Journal of Gastrointestinal Surgery
https://doi.org/10.1007/s11605-019-04118-y

ORIGINAL ARTICLE

Early Infectious Complications After Total Pancreatectomy with Islet Autotransplantation: a Single Center Experience

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Received: 9 October 2018 / Accepted: 9 January 2019

Abstract

Introduction We assessed whether positive microbiological cultures from the islet preparation had any effect on the risk of infectious complications (IC) after total pancreatectomy with islet autotransplantation (TPIAT) in our center.

Methods We analyzed preservation fluid and final islet product surveillance cultures with reference to clinical data of patients undergoing TPIAT. All patients received routine prophylactic broad-spectrum antibiotics.

Results The study involved 10 men and 18 women with a median age of 39 years. Over 30% of surveillance cultures during pancreas processing grew bacterial strains with predominantly polymicrobial contaminations (13 of 22 (59%)). At least one positive culture was identified in almost half of the patients (46%) undergoing TPIAT and a third had both surveillance cultures positive. Infectious complications affected 50% of patients. After excluding cases of PICC line-associated bacteremia/fungemia present on admission, incidence of IC was higher in cases of positive final islet product culture than in those with negative result (57% vs. 21%), which also corresponded with the duration of chronic pancreatitis ($p = 0.04$). Surgical site infections were the most common IC, followed by fever of unknown origin. There was no concordance between pathogens isolated from the pancreas and those identified during the infection.

Conclusions While IC was common among TPIAT patients, we found no concordance between pathogens isolated from the pancreas and those identified during infection. Contamination of the final islet product was of clinical importance and could represent a surrogate marker for higher susceptibility to infection.

Keywords Total pancreatectomy with islet autotransplantation · Infectious complications · Surveillance cultures · Autologous islet transplantation

This abstract was presented at the 27th International Congress of The Transplantation Society.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11605-019-04118-y) contains supplementary material, which is available to authorized users.

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Abbreviations

HbA1c	Hemoglobin A1c
ERCP	Endoscopic retrograde cholangiopancreatography
IEQ	Islet equivalent units
IQR	Interquartile range
TPIAT	Total pancreatectomy with islet autotransplantation

Introduction

Infectious complications after pancreatic resection are the primary cause of postoperative morbidity and continue to represent a major clinical challenge, even in high-volume centers, despite advances in surgical technique, perioperative care and the proper evidence-based use of perioperative, prophylactic antibiotics.[1, 2] Due to the emerging role of infection control as

Published online: 04 February 2019

a metric of quality of surgical care, recent studies have attempted to identify modifiable risk factors and viable prevention strategies that could improve patient outcomes. Surgical site infection was reported to be the second most common reason for readmission following total pancreatectomy with islet autotransplantation (TPIAT).[3] In cases of TPIAT, infections result not only from the surgical procedure itself, but also from the infusion of the potentially contaminated islet tissue into the portal vein. While total pancreatectomy (TP) is considered a therapeutic option for well-selected patients with chronic pancreatitis, simultaneous islet autotransplantation allows for more optimal glucose control with or without the need for exogenous insulin supplementation. Many of these patients undergo multiple prior transampullary endoscopic interventions, including stent placement, and are at additional risk of pre-existent pancreatic and foregut contamination due to gastric antisecretory therapy, antibiotic usage, and chronic opioid use. Here, we examined whether presence of bacteria and positive microbial cultures during islet processing had any effect on the risk of developing infectious complications in our medium-volume transplant center. We also sought to optimize our antimicrobial prophylaxis.

Methods

Patients

Data from 28 consecutive patients undergoing TPIAT at the University of Chicago between January 2014 and June 2018 were prospectively collected and analyzed retrospectively. The study was approved by the University of Chicago Institutional Review Board. All participants provided written informed consent.

All patients received a standard broad-spectrum prophylactic antibiotic during the surgery and for 24 h postoperatively: cefoxitin 2 g (redosed at 2-h intervals during surgery) and ampicillin 2 g (redosed at 2-h intervals during surgery) followed by cefazolin abdominal wash or gentamycin 360 mg with metronidazole 500 mg with subsequent abdominal wash with bacitracin in patients allergic to penicillins/cephalosporins. Blood and/or urine cultures were taken at the discretion of the treating physician, usually whenever symptoms suggested ongoing infection.

After initial analysis of the first 22 cases from our cohort, we extended antibiotic prophylaxis from 24 h to 7 days in subsequent 4 patients with contaminated islet prep.

