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The Impact of Bacterial Colonization on Graft Success after Total Pancreatectomy with Autologous Islet Transplantation: Considerations For Early Definitive Surgical Intervention

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Abstract

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10. Kenneth L. Brayman, M.D., Ph.D.¹: Study conception and design, acquisition of data (performed all islet transplants and a subset of TP operations), drafting and critical revision of the article, final approval

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Objective—The purpose of this study was to determine whether bacterial contamination of islets affects graft success after total pancreatectomy with islet autotransplantation (TPIAT).

Background—Factors associated with insulin independence after TPIAT are inconclusive. Although bacterial contamination does not preclude transplantation, the impact of bacterial contamination on graft success is unknown.

Methods—Patients who received TPIAT at the University of Virginia between January 2007 and January 2016 were reviewed. Patient charts were reviewed for bacterial contamination and patients were prospectively contacted to assess rates of insulin-independence.

Results—There was no significant difference in demographic or perioperative data between patients who achieved insulin-independence and those who did not. However, six of 27 patients analyzed (22.2%) grew bacterial contaminants from culture of the final islet preparations. These patients had significantly lower islet yield and C-peptide at most recent follow-up ($p<0.05$), and none of these patients achieved insulin-independence.

Conclusions—Islet transplant solutions are often culture-positive, likely secondary to pre-procurement pancreatic manipulation and introduction of enteric flora. Although autotransplantation of culture-positive islets is safe, it is associated with higher rates of graft failure and poor islet yield. Consideration should be given to identify patients who may develop refractory chronic pancreatitis and offer early operative management to prevent bacterial colonization.

Introduction

With a prevalence of approximately 50 per 100,000 persons in the United States, chronic pancreatitis places an immense burden on the health care system and can become a debilitating condition for those affected, resulting in both endocrine and exocrine insufficiency, in addition to chronic pain [1,2]. For patients with severe chronic pancreatitis (CP) that is refractory to conservative management, total pancreatectomy (TP) is a definitive operation that effectively treats the source of pain by removing the organ [3,4]. However, TP results in the loss of glucagon-dependent counter-regulation and difficult-to-manage glycemic control, even with supplemental insulin therapy [3,4]. First performed at the University of Minnesota in 1977, autologous pancreatic islet transplantation after total pancreatectomy was developed as a possible solution to this so-called, “brittle diabetes,” with the ability to replace functioning islet cells and potentially, the endocrine function of the pancreas [5,6]. Total pancreatectomy with islet autotransplantation (TPIAT) has demonstrated higher morbidity, but improved overall survival compared to total pancreatectomy without islet autotransplantation [7,8]. Importantly, patient satisfaction and health related quality of life (QoL) is often greatly improved both subjectively, as measured with questionnaires such as the RAND 36-Item Short Form Health Survey and objectively, with decreased opiate requirements postoperatively [3,7–9].

Unfortunately, rates of autologous islet graft failure and subsequent insulin dependence vary from 38 to 87.5% at one year of follow-up, with variable rates of insulin independence as time progresses postoperatively [3,4,9]. Data regarding the factors associated with success, as measured by pain relief and insulin independence are mixed, although studies have shown

correlations with high islet yield (in islet equivalents per kilogram of recipient body weight [IEQ/kg]), lower body surface area (BSA [m²]), and female gender [3,4,10,11].

During the processing of pancreata prior to transplantation, the islets are isolated from the exocrine glandular tissue and routinely washed with antimicrobial agents prior to transplantation. However in a subset of patients, bacterial contamination remains even after this protocol. Although studies are limited, current data suggest that patients with bacterial contamination infrequently develop culture-concordant infections and this contamination should not preclude transplantation [12–14]. The impact of persistent bacterial contamination on graft success is unknown and the purpose of this study was to determine whether bacterial contamination of the final islet preparation affects rates of insulin independence.

Materials and Methods

This study was a single-institution, retrospective and prospective cohort case series reviewed and approved by the University of Virginia Institutional Review Board for Health Sciences Research (IRB-HSR#18380). Patient data was collected from the electronic medical record and patients were prospectively surveyed with a scripted, telephone-based questionnaire developed for this study. Informed verbal consent was obtained for all patients participating in the telephone-based assessment. Only patients greater than 6 months post-TPIAT at the time of study implementation were included in the prospective follow up and subsequent statistical analysis.

