outcomes after TPIAT) is related to this variation in care [26].

Islet processing can take from 5 hours for an islet laboratory co-located with the patient to up to 24 hours in a setting where islets are processed at a distant site. Another variation is how to manage the delay. There are a number of management techniques described. A common approach is to keep the patient in the operating room under anesthesia for the period of time that islets are being processed, infusing islets, then completing closure. Other described approaches include temporary cannulation and closure with removal of the catheter after infusion, percutaneous placement of catheter by IR into the portal system with infusion, or a return to OR for operative infusion of islets (the typical approach for centers utilizing remote processing of islets).

In most cases, the islet preparation is infused into the portal vein or one of its major branches. The authors' technique is to use a 5-French micropuncture kit to place a catheter into the anterior portal vein or splenic vein. Anticoagulation of the patient is necessary as the islet preparation includes injured tissue that will induce a hypercoagulable state [27] and 70 units of heparin per kg body weight administered intravenously is typically utilized. Portal pressures are measured at the beginning and throughout infusion of islets, with infusion held if pressures increase by greater than 25 cm H_2O. Portal pressure increase is expected, as the islet preparation volume is embolizing within the portal venous system, which has a limited capacity for tissue [28] of about 0.25 mL of tissue per kg body weight. In the situation where portal pressures remain elevated during infusion, islets can be safely placed within an omental pouch or other extraportal site [29].

Laparoscopic-assisted, laparoscopic, and robotic total pancreatectomy with islet autotransplant have been described [30–32]. In a case-control series of laparoscopic-assisted total pancreatectomy compared to an open procedure in children (21 patients in each group), perioperative morbidity, operative time, length of stay and outcomes were similar between laparoscopic and open groups, with a higher use of opioids at 2 years post-procedure in the laparoscopic group [30]. Other case series demonstrate the feasibility of both laparoscopic and robotic approaches to TPIAT [31,32]. One issue continues to be the inflammation and scarring associated with CP and the potential effect of this state on the ability to safely perform the dissection via laparoscopy or robotically.

Postoperative Care

Many of the postoperative complications associated with total pancreatectomy and islet autotransplant are common with other similar procedures such as a Whipple procedure. These include anastamotic leak from GI tract or bile duct, postoperative abscess, and postoperative bleeding. Other complications are related to and unique to the islet autotransplant portion of the procedure. Postoperative management of these patients includes close monitoring for these complications and care supportive of the unique features of this operation. In a large, multicenter prospective study of patients after TPIAT [6], complications included need for reoperation for bleeding, portal vein thrombosis, intra-abdominal abscess, and wound infection (Table 66.3).

A common feature in this operation is delayed gastric emptying. In this population of patients this seems to be present for 3–6 weeks after surgery. There is some evidence that laparoscopic or robotic procedures may reduce the duration of this problem, but this has not yet undergone careful study. Current protocol in our institution is to place a gastrojejunostomy tube at the time of surgery, with initiation of tube feedings the morning

Table 66.3 Postoperative complications in a multicenter study of 279 patients after total pancreatectomy with islet autotransplantation [6].

	Incidence: Adults	Incidence: Pediatrics
Complication	***n* = 195**	***n* = 83**
Reoperation within 30 days	11%	7%
Abdominal infection requiring drainage	9%	3%
Bile duct obstruction/leak	2%	2%
Portal venous thrombosis	10%	2%
Mechanical ventilation >24 hours postoperative	3%	1%
Vasopressor use >24 hours postoperative	3%	6%
Pulmonary embolus/deep venous thrombosis	4%	0%

Source: Nathan et al. 2022 [6]/With permission of Elsevier.

after surgery. The patient can be transitioned to oral intake and the gastrojejunostomy tube can be removed several weeks postop. Pancreatic exocrine insufficiency is common in patients with CP in the preoperative state, with nearly 50% of patients on pancreatic enzyme supplementation. Of course, after removal of the pancreas all patients have a lifelong requirement for pancreatic enzyme supplementation. During tube feeds, this deficiency is addressed using an immobilized lipase cartridge in line with the tube feeds (Relizorb R). Pancreatic enzymes are initiated as the patient transitions to oral intake and adjusted as necessary.

Anticoagulation is important in the operating room and postoperatively due to infusion of the hypercoagulable islet tissue. Various regimens include low-dose heparin infusions or moderate doses of low-molecular weight heparin. Patients should be imaged 4–6 days postoperatively for presence of portal vein thrombosis and if this condition is identified, patients should be fully anticoagulated for 3 months postoperatively [33].

