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Pharmacological management of patients undergoing total pancreatectomy with auto-islet transplantation

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ABSTRACT

Chronic pancreatitis results in permanent parenchymal destruction of the pancreas gland leading to anatomical and physiological consequences for patients. Surgical management varies, and some patients require total pancreatectomy with autologous islet cell transplantation (TPIAT). Patients undergoing TPIAT require complex and diligent management after surgery. This encompasses the management of glucose control (endocrine function of the pancreas) and supplementing loss of exocrine function of the pancreas with digestive enzymes. Other areas of management include optimizing pain relief while reducing narcotic usage, providing antimicrobial prophylaxis, and reducing loss of islet cells by improving its integrity through anticoagulation and use of anti-inflammatory agents. Each aspect of care is unique to this population. However, comprehensive reviews on its pharmacological management are scarce. This review will discuss the available literature to date surrounding all aspects of pharmacological management of patients undergoing TPIAT.

1. Introduction

Chronic pancreatitis results in permanent parenchymal destruction of the pancreas gland leading to anatomical and physiological consequences for patients. It often results in chronic pain requiring narcotics, exocrine insufficiency requiring pancreatic enzyme supplement and type 3C diabetes requiring insulin. The prevalence of chronic pancreatitis varies from 5 to 50/100,000 adults [1]. Medical and endoscopic managements are usually the initial treatment approach, and patients are often referred for surgical management upon the failure of these treatments [2]. Surgical management varies from different kinds of parenchymal preserving surgeries like head or tail resections or ductal drainage procedures to some patients requiring total pancreatectomy with/without autologous islet cell transplantation (TPIAT).

TPIAT has been shown to improve quality of life, provide pain relief, and prevent brittle type 3c diabetes [3]. TPIAT is being increasingly utilized for these patients especially in the United States. According to the Collaborative Islet Transplant Registry (CITR), a total of 819 auto-islet patients have been reported between 1999 and 2015 within North America (11 of 23 sites), Europe (4 sites), and Australia contributing 754, 63, and 2 patients, respectively [4]. In short, TPIAT involves performing a total pancreatectomy, isolating the islets of Langerhans by enzymatic

Abbreviations: AI, Anti-inflammatory; ANA, Anakinra; aPTT, activated partical thromboplastin time; CGM, Continuous glucose monitoring; DGE, Delayed gastric emptying; EA, Epidural anesthesia; ERAS, Enhanced recovery after surgery; ETA, Etanercept; GI, Gastrointestinal; GIP, Glucose-dependent insulinotropic; GLP-1, Glucagon-like peptide; HbA1c, Hemoglobin A1c; HCQ, Hydroxychloroquine; IBMIR, Instant blood mediated inflammatory response; IL-1RA, Interleukin-1 receptor antagonist; LMWH, Low molecular weight heparin; MCP-1, Monocyte chemoattractant protein-1; ME, Morphine equivalent; NSAID, Nonsteroidal anti-flammatory drug; PCA, Patient-controlled analgesia; PERT, Pancreatic enzyme replacement therapy; POD, Post-operative day; TNF, Tumor necrosis factor; TPIAT, Total pancreatectomy with autologous islet cell transplantation; TPO, Thrombopoietin.

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digestion of pancreas, and injecting the purified or partially purified islet cells into the portal vein of the liver where they disperse and become lodged in the liver in order to engraft and carry out their function in producing insulin [5–7]. These patients require complex and diligent management after their surgery and management spans the close monitoring and control of glucose (endocrine function of the pancreas), continued pain relief while reducing narcotic usage, optimization of antimicrobial prophylaxis, reduce loss and improve integrity of islet cells through anticoagulation and anti-inflammatory agents, and supplementation of the lack of secreting digestive enzymes (exocrine function of the pancreas) [5,8,9]. Each aspect of care is unique to this population.

There is good amount of data on the outcomes and success of this procedure [3,6–9]. However, there is scarcity of comprehensive reviews on its pharmacological management. As can be imagined, these patients require management at different stages encompassing different areas such as peri-operative anticoagulation, antibiotics, anti-inflammatory medications, anti-glycemic medications, and use of pancreatic enzymes. This review will discuss the available literature to date surrounding all these aspects of the pharmacological management of patients undergoing TPIAT.

2. Anticoagulation management

The surgical procedure of TPIAT requires the dissection to explant the native pancreas, which demands careful hemostasis [8]. In addition, high tissue volume and elevated portal pressure during islet cell infusion increase the risk for portal vein thrombosis [10,11]. Beyond that, pre-existing patient risk factors, such as a hypercoagulable disorder may increase the risk of thrombosis [12]. Hepatic veins are generally not at risk since the size of islet cells are such that they seldom cross the hepatic sinusoids. Instant blood mediated inflammatory response (IBMIR) that happens during islet infusion is restricted to pre-sinusoidal and sinusoidal hepatic circulation and does not involve hepatic veins. Anticoagulants are not only used to lessen the risk of thrombosis, but also to aid with islet engraftment. Balancing the risk of bleeding with thrombosis is critical, and there have been significant variations regarding anticoagulation practices both intra- and post-operatively among centers; specifically, with regard to agent of choice, monitoring, and duration [8,13,14].

