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ORIGINAL ARTICLE

Epidemiology and outcomes of bone and joint infections in solid organ transplant recipients

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Bone and joint infection (BJI) epidemiology and outcomes in solid organ transplant recipients (SOTr) remain largely unknown. We aim to describe BJI in a multi-center cohort of SOTr (Swiss Transplant Cohort Study). All consecutive SOTr with BJI (01.05.2008–31.12.2019) were included. A nested case–control study to identify risk

Abbreviations: BJI, bone and joint infection; CI, confidence interval; CRP, C-reactive protein; DFO, diabetic foot osteomyelitis; ESBL, extended-spectrum beta-lactamases; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; IV, intravenous; MDR, multidrug-resistant; MRSA, methicillin resistant *S. aureus*; OAI, osteosynthesis-associated infection; OR, odds ratio; PJI, peri-prosthetic joint infection; SA, septic arthritis; SOT, solid organ transplant; SOTr, solid organ transplant recipient; SSI, surgical site infection; STCS, Swiss Transplant Cohort Study.

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factors for BJI was performed. Among 4482 patients, 61 SOTr with 82 BJI were included, at an incidence of 1.4% (95% CI 1.1–1.7), higher in heart and kidney-pancreas SOTr (Gray's test $p < .01$). Although BJI were predominately late events (median of 18.5 months post-SOT), most infections occurred during the first year post-transplant in thoracic SOTr. Diabetic foot osteomyelitis was the most frequent infection (38/82, 46.3%), followed by non-vertebral osteomyelitis (26/82, 31.7%). Pathogens included Gram-positive cocci (70/131, 53.4%), Gram-negative bacilli (34/131, 26.0%), and fungi (9/131, 6.9%). BJI predictors included male gender (OR 2.94, 95% CI 1.26–6.89) and diabetes (OR 2.97, 95% CI 1.34–6.56). Treatment failure was observed in 25.9% (21/81) patients and 1-year mortality post-BJI diagnosis was 14.8% (9/61). BJI remain a rare event in SOTr, associated with subtle clinical presentations, high morbidity and relapses, requiring additional studies in the future.

KEYWORDS
BJI, bone and joint infection, epidemiology, solid organ transplant recipients

1 | INTRODUCTION

The number of patients undergoing solid organ transplantation and those undergoing orthopedic surgery with implantation of fracture devices or prosthetic joints is rising worldwide.[1] With the progress attained in the field of transplantation, survival has significantly increased with transplant recipients frequently requiring orthopedic interventions and/or implants.[2,3] The epidemiology and risk factors for osteo-articular and implant infections in the transplant population remain largely unknown. The existing sparse literature almost exclusively reports on unusual pathogens in transplanted patients with prosthetic joint infections and in hematopoietic stem cell transplant (HSCT) recipients.[4–7] Moreover, all available data concern single centre experiences and no nationwide data have been published to date specifically on this topic. There is need for contemporary detailed data on osteo-articular and implant infections in solid organ transplant recipients (SOTr). Using data collected through the Swiss Transplant Cohort Study (STCS) we are reporting on the epidemiology, risk factors and clinical outcomes of osteo-articular and implant infections in a large multi-centre prospective cohort of SOTr.

2 | METHODS

2.1 | Study design and objectives

The STCS is a prospective national cohort and represents >95% of SOTr in Switzerland.[8] A written informed consent was signed by all patients included in this cohort. Patient data are prospectively collected and entered in the STCS database at the time of transplantation, at six and twelve months, and yearly thereafter.[9,10] We performed a retrospective observational cohort study including all adult (≥18 years of age) SOTr with bone and joint infections (BJI) between May 1, 2008 and December 31, 2019, with at least 6 months of follow-up. For patients who received more than one SOT sequentially, only the first SOT was included (censoring at the time of the second SOT). Pediatric patients and patients without a signed informed consent form were excluded. In addition, a nested case–control study was performed to identify risk factors for BJI among SOTr. Patients with BJI were considered as cases and matched at a 1:2 ratio with controls based on: (1) SOT type within 6 months of the index case performed at the same centre, (2) BJI event free during the study period, and (3) time post-SOT as long as the time between transplantation and BJI for the index case. The study was approved by the relevant Ethics Committee (2020–02123).

2.2 | Data collection

Pertinent data were retrospectively collected for all SOTr: (1) using the existing STCS database: demographics: age, gender; underlying disease leading to transplant; SOT-related variables (type of transplant, immunosuppression data [induction, maintenance at BJI-diagnosis], prophylaxis, donor-related data [age, living or dead]) and (2) by chart review for BJI events (date of BJI-diagnosis, BJI-type [septic arthritis, osteomyelitis, peri-prosthetic joint infection or other orthopedic implant infection], origin [primary, hematogenous, surgical site infection, SSI], clinical characteristics [localization, concomitant infection, signs of sepsis], laboratory characteristics, imaging, microbiological diagnosis [samples, pathogens, method of diagnosis], antimicrobial treatment, surgical treatment and clinical outcomes).

2.3 | Definitions

Proven bacterial infections were defined as previously reported and adjusted to international recommendations and guidelines.[11]

Detailed definitions of osteomyelitis, native joint septic arthritis, peri-prosthetic joint infection, and other orthopedic implant infection or osteosynthesis-associated infection are described in Supplementary materials. Osteomyelitis was divided into three groups: osteomyelitis associated with diabetic foot infection (diabetic foot osteomyelitis [DFO]), vertebral osteomyelitis, and non-vertebral osteomyelitis. Sepsis and septic shock were defined according to the Third International Consensus Definitions (Sepsis-3 definition).[12] Success of treatment was adapted from the Delphi-based international multidisciplinary consensus for PJI, with presence of the following criteria to meet favorable outcome[13]: (1) infection eradication, characterized by a healed wound without sinus tract, persisting drainage, or pain, and no infection recurrence caused by the same pathogen; (2) no subsequent surgical intervention for infection after reimplantation surgery in case of implant-associated infection; and (3) no BJI-related mortality. Treatment failure was defined as progression, recurrence with isolation of the same microorganism for the same BJI, or reinfection in case of different pathogen at the same infection site.

2.4 | Statistical analysis

Categorical variables were described by counts and percentages, while mean and standard deviation or median and interquartile range (IQR) were used to summarize continuous variables. Cumulative incidence of BJI was calculated using patients with an infection. If no BJI was observed during follow-up, patients were censored at death, graft failure, next SOT, loss to follow-up or administrative censoring date (June 30, 2020), whatever came first. Risk factor analyses to identify predictors of BJI was carried out on the case–control patient population with univariable and multivariable analyses by conditional logistic regression. For continuous variables, the hypothesis of log-linearity was tested before introducing them into the logistic regression model: if this hypothesis was rejected, the variables were categorized for statistical analysis. Clinically significant variables and variables with a p-value ≤.1 in univariable analyses were introduced in a backward stepwise fashion into a logistic regression model. Results are presented as odds ratios (OR) with 95% confidence intervals (CI), with a p-value <.05 considered as significant. The Pearson correlation coefficient was used to determine the strength of possible correlations between independent variables. Data were analyzed using STATA 16.1 (StataCorp LLC, TX). Charts were created with either Microsoft Excel for Apple Mac (version 16.56) or STATA.

