

Non-viral infections in children after renal transplantation

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Received: 16 January 2011 / Revised: 5 November 2011 / Accepted: 11 November 2011 / Published online: 9 February 2012
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Abstract Renal transplantation has long been recognised as the gold standard treatment for children with end-stage renal failure. There has been an improvement over the years in patient and renal allograft survival because of improved immunosuppression, surgical techniques and living kidney donation. Despite reduced acute allograft rejection rates, non-viral infections continue to be a serious complication for paediatric renal transplant recipients (RTR). The risk of infections in RTR is determined by the pre-transplantation immunisation status, post-transplant exposure to potential pathogens and the amount of immunosuppression. The greatest risk of life-threatening and *Cytomegalovirus* infections is during the first 6 months post-transplant owing to a high immunosuppressive burden. The potential sources of bacterial infections are donor derived, transplant medium fluid, peritoneal and haemodialysis catheter and transplant ureteric stent. Urinary tract infections are frequent in patients with lower urinary tract dysfunction and can result in renal allograft damage. This review outlines the incidence, timing, risk factors, prevention and treatment of non-viral infections in paediatric RTR by critically reviewing current immunosuppressive regimens, their risk–benefit ratio in order to optimise renal allograft survival with reduced rates of rejection and infectious complications.

Keywords Paediatric renal transplantation · Non-viral infection · Immunosuppression minimisation · Risk of infection · Graft survival

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Introduction

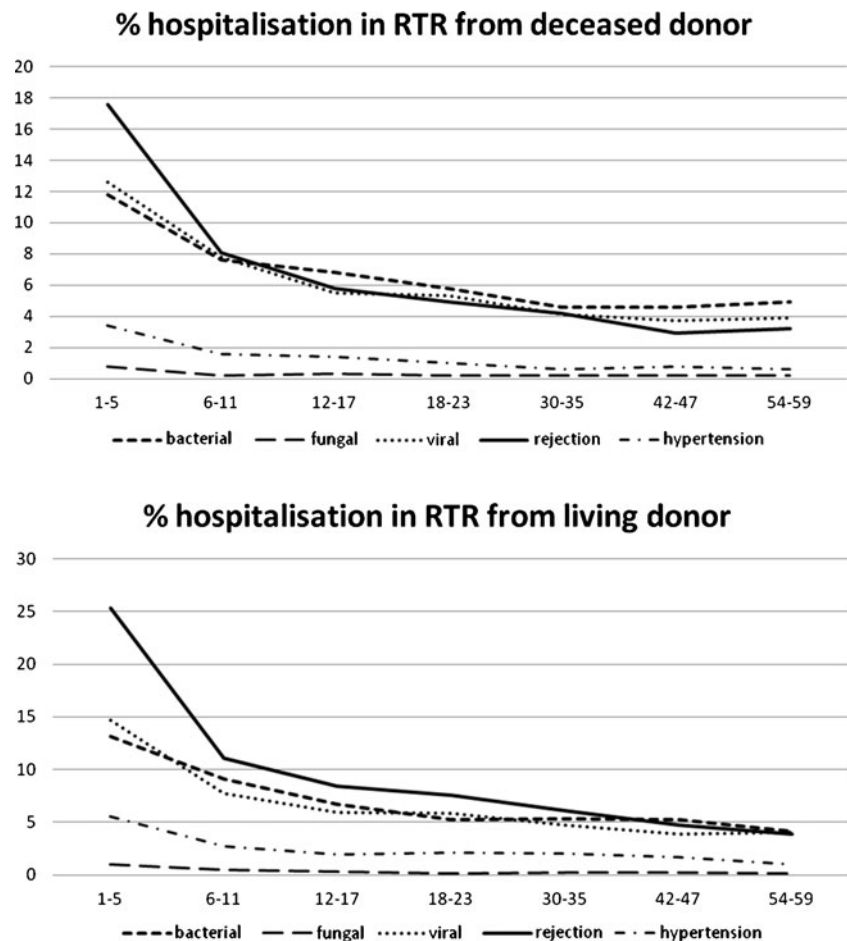
Renal transplantation is the gold standard therapy for children with end-stage renal failure (ESRF). Renal transplantation (RT) frequently restores the potential for normal growth and development with improved morbidity and mortality rates and reduced cardiovascular complications compared with dialysis [1, 2]. Short-term renal allograft survival rates have improved with the advent of newer immunosuppressive medications, but carry the risk of increased infectious complications [3].

