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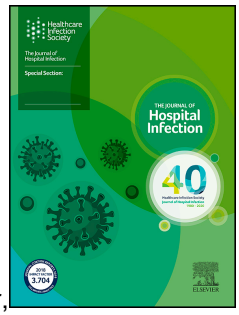

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Surgical site infections after simultaneous pancreas kidney and pancreas transplantation in the Swiss Transplant Cohort Study

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Abstract

Background

Among hospital-acquired infections, surgical site infections (SSI) are common. The occurrence of SSIs in the early post-transplant course poses a relevant threat for simultaneous pancreas kidney transplant (SPK-Tx) or pancreas transplant (P-Tx) recipients.

Methods

Adult SPK-Tx and P-Tx recipients with a follow-up of at least 90 days were identified in the Swiss Transplant Cohort Study (STCS) dataset. Except the categorization of SSIs according to CDC criteria, all other data were prospectively collected. Risk factors for SSIs were investigated with logistic regression. A Weibull accelerated failure-time model was applied to address the impact of SSIs on length of stay, correcting for transplant-related complications and delayed graft function.

Results

Of 130 transplant recipients, 108 SPK-Tx and 22 P-Tx, 18 (14%) individuals developed SSIs within the first 90 days after transplantation. Deep incisional (7, 38.9%) and organ/space infections (8, 44.4%) predominated. In the majority of SSIs (11, 61.1%; 2 SSIs with simultaneous identification of fungal pathogens) bacteria were detected with *Enterococcus* spp. being most frequent. The median duration of hospitalization after transplantation was significantly longer in recipients with SSI (median 26d; IQR [19, 44]) than in patients without SSI (median 17d; IQR [12, 25], P = 0.002). In multivariable analysis, SSIs were significantly associated with an

increased length of stay and prolonged the duration of hospitalization by 36% [95% CI: 4, 79].

Conclusions

SSIs after SPK-Tx and P-Tx were found at a quite low frequency of 14%. Among pathogens, *Enterococcus* spp. predominated. SSIs were independently associated with a longer hospitalization after transplantation.

Introduction

Simultaneous kidney-pancreas (SPK-Tx) or pancreas transplantation (P-Tx) are common treatment strategies for individuals suffering from diabetes mellitus type 1. In 2019, the Organ Procurement and Transplantation Network registered 875 SPK-Tx and 125 P-Tx transplantations in the USA [1], whereas in Switzerland, a total of 340 kidney transplantations and a total of 25 pancreas or islet cell transplantations were performed [2].

Among healthcare-associated infections (HAI), surgical site infections are highly prevalent. Swiss data gathered in a recent point prevalence study reported SSIs as the most common HAI [3]. Similarly, in an US point prevalence study from 2014, SSIs and pneumonia, each detected at a frequency of 20.8%, were the most frequent HAIs [4]. SSIs after SPK-Tx or P-Tx were associated with poorer graft survival [5] and prolonged duration of hospital stay [5-7]. In addition, SSIs often require re-operation contributing to transplant-related morbidity [6]. Data on SSIs after SPK-Tx and P-Tx derived from multicenter studies remain scarce. We sought to address this important infectious complication in the early post-transplant course within the Swiss Transplant Cohort Study (STCS).

Patients and methods

Study design, population, and patient-related data

This study was a nested project within the Swiss Transplant Cohort Study (STCS, www.stcs.ch, ClinicalTrials.gov Identifier: NCT01204944). All Swiss transplant centers (Basel, Bern, Geneva, St. Gallen, Lausanne and Zurich) contribute to the prospective data collection of the STCS. The STCS contains data on all solid organ