3 | RESULTS

3.1 | Patient characteristics

Between 01.05.2008 and 31.12.2019, 4482 patients (2441 kidney, 1048 liver, 442 lung, 359 heart, 177 combined [including 123 kidney-pancreas/islets] and 15 pancreas/islets recipients) were included in the STCS, of which 61 (1.4%) had at least one BJI; 13 patients had >1 BJI. Hence, 61 SOTr with 82 BJI were included in this study. The patient baseline characteristics overall and by SOT type are detailed in Table 1. There was a predominance of male patients (n = 52, 85.2%), with a median age at transplantation of 57.5 years (IQR: 50.4–63.8). The incidence of BJI was 1.4% (95% CI 1.1–1.7) for all patients: 3.4% (95% CI 1.5–7.3), 2.8% (95% CI 1.5–5-1), 1.6% (95% CI 0.8–3.3), 1.4% (95% CI 1.0–2.0) and 0.3% (95% CI 0.1–0.9) in combined (only kidney-pancreas), heart, lung, kidney, and liver transplant recipients, respectively (Figure 1A,B). The incidence rate was 281.4 (95% CI 219.0–361.7) per 100 000 patient-years for any SOTr, and 667.2 (95% CI 299.7–1485.1) for kidney-pancreas, 614.9 (95% CI 330.9–1142.8) for heart, 363.7 (95% CI 173.4–763.0) for lung, 278.3 (95% CI 199.8–387.6) for kidney, and 65.6 (95% CI 21.2–203.4) for liver transplantation per 100 000 patient-years.

3.2 | Bone and joint infection characteristics

Eighty-two BJI were diagnosed at a median time after transplantation of 18.5 months (range 0–123). Most infections in lung and heart transplant recipients occurred during the 1st year post-transplant, at a median time of 5 (IQR 2.5–6.5) and 9 months (IQR 1–33), respectively, while for all other organ recipients BJI median time to diagnosis was during the second year after transplantation (Figure 1C).

The most common infection was DFO (n = 38/82, 46.3%), followed by non-vertebral osteomyelitis (n = 26/82, 31.7%), septic arthritis (n = 8/82, 9.8%), osteosynthesis-associated infection (n = 6/82, 7.3%), peri-prosthetic joint infection (n = 2/82, 2.4%) and vertebral osteomyelitis (n = 2/82, 2.4%), with incidence rates of 119.3 (95% CI 81.2–175.2), 100.8 (95% CI 66.4–153.1), 22.8 (95% CI 9.5–54.9), 22.9 (95% CI 9.5–54.9), 9.1 (95% CI 2.3–36.5), and 4.6 (95% CI 0.6–32.4) per 100 000 patient-years, respectively (Table 2). The distribution of BJI based on SOT category, time to infection since transplantation, and pathogens identified is presented in Figure S1a–c. Kidney and kidney-pancreas recipients were the most frequently SOTr affected by DFO, while non-vertebral osteomyelitis accounted for the majority of infections in lung and heart recipients. All native joint septic arthritis occurred in kidney recipients (Figure 2A). More than two thirds of cases (n = 54/82, 65.9%) were considered as primary infections, while SSI accounted for a quarter of cases (n = 22/82, 26.8%), and only six (7.3%) cases were associated with bloodstream infections. The lower limb was the most frequent site (n = 52/82, 63.4%), particularly the foot (n = 45/82, 54.9%). The sternum was a frequent infection site in thoracic transplant recipients. Details of infections by type of organ transplant are provided in Supplementary materials.

At hospital admission, local inflammation was the most frequent clinical sign (n = 61/79, 77.2%), while fever was present in only one third of patients (n = 23/78, 29.5%), and few had criteria for sepsis (n = 4/79, 5.1%) or septic shock (n = 1/79, 1.3%). C-reactive protein (CRP) was moderately elevated with a median of 70.7 mg/L (range 2.2–440), and white blood cell count were normal or slightly increased in most cases, with a median of 9.6×10^9/L (IQR: 6.8–12.2).

TABLE 1 Baseline patient characteristics

Patient characteristics	All patients, *n* = 61	Heart, *n* = 10 (16.4%)	Kidney, *n* = 35 (57.4%)	Kidney-pancreas[a], *n* = 6 (9.9%)	Liver, *n* = 3 (4.9%)	Lung, *n* = 7 (11.5%)
Sex, female, *n* (%)	9 (14.8)	2 (20)	3 (8.6)	2 (33.3)	0	2 (28.6)
Age at infection (year), median (IQR)	57.5 (51.4–67.0)	51.3 (39.5–57.0)	64.6 (54.2–68.8)	55.0 (40.4–62.9)	54.7 (48.3–59.3)	54.3 (43.6–61.9)
Age at transplantation (year), median (IQR)	57.5 (50.4–63.8)	50.2 (39.5–57.0)	62.7 (54.1–66.8)	53.5 (36.4–60.6)	53.7 (47.3–59.3)	54.3 (43.6–61.9)
Type of donor, *n* (%)						
Cadaveric	48 (78.7)	10 (100)	22 (62.9)	6 (100)	3 (100)	7 (100)
Living	13 (21.3)	0	13 (37.1)	0	0	0
Comorbidities at transplantation						
Diabetes mellitus	33 (54.1)	2 (20.0)	22 (62.9)	6 (100)	1 (33.3)	2 (28.6)
Hypertension	41 (67.6)	2 (20.0)	32 (91.4)	5 (83.3)	2 (66.7)	0
Chronic kidney disease	44 (72.1)	5 (50.0)	33 (94.3)	6 (100)	0	0
without RRT	11 (28.3)	5 (50.0)	6 (17.1)	0	0	0
with RRT	33 (54.1)	0	27 (77.1)	6 (100)	0	0
Coronary artery disease	26 (42.6)	3 (30.0)	22 (62.9)	0	0	1 (14.3)
Peripheral arterial disease	16 (26.2)	1 (10)	13 (37.1)	2 (33.3)	0	0
LVEF<30%	8 (13.1)	7 (70.0)	1 (2.9)	0	0	0
COPD	3 (4.9)	1 (10.0)	1 (2.9)	0	0	1 (14.3)
Immunosuppressive treatments						
Induction, *n* (%)[b]						
Basiliximab	41 (69.5)	10 (100)	30 (88.2)	2 (33.3)	2 (100)	7 (100)
Thymoglobulin[c]	21 (35.6)	10 (100)	7 (20.6)	4 (66.7)	0	0
Rituximab	4 (6.6)	0	5 (14.3)	0	0	0
Other induction	2 (3.3)	1 (10)	1 (2.9)	0	0	0
None	2 (3.3)	0	1 (2.9)	0	1 (33.3)	0
Maintenance, *n* (%)[d]						
Corticosteroid	56 (68.3)	10 (100)	36 (78.3)	2 (15.4)	0	8 (100)
MMF or EC-MPS	71 (86.6)	8 (80.0)	40 (87.0)	12 (97.3)	4 (80.0)	7 (87.5)
Ciclosporine	17 (20.7)	3 (30.0)	10 (21.7)	2 (15.4)	1 (20.0)	1 (12.5)
Tacrolimus	60 (73.2)	5 (50.0)	35 (76.1)	10 (76.9)	3 (60.0)	7 (87.5)
Everolimus	5 (6.1)	3 (30.0)	2 (4.4)	0	0	0
Sirolimus	3 (3.7)	0	1 (2.2)	1 (7.7)	1 (20.0)	0
Azathioprine	4 (4.9)	2 (20.0)	1 (2.2)	0	0	1 (12.5)
PCP prophylaxis by TMP-SMX, *n* (%)[e]	21 (25.6)	5 (50.0)	8 (17.4)	0	2 (40.0)	6 (75.0)