Previously, anticoagulation practices were surveyed among autologous islet cell programs enrolled in the CITR. Roughly one-third of programs completed a hypercoagulability work-up prior to TPIAT with two-third of the programs categorizing patients as high-risk for thrombosis prior to TPIAT based on prior thrombotic events and/or hypercoagulable disorders [13]. The majority of programs used intravenous (IV) heparin bolus before the infusion of islet cells and added heparin to the final islet cell product. The dosing of IV heparin varied among programs ($n = 3$, 0–50 units/kg; $n = 1$, 51–100 units/kg; $n = 2$, 70 units/kg; $n = 1$, 15 units/kg; $n = 1$, 2500 units). A continuous IV heparin drip was the most reported type of anticoagulation in the post-operative period [13,14]. Activated partial thromboplastin time (aPTT) was used for monitoring in 80% of these programs with goal ranges of 45–50 s(s) or >50s, and most programs discontinued the infusion after 24–48 h [13]. Subcutaneous (SQ) low molecular weight heparin (LMWH) is widely used at some phase post-operatively with anti-Xa goal range of 0.4–0.6 IU/mL (60%). The duration of LMWH used for the majority of programs was <1 week (38.5%) or around 2 weeks (30.7%) [13]. Overall, portal vein thrombosis was reported by zero programs while eight bleeding episodes were reported in 120 patients surveyed [13]. Robbins et al. evaluated the use of prophylactic unfractionated heparin as a continuous infusion (~5 units/kg/hr) until post-operative day (POD) 3–5, then transitioned to enoxaparin through POD 7, vs enoxaparin 40 mg SQ twice daily for 7 days and found no statistical difference in portal vein thrombosis (5% vs 8%, $p = 0.5$). Anti-Xa levels were not drawn or reported in this study for enoxaparin. Other thrombotic complications were higher in those receiving enoxaparin (6% vs 0%, $p = 0.02$); however, 3 of the 5 complications were provoked. No difference was found between the two regimens when it came to bleeding complications [14]. Naples and colleagues evaluated heparin dosing of <60 (median dose 52 units/kg) vs > 60 units/kg (median dose of 66 units/kg) in 80 patients on post-operative hemorrhage and portal vein thrombosis. No difference was noted in hemorrhage rates and neither group had any portal vein thrombosis with the author concluding a lower heparin dose closer to 50 units/kg would be preferred [15].

Another aspect of TPIAT is the reactive thrombocytosis, which is concerning for thrombotic events such as portal vein thrombosis due to the platelet hyperaggregation. With the removal of the spleen thrombocytosis is common [16]. The timing of the platelet rise post-TPIAT has been found to be similar to post-splenectomy, but more pronounced [17–19]. An additional contributing factor in TPIAT is the increased secretion of hepatically synthesized thrombopoietin (TPO). TPO is a glycoprotein which regulates platelet production by stimulating the production and differentiation of megakaryocytes. This is believed to potentiate the thrombocytosis and has been shown to be elevated from baseline post-TPIAT [20]. Further, TPO is triggered by significant local inflammatory response, such as IBMIR seen with TPIAT [20]. It is generally recommended to not treat reactive secondary thrombocytosis as it is self-limiting [21]. However, with the need for anticoagulation post-TPIAT and further risks of thrombosis, in particular, portal vein thrombosis, aspirin is used to reduce platelet activation and aggregation [13]. In the adult population, a survey found 5 of 15 centers reported using aspirin post-operatively with its initiation on POD1-7 [13]. Three of the five programs used a dose of 81 mg daily while others used 325 mg daily [13]. The duration of antiplatelet therapy once started is lacking. Once the thrombocytosis resolves, it would be appropriate to discontinue aspirin therapy unless other indications for its use are warranted. Currently, there is no available data on the cardiovascular benefit in this population with aspirin therapy. Considering many patients who undergo TPIAT have diabetes, it would be interesting to gather the data on their cardiovascular comorbidities and role of aspirin in preventing major cardiovascular or cerebrovascular event. In addition to aspirin, hydroxyurea, a ribonucleotide reductase inhibitor, has been studied in pediatric TPIAT patients for its cytoreductive effect for extreme thrombocytosis (>1000 K/μL) [19,22]. Although anagrelide, a phosphodiesterase inhibitor approved for essential thrombocytosis, works by inhibiting the maturation of platelets from megakaryocytes, its use has not been reported post-TPIAT.