transplants performed after 1st May 2008. Each transplant recipient is requested to grant informed consent, prompting enrollment in the STCS and inclusion into research projects. More than 93% of all transplant recipients are enrolled in the STCS allowing comprehensive prospective data collection [8]. The STCS was approved by the Ethic Committees of all participating institutions. A separate approval was obtained for this nested study by the responsible Ethics Committee (Kantonale Ethikkommission Zürich, Req. 2016-01532). Among all individuals enrolled in the STCS between January 2008 and September 2021, we selected adult patients with SPK-Tx or P-Tx and a follow-up of at least 90 days (**Figure 1**). Individuals that received serial transplants (three SPK-Tx followed by a P-Tx, one P-Tx followed by another P-Tx) that were at least one year apart, were treated as separate individuals in our analyses. In predefined time intervals, ranging from twice a week to every 3 months, transplant recipients are followed-up for occurrence of infections by dedicated research assistants. The research assistants are supervised by transplant infectious diseases physicians and predefined criteria for the diagnosis of infections are applied [9]. SSIs were defined according to Centers for Disease Control and Prevention (CDC) criteria [10]. The categorization of the extent of the SSI at diagnosis was retrospectively added by patient chart review, whereas all other data derived from the prospective data collection of the STCS. Chart review was limited to individuals with a documented SSI within 90 days after transplantation in the STCS database. SSIs were categorized into superficial incisional, deep incisional and organ/space infections according to CDC criteria [10]. The collection of these additional data included verification of SSIs reported in the STCS dataset by transplant infectious diseases physicians.

Statistical Analyses

Baseline recipient and donor characteristics were presented for SKP-Tx and P-Tx. We calculated incidence rates for transplant-related SSIs occurring within 90 days after SKP-Tx or P-Tx. Risk factors for SSIs were assessed with univariable and multivariable logistic regression. Based on findings from a previous study [5], we decided to include cold ischemia time and the transplant procedure (SPK-Tx vs. P-Tx) in the multivariable model. The duration of hospitalization in patients with and without SSI was compared with the Wilcoxon-Rank test. In order to adjust for other factors that might alter the length of stay, we fitted a Weibull accelerated failure-time model including the variables SSI, delayed graft function, transplant-related complications, and age. The model allowed us to estimate the event time ratio (ETR) for each of the covariates. Transplant-related complications that were considered likely to prolong hospitalization encompassed vascular complications affecting the graft and revision surgery or interventional drainage. Transplant outcomes, encompassing death, graft loss, need for insulin therapy, and a worsening of renal function to an estimated glomerular filtration rate <15ml/min/1.73m^2 after SKP-Tx and death, graft loss and need for insulin therapy after P-Tx were extracted from the STCS dataset and presented for the entire follow-up. R version 3.6.2 was used for statistical analysis and visualization [11].

Results

Study population

Overall, 108 SPK-Tx and 22 P-Tx recipients of a median age with 45 years [interquartile range (IQR) 37 - 51] and 43 years (IQR 35 - 48) were included, respectively (**Table 1**). Males contributed to 56% of SPK-Tx and to 59% of P-Tx

recipients. All SPK-Tx and P-Tx were performed due to diabetes mellitus type 1. Among SPK-Tx recipients, five (5%) and among P-Tx recipients 15 (68%) individuals had an anteceding transplantation. Among P-Tx recipients, 13 (59%) received the pancreas graft after prior kidney transplant. Among both, SPK-Tx and P-Tx, Caucasian ethnicity was most common (SPK-Tx 94, 88%; P-Tx 21, 96%). Induction immunosuppression was administered in the vast majority of SPK-Tx and P-Tx recipients with thymoglobulin being most frequent (SPK-Tx 85, 79%; P-Tx 22, 100.0%). In the first week after transplantation, most SPK-Tx recipients (91, 84.3%) were started on a tacrolimus-based maintenance immunosuppressive regimen, whereas more than half of P-Tx recipients (12, 54.5%) did neither receive tacrolimus, cyclosporine A or a mammalian target of rapamycin inhibitor. Routine peri-operative antibiotic prophylaxis for SSI prevention consisted of either amoxicillin/clavulanate or piperacillin/tazobactam.