Abbreviations: COPD, chronic obstructive pulmonary disease; EC-MPS, enteric-coated mycophenolate sodium; IQR, interquartile range; LVEF<30%, left ventricular ejection fraction <30%; MMF, mycophenolate mofetil; PCP, *Pneumocystis jirovecii* pneumonia; RRT, renal replacement therapy; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Or islets of Langerhans.

[b]Information for induction was available for 59 patients.

[c]Rabbit anti-thymocyte globulin (ATG) or murine monoclonal anti-T cell antibody (OKT3).

[d]Maintenance immunosuppression was registered at the time of the infection episode.

[e]PCP prophylaxis was registered at the time of the infection episode.

Most BJI were monomicrobial (*n* = 50/82, 61.1%) and rarely associated with bacteraemia (*n* = 11/82, 13.4%). When looking at pathogen categories, Gram-positive cocci were predominant, followed by Gram-negative bacilli, except for lung transplant recipients where fungal infections represented the majority of BJI (Figure 2B). In addition, anaerobic infections were predominately identified in liver, followed by heart transplant recipients. The latter were also commonly infected by aerobic Gram-positive

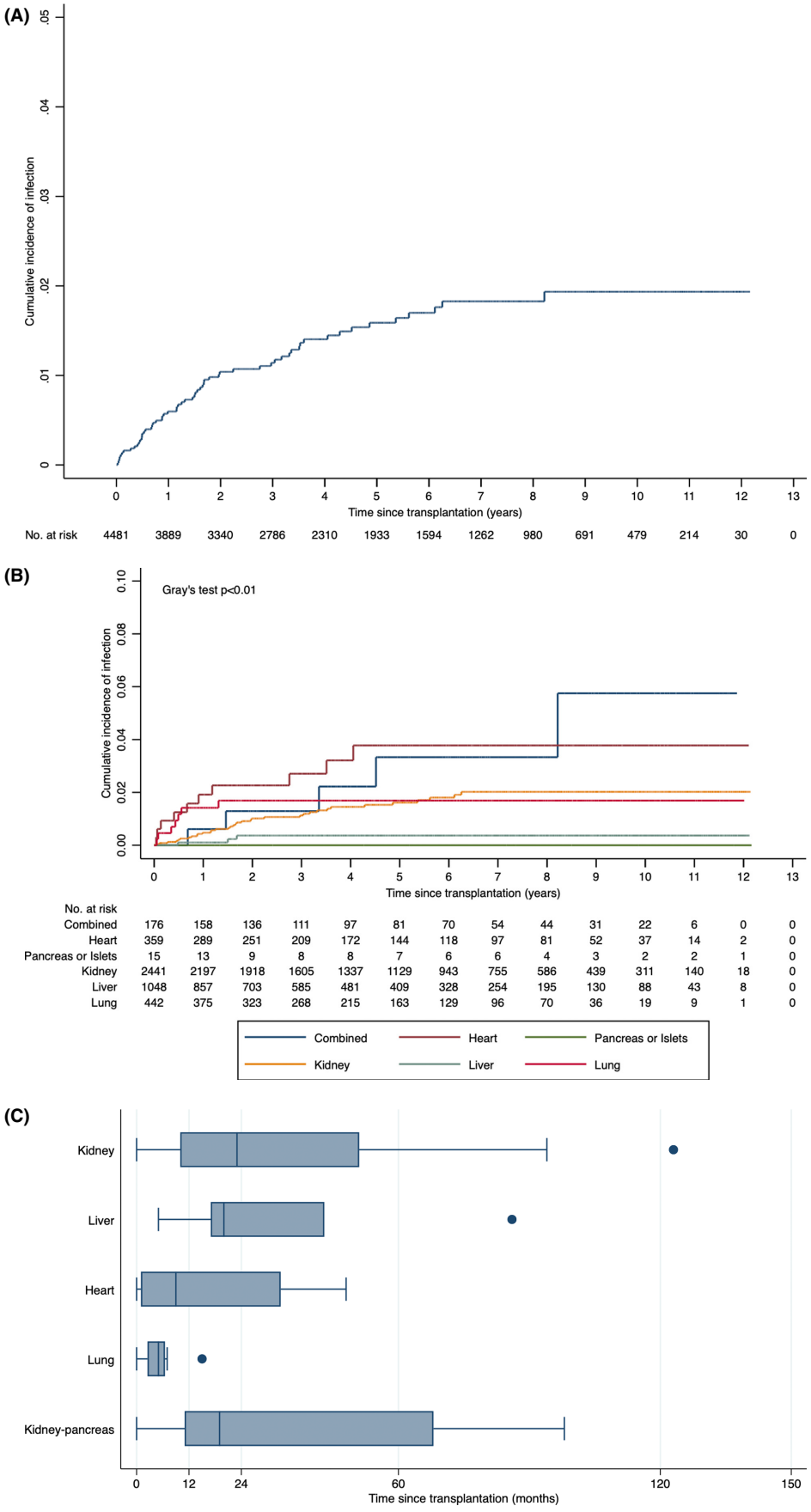

FIGURE 1 Cumulative incidence of bone and joint infection among solid organ transplant recipients: (A) overall and (B) by organ transplanted. Time to infection by organ transplant categories (C). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Bone and joint infection characteristics