Classification

Chronic pancreatitis was considered to be hereditary if patients had genetic mutations consistent with hereditary pancreatitis (i.e., *SPINK1*, *PRSS1*, *CFTR*, *CTRC*) or a suggestive history consisting of early-onset pancreatitis and multiple first-degree relatives with chronic pancreatitis and/or pancreatic cancer. Patients were defined as diabetic based on the following metabolic metrics: HgbA1c ≥ 6.5%, 2-hour GTT ≥ 140 mg/dL, C-peptide below the laboratory reference range (0.50–2.00 ng/mL), or if they were prescribed insulin and/or oral hypoglycemic agents prior to surgical consultation.

Operative Procedure

Preoperatively, all patients were given routine prophylactic antibiotics (Cefazolin 1–2g q4h, Cefoxitin 2g q3h, or Piperacillin-Tazobactam 3.375g q6h). All operations were performed by hepatopancreaticobiliary and transplant surgeons at the University of Virginia (V.Z., R.A., and K.B.). Operative technique involves removal of the pancreas, duodenum, and spleen followed by perfusion of the pancreas with SPS-1® Static Preservation Solution (Organ Recovery Systems, Inc.). All patients received a cholecystectomy if not performed prior. While the pancreas was being perfused and processed, the patients' gastric and biliary anastomoses were completed.

Islet Isolation and Transplantation

Pancreata were packed on ice and transported to the University of Virginia's Current Good Manufacturing Process (cGMP) islet isolation facility on the medical campus. Approximate

time between pancreatectomy and islet infusion was 4 hours. Pancreata were mechanically and enzymatically digested and all enzymes utilized were GMP grade and certified. For the first 2 autologous transplantations, Liberase HI® (Roche Diagnostics, Indianapolis, Indiana) was employed until production was discontinued. Serva Collagenase NB 1® with Thermolysin (Crescent Chemical Company, Islandia, New York) was utilized for the next 5 islet isolations and the laboratory has utilized Roche Liberase MTF® (Roche Diagnostics, Indianapolis, Indiana) since 2010. Islets were isolated using the standard Ricordi method with an average digestion time of 24.6 minutes. Nine of 29 (31%) isolated islet pellets were greater than 15 milliliters (mL) in volume and were purified based on Ficoll gradient purification using a COBE 2991® Cell Purification System (Terumo BCT, Terumo Medical Corporation, Somerset, New Jersey). Islets were loaded into transplant bags containing 250mLs CMRL 1066 Medium (Mediatech Inc., Corning Life Sciences, Corning, New York) supplemented with 2.5% human albumin, glutathione, HEPES (Mediatech Inc., Corning Life Sciences, Corning, New York) and were heparinized (70U/kg body weight) to prevent portal vein thrombosis. Total islet pellet volumes over 10mL were divided between 2 transplant bags to avoid unnecessary increase in portal vein pressure during transplant.

Pancreata were cannulated with an 18g catheter and cleaned with SPS-1® Static Preservation Solution (Organ Recovery Systems, Inc.) before being soaked in 7.5% Betadine solution, followed by an antibiotic solution (80mg Gentamicin, 1g Cefazolin, 100mg Amphotericin). The organs were then rinsed twice in sterile Hanks Balanced Salt Solution (Gibco®, Thermo Fisher Scientific, Waltham, Massachusetts) prior to infusion of digestive enzymes.

To determine sterility, all patients received 2 perioperative cultures. The first culture was of the transportation solution containing the pancreas specimen prior to islet isolation. The second culture was of the final islet preparation solution prior to infusion into the patient. Release criteria prior to transplantation includes a negative endotoxin release assay (< 5 EU/kg body weight), Gram stain of the final islet preparation, islet viability $> 70\%$, islet yield between 4,000 and 20,000 IE/kg body weight, and glucose stimulated secretion (GSIS) assay > 1.0 . Culture results are returned in the days following transplantation and typically resulted within 24-hours. After returning to the operating room, baseline portal venous pressures were measured and islet cells are infused through a portal venotomy. Portal venous pressures were measured and reassessed every 5-minutes, with care taken to prevent an increase of more than 10 mmHg above the baseline. Infusion times ranged from 15 to 60 minutes.