Incidence, categorization and etiology of surgical site infections

Among totally 130 transplant recipients, 18 (13.8%) individuals [15 (13.9%) SPK-Tx recipients and 3 (13.6%) P-Tx recipients] developed SSIs within the first 90 days after transplantation. Three (16.7%) SSIs were categorized as superficial incisional, seven (38.9%) as deep incisional SSIs and eight (44.4%) as organ/space infections. There were nine (50%) bacterial SSIs (1 with detection of multiple bacteria), 5 (27.8%) fungal SSIs (1 with detection of multiple fungi) and 2 (11.1%) SSIs caused by fungi and bacteria. Two (11.1%) SSIs were diagnosed based on clinical findings. After SPK-Tx, in the majority of SSIs bacteria (9/15, 60%) were detected, most frequently enterococci (6/15, 40%) and coagulase-negative staphylococci (CNS) (3/15, 20%) (**Figure 2**). In six SSIs at least one fungus was detected and the

detected species included *Candida albicans* (4/15, 27%), *Candida* non-*albicans* (2/15, 13%) and *Aspergillus fumigatus* (1/15, 7%).

After P-Tx, in two SSIs bacteria were detected, and the species were *Enterococcus* spp., *Streptococcus* spp. and other anaerobic bacteria. In one SSI, a fungus was identified (*Candida* non-*albicans*).

Risk factor analysis for surgical site infections

Using logistic regression to identify possible risk factors for SSI, we did not detect a significant association with type of transplant procedure, recipient age, sex or BMI, donor sex or age, cold ischemia time, different induction therapies, routine peri-operative antibiotic prophylaxis and the variable, if the current transplant was performed after an anteceding transplant (**Table 2**). Similarly, we did not detect a significant association in a multivariable analysis with adjustment for type of transplant procedure and cold ischemia time.

Association of surgical site infections with post-transplant outcomes

Post-transplant outcomes regarding death, graft loss and need for insulin therapy (as well as a worsening of renal function to an estimated glomerular filtration rate <15ml/min/1.73m^2 after SKP-Tx) were similar among transplant recipients with SSI and without SSI (**supplemental Table**). Overall, the median length of hospital stay after transplantation was longer in patients with SSI (median 26d; IQR [19, 44]) than in patients without SSI (median 17d; IQR [12, 25], P= 0.002). This observation was consistent, if we focused exclusively on SPK-Tx (SSI: median 23, IQR [18, 49]; no SSI: 17, IQR [12, 25], P = 0.009) or P-Tx (SSI: median 28, IQR [26, 31]; no SSI: 15, IQR [13, 19], P = 0.055) recipients. When correcting for other possible reasons for a

prolonged length of hospital stay such as delayed graft function, age or transplant-related complications, we found that SSIs, delayed graft function and transplant-related complications significantly were associated with an increase in the length of stay (**Table 3**). After adjustment for the covariates age, transplant-related complications and occurrence of delayed graft function, patients with SSI were found to stay 36% (95% CI: [4, 79]) longer in the hospital than patients without SSI.

Discussion

In the present cohort study on SSIs after SPK-Tx or P-Tx we found an incidence of 14% with a predominance of organ/space infections. The majority of SSIs were caused by bacteria with *Enterococcus* spp. being most frequently identified. Individuals with SSIs were significantly longer hospitalized after transplant compared to recipients without SSIs.

The incidence of SSIs was often higher in prior studies ranging between 20% and 50% [5-7, 12], a single study reported SSIs at a lower frequency with 14% for SPK-Tx and 9% for pancreas after kidney transplantation [13]. One explanation for these differences could be that most studies used older data compared to the present study. It can be speculated that due to improved practices in infection prevention a longitudinal decrease in SSIs could be observed. Furthermore, the country, in which the study was performed, might be also relevant for the incidence of SSIs. The World Health Organization reported an increased burden of HAIs in low- and middle income countries with SSIs being the most frequent HAI [14].

Among all SSIs, deep incisional and organ/space infections are the most relevant SSIs in terms of morbidity and mortality. Besides our study, only few studies addressed this categorization [5, 6]. Resembling the findings of Smets *et al* [6] and

Natori *et al* [5], organ/space infections predominated in the present study. In contrast to Natori *et al* [5], deep incisional SSIs were found more frequent than superficial incisional SSIs. Future studies with inclusion of this highly relevant variable seem desirable.

