Incidence of infectious complications and their risk factors in the first year after renal transplantation

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Abstract

Introduction: Infectious complications significantly increase morbidity and mortality after renal transplantation. The immunosuppression used is the main risk factor and relates directly to the incidence and severity of infectious events. **Methods:** This is a retrospective cohort study, which assessed the incidence of infections and their risk factors among 1,676 kidney transplant recipients during the first year of follow-up. **Results:** Infectious events were observed in 821 (49%) patients. The mean number of infectious episodes among patients with at least one episode was 2.3 (1 - 12). The most prevalent infectious complications were as follows: urinary tract infection (31.3%); cytomegalovirus infection (12%); surgical wound infection (10.3%); herpes virus infection (9.1%); pulmonary infection (5.2%); and bloodstream infection (4.3%). Cold ischemia time and the use of deceased donor grafts were important risk factors for infectious episodes. **Conclusions:** Infections are highly prevalent in the first year following transplantation. The main infectious complication was urinary tract infection.

Keywords: kidney transplantation, infection, cohort studies, logistic models.
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Introduction

Infectious complications significantly increase morbidity and mortality after renal transplantation.[1] Several risk factors related to infectious complications are present after renal transplantation, mainly the need for permanent immunosuppression. Immunosuppression and its modulation are directly related to the incidence and severity of infectious events, mainly in the initial phases of transplantation, when the risk for rejection is also higher.[1-3] Approximately 80% of all renal transplant recipients have an infectious complication in the first year following transplantation.4 Other conditions influence less uniformly the risk for the occurrence of infections after transplantation and are largely dependent on the socioeconomic and hygiene-sanitary status of the population studied. Population studies have shown that the incidence, morbidity, mortality, spectrum, chronological distribution of infectious events and their risk factors have significant differences in the different geographical regions of the world, and are modified over the years. On the other hand, advances in diagnosis and treatment, in addition to better professional qualification, have determined a progressive reduction in the prevalence of infectious episodes in recent years.[1,4-6]

This study was carried out aiming at establishing the incidence of infectious complications and their risk factors after renal transplantation performed at our institution, and at comparing them with the results obtained at other centers.

Methods

This study assessed 1676 medical records of recipients of renal transplantations performed from January 1998 to

March 2004, at the Hospital do Rim e Hipertensão or at the Hospital São Paulo, both affiliated to the Universidade Federal de São Paulo (UNIFESP). The research project had been previously approved by the Committee on Ethics in Research of UNIFESP (Protocol 0666/2005).

Patients

Patients of both sexes, older than 18 years, were studied. The presence, number, and types of all infectious events observed in the first year following transplantation were analyzed. The infectious events were identified through the observation of clinical signs and symptoms and also through complementary laboratory assessment indicated by the assisting medical team. Urinary tract infection (UTI) was defined as the presence of dysuria and/or pollakiuria, accompanied by fever and positive urine culture. Cytomegalovirus infection (CMV) was defined as the presence of fever, abdominal pain, and myalgia, accompanied or not by anemia, leukopenia with or without lymphopenia, confirmed by positive antigenemia in circulating blood, or the histopathologic evidence of the characteristic cytomegalic inclusions in patients undergoing biopsy of the gastrointestinal tract mucosa or of pulmonary tissue. All patients receiving induction immunosuppression with monoclonal or polyclonal antibodies and those considered to be at high risk for primary CMV, because of being CMV-seronegative recipients of grafts originating from seropositive donors, received prophylactic treatment with ganciclovir at the dose of 10 mg/kg/day for 14 days. The presence of purulent secretion at the site of the transplant surgical incision, accompanied or not by fever and positive culture of the secretion, was defined as surgical wound infection. The diagnosis of herpetic infection was based only on clinical criteria. Labial herpes simplex infection was defined as the presence of small vesicles or painful ulcers, of hyperemic ulcer floor, observed in the cutaneous-mucosal junction of one or both lips. Genital herpes infection was defined as the presence of extensive vesicular, vesico-pustular or vesico-ulcerated lesions in the genital region. Herpes zoster infection was defined as the presence of vesicular, vesico-pustular or vesico-ulcerated lesions, of hyperemic ulcer floor, in body regions delimited by specific dermatomes. Pulmonary infections were defined in the presence of respiratory insufficiency of any severity, accompanied by fever and compatible radiologic exam, with or without positive culture of bronchial aspirate. Bloodstream infection was defined as the presence of fever with positive culture of peripheral blood, with no other clinical manifestations.