3. Anti-inflammatory management

IBMIR occurs during the infusion of islets when the islets become subjected to blood, thus causing coagulation and complement activation [23]. Disruption of the islet morphology and function results due to the infiltrating leukocytes, in particular polymorphonuclear cells. These cells are attracted by the upregulation and release of ischemia-induced molecules and by proinflammatory signals [24–26]. This disruption of islet cells than makes the islet cell yield less effective. Anti-inflammatory (AI) agents have been used to improve islet cell function, and regimens include a tumor necrosis factor (TNF) blocker with and without an interleukin-1 receptor antagonist (IL-1RA). These agents overall decrease the effects of proinflammatory cytokines, thus minimizing the harmful effects of IBMIR [27–30].

The majority of studies assessing the use of anti-inflammatory agents have been in the allogenic islet cell transplant population. The use of etanercept (ETA) monotherapy was evaluated in seven studies, all in the allogenic islet cell transplant population [31–37]. However, there are no studies evaluating anakinra (ANA) alone. The combined use of ETA and ANA in allogenic islet cell transplants was evaluated in two studies with one of those being more focused on infectious outcomes [38,39]. Infliximab is no longer the agent of choice for the TNF blocker as one prospective, randomized study did not find clinical benefit with its use [40].

One study evaluated TPIAT patients and compared ETA or ETA and ANA to a control of no anti-inflammatory agents. Both IL-8 and monocyte chemoattractant protein-1 (MCP-1) were significantly reduced back to a baseline level with the administration of ETA and ANA. The use of ETA alone resulted in reduced levels compared to control, but not as pronounced as the combination therapy. Both groups had similar IEQ/kg (islet cell yield) and found the secretory unit of islet transplant objects at six months was significantly better with the combined regimen vs ETA alone; however, there was no difference in these groups compared to the control group. Further, both anti-inflammatory regimens had lower HbA1c at 6 months compared to the control [41]. Safety of these agents was not assessed in the study.

With the use of anti-inflammatory agents, there is a potential of increased infections. Of the studies evaluating anti-inflammatory agents, only one serious infection has been reported (diabetic jaw myonecrosis with associated bone and muscle infection) and noted to be unrelated to the use of an AI agent [36]. Only six of the studies evaluating AI agents have included infectious outcomes [31–42]. Further, the infectious risks of the anti-inflammatory agents are challenging to assess due to most studies being conducted in allogenic islet cell transplant patients where immunosuppression is also used. When using these agents, they do have a warning for serious infections (Table 1) [38,43–45]. Patients using these agents per their United States Food and Drug Administration indication likely will be on them for a longer duration, thus, increasing their infectious risks [43–45]. Recently, the use of hydroxychloroquine (HCQ) for its immunomodulatory effects and reduction of platelet aggregation was studied in a randomized, placebo controlled pilot study where TPIAT patients were given HCQ 200 mg daily for 30 days prior to and 90 days after TPIAT. Their primary endpoint was to assess the *in vivo* islet function using the quotient of C-peptide/glucose 90 min after Mixed Meal Tolerance Testing. Both this primary endpoint and their secondary endpoints were not statistically significant [47]. The use of anti-inflammatory agents provides a reduction in inflammatory markers, thus reducing IBMIR to preserve islet cells' function. The 10th Annual Report of the CITR comments on the use of a TNF blocker with its association in improved clinical outcomes [46]. Further based on Nazziruddin et al., results in TPIAT, the addition of ANA to ETA may be considered along with individual factors, such as their infectious history and risks.

4. Pain management

The ultimate goals of TPIAT are to provide pain relief and improve quality of life. Post-operative pain management is challenging as many patients may have developed central sensitization and opioid induced hyperalgesia due to prolonged opioid exposure [3,48]. In a large single center study (N = 409), 97% of patients undergoing TPIAT used narcotics preoperatively. Narcotic usage decreased post-operatively to 91% at 3 months, 61% at 6 months, 54% at 12 months, and 51% at 24 months [3]. The majority (94%) of patients reported improvement in pain as well as quality of life at one year after TPIAT [3].

In the immediate post-operative period, a multimodal approach to opioid sparing pain control should be utilized [49]. Implementation of an enhanced recovery after surgery (ERAS) program, with post-operative analgesia using a midthoracic epidural or patient-controlled opioid analgesia (PCA) has been associated with a significantly shortened length of stay (hazard ratio 1.61; 95% CI 1.07–2.44) after pancreatectomy without islet autotransplantation [50]. However due to anticoagulation use post-TPIAT, epidural anesthesia (EA) is not an ideal option and not used by centers offering this surgery. Another technique, including thoracic paravertebral blocks, has been used given the potential to cause less hypotension and decreased theoretical risk of epidural hematoma with EA [51]. In a retrospective study of pediatric patients (N = 32) who underwent TPIAT for chronic pancreatitis, a bilateral thoracic paravertebral catheter with continuous ropivacaine 0.2% at a rate of 0.2–0.25 mL/kg/hr was used for 7 days post-operatively. All patients were initiated on a heparin infusion (10 units/kg/hr) for 7 days. Those who received the paravertebral block had significantly decreased opioid utilization within 7 days post-operatively compared to those controlled with a PCA (712 vs 944 mcg morphine, p = 0.043), no differences in complications or cases of bleeding were observed [51].

