Original Research Article

Incidence Rate of Post-Kidney Transplant Infection: A Retrospective Cohort Study Examining Infection Rates at a Large Canadian Multicenter Tertiary-Care Facility

Juthaporn Cowan[1,2,3], Alexandria Bennett[2,4],
Nicholas Fergusson[2], Cheynne McLean[5], Ranjeeta Mallick[2,4],
D. William Cameron[1,2,3,4], and Greg Knoll[2,4,6]

Abstract

Background: Reducing post-operative infections among kidney transplant patients is critical to improve long-term outcomes. With shifting disease demographics and implementation of new transplantation protocols, frequent evaluation of infection rate and type is necessary.

Objective: Our objectives were to assess the incidence and types of post-operative infections in kidney transplant recipients at a large tertiary-care facility and determine sample sizes needed for future intervention trials.

Design: Retrospective cohort study.

Setting: The Ottawa Hospital, Ottawa, Ontario.

Patients: Adult kidney transplant patients, N = 142.

Measurements: Demographic data, transplant protocol, infections up to 2 years following transplantation.

Methods: Infections within 2 years following transplantation in all kidney transplant recipients between January 2011 and December 2012 were reviewed. Sample sizes were determined using all-cause infection rates and infection-free survival data.

Results: Of 142 patients, 44 (31.0%) had at least one infection. The incidence of infection was 36.2 per 100 patient-years by 2 years post-transplant. A total of 32 (22.5%) patients had 56 infection-related hospitalizations with 73.2% occurring in the first year. In the first 2 years, urinary tract infections had the highest incidence (18.1 per 100 patient-years) followed by skin (3.9 per 100 patient-years), cytomegalovirus (3.9 per 100 patient-years), and bacteremia (3.9 per 100 patient-years). Results indicate that 206 patients per study arm would be needed to show a 30% reduction in the 2-year incidence of infection post-transplantation.

Limitations: Infection rates may be slightly underestimated due to the relatively short 2-year follow-up; however, the highest infection-risk period was captured within this time frame.

Conclusions: Infections post-kidney transplant are still common, particularly urinary tract infections. They are associated with significant morbidity and hospitalization. Given the feasible sample sizes calculated in this study, intervention trials are indicated to further reduce infection rates within the first 2 years post-kidney transplantation.

Abrégé

Contexte: La réduction du nombre d'infections post-opératoires contractées par les receveurs d'une greffe rénale est essentielle pour améliorer leurs résultats à long terme. Compte tenu de l'évolution démographique de la maladie et de la mise en œuvre de nouveaux protocoles de transplantation, l'évaluation fréquente des taux d'infections et des types d'infections est nécessaire.

Objectifs: Nous voulions identifier les types d'infections post-opératoires touchant les receveurs d'une greffe rénale et mesurer leur incidence dans un important centre de soins tertiaires. Nous souhaitions également établir la taille de l'échantillon adéquat pour procéder à des études interventionnelles futures.

Type d'étude: Une étude de cohorte rétrospective.

Cadre: L'Hôpital d'Ottawa, en Ontario.

Sujets: Des adultes receveurs d'une greffe rénale (n=142).

Mesures: Les données démographiques des patients, le protocole de transplantation appliqué lors de l'intervention et les infections contractées dans les deux ans suivant la greffe.

Méthodologie: Ont été examinées toutes les infections contractées dans les deux ans suivant l'intervention chez tous les receveurs d'une greffe rénale entre janvier 2011 et décembre 2012. La taille de l'échantillon adéquat pour une étude interventionnelle a été déterminée à l'aide des données sur le taux d'infections toutes causes et le taux de survie sans infections.

Résultats: Des 142 patients retenus pour l'étude, 44 (31,0 %) avaient contracté au moins une infection au cours de la période de suivi. L'incidence des infections se situait à 36,2 par 100 années-patients deux ans après la greffe. Un total de 32 patients (22,5 %) avait contracté 56 infections liées à l'hospitalisation, dont 73,2 % étaient survenues dans la première année. Dans les deux ans suivant la greffe, les infections des voies urinaires se sont avérées les plus prévalentes (18,1 par 100 années-patients), suivies des infections cutanées (3,9 par 100 années-patients), des infections par cytomégalovirus (3,9 par 100 années-patients) et des bactériémies (3,9 par 100 années-patients). Les résultats indiquent que 206 sujets par bras d'étude seraient nécessaires pour démontrer une réduction de 30 % de l'incidence des infections au cours des deux ans suivant une greffe rénale.