Study design and data collection

This is a retrospective cohort study that established the incidence of infectious episodes in renal transplanted patients in the first year following transplantation. Patients were classified according to the infection location in the different body systems, and the related risk factors were identified. In addition, the patient and graft survivals by the end of the first year of transplantation were assessed.

The following variables were analyzed: recipient's age and sex; dialysis time; HLA compatibility; type of donor; previous renal transplantation; occurrence of blood transfusions before transplantation; cold ischemia time for grafts of deceased donors; immunosuppression type; etiology of chronic kidney failure; serology for CMV, hepatitis B, and hepatitis C prior to transplantation; and occurrence and type of the infectious event observed after transplantation. The HLA compatibility with the grafts obtained from living donors was defined as identical when the recipient had HLA A, B, and DR haplotypes compatible with those of the donor; as haploidentical when up to two of those haplotypes were compatible; and distinct when the donor shared none of those HLA haplotypes with the receptor.

Statistical analysis

Data were presented by using absolute and percentage frequencies, means, standard deviations, and minimum and maximum values when appropriate. The chi-square test was used for comparing categorical variables. The Student t test was used for comparing continuous variables. The Kaplan-Meier method was used for univariate analyses of the patient and graft survivals. The log-rank method was used for comparing the survivals of patients with and without infectious episodes. Simple and multiple logistic regression analyses were performed to establish the contributions of the following variables to the risk of infectious episodes after transplantation: recipient's age and sex; dialysis time; HLA compatibility; type of donor; previous renal transplantation; occurrence of blood transfusions prior to transplantation; cold ischemia time for the grafts from deceased donors; type of immunosuppression; etiology of chronic kidney failure; serology for CMV, hepatitis B, and hepatitis C prior to transplantation. Only the variables with a statistically significant association in the

simple logistic regression model were included in the multiple logistic regression model. A p value < 0.05 was considered statistically significant. All statistical analyses were performed by using the SPPS program (version 12.0, SPSS Inc., Chicago, IL, USA, 2003).

Results

Patients

The demographic characteristics of the 1676 patients included in the study according to the presence of infectious episodes are shown in Table 1. Patients with infectious episodes as compared with those with no infectious episodes were as follows: older (41.4 ± 12.2 vs. 37.7 ± 10.4; p < 0.05); predominantly males (55.9% vs. 54.2%; p < 0.05); had a longer dialysis time (47.2 ± 47.2 months vs. 32.5 ± 36.7 months; p < 0.05); had less HLA compatibility with the donor (identical, 12.5%; haploidentical, 31.0%; and distinct, 13.2% vs. identical, 28.8%; haploidentical, 36.7%; and distinct, 15.3%; p < 0.05); received more grafts from deceased donors (41.1% vs. 17.5%; p < 0.05); underwent more retransplantation (2.1% vs. 1.7%; p < 0.05) and more blood transfusion prior to transplantation (51% vs. 49%; p < 0.05); used more calcineurin inhibitors (cyclosporin/tacrolimus, 66.3/28.2% vs. 34.2%/27.8%; p < 0.005), azathioprine (62.1% vs. 71.3%; p < 0.05), methylprednisolone (29.2% vs. 19.1%; p < 0.05), and induction immunosuppression with monoclonal and polyclonal antibodies (9.0%/7.1% vs. 2.6%/1.4%; p < 0.05). No significant difference was observed regarding the cold ischemia time for grafts obtained from deceased donors, the use of prednisone, and the etiology of chronic kidney failure between the groups analyzed.