Perioperative Care

Patients with bacterial contamination were treated empirically with Vancomycin and/or Piperacillin-Tazobactam for Gram-positive organisms and Gram-negative organisms, respectively, and antibiotics were deescalated and tailored after speciation. Patients were generally extubated on post-operative day (POD) 0 and were observed in the intensive care unit (ICU) for close monitoring of vital signs and glucose levels and insulin titration. In order to reduce β -cell stress postoperatively, continuous insulin infusions were titrated to maintain blood glucose levels between 100–150mg/dL. Patients had a C-peptide level drawn

immediately postoperatively to assess graft function. C-peptide and HbA1c were measured during routine clinic follow-up.

Prospective Follow Up

An independent researcher, blinded to retrospective data, contacted patients based on information available in the electronic medical record. Once contacted, patients were recruited for willingness to participate, were verbally consented, and were questioned regarding their pre-and post-operative pain, insulin requirements, and narcotic usage.

Statistical Analysis

Demographic and clinical factors for individual patients were summarized and reported as frequencies and percentages for categorical variables. Continuous variables are reported as a median with an interquartile range (IQR). Distributions of data were tested and found to be non-normally distributed and continuous variables were analyzed using Mann-Whitney *U* test. Categorical variables were analyzed using either Chi-squared or Fischer's exact tests for categorical variables, or Wilcoxon rank-signed test for matched samples. An α level of 0.05 was utilized as a threshold for statistical significance. All statistical analysis was performed using Stata® Version 14.1.

Results

Demographics

Since January 3rd, 2007, the University of Virginia has performed 29 TPIATs and 27 patients were eligible for study inclusion. Each patient had a history of multiple hospital admissions and 25 patients had undergone prior endoscopic interventions. No patient had undergone pancreatic surgery prior to TPIAT. All patients had persistent symptoms despite non-operative management.

The median age at the time of operation was 42 years (range 14–64 years) (Table 1). There were 9 men and 18 women and the mean and median duration of chronic pancreatitis was 7.4 ± 1.8 years and 4.1 years (range 2 months to 42.4 years), respectively. The largest causal etiology was idiopathic chronic pancreatitis (N=9), followed by hereditary/genetic (N=7), biliary, alcoholic, traumatic, and pancreas divisum. 11 of 27 patients (40.7%) had evidence of diabetes and/or insulin resistance, however only 3 were using injectable insulin for glucose control.

Perioperative Data

Median islet equivalent (IEQ) transfused was 192,000 and ranged from 42,000 to 523,000 (Table 2). Median intraoperative blood loss (EBL) and intravenous fluid (IVF) infusion was 500mL and 6,500mL, respectively. Eight cases required intravenous blood product transfusion. Postoperative median ICU stay was 1 day and median hospital length of stay (LOS) was 7 days (ranging from 5 to 52 days).

Clinical Outcomes

Of the 27 patient cohort, 19 patients were successfully contacted via telephone-based survey. 7 of 19 patients (25.9% of the full cohort who received TPIAT) are currently insulin-independent a median of 2.92 years post-transplantation (ranging from 6 months to 7.7 years post-transplant) and 5 of the 7 insulin-independent patients are female (71.4%). Four of 27 patients (14.8%) developed complete islet failure (CIF) postoperatively, defined as fasting C-peptide <0.3ng/mL by the Collaborative Islet Transplant Registry [15]. None of these 4 patients achieved insulin independence. There was no significant difference in demographic data, islet yield transplanted, or perioperative data between the two groups (Table 3). However, patients achieving insulin-independence had significantly fewer stents placed ($p<0.05$) and approached significance for a lower number of ERCPs performed prior to TPIAT ($p=0.051$) (Table 3). Eleven of 19 patients (58%) are currently weaned from narcotic pain medications.