Limites: Les taux d'infections pourraient être sous-estimés compte tenu de la durée relativement courte du suivi (deux ans). Par contre, la durée du suivi couvrait la période où le risque de contracter une infection est le plus élevé.

Conclusion: Les infections consécutives à une greffe rénale sont encore fréquentes, particulièrement les infections des voies urinaires, et sont associées à plus de morbidité et à un important taux d'hospitalisation. La taille de l'échantillon adéquat étant facilement réalisable, des études interventionnelles sont indiquées pour réduire davantage les taux d'infections contractées au cours des deux ans suivant une greffe rénale.

What was known before

Infection rates following kidney transplantation are likely to fluctuate with changing patient demographics (eg, number of patients with comorbid diabetes) and changes to transplantation protocols. Although previous data had shown decreasing infection rates following kidney transplantation, there are limited data regarding all-cause infection rate in a more recent era since 2010.

What this adds

This study provides modern infection rates for comparison by other institutions and highlights the need for targeted trials aimed at reducing specific infections (such as urinary tract infections) following kidney transplantation. Moreover, sample sizes calculated within this study can be used to help guide these future trials.

Introduction

Kidney transplantation is the preferred treatment for end-stage kidney disease as it improves both survival and quality of life.[1,2] Long-term immunosuppression is necessary to prevent organ rejection but is associated with an increased risk of infection and cancer. Infection is the second leading cause of death in kidney transplant recipients and is associated with decreased allograft survival.[3,4] Estimates from the US Renal Data System suggested a rate of first infections in the initial 3 years following kidney transplant of 45 per 100 patient-years of follow-up using data from 1995-2003.[5]

Advanced donor age, deceased donor status, cytomegalovirus (CMV) positive donor, recipient age ≤18 or ≥50 years, female sex of recipient, number of years on dialysis, and systemic lupus erythematosus or diabetes mellitus as the cause of kidney disease have been identified as factors that increase

[1]Division of Infectious Diseases, Department of Medicine, University of Ottawa, ON, Canada
[2]Clinical Epidemiology Program, The Ottawa Hospital Research Institute, ON, Canada
[3]Department of Biochemistry, Microbiology and Immunology, University of Ottawa, ON, Canada
[4]School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, ON, Canada
[5]Faculty of Medicine, University of Ottawa, ON, Canada
[6]Division of Nephrology, Department of Medicine, University of Ottawa, ON, Canada

Corresponding Author:
Juthaporn Cowan, Department of Medicine, Division of Infectious Diseases, University of Ottawa, 501 Smyth Road, Box 223, Ottawa, ON, Canada K1H 8L6.
Email: jcowan@toh.ca

the risk of post-transplant infection.[6] These factors, however, change over time. For example in 2013, 42% of kidney transplant recipients were greater than 60 years of age compared with only 31% in 2004.[7] Therefore, as disease distribution, population demographics, disease treatments, and transplant protocols change over time, one can reason that infection rates following kidney transplantation will as well. Although a number of studies have recently assessed specific post-transplant infections,[8-13] few recent studies have evaluated overall infection rates in kidney transplant patients.[14,15]

Interventions such as changes to pretransplant screening of recipient and donor, vaccination and prophylaxis, and post-transplant surveillance may effectively decrease infection rates following kidney transplantation. In addition to scientific justification and validity, sample size calculation aids in the assessment of the feasibility of intervention trials.

The primary objectives of this retrospective study were to determine the incidence of clinically or microbiologically confirmed infections within a cohort of North American kidney transplant recipients, results from which would aid in influencing program and policy changes at our own institution and serve as comparison values for assessment of infection rates at other institutions. We conducted a secondary analysis whereby we used these data to estimate sample sizes requirements to detect a desired effect size for future intervention trials aimed at preventing or reducing post-kidney transplant infections.

Methods

Study Design and Data Collection

This study was a retrospective cohort study conducted at The Ottawa Hospital (TOH), a large multicenter tertiary-care facility of approximately 1000 in-patient beds. The patient cohort was defined as adult patients (age ⩾18 years) who had undergone kidney transplantation between January 1, 2011, and December 31, 2012, regardless of history of previous transplantation. Combined organ transplantation was excluded. Medical records were reviewed for demographic data, transplant protocol, and infections up to 2 years following transplantation. A list of patients whom had a kidney transplant during this period was obtained from TOH Renal Transplantation Program.