Incidence of infectious episodes

The infectious episodes had an incidence of 49% (821 patients), and were more frequent in the first months following transplantation. The number of infectious episodes was 1882, of which, 588 (31.3%) occurred in the first month after transplantation, 452 (24%) in the second month, 230 (12.2%) in the third month, and 612 (32.5%) after the third month (Figure 1). The mean number of infectious episodes among patients who had at least one infectious episode was 2.3 episodes per patient, ranging from one to 12 during the follow-up period. The number of deaths during the follow-up period was 64 (7.9%) in the group with infection and 16 (1.9%) in the group without infection (p > 0.001).

Types and etiology of the infectious complications

The distribution of the 1882 infectious episodes according to types is as follows: UTI, 588 (31.3%); CMV infections, 225 (12%); surgical wound infections, 194 (10.3%); herpetic infections, 172 (9.1%); pulmonary infections, 99 (5.2%); bloodstream infections, 81 (4.3%); infections at other sites, 523 (27.8%).

Of the 588 episodes of UTI, etiology was attributed to Escherichia coli in 217 (37%), to Enterobacter sp in 112 (19%), to Klebsiella pnemumoniae in 65 (11%), to Pseudomonas aeruginosa in 35 (6%), and to other agents in 159 (27%). Of the 225 episodes of CMV infection, 178 (79%) had positive antigenemia only in peripheral blood samples, 37 (16%) also had cytomegalic inclusions in biopsy of the gastrointestinal tract, 8 (4%) had cytomegalic inclusions in pulmonary biopsy, and 2 (1%) had them in samples obtained at other sites. The 194 episodes of surgical wound infection were attributed to the following agents: coagulase-negative Staphylococcus, 47 (24%); Staphylococcus aureus, 23 (12%); Enterobacter sp, 23 (12%); Enterococcus, 17 (9%); and others, 47 (24%). The 172 episodes of herpetic infections were attributed to the following agents: genital herpes simplex, 43 (25%) patients; labial herpes simplex, 42 (24%); herpes zoster on the thoracic region, 48 (29%); and herpes zoster on other locations, 23 (13%). Varicella was the clinical presentation of 16 (9%) patients with episodes of herpetic infections. The 99 episodes of pulmonary infection included six (6%) infections by coagulase-negative Staphylococcus, two (2%) by Pseudomonas aeruginosa, two (2%) by Pneumocisti carinii, and 30 (30.3%) by others. The etiology of 59 episodes of pulmonary infections (59.9%) has not been established. The etiology of 81 episodes of bloodstream infection was attributed to Escherichia coli, coagulase-negative Staphylococcus, Enterobacter sp, Acinetobacter baumannii, and Staphylococcus aureus in 15 (19%), 10 (12%), 8 (10%), 7 (9%), and 7

Figure 1. Number of infectious episodes according to time elapsed after transplantation.

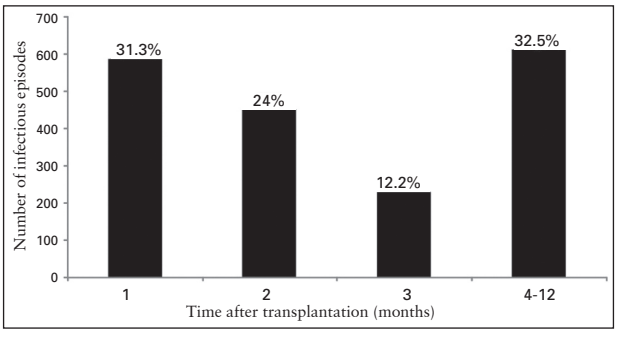


Table 1 Demographic characteristics of patients with and without infectious episodes following renal transplantation

