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The Impact of Infectious Complications on the Outcome of Kidney Transplant Patients.

KEYWORDS: Kidney, transplantation, immunosuppression, infection.

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ABSTRACT *Infections remain a frequent, potentially life-threatening complication of kidney transplantation. Subjects and Methods: Between 1998 and 2006 we evaluated the incidence of infections in 114 renal transplant patients, with a 1-year follow-up. All patients received a posttransplant anti-infectious prophylaxis regimen. Induction therapy was given to 94 patients (82.4%) and maintenance immunosuppression consisted of cyclosporin microemulsion in 61 (53.5%) patients, or Tacrolimus in 49 (42.9%) patients, associated to mycophenolate mofetil and prednisone. All demographic, clinical, and surgical data were analyzed by SPSS 13.0. Results: In total, 56 (49.1%) patients developed a total of 95 infections up to 1 year after kidney transplantation, including 46 in-hospital infections in 38 patients. Bacterial infections were the most frequent (97.8%), and were mainly urinary, followed by drain, central line catheter and pulmonary infections. The most frequent isolated bacteria were E.coli, followed by Klebsiella, Acinetobacter and Pseudomonas. No viral infections were detected. Up to 1 year after discharge from the hospital, 49 infections occurred in 26 patients, of which 79.5% were bacterial, mainly urinary tract infections due to E.coli, in addition to 7 cases of Cytomegalovirus, 1 herpes, and 2 cases of fungal infections. Conclusions: To our knowledge, this is the first Lebanese study that deals with posttransplant infections up to 1 year in transplant patients. It shows the importance of close patient monitoring and follow up. Comparison with international data shows similar patterns.*

INTRODUCTION

While kidney transplantation (KT) has become the treatment of choice for patients with end stage renal disease (ESRD), infection remain one of the major concerns in renal transplant (RT) patients (1,2) It represents a significant cause of morbidity and mortality, and a major reason of chronic graft dysfunction and graft loss (3-7).

The success of KT in the early post operative period depends on a compromise between achieving sufficient immunosuppression to avoid rejection of the graft and maintaining a sufficient level of immune competence to protect the recipient from infection. Despite the progressive improvements in patient and graft survival made in the previous 2 decades (7,8), RT recipients remain at risk of contracting infection, which resides in the state of immunosuppression associated with anti-rejection medications (6), together with the need for external devices dictated by technical or anatomic abnormalities (1), exposure to pathogens, and in the disturbance in the patient's normal bacterial balance, which in turn facilitates the establishment of opportunistic, potentially antibiotic-resistant infections (9,10).

In the early years of transplantation, the incidence of severe and lethal infections was high and discouraging. Peterson found in his study that 32% of his patients suffered a clinically significant infection. Seven per cent of them died and in 87% of these deaths, infection was an important contributing factor (11). With increasing experience, the incidence of serious and lethal infections has fallen dramatically due to improvements in general clinical care, methods of organ procurement, surgical technique, recipient selection in addition to a greater awareness of the type and timing of infections. Current studies report graft and patient survival of 85% and 95% at 1 year and 80% and 90% at 5 years with cardiovascular events overtaking infection as the leading cause of death (12,13). However, the problem of infection remains a major concern and contributes substantially to the morbidity, allograft loss and mortality of KT particularly in patients who have suffered primary graft failure and undergo repeat transplantation (14).

This link between the need for immunosuppressive therapy and the potential for development of infection necessitates the development of effective preventive strategies, which depends on familiarity with the site and time line of post transplant infections (10,15). As such, infections in high-risk RT recipients may be deduced according to the time period post transplant, the patient's state of immunosuppression, and their environmental exposures (6,16,17). While infections occurring in the first month are similar to those seen in the general surgical patient, unusual nosocomial infection outbreaks of Aspergillus, Legionella, vancomycin-resistant enterococcus, respiratory syncytial virus, among others, were reported (18-20). Viral (Cytomegalovirus (CMV), Herpes simplex virus (HSV), and Epstein-Bar virus (HSV)), Listeria, and Nocardia are infections frequently encountered at 1 month post-tranplant, of which CMV infection is of significance given its immune-modulating effects (2,21). Community-acquired infections, including those secondary to respiratory viruses, and syndromes related to chronic viral infections (CMV, EBV, etc.) are detected after the sixth month (22). Due to prophylaxis, newer immuno-suppressive regimens, and emergence of antibiotic resistance and newer pathogens (BK polyomavirus) have altered the form and timing of some infections (23), thus underscoring preoperative screening of high-risk patients.

