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Infection Risk in the First Year After ABO-incompatible Kidney Transplantation: A Nationwide Prospective Cohort Study

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Background. ABO-incompatible (ABOi) kidney transplantation (KT) expands the kidney donor pool and may help to overcome organ shortage. Nonetheless, concerns about infectious complications associated with ABOi-KT have been raised. **Methods.** In a nationwide cohort (Swiss Transplant Cohort Study), we compared the risk for infectious complications among ABOi and ABO-compatible (ABOc) renal transplant recipients. Infections needed to fulfill rigorous, prespecified criteria to be classified as clinically relevant. Unadjusted and adjusted competing risk regression models were used to compare the time to the first clinically relevant infection among ABOi-KT and ABOc-KT recipients. Inverse probability weighted generalized mixed-effects Poisson regression was used to estimate incidence rate ratios for infection. **Results.** We included 757 living-donor KT recipients (639 ABOc; 118 ABOi) and identified 717 infection episodes. The spectrum of causative pathogens and the anatomical sites affected by infections were similar between ABOi-KT and ABOc-KT recipients. There was no significant difference in time to first posttransplant infection between ABOi-KT and ABOc-KT recipients (subhazard ratio, 1.24; 95% confidence interval [CI], 0.93-1.66; $P=0.142$). At 1 y, the crude infection rate was 1.11 (95% CI, 0.93-1.33) episodes per patient-year for ABOi patients and 0.94 (95% CI, 0.86-1.01) for ABOc-KT recipients. Inverse probability weighted infection rates were similar between groups (adjusted incidence rate ratio, 1.12; 95% CI, 0.83-1.52; $P=0.461$). **Conclusions.** The burden of infections during the first year posttransplant was high but not relevantly different in ABOi-KT and ABOc-KT recipients. Our results highlight that concerns regarding infectious complications should not affect the implementation of ABOi-KT programs.

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INTRODUCTION

At the current time, kidney transplantation (KT) is the most valuable option for patients with end-stage renal disease.[1] Nonetheless, there is still a significant gap between the demand and supply of organs and many patients have to endure a long period on dialysis because of growing transplant waiting lists. In 1987, Alexandre et al[2] first published a case series of 26 patients, who successfully underwent ABO-incompatible (ABOi) living-donor KT. ABOi-KT expands the donor pool considerably and is increasingly used to overcome organ shortage. Pretransplant desensitization strategies, such as plasmapheresis or immunoadsorption to remove anti-A and anti-B blood group antibodies, depletion of B cells with rituximab, and pharmacological immunosuppression before transplantation, have enabled ABOi-KT.[2,3]

Compared with ABO-compatible (ABOc)-KT, immunosuppression is more pronounced in ABOi-KT, and desensitization is associated with additional immunosuppression.[4] There is conflicting evidence about the risk for infectious complications associated with ABOi-KT. Although some studies reported an increased susceptibility to infections in patients undergoing ABOi-KT compared with ABOc-KT,[5-9] other studies did not support these findings.[10-12] Therefore, uncertainty about safety of ABOi-KT with regard to infectious complications still remains and may affect its implementation by transplant centers.

Since May 2008, the Swiss Transplant Cohort Study (STCS) has enrolled 93% of all solid organ transplant recipients in Switzerland and provides an ideal source to extract data on all aspects of transplantation including infections.[13] Using STCS data, we sought to investigate the risk for infectious complications associated with ABOi-KT applying rigorous prespecified definitions for infectious diseases.[13,14] In particular, we aimed to determine whether ABOi-KT was associated with an increased risk for clinically relevant infections compared with ABOc-KT.

MATERIALS AND METHODS

Study Design and Patients

We conducted a nested project based on the data from the multicenter nationwide STCS.[13] We included all adult (aged ≥18 y) ABOi and ABOc living-donor KT recipients with a first transplant and complete infectious diseases follow-up enrolled in the STCS from May 2008 to January 2017. All 6 Swiss transplant centers participated in the STCS. The STCS central data center performs regular data monitoring and data quality audits. In this process, all types of transplants are assessed by a thorough review of randomly sampled patients. The STCS and the current subproject were approved by the local ethics committee of each participating center (Ethics Commission of the Canton of Bern, Bern, Switzerland, No. 2017-00292). All study participants provided written informed consent.

The primary endpoint was the incidence rates of clinically relevant infections after ABOi-KT and ABOc-KT during the first year posttransplant. Secondary endpoints were the time to occurrence of the first clinically relevant infection and the comparison of the infectious diseases pattern between ABOi-KT and ABOc-KT recipients.

Desensitization Protocol for ABOi Renal Transplantation

In Switzerland, all ABOi-KT recipients undergo an identical desensitization procedure, including a single dose of rituximab (375 mg/m^2, 4 wk before transplantation), standardized initial immunosuppression started before transplantation (preferably tacrolimus, mycophenolate mofetil, and prednisone), basiliximab induction (d 0 and 4), and antigen-specific perioperative immunoadsorption.[15] Selective blood group antibody removal is performed with a low-molecular carbohydrate column containing A or B blood group antigens linked to a sepharose matrix until the immunoglobulin (immunoglobulin G) and isoagglutinin (immunoglobulin M) antibody titers against donor erythrocytes are ≤1:8. Target tacrolimus trough levels were 8 to 10 ng/mL from day 14 before transplantation to day 90 after transplantation and 6 to 8 ng/mL from day 90 to 365. Target mycophenolate mofetil trough level was >2 mg/mL.

