Infectious complications after kidney transplantation: a single-center experience


Abstract: Infectious complications after renal transplantation are associated with significant morbidity and mortality. The prevalence of infections in transplant recipients varies from country to country. This study sought to assess the overall incidence of post-transplant infectious complications at our research center in Iran, compared with other centers in the world. Between 2002 and 2004, 179 renal transplantsations were performed in our center. Of these, 142 were studied and followed for 1 year. Immunosuppressive regimens were cyclosporine, mycophenolate mofetil, and prednisolone. The overall incidence of infections was 54.2%. The most common sites of infections were the urinary tract (41.5%) and the respiratory tract (6.3%). The most frequent causes of infections were *Klebsiella* (24%) and cytomegalovirus (CMV) (17.6%). Wound infection occurred in 4.9% of the patients. Three (2.1%) patients developed hepatitis C and 2 (1.4%) had mycobacterial infections. There was no case of *Pneumocystis* pneumonia. Overall mortality was 7.7%. Infection-related mortality was 3.5%. In conclusion, this study identifies infections as the cause of morbidity and mortality in the post-transplant period. There was a low incidence of tuberculosis (<2% yearly) and a high incidence of CMV disease in our recipients.

Renal transplantation has become a well-established, definitive, highly successful therapy for chronic end-stage renal disease (ESRD) and is more widely accessible now than in previous decades. Infectious complications after renal transplantation are associated with significant morbidity and continue to be the most frequent cause of death in the early post-transplant period (1–4). Under standard immunosuppression, nearly 80% of all renal transplant recipients suffer at least 1 episode of infection during the first year after engraftment (5, 6). In developing countries, the morbidity, mortality, spectrum of infections, their chronological occurrence, and risk factors seem to be different from those in developed regions (7, 8). Because of the progress that has been made in the treatment of infections and the increasing expertise of the transplant community, death resulting from infections has decreased from 73% before 1976 to 20% between 1994 and 1996 (1, 3, 7). In the United States (1998), mortality rate due to infections was close to 0.3% in a year, or 20% of deaths in all transplant patients, and the Medicare spending during the first year after transplantation was about US $88,000 for each patient, and an estimated 20% of this was used for the diagnosis and treatment of infection (3, 7).

Owing to the differences in the fields of environmental, social, and financial facilities, between our country and developed regions, we assume that post-transplant infectious patterns and percentages differ from those countries. Therefore, we planned this study to assess the overall incidence of infectious complications in kidney transplantation recipients at our hospital and to evaluate the difference between our center in Iran and other centers.

Patients and methods

Patient population

From February 2002 to February 2004, 179 consecutive ESRD patients underwent renal transplantation at Sina Hospital. Of these, 142, who had attended follow-up visits
regularly, were assessed prospectively for a period of 1 year. Thirty-seven patients were lost to follow-up and were excluded from the study. Pre-transplantation data, including age, sex, donor type, and underlying causes of ESRD, as well as the postoperative data, regarding graft function (creatinine level), infectious episodes (type and time), episodes of acute rejection, dosage of immunosuppressive drugs, and graft and patient survival, were collected and recorded. Serological screening for cytomegalovirus (CMV), hepatitis B antigens and antibodies, human immunodeficiency virus (HIV) antibody, and hepatitis C antibody were performed for donors and recipients. Patients with a positive serological test for HIV were excluded from transplantation.

Immunosuppression and surgical procedure

All patients received prednisolone (1 mg/kg/day and tapered 5 mg weekly), cyclosporine A (5 mg/kg/day), and mycophenolate mofetil (2 g/day). Acute rejection was managed with antithymocyte globulin (ATG) or a pulse of methylprednisolone. Furthermore, in high-risk cases (second or third transplantation or positive panel-reactive antibodies [>25%]) and cadaveric renal allograft, ATG was prescribed as prophylaxis.

The kidney graft was placed retroperitoneally in the right or left iliac fossa. The ureter was anastomosed to the recipient’s bladder. Native kidneys of the recipients were left in situ and ureters were anastomosed to the graft and radioisotope scan, was done.

Prophylactic regimen

All donors and recipients were administered a single dose of an intravenous prophylactic antibiotic 1 h preoperatively (ceftriaxone 1 g). All transplanted patients received cefuroxime for 4 days during the hospital stay and trimethoprim-sulfamethoxazole (TMP-SMX) (1 double-strength tablet twice a day during hospitalization, and then 1 double-strength tablet once a day for 6 months postoperatively) as prophylaxis. No prophylactic agents were used for CMV and Mycobacterium tuberculosis (TB).