	With infection	No infection	p
Total of patients	821 (49%)	855 (51%)	< 0.001
Age (years)	41.4 ± 12.2	37.7 ± 10.4	< 0.001
Sex			
Male	459 (55.9%)	541 (63.3%)	< 0.002
Female	362 (44.1%)	314 (36.7%)	< 0.002
Dialysis time (months)	47.2 ± 47.2	32.5 ± 36.7	< 0.001
HLA compatibility			
Identical	103 (12.5%)	246 (28.8%)	< 0.001
Haploidentical	254 (31.0%)	314 (36.7%)	< 0.001
Distinct	109 (13.2%)	131 (15.3%)	< 0.001
Deceased donor	338 (41.2%)	149 (17.5%)	< 0.001
Retransplantation	17 (2.1%)	15 (1.7%)	< 0.001
Blood transfusions prior to transplantation	611 (51%)	586 (49%)	0.008
CIT/DD (minutes)	1276 (± 488.6)	1217 (± 470.6)	NS
Immunosuppression			
Calcineurin inhibitors			
Cyclosporin	545 (66.3%)	241 (28.2%)	0.016
Tacrolimus	281 (34.2%)	238 (27.8%)	0.005
Adjuvant drug			
Azathioprine	510 (62.1%)	610 (71.3%)	< 0.001
MMF	301 (36.6%)	170 (19.9%)	< 0.001
Prednisone	815 (99.2%)	847 (99.1%)	NS
Methylprednisolone	240 (29.2%)	163 (19.1%)	< 0.001
Sirolimus	42 (5.1%)	81 (9.4%)	0.001
Monoclonal and polyclonal antibodies			
Anti-CD3	74 (9.0%)	22 (2.6%)	< 0.001
Antithymocyte globulin	59 (7.1%)	12 (1.4%)	< 0.001
Etiology of CRF			
SAH	164 (20.0%)	162 (19.0%)	NS
Diabetes	49 (5.9%)	38 (4.5%)	NS
GMN	155 (18.8%)	183 (21.4%)	NS
Polycystic kidneys	48 (5.8%)	35 (4.1%)	NS
Lupus	32 (3.9%)	24 (2.8%)	NS
Undetermined	317 (38.6%)	363 (42.4%)	NS
Others	56 (6.8%)	50 (5.8%)	NS

HLA compatibility: identical - A, B, and DR HLA haplotypes of the donor compatible with those of the recipient; haploidentical - compatibility in up to two of those haplotypes; distinct - no compatibility among those haplotypes. CIT/DD = cold ischemia time/deceased donors; MMF = mycophenolate mofetil; SAH = systemic arterial hypertension; GMN = glomerulonephrites; NS = nonsignificant.

(9%) of those episodes, respectively. Other infectious agents were responsible for the remaining 33 (41%) episodes. The distributions of the infectious episodes according to the different types identified and the etiological agents identified are shown in Figure 2.

Survival analyses

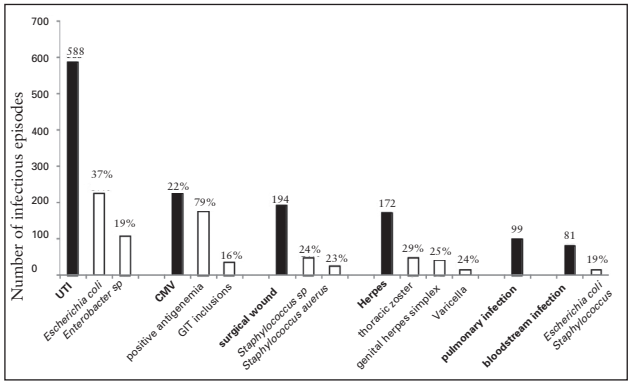
The patient and graft survival curves, including all losses, are shown in Figure 3. The patient's survival rates 6 and 12 months after transplantation were significantly lower among patients with infectious episodes than among those with no infection: 94.3% and 92.3% vs. 98.1% and 98.1%, respectively ($p < 0.05$). Comparing patients with and without infectious episodes, the graft survival analysis showed survival rates 6 and 12 months after transplantation of 94.5% and 93.2% vs. 97.6% and 97.5%, respectively ($p < 0.05$).