There were no prespecified uniform tacrolimus and mycophenolate mofetil trough levels for ABOc-KT recipients across centers. However, in general, physicians aimed for lower levels in ABOc-KT recipients.

Clinical Definitions

All infections were identified by transplant infectious diseases physicians using electronic patient charts and referral documentation. Both inpatient and outpatient infectious diseases episodes were considered. Infectious diseases definitions were developed by the STCS Infectious Diseases Working Group based on guidelines of the *American Society of Transplantation Infectious Disease Community of Practice* and the *European Conference on Infections in Leukemia*.[16,17] Infections needed to fulfill rigorous criteria to be classified as clinically relevant: Bacterial infections require isolation of a bacterial pathogen, clinical signs/symptoms, and specific antibiotic treatment. Clinically relevant viral infections are defined by detection of viral replication (by polymerase chain reaction or viral culture) together with clinical signs/symptoms. Cytomegalovirus (CMV) infection was considered clinically relevant when fulfilling the criteria for CMV viral syndrome or a tissue invasive disease.[18] Polyomavirus BK infection was classified as clinically relevant if there was biopsy-proven polyomavirus-associated nephropathy or presumptive biopsy-proven polyomavirus-associated nephropathy.[16] Clinically relevant fungal infections require histopathology of a tissue biopsy showing invading fungal hyphae or yeasts (proven invasive fungal infection by European Organization for Research and Treatment of Cancer definition), or clinical and microbiological criteria (probable invasive fungal infection by European Organization for Research and Treatment of Cancer definition).[17] Mucocutaneous candida infection was not taken into account.

Anatomical localizations affected by an infection were systematically recorded. One single infection episode could affect different anatomical sites (eg, urinary tract infection with concomitant bloodstream infection). Polymicrobial infections (eg, viral respiratory tract infections with >1 isolated respiratory virus) were considered 1 infection episode with >1 causing pathogen.

The way of capturing rejection episodes by the STCS changed during the study period. At the beginning, the STCS did not record detailed Banff lesion scores.[19] Therefore, we cannot differentiate between borderline rejections (with unclear clinical significance) and true rejections fulfilling the Banff classification criteria for the initial study period. However, the STCS consistently recorded if rejection episodes required treatment throughout the complete study period. To keep consistency, we decided to report data on *rejection treatment episodes* rather than rejection episodes.

Statistical Analyses

We performed a descriptive analysis to determine patients' baseline characteristics (chi-square test for categorical variables and the Mann-Whitney U test for continuous variables). To adequately reflect the *burden of infection*, we performed 2 types of analyses: *time-to-event analyses* to test for the length of time until occurrence of the first clinically significant infection and analysis of the incidence rate ratios (IRRs) of infections. By analyzing IRR, we take into account that each individual may experience multiple infection episodes.

For *time-to-event analysis*, we first used the Kaplan-Meier method to describe the infection-free survival at 100 d and 365 d posttransplant, and differences in infection-free survival were assessed using log-rank tests. We treated death, early exit from the study, and graft loss as censoring events. We then refined this by performing unadjusted and adjusted competing risk regression models.

Unadjusted and adjusted competing risk regression models (with death and graft loss as competing risk factors for infection) were used to compare the time to the first clinically relevant infection among ABOi-KT and ABOc-KT recipients.[20] Sandwich-type standard errors were calculated to account for multiple records per patient. In the adjusted analysis, we included predefined previously published risk factors for infection at baseline, including gender,[21,22] number of HLA mismatches,[23] body mass index,[24] age at transplantation,[22] CMV risk status,[18] diabetes,[22,25] adult polycystic kidney disease,[26] and being on dialysis before transplantation.[22] In addition, the use of trimethoprim/sulfamethoxazole prophylaxis was included as a time-varying covariate.[27]

Unadjusted IRRs for infection were calculated using Quasi-Poisson regression with sandwich-type standard errors. We used Quasi-Poisson regression because of overdispersion of our data. To adjust for potential confounding factors, we fitted a multivariable logistic regression model of treatment allocation (ABOi versus ABOc renal transplantation) using the same variables as for the competing risk analysis. Predicted probabilities of the model were used to calculate stabilized inverse probability weights,[28] and a weighted generalized mixed-effects Poisson regression was used to estimate weighted IRRs for infection. We added a random intercept for each individual to account for multiple records per patient. The balance of covariates after weighting was assessed by calculating the mean standardized difference in covariates across treatment groups (**Figure S1, SDC**, http://links.lww.com/TP/C383) and by visualization using density plots of continuous covariates (**Figure S2, SDC**, http://links.lww.com/TP/C383).[29]

Statistical analyses were performed using Stata software version 16 (Stata Corp., College Station, TX) and R version 4.0.3.

