ORIGINAL ARTICLE

Clinical and microbiological epidemiology of early and late infectious complications among solid-organ transplant recipients requiring hospitalization

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SUMMARY

There is limited literature describing the clinical and microbiological characteristics of solid-organ transplant recipients requiring hospitalization for infectious complications. This study reports on the rate and timing of these syndromes and describes the associated microbiological epidemiology. This prevalence cohort study evaluated solid-organ transplant recipients requiring hospitalization during 2007–2011. We reported infectious complications requiring hospitalization in 603 of 1414 readmissions at a rate of 0.43 episodes per 1000 transplant-days (95% CI, 0.40–0.47), with 85% occurring >6 months post-transplantation. The most frequent infectious complications were as follows: respiratory (27%), sepsis or bacteremia (13%), liver or biliary tract (12%), genitourinary (12%), and cytomegalovirus related (9%). Approximately 53% presented without fever, 45% had no pathogen isolated, and multidrug-resistant organisms were isolated in 27% of those with an identified microbiological etiology. Infectious-related complications continue to pose a high clinical burden on our acute care center, with the majority occurring in the late transplant period. Clinicians are faced with the difficult task of prescribing adequate antimicrobial therapy.

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Introduction

Solid-organ transplantation is a well-established therapy for many end-stage organ diseases, with over 29 000 transplants performed in 2014 according to the United Network for Organ Sharing (UNOS). While improvements in medical management, surgical techniques, and immunosuppressant therapy have enhanced graft and patient survival rates among solid-organ transplant (SOT) recipients, post-transplant infection continues to cause substantial morbidity and mortality [1–4]. Bacterial infections occur in 21–30% of heart, 33–68% of liver, 47% of kidney, and 54% of lung transplant recipients [5]. Infections are a common cause of death, varying from 21% in heart to 63% in lung recipients [6]. Infections may also have indirect adverse effects in SOT recipients, including increased immunosuppression, development of chronic allograft rejection, and malignancy [7].

The risk of infection post-transplantation is generally determined by the balance between two factors: the

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patient's net state of immunosuppression and their risk of epidemiological exposure [8]. As a result, antimicrobial prophylaxis and preemptive treatment strategies are targeted to the first 6 months post-transplantation. However, some evidence suggests that changes in immunosuppressive and prophylaxis regimens have altered the predictability of infections post-transplantation, resulting in later infections with viral, fungal and other opportunistic pathogens [9]. Additionally, although the risk of infection diminishes 6 months after transplantation, the risk may increase for patients treated for rejection with potent agents such as antithymocyte globulin supplemented with an increase in maintenance immunosuppression [7].

The majority of transplant recipients will require an emergency department visit within 5 years post-transplantation, with approximately 25% requiring hospitalization for an infectious diagnosis [10]. Despite the associated morbidity and mortality, there are few current-era studies describing the clinical and microbiological characteristics of late infectious complications in SOT recipients. Furthermore, although several studies have assessed overall incidence and trends in early and late infections, the majority of these reports have combined both ambulatory and acute care settings, with limited literature focussing solely on the epidemiology for those hospitalized [9–14]. Therefore, the primary objective of this study was to determine the rate and relative contribution of specific infectious disease syndromes among hospitalized SOT recipients after their initial discharge from the hospital. Other objectives include describing patient symptoms and other clinical or transplant characteristics and reporting the microbiological epidemiology of early and late infectious complications.

Methods

Study design and setting

Using a prevalent cohort study design, we reviewed the electronic and paper medical records using standard data collection forms. The study was conducted at the Toronto General Hospital, University Health Network, Toronto, Canada, providing follow-up care to approximately 5000 recipients of heart, lung, liver, kidney, pancreas, and small bowel transplants. The majority of transplant recipients continue their primary care with our institution following their transplant surgery. This study received approval from the institution's Research Ethics Board.

Data collection

We reviewed the health records of patients admitted to the multi-organ transplant unit during 2007–2011. We excluded the initial admission for the transplant surgery itself. Hospital visit documentation consisted of clinical notes by members of a multidisciplinary healthcare team, scanned into the patients' electronic medical records. Laboratory, microbiology, and medication history were integrated into the patients' electronic medical records. Transplant-related data were obtained from a stand-alone computerized data management system using the Outpatient Transplant Tracking Record (OTTR Chronic Care Solutions, Omaha, NE, USA). Trained abstractors collected and entered all data into a computerized database using MS ACCESS 2007 (Microsoft Corporation, Redmond, WA, USA). Data variables included patient demographics, symptoms on admission, comorbidities, organ transplanted, clinical or biopsy-proven rejection within 6 months of admission, concomitant immunosuppression, infection-related diagnoses, and isolated pathogens.