Postoperative care

During the hospital stay, clinical examinations and laboratory investigations (including complete blood count [CBC] with differentials, serum urea, creatinine, and electrolytes) were performed daily. Urinalysis and urine culture were performed twice per week. Furthermore, in case of the presence of signs and symptoms (such as fever, leukocytosis, urinary symptoms, respiratory symptoms, diarrhea, abdominal pain, tenderness of the graft, discharge from the wound or catheter site, rise in the creatinine level, or decrease in the consciousness level), 1 or more of the following investigations were performed, according to the clinical status: smear and cultures of blood, urine, throat, sputum, synovial fluid, cerebrospinal fluid (CSF), and bronchoalveolar lavage (BAL). Moreover, the following assays were used for viral diagnostic studies: anti-CMV antibody (IgG, IgM with ELISA method) (Dade Behring, Marburg, Germany), CMV antigen (pp65) (IQproducts, Brite™ Turbo, the Netherlands), CMV DNA (polymerase chain reaction [PCR] method) (Sacace, Italy), hepatitis B surface (HBs) antigen (Dade Behring), anti-HBC antibody (Dade Behring), hepatitis B virus (HBV) DNA (PCR method) (Qiagen, QiAamp, Hilden, Germany), anti-hepatitis C virus (HCV) antibody (Cinnagen, Tehran, Iran), and HCV RNA (PCR method) (Cinnagen).

The Foley catheter and ureteral JJ stent were usually removed after 7 and 40 days of transplantation, respectively. Blood cyclosporine levels were checked on the seventh postoperative day and monthly afterwards.

During the follow-up period, patients were visited weekly for the first month, every 2 weeks in the second month, monthly up to the sixth month, and subsequently every 3 months. Laboratory investigations (CBC with differentials, urea, creatinine, electrolytes, and urinalysis), and if necessary, imaging techniques, such as ultrasonography of the graft and radioisotope scan, were carried out.

Bacterial infections were diagnosed by routine methods. Although the presence of bacteriuria (>10^5 CFU/mL) would fulfill the criteria for urinary tract infection (UTI) in renal transplant recipients (9), other criteria, such as pyuria (>10 leukocytes/mL) and fever, are frequently used for diagnosing UTI. In the present study, the Centers for Disease Control (CDC) criteria were used as a definition for this infection. Respiratory tract infection (RTI) was diagnosed according to the CDC criteria (10). Wound infection was defined as the presence of a purulent discharge from a surgical wound (confirmed by culture). The diagnosis of fungal infection required histologic evidence of tissue invasion or isolation from blood or an otherwise sterile site. The diagnosis of viral infection required a significant rise in serological test titer (a 4-fold increase), as mentioned above, and/or 1 of the following: a newly positive IgM antibody titer associated with clinical evidence of disease requiring antiviral therapy; seroconversion; virus isolation; or histopathologic evidence of the virus. In this study, CMV infection was defined as the detection of CMV antigen (pp65) in peripheral blood leukocytes, or CMV DNA in clinical samples (such as blood and BAL fluid). CMV disease was defined according to Ljungman et al. (11) and included either CMV syndrome (the occurrence of CMV infection, accompanied by fever [>38°C] on at least 2 consecutive days, malaise, arthralgias, myalgias, leukopenia <3000 white
blood cells [WBC]/mm$^2$ and/or thrombocytopenia <100,000 pL/mm$^3$), or tissue-invasive disease (compatible symptoms or signs of organ involvement with evidence of the localized CMV infection in an appropriate specimen). The isolated finding of an increase in serological test titer without signs or symptoms and not requiring antiviral therapy was not used as a criterion of active viral infection. Varicella zoster virus (VZV) was identified after the appearance of typical papulo-vesicular cutaneous eruptions, confirmed by a dermatologist. Also, the same method is used for herpes simplex virus (HSV) identification. Sepsis was diagnosed when positive blood cultures were accompanied by fever, chills, and/or hypotension.

No programmed or periodic laboratory evaluations were performed for diagnosis of the specific infections (such as CMV, HBV, HCV, HSV, VZV, etc.), unless the clinical manifestations of the disease occurred. All consecutive infectious episodes in each transplant recipient were included.