PCA is commonly initiated post-operatively. In a Cochrane review, post-operative patients receiving a PCA had decreased pain intensity scores and improved patient satisfaction compared to those who received non-PCA analgesia [52]. Commonly used opioids in PCAs (ie: morphine, fentanyl, hydromorphone) are described in Table 2. After TPIAT, opioid dose requirements are expected to increase compared to baseline to address surgical pain. The patient's home pain medication regimen and dose requirements should be considered when managing pain post-operatively.

To provide a multi-modal opioid sparing approach, adjuvant agents such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and gabapentinoids (ie: gabapentin, pregabalin)

Table 1
Anti-inflammatory agents [44,45].

Anti-inflammatory agent	Dosing for TPIAT (non-FDA approved)	Infectious considerations	Pertinent drug interactions
TNF blocker		Testing for latent TB prior to use. Testing for hepatitis B prior to its use, during, and several months after TPIAT for potential reactivation in patients previously infected with hepatitis B (hepatitis B carriers). Due to the potential risk of invasive fungal infections with etanercept noted, anti-fungal coverage may be advised.	A higher rate of serious infections has been observed in RA patients treated with concurrent anakinra and etanercept therapy than in patients treated with etanercept alone. The combined use is not recommended. Live vaccinations should be avoided.
Etanercept	50 mg IV, 1 h prior to islet cell infusion, then 25 mg SQ on POD 3, 7, 10		
IL-1 receptor antagonist			
Anakinra	100 mg IV or SQ intra-operatively, then 100 mg SQ daily from POD1-POD7		

IL-1 = interleukin-1; IV = intravenous; POD = post-operative day; RA = rheumatoid arthritis; SQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor.

Table 2
Common analgesics for acute post-operative pain [57].

Drug	Administration route(s)	Mechanism of analgesia	Considerations/Cautions
Common Opioid Analgesics			
Morphine	IV, PO, SC	Pure μ receptor agonist	Active metabolites accumulate in renal impairment Causes histamine release (hypotension, urticaria, pruritus, and tachycardia)
Fentanyl	IV, transdermal	Pure μ receptor agonist, synthetic opioid	Quick onset Short duration Less hemodynamic disturbance Preferred in hepatic impairment
Hydromorphone	IV, PO, SC	Pure μ receptor agonist	Morphine derivative Preferred in renal impairment
Oxycodone	PO	Pure μ receptor agonist	
Tramadol	PO	Synthetic opioid, inhibits uptake of NE and 5HT	May interact with serotonergic medications
Non-opioid analgesics			
Acetaminophen	IV, PO	Various (inhibition of COX, activation of descending serotonergic pathways)	Hepatotoxicity Maximum dose 3000–4000 mg/day (2000 mg/day in those with hepatic impairment)
NSAIDs (ibuprofen, celecoxib, ketorolac)	PO, IV (ketorolac)	Cyclooxygenase-1 and 2 inhibitor (ibuprofen, ketorolac) COX-2 inhibitor (celecoxib)	Gastrointestinal bleeding Renal impairment Cardiovascular events (decreased with COX-2 selective inhibitors) Maximum of 5 day duration (ketorolac)
Gabapentinoids (Gabapentin, pregabalin)	PO	Voltage gated Ca2+ channel inhibitors	Accumulation in renal impairment Sedation, mental status changes
Ketamine	IV, PO, intranasal, SL, rectal, topical	NMDA receptor antagonist	Dose dependent adverse effects (hallucinations, euphoria, nightmares, dissociation, hypertension, tachycardia, hypersalivation) Contraindicated in pregnancy, uncontrolled psychiatric, cardiac, or severe hepatic disease

should be initiated post-operatively. The American Pain Society Guidelines on the Management of Post-operative Pain recommend that all patients be initiated on acetaminophen and/or NSAIDs post-operatively, unless contraindicated and gabapentinoids be considered, particularly in those on opioids prior to surgery [53]. Addition of these agents has been associated with decreased post-operative pain and opioid use compared to opioids alone [54].