Definition of Infection

In order to enable the direct comparison of infection rates in our study with those from other reports, we adopted the "definition of infection" published by Berger at al.[4] For the same reason, we regarded a "fever of unknown origin" as infection, whenever empiric antibiotic therapy led to clinical improvement.[4]

Surgical Technique: Islet Isolation

Open TP with excision of the duodenum and pancreas was performed according to the previously described standard technique.[5, 6] After trimming, the pancreas was decontaminated with 10% povidone-iodine solution followed by two washes in 1× Hank's Balanced Salt Solution (HBSS) with cefazolin. In 2018, we ceased washing the pancreas in HBSS containing cephalosporin. Islets were isolated using the Ricordi method at the University of Chicago Good Manufacturing Practice (GMP) facility.[5, 6] Islet purification was performed after digestion only when necessary in order to reduce tissue volume to below 20 mL. Islets were infused into the portal vein cannulated under direct vision prior to the end of the operation. The Endosafe®—spectrophotometric portable test system was used to measure endotoxin concentration.

Microbiological Sampling and Analysis

Culture material was transported in anaerobic conditions to the microbiology laboratory and cultured for the detection of aerobic and anaerobic microbes. For the aerobic culture, chocolate, trypticase soy agar with 5% sheep blood, CNA, and MacConkey agars were inoculated and incubated for 72 h at 35 °C in 5% CO_2. For the anaerobic culture, *Brucella*, CNA, egg yolk, and BBE agars were inoculated and incubated at 35 °C for 6 days under anaerobic conditions. In addition, a chopped meat broth was inoculated and incubated at 35 °C for 14 days. A cytospin slide was made for Gram stain. If the culture grew organisms that were suspected to be contaminants, the original specimen was re-inoculated onto the same media and incubated for 14 days. Since March 2017, culture material has been instead inoculated in the BACTEC™ PLUS Aerobic/F and BACTEC™ Lytic/10 Anaerobic/F blood culture bottles (Becton Dickinson, Sparks, MD), which were incubated in a BACTEC™ FX continuous blood culture monitoring instrument until growth was detected or 14 days had elapsed. A separate specimen was submitted for the cytospin slide. Bacteria and yeast were identified using the Vitek® MS (MALDI-TOF) (bioMérieux, Inc., Durham, NC).

Metabolic Evaluation

Patients were evaluated for metabolic outcomes at baseline prior to TPIAT, at day 75 and 1 year post-TPIAT.

Assessment of islet function and glycemic control included fasting and stimulated plasma glucose, C-peptide, and HbA1c levels. Daily insulin requirements were calculated as the mean of doses in a patient's log during a 3-day period 1 week prior to each follow-up visit. Criteria previously established for allogeneic-islet transplant recipients were used to decide whether to discontinue or resume exogenous insulin.[7]

Statistical Analysis

All analyses were performed using Statistica 12.0 (StatSoft) software. Data was tested for normality. Descriptive statistics included: median, range, and percentages. The Mann-Whitney *U* test was used to compare continuous variables, and Fischer's exact test was used to compare proportions. $p \leq 0.05$ was considered to be statistically significant.

Results

Patients

This study involved 10 male and 18 female TPIAT recipients with a median age of 39 years, including four adolescents with ages 9, 15, 16, and 17. Detailed baseline characteristics of patients are presented in Table 1.

Microbiological Contamination of Preservation Media

Pancreas preservation solution was found to be contaminated in 11 of the 28 (39%) patients. *Streptococcus* spp., *Enterococcus* spp., and *Klebsiella* spp. were the most common microorganisms found in surveillance cultures, which represented skin or gastrointestinal tract normal flora (Fig. 1). No fungal growth or multidrug resistant strains were identified. One, two, and three bacterial species were identified in 6/28 (21%), 4/28 (14%), and 1/28 (4%) of cases, respectively. In two cases of positive preservation solution, surveillance culture of final islet product produced no growth. In the first case, the contaminants were *Escherichia coli*, *Enterobacter cloacae*, alpha hemolytic streptococci, *Parvimonas micra*, *Fusobacterium nucleatum*, and in the second case Gram-positive cocci. In the remaining 9 cases, culture results from the preservation media were concordant with those from the final islet product, except 4 cases, when additional bacteria/fungi were identified in the final islet preparation.