**Statistical analysis**

Data were analyzed by the $\chi^2$ or Fisher exact test for dichotomous variables, and the Student $t$ test for continuous variables with SPSS-software. A value of $P<0.05$ was considered to be significant.

The study was performed in accordance with the Declaration of Helsinki and subsequent revisions, and approved by the ethics committee at Tehran University of Medical Sciences. Meanwhile, written informed consents were obtained from the patients.

**Results**

**Patients**

From 2002 to 2004, 179 renal transplantations were performed in our center. Of these, 142 were studied and followed for 1 year. Patient characteristics are summarized in Table 1.

**Infectious complications**

During the study period, 125 infectious episodes in 77 (54.2%) of all 142 patients with a mean of 0.9 episodes per recipient and 1.6 per infected patient were recorded. All infectious episodes are monitored and charted in Table 2.

**Bacterial infections**

UTI developed in 59 (41.5%) patients (33 males, 26 females); 37% were hypertensive and 10% were diabetic. Of the cases that developed UTI, acute rejection occurred in 13 ($P=0.54$), graft loss was seen in 2, and 5 patients died. The mean level of serum creatinine at the time of acute rejection in patients with and without previous urinary infection was 6.73 and 3.98 mg/dL, respectively. The average of the first urinary infection occurrence and the mean level of creatinine at that time was in sequence as 58 days and 2.56 mg/dL. Pyelonephritis occurred in 2 patients and was caused by *Klebsiella* and *Escherichia coli* (the second patient was diabetic). Variables such as age, female gender, cadaveric kidney, and underlying cause of ESRD (especially diabetes mellitus and polycystic kidney disease) were not associated with UTI. Thirty-eight percent of UTIs occurred during the hospital stay.
RTIs occurred in 9 (6.3%) patients. There were 8 episodes of bacterial infections, which occurred at the mean time of 69 days after transplantation. The average age of the patients was 36 years. None of them was diabetic. Forty-three percent of RTIs occurred during the hospital stay.

Wound infection developed in 7 (4.9%) patients, 57% of whom were diabetic. The mean time of the infection occurrence was 147 (10^355) days after transplantation, and the average age was 44 years.

The other sites of bacterial infections were osteomyelitis (Staphylococcus aureus, 1 case), endocarditis (Enterococcus, 1 case), perirenal abscess (Klebsiella, 1 case), epididymio-orchitis (E. coli, 1 case), and otitis media (coagulase-negative Staphylococcus, 1 case; Mycoplasma, 1 case).

Sepsis was diagnosed in 11 (7.7%) patients. Enterobacteriaceae (5 cases), Staphylococci (3), Pseudomonas (I), and Enterococcus (I) were the causative pathogens in 10 of them. The male/female ratio was 1. The average age of the patients was 44 years. The mean time of the sepsis occurrence was 119 days post transplantation.

Viral infections
One hundred twenty-three (86.6%) of 142 recipients (R) and 119 (90.8%) of 131 available donors (D) were positive for CMV-specific IgG antibodies. Twenty-five (17.6%) patients (17 males, 8 females) developed CMV disease; 16 were D+/R+4 D+/R−2 D−/R−, and 1 D−/R−, and in 2 patients serologic tests were unclear. The average time to developing CMV disease was 136 days (14–331) after transplantation. At the time of positive CMV antigen, the mean level of serum creatinine was 2.18 mg/dL. Among these 25 patients, 15 (60%) had experienced UTI before (P \leq 0.03) (Klebsiella, 9 cases, and E. coli, 3 cases, were the most frequent causative organisms), acute rejection occurred in 8 (32%), and 2 (8%) patients died. Only 2 (8%) of the patients with CMV disease had received a cadaveric kidney. None of the symptomatic patients had tissue-invasive disease. CMV was not associated with acute rejection (P \leq 0.34). Nineteen percent of CMV diseases occurred during hospitalization.

HCV serologic tests, at the time of transplantation, revealed a positive HCV antibody in only 1 patient (HCV RNA was negative). Three patients developed HCV infection (positive ELISA and PCR) after transplantation. Acute rejection occurred in 2 cases after 171 days on average, in the post-transplant period. At the time of transplantation, only 1 patient had a positive HBs antigen in serologic tests. Two patients developed HB infection, after transplantation. UTI occurred in both.