RESULTS

Study Population

From May 2008 to January 2017, the STCS enrolled 797 living KT recipients with a first transplant, 675 ABOc and 122 ABOi. We excluded 40 patients because of missing data on infection (36 ABOc and 4 ABOi, respectively). The final cohort consisted of 757 living renal transplant recipients, 639 ABOc-KTs, and 118 ABOi- KTs (Table 1).

Most patients were male (ABOc: 65.4%; ABOi: 76.3%) and the median age at transplantation was 51.2 y (interquartile range [IQR], 38.3–61.5). Glomerulonephritis (208 of 757, 27.5%) and adult polycystic kidney disease (167 of 757, 22.1%) were the most common causes for end-stage renal disease. There were no differences in CMV donor/recipient serostatus or number of HLA mismatches for ABOc and ABOi patients (Table 1). However, ABOi-KT recipients were more likely to be on dialysis before transplantation (72.9% versus 61.5%, $P = 0.018$). Most patients were on tacrolimus-based immunosuppressive regimens (ABOc: 73.2%; ABOi: 96.6%). Of note, there was a shift toward a more frequent use of tacrolimus instead of cyclosporine in ABOc patients over time during the study period (**Figure S3, SDC**, http://links.lww.com/TP/C383).

Time to First Posttransplant Clinically Relevant Infection

By Kaplan-Meier estimate the probability of infection-free survival 100 d posttransplantation was found to be 60.2% (ABOi) and 71.3% (ABOc) ($P = 0.021$), respectively, which decreased to 46.5% (ABOi) and 52.7% (ABOc) ($P = 0.080$), respectively, after 1 y (Figure 1).

In univariate (competing risk regression; ABOi n = 118, ABOc n = 639) and adjusted analyses (ABOi n = 114; ABOc = 599), a trend toward an increased risk for earlier occurrence of the first clinically relevant infection was seen in ABOi patients (univariate subhazard ratio [SHR], 1.28; 95% confidence interval [CI], 0.96-1.69; $P = 0.089$; adjusted SHR, 1.24; 95% CI, 0.93-1.66; $P = 0.139$; **Table S1, SDC**, http://links.lww.com/TP/C383).

Incidence Rate of Clinically Relevant Infections

Within 12 mo posttransplant, 717 clinically relevant infection episodes occurred in 757 patients (**Figure S4, SDC**, http://links.lww.com/TP/C383).

At 1 y, the crude infection rate was 1.11 (95% CI, 0.93-1.33) episodes per patient-year for ABOi patients and 0.94 (95% CI, 0.86-1.01) for ABOc-KT recipients. The unadjusted IRR for clinically relevant infections was 1.19 (95% CI, 0.92-1.55; $P = 0.191$) for ABOi-KT recipients compared with ABOc-KT patients.

In the inverse probability weighted model (ABOi n = 114, ABOc n = 599), there was no significant difference in infection rates between ABOi-KT and ABOc-KT recipients (adjusted IRR, 1.12; 95% CI, 0.83-1.52; $P = 0.461$).

In both ABOc-KT and ABOi-KT recipients, most infectious diseases events occurred in the first month posttransplant and were less frequent thereafter (ABOi: 26.6% [34 of 128] of infections occurred within the first mo; ABOc: 19.0% [112 of 589] of infections occurred within the first mo; Figure 2). The shift toward a more frequent use of tacrolimus in ABOc-KT patients during the study

TABLE 1.
Demographics

Characteristics	ABO compatible (n = 639)	ABO incompatible (n = 118)	*P*
Male, sex, n (%)	418 (65.4)	90 (76.3)	0.021
Age at transplantation, y, median (IQR)	50.6 (37.9–61.3)	53.4 (43.5–62.6)	0.050
Ethnicity, n (%)			
African	17 (2.7)	0 (0.0)	
Asian	20 (3.1)	3 (2.5)	
Caucasian	594 (93.0)	109 (92.4)	
Other	8 (1.3)	6 (5.1)	0.014
Cause of ESRD, n (%)			
ADPKD	134 (21.0)	33 (28.0)	0.344
Diabetic nephropathy	43 (6.7)	7 (5.9)	
ESRD of unknown cause	39 (6.1)	6 (5.1)	
Glomerulonephritis	182 (28.5)	26 (22.0)	
Nephrosclerosis	67 (10.5)	17 (14.4)	
Other	174 (27.2)	29 (24.6)	
Dialysis before transplantation, n (%)	393 (61.5)	86 (72.9)	0.018
Time on dialysis before transplantation, d, median (IQR)	390 (290–723)	384 (192–723)	0.941
BMI, median (IQR)	24.9 (22.1–27.8) (n = 605)	26.1 (22.4–29.5) (n = 114)	0.044
Diabetes, n (%)	75 (11.7)	12 (10.2)	0.624
CMV D^+/R^-, n (%)	123 (19.2)	22 (18.6)	0.878
Primary CMV prophylaxis (valgancyclovir), n (%)	239 (37.4)	35 (29.7)	0.108
TMP-SMX prophylaxis duration, d, median (IQR)	178.0 (155.0–199.0)	181.5 (157.0–207.0)	0.293
HLA mismatches			
0–2	162 (25.4%)	25 (21.2%)	0.576
3–4	244 (38.2%)	49 (41.5%)	
5–6	228 (35.7%)	44 (37.3%)	
Unknown	5 (0.8%)	0 (0.0%)	
Induction therapy			
Basiliximab and rituximab and immunoadsorption	–	118 (100.0%)	<0.001
Antithymocyte globulin	78 (12.2%)	–	
Basiliximab	480 (75.1%)	–	
Other	26 (4.1%)	–	
Unknown	55 (8.6%)	–	
Maintenance immunosuppression			
Cyclosporine	147 (23.0%)	4 (3.4%)	<0.001
Tacrolimus	468 (73.2%)	114 (96.6%)	<0.001
Sirolimus/everolimus	23 (3.6%)	0 (0.0%)	0.036
Glucocorticoid	632 (98.9%)	116 (98.3%)	0.581
Mycophenolate	603 (94.4%)	114 (96.6%)	0.317
Azathioprine	33 (5.2%)	4 (3.4%)	0.406
Donor characteristics			
Male, sex, n (%)	240 (37.6)	40 (33.9)	0.442
Age, y, median (IQR)	54.0 (46.0–61.0)	52.0 (45.0–60.0)	0.448
Related donor, n (%)	308 (48.2)	41 (34.7)	0.007