For patients with pain refractory to standard analgesics, alternative analgesics should be considered. Ketamine is a *N*-methyl-D-aspartate receptor antagonist with anesthetic and analgesic properties [55]. Ketamine is an ideal analgesic post-operatively as it preserves cardiac output, gut motility, and respiratory function. It is particularly useful for those undergoing painful surgeries (ie: upper abdominal, thoracic), opioid-tolerant patients, and those unable to use opioids (ie: obstructive sleep apnea or history of abuse) [56]. At low doses (<0.35 mg/kg bolus or <1 mg/kg/hour infusion), ketamine provides analgesia, while at higher doses it provides both anesthesia and analgesia. Adverse effects are dose dependent and are reviewed in Table 2. A low-dose ketamine infusion is utilized at our institution after TPIAT for post-operative pain control. Starting doses for analgesia vary and range from 0.05 to 0.5 mg/kg/hour [55,57]. While no studies have been conducted specific to TPIAT, ketamine has been shown to decrease pain scores, opioid requirements, and the incidence of nausea/vomiting post-operatively in several meta-analyses and systematic reviews [58–60]. Alternative analgesic agents such as alpha 2 agonists (dexmedetomidine, clonidine), magnesium, dexamethasone, and methadone may be considered for refractory pain [57].

Pain management post-operatively requires a slow and controlled opioid wean for those with opioid dependence prior to TPIAT. In a review of 33 patients who underwent TPIAT, daily oral morphine equivalents (ME) increased by 50%, from an average of 357 mg (range 0–1492 mg) preoperatively to 536 mg (8-2518) post-operatively at discharge. In most patients, opioid weaning began at 3 months post-operatively and opioids were tapered outpatient on a monthly cadence. By 6 and 12 months, the average daily ME decreased by 55% (161 mg) and 64% (128 mg) from pre-operative requirements, with 23% of patients achieving opioid independence [61]. Given the gradual nature of opioid weaning after TPIAT, it is critical that a pain management specialist be included in the patient's care after surgery to facilitate narcotics tapering in a safe manner [62]. While the goal of TPIAT is to relieve pain, approximately 10–20% of patients will still have chronic pain post-TPIAT. This may be due to various causes such as neuropathy, pain centralization, or opioid-induced hyperalgesia [62,63].

5. Glycemic control management

The purpose of TPIAT is to prevent brittle diabetes and achieve euglycemic state. Strict glycemic control with insulin therapy is needed post-operatively as it takes time for the transplanted islet cells to recover and engraft, which typically occurs over the first 2–4 weeks [64,65]. Islet cell engraftment and survival is highly dependent on the islet mass infused and achievement of euglycemia post-operatively [3].

5.1. Post-operative glycemic control

In the immediate post-operative period, an IV continuous insulin infusion should be initiated and titrated to achieve target blood glucose as close as possible to physiologic values, while minimizing the risk of hypoglycemia [66]. The University of Minnesota shared their experience using a post-TPAIT insulin infusion protocol in pediatric patients. In this protocol, the IV insulin infusion is usually initiated at a rate of 0.025–0.05 units/kg/hour (maximum 2 u/kg/hour) and titrated to achieve a target blood glucose of 100–120 mg/dl. Blood glucose is monitored every 1 h for the first 48 h and the insulin infusion is adjusted [66]. Once tolerating full enteral feeds, patients are transitioned to subcutaneous insulin (median 6.9 days post-TPIAT). Long acting insulin dosages calculated using 100–120% of total daily IV insulin dosed. Rapid acting insulin is given every 4 h as needed using an insulin to

correction ratio of 1 unit for every 25–50 mg/dl over 125 mg/dl. An insulin to carbohydrate ratio of 0.5–1 units for every 15 g was initiated once the patient was eating. When comparing blood glucose control between IV and SQ insulin administration, one study reported theIV insulin therapy was associated with significantly lower glucose values (116 vs 128 mg/dl) and glucose variability compared to SQ therapy with multiple daily injections [66].

Forlenza et al. explored the feasibility of using a closed loop system with an insulin pump and continuous glucose monitor postoperatively. In this randomized controlled pilot study, 14 adult patients were randomized to a closed-loop therapy with an insulin pump and continuous glucose meter (CGM) or multiple SQ daily injections (basal and boluses every 4 h as needed) with blinded CGM for 72 h at transition from IV to SQ insulin (about 4–8 days after surgery once reached full enteral nutrition). Blood glucose was titrated to a goal of 80–125 mg/dl. In the closed loop group, mean blood glucose concentrations were significantly lower (111 vs 130, $p = 0.003$); no difference in percentage of time with hypoglycemia was observed (1.9% vs 4.8%, $p = 0.48$) [67]. Similarly, in the pediatric population, early transition from IV insulin to pump therapy after TPIAT has been associated with significantly less glucose variability, improved glucose control, and a decreased length of stay by 5 days [68].

5.2. Outpatient glycemic control

Typically, exogenous insulin therapy is needed for at least 3 months post-operatively and should be weaned gradually based on blood glucose control and HbA1c values [65]. Achievement of insulin independence post-TPIAT is often marginal. In a meta-analysis of 15 observational TPIAT studies, only 30% achieved insulin independence at 1-year after TPIAT [69]. In another large study of 409 patients undergoing TPIAT, at 3 years 30% achieved insulin independence and 30% had partial graft function (defined as a positive blood C-peptide > 0.6 ng/mL or ability to maintain target glucose control with once daily basal insulin) [3].