Variable Definitions

Infection in this study was typically defined as documented clinical infectious signs and symptoms confirmed by positive microbiological testing. However, urinary tract infections (UTIs) were defined as significant bacteriuria (bacterial load $> 1 \times 10^5$ CFU [colony-forming unit]/mL) with either pyuria (white bed cells [WBC] > 10 cells/high power field) or at least 2+ positive leukocyte esterase on urine-dipstick testing. Urinalysis was surveilled at every clinic visit (twice weekly during the first month, weekly during the second month, every 2 to 3 weeks until 6 months post-transplant, monthly during month 6 to 12, and then every 3 months afterward). However, urine cultures were only performed in symptomatic cases. Microbiological confirmation of infection was infrequently provided for patient with pneumonias and therefore the definition used for analysis was clinical and radiographic evidence of pneumonia that required hospitalization. CMV infection was defined as CMV viremia with associated symptoms. CMV viremia was considered when CMV DNA $> 1.32 \times 10^2$ IU (international units)/mL in at least 2 measurements with at least 1-week interval. Invasive CMV disease was a subset of CMV infection but had histologically proven CMV disease in a biopsied tissue sample. BK or JC polyomavirus viremia was considered clinically significant infections if viremia led to changes in immunosuppression and/or the addition of antiviral treatment.

The following demographic and clinical data were collected: patient sex (female vs male) and age (measured continuously), cause of end-stage renal disease, donor status (living or deceased), preoperative antimicrobial prophylactic regimen, immunosuppressive regimen, CMV serology of donor and recipient, clinically or microbiologically confirmed infections, infection-associated hospitalization, and mortality. Causes of end-stage renal disease were classified as glomerulonephritis, diabetic nephropathy, autosomal dominant polycystic kidney disease (ADPKD), ischemic nephropathy, obstructive nephropathy, other, or unknown.

Statistical Analyses

Data analyses were conducted using Microsoft Excel and presented with proportions and percentages for categorical variables and means and standard deviations (SD) for continuous variables. Event rates were calculated as the ratio of number of events and total patient-years of follow-up.

Study sample size calculation for future trials aimed at reducing the 1-year and 2-year overall infection rate was performed assuming $\alpha = 0.05$ with 80% power. Power calculation was conducted using PROC GLIMMIX (for Poisson regression) by SAS 9.3, SAS Institute Inc, Cary, North Carolina. A second power calculation based on the infection-free survival data was performed using PASS 2008, NCSS, LLC, Kaysville, Utah. For this analysis, a control hazard of 0.03 was used (median survival, 24 months), pursuant to previously reported data.[16] Other assumptions were as follows: the accrual pattern across time periods is uniform (all periods equal); no subjects drop out of the control or the treatment group; the proportion switching from the control group to another group with a hazard rate equal to the treatment group is 0; the proportion switching from the treatment group to another group with a hazard rate equal to the control group is 0.

Results

In total, 142 patients underwent kidney transplantation at TOH during the 2-year study period. Transplant recipients were predominantly male (67.6%) with a mean age at the time of transplantation of 51.2 (SD: ±13.8 years) (Table 1). The most common causes of end-stage renal disease were glomerulonephritis (25.4%), diabetic nephropathy (21.8%), and ADPKD (14.8%). Approximately half of transplanted kidneys were from deceased donors (51.4%).

All patients received some form of induction immunosuppression. Methylprednisolone was most commonly used (97.9%), followed by basiliximab (72.5%), and anti-thymocyte globulin (38%). Approximately 57% of patients received combined induction immunosuppressive therapy with basiliximab and methylprednisolone while a minority received methylprednisolone only (2.8%) or basiliximab only (2.1%). All CMV seropositive donors/seronegative recipients (D+/R–) and all CMV seropositive recipients (R+) who received anti-thymocyte globulin were given 6-month valganciclovir prophylaxis (40.1%). Patients who did not get valganciclovir prophylaxis but were at high risk for EBV reactivation, eg, EBV D+/R–, had monthly EBV viral load monitoring for 1 year. All patients received UTI and *Pneumocystis jeroveci* pneumonia prophylaxis with Trimethoprim/Sulfamethoxazole 80 mg/400 mg one tablet daily for 1 year. Antifungal prophylaxis was not routinely used. The most common post-operative immunosuppressive regimen was a combination of mycophenolate mofetil, prednisone, and tacrolimus (75.4%) followed by a combination of mycophenolate mofetil, prednisone, and cyclosporin (24.6%). Urinary stent was removed 4 to 6 weeks post-transplant in all cases.