Two patients developed herpes zoster, and 1 patient developed HSV infection.

Other infections
There were 3 fungal infections of the urinary tract system, which were caused by undefined yeast. Candida albicans was the causative pathogen in another case with a positive CMV antigen. One patient had invasive aspergillosis, who died 125 days post transplantation. Entamoeba histolytica caused dysentery in 2 patients, 46 and 128 days after transplantation. Only 2 patients developed overt TB (1 pulmonary, 1 peritoneal) after 311 and 345 days post-transplantation, respectively.

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Urinary tract</th>
<th>Respiratory tract</th>
<th>Wound</th>
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<td></td>
<td></td>
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<td></td>
</tr>
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</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>9</td>
<td>8</td>
<td>45</td>
<td>125</td>
</tr>
</tbody>
</table>

Table 2

Pourmand et al: Infections after kidney transplantation
Acute rejection, mortality rate, and graft loss

There were 35 (24.6%) cases of acute rejection. The mean time of the rejection was 85 days after transplantation. Simultaneous rejection and infection occurred in 10 (7%) cases and were caused by UTI (5), CMV (2), sepsis (2), and HCV (1). Among these 35 patients, 14 cases were administered ATG before rejection ($P < 0.05$), 4 received cadaveric renal allograft, and 3 patients died.

Overall mortality was 7.7% (11 patients; 7 males, 4 females). Infection-related mortality was 3.5% (5 cases). All of these 5 patients developed sepsis. Mortality was associated with gram-negative Enterobacteriaceae (2 cases), S. aureus (1), coagulase-negative Staphylococcus (1), and aspergillosis (1). The average age, time of death (after transplantation), and serum creatinine level were 43 years, 53 days, and 5.61 mg/dL, in sequence at the time of death. Among these 11 patients, 3 cases had received a cadaveric kidney ($P = 0.01$).

There were 16 (11.3%) cases of graft loss in our study (5 cases due to rejection and 11 because of death). Of these 16 patients, 2 had developed CMV disease, 2 experienced UTI, and 5 developed sepsis. The average age of the patients and the mean time of graft loss (post transplantation) were 43 years and 151 days, respectively.

A time table of major infectious complications during 1 year after transplantation is shown in Figure 1.

Discussion

The prevalence of infection in transplant patients usually varies from country to country. There are many factors that may interact to determine the risk of infection as the net state of immunosuppression, postoperative care, and epidemiologic exposure. Furthermore, poorer socioeconomic conditions and lower standards of hygiene contribute to higher infectious complications in developing countries (1, 2, 7, 12). There are different studies with different results on the overall incidence and the most common sites of post-transplant infections. A comparison of patient characteristics and incidence of infectious complications after transplantation including those series published after 1995 is listed in Table 3 (13–20).

Overall, 47% of kidney transplant recipients develop bacterial infections, which often occur in the first post-transplantation month (1, 2, 7, 21). The reported incidence of UTI as the most common bacterial infection in kidney recipients ranges widely between 35% and 80%; the majority of these UTIs are uncomplicated and occur during the early post-transplant period. The main bacteria isolated in culture are E. coli, Klebsiella, Enterococcus, Staphylococcus, Streptococcus, and Pseudomonas aeruginosa (22–24). In our study, there were 83 (66.4%) bacterial infectious episodes. UTI was the major site of infection and appeared in the first 2 months after transplantation. Klebsiella was the most common causative organism in UTI and the most common in the whole study, which was consistent with other reports from our country (25, 26). Although post-transplant prophylactic antibiotics, especially TMP-SMX, provide some protection against UTI and urosepsis, increased resistance of urinary pathogens, particularly Klebsiella, has been found and is considered to be of major concern (24, 27). In other words, isolated Klebsiella exhibited the highest frequencies of resistance, with more than 61% resistant in this country (26, 28). As reported in other studies, we did not find female gender and pre-transplant diabetes to be associated with an increased incidence of UTIs (22), although this finding is in contrast with some other reports (2, 13). Renal transplant recipients are reported to have 28% to more than 90% incidence of UTI occurring after hospital discharge (1), while in our study we found 68%. In line with Charfeddine et al. (19), we were not able to find a significant correlation between UTI and rejection in our series.

