

Infections in Paediatric Renal Transplant Recipients

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Abstract

A retrospective study of all children who had undergone renal transplantation at the National University Hospital was undertaken in order to investigate the types and frequency of infections in paediatric renal transplant recipients. A total of 13 children ranging in age from 3 to 17 years were transplanted over a 7-year period from 1989 to 1996. The mean follow-up period was 40.5 months. Ten patients (77%) had at least one episode of infection post-transplant, 70% of which occurred within the first 6 months post-transplant.

These infections included urinary infections (8), disseminated cytomegalovirus (CMV) disease (4), Pneumocystis carinii pneumonia (1) and mycoplasma pneumonia (1). Urinary tract infections were significantly associated with the presence of ureteral stents. CMV disease was significantly associated with the use of mycophenolic acid in the early post-transplant period. Infection therefore continues to be a major cause of morbidity in paediatric renal transplant recipients.

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Introduction

Renal transplantation has become established as the treatment of choice in children with end-stage renal disease. Living donor graft and cadaveric graft survival rates are much improved and are presently 75% and 62% at 5 years post-transplant, respectively.* Overall mortality post-transplantation continues to be low, at 6.8% and 4% for cadaveric and living donor grafts, respectively.¹ However, infection continues to be a leading cause of death and is also one of the most common reasons for re-hospitalisation within the first six months post-transplantation. In fact, in a study of 247 paediatric renal transplant recipients, Harmon² found that 84% of deaths within the first six months after transplantation were attributable to infection. Therefore, the prevention and early treatment of post-transplant infection might well yield significant improvements in graft and patient survival. The aims of this study were to examine the frequency and types of post-transplant infections in children and possible predisposing factors.

Patients and Methods

Patient Profile

A total of 13 children were transplanted over a 7-year period from 1989 to 1996. They consisted of 6 females and 7 males ranging from 3 to 17 years of age at the time of transplantation. Eight received kidneys from living related donors while the other 5 received cadaveric transplants. Of the latter group, 2 had their cadaveric transplants performed in China. The mean follow-up period was 40.5 months after transplantation. These children suffered from a variety of diseases which had caused end-stage renal failure (Table I). The three most common diagnoses were focal segmental glomerulosclerosis, diffuse sclerosing glomerulonephritis and renal dysplasia. In terms of dialysis modality, 7 patients were receiving haemodialysis (HD) prior to transplantation, 4 were receiving continuous cycling peritoneal dialysis (CCPD) and 2 were on chronic ambulatory peritoneal dialysis (CAFD). Almost all (12 out of 13) had had at least one episode of peritonitis and/or exit site infection

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TABLE I: AETIOLOGY OF END-STAGE RENAL DISEASE

Type of Renal Disease	Number of Patients
Focal segmental glomerulosclerosis	3
Diffuse sclerosing glomerulonephritis	2
Renal dysplasia	2
ImmunoglobulinA nephropathy	1
Diffuse mesangio-proliferative glomerulonephritis	1
Focal global sclerosis	1
Unknown	3

prior to transplantation.

Pre-Transplant Investigation Status

All patients underwent a comprehensive series of pre-transplant investigations which included the following: urine microscopy and culture, Venereal Disease Research Laboratory (VDRL) test, chest radiograph, human immunodeficiency virus (HIV) serology, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis C immunoglobulin M (HCV IgM), cytomegalovirus (CMV) IgG, CMV IgM, measles IgG, mumps IgG, rubella IgG, varicella-zoster (VZ) IgG and Epstein-Barr viral capsid immunoglobulin G (EBV VCA IgG). In terms of CMV immune status, 10 of the 13 transplants were from seropositive donors to seropositive recipients, and only 3 were from seropositive donors to seronegative recipients.

Hepatitis B and measles/mumps/rubella boosters and VZ vaccine using attenuated OKA strain (SmithKline Beecham Biologicals varivix) were given to non-immune patients before transplantation. However, 2 patients who did not have naturally-acquired immunity to VZ had their transplants before the VZ vaccine became available and therefore remained non-immune to varicella-zoster. Post-transplant, 6 patients identified as high risk due either to pre-transplant CMV immune status or use of monoclonal or polyclonal antibodies as part of their immunosuppressive regimen received both intravenous ganciclovir and intravenous (IV) IgG as CMV prophylaxis, 3 received only intravenous Ig and 4 did not receive any CMV prophylaxis. *Pneumocystis carinii* chemoprophylaxis consisted of oral cotrimoxazole while antibiotic prophylaxis for indwelling urinary catheterisation and /or ureteral stent consisted of cephazolin.