In this study, we evaluated retrospectively bacterial, viral, and fungal infections up to 1 year post-transplantation in 114 RT Lebanese patients between 1998-2006. The study clearly demonstrated changes in the pattern of infection from hospital discharge to one year post-operatively.

Subjects and Methods

Patients and Donors. Between 1998-2006, 114 adult patients (89 males and 25 females; mean age 42.0 ± 13.8 years) were operated for KT by or team. All patients were

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Caucasians. Of these, 105 were first transplants, and the others having a second re-transplant. Nine patients received kidney grafts from brain deceased donors and the remaining 109 patients from living donors after getting the approval from the local ethics committee in accordance to the Lebanese rules and regulations. Donor age (34.6 ± 9.9 years; range from 18 to 62 years) and gender distribution (75 males and 39 females) were comparable to those of recipients. Ninety seven patients received a kidney from identical and the remaining 17 from compatible blood group donors.

Donor-recipient HLA AB/DR matching is shown in Figure 1. Sensitized patients were defined as those who had more than 4 pregnancies (n=5), received more than 4 blood transfusions (n=7), those having a retransplant (n=9), and those who had a panel-reactive antibody score (anti-HLA class 1 and 2 antibodies) more than 50% (n=1). One patient had both multiple pregnancies and blood transfusions. While chronic glomerulonephritis and pyelonephritis were the most common, the etiology of renal disease was not clear because of late diagnosis in 36 patients (Table 1). The pre-transplant dialysis duration ranged from 0 to 115 months (mean 17.9 ± 19.6 months). Twelve patients had a preemptive KT.

Operation. All transplants were heterotopic inserted in the iliac fossa. Vascular anastomoses were done with the recipient external iliac vessels in an end-to-side manner, the vein first then the artery using prolene 5-0 for the vein and 6-0 for the artery. Vesico-ureteral anastomosis was done as described by Shanfield (24). To minimize urological complications, an internal double-J ureteric stent was inserted before ending the uretero-neocystostomy, then removed 6 weeks after KT by cystoscopy (6). A closed drain was left in the operative area before wound closure, and removed when the drainage is <50 ml/day. Foley catheters were removed on day 4 after KT and urine culture was routinely obtained.

Perioperative Antibiotic Prophylaxis. Intra-operative antibiotic prophylaxis with intravenous first-generation cephalosporin (or others in case of specific preoperative infections or drug allergies) was instituted for all patients, and continued for 48 hours thereafter. Intravenous ganciclovir was administered during hospitalization, and the dose adjusted according to the renal graft function (glomerular filtration rate). Oral valacyclovir was then administered for 3 months after hospital discharge, or for 6-month period in CMV high-risk patients (ATG-F extended protocol, multiple AR episodes needing high dose of steroids, or CMV-negative recipient receiving a kidney from a CMV-positive donor). In addition, trimethoprine/sulfametoxazole was given for 1 year after the transplant for *Pneumocystis carinii* prophylaxis.