Definitions related to infectious syndromes

Infectious syndromes were defined and categorized according to established consensus recommendations or Centers for Disease Control and Prevention criteria [15,16]. Based on clinical and microbiological documentation from the patients' medical records, all infectious syndromes were categorized into one of the following: respiratory, sepsis or primary bacteremia, genitourinary, liver and biliary tract, cytomegalovirus (CMV) infection, fever of unknown origin, gastrointestinal, skin and soft tissue, intra-abdominal, osteomuscular and "other" if none of the previous applied. In cases where no microbiological etiology was established, clinical and radiological documentation were used to categorize the infections. Where abstractors differed on categorization, consensus agreement was reached among the principal investigators, which included a transplant pharmacist and infectious disease specialist. If patients presented with multiple syndromes, the one most responsible for the majority of their hospitalization was selected. Organisms found to have *in vitro* resistance to three or more antimicrobial categories to which they would normally be susceptible were classified as being multidrug resistant [17]. Infections were classified according to the post-transplant period as "early" (within 6 months post-transplant) or "late" (>6 months post-transplant).

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Immunosuppression and infection prevention

Maintenance immunosuppression consisted of a dual or triple therapy regimen according to organ-specific protocols, including the use of a calcineurin inhibitor and corticosteroids, with the majority of patients also prescribed an antimetabolite that generally consisted of a mycophenolic acid derivative, although some patients may have also received azathioprine. All patients received high-dose corticosteroids in the immediate postoperative period. Use of more potent induction agents included antithymocyte globulin in all heart, all pancreas, the majority of kidney, and some liver transplant recipients, in addition to basiliximab, an interleukin-2 receptor antagonist, which was prescribed to a limited number of kidney and liver transplant recipients. Treatment of acute rejection episodes usually consisted of a short course of high-dose corticosteroids or antithymocyte globulin for steroid-resistant and more severe episodes.

In addition to prescribing antibiotics for prevention of postoperative surgical site infections, our institution's protocol uses a *targeted prophylaxis* approach to prevent CMV infection post-transplantation. This involves administration of ganciclovir/valganciclovir to a subset of high-risk patients for a period of 3–9 months post-transplantation followed by surveillance monitoring until one year post-transplantation. These patients include those receiving antithymocyte globulin, recipients with donor-positive and recipient-negative serology, or others deemed at high risk. Trimethoprim/sulfamethoxazole or dapsone directed against *Pneumocystis jirovecii,* along with nystatin for prevention of oropharyngeal candidiasis, was routinely administered. Antifungal prophylaxis was not routinely prescribed, although previously colonized lung transplant recipients may have received targeted or preemptive antifungal therapy post-transplantation.

Outcomes

The primary objective of this study was to report the number and rate of hospitalizations in SOT recipients experiencing infectious-related complications. Other objectives included describing patient symptoms and other clinical or transplant characteristics and reporting specific infectious complications along with the microbiological epidemiology.

Statistical analysis

Values were expressed as the mean (standard deviation) or median (interquartile range) for continuous variables depending on the distribution or as a mean (percent) for binary variables. We compared variables between groups using the Student's *t*-test, chi-squared, or Wilcoxon signed-rank tests as appropriate. We assumed a Poisson distribution for the number of hospitalizations per 1000 transplant-days to calculate the 95% confidence intervals for these parameters. The criterion for statistical significance was set *a priori* at $\alpha = 0.05$, with all tests of significance being two tailed. All data were analyzed using STATAMP 12 (StataCorp LP, College Station, TX, USA) and MS EXCEL 2007 (Microsoft).

Results

A total of 531 transplant recipients were admitted with 1414 hospitalizations over a total follow-up of 3802 patient-years. Infectious-related complications resulted in a total of 603 (42.6%) hospitalizations from 306 (57.6%) unique patients. Cardiovascular (18.0%), acute rejection (11.5%), gastrointestinal (11.4%), and graft dysfunction or failure (7.2%) were the most common noninfectious complications among the 1414 hospitalizations. Demographic, transplant-related, and clinical characteristics of the cohort admitted for infectious complications are reported in Table 1. The overall rate of hospitalization for infectious complications was 0.43 episodes per 1000 transplant-days (95% CI, 0.40–0.47); however, the rate varied when stratified by organ group. Rates were lowest among kidney and highest among lung transplant recipients (Fig. 1). Eighty-five percent of the hospitalizations occurred more than 6 months post-transplantation. The overall median time from transplantation to hospitalization was 4.2 years, with lung (2.2 years) and liver (2.8 years) being admitted relatively earlier compared to kidney (6.4 years) and heart (8.6 years) transplant recipients. One-hundred and thirty-eight patients (45.1%) required more than one hospitalization for infectious complications. Patients admitted with late infections were less likely to have received induction with antithymocyte globulin, be prescribed cyclosporine or mycophenolic acid, be diagnosed with acute rejection within the previous 6-months, be prescribed an antibiotic within the previous 30-days, and be admitted with a polymicrobial infection when compared to patients admitted with early infections (Table 1). Conversely, a greater proportion of these patients were prescribed sirolimus and diagnosed with chronic renal failure.

Across all transplant types, the most common presenting complaint was fever, reported just prior to or at admission in 52.6% of all admissions for infections. The

Table 1. Demographic, transplant, and selected clinical characteristics among patients admitted for infectious-related complications.