Microbiological Contamination of Final Islet Products

Bacterial strains grew in 11/28 (39%) of the final islet products. *Enterococcus* spp., *Klebsiella* spp., and streptococcal species were the most common isolates identified (Fig. 1). There were no multidrug resistant strains. Mixed culture results were obtained from 8 patients (29%). All grew organisms consistent with either skin or gastrointestinal tract normal flora. Fungal growth (*Candida tropicalis*, *Candida albicans*) was present in only 2 cases (7%). There were two cases of positive final islet product culture with negative preservation solution surveillance culture. *Granulicatella adiacens*, which represents Gram-positive cocci normal flora of the upper respiratory, gastrointestinal, and urogenital tracts, was identified in the first case. In the second case, multiple organisms were noted to be present on both Gram stain and final product culture results, including *Klebsiella oxytoca*, *Serratia marcescens*,

Table 1 Demographic and baseline patient characteristics

	Median (*n*)	Range
Age at TPIAT, year	39	9–60
BMI at TPIAT, kg/m^2	26	18.2–38.8
Duration of diagnosed pancreatitis, year	7	1–39
Etiology (*n*)		
Genetic		
Cationic trypsinogen (PRSS1)	8	
Cystic fibrosis transmembrane conductance regulator gene (CFTR)	10	
Pancreatic secretory trypsin inhibitor gene (SPINK1)	1	
Autoimmune	1	
Pancreas divisum	5	
Unknown etiology	2	
Necrotizing gallstone pancreatitis	1	
Islet mass transplanted		
Total islet equivalent (IEQ)	217,255	2539–379,109
IEQ/kg body weight	2926	33.8–5193

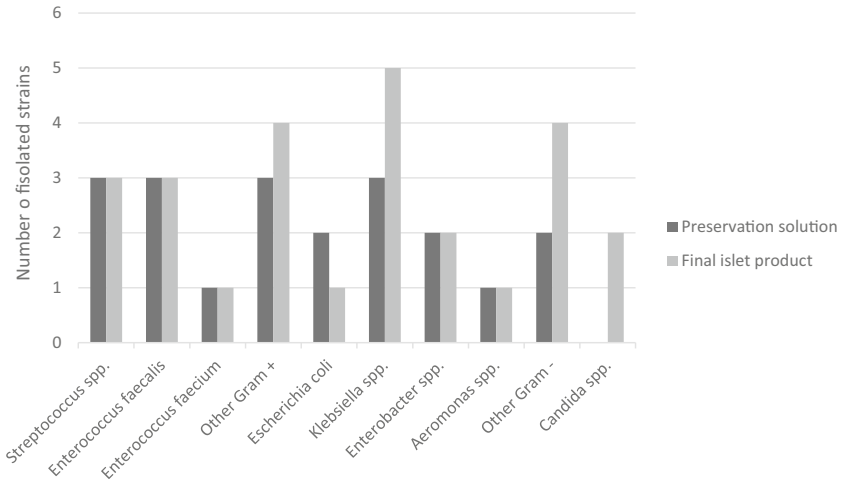

Fig. 1 Microorganisms isolated from preservation solution and final islet product cultures

Streptococcus anginosus, *Pseudomonas aeruginosa*, and *Fusobacterium necrophorum*. Additional microorganisms, which were not present in contaminated preservation media, including *Enterobacter cloacae*, *Klebsiella oxytoca*, *Candida tropicalis*, and *Candida albicans*, were identified in the final islet preparation in 4/28 (14%) cases.

Endotoxin was negative in all cases, regardless of the presence or absence of microbial contamination.

Infectious Complications after TPIAT

Microbial contamination was detected in at least one surveillance culture in 13 out of 28 (46%) patients and both surveillance cultures in 9 out of 28 (32%). Two patients had microbial growth in preservation solution only and another two only in the final islet product.

Initially, we assessed the incidence of infectious complications after TPIAT in our first 22 consecutive patients who received antibiotic prophylaxis for up to 24 h during and after the surgery as described in "Methods." Both preservation solution and final islet product were contaminated in 5 of those 22 (23%) individuals (Fig. 2). Three of those five patients (60%) developed infectious complications: fever of unknown origin and possibly aspiration pneumonia, wound infection, and sepsis with bowel perforation. One in two (50%) patients with contaminated final islet preparation presented with fever and in-hospital wound infection. One patient with contaminated preservation solution developed a superficial surgical site infection after discharge from the hospital, but did not require readmission.

Six out of 14 (43%) patients with sterile both preservation media and islet surveillance cultures developed infections. Three of those 6 patients experienced bacteremia/fungemia due to the peripherally inserted central catheter (PICC line) for vascular access some time prior to surgery, including one patient with an additional surgical site infection. The blood cultures drawn from those catheters were positive for contamination. There were two cases of catheter-associated urinary tract infections (CAUTI) and one surgical site infection (Fig. 3).