Risk factors for infection

Simple logistic regression analysis has identified the following variables as risk factors for infectious episodes: female sex (OR 1.32, CI 1.038 – 1.69); age (1.02, CI 1.01 – 1.03); compatibility with haploidentical living donor (OR 1.93, CI 1.45 – 2.56) and distinct living donor (OR 1.98, CI 1.41 – 2.80); retransplantation (OR 2.75, CI 1.26 – 5.99); transplantation from deceased donor (OR 5.41, CI 4.01 – 7.31); blood transfusion prior to transplantation (OR 1.34, CI 1.08 – 1.67); positive serology for hepatitis C prior to transplantation (OR 1.96, CI 1.42 – 2.71); dialysis time (OR 1.06, CI 1.04 – 1.08); cold ischemia time (30-minute increments) (OR 1.02, CI 1.02 – 1.03); use of cyclosporin (OR 0.77, CI 0.63 – 0.95), tacrolimus (OR 1.34, CI 1.09 – 1.66); azathioprine (OR 0.65, CI 0.53 – 0.80), mycophenolate mofetil (OR 2.33, CI 1.87 – 2.90); methylprednisolone (OR 1.75, CI 1.39 – 2.20); sirolimus (OR 0.51, CI 0.35 – 0.75); and monoclonal antibodies (OR 3.75, CI 2.30 – 6.09) and polyclonal antibodies (OR 5.43, CI 2.90 – 10.19).

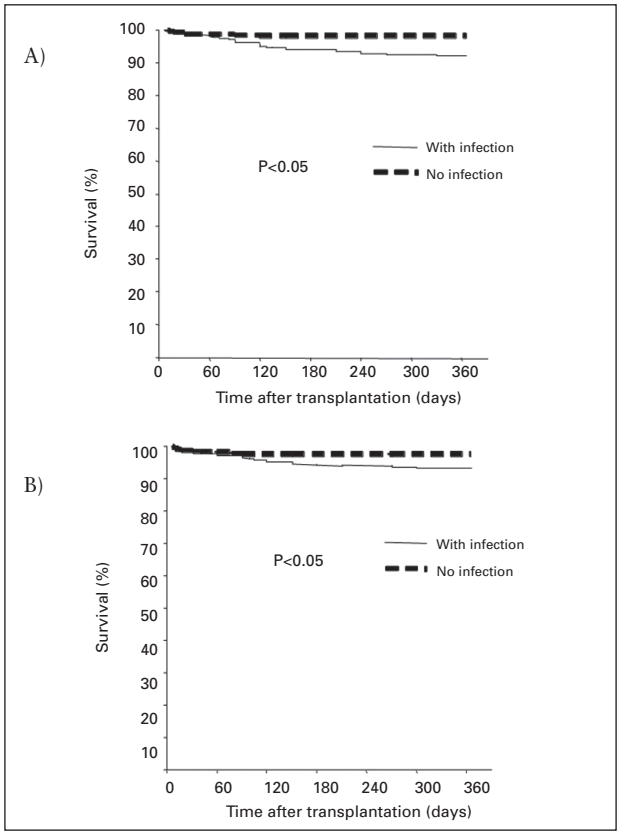
Multiple logistic regression analysis is shown in Table 2. The variables that remained as significant risk factors associated with infectious episodes in that analysis are as follows: female sex (OR 1.28, CI 1.04 – 1.59); age (OR 1.02, CI 1.01 – 1.03); haploidentical HLA compatibility (OR 1.71, CI 1.27 – 2.32); transplantation from deceased donor (OR 3.29, CI 2.37 – 4.58); use of immunosuppression with mycophenolate mofetil (OR 1.46, CI 1.14 – 1.86); use of immunosuppression with anti-CD3 induction therapy (OR 2.38, CI 1.40 – 4.04); and use of immunosuppression with antithymocyte globulin induction therapy (OR 2.90, CI 1.51 – 5.57).