ADPKD, autosomal-dominant polycystic kidney disease; BMI, body mass index; CMV, cytomegalovirus; D/R, donor/recipient; ESRD, end-stage renal disease; IQR, interquartile range; TMP-SMX, trimethoprim/sulfamethoxazole.

period had no effect on infection rates (**Table S2, SDC**, http://links.lww.com/TP/C383).

Infections by Pathogens

Bacterial pathogens accounted for most of the clinically relevant infection episodes in the overall cohort (62.3%; 447 of 717 infections) followed by viruses (34.7%; 249 of 717 infections), fungi (2.2%; 16 of 717 infections), and parasites (0.7%; 5 of 717 infections).

Five hundred seven bacteria were isolated and accounted for the 447 bacterial infection episodes. Most bacterial infection episodes were caused by a single bacterial pathogen (88.4%; 395 of 447), but a minority of bacterial infections were polymicrobial (11.6%; 52 of 447). *Escherichia coli* was the most common isolated bacterial pathogen in ABOi-KT (43.3%; 45 of 104) and ABOc-KT recipients (40.7%; 164 of 403; Figure 3A). *Enterococcus* spp. (ABOi: 14.4%, 15 of 104; ABOc: 14.4%, 58 of 403) and *Klebsiella* spp. (ABOi: 7.7%, 8 of 104; ABOc: 13.7%, 55 of 403) were also frequently detected in both patient groups. The frequency distribution of isolated bacteria was similar among ABOi and ABOc patients (Figure 3A).

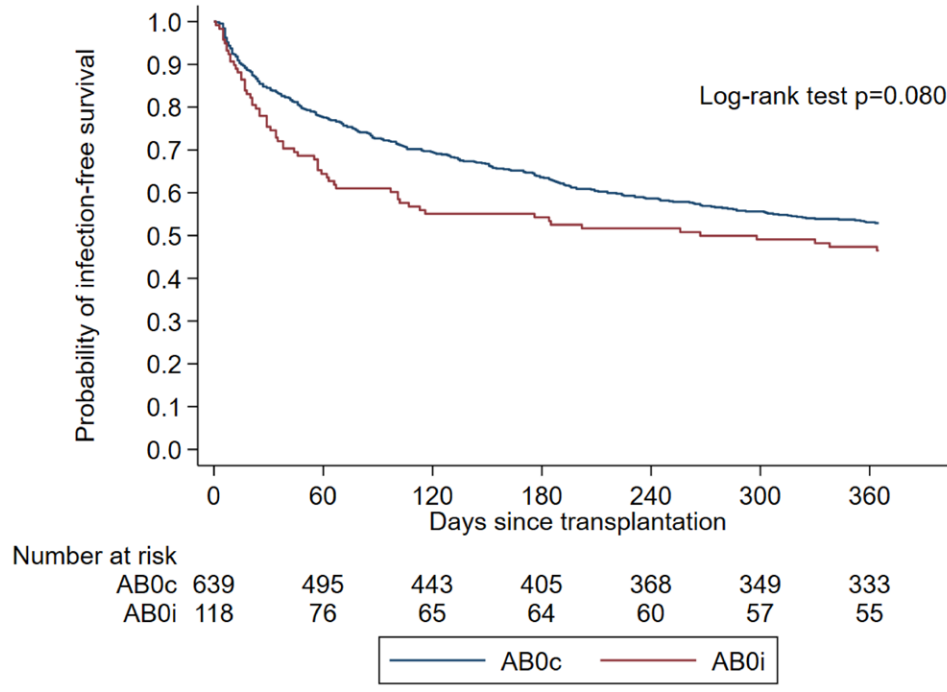

FIGURE 1. Kaplan-Meier estimate for infection-free survival. ABOc, ABO-compatible; ABOi, ABO-incompatible.