59.3% of patients grew microbial flora in the transportation solution, often coagulase-negative staphylococcus species, α -hemolytic streptococci, or flora reported as mixed unspciated flora by our laboratory. Six of 27 patients (22.2%) grew bacterial contaminants in the final islet preparation. Patients with bacterial contamination in the final islet preparation had significantly lower IEQ/kg patient body weight, IEQ/BMI, IEQ/BSA, and C-peptide at most recent follow up ($p<0.05$) (Table 4). Of note, no patient with bacterial contamination was diabetic prior to his or her operation ($p=0.041$). All patients with bacterial contaminants in the final islet preparation are currently insulin-dependent. The bacteria grown in culture were diverse and polymicrobial, and despite all patients passing release criteria with 5EU/kg of endotoxin released, 5 of 6 grew Gram-negative rods in culture (Table 5). There was no significant difference in number of ERCPs or stents amongst patients who grew bacterial contaminants and those who did not. However, patients with bacterial contamination approached significance for an increased number of stents present compared to patients who would ultimately become insulin-independent ($p=0.053$).

Five of 6 patients with bacterial contaminants did not experience any infectious complications during their hospitalization. The second patient transplanted with contaminated islets developed hospital acquired pneumonia (HAP), however their sputum culture grew *Enterobacter cloacae* and *Staphylococcus aureus* (coagulase-positive staphylococci), a finding discordant from the islet culture which speciated as *Staphylococcus haemolyticus* (coagulase-negative staphylococci) (Table 5).

Discussion

Total pancreatectomy (TP) is a potential solution to the unremitting and multifactorial pain of chronic pancreatitis and islet autotransplantation (IAT) has been utilized to preserve patients' endogenous β -cell function. Data regarding factors leading to successful outcomes after TPIAT are mixed. Despite the series size, current rates of insulin independence at the University of Virginia are comparable to previously published data, which report insulin independence in 21.7–34.2% of patients after TPIAT [4,8,16]. Unlike prior studies, this is the first series to demonstrate the potential adverse impact of bacterial colonization, resulting in a statistically significant difference in islet yield, insulin independence, and

subsequent graft function as measured by C-peptide and consequently, the overall success of performing TPIAT on patients with chronic pancreatitis.

Prior to transplantation, established release criteria for islet products must include sterility metrics such as the absence of bacteria on Gram stain and acceptably low levels of endotoxins in the final preparation. Contamination in the pancreatic transport solution is reported as high as 61–68% with only 5.5 to 32.3% of final islet preparations growing bacterial contaminants after rigorous GMP isolation and antimicrobial protocols [12,17–19]. Our rate of contaminated transportation solution was comparable at 59.3% and contamination was substantially reduced to 22.2% in the final islet preparation with the aforementioned protocols.

Studies have demonstrated the sterility and antimicrobial capacity of pancreatic fluid and researchers have postulated that any bacterial colonization of pancreatic tissue is likely due to iatrogenic manipulation of the pancreatic duct [14,20,21]. Ascending bacterial colonization can occur through retrograde migration from the intestinal lumen (more likely after pancreatic surgery) or through the formation of a biofilm on the surface of pancreatic duct stents [14,20,22]. More specifically, a recent study by Hill *et al* cultured pancreatic duct stents placed by a single operator at a tertiary referral center and reported that 28 of 47 stents grew clinically significant bacteria, the majority of which belonged to the Enterobacteriaceae family of Gram-negative bacteria, a finding consistent with our report [23].

Bacterial colonization alone may impact islet engraftment by eliciting an inflammatory response upon transplantation [14]. Recent data has demonstrated the ability of lipopolysaccharide (LPS), a component of Gram-negative bacterial cell membranes, to increase β -cell apoptosis in-vitro. The same researchers found that by inhibiting toll-like receptor-4 (TLR4), the key receptor for LPS, in-vivo, they could achieve increased islet mass engraftment and allogeneic islet graft survival [24]. Whereas prior studies have demonstrated a preponderance of Gram-positive organisms such as *Staphylococcal*, *Streptococci*, and *Enterococcal* species, 5 of 6 patients with bacterial contamination also grew Gram-negative bacteria, predominantly *Klebsiella pneumoniae* [12,17,18]. This dichotomy alone may provide a microbial milieu leading to greater β -cell death and our observed findings of lower islet yield, and higher rates of graft failure than non-contaminated patients.