Bone and joint infection characteristics	Total, *n* = 82	Diabetic foot osteomyelitis, *n* = 38 (46.3%)	Non-vertebral osteomyelitis, *n* = 26 (31.7%)	Vertebral osteomyelitis, *n* = 2 (2.4%)	Septic arthritis, *n* = 8 (9.8%)	Osteosynthesis-associated infection, *n* = 6 (7.3%)	Peri-prosthetic joint infection, *n* = 2 (2.4%)
Sex, female, *n* (%)	10 (12.2)	6 (15.8)	3 (11.5)	0	0	1 (16.7)	0
Age at infection (year), median (IQR)	59.6 (53.4–67.0)	60.7 (54.3–67.0)	54.3 (49.8–65.4)	63.9 (59.9–67.9)	65.1 (51.9–68.4)	60.0 (57.5–62.7)	44.5 (34.3–54.7)
Age at infection (year), mean (range, ± SD)	57.8 (25.1–76.1, 11.1)	59.2 (31.5–76.1, 10.3)	54.8 (25.1–73.1, 12.7)	63.9 (59.9–67.9, 5.7)	60.1 (41.1–68.8, 10.7)	61.6 (54.2–75.3, 7.3)	44.5 (34.4–54.7, 14.3)
Type of transplant, *n* (%)							
Heart	10 (12.2)	1 (2.6)	7 (26.9)	0	0	2 (33.3)	0
Kidney	46 (56.1)	22 (57.9)	9 (34.6)	2 (100)	8 (100)	4 (66.7)	1 (50.0)
Kidney-pancreas[a]	13 (15.9)	13 (34.2)	0	0	0	0	0
Liver	5 (6.1)	2 (5.3)	2 (7.7)	0	0	0	1 (50.0)
Lung	8 (9.8)	0	8 (30.8)	0	0	0	0
Origin of infection, *n* (%)							
Primary	54 (65.9)	37 (97.4)	12 (46.2)	1 (50.0)	3 (37.5)	1 (16.7)	0
Hematogenous	6 (7.3)	0	2 (7.7)	1 (50.0)	3 (37.5)	0	0
Surgical site infection	22 (26.8)	1 (2.6)	12 (46.2)	0	2 (25.0)	5 (83.3)	2 (100)
Site of infection, *n* (%)							
Lower limb	52 (63.4)	38 (100)	7 (26.9)	NA	3 (37.5)	2 (33.3)	2
Incl. foot	45 (54.9)	38 (100)	5 (19.2)	NA	0	2 (33.3)	0
Upper limb	8 (9.8)	NA	3 (11.5)	NA	4 (50.0)	1 (16.7)	0
Incl. hand	3 (3.7)	NA	2 (7.7)	NA	1 (12.5)	0	0
Vertebral	4 (4.9)	NA	NA	2 (100)	0	2 (33.3)	NA
Sternum	13 (15.6)	NA	11 (42.3)	NA	1 (12.5)	1 (16.7)	NA
ENT	2 (2.4)	NA	2 (7.7)	NA	0	0	NA
Other[b]	3 (3.7)	NA	3 (11.5)	NA	0	0	NA
Concomitant infection, *n* (%)[c]	22 (26.8)	8 (21.1)	8 (30.8)	2 (50.0)	4 (50.0)	0	0
Time to BJI (months), median (IQR, range)	18.5 (7–43, 0–123)	19.5 (10–54, 0–98)	9.5 (4–35, 0–123)	26.5 (10–43, 10–43)	36 (17–42.5, 5–94)	20.5 (6–64, 1–80)	42 (17–67, 17–67)
Clinical characteristics at hospital entry, *n* (%)[d]							
Fever	23/78 (29.5)	16/36 (44.4)	5 (19.2)	0	0/7	0/5	2 (100)
Sepsis	4/79 (5.1)	1/36 (2.8)	1 (3.9)	0	0/7	0	2 (100)
Septic shock	1/79 (1.3)	0/36	0	0	0/7	1 (16.7)	0

TABLE 2 (Continued)

Bone and joint infection characteristics	Total, *n* = 82	Diabetic foot osteomyelitis, *n* = 38 (46.3%)	Non-vertebral osteomyelitis, *n* = 26 (31.7%)	Vertebral osteomyelitis, *n* = 2 (2.4%)	Septic arthritis, *n* = 8 (9.8%)	Osteosynthesis-associated infection, *n* = 6 (7.3%)	Peri-prosthetic joint infection, *n* = 2 (2.4%)
Local inflammation	61/79 (77.2)	30/37 (81.1)	21 (80.8)	0	5/7 (71.4)	3/5 (60.0)	2 (100)
Necrosis	19/80 (23.8)	12/37 (32.4)	6 (23.1)	0	1/7 (14.3)	0	0
Laboratory characteristics at hospital entry, median (IQR, range)[e]							
C-reactive protein (mg/L)	70.7 (27.7–175.6, 2.2–440.0)	50.0 (16.7–126.3, 3.0–363.0)	45 (23.9–95.0, 2.2–292.0)	317.0 (289.0–345.0, 289.0–345.0)	209.5 (164.6–291.0, 125.0–300.0)	89.0 (80.0–287.0, 11.5–336.0)	357.0 (274.0–440.0, 274.0–440.0)
Procalcitonin (ng/ml)	0.85 (0.35–3.9, 0.11–40.0)	1.97 (0.52–3.42, 0.52–3.42)	4.42 (NA)	1.02 (NA)	20.09 (0.17–40.0, 0.17, 40.0)	0.11 (NA)	0.68 (NA)
Leukocytes (x10^9/L)	9.6 (6.8–12.2, 1.92–37.6)	9.9 (6.7–11.8, 2.4–23.1)	9.5 (6.3–14.2, 2–37.6)	5.0 (1.2–8.0, 1.2–8.0)	10.7 (9.3–15.0, 8.0–24.7)	8.8 (5.9–9.0, 5.0–11.1)	16.8 (13.8–19.8, 13.8–19.8)
Imaging, *n* (%)[g]							
X-ray	27/78 (34.6)	17/37 (46.0)	5/25 (20.0)	0	3/7 (42.9)	0/5	2 (100)
Computed tomography scan	21/78 (26.9)	7/37 (18.9)	11/25 (44.0)	0	1/7 (14.3)	2/5 (40.0)	0
MRI	31/78 (39.7)	17/37 (46.0)	8/25 (32.0)	2 (100)	3/7 (42.9)	1/5 (20.0)	0
PET-CT	1/77 (1.3)	0/37	0/25	0	0/7	1/5 (20.0)	0
Other[h]	3/76 (4.0)	1/37 (2.7)	1/23 (4.4)	1 (50.0)	0/7	0/5	0
Diagnosis, *n* (%)							
Samples							
Surgical sample	58 (70.7)	25 (65.8)	21 (80.8)	1 (50.0)	4 (50.0)	5 (83.3)	2 (100)
Bone	38 (46.3)	17 (44.7)	18 (69.2)	0	0	3 (50)	0
Tissue	42 (51.2)	14 (36.8)	16 (61.5)	1 (50.0)	4 (50.0)	5 (83.3)	2 (100)
Bone biopsy	10 (12.2)	4 (10.5)	5 (19.2)	0	1 (12.5)	0	0
Joint aspiration, n (%)	5 (6.1)	0	0	1 (50.0)	4 (50.0)	0	0
Synovial leukocytes (cells/mm3), median (IQR)[i]	71 800 (32700-104 100)	ND	ND	71 800 (NA)	68 400 (32700-104 100)	ND	ND
Wound Swab	21 (25.6)	13 (34.2)	7 (26.9)	0	0	0	1 (50.0)
Other[f]	6 (7.3)	2 (5.3)	2)8.0)	0	1 (14.3)	1 (16.7)	0
Methods							
Culture	82 (100)	38 (100)	26 (100)	26 (100)	2 (100)	8 (100)	2 (100)
PCR/Molecular technique	3 (3.7)	1 (2.6)	1 (3.9)	1 (50.0)	0	0	0
Pathology	11 (13.4)	5 (13.2)	6 (23.1)	0	0	0	0