Immunosuppressive Regimen. Induction therapy was given to 94 patients: 38 patients received a single intraoperative Anti-Thymogobulin globulin-Fresenius (ATG-F) bolus (6 mg/kg), 35 had 1 dose of Daclizumab (1 mg/kg) and 3 patients received 2 doses of 1 mg/kg of Daclizumab. Eighteen patients received the extended protocol of ATG-F (6 mg/kg during the surgery followed by 4 mg/kg every other day for 3 doses) for high sensitization status. In 20 patients, no induction therapy was used. Maintenance immnusuppression consisted of intravenous methylprednisolone (500 mg), given during surgery than tapered progressively over the next four weeks to 0.2 mg/kg/day of prednisone (Pred). Cyclosporine microemulsion (CyA-me) was given after the transplant (5 mg/kg bid), or was delayed in case of slow graft function (SGF) or delayed graft function (DGF); the dose adjusted to a C2 levels of 1700 ng/ml (using the monoclonal radioimmunoassay on whole blood) during the first month. Tacrolimus (Tacro) was given at a dose of 0.1 mg/kg bid, and monitored for a trough level of 12-15 ng/ml during the first month. Mycophenolate mofetil (MMF) was started 48 hours before KT at 1 gm twice a day (in CyA-me patients) or 500 mg bid (in Tacro patients).

Diagnosis of infections. Urine, throat, nose, peritoneal fluid (in peritoneal dialysis patients) and blood (in case of hemodialysis catheter) cultures were obtained before KT. They were all negative. Serology for CMV, HSV, herpes zoster (HZ), EBV and Toxoplasmosis virus were obtained before transplantation. Active infections excluded KT. After KT, blood, urine and sputum cultures for bacteria and fungi were done when indicated. The indwelling arterial and central venous monitoring catheters were removed in all patients as soon as possible and their tips were cultured. Similarly, intravascular catheters used for hemodialysis access were also cultured. Cultures were also taken from other sites (e.g. drains, peritoneal catheters) when patients had persistently elevated leucocytes counts or episodes of fever. Intravascular catheters were regarded infected, using the semi-quantitative culture method of Maki technique (25), if more than 15 organisms were cultured from the tip of the removed catheters regardless if fever was present or whether blood cultures were positive. The urine was considered infected if greater than 100.000 organisms/ml were present. Viral infections were diagnosed on the basis of polymerase chain reaction (PCR) in blood, urine or tissue specimen, or histological proof of tissue invasion. CMV testing was performed only in symptomatic patients (CMV disease or suspicion of CMV syndrome). Detection of BK virus also was requested in case of occurrence of symptoms, or a rise in serum creatinine. In this case, kidney graft biopsy and urine BK-PCR tests were performed. Specific immunohistochemistry coloration was done systematically in all kidney graft biopsies. Bronchoscopy and bronchial lavage were performed when a pulmonary infiltrate was present and sputum samples were inadequate. Chest X-rays were taken daily until extubation, then when indicated.

All episodes of infections during the first year after KT, whether symptomatic or asymptomatic, were analyzed. These infections were divided into 2 groups: In hospital infections and out of hospital infections.

Diagnosis of rejection. Kidney biopsies were performed when abnormal renal graft function tests occurred, after ruling out surgical complications by appropriate radiological investigations. The histological criteria for acute rejection (AR) proposed by the Banff classification were used (7). AR episodes were treated with a 3-day course of bolus steroids. Steroid-resistant rejection was treated by an additional course of ATG-F.

Statistical Analysis. The data were analyzed using SPSS software for Windows (Statistical Product and Service Solutions, version 13.0, SSPS Inc., Chicago, IL, USA). Data are reported as the mean ± SD or percentage of the total. Intergroup significance was determined by Student *t*-test (continuous variables) and the Fisher's exact test (categorical variables). Statistical significance set at $P < 0.05$.

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RESULTS

Infections. Fifty six out of 114 patients (49.1%) developed infection during or up to 1 year after hospitalization. Thirty of them (53.5%) developed the infection during their stay in the hospital, 18 patients (32.2%) after their discharge, and the remaining 8 patients (14.3%) were infected during and after hospitalization. In total, 95 infectious episodes at a rate of 1.69 infectious episode / patient were diagnosed. These included 46 infections occurring during the patient's hospital stay (Group I) and 49 infections up to 1 year later (Group II). There infections consisted of 84 bacterial (88.4%), 8 viral (8.4%) and 3 fungal infections (3.2%).