In line with prior studies, the vast majority of SSIs was caused by bacteria with common detection of *Enterococcus* spp. and CNS [5, 6, 12, 15]. In contrast, Perdiz *et al* reported a high proportion of gram-negative pathogens causing SSIs [7]. Fungal SSIs were predominantly due to *Candida* spp., resembling the findings from Kawecki *et al* [15] and Natori *et al* [5].

A recent mono-centric study from Canada with inclusion of 445 patients aimed at identification of risk factors for SSIs after SPK-Tx and pancreas after kidney transplantation [5]. The authors found an increased SSI risk for SPK-Tx recipients and longer cold ischemia time. Perdiz *et al* identified acute tubular necrosis, post-transplant fistulas and an episode of rejection as independent risk factors [7], whereas Smets *et a*l identified cefamandole prophylaxis as independent risk factor [6]. Among the addressed variables, we did not identify any significant risk factor for SSIs. However, our analysis might be hampered by the low frequency of SSIs in our cohort and the overall limited number of SPK-Tx and P-Tx recipients. Our cohort did not include data on the individually administered peri-operative antibiotic prophylaxis, but if we considered the different routinely administered peri-operative prophylaxis, we didn’t find a significant association with SSIs.

Data on transplant outcomes due to SSIs among SPK-Tx and P-Tx patients are still scarce. In a Canadian cohort of SPK and pancreas after kidney recipients, a longer hospital stay and 16-fold odds for graft loss within 3 months post-transplant was reported [5]. Smets *et al* observed two graft losses in direct relation to a SSIs among

20 patients with SSIs and a significant longer hospital stay in recipients with SSIs [6]. In line with prior studies [5-7], we confirmed a prolonged duration of hospitalization for transplant recipients with SSIs. The application of a Weibull accelerated failure-time model allowed us to provide a more accurate estimate of the association between the investigated variables and prolongation of hospital stay. These findings might be helpful for identification of individuals with likely prolonged hospital stay and the expected extent of prolongation by the occurrence of associated variables. A better understanding of these associations could be crucial for optimized allocation of resources in health care. We did not identify any significant differences among the further assessed outcome variables.

Strengths of the current study are the multi-centric design with almost exclusive use of prospectively collected data. The STCS dataset is highly representative for transplantations performed in Switzerland given an enrolment of more than 90% of all solid organ transplantations performed in Switzerland [8]. The use of widely established CDC definitions for SSIs enables insights into severity of SSIs and will allow comparisons with future studies.

The present study also has some limitations. The categorization of SSIs was assessed retrospectively. The overall low number of SSIs limited statistical power and thus hindered more detailed statistical analyses. We did not collect information on the administration of peri-operative prophylaxis per individual patient. We provided data on routinely used peri-operative antibiotic prophylaxis, but there might have been adaptions due to pre-transplant colonization of transplant recipients.

To conclude, SSIs were detected at a similar frequency after SPK-Tx and P-Tx. SSIs were associated with a significant longer hospitalization after transplant procedure.

Conflicts of interest statement

PWS received travel grants from Pfizer and Gilead, speaker's honorary from Pfizer and fees for advisory board activity from Pfizer and Gilead outside of the submitted work. All other authors declared no conflicts of interest.

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Tables and Figures

Table 1: Baseline characteristics of 108 simultaneous kidney-pancreas recipients and 22 pancreas recipients.