(Continues)

TABLE 2 (Continued)

Bone and joint infection characteristics	Total, *n* = 82	Diabetic foot osteomyelitis, *n* = 38 (46.3%)	Non-vertebral osteomyelitis, *n* = 26 (31.7%)	Vertebral osteomyelitis, *n* = 2 (2.4%)	Septic arthritis, *n* = 8 (9.8%)	Osteosynthesis-associated infection, *n* = 6 (7.3%)	Peri-prosthetic joint infection, *n* = 2 (2.4%)
Monomicrobial, n (%)	49 (59.8)	17 (44.7)	15 (57.7)	2 (100)	8 (100)	6 (100)	1 (50)
Fungal infection	9 (11.0)	0	8 (30.8)	0	0	1 (16.7)	0
Associated bacteraemia, n (%)	11 (13.4)	5 (13.2)	2 (7.7)	1 (50.0)	3 (37.5)	0	0
Antibiotic duration (days), median (IQR, range)							
Total	50 (37–85, 7–405)	52.5 (39–85, 11–270)	43 (16–85, 7–371)	62 (43–81, 43–81)	44 (42–70, 34–405)	57 (42–101, 40–225)	89 (85–93, 85–93)
IV	19 (13–37, 0–405)	15 (9–25, 0–78)	20 (15–37, 7–371)	62 (43–81, 43–81)	34.5 (18.5–42.5, 13–405)	44 (16–52, 8–163)	18.5 (0–37, 0–37)
Antifungals duration (days), median (IQR, range)							
Total	204 (36–366, 15–783)	15 (ND)	213 (99–366, 99–366))	NA	NA	36 (NA)	NA
IV	16 (0–26, 0–204)	0	16 (1–23, 0–244)	NA	NA	30 (NA)	NA
Surgical procedures, n (%)							
Irrigation/drainage/debridement	39 (47.6)	11 (29.0)	15 (57.7)	2 (100)	6 (75.0)	4 (66.7)	1 (50.0)
Implant removal/exchange	4 (4.9)	NA	1 (3.9)	NA	NA	2 (33.3)	1 (50.0)
Amputation	26 (31.7)	19 (50.0)	6 (23.1)	NA	1 (12.5)	0	0
Other surgical procedure[j]	4 (4.9)	1 (2.6)	2 (7.7)	0	1 (12.5)	0	0
No surgery	9 (11.0)	7 (18.4)	2 (7.7)	0	0	0	0
Multiple procedures	33/73 (45.2)	8/31 (25.8)	15/24 (62.5)	1 (50.0)	4 (50.0)	4 (66.7)	1 (50.0)
Outcome, *n* (%)							
Favorable[k]	60/81 (74.1)	23/37 (62.2)	23 (88.5)	1 (50.0)	7 (87.5)	4 (66.7)	2 (100)
Failure							
Relapse	13/81 (16.0)	10/37 (27.0)	1 (3.9)	0	0	2 (33.3)	0
Progression	7/81 (8.6)	4/37 (10.8)	2 (7.7)	0	1 (12.5)	0	0
Reinfection	1/81 (1.2)	0	0	1 (50.0)	0	0	0
Mortality[l]							
30 days	0	0	0	0	0	0	0
90 days	4/61 (6.6)	0	3/22 (13.6)	0	1/4 (25.0)	0	0

TABLE 2 (Continued)

Bone and joint infection characteristics	Total, *n* = 82	Diabetic foot osteomyelitis, *n* = 38 (46.3%)	Non-vertebral osteomyelitis, *n* = 26 (31.7%)	Vertebral osteomyelitis, *n* = 2 (2.4%)	Septic arthritis, *n* = 8 (9.8%)	Osteosynthesis-associated infection, *n* = 6 (7.3%)	Peri-prosthetic joint infection, *n* = 2 (2.4%)
6 months	6/61 (9.8)	0	3/22 (13.6)	0	2/4 (50.0)	1 (16.7)	0
1 year	9/61 (14.8)	2/25 (8.0)	4/22 (18.2)	0	2/4 (50.0)	1 (16.7)	0

Abbreviations: BJI, bone and joint infection; ENT, ear, nose, and throat; IQR, interquartile range; IV, intravenous; MRI, magnetic resonance imaging; NA, not applicable; ND, not done; PCR, polymerase chain reaction; PET-CT, positron emission tomography-computed tomography; SD, standard deviation.

[a]Or islets of Langerhans.

[b]Other localizations included: pubic symphysis, os temporale, scapula, base of skull.

[c]Concomitant infections included: other BJI (6), cellulitis or other complex skin and skin structure infection (cSSSI) (5), bacteraemia of other origin (2), endocarditis (3), pneumonia or lung empyema (3), disseminated nocardiosis with brain abscess and pneumonia (1), mediastinitis (1), cytomegalovirus (CMV) reactivation (1).

[d]For clinical characteristics, information for fever, sepsis, septic shock, local inflammation and necrosis, was available for: 78, 79, 79, 79, and 80 cases respectively.

[e]For laboratory characteristics, information for C-reactive protein, procalcitonin and leucocyte count, information was available for: 72, 8, and 73 cases, respectively.

[f]Other diagnostic samples included: abscess puncture (2), osteosynthesis culture (2), blood culture (1), maxillary sinus aspiration (1).

[g]For imaging, information for X-ray, CT, MRI, PET-CT and other, was available for: 78, 78 78, 77, and 76, respectively.

[h]Other imaging included: ultrasound, SPECT/CT (single photon emission computed tomography/computed tomography), arteriography.

[i]For synovial leucocyte count, information was available for 3 cases.

[j]Other surgical procedure included: resection arthrodesis, Girdlestone procedure (hip excision arthroplasty), petrosectomy, and meatotomy, sphenoidectomy and ethmoidectomy.

[k]For clinical outcome, information was available for 81 cases.

[l]For mortality, only the last BJI episode was considered.