	All (n = 603)	Early period* (n = 93)	Late period† (n = 510)	P value
Age (years) – mean (SD)	52.9 (14.4)	52.1 (13.9)	53.0 (14.6)	0.57
Male	372 (61.7)	61 (65.6)	311 (61.0)	0.4
Organ				
Kidney	190 (31.5)	25 (26.9)	165 (32.4)	0.028
Liver	183 (30.4)	38 (40.9)	145 (28.4)	
Lung	154 (25.5)	23 (24.7)	131 (25.7)	
Heart	64 (10.6)	5 (5.4)	59 (11.6)	
Kidney/Pancreas	12 (2.0)	2 (2.2)	10 (2.0)	
Immunosuppression				
Tacrolimus	309 (51.2)	47 (50.5)	262 (51.4)	0.88
Cyclosporine	215 (35.7)	44 (47.3)	171 (33.5)	0.011
Steroid	498 (82.6)	81 (87.1)	417 (81.8)	0.21
Mycophenolic acid	379 (68.6)	70 (75.3)	309 (60.6)	0.007
Sirolimus	28 (9.1)	2 (2.2)	47 (9.2)	0.022
Antithymocyte induction	131 (21.7)	32 (34.4)	99 (19.4)	0.001
Rejection (previous 6 months)	64 (10.6)	19 (20.4)	45 (8.8)	0.001
Chronic renal failure	166 (27.5)	15 (16.1)	151 (29.6)	0.007
Dialysis dependent	58 (9.6)	6 (6.5)	52 (10.2)	0.26
Central venous access	211 (35.0)	32 (34.4)	179 (35.1)	0.9
Leukopenia	245 (40.6)	43 (46.2)	202 (39.6)	0.23
Fever on admission	193 (32.0)	34 (36.6)	159 (31.2)	0.31
Antibiotic treatment (previous 30 days)	319 (52.9)	88 (94.6)	392 (76.9)	0.001
Microbiologically positive infections	333 (55.2)	57 (61.3)	276 (54.1)	0.2
Polymicrobial infection	90 (14.9)	21 (22.6)	69 (13.5)	0.024
Multidrug-resistant infection	90 (14.9)	18 (19.4)	72 (14.1)	0.192

Note: Data are number or percentage (in parentheses) unless otherwise stated.

*Early period defined as occurring within 6 months post-transplantation.

†Late period defined as occurring after 6 months post-transplantation.

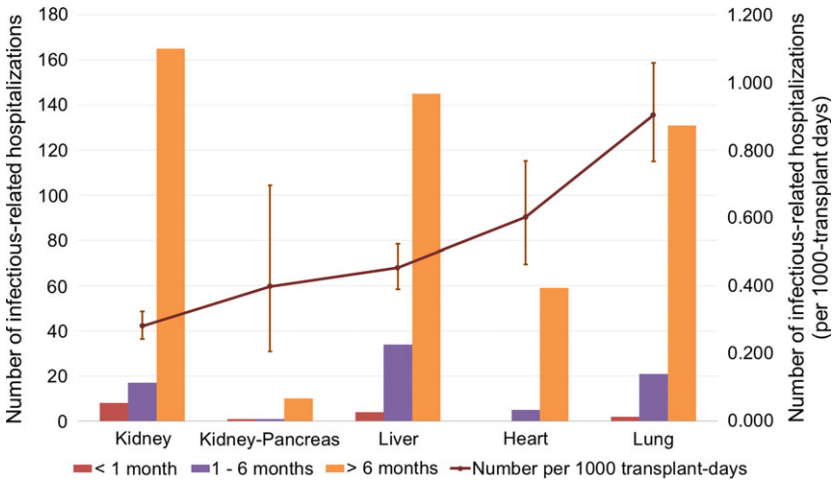

Figure 1 Number of infectious-related hospitalizations per post-transplant time period and total rate by transplanted organ. (Note: For number of hospitalizations per 1000 transplant-days, the error bars represent 95% confidence intervals based on a Poisson distribution).

proportion of patients being afebrile was not significantly different with respect to age, gender, or time post-transplantation; however, we did find that use of mycophenolic acid derivatives or azathioprine was associated with a higher proportion of afebrile patients (54.1% vs. 36.2%, $P < 0.001$). In addition, the

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proportion of afebrile patients was relatively greater among lung transplant recipients (69.4%) and those diagnosed with osteomuscular (88.9%), CMV (71.7%), skin/soft tissue (69.0%) and gastrointestinal (68.3%) infections. Other common symptoms included cough (16.1%), abdominal pain (15.9%), chills (15.6%), shortness of breath (15.6%), diarrhea (13.1%), vomiting (9.3%), and nausea (8.3%). Respiratory infections were reported most often in lung and heart recipients, with genitourinary tract infections most frequently diagnosed in kidney recipients, and liver recipients most frequently admitted with biliary tract or liver infections (Table 2). Sepsis or bacteremia and CMV infections tended to be evenly distributed among all organ groups. Overall, respiratory, sepsis or bacteremia, liver and biliary tract, genitourinary, and CMV infectious syndromes were the most common causes of infectious-related hospitalizations (Fig. 2). The median time (in years) post-transplantation varied by infectious syndrome, with CMV (1.0) and other viral (1.4) infections presenting earlier, and liver and biliary tract (4.9), gastrointestinal (6.6), and skin/soft tissue (7.9) infections occurring later. The CMV cases included 24 patients with asymptomatic viremia, 12 patients with CMV syndrome, and 17 patients with invasive disease (12 of which were diagnosed with CMV gastroenteritis or colitis).