	Kidney - Pancreas (N=108)	Pancreas (N=22)	Total (N=130)
Recipient sex			
Male	61 (56.0%)	13 (59.1%)	74 (56.5%)
Female	47 (43.5%)	9 (40.9%)	56 (43.5%)
Recipient age at transplantation (median [IQR])	44.7 [37.0, 51.0]	42.6 [34.9, 48.4]	44.4 [36.6, 50.1]
Recipient ethnicity			
African	6 (5.6%)	1 (4.5%)	7 (5.4%)
Asian	1 (0.9%)	0 (0.0%)	1 (0.8%)
Caucasian	94 (87.9%)	21 (95.5%)	115 (89.1%)
Other	6 (5.6%)	0 (0.0%)	6 (4.7%)
Recipient BMI (median [IQR])	23.1 [21.1, 25.3]	22.8 [20.5, 25.0]	23.1 [21.1, 25.3]
Tx history	5 (4.6%)	15 (68.2%)	20 (15.4%)
Induction immunosuppression			
None	3 (2.8%)	0 (0.0%)	3 (2.3%)
Basiliximab	20 (18.5%)	0 (0.0%)	20 (15.3%)
Thymoglobulin	83 (76.9%)	19 (86.4%)	102 (78.5%)
Basiliximab and thymoglobulin	2 (1.9%)	1 (4.5%)	3 (2.3%)
Rituximab and thymoglobulin	0 (0.0%)	2 (9.1%)	2 (1.5%)
Maintenance immunosuppression*			
Tacrolimus-based regimen	91 (84.3%)	10 (45.5%)	**101 (77.7%)**
mTOR inhibitor-based regimen	1 (0.9%)	0 (0.0%)	1 (0.8%)
Other	16 (14.8%)	12 (54.5%)	28 (21.5%)
CIT (median [IQR], h)			
Kidney	10.38 [8.92, 11.66]		10.38 [8.92, 11.66]
Pancreas	8.49 [7.18, 9.57]	7.95 [6.77, 9.43]	8.33 [7.08, 9.55]
Donor sex			
Male	70 (64.8%)	15 (68.2%)	85 (65.4%)
Female	38 (35.2%)	7 (31.8%)	45 (34.6%)
Donor age (median [IQR])	33.0 (22.8, 44.0)	30.5 (24.0, 36.8)	33.0 (23.3, 41.0)
Donor type			
DBD	**108 (100.0%)**	**22 (100.0%)**	130 (100.0%)

Abbreviations: CIT cold ischemia time, DBD donation after brain death, Tx history prior solid organ transplant

* Maintenance immunosuppressive regimen that was administered within the first week after transplantation. Other maintenance immunosuppression referred to a maintenance regimen that did not include cyclosporine A, tacrolimus or a mammalian target of rapamycin inhibitor (mTOR inhibitor).

Table 2: Univariable and multivariable logistic regression for identification of risk factors for SSIs 90 days post-transplant

	univariable		multivariable	
	OR [95% CI]	p-value	OR [95% CI]	p-value
Transplant procedure				
Kidney - Pancreas	reference		reference	
Pancreas	0.98 [0.21, 3.34]	0.98	0.99 [0.26, 3.8]	0.99
Recipient sex				
Female	reference			
Male	0.72 [0.26, 1.99]	0.52		
Recipient age (years)	0.96 [0.91, 1.02]	0.19		
Recipient BMI (kg/m^2)	1.03 [0.89, 1.19]	0.68		
Tx history	1.12 [0.24, 3.86]	0.87		
CIT pancreas (minutes)	1.00 [0.99, 1.00]	0.70	1.00 [0.99, 1.00]	0.70
Induction immunosuppression with thymoglobuline	1.09 [0.32, 5.00]	0.90		
Routine peri-operative antibiotic prophylaxis				
Piperacillin/tazobactam	reference			
Amoxicillin/clavulanate	1.50 [0.52, 4.95]	0.47		
Donor sex				
Female	reference			
Male	0.62 [0.22, 1.74]	0.35		
Donor age (years)	1.02 [0.97, 1.06]	0.51		

Abbreviations: BMI body mass index, CI confidence interval, CIT cold ischemia time, OR odds ratio, Tx history prior solid organ transplant

383 **Table 3:** Multivariable accelerated failure time model predicting time to discharge

	ETR [95% CI]	p-value
Surgical site infection	1.36 [1.04, 1.79]	0.025
Transplant-related complication	1.68 [1.37, 2.07]	<0.001
Delayed graft function	1.40 [1.04, 1.97]	0.029
Age (year)	1.00 [0.9, 1.01]	0.767