Bacterial infections. Most of the infections In Group I patients were bacterial (45 out of 46 infections; 97.8%). Urinary tract infections were the most frequent (55.5%) followed by external drainage catheter (13.3%) and intravascular catheter-related infections (11.1%). E. Coli and Klebsiella were the most common organism isolated from the urinary infections, while E. Coli and S. epidermidis or S. aureus were isolated in the external drainage catheter infections and intravascular catheter-related infections. In Group II patients, there were fewer bacterial infections (34 episodes; 79.5%) than in Group I (p = N.S.), and their distribution was different except for the urinary tract infections which were similar with respect to frequency (87.1%) and causative organisms (Table 2).

Viral infections: All 8 viral infections were acquired after patients' discharge (Group II). There were 1 case of oral herpes occurring on day 210 after KT which responded well to acyclovir treatment and 7 CMV infections (87.5%). All the CMV infections are described in Table 3 in accordance to the donor and recipient CMV status. All these infections were diagnosed by positive CMV-PCR testing or tissue biopsy and all the patients responded well to IV ganciclovir for 2 weeks followed by oral ganciclovir for a 3 month period.

Fungal infections: There were 3 cases of fungal infections: 1 case of esophageal mycotic infection diagnosed in Group I and 2 cases of ungueal candidiasis seen in Group II. All 3 cases were treated with oral Fluconazole.

Acute Rejection. AR occurred in 30 patients (26.3%) between day 2 and day 11 after KT. All the AR cases responded well to treatment. Nine episodes of steroid-resistant acute rejection occurred in 9 patients (30%) and required ATG-F therapy.

Patients and Grafts outcome. Excellent actuarial 1-year patient and graft survival rates were obtained. While the patient's hospital stay duration was longer in the infection than in the non-infection group (14 ± 7 vs. 11.9 ± 3.5 days), the rates of SGF (5.2% vs. 7.1%) and DGF (5.2% vs. 8.9%) were comparable between the two groups (Table 4). Slow graft function cases comprised 2 cases of drug-induced acute tubular necrosis and 1 case of early AR in the no infection group, and 4 cases related to drug toxicity and 1 case owing to acute tubular necrosis in the infection group. The DGF cases consisted of 2 cases of drug-induced acute tubular necrosis and 1 case of early AR in the non infected group, compared to 3 cases of drug-induced acute tubular necrosis, 1 case of double-J ureteric stent obstruction, and 1 case related to early AR in the infected patients (day 3 after KT). There was a steady decline in serum creatinine levels from 1.54 ± 0.8 mg/dl upon discharge, to 1.44 ± 0.55 mg/dl and 1.31 ± 0.48 mg/dl at 1 month and 12 months after discharge (Table 4). In general, serum creatinine levels were comparable between the infection and no infection patient groups (Table 5).

DISCUSSION

Despite progressive improvements in RT outcomes, infection remains a frequent cause of allograft failure, and patient morbidity and mortality in early and late stages after KT (17-19,25,26), with postoperative infections reportedly occurring in 10 to 50% of recipients depending on the definition of infection and the type of immunosuppressive regimen employed (1,27,28). This necessitated the need for effective treatment regimen, which reduces rejection rates, while minimizing morbidity and mortality from infection. Moreover, the definition of infection varies from the clinically significant and laboratory-proven episode, to the asymptomatic positive culture.

The immunosuppressive protocol instituted was based on the extent of immunosensitization, with extended ATG-F given to highly sensitized but not immunologically low-risk patients, and in post-transplant SGF or DGF (to minimize toxicity of calcineurin inhibitors). This translated to acceptable AR rate (26.3.%), and the steroid resistant AR needing ATG-F as rescue therapy (30%), in a population where 20% of patients are highly sensitized.