Insulin should be titrated and adjusted to achieve target blood glucose values. Target blood glucose values range from 70 to 130 mg/dl fasting and <180 mg/dl postprandial. The American Diabetes Association recommends a goal HbA1c value of <7% for most adults but endorses select individuals may benefit from more intensive glucose control. Data in TPIAT suggests these patients may benefit from even tighter control with a goal HbA1c of <6.5% to prevent islet cell damage from hyperglycemic stress [3,65].

Non-insulin antihyperglycemic agents aimed at improving islet cell survival and metabolic outcomes post-TPIAT have been studied. Glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP) both play a role in stimulating beta cell insulin secretion as well as beta cell health. GLP-1 agonists such as exenatide have been studied in islet transplant patients with graft dysfunction and have demonstrated positive effects on glucose control and islet cell function [33]. These agents are notorious for causing gastrointestinal upset (ie: nausea, vomiting, delayed gastric emptying), which is problematic after TPIAT. The dipeptidyl peptidase 4 (DPP-4) inhibitors have improved tolerability compared to GLP-1 agonists. DPP-4 is the enzyme that degrades GLP-1. Consequently, these agents not only increase endogenous GLP-1 and GIP, but also have been shown to increase beta cell mass through inhibition of beta cell apoptosis and induction of proliferation [70]. Bellin et al. reported the use of sitagliptin, a DPP-4 inhibitor, after TPIAT. In this randomized double-blind placebo-controlled trial, 83 adult TPIAT patients were randomized to sitagliptin 100 mg daily or placebo for 12 months. At 12 and 18 months, there was no significant difference in insulin independence, insulin dose, HbA1c levels, or insulin secretory measures. Adverse events were similar [71]. Another study conducted by Senior et al. investigated the effect of sitagliptin, in combination with a proton-pump inhibitor as the gastrointestinal hormones, gastrin and incretin, may play a role in beta cell survival. In this single center, open label trial, 8 islet transplant patients with early graft insufficiency were initiated on sitagliptin 100 mg daily and pantoprazole 40 mg twice daily for 6 months. The authors reported improvement in islet cell function with achievement of insulin independence in 2 of 8 participants and reduced insulin doses in others. This benefit was lost once the agent was discontinued [72].

Recent advancements in technology have made continuous glucose monitoring (CGM) systems an accurate and extremely useful monitoring tool for analyzing blood glucose trends and detecting hypoglycemia. CGM devices such as the Dexcom (G4, G5, G6) and Medtronic (Enlite 2) have been used in the immediate post-operative period in TPIAT populations. These systems have been associated with acceptable accuracy compared to serum glucose values [73–76]. Use of CGM in the post-operative period after TPIAT has been associated with lower blood glucose values and higher satisfaction rates compared to controls self-monitoring blood glucose [77]. They also aid in detection of spontaneous hypoglycemia, a known complication of TPIAT. Cases of spontaneous, fasting, post-prandial, and exercise induced hypoglycemia have been reported post-TPIAT, despite no exogenous insulin administration [78,79]. Abnormalities in alpha cell function resulting in decreased glucagon response are thought to play a role in the development of this. This may be responsive to changes in dietary intake such as minimizing fasting durations, intake of lower glycemic index carbohydrates, and higher protein content food [78,79]. CGMs may be particularly useful in these situations as they can help to predict and identify trends in hypoglycemia, allowing for a more comprehensive understanding of islet cell function after TPIAT [76]. One caveat of CGM systems is that they should not be used in those receiving hydroxyurea, as this can result in artificially elevated blood glucose readings [80].

6. Antimicrobial prophylaxis

Contaminant of the islet cell product could arise during the surgery of pancreatectomy, the transport to the isolation facility in preservation solution, the cannulation of pancreatic duct with enzymes, and the isolation process [81]. Further, some patients are at increased risk of being colonized with bacteria due to prior endoscopic interventions, such as stent placements. Microbiological testing is commonly acquired from the preservation solution, cannulation solution, and of the final islet cell product with the primary focus being on the culture results of the final islet cell product as those are being infused back into the patient.