Another factor, longer duration of chronic pancreatitis, has been associated with lower islet yield, and worse metabolic outcomes [25]. This phenomenon could be due to a multitude of factors including pancreatic burnout and β -cell death, greater number of endoscopic interventions, longer indwelling duration of stents (regardless of number), or persistent colonization due to the reduced inherent antimicrobial capabilities of patients with chronic pancreatitis [20,21]. The confounding variable of duration may explain the lower islet yield in patients with bacterial colonization and subsequent rates of insulin independence, however many studies' data have disputed the causal relationship of islet yield and insulin-independence [9,25]. A recent study by Schneider *et al* found Gram-negative organisms such as *Enterobacteriaceae* were significantly more prevalent on stents with a longer

indwelling time [20]. Although not statistically significant in this study, patients with bacterial contamination experienced a longer median duration of chronic pancreatitis (6.3 vs. 3.9 years, $p=0.30$), a factor that may have contributed to the number of *Enterobacteriaceae* isolated in culture.

Data from larger series has demonstrated the adverse impact of endoscopic interventions [4]. Although our data does not demonstrate a difference in endoscopic interventions between patients with bacterial contamination and those without, possibly due to low sample size, sub-group comparison reveals a significant difference in the number of stents placed between insulin-independent and insulin-dependent patients and approaches significance for patients with bacterial contamination (all of whom are insulin-dependent) and insulin-independent patients ($p=0.053$). We believe this demonstrates that the cause of persistent bacterial infection is likely multifactorial and is affected by the number of endoscopic interventions and/or stents placed as well as the duration of stent placement and the ineffective antimicrobial milieu of patients with chronic pancreatitis. Further, although some bacteria may plausibly be introduced iatrogenically during the digestion process, it is more likely that enteric flora, such as *Enterobacteriaceae* are hidden in the pancreatic duct until after islet isolation, allowing them to be transplanted with the final preparation [14].

Regardless of the initiating event and despite the small sample size, patients in this series with bacterial contamination experienced a lower islet yield and higher rates of graft failure than their non-contaminated counterparts. Bacterial contamination may be a tangible threat to the success of autologous islet transplantation. Further research should be undertaken to identify patients with contaminated pancreata, to methods of pancreatic decontamination prior to transplantation, and whether this bears any impact on clinical outcomes. Although antibiotics are routinely used both during digestion and intraoperatively, it is currently difficult to completely eliminate all microbial threats prior to transplantation. Moreover, given the inverse relationship with duration of chronic pancreatitis, stent placement, and outcomes, we advocate for earlier operation on patients with chronic pancreatitis in an effort to prevent languishing with recurrent flairs of pancreatitis and to prevent multiple endoscopic interventions, which have highly variable reported rates of pain relief [26]. Moving forward, continued research should also be done to identify which patients may be refractory to non-operative therapy, thereby allowing referral to experienced transplant surgeons and consideration for earlier TPIAT.