Pre-transplant Urological Status

Urological evaluation consisting of ultrasonography, micturating cysto-urethrogram (MCU), dimercaptosuccinic acid-labelled technetium (DMSA)/diethylenetriaminepenta-acetate (DTPA) scans, and urodynamic studies (when required) was carried out. Only 2 of the 13 patients were found to have urological abnormalities consisting of bilateral vesico-ureteric

reflux. Of the 2 patients with vesico-ureteric reflux, 1 had a bilateral re-implantation done which resulted in a complete cure. The other underwent a sub-ureteric teflon injection (STING) procedure which improved the degree of vesico-ureteric reflux from moderate to very mild.

Immunosuppressive Protocol

All 13 patients received cyclosporin as the mainstay of their primary immunosuppressive regimen. Ten had conventional triple agent immunosuppression with cyclosporin, azathioprine and prednisolone. Three had cyclosporin and prednisolone with mycophenolate instead of azathioprine. The maintenance dose of mycophenolate given was between 15 to 23 mg/kg/dose bid. Nine patients received ATG or OKT3; 6 as part of induction immunosuppression and 2 as rescue therapy for acute allograft rejection. The remaining patient received OKT3 as part of induction as well as treatment for rejection in a primary non-functioning allograft. The induction dose of ATG was 2 mg/kg given for 5 to 14 days depending on the post-transplant serum creatinine level. When used as rescue therapy for acute rejection, a single dose of 3 to 5 mg of OKT3 was given for 10 to 14 days.

Statistical Analysis

Review of the records of all 13 patients was carried out. Post-transplant infections were characterised in terms of anatomical site, pathogen and timing of the infection post-transplant. The presence and duration of post-transplant acute tubular necrosis and the presence of an indwelling ureteral stent and previous urological abnormalities were correlated with the subsequent development of urinary tract infections. The donor and recipient CMV status, type of CMV prophylaxis, use of OKT3, use of mycophenolate and graft function were correlated with development of CMV disease. Univariate analysis was carried out using the statistical package SPSS for Windows (version 1.0) to determine the relationship between the presence of infections and the abovementioned risk factors. Statistical significance was defined as a *P* value of less than 0.05. However, meaningful statistical analysis was constrained by the small number of patients.

Results

Over the 7-year period, there were 18 separate episodes of infection after renal transplantation. Ten out of thirteen patients had at least one episode of infection while 3 patients remained free of infection. There were no deaths among these patients. The various types of infections and their frequency are shown in Table II. The most common infection was urinary tract infection (UTI), *Pseudomonas aeruginosa* was the commonest pathogen causing UTI (5 episodes), followed by *Escherichia*

coli (2 episodes) and *Klebsiella pneumoniae* (1 episode). Most of the UTIs occurred within the first one month after transplantation (Table III). UTI was significantly associated with the presence of an indwelling ureteral stent. However, no association was found between abnormal urinary tract anatomy and the subsequent development of UTIs. This is probably due to the fact that only 2 patients had urological abnormalities pre-transplant. Among the patients who developed UTI were 2 patients who had normal urinary tract anatomy before transplantation but developed stenosis of the donor ureter more than 2 years after transplantation.

There were 5 episodes of disseminated CMV disease. Most of these (4/5) occurred after the first month of transplantation. CMV disease manifested as prolonged fever, pneumonitis and chorioretinitis. One patient was unfortunate enough to develop CMV encephalitis. A significant association was found between early administration of mycophenolate i.e. when it was given as part of the primary immunosuppressive regimen and the development of CMV disease ($P < 0.02$). We were unable to demonstrate significant association between donor or recipient CMV status, type of CMV prophylaxis given and administration of OKT3 and the subsequent development of CMV disease. There was also no significant difference in the eventual allograft function between those with and those without CMV disease. However, it is noteworthy that of the 4 patients who did not receive OKT3, none developed CMV disease.