Two hundred fifty-five viruses were detected and accounted for the 249 viral infection episodes. More than 1 concomitant virus was present in 2.0% (5 of 249) of clinically relevant viral infection episodes (4 patients with 2 concomitant viruses, 1 patient with 3 concomitant viruses). Herpes simplex viruses were the most frequent viral pathogens in both ABOi-KT (39.5%, 17 of 43) and ABOc-KT (25.9%, 55 of 212) recipients (Figure 3B). Other viruses of the *herpesviridae* group were also common (CMV: 9.2% [4 of 43] in ABOi; 19.8% [42 of 212] in ABOc and varicella zoster virus: 14.0% [6 of 43] in ABOi; 8.5% [18 of 212] in ABOc). BK viruses (presumptive and proven polyomavirus-associated nephropathy only) also accounted for a relevant proportion of viral pathogens (ABOi: 11.6% [5 of 43]; ABOc: 19.3% [41 of 212]). However, proven and presumptive polyomavirus-associated nephropathy was a rare event in ABOi-KT (4.2%, 5 of 118) and ABOc-KT (6.4%, 41 of 639) recipients.

Sixteen fungal pathogens were isolated: *Aspergillus* spp. (ABOi: 2 cases; ABOc: 3 cases), *Candida* spp. (ABOi: 0 cases; ABOc: 5 cases), and *Pneumocystis jirovecii* (ABOi: 0 cases; ABOc: 6 cases) accounted for these infections.

Parasitic pathogens were rarely isolated: 4 cases of *Cryptosporidium* spp. (ABOi: 2 cases; ABOc: 2 cases) and 1 *Giardia lamblia* case (in a ABOc-KT recipient) occurred.

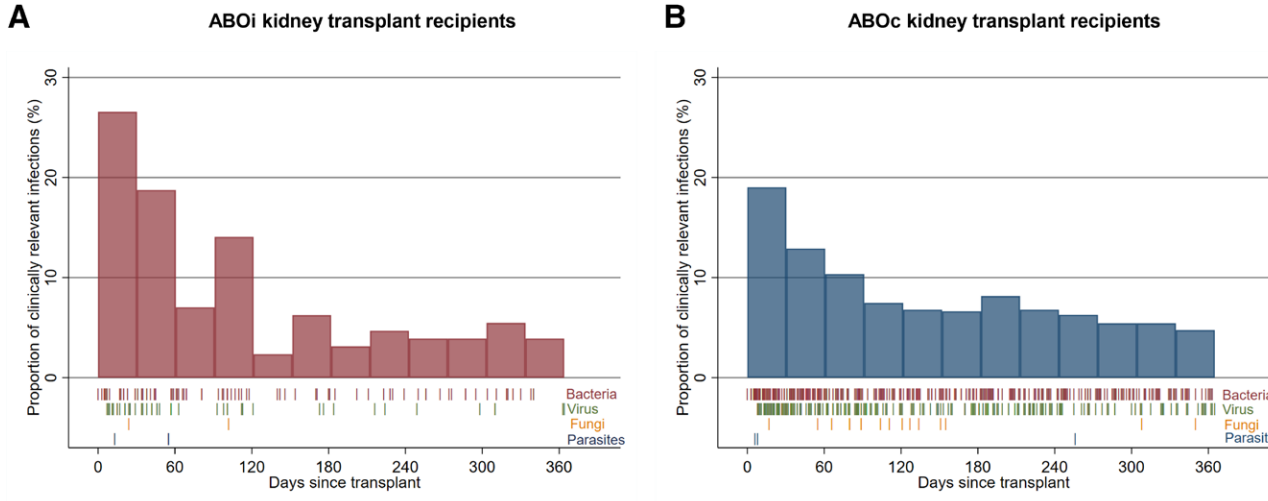

FIGURE 2. Timeline of clinically relevant infections. A, Timeline of clinically relevant infections (n = 128) in ABOi kidney transplant recipients. B, Timeline of clinically relevant infections (n = 589) in ABO-compatible kidney transplant recipients. Bars represent proportions of clinically relevant infections occurring during the corresponding 30-d period. Colored horizontal ticks below bars represent an individual infection event. ABOc, ABO-compatible; ABOi, ABO-incompatible.