Pancreatic islets are routinely cultured for presence of bacterial contamination prior to infusion. If these cultures return positive (this occurs in 40–60% of cases), appropriate tailored antibiotic therapy is initiated and continued for 7 days to treat the positive cultures. In one series of more than 250 patients, this approach resulted in no concordant bacterial infections [34].

Pain management after TPIAT is a vexing problem. Essentially every patient is habituated to narcotics, and appropriate control of pain without oversedation is challenging. An epidural catheter is contraindicated, due to the need for intraoperative anticoagulation. Typical therapy includes a multimodal management approach that can include i.v. narcotics, adjuncts such as ketamine or dexmetatomidine, and local therapies including paravertebral catheters or long-acting abdominal wall blocks. A key component of this management is in counselling of the patient and their support persons on the difficulty of achieving adequate pain control for the first several days following surgery. As the patient recovers from surgery, transition to long-acting narcotics to treat both the narcotic dependency and postop pain is appropriate, with weaning of narcotics over the months following surgery.

Glycemic Management

The important concept to preserve islet function after autotransplantation is maintainance of normoglycemia. Hyperglycemia can lead to both poor engraftment of cells in the perioperative period, and loss of islet cells after TPIAT [35,36]. Management of blood glucose to promote optimal islet function begins in the operating room. Solutions containing dextrose should be minimized in the intraoperative period as this has been shown to be associated with sustained intraoperative and postoperative hyperglycemia. Insulin should be administered to maintain blood glucose levels between 80 and 120 mg/dL and postoperatively an insulin infusion should be maintained to keep blood glucose within this range. Patients are typically transitioned to long-acting insulin preparations as enteral nutritional requirements are met. Most patients are maintained on insulin for the first 3 months after islet autotransplant with gradual weaning of insulin as tolerated.

Outcomes after Total Pancreatectomy and Islet Autotransplantation

The major outcome of interest in patients receiving TPIAT is relief of pain, with other outcomes including need for insulin and quality of life. Studies from multiple centers have recently been evaluated in a meta-analysis from the Dutch Pancreatitis Study Group [37] where outcomes from 14 studies that included 1255 patients were evaluated. In this meta-analysis, at 1 year after total pancreatectomy with islet cell autotransplantation, opioid-free rate had improved from between 0% and 15% to 63% (95% CI: 46–77), and the insulin-free rate had decreased from between 89.5% and 100% to 30% (95% CI: 20–43). Alcohol as the cause of pancreatitis was associated with lower insulin-free rate. Quality of life significantly improved after TPIAT.

In one of the largest single center studies published to date, Chinnakotla and coauthors reported long-term outcomes in adults ($n = 490$) and children ($n = 91$) after TPIAT [38]. They reported 10-year survival of 90%, with 1 year narcotic-free rates of 67% and insulin-free rates of 18% (adults) and 31% (children) (Fig. 66.2). Pediatric patients had significantly improved outcomes compared to adults. Other larger series have shown comparable results [39,40] An ongoing prospective multicenter trial is actively enrolling patients from nearly a dozen institutions to evaluate postoperative outcomes and relationship to preoperative findings [6,41].

There have been two long-term studies examining the durability of TPIAT for resolution of pain, glycemic control, and quality of life. In a 5-year follow-up study, Wilson and coauthors report their results in 195 patients [40]. Annual visits and hospitalizations decreased from 6 and 4, respectively, to 0 for each of years 1, 2, and 5 after surgery. Postoperative quality of life scores significantly improved with a durable improvement at 5 years for both physical and mental well-being. Finally, median oral morphine equivalents were significantly reduced and remained significantly lower than preop (214 mg/kg before surgery, 69 mg/kg at 5 years postoperatively). A second study, reporting 10-year