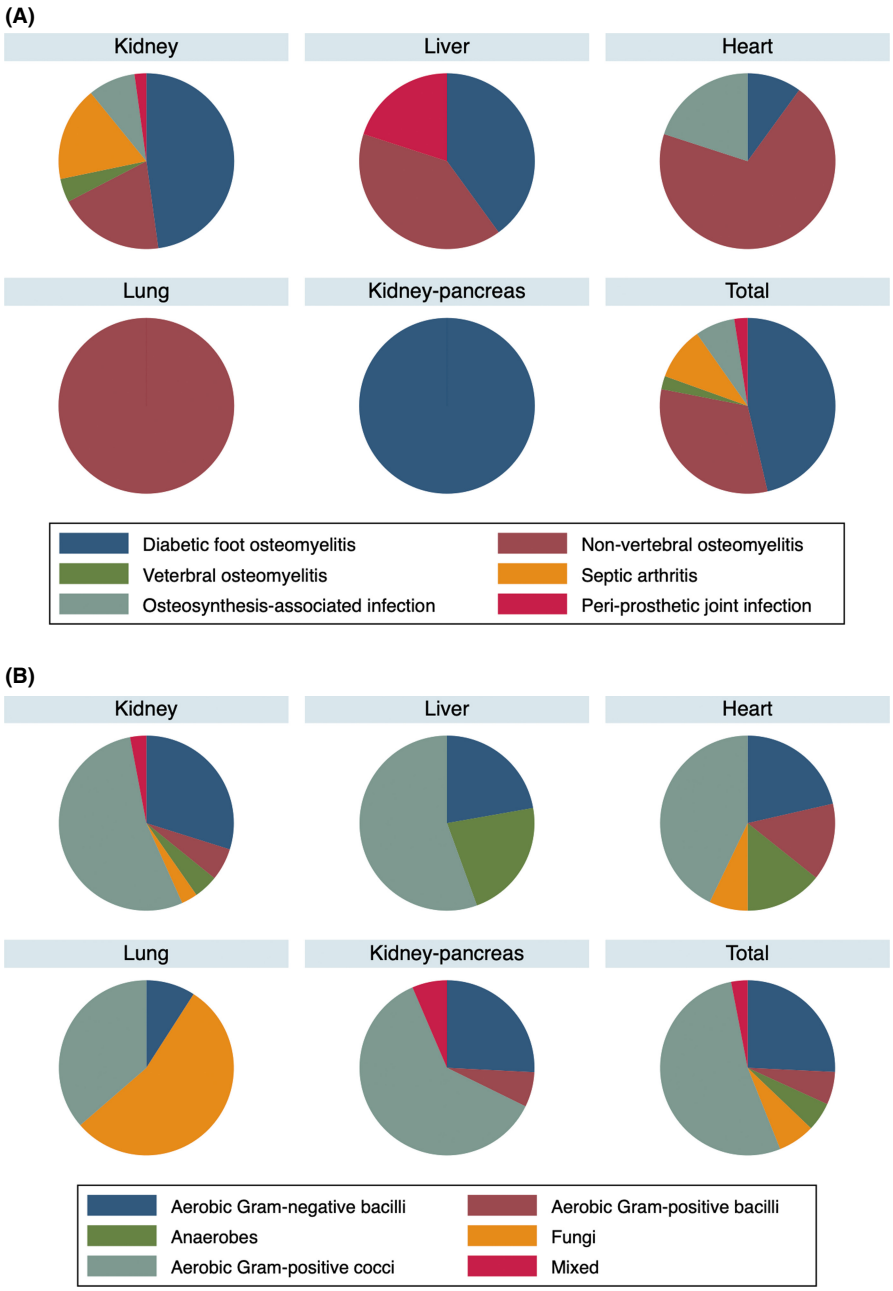

FIGURE 2 Distribution of bone and joint infections (A) and pathogens (B), by organ transplanted. [Color figure can be viewed at wileyonlinelibrary.com]

bacilli. Overall, 132 pathogens were isolated as detailed in Table S1 and Figure S2a. *Staphylococcus aureus* was the most frequent (*n* = 28/132, 21.2%), followed by Enterobacterales (*n* = 20/132, 15.3%), *Streptococcus* spp. (*n* = 20/132, 15.3%) and coagulase-negative *Staphylococcus* (*n* = 14/132, 10.6%). *Pseudomonas aeruginosa* (*n* = 11/132, 8.4%) and enterococci (*n* = 8/132, 6.1%) were less frequently encountered. Of particular interest, *Nocardia farcinica/kroppenstedtii* was responsible for one infection (olecranon osteomyelitis in a heart transplant recipient), and fungal infections were identified in eight cases: *Candida albicans* in 6/132 (4.5%) and *Aspergillus fumigatus* in 2/132 (1.5%).

A detailed list of antimicrobial therapies administered is described in Table S2. Penicillin antibiotics were the most frequently prescribed antimicrobial therapies (*n* = 111/303, 36.6%), followed by fluoroquinolones (*n* = 41/303, 13.5%), and glycopeptides or daptomycin (*n* = 37/303, 12.2%); a large variety of other antimicrobial agents were used (Figure 3A). Amoxicillin-clavulanate was the most commonly used antibiotic and accounted for almost half of first-line therapies (*n* = 34/82, 41.5%), followed by piperacillin-tazobactam (*n* = 18/82, 22.0%) (Figure S2b). A surgical intervention was performed in most cases (*n* = 73/82, 89.0%), with an irrigation/drainage/debridement being the most frequently observed intervention (*n* = 39/82, 47.6%; Figure 3B), followed by amputation (*n* = 26/82, 21.7%), which was the first choice for patient with DFO (*n* = 19/38, 50%). Among cases requiring a surgical procedure, multiple surgical interventions were necessary for almost half of them (*n* = 33/73, 45.8%).