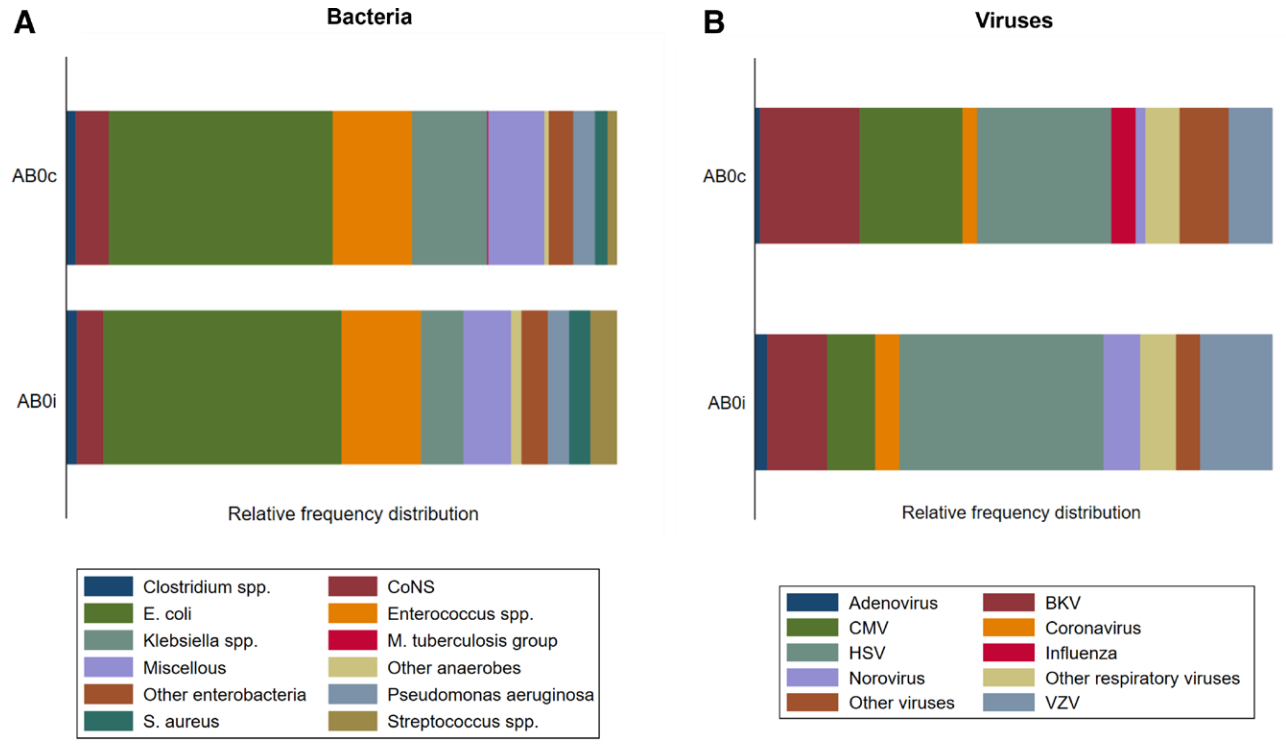

FIGURE 3. Relative frequency distribution of pathogens. A, Bacterial pathogens (ABOc: n = 403; ABOi: n = 104). B, Viral pathogens (ABOc: n = 212; ABOi: n = 43). ABOc, ABO-compatible; ABOi, ABO-incompatible; BKV, BK polyomavirus; CMV, cytomegalovirus; CoNS, coagulase-negative Staphylococci; *E coli*, *Escherichia coli*; HSV, herpes simplex virus; *M tuberculosis* group, *Mycobacterium tuberculosis* group; *S aureus*, *Staphylococcus aureus*; VZV, varicella zoster virus.

Infections by Anatomical Site

Overall, the urinary tract was the most common anatomical site affected by any type of infection in ABOi-KT (61 of 138; 44.2%) and ABOc-KT recipients (317 of 627; 50.6%) followed by the bloodstream (ABOi: 23 of 138; 16.7%; ABOc: 78 of 627; 12.4%). The pattern of anatomical localizations affected by bacterial and viral pathogens was similar among ABOc and ABOi transplant recipients

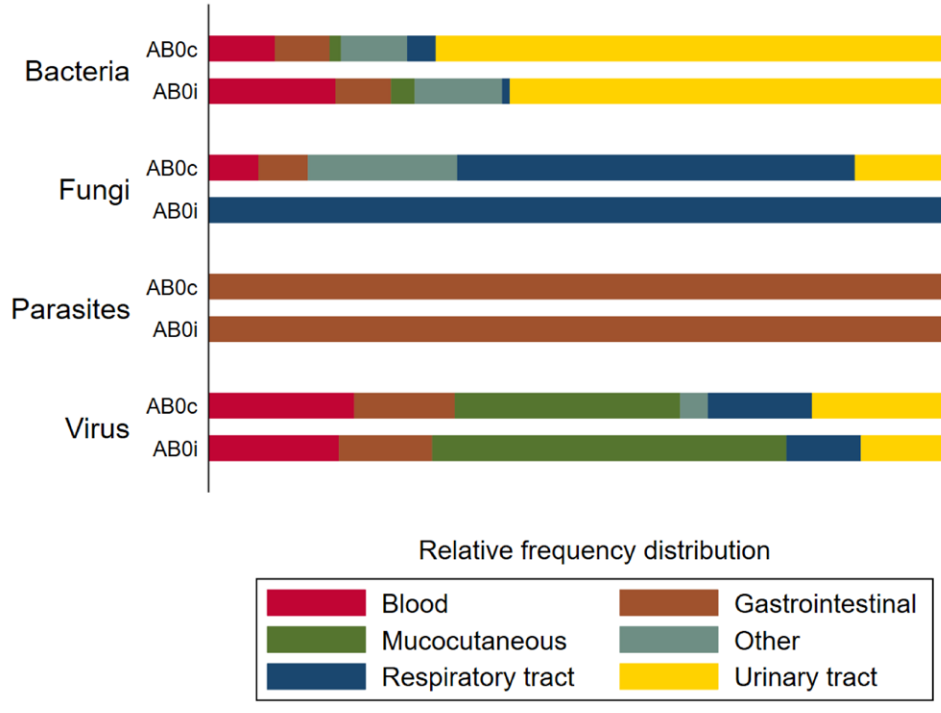

FIGURE 4. Relative frequency distribution of anatomical location of infection. Number of affected anatomical locations by bacteria: ABOc (n = 394) and ABOi (n = 94). Number of affected anatomical locations by fungi: ABOc (n = 15) and ABOi (n = 2). Number of affected anatomical locations by parasites: ABOc (n = 3) and ABOi (n = 2). Number of affected anatomical locations by viruses: ABOc (n = 215) and ABOi (n = 40). ABOc, ABO-compatible; ABOi, ABO-incompatible.