Overall, when the final islet product was found to be contaminated, 4 out of 7 (57%) patients developed infectious complications. When both surveillance cultures were sterile, 6 out of 14 (43%) patients were diagnosed with various infections. However, when we excluded 3 patients with infectious complications due to PICC lines that preceded surgery, the infection rate was instead 3 out of 11, so 27%. Although, the difference was not statistically significant, we considered it clinically significant enough to prolong antibiotic prophylaxis up to 7 days in subsequent patients with positive final islet product cultures. Since then, 6 TPIATs were performed with the new prophylaxis scheme implemented in 4 out of those 6 patients who had contaminated islets. Upon detection of microbial contamination via the Gram stain or when preliminary cultures were positive, these patients received a broad-spectrum antibiotic until microbial susceptibility profiles guided narrowed therapy. In contrast to the high incidence of infections (57%), when antibiotic prophylaxis was applied for only 24 h postoperatively, none of the patients receiving 7 days of prophylaxis experienced IC (Table 3). The remaining 2 out of 6 patients had both surveillance cultures sterile and received standard 24-h prophylaxis.

In most cases, blood and urine cultures taken upon the suspicion of infection were negative and the diagnosis was solely based on clinical symptoms. In a case of a patient with infectious complications and multiple positive cultures, all pathogens isolated were discordant with pathogens found in pancreas preservation fluid and final islet product. Of note, one patient, who in addition to have both surveillance cultures positive and had poorly controlled diabetes prior to surgery (HbA1c 9.6), developed severe sepsis, which lead to multi-organ failure with bowel perforation despite intensive treatment. All three additional patients, who were prediabetic prior to surgery (HbA1c

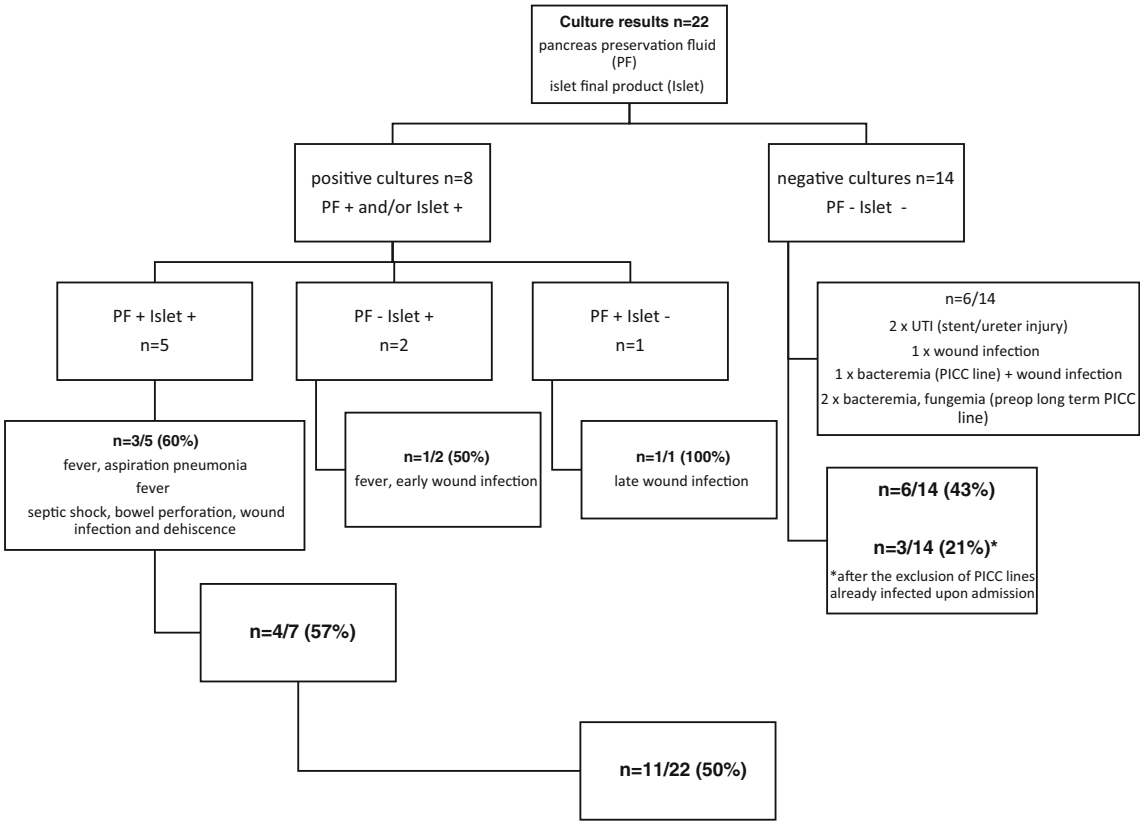

Fig. 2 Flowchart of the infectious outcomes with reference to the surveillance cultures in a group of 22 patients before the implementation of a new prolonged perioperative antibiotic prophylaxis