Figure 2. Absolute frequencies of the infectious episodes identified in the first year after renal transplantation and percentage frequencies of the corresponding etiological agents identified. UTI, urinary tract infection; CMV, cytomegalovirus; GIT, gastrointestinal tract.



ITU, infecção do trato urinário; CMV, citomegalovírus; TGI, trato gastrointestinal.

Figure 3. Patient (A) and graft (B) survival curves, including all losses, of renal transplant recipients with and without infectious episodes identified in the first year of follow-up.



Discussion

This study assesses the incidence of infectious episodes among a significant number of renal transplant recipients followed up at the same institution. The prevalence of infections in transplanted patients varies in the different regions and countries. Many factors can interact modifying the risk for infections, such as the immunosuppression profile used, the post-operative care, and the profile of epidemiological exposures to the different infectious-contagious diseases. In addition, the unfavorable socioeconomic profile contributes to increase the incidence of those complications in developing countries.[1,5,7] Although the incidence of infectious episodes varies significantly in different studies, the incidence of infection is usually higher in the first months following transplantation and is directly related to the immunosuppression dose used. In the first months following renal transplantation, hospital infections predominate, mainly those located in the urinary tract and surgical wound. Between the second and sixth months, viral and fungal opportunistic infections predominate. After the sixth month, community infections prevail.[1-5]

In our case series, the incidence of infectious episodes during the first year following transplantation was 49%. Comparatively, this result indicates that the incidence of infectious episodes in renal transplant recipients among us is equivalent to that observed in other countries of different regions in the world. In 2006, Alangaden *et al.*[8] studied 127 renal transplanted patients at a North-American center and reported infectious complications in 51% of those recipients. Similarly, in 2007, Pourmand *et al.*[9] reported a 54.2% frequency of infectious episodes in 172 patients followed up at an Iranian center.

Of all different conditions studied significantly associated with the risk of developing infectious episodes after renal transplantation, those related to the graft cold ischemia time and to immunological factors stand out. In the logistic regression analysis, the variable most significantly associated with that risk was the use of deceased donors (OR 3.29, CI 2.37 – 4.58). Each 30-minute increment in the cold ischemia time of the graft obtained from a deceased donor also showed a significant and independent association with the risk of developing infectious episodes (OR 1.02, CI 1.02 – 1.03). Prolonged tissue ischemia is known to facilitate and amplify the exposure of class I and II MHC antigens of the transplanted organ to the recipient's immune system, favoring immune recognition and increasing the chances of triggering the rejection process.[10] The use of additional doses of immunosuppression for treating those rejections also increases the chances of infectious episodes, and this may justify the association between that variable and the risk for developing infectious episodes. In accordance with that supposition, the use of methylprednisolone has also been significantly associated with a higher risk for developing infectious episodes (OR 1.29, CI 1 – 1.68). The transplantation from a deceased donor has also been observed to have 5.4 times more chance to develop infection as compared with the transplantation from a living HLA-identical sibling donor. The significant association of that variable with the risk for developing infection may be

Table 2 Risk factors for the development of infection after transplantation – multiple logistic regression analysis

	Odds Ratio	CI 95%	p
Female sex	1.288	[1.043 - 1.592]	0.019
Age (years)	1.022	[1.013 - 1.032]	< 0.001
HLA compatibility			
Haploidentical	1.719	[1.271 - 2.324]	< 0.001
Distinct	1.442	[0.998 - 2.082]	0.051
Retransplantation	2.212	[0.987 - 4.956]	0.054
Deceased donor	3.299	[2.373 - 4.585]	< 0.001
Immunosuppression			
MMF	1.462	[1.143 - 1.869]	0.002
Methylprednisolone	1.299	[1.003 - 1.681]	0.047
Anti-CD3	2.380	[1.400 - 4.045]	0.001
Antithymocyte	2.907	[1.515 - 5.579]	0.001

justified by the longer cold ischemia time usually observed when renal transplantation is performed with that type of donor, thus, increasing the incidences of graft function delay and acute rejection.[2]