(Figure 4). The most common anatomical localization affected by bacterial pathogens in both patient groups was the urinary tract (ABOi: 56 of 94, 59.6%; ABOc: 274 of 394, 69.5%; Figure 3). Viruses were most commonly detected on mucocutaneous membranes (ABOi: 19 of 40, 47.5%; ABOc: 65 of 215; 30.2%) and in blood (ABOi: 7 of 40; 17.5%; ABOc: 42 of 215; 19.5%). The majority of herpes simplex virus (84.7%; 61 of 72) and VZV infections (95.8%; 23 of 24) were mucocutaneous (**Table S3**, **SDC**, http://links.lww.com/TP/C383). The number of fungal and parasitic infections was low; therefore, the distribution of anatomical sites affected was more variable between the 2 patient groups (Figure 4).

Survival, Graft Function, and Rejection Treatment Episodes

Nine patients (1.19%) died within the first 12 mo posttransplant (ABOc: 8 of 639, 1.25%; ABOi: 1 of 118, 0.85%; $P = 1.000$). Infection was the cause of death in 2 patients (both ABOc; 1 patient with an invasive aspergillosis and 1 patient with sepsis because of an intra-abdominal infection). Six additional patients (ABOc: 4 of 639, 0.63%; ABOi: 2 of 118, 1.69%; $P = 0.237$) experienced a graft loss within 12 mo.

Within 12 mo posttransplant, 26.4% (169 of 639) of ABOc patients experienced 202 different rejection treatment episodes and 34.7% (41 of 118) of ABOi patients had 53 treated rejection episodes. Details on rejection treatment modalities are provided in **Table S4** (**SDC**, http://links.lww.com/TP/C383). The probability of rejection treatment–free survival was higher in ABOc patients compared with ABOi patients (log-rank test $P = 0.039$; **Figure S5**, **SDC**, http://links.lww.com/TP/C383). The rejection treatment rate was also higher in ABOi patients (incidence rate: 0.46 per patient-y) compared with ABOc patients (incidence rate, 0.32 per patient-y; IRR, 1.44 [95% CI, 1.03-1.97]; $P = 0.0283$).

Serum creatinine values 1 y posttransplant were available for all ABOi-KT (115 of 115) and for 99.7% (625 of 627) of ABOi-KT recipients with functioning graft. Estimated glomerular filtration rates (eGFRs) (by Modification of Diet in Renal Disease formula[26]) were similar across ABOi-KT (median eGFR, 53.0 [IQR, 63.1–44.4] mL/min/1.73 m^2) and ABOc-KT recipients (median eGFR, 53.8 [IQR, 64.0–44.4] mL/min/1.73 m^2; $P = 0.992$). However, patients without infection had a significantly higher eGFR at 1 y (median, 55.0 [IQR, 47.4–65.5] mL/min/1.73 m^2) compared with patients who experienced at least 1 clinically relevant infection (median, 51.4 [IQR, 42.6–62.6] mL/min/1.73 m^2; $P < 0.001$).

DISCUSSION

In this nationwide cohort study, we evaluated whether ABOi-KT is associated with an increased risk for clinically relevant infection compared with ABOc living-donor KT. The major findings of our study were as follows: (1) there was no statistically significant difference in time to first posttransplant infection between ABOi-KT and ABOc-KT recipients (SHR adjusted analysis, 1.24; 95% CI, 0.93-1.66; $P = 0.142$); (2) at 1 y posttransplant, the infection rate was 1.11 (95% CI, 0.93-1.33) episodes per patient-year for ABOi-KT patients and 0.94 (95% CI, 0.86-1.01) for ABOc-KT recipients. There was no significant difference in infection rates between ABOi-KT recipients and ABOc-KT patients (inverse probability weighted IRR, 1.12; 95% CI, 0.83-1.52; $P = 0.461$); (3) in both ABOc-KT and ABOi-KT recipients the frequency of infectious diseases events was highest in the first month posttransplant and gradually decreased thereafter; and (4) in both patient groups, bacterial pathogens were responsible for >60% of infection episodes. The spectrum of causative pathogens and the anatomical sites affected by infections were similar among ABOi-KT and ABOc-KT recipients.