Data is limited on the clinical impact of the islet product's microbiological results [81–87]. Growth from final islet cell products have included gram positive organisms, such as *Enterococcus* spp *to Staphylococcus and Streptococcus* spp along with gram negative bacteria, such as *Klebsiella pneumoniae, Escherichia coli,* and *Citrobacter* spp. Anaerobic bacteria in addition to *Candida* spp are also reported [81,88]. Clinical practice guidelines for antimicrobial prophylaxis in surgery do not include islet cell transplant. There are recommendations regarding antimicrobial prophylaxis for pancreas transplant (use of cefazolin and fluconazole if high-risk for fungal infection) and pancreaticoduodenectomy (use of cefazolin) [89]. Antimicrobial prophylaxis regimens reported intra- and post-operatively in TPIAT studies are inconsistent. Studies have highlighted the use of various antibiotics. Some report use of more narrow agents, such as cefoxitin, ciprofloxacin, and metronidazole while others use broader antibiotics, such as vancomycin, piperacillin/tazobactam, and ertapenem [81,86,88]. Combinations of the

agents are generally reported as empiric regimens peri-operatively and initially post-operatively, likely include an agent(s) that would cover gram positive and negative along with anaerobic bacteria. Some examples would include piperacillin/tazobactam or the combination of metronidazole, ciprofloxacin, and cefazolin [81,88]. Empiric coverage for methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcus has not been assessed in this population. With the use of AI agents and patient's risks for fungal infections (ex. history of multiple abdominal surgeries, diabetes), the addition of an anti-fungal agent, such as fluconazole, may be selected.

The post-operative duration and the additional need to provide further antimicrobial coverage based on culture results of the islet cell product is not standardized. Depending on the islet cell facility, the turnaround time for final islet cell product culture results could take up to, if not longer, than 72 h. Some centers may decide to continue empiric coverage until the final islet cell product is known or re-initiate appropriate antimicrobial agent(s).

7. Post-splenectomy vaccines

Removal of the spleen during TPIAT is often necessary, but rates of splenectomy vary across institutions [90]. Leaving the spleen intact may prevent post-splenectomy infection; however, spleen-sparing pancreatectomy carries risks of gastrointestinal bleeding, portal vein thrombosis, splenomegaly, infarcts and persistent pain [90]. As such, the patient's immunization status should be evaluated prior to TPIAT. Without a spleen, risk of infections from encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type B (Hib), and *Neisseria meningitidis*, is a major concern [91]. Overwhelming post-splenectomy infection is a syndrome occurring after spleen removal that carries a high mortality rate, with the highest rates of severe infections occurring in the first two years after splenectomy [91].

Currently, three types of vaccines are recommended for adult patients with asplenia: pneumococcal, Hib, and meningococcal vaccines (Table 3) [92,93]. Additionally, yearly vaccination with inactivated influenza vaccine is recommended for all immunocompromised individuals greater than 6 months of age [92]. Ideally, vaccinations would be given at least two weeks prior to TPIAT [92,93]. If vaccinations cannot be administered prior to the splenectomy, it is recommended to wait to administer the vaccines until after antibody response returns, typically at least two weeks after the procedure [92]. However, if patient compliance is a concern, then the first dose of these vaccinations should be administered prior to hospital discharge [94].

7.1. Pancreatic enzyme replacement

Pancreatic enzyme replacement therapy (PERT) is indicated in TPIAT patients as the pancreas is fully removed resulting in loss of its exocrine function [95]. Standard PERT contains three digestive enzymes: amylase, protease, and lipase to aid in digestion and subsequent absorption of carbohydrates, proteins, and fats. Without PERT, these patients can experience malabsorption, weight loss, fat soluble vitamin deficiencies and malnutrition [96]. PERT is initiated as soon as the patient can be started on a diet. Details of different products and dosages are described in Table 4. Of note, TPIAT patients may require enteral nutritional support if they are unable to meet their nutrition needs orally. There are several reasons oral enzymes are generally not recommended for use with enteral nutrition [97]. Adding crushed oral enzymes to enteral formula in tubes less than 14 French in diameter is contraindicated as this leads to the tubes becoming clogged. Also, oral enzymes will not provide adequate coverage for continuous or cycled feeds as activity peaks at 30 min and wanes over the next 2 h. Immobilized lipase cartridge (Relizorb®) is the only FDA approved enzyme to be used in line with enteral feeds.

7.2. Gastrointestinal symptoms management

In addition to pancreatic exocrine insufficiency, other gastrointestinal (GI) complications may occur after TPIAT. Up to 69% of patients report GI symptoms severe enough to interfere with daily life in the months following surgery [95]. In another study, GI problems, specifically delayed gastric emptying (DGE), were the most commonly cited reasons for re-admission after TPIAT [98].

DGE is associated with symptoms of nausea, vomiting, early

Table 3
Post-splenectomy vaccines [93].