The UTI frequency was 31.3% of all infectious episodes identified, and the most frequently found etiological agents were Escherichia coli (37%), Enterobacter sp (19%), and Klebsiella sp (11%). Urinary tract infection is the most common infection among renal transplanted patients, with prevalence ranging from 35% to 80%, being mainly observed in the first three months following transplantation.[4] A prospective study carried out by Heilberg in Brazil in 2003 showed a 63% prevalence of UTI in renal transplanted children, the most frequently found etiological agent being Escherichia coli (57%).11 In Spain, a prospective analysis involving 159 recipients with a follow-up time of two years has shown a frequency of infections of 1.1 episode per patient, UTI accounting for 46.6% of the infectious episodes identified, and Escherichia coli being the most frequently found etiological agent.[12]

Only 12% of the infectious episodes were attributed to CMV. Cytomegalovirus infection is usually observed in 50% to 80% of the renal transplanted patients and usually occurs in the first six months following transplantation.[2] The serological conditions of donors and recipients regarding CMV are routinely assessed at the UNIFESP renal transplantation units, significantly contributing to the prevention and treatment of CMV infections. A study carried out in France by Giral *et al.*[13] in 2001 compared the incidence of CMV disease in a group of 319 renal transplanted patients who used azathioprine with that observed in another group of 126 patients who used mycophenolate mofetil. Those authors reported a similar result regarding the incidence of CMV in both groups studied (21.6% vs. 24.1%, respectively).[13] It is worth emphasizing that all patients of that case series received gancyclovir for at least 14 days with doses corrected according to the renal function.

Surgical wound infections corresponded to 10.3% of all infectious episodes analyzed. In 2006, Alangaden *et al*[8] reported a 7% incidence of infectious episodes in the surgical wound in a cohort of 127 renal transplanted patients. This result is also similar to that obtained in 2009 by a Spanish group reporting a 7.9% incidence of that same complication.[12]

Herpes virus infections, comprising both herpes simplex infections and severe clinical findings of herpes zoster, corresponded to 9.1% of all infectious episodes identified. Recent studies have shown that the incidence of herpes zoster may reach 0.5%, 1.9%, 5.6% and 11.2%, by the end of the sixth month, first year, second year, and forth year after renal transplantation, respectively.[14] A significant correlation between the type of immunosuppression used and variations in the incidence and severity of herpetic infections has also been shown in renal transplant recipients. In 2008, Gaber *et al.*[15] compared a group of 224 renal transplanted patients using sirolimus and tacrolimus with another group of 224 patients using sirolimus and cyclosporin, both on corticosteroids for 12 months. Those authors reported a higher incidence of herpes simplex infection among patients using sirolimus and tacrolimus as compared with that of the group using sirolimus and cyclosporin (4.5% and 0.4%, respectively; $p = 0.01$).

Respiratory tract infections corresponded to 8.9% of all infectious episodes identified. The option for the prophylactic use of antibiotics may justify the differences observed in the different studies regarding the incidence of respiratory tract infections, which has ranged from 6.3%8,9 to 2.2%16 at the end of the first year following transplantation.

It is worth emphasizing the significant reductions observed in both the patient and graft short-term survivals in recipients with infectious episodes, independently from the type and site of the infectious episodes and agents identified. The UTI in renal transplant recipients with urologic complications,[17] seropositivity for hepatitis B virus,[18] and herpes simplex infection[19] have not determined a significant reduction in long-term survival. Nevertheless, the influence of infectious episodes on the results of renal transplantation has not been systematically analyzed in recent studies.

In conclusion, this study established the incidence of infectious episodes in the first year following transplantation at a single center. The most prevalent infectious complications after renal transplantation among us are UTI, CMV, and surgical wound infection. Infections after renal transplantation cause significant morbidity and mortality, justifying measures directed at the identification of risk factors and early treatment. A prolonged cold ischemia time and renal transplants from deceased donors were important risk factors for infections following renal transplantation.

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