Infections and Hospitalization

Of 142 patients, 40 (28.2%) had at least one infection within the first year and 44 (31.0%) had at least one infection within 2 years (Table 2). Within these 44 patients, the number of infection episodes ranged from 1 to 10 per patient with median and mean numbers of infection of 1 and 2.3, respectively. Overall, there were 102 episodes of infection throughout the 2-year study period, 75 of which occurred within the first year. Incidence of all-cause infection within the first year was 52.8 per 100 patient-years, and incidence of infection was 36.2 per 100 patient-years by 2 years post-transplant (52.8 in year 1 and 19.3 in year 2). The probability of being infection-free was 72% at 1 year and 67% at 2 years. Bacterial infections were more common than viral infections. Interestingly, despite intensive immunosuppressive therapy, there were no documented fungal or parasitic infections.

Throughout the study period, there were 56 infectious episodes that resulted in hospitalization among kidney transplant patients, of which 73.2% occurred within 1 year following transplantation. Infection-related admission to the intensive

Table 1. Demographic Characteristics of Kidney Transplant Patients (n = 142).

Variables	n (%)
Sex	
Male	96 (67.6)
Female	46 (32.4)
Age, mean years ± SD	51.2 ± 13.8
Cause of end-stage renal disease	
Glomerulonephritis	36 (25.4)
Diabetic nephropathy	31 (21.8)
ADPKD	21 (14.8)
Ischemic nephropathy	7 (4.9)
Obstructive nephropathy	2 (1.4)
Other	29 (20.4)
Unknown	16 (11.3)
Donor status	
Deceased donor	73 (51.4)
Living donor	69 (48.6)
CMV serostatus	
D+R+	41 (28.9)
D+R–	31 (21.8)
D–R+	24 (16.9)
D–R–	38 (26.8)
Induction immunosuppression	
ATG only	0 (0)
Basiliximab only	3 (2.1)
Methylprednisolone only	4 (2.8)
Basiliximab + Methylprednisolone	81 (57)
ATG + Methylprednisolone	35 (24.6)
ATG + Basiliximab	0 (0)
ATG + Basiliximab + Methylprednisolone	19 (13.4)
Post-operative immunosuppressive regimen	
MMF, prednisone, and tacrolimus	107 (75.4)
MMF, prednisone, and cyclosporin	35 (24.6)
Acute graft rejection	7 (4.9)

Note. ADPKD = autosomal dominant polycystic kidney disease; CMV = cytomegalovirus; D = donor; R = recipient; ATG = anti-thymocyte globulin; MMF = mycophenolate mofetil.

care unit occurred twice, and both admissions were due to sepsis secondary to UTI. Mean length of infection-related hospitalization was 11.7 (range: 1-87 days). Of the infection-related hospitalizations, 22 (39.3%) were associated with UTI, 13 (23.2%) were associated with bacteremia, 6 (10.7%) were associated with bronchitis/pneumonia, and 15 (26.8%) were associated with miscellaneous infections such as *C difficile* infection, CMV infection, skin and soft tissue infection.

Bacteremia was mainly caused by UTI (81.8%). Microorganisms of all 11 bacteremia episodes included *Escherichia coli* (n = 7), *Acinetobacter baumannii* (n = 1), *Enterobacter cloacae* (n = 1), *Morganella morganii* (n = 1), and *Pseudomonas aeruginosa* (n = 1). None of the *E coli* isolates had extended spectrum beta-lactamases. Both the *M morganii* and *P aeruginosa* isolates were also reported not to be multidrug resistant (MDR, resistant to ≥2 classes). There were

Table 2. Number and Incidence of Infections by Type Within Kidney Transplant Patients During the First and Second Year Following Transplantation.