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References

1. Bliss LA, Yang CJ, Eskander MF, et al. Surgical management of chronic pancreatitis: current utilization in the United States. *HPB (Oxford)*. 2015; 17(9):804–810. [PubMed: 26216570]
2. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013; 144(6):1252–1261. [PubMed: 23622135]
3. Witkowski P, Savari O, Matthews JB. Islet autotransplantation and total pancreatectomy. *Adv Surg*. 2014; 48:223–233. [PubMed: 25293618]
4. Chinnakotla S, Beilman GJ, Dunn TB, et al. Factors Predicting Outcomes After a Total Pancreatectomy and Islet Autotransplantation Lessons Learned From Over 500 Cases. *Ann Surg*. 2015; 262(4):610–622. [PubMed: 26366540]
5. Kim SJ, Joh JW, Lee SK, et al. Pancreatic islet cell autotransplantation in the canine model. *Transplant Proc*. 2000; 32(7):2473–2474. [PubMed: 11120251]
6. Najarian JS, Sutherland DE, Matas AJ, et al. Human islet autotransplantation following pancreatectomy. *Transplant Proc*. 1979; 11:336–340. [PubMed: 109963]
7. Bhayani NH, Enomoto LM, Miller JL, et al. Morbidity of total pancreatectomy with islet cell autotransplantation compared to total pancreatectomy alone. *HPB (Oxford)*. 2014; 16(6):522–527. [PubMed: 23992021]
8. Garcea G, Pollard CA, Illouz S, Webb M, Metcalfe MS, Dennison AR. Patient satisfaction and cost-effectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis. *Pancreas*. 2013; 42(2):322–328. [PubMed: 23407482]
9. Wilson GC, Sutton JM, Abbott DE, et al. Long-term outcomes after total pancreatectomy and islet cell autotransplantation: is it a durable operation? *Ann Surg*. 2014; 260(4):659–665. [PubMed: 25203883]
10. Chinnakotla S, Bellin MD, Schwarzenberg SJ, et al. Total pancreatectomy and islet autotransplantation in children for chronic pancreatitis: indication, surgical techniques, postoperative management, and long-term outcomes. *Ann Surg*. 2014; 260(1):56–64. [PubMed: 24509206]
11. Ahmad SA, Lowy AM, Wray CJ, et al. Factors associated with insulin and narcotic independence after islet autotransplantation in patients with severe chronic pancreatitis. *J Am Coll Surg*. 2005; 201(5):680–687. [PubMed: 16256909]
12. Colling KP, Blondet JJ, Balamurugan AN, et al. Positive sterility cultures of transplant solutions during pancreatic islet autotransplantation are associated infrequently with clinical infection. *Surg Infect (Larchmt)*. 2015; 16(2):115–123. [PubMed: 25668050]
13. Johnson CN, Morgan KA, Owczarski SM, Wang H, Fried J, Adams DB. Autotransplantation of culture-positive islet product: is dirty always bad? *HPB (Oxford)*. 2014; 16(7):665–669. [PubMed: 24308511]
14. Berger MG, Majumder K, Hodges JS, et al. Microbial contamination of transplant solutions during pancreatic islet autotransplants is not associated with clinical infection in a pediatric population. *Pancreatology*. 2016
15. Center CC. Eighth annual report of the Collaborative Islet Transplant Registry. 2014 [Accessed November 8th, 2015] Available at: <http://www.citregistry.org>.
16. Johnston PC, Lin YK, Walsh RM, et al. Factors associated with islet yield and insulin independence after total pancreatectomy and islet cell autotransplantation in patients with chronic pancreatitis utilizing off-site islet isolation: Cleveland Clinic experience. *J Clin Endocrinol Metab*. 2015; 100(5):1765–1770. [PubMed: 25781357]
17. Gala-lopez B, Kin T, O'gorman D, et al. Microbial contamination of clinical islet transplant preparations is associated with very low risk of infection. *Diabetes Technol Ther*. 2013; 15(4):323–327. [PubMed: 23438305]
18. Bucher P, Mathe Z, Bosco D, et al. Microbial surveillance during human pancreatic islet isolation. *Transplant Proc*. 2004; 36(4):1147–1148. [PubMed: 15194400]
19. Carroll PB, Ricordi C, Fontes P, et al. Microbiologic surveillance as part of human islet transplantation: results of the first 26 patients. *Transplant Proc*. 1992; 24(6):2798–2799. [PubMed: 1465945]

20. Schneider J, Schenk P, Obermeier A, et al. Microbial colonization of pancreatic duct stents: a prospective analysis. *Pancreas*. 2015; 44(5):786–790. [PubMed: 25906452]
21. Marotta F, Tajiri H, Li ZL, Barreto R, Bellini O, Barbi G. Pure pancreatic juice from patients with chronic pancreatitis has an impaired antibacterial activity. *Int J Pancreatol*. 1997; 22(3):215–220. [PubMed: 9444553]
22. Szary NM, Al-kawas FH. Complications of endoscopic retrograde cholangiopancreatography: how to avoid and manage them. *Gastroenterol Hepatol (N Y)*. 2013; 9(8):496–504. [PubMed: 24719597]
23. Hill SK, Bhalla C, Thomson A. Risk of bacterial colonization of pancreatic stents used in endoscopic retrograde cholangiopancreatography. *J Clin Gastroenterol*. 2012; 46(4):324–327. [PubMed: 22138843]
24. Giovannoni L, Muller YD, Lacotte S, et al. Enhancement of islet engraftment and achievement of long-term islet allograft survival by Toll-like receptor 4 blockade. *Transplantation*. 2015; 99(1): 29–35. [PubMed: 25340601]
25. Takita M, Lara LF, Naziruddin B, et al. Effect of the duration of chronic pancreatitis on pancreas islet yield and metabolic outcome following islet autotransplantation. *J Gastrointest Surg*. 2015; 19:1236–1246. [PubMed: 25933581]
26. Goodman AJ, Gress FG. The endoscopic management of pain in chronic pancreatitis. *Gastroenterol Res Pract*. 2012; 2012:860879. [PubMed: 22550479]