TABLE II: TYPES OF POST-TRANSPLANT INFECTIONS

Type of Infection	Number of Episodes
Urinary tract infection	8
Disseminated cytomegalovirus disease	5
Bacterial pneumonia	2
<i>Pneumocystis carinii</i> pneumonia	1
Hepatitis B	1
Bacterial septicaemia	1

TABLE III: TIMING OF INFECTIONS DURING THE POST-TRANSPLANT PERIOD

Time (post-transplant)	No of Episodes	Type of Infection
≤ 1 month	7	UTI (5 episodes) Pneumonia (1 episode) CMV (1 episode)
1 to 6 months	6	CMV (4 episodes) PCP (1 episode) Bacterial septicaemia (1 episode)
> 6 months	5	UTI (3 episodes) Hepatitis B (1 episode) Pneumonia (1 episode)

CMV: cytomegalovirus disease; UTI: urinary tract infection

PCP: pneumocystis carinii pneumonia

There were 3 episodes of pneumonia, of which one was due to *Pneumocystis carinii*. One patient who had her cadaveric transplant done in China developed hepatitis B seven months after transplantation although she had been found to have an adequate titre of antibody during the pre-transplant work-up. There was 1 episode of prolonged *Xanthomonas maltophilia* septicaemia in a patient who had previously been on a prolonged course of imipenem.

Discussion

Historically, infections from the genito-urinary tract have been the most common infection complicating renal transplantation.³ The incidence of UTIs after renal transplantation ranged from 22%⁴ to 40%.³ As such, the high incidence of UTIs in our series is to be expected.

The timing of UTIs within the first month post-transplant is also well recognised. These "early" UTIs (occurring within the first 6 months post-transplant) should not be taken lightly as they have been associated with overt pyelonephritis, bacteraemia, allograft function and a high rate of relapse.⁵ In contrast, "late" UTIs (occurring more than 6 months post-transplant) are usually asymptomatic and generally benign. The incidence of UTIs falls progressively during the first years following transplantation and subsequently does not differ from that of UTIs in the general population.⁶

Predisposing factors to UTI include genito-urinary manipulation during surgery, bladder catheterisation, anatomic abnormalities (uretero-vesical stenosis, ureteral stricture and vesico-ureteric reflux) and neurogenic bladder. An interesting point is the finding that the presence of indwelling ureteral stents predisposed to UTI. This has not been reported widely elsewhere, though it is well established that the duration of bladder catheterisation correlates with the incidence of UTIs in post-transplant patients. In fact, Nicol et al⁷ found that there was no significant increase in UTI in patients with indwelling ureteral stents. However, they found that in a significant percentage of patients, resistant UTIs did develop, and which only responded to antibiotics after removal of the ureteral stents. Measures that should be taken to minimise UTIs post-transplant include: surveillance and treatment of any UTIs prior to transplantation, correction of existing urological abnormalities predisposing to UTI prior to transplantation, use of perioperative chemoprophylaxis, improved surgical techniques in order to reduce donor kidney and wound contamination and postoperative chemoprophylaxis for the duration of bladder catheterisation.

CMV is among the most important microbial pathogens affecting renal transplant recipients. As many as 40% of paediatric renal transplant recipients had CMV infection and 15% developed clinical CMV disease.⁸ As

such, the 38% incidence of CMV disease in our series is similar to that reported elsewhere. Paediatric renal transplant recipients would be expected to be more susceptible to CMV since at their young age they have not had previous exposure to the virus. This consideration was not particularly significant in our patients as 10 out of 13 recipients were in fact seropositive for CMV before transplant. CMV is responsible for the direct causation of infectious disease syndromes such as prolonged fevers, pneumonia, hepatitis, gastro-intestinal ulceration and chorioretinitis. In addition, CMV causes immunosuppression predisposing to opportunistic superinfection. The single patient in our series who developed *Pneumocystis carinii* infection also had disseminated CMV infection. In addition, CMV is postulated to produce acute and chronic allograft injury although we were unable to demonstrate a difference in the graft function between those with and without CMV disease.

The finding of an association between the use of mycophenolate in primary immunosuppression and the subsequent development of CMV disease is of concern. Previous studies have suggested the possibility that tissue invasive CMV disease may be more common in patients treated with mycophenolate.⁹ Consequently, as the use of mycophenolate as an alternative agent to azathioprine becomes more widespread, careful monitoring for evidence of increased CMV disease is required.

In contrast to the UTI which mostly occurred during the early post-transplant period, most of the opportunistic infections viz CMV and *Pneumocystis carinii* occurred after the first month post-transplant. This is probably because the immunosuppressive agents have to be given some time before the net state of immunosuppression permits these types of infection. This particular temporal sequence of infections is well

recognised and should be borne in mind when confronted with fever in the post-transplant patient.

In conclusion, infections are a cause of significant morbidity in paediatric renal transplant recipients. Urinary tract infections are numerically the biggest group of post-transplant infections. Cytomegalovirus disease is less common but is apt to require prolonged treatment with anti-viral agents and significantly lengthen hospitalisation. Moreover, their effects on long-term allograft function are cause for concern.

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