Overall, the microbiological etiology was established in 333 of 603 (55%) hospitalizations, with 475 isolated or identified pathogens (Table 3). Table S1 reports the microbiological etiology of pathogens identified or isolated among patients with the most common syndromes. The most common syndromes among cases with no microbiological etiology were classified as respiratory (30%), liver or biliary tract (16%), fever of unknown origin (14%), and urinary tract (11%). The number of Gram-negative and Gram-positive bacteria

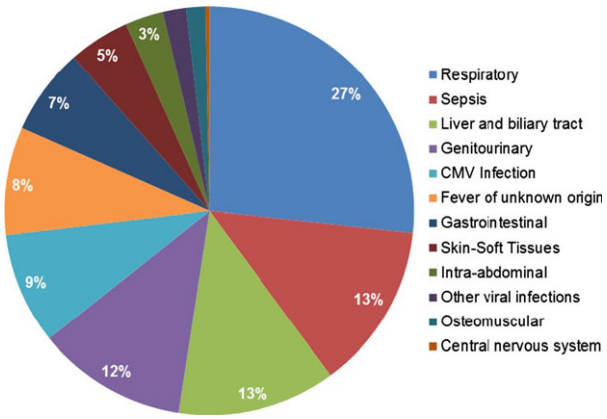

Figure 2 Most frequently diagnosed infectious syndromes as a percent of all infectious-related hospitalizations.

Table 2. Most frequently diagnosed infectious syndromes as a percent of all infectious-related hospitalizations overall, by time period, and by organ transplanted.

Infectious syndrome	All (n = 603)	Early period* (n = 93)	Late period† (n = 510)	P value	Kidney (n = 190)	Liver (n = 183)	Lung (n = 154)	Heart (n = 64)	Kidney/ Pancreas (n = 12)
Respiratory	160 (26.5)	23 (24.7)	137 (26.9)	0.67	18 (9.5)	15 (8.2)	93 (60.4)	33 (51.6)	1 (8.3)
Sepsis/Bacteremia	79 (13.1)	12 (12.9)	67 (13.1)	0.95	25 (13.2)	25 (13.7)	21 (13.6)	6 (9.4)	2 (16.7)
Liver and biliary tract	75 (12.4)	12 (12.9)	63 (12.4)	0.88	3 (1.6)	68 (37.2)	4 (2.6)	0 (0.0)	0 (0.0)
Genitourinary	71 (11.8)	9 (9.7)	62 (12.2)	0.50	61 (32.1)	5 (2.7)	1 (0.7)	0 (0.0)	4 (33.3)
CMV infection	53 (8.8)	15 (16.1)	38 (7.5)	0.007	15 (7.9)	10 (5.5)	17 (11.0)	8 (12.5)	3 (25.0)
Fever of unknown origin	51 (8.5)	10 (18.8)	41 (8.0)	0.39	16 (8.4)	24 (13.1)	7 (4.6)	3 (4.7)	1 (8.3)
Gastrointestinal	41 (6.8)	2 (2.2)	39 (7.7)	0.050	18 (9.5)	13 (7.1)	4 (2.6)	5 (7.8)	1 (8.3)
Skin and soft tissues	29 (4.8)	3 (3.2)	26 (5.1)	0.44	13 (6.8)	6 (3.3)	5 (3.3)	5 (7.8)	0 (0.0)
Intra-abdominal	18 (3.0)	4 (4.3)	14 (2.8)	0.42	5 (2.6)	10 (5.5)	0 (0.0)	3 (4.7)	0 (0.0)
Other viral infection	11 (1.8)	3 (3.2)	8 (1.6)	0.27	6 (3.2)	4 (2.2)	1 (0.7)	0 (0.0)	0 (0.0)
Osteomuscular	9 (1.5)	0 (0.0)	9 (1.8)	0.20	7 (3.7)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical site infection	4 (0.7)	0 (0.0)	4 (0.8)	0.40	3 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Central nervous system	2 (0.3)	0 (0.0)	2 (0.4)	0.55	0 (0.0)	1 (0.6)	0 (0.0)	1 (1.6)	0 (0.0)

Note: Data are number or percentage (in parentheses) of hospitalizations within total or organ group.

*Early period defined as occurring within 6 months post-transplantation.

†Late period defined as occurring after 6 months post-transplantation.

Table 3. Microbiological etiology of 475 pathogens identified overall and by time period.