Abbreviations

BSA	body surface area
GMP	good manufacturing process
CIF	complete islet failure
CLL	chronic lymphocytic leukemia
CP	chronic pancreatitis
DVT	deep vein thrombosis
EBL	estimated blood loss
GSIS	glucose-stimulated insulin secretion
GTT	glucose tolerance test
HbA1c	hemoglobin A1c
ICU	intensive care unit
IEQ	islet equivalents
IEQ/BSA	IEQ per patient body surface area
IEQ/kg	islet equivalents per kilogram patient body weight
IQR	interquartile range
IVF	intravenous fluids
LOS	length of stay

PE	pulmonary embolus
POD	postoperative day
QoL	quality of life
TP	total pancreatectomy
TPIAT	total pancreatectomy with islet autotransplantation
VAS	verbal analog score

Table 1

Patient Demographics (N=29)

Variable	Data
Number of patients, N	27
Median age at surgery (range)	42 (14–64)
Median duration of chronic pancreatitis (years) (range)	4.13 (0.17– 42.4 years) *
Gender, N, (%)	
Male	9 (33.33)
Female	18 (66.67)
Median preoperative BMI (kg/m ²) (range)	24.5 (15.5–36.9)
Underweight (<18.50 kg/m ²), N, (%)	4 (14.8)
Normal (18.50–24.99 kg/m ²), N (%)	11 (40.7)
Overweight (25.00 kg/m ²), N (%)	9 (33.3)
Obese (30.00 kg/m ²), N, (%)	3 (11.1)
Median preoperative BSA (m ²) (range)	1.82 (1.4–2.3)
Etiology	
Idiopathic, N, (%)	9 (33.3)
Hereditary, N, (%)	7 (25.9)
Biliary, N, (%)	4 (14.8)
Alcoholic, N, (%)	4 (14.8)
Trauma, N, (%)	2 (7.4)
Pancreas divisum, N, (%)	1 (3.7)

BMI=body mass index; BSA=body surface area

* N=26 for years with CP due to inability to determine one patient's duration of symptoms

Table 2

Islet Transplantation Characteristics, Perioperative Data (N=27)

Variable	Data
Median IEQ (range)	192,000 (42,000–523,000)
Median IEQ/body weight (IEQ/kg) (range)	2,388 (745–5,714)
Median IEQ/BMI (IEQ/kg/m ²) (range)	7,306 (2,223–16,348)
Median IEQ/BSA (IEQ/m ²) (range)	92,720 (29,676–229,160)
Median intraoperative estimated blood loss (mL) (range)	500 (200–4,500)
Median intraoperative intravenous fluid infused (mL) (range)	6,500 (3500–20758)
Cases requiring blood product transfusion, N (%)	8 (29.6)
Median ICU stay (days) (range)	1 (0–13)
Median Hospital Length of Stay (LOS) (days) (range)	7 (5–52)

BMI=body mass index; BSA=body surface area; ICU=intensive care unit; IEQ=islet equivalents; LOS=length of stay

Table 3

Comparing Insulin-Independent to Insulin-Dependent Patients (N=19)