384 ETR: event time ratio

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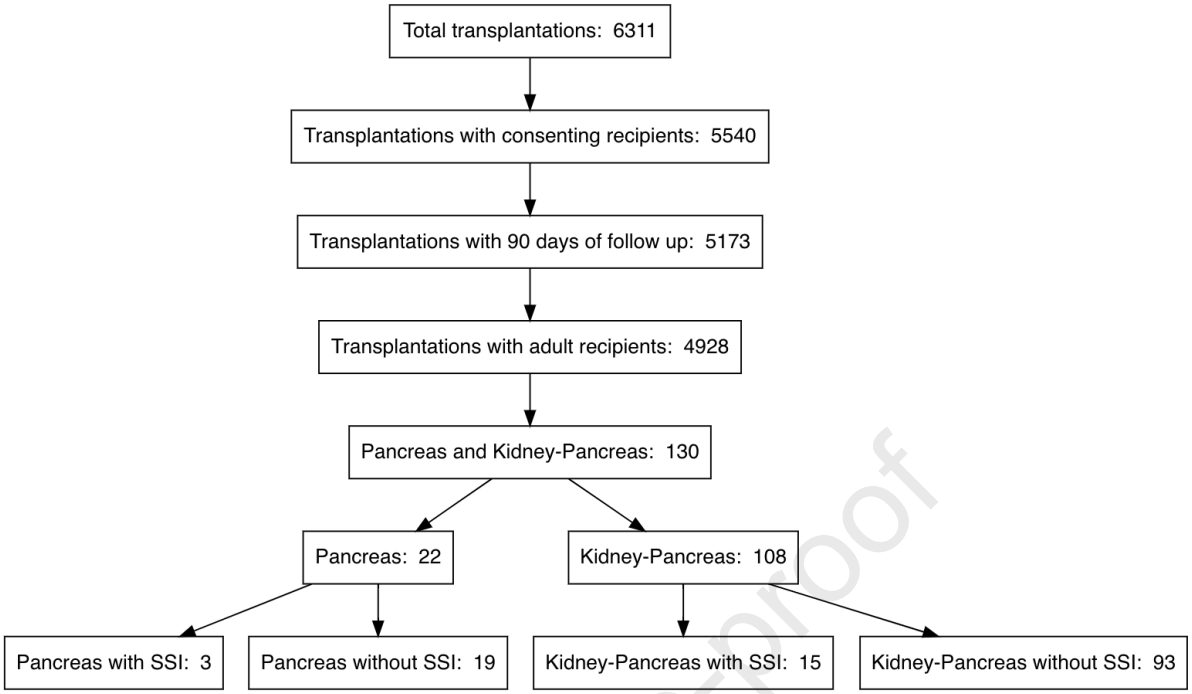

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388 **Figure 1: Flowchart of the study population selection**