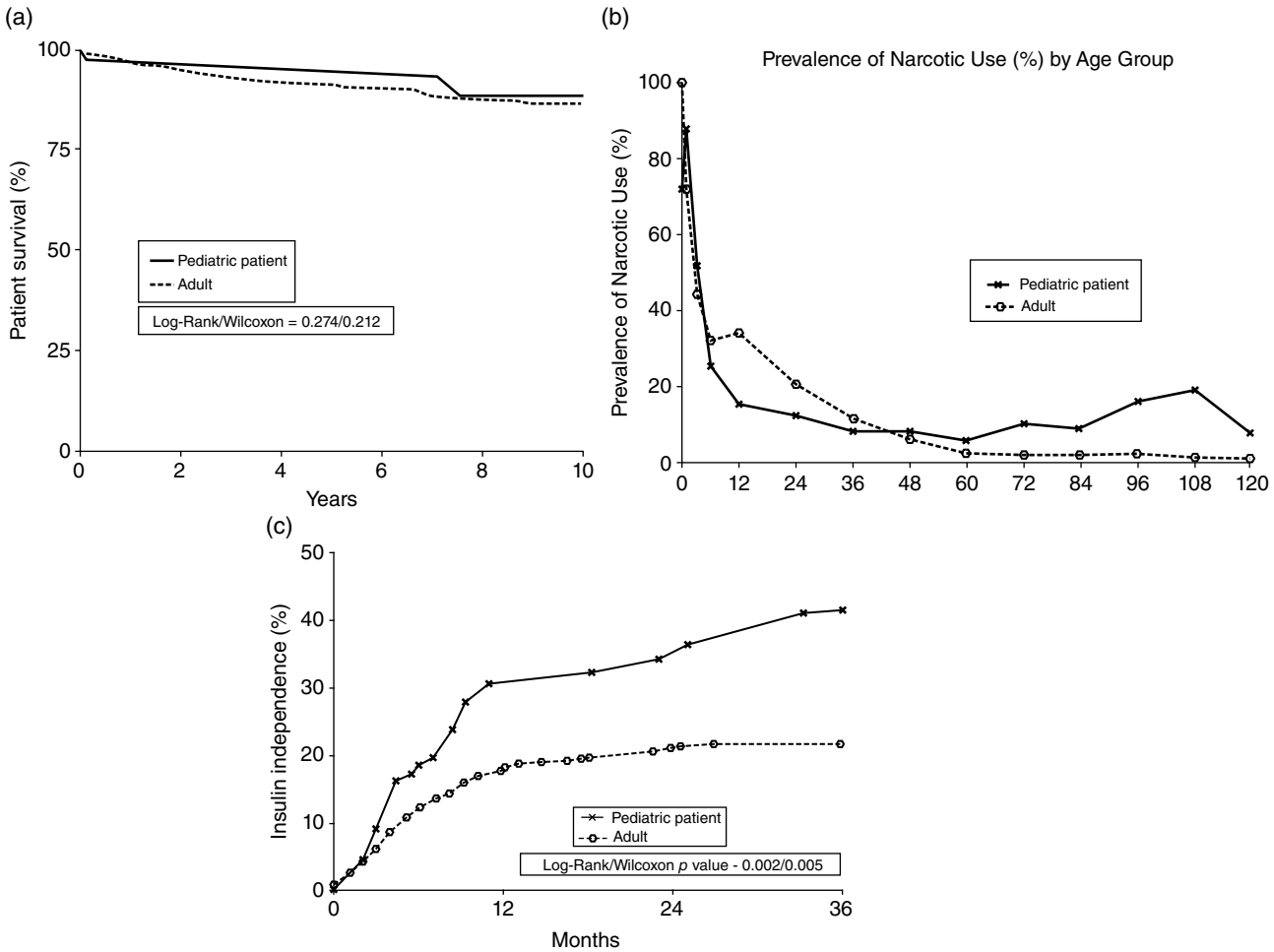

Figure 66.2 Outcomes after total pancreatectomy with islet autotransplant (TPIAT) in 581 patients at a single center [38]. (a) Ten-year actuarial survival in adults and children after TPIAT. (b) Narcotic-free percent in adults and children after TPIAT. (c) Insulin-independence in adults and children after TPIAT. *Source:* Chinnakotla et al. 2015 [38]. Reproduced with permission.

outcomes in 215 patients [42], noted a 10-year actuarial survival rate of 72%. Narcotic use declined with time: the rates were 50% at 5 years and 37% at 10 years. At 10 years, the rate of insulin independence was 20%; the rate of partial graft function, 32%. Transplantation of islet equivalents/kg >4000 was the strongest predictor of islet graft function at 10 years. Health-related quality of life continued to improve at 10 years, even in patients on narcotics.

In conclusion, total pancreatectomy with islet autotransplantation has become a viable option for selected patients with painful chronic pancreatitis, with long-term success in terms of pain relief and glycemic control.

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