	First year No. of infections (incidence per 100 patient-years)	Second year No. of infections (incidence per 100 patient-years)
Overall infection	75 (52.8)	27 (36.2)
Bacterial infections		
Urinary tract	37 (26.1)	14 (10.0)
Skin/soft tissue	9 (6.3)	2 (1.4)
Bacteremia	7 (4.9)	4 (2.9)
Colitis (*Clostridium difficile*)	5 (3.5)	0 (0.0)
Pneumonia	4 (2.8)	3 (2.1)
Bone/joint	2 (1.4)	1 (0.7)
Cholecystitis	0 (0.0)	2 (1.4)
Viral infections		
CMV	9 (6.3)	2 (1.4)
BK viremia	3 (2.1)	0 (0.0)
BK nephropathy	1 (0.7)	0 (0.0)
PTLD	1 (0.7)	0 (0.0)
HCV	1 (0.7)	0 (0.0)
Gastroenteritis	1 (0.7)	0 (0.0)
HMPV	1 (0.7)	0 (0.0)
JC viremia	1 (0.7)	0 (0.0)

Note. First year, n = 142; second year, n = 140 (excluded 2 deaths in the first year). CMV = cytomegalovirus; PTLD = post-transplant lymphoproliferative disease; HCV = hepatitis C virus; HMPV = human metapneumovirus.

5 episodes of *C difficile* infection within 5 patients, and 4 of these episodes occurred within the first week following kidney transplantation. Three patients had clinically significant BK viremia (2 of which had viral load > 10 000 copies/mL) and one patient had clinically significant JC viremia within the 2-year study period. Furthermore, 11 CMV infections were recorded in 10 patients. None had biopsy-proven CMV disease. CMV serostatus of donors and recipients were discordant in 8 of 9 pairs with known CMV serostatus. One of the patients with CMV infection was CMV seronegative but received an organ from a donor with an unknown CMV status.

To capture post-operative infection outcome, we analyzed incidence of overall infection rates at 30 days and 90 days post-transplant. There were 18 infection episodes from 16 patients in 30-day period, and 30 infection episodes from 19 patients in 90-day period. This resulted in the infection incidence of 152.1 and 84.5 per-patient-years, at 30 days and 90 days post-transplant, respectively. UTI was the most common infection (12/18 [66.7%] at 30 days, and 21/30 [70%] episodes at 90 days post-transplant).

Three deaths occurred over the 2-year study period, causes of which included urosepsis, intracerebral hemorrhage, and congestive heart failure. One-year and 2-year mortality rate was 1.4% and 2.1%, respectively.

Sample Size Calculation

Sample size calculations using the 1- and 2-year rates of all-cause infection found within this study are presented in detail in Table 3 and vary substantially based on the percent reduction desired and treatment rate. Using a baseline infection rate from this study of 52.8 per 100 patient-years in year 1, the sample size can range from 12 187 per group (cases vs controls) for a 5% reduction in infection to 95 per group for a 50% reduction in infection. Using the year 2 infection rate of 36.2 per 100 patient-years, the calculated sample size ranges from 8715 per group to detect a 5% reduction in infection to 68 per group to detect a 50% reduction in infection. Based on the number of annual kidney transplantation at our hospital, we estimate that it would take at least 5 years to conduct a trial to demonstrate a clinically significant effect of an intervention, ie, 30% reduction of 2-year infection rate.

Calculated sample sizes using time to first infection assuming 1-year accrual are presented in Table 4 and vary considerably based off of the selected hazard ratio. For a 1-year follow-up time, the calculated sample size ranges from 11 570 per group for a 0.95 hazard ratio to 81 per group for a 0.5 hazard ratio. For a 2-year follow-up time, calculated sample size ranges from 8077 per group for a 0.95 hazard ratio to 55 per group for a 0.5 hazard ratio.

Discussion

This study reports the overall infection rate at 1- and 2-year post-kidney transplant at TOH in Canada. Among our study cohort, bacterial infections were noted most frequently followed by viral infections, and no fungal or parasitic infections were documented. Overall incidence of infection was

Table 3. Calculated Sample Sizes Using 1- and 2-Year Rates of All-Cause Infection.

	% reduction	Treatment rate	n per group
1 year[a]	5	0.502	12 187
	10	0.475	2855
	15	0.449	1250
	20	0.422	674
	25	0.396	422
	30	0.37	286
	40	0.317	155
	50	0.264	95
2 years[b]	5	0.344	8715
	10	0.326	2122
	15	0.308	917
	20	0.29	501
	25	0.272	311
	30	0.253	206
	40	0.217	111
	50	0.181	68

[a]Control rate = 0.528.
[b]Control rate = 0.362.