between 6 and 6.5), had at least one contaminated islet culture and developed infectious complications despite standard perioperative antibiotic prophylaxis.

Analysis of patients' baseline characteristics revealed three major statistically significant differences. Patients with positive final islet product cultures had longer chronic pancreatitis duration than those with sterile islet cultures, which was 14.54 ± 10.32 vs 7.88 ± 8.26 years ($p = 0.04$), respectively (Table 2). Patients with a history of at least three stent placements or at least five ERCPs (endoscopic retrograde cholangiopancreatography) were more likely to have contaminated islets ($p = 0.003$ and $p = 0.02$, respectively), but the timing of the endoscopic procedure did not influence the outcome.

Also, patients with a diagnosis of a hereditary or familial pancreatitis more often had positive final islet product culture, most likely as a result of a longer disease duration compared to those with other etiologic risk factors ($p = 0.005$).

Metabolic Outcomes

Twenty-eight patients were evaluated 75 days after TPIAT and 21 of them at 1 year. Four patients (14%), who required insulin support prior to the TPIAT remained insulin

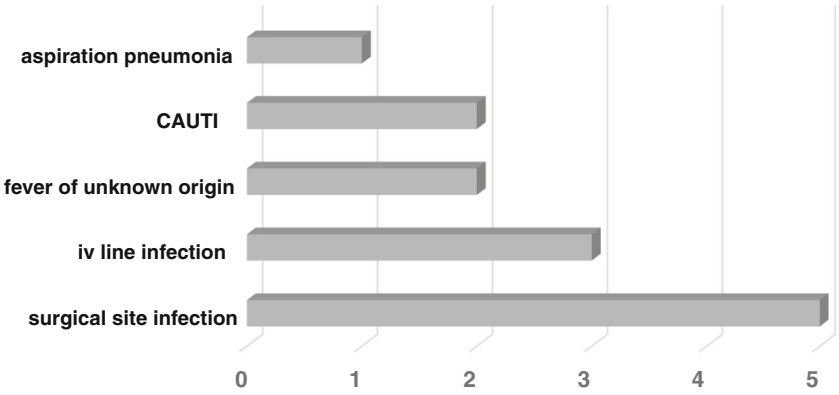

Fig. 3 Prevalence of various types of infections post-TPIAT

Table 2 Demographic and clinical characteristics of patients with negative versus positive sterility cultures of final islet product

Variable	Negative final islet product culture ($n = 17$)	Positive final islet product culture ($n = 11$)	p
Age at TPIAT, year	41 (9–60)	36 (15–51)	0.46
Sex M/F	7/10	3/8	0.69
BMI at TPIAT, kg/m^2	25.7 (18.8–38.8)	26.4 (18.2–38.7)	0.55
Duration of diagnosed pancreatitis, year	5 (1–31)	15 (3–39)	0.04
Genetic mutation	7/17 (41%)	10/11 (91%)	0.02
Number of previous ERCPs ≥ 5	2/17 (12%)	8/11 (73%)	0.003
Number of previous stents ≥ 3	1/17 (6%)	5/11 (45%)	0.02
Stent placement or surgical interventions within 1 year before TPIAT	5/17 (29%)	7/11 (64%)	0.12
Number of previous surgical interventions	3/17 (18%)	1/11 (9%)	1.0
Islet mass transplanted			
Total islet equivalent (IEQ)	235,835 (2539–379,109)	152,202 (52,926–306,194)	0.12
IEQ/kg body weight	3496 (34–5193)	1512 (680–4502)	0.15
ICU length of stay	4 (3–15)	5 (2–13)	0.33
Total hospital length of stay	8 (6–21)	10 (6–68)	0.4
Endotoxin in final product, EU/kg	0.4 (0.2–1.4)	0.3 (0.2–0.5)	0.49
Insulin independence on day 75 ($n = 28$)	4/17 (23.5%)	1/11 (10%)	0.62
Insulin independence at 1 year ($n = 21$)	9/14 (64.3%)	1/7 (14.3%)	0.06
HbA1c on day 75 ($n = 28$)	6.2 (4.8–9.3)	6.5 (5.8–12.4)	0.14
HbA1c at 1 year ($n = 21$)	6.25 (5.3–12.9)	7.3 (5.5–10.9)	0.49

dependent after the surgery. Two of those patients had contaminated final islet preparation and three of them displayed partial islet function with detectable serum c-peptide with median HbA1c 7.5 (7.3–10.2) at 1 year.