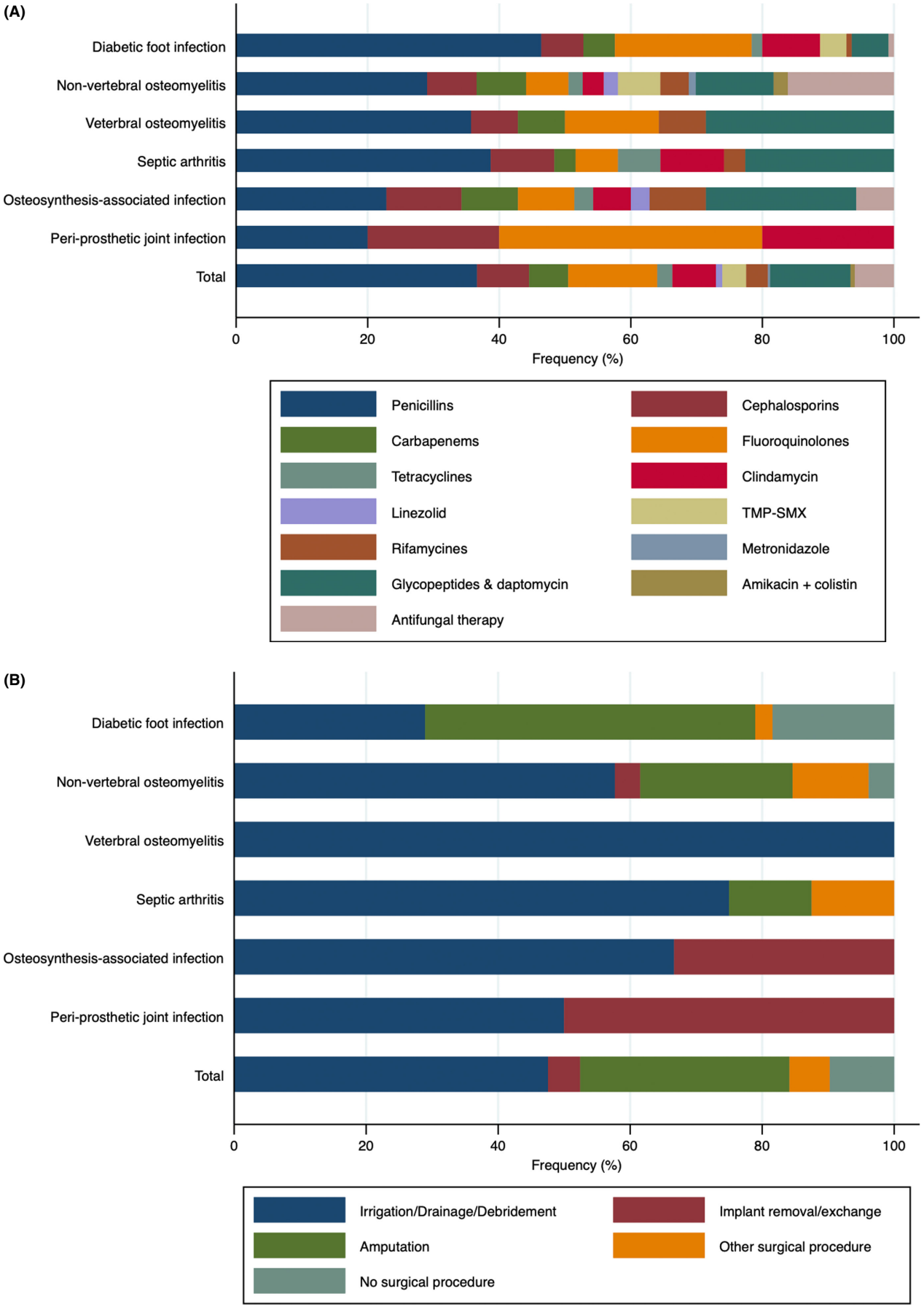

FIGURE 3 Presentation of bone and joint infection treatments, based on (A) antimicrobial treatments administered and (B) surgical procedure. [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | Risk factor for bone and joint infection

An analysis of risk factors for developing BJI in SOTr was performed using patient demographics, comorbidities, and transplant-related variables in the case–control population (Table 3). In univariable analysis, male gender (OR: 3.24, 95% CI 1.51–6.92, $p = .002$), diabetes (OR: 3.40, 95% CI 1.73–6.69, $p < .001$), coronary artery disease (OR: 2.33, 95% CI 1.12–4.86, $p = .024$) and peripheral arterial disease (OR: 2.98, 95% CI 1.30–6.86, $p = .01$) were associated with an increased risk of BJI, without detection of any multicollinearity. Multivariable analysis revealed male gender (OR: 2.94, 95% CI 1.26–6,89, $p = .013$) and diabetes (OR: 2.97, 95% CI 1.34–6.56, $p = .007$) as the only significant predictors of BJI.

TABLE 3 Risk factor analysis for bone and joint infections in solid organ transplant recipients

Variable	Univariate analysis			Multivariable analysis[a]		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Demographics						
Gender, male	3.24	1.51–6.92	.002	2.94	1.26–6.89	.013
Age at transplantation						
≤45	1	(ref.)				
45–65	1.14	0.48–2.71	.76			
>65	1.52	0.57–4.08	.41			
Diabetes mellitus	3.40	1.73–6.69	<.001	2.97	1.34–6.56	.007
Hypertension	0.95	0.43–2.10	.89			
CKD without RRT	1.38	0.59–3.22	.46			
CKD with RRT	1	0.39–2.53	1			
Coronary artery disease	2.33	1.12–4.86	.024	1.14	0.49–2.63	.764
Peripheral arterial disease	2.98	1.30–6.86	.01	2.29	0.82–6.38	.11
LVEF<30%	4.00	0.41–39.00	.23			
COPD	1	0.16–6.42	1			
Transplant characteristics						
Donor type, cadaveric	1.19	0.76–1.87	.44			
Maintenance IS						
Azathioprine	0.67	0.13–3.30	.62			
Ciclosporine	1.10	0.39–3.10	.86			
EC-MPS	0.41	0.215–1.18	.10	0.44	0.13–1.55	.20
Everolimus	1.62	0.31–8.40	.57			
MMF	1.67	0.70–3.99	.25			
Sirolimus	2.00	0.28–14.20	.49			
Steroids	2.41	0.97–5.98	.058	2.04	0.69–6.04	.20
Tacrolimus	1.73	0.60–4.94	.31			
Induction IS						
Basiliximab	0.85	0.22–3.33	.81			
Thymoglobulin	1.44	0.49–4.27	.51			
Any induction	1.50	0.34–6.70	.60			
Prophylaxis						
TMP-SMX	0.68	0.23–1.98	.48			

Abbreviations: CI, confidence interval; CKD, chronic kidney disease defined as creatinine clearance<60 ml/min/1.73 m^2; COPD, chronic obstructive pulmonary disease; EC-MPS, enteric-coated mycophenolate sodium; IS, immunosuppression; LVEF<30%, left ventricular ejection fraction <30%; MMF, mycophenolate mofetil; NA, not applicable; OR, odds ratio; RRT, renal replacement therapy; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Only small correlations were identified between DM and PAD, and between gender and CAD (Pearson correlation coefficients: $r = 0.2973$, $p < .001$, and $r = 0.2367$, $p = .001$, respectively).

3.4 | Clinical outcomes

Clinical response was known in 81 of 82 cases. Successful treatment was reported in 60/81 (74.1%) patients, while treatment failure was observed in the rest of cases due to: infection recurrence (n = 13/81, 16.0%), progression (n = 7/81, 8.6%), and reinfection (n = 1/81, 1.2%). Most failures were observed in patients with DFOs (n = 14/21, 66.7%), predominately affecting kidney (n = 8/21, 38.1%) or kidney-pancreas transplant recipients (n = 9/21, 42.9%). There were no deaths at 30 days post-BJI diagnosis, but three patients died because of progression of their initial BJI, at 36, 38, and 46 days. All-cause mortality at 90 days, 180 days, and 1 year post-BJI diagnosis was 4.9% (n = 3/61), 9.8% (n = 6/61), and 14.8% (n = 9/61), respectively, considering the last BJI for patients with >1 BJI. Among the 9 patients who were dead by 1-year post-BJI, three had >1 BJI and four were labeled as treatment failure.

All relevant independent variables, including demographics, SOT characteristics, type and presentation of BJI as well as medical and surgical treatment variables were analyzed in univariable analyses to identify potential predictors of clinical failure. The type of SOT was associated with clinical failure (OR: 1.56, 95% CI 1.19–2.05, p = .001), with more failures in kidney-pancreas transplant recipients (9/13, 69%) compared to other organs (12/68, 17.6%; p < .0001).

4 | DISCUSSION

In this largest cohort to date, we report that BJI remain a relatively rare and late event in SOTr, with some variability in the type of BJI and pathogens identified across different SOT types. Clinical presentations were subtle and could lead to delays in medical care. Treatment includes a large variety of antibiotic agents and almost universally some type of surgical intervention. Clinical outcomes remain rather favorable in their majority with very low mortality observed, albeit with rather frequent recurrences.