	All (n = 475)	Early period* (n = 69)	Late period† (n = 406)
Gram-negative bacteria	**178 (37.4)**	**23 (33.3)**	**155 (38.2)**
Escherichia coli	62 (13)	8 (11.6)	54 (13.3)
Klebsiella species	44 (9.2)	9 (13)	35 (8.6)
Pseudomonas aeruginosa	26 (5.5)	0 (0)	26 (6.4)
Enterobacter species	12 (2.5)	3 (4.3)	9 (2.2)
Citrobacter species	7 (1.5)	2 (2.9)	5 (1.2)
Stenotrophomonas maltophilia	5 (1.1)	1 (1.4)	4 (1)
Bacteroides species	5 (1.1)	0 (0)	5 (1.2)
Other Gram-negative bacteria	17 (3.6)	0 (0)	17 (4.2)
Gram-positive bacteria	**174 (36.6)**	**26 (37.7)**	**148 (36.5)**
Enterococcus species	45 (9.5)	8 (11.6)	37 (9.1)
Coagulase-negative staphylococci	37 (7.8)	5 (7.2)	32 (7.9)
Streptococcus species	26 (5.5)	3 (4.3)	23 (5.7)
Staphylococcus aureus	21 (4.4)	3 (4.3)	18 (4.4)
Clostridium difficile	15 (3.2)	1 (1.4)	14 (3.4)
Bacillus species	8 (1.7)	2 (2.9)	6 (1.5)
Mycobacterium species	7 (1.5)	0 (0)	7 (1.7)
Corynebacterium species	5 (1.1)	2 (2.9)	3 (0.7)
Other Gram-positive bacteria	10 (2.1)	2 (2.9)	8 (2.0)
Viruses	**82 (17.2)**	**17 (24.6)**	**65 (16)**
Cytomegalovirus	53 (11.1)	13 (18.8)	40 (9.9)
Herpes simplex virus	9 (1.9)	0 (0)	9 (2.2)
Epstein–Barr virus	8 (1.7)	0 (0)	8 (2.0)
Enterovirus/Rhinovirus	4 (0.8)	0 (0)	4 (1.0)
Other viruses	8 (1.7)	4 (5.8)	4 (1.0)
Fungi	**41 (8.6)**	**3 (4.3)**	**38 (9.4)**
Candida albicans	15 (3.2)	3 (4.3)	12 (3.0)
Aspergillus species	11 (2.3)	0 (0)	11 (2.7)
Other yeast	9 (1.9)	0 (0)	9 (2.2)
Other fungi	6 (1.3)	0 (0)	6 (1.5)

Note: Data are number or percentage (in parentheses) of hospitalizations within total or time period group.

*Early period defined as occurring within 6 months post-transplantation.

†Late period defined as occurring after 6 months post-transplantation.

were split relatively equally among the 352 identified bacteria, with *E. coli*, *Enterococcus* species, *Klebsiella* species, and coagulase-negative staphylococci most commonly isolated. We identified four episodes of MRSA among the 21 *S. aureus* isolated, and four vancomycin-resistant enterococci among the 45 *Enterococcus* species isolated, all of which were determined to be *E. faecium*. Among *Enterobacteriaceae* species, 26 isolates (19%) were determined to be resistant to third-generation cephalosporins. We also identified four cases of carbapenem resistance, among them, three isolates of *P. aeruginosa* and one *E. coli*. In total, 90 infectious episodes were caused by a multidrug-resistant organism. The most common viral pathogen was CMV, accounting for over half of the 82 viral pathogens identified. Twenty-two of the 53 episodes of CMV infection occurred in recipients at high risk of CMV infection (donor-positive, recipient-negative serology), with six patients actively receiving antiviral prophylaxis at the time of infection. We also identified three cases of ganciclovir-resistant CMV. Among the 41 fungal pathogens identified, the most commonly isolated were *C. albicans* and *Aspergillus* species, with all of the *Aspergillus* infections being diagnosed in thoracic recipients. Patients admitted in the late period were diagnosed with a greater proportion of Gram-negative bacterial and fungal infections compared to those in the early period.

Thirty-two patients died in-hospital; however, the mortality rate did not differ significantly between those admitted with early compared to late infections (6.5% and 5.1%, respectively). Pathogens were identified in 22 (69%) of the 32 deaths, 14 of 22 (64%) being polymicrobial, and 12 of 22 (55%) considered to be multidrug resistant. Additionally, 26 of 32 (81%) patients had

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received antibiotic therapy within 30 days prior to admission. Median hospital length of stay was 5.5 days, and 23% of patients required rehospitalization within 30 days of their infectious complication visit; however, these did not differ significantly between patients admitted during the early and late periods.

Discussion

To our knowledge, this is the largest single-center study containing a detailed description of severe infections leading to hospitalization in a prevalent cohort of solid-organ transplant recipients. The data presented are important not only for the clinical, microbiological, and epidemiological description that they provide, but also summarize the burden of infections in this population. We observed a rate of 0.43 hospitalizations per 1000 transplant-days among those admitted for an infectious complication, accounting for approximately 43% of all admissions, exceeding cardiovascular and allograft rejection-related admissions combined. This rate is likely a conservative estimate as our institution has a relatively large catchment area, and some patients may have been admitted to their local hospital. This is especially true for our lung recipients (including a substantial number of out-of-province residents) who had the highest rates of hospitalization for infectious complications. Previous reports confirm this shift in burden from graft failure and cardiovascular disease to infectious disease as a primary cause of hospitalization as well as death during the first year post-transplantation [18–20]. The increase in the burden of infectious complications may be related to the concurrent use of more potent immunosuppressive agents early post-transplantation along with more aggressive maintenance immunosuppressive strategies to prevent acute graft dysfunction [21–23]. With a median time from transplantation of 4.2 years, our data describes the clinical burden of infectious complications not only during the early post-transplant period as previously reported, but also long afterward [20,24,25].