Renal transplant patients are susceptible to infection, partly for the immunosuppressive treatment they receive, and also for uremia, anemia, and coagulation defects with delayed wound healing (29,30). In addition, vascular and urological manipulations (urinary catheters, intravenous cannulae and peritoneal dialysis catheters), increase the susceptibility to contracting infections by non-specifically lowering their immunity (31). In view of the contribution of these and other factors to the development of infectious episodes, we analyzed both immunological and non-immunological contributing factors, and except for the degree of sensitization, did not identify any additional predisposing factor linked to the rate of post transplant infections, or to the need for ATG-F as a rescue (steroid-resistant AR) or hospital stay.

In this retrospective study, the rate of infectious episodes was stable during the 1-year follow-up, and was lower than that reported by others studies (3,5,31). Compared to other studies (4), excellent graft and patient survival were seen, which is due to effective infection control policy adopted at our institution. This includes early removal of central venous line, drainage and urinary catheters, as suggested elsewhere (16,17,31). As the routine use of antibiotic prophylaxis in RT recipients is still debatable (4,32), coupled with the possibility of emergence of antibiotic-resistant infections (1,9), together with patient's factors (primary kidney disease and immunosuppression protocol) (4,21), care was exercised in administering antibiotic therapy, unless justified by development of clear signs and symptoms of infection. Insofar as minor infections have the potential to progress to major invasive sepsis in high-risk patients, this supports the need for detailed diagnosis and monitoring of infection, before precipitation of morbidity and mortality.

Despite close monitoring and progressive reduction of the dosage of immunosuppressive medication, more infectious episodes were noted to occur outside than inside the hospital (51.5% vs. 48.5%), of which CMV infections were

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the most prominent. Most CMV infections occurred 3 to 4 months after CMV prophylaxis, and did not compromise graft or patient survival, and generally responded well to ganciclovir therapy. This was in agreement with a recent Turkish study documenting increased CMV infection following hospital discharge (21).

Insofar as CMV testing was done only on symptomatic patients, and hence may have underestimated the number of infected patients, it is likely that this number would increase if routine tests were also adopted for asymptomatic patients, as shown elsewhere (33). While urinary tract infections remain the most common type of bacterial infection contracted by RT recipients (1,16), the relatively high rate of urinary infections seen here (62%) and elsewhere recommends adopting effective preventive measures, including using closed-bladder drainage, with less manipulation and its early removal (17), as well as regular urine analysis and culture to detect urinary infections, which are frequent but often asymptomatic (1,16).

The incidence of (bacterial and viral) infectious complications remains high, and a major cause of morbidity and mortality in RT recipients. However, they may be controlled by adoption of strict infection control measures, appropriate use of prophylactic antibiotic therapy, careful monitoring for allograft function, and routine but sensitive laboratory monitoring.

SUMMARY

In summary, infections occurring after transplantation reflect the intricate relationship between the net state of immunosuppression and environmental exposure. The introduction of new immunosuppressive agents has led to changes in the spectrum of posttransplant infections. Familiarity with the time line of infections is necessary to avoid diagnostic delays and serves as a framework for developing preventive strategies. Moreover, to avoid delays in diagnosis and institution of appropriate antimicrobial therapy, clinicians should be aware of the blunted inflammatory response in transplant recipients. Such patients may have overwhelming sepsis, and yet fail to display any signs or symptoms suggestive of an ongoing infection. The high rate of infection among this group of patients directly reflects the intricate relationship between the net state of immunosuppression and environmental exposure. For the transplant recipient, the therapeutic prescription must create a balance between immunosuppression to reduce the risk of graft rejection and antimicrobial therapy to keep the immunosuppressed patient safe from infection. The first steps in the establishment of a therapeutic prescription are to ascertain any recent and remote exposures, identify any infections that are present, and eradicate those infections before transplantation (10,34).

In our study, almost half of our transplant population presents an infectious episode some time during 1 year after the transplantation without any negative impact on the outcome of the kidney graft or the patient survival. The absence of predisposing factor is related to good patient selection and preparation before transplantation. We believe that we should look to an effective anti-bacterial prophylaxis in the same way we are using a good anti-rejection therapy.