Pulmonary infection occurs in 4.5–16% of all kidney recipients (2, 17, 19, 29). The main causative agents are Streptococcus pneumonia, P. aeruginosa, Staphylococci,
Pneumocystis jiroveci, Legionella, M. tuberculosis, CMV, and fungi (1, 2, 29). P. jiroveci, with an infectious rate of 1.6–11.5%, is an extracellular pathogen that causes infection in kidney transplant recipients by reactivation and direct person-to-person transmission (1, 13, 29). The investigations indicated that the rate of this infection is reduced significantly by using TMP-SMX as prophylaxis (1, 2). In this study, RTI as the second most common site of infections occurred in 6.3% of patients. S. pneumonia was observed in 2 (22.2%) of them. We encountered no P. jiroveci infection, owing to the use of TMP-SMX as prophylaxis.

Generally, CMV is the single main cause of Infectious complications from the second to the sixth month after kidney transplantation; however, less than 20% of patients develop its typical symptoms (1, 2, 7, 30–32). In our study, the incidence of viral infection was 26.4%. CMV, being the most frequent opportunistic pathogen, occurred in the first 6 months post operation. Similar to some other series (32), we found no association between CMV disease and an acute rejection episode during a 1-year follow-up, while this fact is in contrast with other studies (1, 2). CMV disease was prevalent in our recipients with an incidence of 17.6%. The reason, in our opinion, is that most donors in this study were positive for anti-CMV IgG and we did not use CMV prophylactic medication (31).

Hepatitis B and C are the major causes of liver disease in transplanted patients (33, 34). In Asian-Pacific countries, the carrier rate for HBV varies from 1–10%, and from 1–25% in kidney transplant recipients (35). There is a low incidence of HBV and HCV infection in the Iranian population (36). In the current study, only 1.4% of patients developed HBV infection, which was in line with the reports from Iran and other countries (18, 33, 36). The incidence of HCV infection was lower than that of other reports (33–35).

Mycobacterial infections, especially in developing countries, are one of the serious infectious diseases (37). Tuberculosis is endemic, with a prevalence of 122 cases/100,000 in the Iranian population; however, BCG vaccination in childhood is routine (38). Transplant patients show a 50–100 times increased risk of developing TB (39). The prevalence of TB among renal transplant recipients varies widely in different parts of the world and is <1% in the United States, 1–4% in Europe, 5.2% in China, 3.6% in Argentina,

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<td>29</td>
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<td>2/119</td>
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<td>10/57</td>
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<td>Bacterial IEs (%)</td>
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<td>64.4</td>
<td>88</td>
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<td>CMV (%)</td>
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<td>16 (33.3)</td>
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<td>70 (12.5)</td>
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<td>9 (6.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Infection-related mortality (%)</td>
<td>5 (3.5)</td>
<td>2 (4.2)</td>
<td>NA</td>
<td>12 (17.9)</td>
<td>5 (2.6)</td>
<td>34 (3.6)</td>
<td>6 (4.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Pros, prospective; Retro, retrospective; Rev, review; NA, not available; IEs, infectious episodes; UTI, urinary tract infection; TB, tuberculosis; CMV, cytomegalovirus.
3.5% in Saudi Arabia, 1–1.4% in Iran, and 11–15% in India (20, 37, 40–45). Compared with other countries, the posttransplant TB in our center with an incidence of 1.4% is similar to other series from Iran and those of European countries, higher than the United States but lower than East Asia, South America, Middle East countries, and India.

Kidney recipients who develop opportunistic infections during the first year of transplantation usually have higher serum creatinine levels, receive higher dosage of immunosuppressive drugs, and have more recurrent rejection episodes (3, 7). The overall incidence of mortality in the first year after transplantation is 5–10%, half of which is caused by infectious complications (3, 12, 46). Our results suggest a specific correlation between ATG administration and acute rejection. Eleven patients died during the first year of transplantation; 5 of these (45.5%) had developed an episode of infection before death. We found an association between cadaveric kidney recipients and mortality in the first year after transplantation. In this study, no particular underlying disease was related to a particular infectious complication. Justification of these results needs further well-designed studies.

In conclusion, this study identifies infections as the important cause of morbidity and mortality in the post-transplant period. The overall spectrum of infections, with UTI and CMV infections being predominant, is similar to that of other countries. Our kidney transplant patients did not receive prophylactic agents for TB and CMV. There was a low incidence of TB (<2% yearly) and HCV infection, and a high incidence of CMV disease in our center, compared with other studies.

References