Table 4. Calculated Sample Sizes Using Time to First Infection Assuming 1-Year Accrual.

	Hazard ratio	n per group
1 year	0.95	11 570
	0.9	2799
	0.85	1202
	0.8	653
	0.75	402
	0.7	269
	0.6	139
	0.5	81
2 years	0.95	8077
	0.9	1947
	0.85	834
	0.8	451
	0.75	277
	0.7	185
	0.6	95
	0.5	55

Note. Control hazard rate = 0.03.

highest within the first year following renal transplant at 52.8 per 100 patient-years. Fewer infections were noted within the second year following transplantation resulting in a combined incidence of infection across the first 2 years following transplantation of 36.2 per 100 patient-years. Infections resulting in hospitalization were highest within the first year following transplantation and UTI was identified as both the leading overall cause of infection and leading cause of infection-related hospitalization within renal transplant patients.

Here, we report an infection rate that is lower than values reported using 1995-2003 data from the United States.[5] Previously, Snyder et al reported an overall infection rate of 74.7 and 33.1 per 100 patient-years during years 1 and 2 post-transplant, while we report infection rates of 52.8 and 19.3 per 100 patient-years during this time frame. There are no data regarding all-cause infection rate in a more recent era since 2010. However, the risk of death due to infectious causes declined overtime from 1990 to 2012 in Finland.[17] We were not able to compare infection rates with the previous era at our center to conclude whether the infection rates may be falling. The difference in infection rates between our study and the study by Snyder et al could be due to differences in induction therapy regimen or patient population in the Medicare system versus general population in Ottawa, Canada, among others.

UTIs were the most common cause of infectious complication within our study cohort and were the most referenced reason for infection-related hospitalizations early post-transplantation, even though our rate may be underestimated due to the exclusion of symptomatic but nondocumented bacteriuria. The finding of UTI as the primary cause of post-operative infection following kidney transplantation is

consistent with previous reports spanning decades.[5,18,19] Sepsis secondary to UTI resulted in the only 2 intensive care unit admissions found among transplant patients and urosepsis was the only infection causing death. These results underscore that UTI remains a leading cause of post-operative morbidity and mortality and should, therefore, be the focus of rigorous interventional trials to decrease the risk of infection. Indeed, investigations regarding therapeutic interventions are underway. The identification of virulence determinants in UTI has allowed for the development of targeted therapies that effectively neutralize pathogenic bacteria and prevent diseases in animal models; however, these new therapies have yet to be tested in clinical trials.[20] We did not look at risk factors associated with UTI in this study but female sex, older age of the recipient, long duration of catheter placement, acute rejection episodes, and deceased donor are reported to be associated with higher risk of UTI.[18]

MDR organisms as a cause of bacterial infection were not common in our patient population as compared with other reported studies which showed an increasing trend of MDR organisms in kidney transplant recipients.[21,22] Our findings are likely due to the overall lower prevalence of MDR organisms in Canada as compared with other geographic regions, and it is likely a matter of time until we see an increase in MDR organisms in our kidney transplant population.[23]

The second and third most common sites of infection found within our patient cohort were skin and soft tissue and lung, respectively. Interestingly, the sites of skin and soft tissue infections documented within our patient population were not generally located at the operative incision or previous peritoneal catheter exit site. Skin and soft tissue infections only affected patients with a diabetic cause of end-stage renal disease, likely due to impaired circulation and reduced

immunological defenses within this patient population. The incidence of pneumonia was approximately 7%, which is consistent with 8% reported by Alangaden et al.[14] However, the frequency and rate of pneumonia may be underrepresented due to difficulty in the identification of microbiologically negative pneumonia through a retrospective chart review and potentially missing mild cases of pneumonia that did not require medical attention.

We report 5 episodes of *C difficile* infection during the first year post-transplant, 4 of which occurred within 1 week following kidney transplantation. This period likely represents the most vulnerable time due to a heightened degree of immunosuppression. It is interesting that 2 cases occurred at around the same period likely indicating a hospital-acquired infection. The first patient had documented *C difficile* infection on the second day post-transplant, which was the day of transplantation for the second patient, whom had a documented *C difficile* infection 6 days later. Increased *C difficile* infection has been reported in kidney transplant recipients with a frequency of 3.7% in 2008 to 9.4% in 2010 in a single institution in the United States.[24]

Viral infection was not common during our study period. However, despite prophylactic valganciclovir in high-risk patients, there were 11 CMV infectious episodes in our study patients. All but one cases occurred late, after prophylaxis had stopped. Nevertheless, there was no documented invasive CMV disease in our cohort.