One year post-TPIAT, 14 out of 18 remaining patients (78%) had well-controlled blood glucose. Ten (56%) were off insulin with HbA1c of 6 ± 0.43 and an additional 4 patients (22%) with HbA1c < 6.3 required a low dose of insulin support. The remaining 4 individuals (22%) had inadequate glucose control despite insulin supplementation (HbA1c > 7). We did not observe a statistically significant difference in the insulin independence rates on day 75 post-TPIAT in patients with and without final islet product contamination. However, 1 year after surgery, only 1 out of 7 patients (14%) who received contaminated final islet preparation was off insulin, while 9 in 14 (64%) patients without final islet product contamination did not require any insulin support ($p = 0.06$). The median HbA1c did not differ significantly between those two groups of patients 75 days and 1 year after the procedure. The difference in the total islet yield and the number of transplanted IEQ/kg between patients with and without contamination was not statistically significant (Table 2). However, the total number of IEQ and IEQ/kg was significantly higher in patients who did not require insulin support when compared to those needing insulin 1 year post-TPIAT (264,757 ± 64,697 vs. 146,046 ± 76,716 with $p = 0.005$ and 3995 ± 1056 vs. 2032 ± 1346 with $p = 0.002$, respectively).

Discussion

This study aimed to assess the incidence and severity of infectious complications after TPIAT and their association with microbial contamination of pancreas preservation media and/or final islet product. Over one-third of surveillance cultures from pancreas processing grew bacterial strains including those often found in clean-contaminated procedures and typical skin and gastrointestinal flora such as streptococci, staphylococci, and with the predominant Gram-negative bacilli and enterococci.

Pathogens isolated from both preservation solution and final islet product in our study were similar to those reported by others, including species often identified from surgical site infections after gastroduodenal procedures, i.e., Gram-positive cocci or/and Gram-negative bacilli. Bacteria present in our final islet products also mirrored those found by Schneider et al. in biofilm covering pancreatic duct stents.[8] This finding is of clinical importance due to the known impact of bacterial colonization on patient outcomes. Hill et al. reported a significant association between bacterial colonization and stent time in situ.[9] Kozarek et al. reported a significant contamination of the pancreatic ductal system

by enteric flora in all patients with pancreatic stents, although antibiotic prophylaxis was used with every stent placement.[10] We found islet contamination to be associated not only with the number of stents placed, but also with the number of ERCPs irrespective of pancreatic duct stent placement. This could help to explain the observed correlation between disease duration and contamination of the final islet product.

The rates of pancreas preservation solution contamination observed in our study are similar to those previously reported (ranging from 32 to 89% in cultures from product during processing and 0 to 64% in cultures from product post-processing) (Supplementary Table 1).[4, 11–16] Contamination rates of the final islet product in islet autotransplantation are much higher than reported in allotransplantation (ranging from 0 to 9.4%) (Supplementary Table 1).[11, 16–23] This discrepancy suggests that contamination of the final auto-islet product may result from colonization of the pancreatic ductal system due to obstruction, frequent instrumentation, and/or chronic stenting. In allotransplantation, even if preservation fluid surrounding pancreas is contaminated during the procurement, the islet isolation procedure usually provides clearance and the final product is usually pathogen free. Unlike in the previously published studies, islet processing did not decrease the rates of contamination observed in our patients. In addition, we observed two cases with contaminated final islet product culture and sterile preservation solution, which strongly supports the hypothesis of microbial seeding of the pancreatic duct and surrounding internal pancreatic tissue prior to resection, with normal flora of the gastrointestinal tract. Indeed, the isolation of such flora from these patients provides further evidence. Seeding of gastrointestinal flora may also have occurred in an additional four cases, when a new additional microorganism typical for gastrointestinal microbiota was found in the final islet preparation but was not present in the preservation media. This de novo contamination probably resulted from the release of pathogens residing deep within the pancreatic ductal system and tissue and not from external contamination. Notably, endotoxin test was negative in all final product samples and therefore not useful for distinguishing between contaminated and non-contaminated islet products.[15, 20, 21]

Infectious complications were common, especially in TPIAT patients that experienced a long duration of chronic pancreatitis. Our overall infection rate of 50% was comparable to that of 48% in a group of 83 children reported by Berger et al.[4] Surgical site infections were found by various authors to be the most common infectious complications post-TPIAT, followed by fevers of unknown origin, and urinary tract infections.[3, 4] A similar spectrum of infection complications were identified in our study.