With an incidence as low as 1.4% and some variability across different SOT types, BJI remain a rare event in SOTr. This is pertinent, when considering that this observation was made in a large national multi-center cohort of >4000 SOTr, suggesting that indeed BJI are rarely encountered in SOTr. Combined kidney-pancreas and heart transplant recipients appeared to have higher rates of BJI than other SOT categories. This could be attributed to the type of different infections encountered in these two patient populations: DFO in kidney-pancreas transplant recipients, patients often suffering and transplanted for diabetes complications and SSI in thoracic transplant recipients, with surgical intervention requiring sternal incision. The above come to add to the existing body of literature, showing some variability of bacterial complications across the different SOT categories.[10] For instance, in another study using the STCS database on bloodstream infections in SOTr, higher rates of bacteraemia were observed in lung transplant recipients, followed by heart, liver and kidney-pancreas transplant recipients.[10] Similarly, the Spanish cohort study RESITRA reported highest incidence rates of bacteraemia in lung and pancreas transplant recipients.[14] In contrast, a Danish national cohort study reported higher incidence of bacteraemia in liver and kidney SOTr as compared to other SOT categories.[15]

Most BJI were rather late post-transplant complications, with the exception of thoracic organ transplant recipients, who developed an infection within the 1st year post-transplant, predominately non-vertebral osteomyelitis. In fact, when we looked at time to infection for thoracic (heart and lung) versus abdominal (liver, kidney, kidney-pancreas) transplant recipients, BJI occurred significantly earlier in the former (median 5.5 months, IQR: 1–14 versus 22 months, IQR: 10.5–54.5; p = .0001). It is likely that a number of those infections of thoracic SOTr were post-operative infections, a rather common complication in non-transplant cardiothoracic surgical patients.[16,17] The above could inform clinical practice and alert clinicians to early identification of such complications during the 1st year after a thoracic transplant. In contrast, BJI was a rather late event in abdominal organ transplant recipients presenting predominately with DFO, followed by non-vertebral osteomyelitis. The incidence of DFO and non-vertebral osteomyelitis in this transplant cohort was higher compared to the general population.[18–21] This may be related to the higher proportion of patients with diabetes, frequently observed in kidney and kidney-pancreas transplant patients. Furthermore, patients requiring kidney and/or pancreas or islet transplantation are frequently patients who have been on dialysis for many years with macro- and/or micro-angiopathy, and polyneuropathy, all predisposing factors for DFO.[22–24] In fact, diabetes was identified as one of the strongest predictors for BJI in this cohort, in addition, to male gender, both well-known risk factors for developing a BJI.[25–27] This may, in part, be due to the higher proportion of DFO in our SOTr cohort, as compared to another study in HSCT recipients, where septic arthritis was the most common BJI.[7]

Most BJI were due to Gram-positive cocci, followed by aerobic Gram-negative bacilli, consistent with data in the general population.[18,28–35] Overall, *S. aureus*, *Streptococcus* spp. and Enterobacterales represented the vast majority of pathogens identified. Infections due to antibiotic resistant pathogens were rarely encountered. Data on antimicrobial resistance were not recorded in the STCS database until 2012 and since then resistance data reporting might have not been complete. Nevertheless, given the low number of carbapenem administration, it is likely that infections due to multidrug-resistant (MDR) Gram-negative pathogens, such as those producing extended-spectrum beta-lactamases (ESBL), were rarely encountered in our series. These data are consistent with data from the ANRESIS Swiss antibacterial resistance network, showing relatively low rates of ESBL and MDR Gram-negative bacteria in Switzerland.[36,37] Similarly, there were no methicillin resistant *S. aureus* (MRSA) bloodstream infection observed, consistent with the low prevalence MRSA in Switzerland.

Treatment duration was considered appropriate for most BJI categories, except for DFO where treatment was longer than the recommended 4–6 weeks.[38–43] Particularly, when 80% of the patients with DFO were surgically treated and half of the cases

required amputation, which should have shortened treatment duration.[31,44] The above could, in part, be attributed to lack of clinical response and/or problematic wound healing leading clinicians to prolong the duration of antibiotic treatment. Notably, the duration of IV treatment was relatively short, with a median of 19 days for antibiotics and 16 days for antifungals. This may simply reflect a national practice to transition antibiotic treatment of BJI to highly bioavailable orally administered agents as soon as possible. The latter has been reinforced by a recent randomized controlled study on BJI showing non-inferiority of early oral step-down versus prolonged IV therapies.[45] The majority of patients were treated surgically as well, including two cases of vertebral osteomyelitis, usually treated conservatively in most cases.[46] Clinicians in charge of SOTr with BJI may have a lower threshold to consider a surgical intervention for their patients, in order to rapidly decrease the bacterial (or fungal) load and avoid potential complications. Thus, multidisciplinary approach should be encouraged for the treatment of BJI in SOTr: indeed, it is well known that interdisciplinary teams decrease reoperation rates for infection recurrence, improve survival, lower number of surgeries, and reduce days of total antibiotic treatment and amputation rates.[20,47–49]

Despite long treatment courses and the fact that most patents underwent a surgical intervention for the management of their BJI, including a high number of amputations for DFO, treatment failure rate was relatively high at 25.9%. The risk of recurrence among infections related to arthroplasties and other implants is reported to be between 5 and 15%, depending on the context and completeness of surgical debridement and antibiotic duration.[42,50] Only difficult-to-operate osteomyelitis and DFO might have higher risks of failure.[51,52] The less favorable clinical outcomes observed in this cohort could, in part, be explained by the concomitant comorbidities and administration of immunosuppressive treatments in SOTr, potentially hindering tissue healing, and/or the rather indolent clinical presentation of BJI in this population. Indeed, our data suggest that clinical presentation of BJI in SOT recipients can be subtle. Most patients in this cohort were afebrile with low white blood cell counts and inflammatory markers. The above may be due to the administration of immunosuppression including low-dose steroids, which may have not allowed patients to mount a significant inflammatory reaction to their infection. This observation could alert clinicians caring for these patients to promptly respond to -even minor- signs and symptoms potentially suggestive of a BJI.

Our study has several limitations, mainly associated with its retrospective observational design. Only BJI due to an identified pathogen were included, therefore it is possible that the number of cases might have been underestimated. Pertinent information on diabetes management, particularly considering the high numbers of DFO, including A1C was not recorded in the STCS database, and hence this information was not included in the manuscript. Only patients with their first transplant were included in the study: recipients of a second or more organ transplant were excluded from the study, potentially decreasing the number of cases. Last, SOT practices and prophylactic strategies but also BJI diagnostic and treatment modalities might have differed across the different centers.

In conclusion, BJI remain rare and late complications in SOTr. The clinical presentation can be subtle and the risk of treatment failure high, probably related to the immunosuppression and frequent comorbidities of SOTr patients. Thoracic organ transplant recipients appear to be at higher risk of developing early onset BJI due to fungal and other pathogens, suggesting increased vigilance and high degree of clinical suspicion should be applied in this patient population. The relative rarity of BJI, even in the setting of multi-center cohort studies, makes clinical research complicated in SOTr.

AUTHOR CONTRIBUTIONS

Study design: TTP, DOA, CvD, IU, DN. Data collection: TTP, DOA, SHB, CH, JT, KU, CS, PWS, DS. Data analysis: TTP, DOA, IU, DN. Statistics: TTP, SS, DN. Drafting article: TTP. Critical revision of the article: all authors.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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