Infection-related hospitalization remains high and we noted a total infection-related length of stay among kidney transplant patients of 554 days over the 2-year observation period. Approximately one in 5 transplant recipients required hospitalization because of infection. Hospitalization not only reduces patient quality of life but also increases the likelihood of additional infections, adding to the clinical and cost burden. For example, previous work reports that infection during the first year post-transplant significantly increased first-year costs from US$17 691 marginal cost increase for UTI alone, to US$40 000-US$50 000 for pneumonia or sepsis alone, and to US$135 000 for those with UTI, pneumonia, and sepsis.[25]

Alternative prophylactic or therapeutic approaches are needed to minimize the risk of infection in this population. To aid in the design of trials testing new approaches to infection reduction, we calculated sample sizes using infection data obtained in this study. Interventions/approaches that could be tested include new immunosuppressive regimen, antimicrobial prophylaxis, vaccination, infection control measures, or innovative surgical techniques. Given that a standard minimal clinically important difference has not been identified for infection outcomes in kidney transplantation, we reported sample sizes for a wide variety of assumptions. The sample sizes presented in this study will allow researchers to estimate the feasibility of conducting an interventional trial by selecting either a percent reduction in infection or hazard ratio that would be required to implement protocol changes at their institution. Although we present sample sizes that can be referenced for assessment of study feasibility and estimates for initial ethics approval, we recommend that researchers conduct a pilot or pretest study to help refine sample sizes for the particular hypothesis.

Limitations to this study should be noted. First, the majority of infections were identified by positive microbiology data that likely resulted in an underestimation of infection rate. Nevertheless, based on our electronic medical record system, we could identify hospitalization due to pneumonia even though microbiological data were not available or were negative. Second, infections and hospitalizations that occurred outside of our center were not captured. However, we estimate this number to be small as our transplant patients are rarely, if ever, treated at other institutions. Third, the study results cannot be generalized because this is a single-center study. Finally, the 2-year follow-up period was relatively short. Although we cannot comment on long-term infection rates, the highest infection-risk period occurred within the time frame of our study.

Conclusions

In summary, our study reports infection rates at 1- and 2-year post-kidney transplant and shown that infections are still associated with significant morbidity in terms of need for hospitalization. Intervention trials are needed to test strategies aimed at reducing infection rates further. Such studies should be pursued given the feasible sample sizes we have reported using realistic clinically important differences.

Ethics Approval and Consent to Participate

This study was approved by the Ottawa Hospital Research Ethics Board (OHREB#20150331).

Consent for Publication

All authors read and approved the final version of this manuscript.

Availability of Data and Materials

Data are available upon request.

Author Contributions

JC contributed to the study conception, data collection, data analysis, data interpretation, and manuscript drafting and revision; AB and NF contributed to the data collection; CM contributed to the manuscript drafting and revision; RM contributed to the data analysis; DWC contributed to the study conception and intellectual content; GK contributed to the study conception, data interpretation, intellectual content, and manuscript revision.

Declaration of Conflicting Interests

Funding

References

1. Overbeck I, Bartels M, Decker O, Harms J, Hauss J, Fangmann J. Changes in quality of life after renal transplantation. *Transplant Proc*. 2005;37:1618-1621.

2. Cameron JI, Whiteside C, Katz J, Devins GM. Differences in quality of life across renal replacement therapies: a meta-analytic comparison. *Am J Kidney Dis*. 2000;35:629-637.

3. Bige N, Zafrani L, Lambert J, et al. Severe infections requiring intensive care unit admission in kidney transplant recipients: impact on graft outcome. *Transpl Infect Dis*. 2014;16:588-596.

4. Shen T-C, Wang I-K, Wei C-C, et al. The risk of septicemia in end-stage renal disease with and without renal transplantation: a propensity-matched cohort study. *Medicine*. 2015;94:e1437.

5. Snyder JJ, Israni AK, Peng Y, Zhang L, Simon TA, Kasiske BL. Rates of first infection following kidney transplant in the United States. *Kidney Int*. 2009;75:317-326.