Variable	Insulin-Independent (N=7)	Insulin-Dependent (N=12)	p-value
BMI (kg/m ²), Median (IQR)	25.1 (22.1–27.6)	25.7 (21.9–30.3)	0.64
BSA (m ²), Median (IQR)	1.8 (1.5–1.9)	1.8 (1.6–2.2)	0.47
Female sex, N (%)	5 (71.4)	7 (58.3)	0.66
Duration of CP (years), Median (IQR)	3.2 (0.4–11.3)	4.0 (2.7–9.5)	0.58
Intraoperative EBL (mL), Median (IQR)	400 (225–800)	600 (400–900)	0.17
Intraoperative transfusion, N (%)	1 (14.3)	4 (33.3)	0.60
IEQ, Median (IQR)	173,000 (123,000–314,000)	202,500 (98,500–229,500)	0.74
IEQ/kg, Median (IQR)	3145 (1587–4618)	2512 (1507–4055)	0.67
IEQ/BMI, Median (IQR)	7306 (4877–12,939)	7184 (4394–10,650)	1.00
IEQ/BSA, Median (IQR)	113,376 (62,762–172,558)	100,914 (60,923–143,538)	0.80
Preoperative Diabetes, N (%)	3 (42.9)	6 (50.0)	1.00
C-peptide at most recent follow-up (ng/mL), Median (IQR)	2.2 (1.4–5.7)	0.54 (0.26–1.9)	0.028*
Number of ERCs, Median (IQR)	1 (0–1)	2 (1–6)	0.051
Number of stents, Median (IQR)	0 (0–1)	2 (0–4)	0.046*

BMI = body mass index; IQR = interquartile range; BSA = body surface area; CP = chronic pancreatitis

* Statistically significant, p < 0.05

Table 4Comparing Bacterial-Contamination to Non-Contaminated Patients (N=26)[/]

Variable	Bacterial-Contamination (N=6)	Non-Contaminated (N=20)	p-value *
BMI (kg/m ²), Median (IQR)	26.3 (21.3–29.7)	24.2 (22.1–26.2)	0.38
BSA, Median (IQR)	1.8 (1.7–2.2)	1.8 (1.6–1.9)	0.56
Female sex, N (%)	5 (83.3)	13 (61.9)	0.63
Duration of CP (years), Median (IQR)	6.3 (4.0–8.3)	3.9 (0.96–11.0)	0.30
Intraoperative EBL (mL), Median (IQR)	800 (450–1100)	400 (300–800)	0.15
Intraoperative transfusion, N (%)	2 (33.3)	6 (28.6)	1.00
IEQ, Median (IQR)	84,500 (78,000–192,000)	200,000 (125,000–249,000)	0.071
IEQ/kg, Median (IQR)	1335 (988–2021)	2958 (1667–4292)	0.017 *
IEQ/BMI, Median (IQR)	3478 (2632–7334)	8277 (5501–12432)	0.031 *
IEQ/BSA, Median (IQR)	49,623 (35,696–85,633)	113,377 (69,213–149,451)	0.036 *
Preoperative Diabetes, N (%)	0 (0)	12 (57.1)	0.020 *
C-peptide at most recent follow-up (ng/mL), Median (IQR)	0.47 (0.2–1.1)	1.4 (0.55–3.0)	0.041 *
Number of ERCPs, Median (IQR)	2 (1–8)	1.5 (1–3)	0.30
Number of stents, Median (IQR)	2 (1–4)	0.5 (0–1.5)	0.14

BMI=body mass index; BSA=body surface area; CP=chronic pancreatitis; IQR=interquartile range

[/] One patient excluded from “non-contaminated” group due to missing information (duration of symptoms);

* Statistically significant, p<0.05

Table 5

Bacterial speciation for contaminated pancreata (N=6)

Variable	Infectious Sequelae
<i>Klebsiella pneumoniae</i> and <i>Enterococcus faecalis</i> (N=1)	None
<i>Staphylococcus haemolyticus</i> (N=1)	<i>Enterobacter cloacae</i> and <i>Staphylococcus aureus</i> pneumonia
<i>Klebsiella pneumoniae</i> and non-hemolytic Streptococci spp. (N=1)	None
<i>Escherichia coli</i> and alpha-hemolytic Streptococci spp. (N=1)	None
<i>Klebsiella pneumoniae</i> and <i>Staphylococcus aureus</i> ¹ (N=1)	None
<i>Klebsiella pneumoniae</i> and <i>Enterococcus faecalis</i> ² (N=1)	None

¹ Stent present at the time of TPIAT with *Klebsiella pneumoniae* and *Staphylococcus aureus* growth from stent culture

² Stent present at the time of TPIAT with no growth from stent culture