389 Abbreviation: SSI surgical site infection

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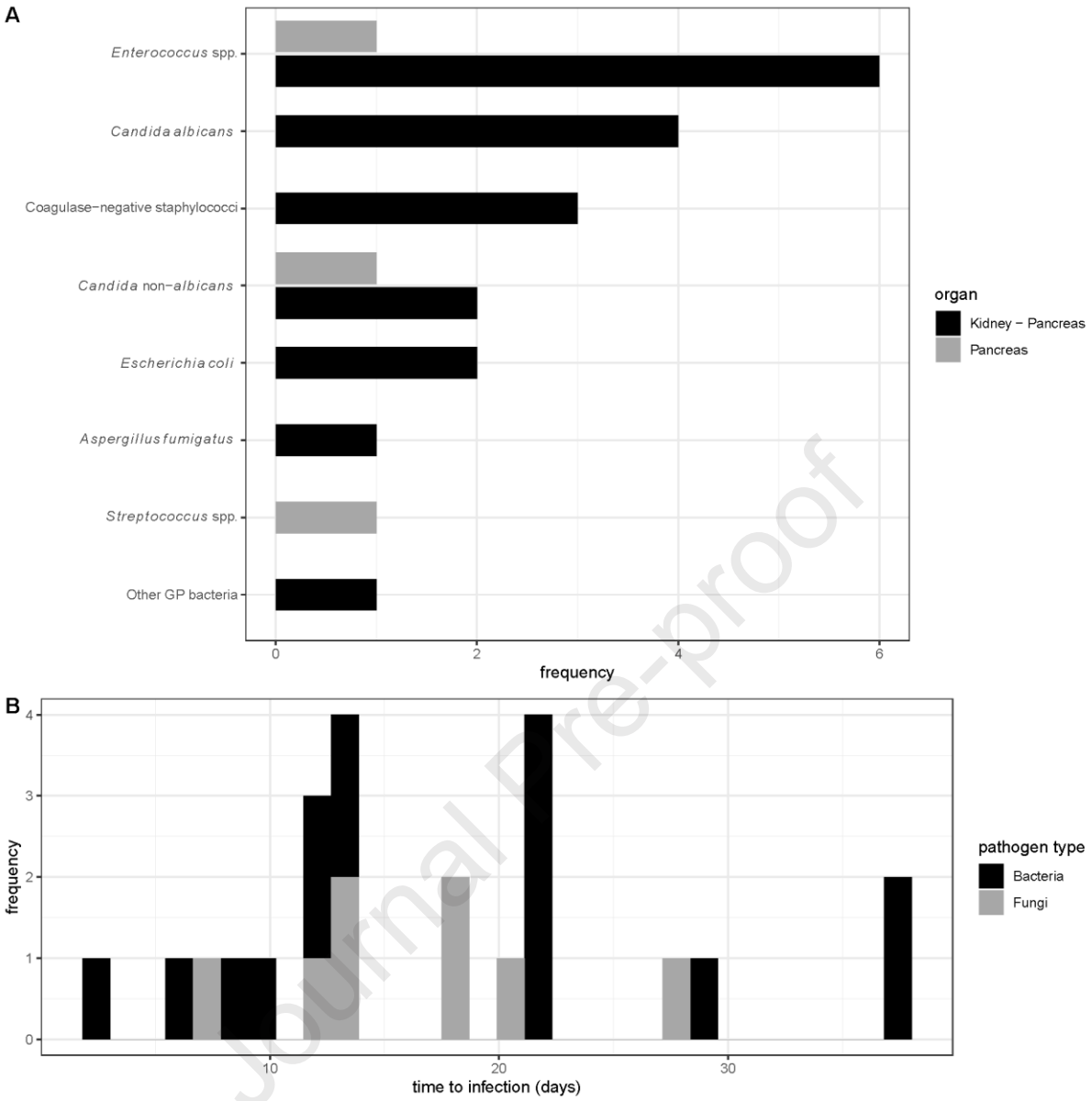

Figure 2: Frequency of detected pathogens in surgical site infections after simultaneous pancreas-kidney and pancreas transplantation (A) and time to occurrence of surgical site infection by pathogen (B)

In two surgical site infections after simultaneous pancreas-kidney transplantation and in one surgical site infection after pancreas transplantation multiple pathogens were detected.

Table 1: Baseline characteristics of 108 simultaneous kidney-pancreas recipients and 22 pancreas recipients.