6. Dharnidharka VR, Agodoa LY, Abbott KC. Risk factors for hospitalization for bacterial or viral infection in renal transplant recipients? an Analysis of USRDS data. *Am J Transplant*. 2007;7:653-661.

7. Canadian Institute for Health Information. *Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2004 to 2013*. Canada: CIHI; April 2014.

8. Sharma R, Tzetzo S, Patel S, Zachariah M, Sharma S, Melendy T. BK virus in kidney transplant: current concepts, recent advances, and future directions. *Exp Clin Transplant*. 2016;14:377-384.

9. El Ansary M, Abd Elhamid S, Saadi G, et al. Prevalence of polyoma BK virus infection among living-donor renal transplant recipients. *Transpl Infect Dis*. 2016;18:529-537.

10. Song T-R, Rao Z-S, Qiu Y, et al. Fluoroquinolone prophylaxis in preventing BK polyomavirus infection after renal transplant: a systematic review and meta-analysis. *Kaohsiung J Med Sci*. 2016;32:152-159.

11. Kaminski H, Couzi L, Garrigue I, Moreau J-F, Dechanet-Merville J, Merville P. Easier control of late-onset cytomegalovirus disease following universal prophylaxis through an early antiviral immune response in donor-positive, recipient-negative kidney transplants. *Am J Transplant*. 2016;16:2384-2394.

12. Leone F, Gigliotti P, Mauro MV, et al. Early cytomegalovirus-specific T-cell response and estimated glomerular filtration rate identify patients at high risk of infection after renal transplantation. *Transpl Infect Dis*. 2016;18:191-201.

13. Radtke J, Dietze N, Spetzler VN, et al. Fewer cytomegalovirus complications after kidney transplantation by de novo use of mTOR inhibitors in comparison to mycophenolic acid. *Transpl Infect Dis*. 2016;18:79-88.

14. Alangaden GJ, Thyagarajan R, Gruber SA, et al. Infectious complications after kidney transplantation: current epidemiology and associated risk factors. *Clin Transplant*. 2006;20:401-409.

15. Dharnidharka VR, Caillard S, Agodoa LY, Abbott KC. Infection frequency and profile in different age groups of kidney transplant recipients. *Transplantation*. 2006;81:1662-1667.

16. Kahwaji J, Sinha A, Toyoda M, et al. Infectious complications in kidney-transplant recipients desensitized with rituximab and intravenous immunoglobulin. *Clin J Am Soc Nephrol*. 2011;6:2894-2900.

17. Kinnunen S, Karhapää P, Juutilainen A, Finne P, Helanterä I. Secular trends in infection-related mortality after kidney transplantation. *Clin J Am Soc Nephrol*. 2018;13:755-762.

18. Wu X, Dong Y, Liu Y, et al. The prevalence and predictive factors of urinary tract infection in patients undergoing renal transplantation: a meta-analysis. *Am J Infect Control*. 2016;44:1261-1268.

19. Maraha B, Bonten H, van Hooff H, Fiolet H, Buiting AG, Stobberingh EE. Infectious complications and antibiotic use in renal transplant recipients during a 1-year follow-up. *Clin Microbiol Infect*. 2001;7:619-625.

20. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol*. 2015;13: 269-284.

21. Kawecki D, Wszola M, Kwiatkowski A, et al. Bacterial and fungal infections in the early post-transplant period after kidney transplantation: etiological agents and their susceptibility. *Transplant Proc*. 2014;46:2733-2737.

22. Pinheiro HS, Mituiassu AM, Carminatti M, Braga AM, Bastos MG. Urinary tract infection caused by extended-spectrum beta-lactamase-producing bacteria in kidney transplant patients. *Transplant Proc*. 2010;42:486-487.

23. Molton JS, Tambyah PA, Ang BSP, Ling ML, Fisher DA. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. *Clin Infect Dis*. 2013;56:1310-1318.

24. Neofytos D, Kobayashi K, Alonso CD, et al. Epidemiology, risk factors, and outcomes of Clostridium difficile infection in kidney transplant recipients. *Transpl Infect Dis*. 2013;15:134-141.

25. Naik AS, Dharnidharka VR, Schnitzler MA, et al. Clinical and economic consequences of first-year urinary tract infections, sepsis, and pneumonia in contemporary kidney transplantation practice. *Transpl Int*. 2016;29:241-252.