To our knowledge, this work represents the most comprehensive study that systematically compares the risk for posttransplant infection among ABOi-KT and ABOc-KT recipients. The framework of the STCS and the introduction of a nationwide uniform desensitization protocol made it possible to analyze the infection risk associated with ABOi-KT after desensitization with immunoadsorption and without splenectomy. Our results are different from the findings of some previous studies. In a small study (ABOi n = 21, ABOc n = 47), Habicht et al[5] reported that ABOi-KT was associated with an increased risk for infectious complications, in particular, viral infections were more common in ABOi patients. Using Medicare claims data and information collected by the Organ Procurement and Transplantation Network, Lentine et al[6] reported that ABOi transplantation was associated with an increased risk for pneumonia and urinary tract infection in the first 90 d posttransplantation and a higher risk of wound infections in the period 91 to 365 d posttransplantation. In a large multicenter cohort study including >1400 ABOi patients, a small but significant survival difference became apparent between recipients of ABOi grafts and ABOc recipients (97.0% versus 98.6%).[7] This was because of a significantly higher rate of early death from infection in recipients of ABOi grafts.[7] In our cohort, infection was the cause of death in 2 patients (both ABOc). In contrast, and in line with our findings, Kakuta et al,[12] Zschiedrich et al,[10] and Hamano et al[11] did not observe a higher risk for overall infectious complications and viral infections in ABOi-KT recipients, respectively. A Japanese study reported outcomes of ABOi-KT recipients in the present era (2005–2013) without splenectomy and in the early era of ABOi-KT (1989–2004) with splenectomy at the time of transplantation.[30] In the early era, ABOi patients had higher rates of CMV and adenovirus infection compared with ABOc-KT recipients, whereas there were no differences in the present era. A recent meta-analysis reported a higher proportion of patients with sepsis after ABOi-KT.[31] No statistically significant difference in the risk of urinary tract infection, CMV infection, BK polyomavirus infection, and *P jirovecii* pneumonia was observed in this meta-analysis.[31] However, the results of these different studies might be difficult to interpret because of small sample sizes,[5,11,12] not reporting concise definitions for infectious diseases (mostly because of primary outcomes other than infections),[5-7,11,12,30,31] and nonuniform desensitization protocols.[6-8,10,31]

In our study, infectious complications tended to occur earlier in ABOi patients. Therefore, increased awareness of the potential of infections is warranted in the early posttransplant period in this patient population.

The type of desensitization protocol used for ABOi transplantation may affect the risk for posttransplant

infectious complications. ABOi patients who receive rituximab-based desensitization instead of splenectomy at time of transplantation have a lower risk for infection.[30,31] Additionally, the susceptibility for infection might also be different depending on whether plasmapheresis or immunoadsorption is used. A recent study examined the impact of desensitization intensity (as by the number of plasmaphereses) for incompatible KT (pooled HLA-incompatible and ABOi) on infection risks.[32] The cumulative risk for infection increased with desensitization intensity.[32] When interpreting the results of our study, it is important to consider that all ABOi patients in our cohort had rituximab-based desensitization in combination with immunoadsorption. Therefore, our findings might not apply if other desensitization protocols are used.

We assessed if the types of infection differ after ABOi and ABOc renal transplantation. In both groups, bacterial pathogens accounted for most infection episodes, and the urinary tract was the most commonly affected site. Classical opportunistic fungal and bacterial infections were rare in ABOi-KT and ABOc-KT recipients. These findings are consistent with earlier observations wherein bacterial pathogens also accounted for most infections in renal transplant recipients.[22] We did not identify any relevant difference in the infection pattern among ABOi-KT and ABOc-KT recipients.

We wish to acknowledge potential limitations. First, findings of observational studies are inherently limited by the lack of randomization of exposure. Therefore, it is difficult to rule out that our results were affected by confounding effects. However, we tried to minimize this by either adjusting or weighting our analysis. For adjusting and weighting, we used predefined potential confounding factors, which have previously been associated with increased risk for infection in KT recipients. Second, despite efforts to identify all inpatient and outpatient events, some infections may have not been captured. Third, there were missing data for variables used to adjust/weight the analysis. This decreased the sample size of the adjusted/weighted analysis. However, complete data for adjusting/weighting were available for >90% of patients; therefore, we are confident that the adjusted/weighted analysis was not significantly compromised by missing data. Fourth, the point estimates of our study indicate toward an increased risk for clinically relevant infections in ABOi-KT recipients. We acknowledge that a larger sample size might have shown statistically significant results. Nevertheless, we expect the size of our cohort to be large enough to reveal clinically relevant differences in infectious complications. Fifth, our study population mirrors the ethnic distribution of Western Europe. More than 90% of participants were of Caucasian ethnicity. It is therefore unclear if our findings also apply to a non-Caucasian patient population. Sixth, immunoadsorption is unfortunately not widely available in many countries, and if unavailable, plasmapheresis is used instead. In our study, all patients were desensitized using an immunoadsorption protocol and our findings may not apply when plasmapheresis is used.

In summary, the burden of clinically relevant infections during the first year posttransplant was high in living-donor KT recipients. However, the risk for infection was not significantly different after ABOi-KT compared with ABOc-KT and the spectrum of infectious diseases was similar between these 2 groups. Our results highlight that concerns regarding infectious complications should not affect the implementation of ABOi-KT programs. This is especially true for settings where administrative barriers or demographic conditions (such as small countries with low population) complicate the successful launch of paired kidney exchange programs.

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