There is a limited published literature describing the contribution of infection to hospitalization post-transplantation [9–14,26]. Similar findings were reported in a cohort of renal transplant recipients from a hospital in Mexico, with an incidence rate of 0.46 episodes per 1000 transplant-days [26]. A chart review of liver and renal SOT visits to an emergency department reported a slightly higher rate (0.5 per 1000 transplant-days), although they also reported a higher overall hospitalization rate [10]. They also reported infection to be the most common cause of hospitalization, contributing to about 35% of all admissions [10]. A descriptive analysis of liver recipient visits to an emergency department reported a total hospitalization rate of 0.75 per 1000 transplant-days, with an infectious diagnosis (including fever of unknown origin) in 38% of patient visits [13]. Apart from the data presented in this study, one of the few other studies to include patients from across all solid-organ transplants is the prospective RESITRA cohort, which reported that late infections occurred at a rate of 0.4 per 1000 transplant-days, ranging from 0.3 per 1000 days in kidney to 1.4 per 1000 days in lung recipients [9]. Lastly, a review of infections up to 3 years post-kidney transplantation using the United States Renal Data System (USRDS) and Medicare claims documented an infectious discharge diagnosis rate of 0.69 per 1000 transplant-days [14]. This higher rate may be a result of a higher overall incidence of infection in the early post-transplant period, along with a population that included both ambulatory and hospitalized patients. In contrast to these studies, our data included patients with infections severe enough to warrant hospitalization, with many well beyond the first 3 years post-transplantation.

The most frequent hospitalizations were attributable to respiratory, sepsis or bacteremia, liver and biliary, urinary tract, and CMV infections, a finding similar to that of the USRDS Medicare study [14]. We reported that the median time post-transplantation varied by infectious syndrome, but overall, we found the majority of patients were admitted well beyond the first year of transplantation. This may be a result of the use of antimicrobial prophylaxis targeted against post-transplant surgical infections and other infections expected in the early period, including oral/esophageal candidiasis, pneumocystis pneumonia, CMV, and herpes infections. We reported mainly late-onset CMV infection (including several cases of tissue-invasive disease), perhaps a result of our institution's hybrid approach with antiviral prophylaxis in the early post-transplant period followed by surveillance monitoring until one year post-transplantation. This observation is similar to two other reports [27,28] that antiviral prophylaxis has minimized the burden of CMV in the early period, but has pushed its occurrence beyond prophylaxis cessation. Strategies to prevent late-onset CMV, including prolongation of prophylaxis and preemptive therapy after prophylaxis cessation, have been suggested but have yet to be fully adopted in clinical practice [29]. Alternatively, a preemptive approach has been associated with lower rates of late CMV infection, more selective use of antivirals and decreased drug costs, along with reduced risks of drug-related toxicities, although one concern is that

preemptive therapy may not prevent the indirect effects of CMV infection, including effects on graft survival [29].

We also reported that patients admitted in the late period were diagnosed with a greater proportion of fungal and Gram-negative bacterial infections compared to those in the early period, with all *Aspergillus* and *Pseudomonas* species being isolated in the late period. The use of prophylaxis and preemptive strategies has decreased the incidence and likely pushed the onset of invasive aspergillosis well into the late period, with a previously reported median time to onset in lung transplant recipients at 1.4 years [3,30]. The isolation of *Pseudomonas* species only in the late period is in contrast to previous studies, which showed a similar proportion of nonfermenting Gram-negative bacilli isolated from early compared to late infections [9,31]. In lung transplant recipients, especially those diagnosed with cystic fibrosis, the use of a variety of preventative and treatment strategies, including combination and inhaled antibiotics, may have played a role in reducing the burden in the early period [32]. Bacterial pathogens were responsible for approximately 50% of isolates reported for the late period in the RESITRA study, compared to our reported 75%; furthermore, we were unable to identify or isolate a pathogen in 45% of the infectious cases during the late period [9]. This, along with the substantial proportion of opportunistic microorganisms, poses a clinical problem when attempting to initiate empiric antimicrobials and only adds to the complexity and risk of serious infections.