	Kidney - Pancreas (N=108)	Pancreas (N=22)	Total (N=130)
Recipient sex			
Male	61 (56.0%)	13 (59.1%)	74 (56.5%)
Female	47 (43.5%)	9 (40.9%)	56 (43.5%)
Recipient age at transplantation (median [IQR])	44.7 [37.0, 51.0]	42.6 [34.9, 48.4]	44.4 [36.6, 50.1]
Recipient ethnicity			
African	6 (5.6%)	1 (4.5%)	7 (5.4%)
Asian	1 (0.9%)	0 (0.0%)	1 (0.8%)
Caucasian	94 (87.9%)	21 (95.5%)	115 (89.1%)
Other	6 (5.6%)	0 (0.0%)	6 (4.7%)
Recipient BMI (median [IQR])	23.1 [21.1, 25.3]	22.8 [20.5, 25.0]	23.1 [21.1, 25.3]
Tx history	5 (4.6%)	15 (68.2%)	20 (15.4%)
Induction immunosuppression			
None	3 (2.8%)	0 (0.0%)	3 (2.3%)
Basiliximab	20 (18.5%)	0 (0.0%)	20 (15.3%)
Thymoglobulin	83 (76.9%)	19 (86.4%)	102 (78.5%)
Basiliximab and thymoglobulin	2 (1.9%)	1 (4.5%)	3 (2.3%)
Rituximab and thymoglobulin	0 (0.0%)	2 (9.1%)	2 (1.5%)
Maintenance immunosuppression*			
Tacrolimus-based regimen	91 (84.3%)	10 (45.5%)	**101 (77.7%)**
mTOR inhibitor-based regimen	1 (0.9%)	0 (0.0%)	1 (0.8%)
Other	16 (14.8%)	12 (54.5%)	28 (21.5%)
CIT (median [IQR], h)			
Kidney	10.38 [8.92, 11.66]		10.38 [8.92, 11.66]
Pancreas	8.49 [7.18, 9.57]	7.95 [6.77, 9.43]	8.33 [7.08, 9.55]
Donor sex			
Male	70 (64.8%)	15 (68.2%)	85 (65.4%)
Female	38 (35.2%)	7 (31.8%)	45 (34.6%)
Donor age (median [IQR])	33.0 (22.8, 44.0)	30.5 (24.0, 36.8)	33.0 (23.3, 41.0)
Donor type			
DBD	**108 (100.0%)**	**22 (100.0%)**	130 (100.0%)

Abbreviations: CIT cold ischemia time, DBD donation after brain death, Tx history prior solid organ transplant

* Maintenance immunosuppressive regimen that was administered within the first week after transplantation. Other maintenance immunosuppression referred to a maintenance regimen that did not include cyclosporine A, tacrolimus or a mammalian target of rapamycin inhibitor (mTOR inhibitor).

Table 2: Univariable and multivariable logistic regression for identification of risk factors for SSIs 90 days post-transplant

	univariable		multivariable	
	OR [95% CI]	p-value	OR [95% CI]	p-value
Transplant procedure				
Kidney - Pancreas	reference		reference	
Pancreas	0.98 [0.21, 3.34]	0.98	0.99 [0.26, 3.8]	0.99
Recipient sex				
Female	reference			
Male	0.72 [0.26, 1.99]	0.52		
Recipient age (years)	0.96 [0.91, 1.02]	0.19		
Recipient BMI (kg/m^2)	1.03 [0.89, 1.19]	0.68		
Tx history	1.12 [0.24, 3.86]	0.87		
CIT pancreas (minutes)	1.00 [0.99, 1.00]	0.70	1.00 [0.99, 1.00]	0.70
Induction immunosuppression with thymoglobuline	1.09 [0.32, 5.00]	0.90		
Routine peri-operative antibiotic prophylaxis				
Piperacillin/tazobactam	reference			
Amoxicillin/clavulanate	1.50 [0.52, 4.95]	0.47		
Donor sex				
Female	reference			
Male	0.62 [0.22, 1.74]	0.35		
Donor age (years)	1.02 [0.97, 1.06]	0.51		

Abbreviations: BMI body mass index, CI confidence interval, CIT cold ischemia time, OR odds ratio, Tx history prior solid organ transplant

Table 3: Multivariable accelerated failure time model predicting time to discharge

	ETR [95% CI]	p-value
Surgical site infection	1.36 [1.04, 1.79]	0.025
Transplant-related complication	1.68 [1.37, 2.07]	<0.001
Delayed graft function	1.40 [1.04, 1.97]	0.029
Age (year)	1.00 [0.9, 1.01]	0.767

ETR: event time ratio