In contrast to the preservation solution, contamination of the final islet product culture seemed to be of clinical importance which was further supported by the clear clinical improvement and lack of infectious complications of four patients, who received contaminated final islet product after the implmantation of a 7-day antibiotic prophylaxis regime (Table 3), and it corresponded with the duration of chronic pancreatitis. Due to the limited number of patients, we observed only a trend between the incidence of infection and insulin independence at 1 year post-TPIAT. Interestingly, we found no concordance between pathogens isolated from the pancreas and those found at the infection site. Some authors have reported cases of post-TPIAT infections with causative pathogens concordant with those present in the final islet product (Supplementary Table 2).[4, 12–14, 17] However, no genotyping of bacterial strains was performed in any of these studies, and the assumed concordance could have been coincidence, when in fact two different bacterial strains of the same species were isolated from the patient and sterility culture. A study of 251 patients by Colling and colleagues found that the presence of bacteria in the final islet preparation did not increase the likelihood of postoperative infection compared with those patients with negative islet cultures.[14] When contaminated islets were transplanted, the rate of postoperative infections was reported to be higher in autotransplantation than in allotransplantation. We hypothesize that colonization of the pancreatic ductal system leading to positive post-processing surveillance culture might be a surrogate marker for higher susceptibility to infection, which could be due to altered immunity resulting from preoperative chronic inflammation, more advanced pancreatic disease, malnutrition, diabetes, and chronic opioid usage. Exocrine insufficiency in chronic pancreatitis leads to maldigestion and malabsorption, which can result in nutrition deficiencies that may impair immunity and increase the risk of infections.[24, 25] We found the difference in the islet yield and insulin independence rates between patients with and without microbial contamination in the final islet preparation of borderline significance. Other authors have observed a significantly lower islet yield[4, 14] and worse metabolic outcomes when the final islet product culture was contaminated.[15] We believe that this may help account for the association between the presence of microorganisms in final islet product and the severity of chronic pancreatitis upon TPIAT. The discrepancy in the rate of symptomatic infections after allotransplantation and autotransplantation of contaminated islets could have resulted from the difference in the invasiveness of the procedure or resulted from different antibiotic prophylaxis applied.

According to clinical practice guidelines for antimicrobial prophylaxis in surgery developed jointly by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA), the

Table 3 Case description of infectious complications after TPIAT in patients with positive final islet product culture ($n = 11$)

No.	Antibiotic (days)	Preservation fluid culture	Final islet product culture	Splenectomy	Type of postoperative infection	Blood/urine culture	ICU/hospital stay (days)
1	Cefoxitin (1) Ampicillin (1)	*Escherichia coli*, alpha hemolytic *streptococci*	*Escherichia coli*, alpha hemolytic *streptococci*	No	None	None	6/15
2	Cefoxitin (1) Ampicillin (1)	*Klebsiella pneumoniae*, *Enterococcus faecalis*	*Klebsiella pneumoniae*, *Enterococcus faecalis*	Yes	Fever of unknown origin	Intra-abdominal fluid: negative; 2× urine: negative 2× blood: negative	4/8
3	Cefoxitin (1) Ampicillin (1)	Negative	*Granulicatella adiacens*	No	None	None	6/16
4	Cefoxitin (1) Ampicillin (1)	*Raoultella* spp., *Streptococcus anginosus*	*Raoultella* spp., *Streptococcus anginosus*	No	None	None	10/11
5	Cefoxitin (1) Ampicillin (1)	Negative	*Klebsiella oxytoca*, *Serratia marcescens*, *Streptococcus anginosus*, *Pseudomonas aeruginosa*, *Fusobacterium necrophorum*	Yes	Fever of unknown origin; wound infection	2× blood negative	8/10
6	Cefoxitin (1) Ampicillin (1)	*Enterococcus faecalis*	*Enterococcus faecalis*, *Enterobacter cloacae*	Yes	Hospital acquired pneumonia likely from aspiration	Blood: negative	5/9
7	Gentamycin (1) Metronidazole (1)	*Enterococcus faecalis*, *Enterococcus faecium*	*Enterococcus faecalis*, *Enterococcus faecium*	No	Septic shock, bowel perforation, wound infection and dehiscence	Blood: *Klebsiella oxytoca*; iv line tip: *Klebsiella oxytoca* Wound: *Enterococcus faecalis* + *Enterobacter cloacae*, Sputum: *Candida glabrata*, Endotracheal aspirate: *Candida dubliniensis and glabrata*	13/68
After the implementation of 7-day antibiotic prophylaxis in case of positive final islet product cultures							
8	Cefoxitin (1) Ampicillin (1) Cefepime (6)	*Klebsiella oxytoca*	*Klebsiella oxytoca*	Yes	None	None	4/8
9	Cefoxitin (2) Ampicillin (2) Cefepime (5) Fluconazole (4)	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*, *Candida tropicalis*	Yes	None	None	5/11
10	Cefoxitin (2) Ampicillin (2) Cefepime (5) Metronidazole (7)	*Citrobacter freundii*, *Aeromonas* spp., *Enterobacter cloacae*	*Aeromonas* spp., *Enterobacter cloacae*, *Klebsiella oxytoca*	Yes	None	None	3/7
11	Gentamycin (1) Metronidazole (1) Vancomycin (3) Daptomycin (2) Fluconazole (3)	Gram-positive cocci	Gram-positive cocci, *Candida albicans*	No	None	None	2/6