Multidrug-resistant organisms were isolated in about 27% of episodes with an identified microbiological etiology, lower than that reported in a cohort of lung transplant recipients, where bacteria demonstrating multidrug resistance were found to be responsible for 48% of bloodstream infections [3]. We also reported third-generation cephalosporin resistance among 19% of all *Enterobacteriaceae* species, and methicillin resistance among 19% of *S. aureus* species, rates similar to those found in a study of bloodstream infections among patients in the RESITRA cohort [33]. In the aforementioned cohort, investigators found increased mortality among those infected with multidrug-resistant nonfermentative bacilli [33]. This was also evident in our study, with multidrug-resistant infections occurring in 93% of identified pathogens among patients who died in-hospital. We previously demonstrated that approximately one-quarter of patients receiving inadequate empiric antimicrobial therapy did not survive their hospital stay, and this was especially problematic in the context of polymicrobial and multidrug-resistant isolates [2]. It may also be more difficult to diagnose infection in transplant recipients versus nonimmunosuppressed individuals, as signs and symptoms of infection, such as fever, can often be muted [1]. We reported that only 53% of those diagnosed with an infection actually presented with a febrile episode, similar to Savitsky *et al.* [13] who reported that 49% of patients with serious infections were febrile at the time of their initial evaluation. Although the proportion of patients presenting without fever may be related to the underlying infectious syndrome, we also found that those prescribed mycophenolic acid or azathioprine was more likely to have a blunted febrile response. This may not be surprising given the known myelosuppressive effect of these drugs and is similar to a previous finding where patients receiving mycophenolate or azathioprine had significantly lower maximum temperatures and leukocyte counts, while corticosteroids appeared to have little effect on the systemic inflammatory response [34]. Furthermore, fever may be a marker of noninfectious processes such as allograft rejection. With a large proportion of our patients receiving induction immunosuppression with antithymocyte globulin, and over 10% receiving treatment for clinical or biopsy-proven rejection within six months of admission, our current-era patients may be at higher risk of infections in the late period post-transplantation. These findings underscore the need for careful evaluation of infection in this population. Despite limited literature describing its application in medicine, the use of data mining and machine learning techniques for analyzing longitudinal health data can potentially identify patterns and provide an alternate approach to generating clinically relevant knowledge that can inform patient-specific clinical decision making [35]. Such techniques could possibly incorporate reports of antibiotic susceptibility patterns for commonly encountered infectious syndromes and capture local temporal pattern changes that could help in the timing of the initiation of empiric therapy. Such information may help clinicians develop more rational prescribing practices that may avoid inadequate antibiotic treatment in the most vulnerable hospitalized patients [2].

Study limitations

As this study utilized retrospectively collected data, there is a possibility of recall bias when data were collected from the respective data sources. We attempted to overcome these biases through various efforts. Study inclusion criteria were clearly stated and thoroughly observed. A standardized data abstraction form was

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used for all data entry, and a consistent protocol was followed for missing or contradictory data. As previously alluded to, our institution's patients come from a large geographic area and as a result, not all post-transplant hospitalizations may have been captured in this study. This may have resulted in a more conservative estimate documented in this study, although it is likely that we have captured the most severe infections as these patients would most probably be transferred to our institution. Furthermore, use of a control group may have been informative and provided further comparisons between SOT recipients and the general population for more common infectious complications. Finally, given that this study was conducted in a single center using a prevalent cohort of SOT recipients, the results reported are reflective of institutional-specific practices and standards of care, which may differ from other centers. The setting of this study may have resulted in a cohort of more severely ill SOT recipients, and although it may limit its external validity to other acute care centers, it does provide a more pragmatic and real-world experience.

The findings in this cohort study suggest that infectious-related complications continue to pose a high clinical burden on our acute care center, with the majority of cases occurring in the late transplant period. Given the proportion of episodes where patients may not present with classical symptoms and the inability to identify causative pathogens, clinicians are faced with the difficult task of prescribing adequate antimicrobial therapy. This task is made further demanding given the proportion of polymicrobial and multidrug-resistant organisms identified. Careful evaluation of infection in this population is needed, with empiric treatment strategies that consider the timing post-transplantation along with the associated microbiological etiology.

Authorship

BH: participated in design and performance of the research, statistical/data analysis and interpretation, and writing and reviewing of the manuscript for final publication. SH: participated in design of the research, interpretation of the results, critical revisions of the paper draft, and critically reviewing of the manuscript for final publication. PG and EAP: participated in interpretation of the results and critically reviewing of the manuscript for final publication.

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Conflict of interest

The authors declared that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Microbiological etiology of pathogens identified or isolated among patients with respiratory, sepsis, liver and biliary tract, genitourinary, and intra-abdominal infections.

REFERENCES

1. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007; **357**: 2601.
2. Hamandi B, Holbrook AM, Humar A, *et al.* Delay of adequate empiric antibiotic therapy is associated with increased mortality among solid-organ transplant patients. *Am J Transplant* 2009; **9**: 1657.
3. Husain S, Chan KM, Palmer SM, *et al.* Bacteremia in lung transplant recipients in the current era. *Am J Transplant* 2006; **6**: 3000.
4. Lupei MI, Mann HJ, Beilman GJ, Oancea C, Chipman JG. Inadequate antibiotic therapy in solid organ transplant recipients is associated with a higher mortality rate. *Surg Infect* 2010; **11**: 33.
5. Patel R, Paya CV. Infections in solid-organ transplant recipients. *Clin Microbiol Rev* 1997; **10**: 86.
6. Sanromán Budiño B, Vázquez Martul E, Pértega Díaz S, Veiga Barreiro A, Carro Rey E, Mosquera Reboredo J. Autopsy-determined causes of death in solid organ transplant recipients. *Transplant Proc* 2004; **36**: 787.
7. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998; **338**: 1741.
8. Rubin RH. *Infection in the Organ Transplant Recipient: In Rubin RH Young LS (eds): Clinical Approach to Infection in the Compromised Host*. New York: Plenum Medical Book Company, 1994.
9. San Juan R, Aguado JM, Lumbreras C, *et al.* Incidence, clinical characteristics and risk factors of late infection in solid