FIGURE LEGEND

FIGURE ONE: The HLA AB-DR matching between donors and recipients (MM = Mismatching)

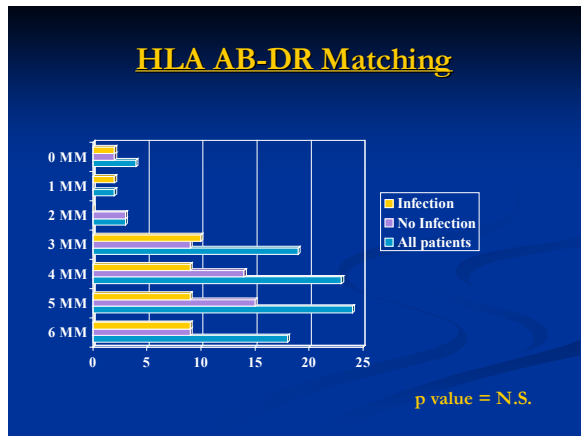

TABLE 1

Indications for Kidney Transplantation

Cause	All patients (114)	No Infection (58)	Infection (56)
Unknown	36	22	14
Chronic pyelonephritis	12	6	6
Chronic glomerulonephritis	17	9	8
Polycystic kidney disease	10	3	7
Diabetes	4	1	3
Arterial hypertension	6	4	2
Berger disease	5	2	3
Alport disease	2	2	-
Interstitial nephritis	4	2	2
Amyloidosis	1	-	1
Retransplant	9	3	6
FSGS	7	3	4
Renal hypolasia	1	1	0

P = N.S.

Abbreviation: FSGS, focal segmental glomerulosclerosis

TABLE 2

Distribution of Postoperative Bacterial Infections

Site of Infection (Bacterial)	Group I (n = 45)	Group II (n = 39)
Urinary	25 (55.5%)	34 (87.1%)
External drainage catheter	6 (13.3%)	—
Intravascular catheter	5 (11.1%)	—
Respiratory	4 (8.8%)	—
Colitis	3 (6.6%)	—
Wound	1 (2.3%)	2 (5.1%) skin
Others	1 (2.3%)	3 (7.8%)

P = N.S.

TABLE 3

CMV Infections

D → R	All patients	No Infection (Disease)	Infection (Disease)	Infection (Site)
N -> P	9	3 (0)	6 (0)	
P → N	6	3 (0)	3 (2)	1 GI; day 90 1 Urinary; day 92
P → P	99	52 (0)	47 (5)	3 GI; day 70,90,310 1 Pneumonia; day 70 1 Urinary; day 125

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D: Donor
R: Recipient
N: Anti-CMV IgG negative
P: Anti—CMV IgG positive
GI: Gastro-intestinal

TABLE 4
Patient and Graft Outcome

	All patients	No Infection	Infection	P[1]
Hospital stay Mean ± SD (days) Range (days)	12.9 ± 5.6 6 – 48	11.9 ± 3.5 6 – 24	14 +/- 7 6 – 48	0.047
SGF	7 (6.1%)	3 (5.2%)	4 (7.1%)	N.S
DGF	8 (7%)	3 (5.2%)	5 (8.9%)	N.S

1. Student *t*-test for continuous variables, Fisher's exact test for categorical variables.

TABLE 5
Serum Creatinine Levels (mg/dl)

	All patients	No Infection	Infection
Upon discharge	1.54 ± 0.8	1.56 ± 0.68	1.53 ± 0.92
1 month	1.44 ± 0.55	1.47 ± 0.48	1.41 ± 0.61
3 months	1.38 ± 0.53	1.38 ± 0.38	1.37 ± 0.65
6 months	1.32 ± 0.47	1.33 ± 0.29	1.32 ± 0.61
12 months	1.31 ± 0.48	1.32 ± 0.33	1.3 ± 0.6

P= N.S.

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