Vaccines	Dosing	Additional information and considerations
Pneumococcal		
pneumococcal 20-valent conjugate vaccine (PCV20) **or** pneumococcal 15-valent conjugate vaccine (PCV15) **and** pneumococcal polysaccharide vaccine (PPSV23)	One dose of PCV15 or PCV20. If PCV15 is used, it should be followed by at least 8 weeks before a dose of PPSV23; otherwise, if PPSV23 is given first, then PCV15 or PCV20 can be given at least one year later.	For patients that have previously received a pneumococcal 13-valent conjugate vaccine (PCV13) only or both PCV13 and PPSV23, the previously recommended PPSV23 series should be completed. No data are available on the co-administration of PCV15 and PCV20 with other vaccines.
Haemophilus influenzae		
Haemophilus influenzae type B (Hib)	One dose	Can be administered along with other vaccines (different injection site)
Meningococcal		
Conjugate (Menactra®, Menveo®, MedQuadfi®) **and** Recombinant (Bexsero®, Trumenba®)	Two doses, spaced at least 8 weeks apart	Quadrivalent and provide protection against serogroup A, C, W, and Y; can receive the recombinant meningococcal vaccine at the same visit (different injection site)
	Bexsero®: two dose series, spaced at least 4 weeks apart; Trumenba®: three dose series at 0, 1–2, and 6 months	Monovalent and provide protection against serogroup B

Table 4
Pancreatic enzyme replacements [2,96].

Medication	Dosing	Timing of Dosing	Additional information and considerations
pancrealipase (Creon®, Zenpep®, Pancreaze®, Pertzye®, Ultresa®, and Viokase®)	Dosing for older children and adults is 500–4000 units lipase per gram of fat ingested or 500–2500 units lipase per kilogram of body weight per meal. Snack doses are generally considered 50% of a meal dose. Recommended upper limit for PERT dosing is less than 10,000 lipase units per kilogram per day, 4000 lipase units per gram of fat or 2500 lipase units per kilogram per meal. Dosing at or above these levels have been shown to cause increased risk of fibrosing colonopathy.	Beginning of each meal and snack. Some recommend breaking up the dose depending on meal length. For example, for a 15-min meal, may take full dose at beginning of meal, for a 30-min meal may take half of the enzyme capsules with the first bite and the other half in the middle of the meal.	Non-enteric coated enzymes are not effective when the gastric pH < 4.0 whereas enteric coated enzymes are designed to dissolve when the small intestinal pH ≥ 5.5. Patients who take pancrealipase (Viokase®), the only non-enteric coated pancrealipase, will also need concurrent treatment with an acid reducing agent, such as a proton pump inhibitor.
immobilized lipase cartridge (Relizorb®)	1 cartridge per 500 mL of enteral formula		Studied in the cystic fibrosis population with results showing positive effects in decreasing steatorrhea, bloating, and abdominal pain. Enteral nutrition formulas containing insoluble fiber or food particles have been deemed to be incompatible.

satiety and/or abdominal pain Readmission rates after TPIAT for patients with DGE were three times higher than for patients without DGE [98]. Several pathophysiologic mechanisms for DGE after pancreatoduodenectomy have been proposed: decreased secretion of motilin, dysfunction of the migrating motor complexes in the stomach and intestines, iatrogenic injury to the vagus nerve, and post-operative sequelae such as infection and fluid collections [99]. Use of opioids in the post-operative period may also worsen intestinal dysmotility [95]. Prokinetic medications such as erythromycin or metoclopramide are considered a key part of therapy for symptoms of delayed gastric emptying [100]. The efficacy of metoclopramide and erythromycin for DGE has been demonstrated in several trials, but little data exists on the long-term use of these agents [100]. Additionally, metoclopramide can cause numerous side effects, particularly dystonic reactions; while erythromycin has significant drug interactions through its metabolism by CYP3A4, both of which may limit use of these agents. Bile acid sequestrants, such as cholestyramine, may be used to improve bile reflux, which could occur post-TPIAT. Cholestyramine along with prokinetic agents will assist with reducing and preventing biliary reflux.

While prokinetic medications may alleviate symptoms of nausea and vomiting, additional therapy with anti-emetics may be indicated for refractory symptoms. 5HT-3 antagonists (ondansetron, granisetron) and phenothiazine derivatives (promethazine, prochlorperazine) have demonstrated efficacy in treatment of chemotherapy induced nausea and vomiting as well as several other indications [100]. In our experience, scheduling anti-emetic regimens around the clock may be beneficial in the early post-operative period to reduce nausea and vomiting.

Diarrhea was reported in 80% of patients in the first year after surgery in one study [95]. While other GI symptoms such as constipation and steatorrhea are correlated with adherence and dose of pancreatic enzymes, the incidence of diarrhea was not correlated with pancreatic enzyme dose, even at higher prescribed doses [95]. For diarrhea refractory to non-pharmacologic interventions, anti-diarrheal agents such as loperamide or diphenoxylate/atropine may provide some benefit.

8. Conclusion

Although the surgical and post-operative management of splenectomy and pancreatectomy have been more widely studied, aspects of TPIAT make its management unique. Literature surrounding the pharmacological management of these patients is limited as described in this review. With the variation among centers in practice, there is a lack of much needed consensus guidelines.

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