organ transplant recipients: data from the RESITRA Study Group. *Am J Transplant* 2007; **7**: 964.
10. Unterman S, Zimmerman M, Tyo C, *et al.* A descriptive analysis of 1251 solid organ transplant visits to the emergency department. *West J Emerg Med* 2009; **10**: 48.
11. Vera A, Contreras F, Guevara F. Incidence and risk factors for infections after liver transplant: single-center experience at the University Hospital Fundación Santa Fe De Bogotá, Colombia. *Transpl Infect Dis* 2011; **13**: 608.
12. Cervera C, Fernández-Ruiz M, Valledor A, *et al.* Epidemiology and risk factors for late infection in solid organ transplant recipients. *Transpl Infect Dis* 2011; **13**: 598.
13. Savitsky EA, Votey SR, Mebust DP, Schwartz E, Uner AB, McCain S. A descriptive analysis of 290 liver transplant patient visits to an emergency department. *Acad Emerg Med* 2000; **7**: 898.
14. 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.
15. Humar A, Michaels M. American society of transplantation recommendations for screening, monitoring and reporting of infectious complications in immunosuppression trials in recipients of organ transplantation. *Am J Transplant* 2006; **6**: 262.
16. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC Definitions for Nosocomial Infections, P. A1-A20. 1996.
17. Magiorakos A-, Srinivasan A, Carey RB, *et al.* Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**: 268.
18. Dharnidharka VR, Stablein DM, Harmon WE. Post-transplant infections now exceed acute rejection as cause for hospitalization: a report of the NAPRTCS1. *Am J Transplant* 2004; **4**: 384.
19. Parasuraman R, Abouljoud M, Jacobsen G, Reddy G, Koffron A, Venkat KK. Increasing trend in infection-related death-censored graft failure in renal transplantation. *Transplantation* 2011; **91**: 94.
20. Kosmadakis G, Daikos GL, Pavlopoulou ID, *et al.* Infectious complications in the first year post renal transplantation. *Transplant Proc* 2013; **45**: 1579.
21. Åsberg A, Jardine AG, Bignamini AA, *et al.* Effects of the intensity of immunosuppressive therapy on outcome of treatment for CMV disease in organ transplant recipients. *Am J Transplant* 2010; **10**: 1881.
22. Brennan DC, Agha I, Bohl DL, *et al.* Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant* 2005; **5**: 582.
23. Dharnidharka VR, Stevens G. Risk for post-transplant lymphoproliferative disorder after polyclonal antibody induction in kidney transplantation. *Pediatr Transplant* 2005; **9**: 622.
24. Alangaden GJ, Thyagarajan R, Gruber SA, *et al.* Infectious complications after kidney transplantation: current epidemiology and associated risk factors. *Clin Transplant* 2006; **20**: 401.
25. Sacristán PG, Marfil AP, Moratalla JO, *et al.* Predictive factors of infection in the first year after kidney transplantation. *Transpl Proc* 2013; **45**: 3620.
26. Valdez-Ortiz R, Sifuentes-Osornio J, Morales-Buenrostro LE, *et al.* Risk factors for infections requiring hospitalization in renal transplant recipients: a cohort study. *Int J Infect Dis* 2011; **15**: 188.
27. Paya C, Humar A, Dominguez E, *et al.* Efficacy and safety of valganciclovir versus oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4**: 611.
28. Murray BM, Subramaniam S. Late cytomegalovirus infection after oral ganciclovir prophylaxis in renal transplant recipients. *Transpl Infect Dis* 2004; **6**: 3.
29. Kotton CN, Kumar D, Caliendo AM, *et al.* Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2013; **96**: 333.
30. Neofytos D, Fishman JA, Horn D, *et al.* Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis* 2010; **12**: 220.
31. Parada MT, Alba A, Sepulveda C. Early and late infections in lung transplantation patients. *Transplant Proc* 2010; **42**: 333.
32. Gilljam M, Scherstén H, Silverborn M, Jönsson B, Hollsing AE. Lung transplantation in patients with cystic fibrosis and mycobacterium abscessus infection. *J Cyst Fibros* 2010; **9**: 272.
33. Moreno A, Cervera C, Gavaldá J, *et al.* Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. *Am J Transplant* 2007; **7**: 2579.
34. Sawyer RG, Crabtree TD, Gleason TG, Antevil JL, Pruett TL. Impact of solid organ transplantation and immunosuppression on fever, leukocytosis, and physiologic response during bacterial and fungal infections. *Clin Transplant* 1999; **13**: 260.
35. Wojciuk B, Myślak M, Pabisiak K, Ciechanowski K, Giedrys-Kalemba S. Epidemiology of infections in kidney transplant recipients – data miner's approach. *Transpl Int* 2015; **28**: 729.