postoperative course of antibiotics should only involve either a single dose of antibiotic or a duration be continued for less than 24 h in order to minimize adverse effects including these secondary to dysbiosis, the development of resistance, and costs.[26] It is generally acknowledged that positive surveillance cultures do not translate into infectious complications of major clinical significance after TPIAT. Currently, there are no evidence-based recommendations on the type and length of antimicrobial prophylaxis in patients undergoing TPIAT due to insufficient data. In our study, a standard 24-h antibiotic prophylaxis appeared to have limited efficacy for preventing infectious complications in patients that received a contaminated final islet product. Based upon an analysis of the clinical course and postoperative infectious complication of our first 22 patients, we decided to extend the antimicrobial prophylaxis from 24 h to 7 days for subsequent patients receiving contaminated final islet product. This strategy has been successfully applied to the treatment of pediatric and adult TPIAT patients[4, 14] and has dramatically reduced the incidence of infectious complications in our small cohort of patients. The reported postoperative infection rate due to infusion of bacteria and/or fungi directly into the portal system was 39% when a standard 24-h antibiotic prophylaxis was used,[12] 57.1% when antibiotics were administered for 3 days,[13] and 15–36% when extended 7-day prophylaxis was applied.[4, 14] The appropriate duration of antibiotic treatment in the setting of TPAIT with contaminated islet preparation remains to be determined.

Major limitations of our study include the highly specific strategies for patient clinical management, islet isolation, and transplantation, which may differ from practices employed at other institutions, and the nature of results, which are retrospective and derived from a single center. The number of patients included in our study was limited and therefore reduced statistical power and the strength of associations. Regardless, we identified results of potential clinical importance that may lead to improved treatment strategies. The granularity gained from a single center with low volumes may be used as a guide for centers interested in starting their own program.

In aggregate, our observations and the analysis of the published data lead to the conclusion that patient-related risk factors, rather than direct contamination of islet preparation, most strongly predicts the development of infectious complications after TPIAT. Nevertheless, the presence of microbes in the final islet preparation appears to be a surrogate marker for the impact of chronic pancreatitis on patient immunity and warrants closer attention to the patient's general condition. This is also an argument in favor of earlier referral for TPIAT instead of prolonged non-operative and especially endoscopic therapy, which has limited pain relief efficacy in patients with small duct disease or without evident pancreatic duct stricture.

Acknowledgments We would like to thank the European Society for Organ Transplantation, which supported the training for Justyna Gołębiewska with ESOT Study Scholarship 2017. Martin Tibudan was supported by the University of Chicago Diabetes Research and Training Center, US Public Health Service Grant P30DK020595.

Author Contributions Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content as per the guidelines of the International Committee of Medical Journal Editors.

Funding Justyna Gołębiewska received the ESOT Study Scholarship from the European Society for Organ Transplantation, Martin Tibudan was partially supported by the University of Chicago Diabetes Research and Training Center, US Public Health Service Grant P30DK020595.

Compliance with Ethical Standards

The study was approved by the University of Chicago Institutional Review Board. All participants provided written informed consent.

Conflict of Interest The authors declare that they have no conflict of interest.

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