Infection is the most common cause of death after transplantation in 24–56% of cases, with cardiovascular disease accounting for 30–36% and malignancy 11–20% respectively [4–9]. In a recent analysis of the North American Pediatric Renal Trials and Collaborative Study (NAPRTCS), post-transplant infections exceed acute rejection as the cause of hospitalisation in the first 2 years following RT (Fig. 1) [10]. In 2000, the risk of hospitalisation for post-transplant infection was twice that for acute rejection. The optimal approach for patient and renal allograft survival is a balance between the prophylaxis and treatment of rejection and the risk of infections using minimal immunosuppression.

Complications of immunosuppression account for the most significant morbidity and mortality following organ transplantation. Infection, both sepsis-related and due to opportunistic organisms, have increased with the use of more potent immunosuppressive agents. Opportunistic infections are the most severe of these complications and are most frequent in the early post-transplant period when RTR are highly immunosuppressed [11].

There are a broad range of potential sources of infection (latent viruses, hospital and community acquired) in a host that has an impaired inflammatory response by immunosuppression, which attenuates the signs and symptoms of invasive infections. This has to be balanced with the toxicity of

Fig. 1 Post-transplant reasons for hospitalisation for living and deceased donor source renal transplant recipients (RTR) in the first 59 months of follow-up. (Data derived from North American Pediatric Renal Trials and Collaborative Study (NAPRTCS) Annual Report 2008.)



antimicrobial medications and their interaction with immunosuppressive therapy [12].

Increasingly, potent immunosuppressive agents have dramatically reduced the incidence of biopsy-proven acute cellular rejection of transplanted organs while increasing patients' susceptibility to opportunistic infections and malignancy. There is also an increased number of infections due to organisms with antimicrobial resistance [13].

Paediatric RT carries a higher risk of infectious complications compared with adult counterparts, due to reduced exposure in a developing immune system. Children with chronic kidney disease (CKD) and ESRF requiring dialysis may have inadequate nutrition and growth, leaving them compromised at the time of transplantation. Their small size makes surgical procedures more complex and predisposes them to gastrointestinal, pulmonary and vascular complications that can increase the risk of infection [11].

Risk of infection in renal transplant recipients (RTR)

The risk of infections in RTR is determined by the interaction between the exposure to potential pathogens the individual encounters and the individual's net state

of immunosuppression [14–16]. This refers to all factors that contribute to the patient's risk of infection, including the dose, duration and type of immunosuppressive therapies, the presence of metabolic factors like malnutrition and uraemia, the presence of immunomodulating viral infections (including *Cytomegalovirus* [CMV] and Epstein–Barr virus [EBV]; Table 1) [17]. Even minimal environmental exposure to organisms of low virulence can cause an invasive infection that is most likely early post-transplantation when the immunosuppressive burden is greatest [14]. CMV infection may cause both invasive disease and a variety of secondary immune phenomena in RT, increasing the risk of opportunistic infections [15, 18, 19].

Timing for infection after transplantation

Early post transplant infections

Opportunistic infections (viral, fungal, nocardial and protozoal) are almost non-existent in the first month after transplantation (Fig. 2). The major causes of infection are bacterial wound, pulmonary, urinary tract and intravenous line and catheter-related infections seen in patients after any

Table 1 Factors affecting the net state of immunosuppression in renal transplant recipients (RTR). Reproduced with permission from [17]

Factors affecting the net state of immunosuppression in RTR
Immunosuppressive therapy: dose, duration and temporal sequence
Haematological features: neutropaenia, lymphopaenia
Underlying immunodeficiency: autoimmune disease, functional immune deficits
Integrity of the mucocutaneous barrier: catheters, epithelial surfaces, devitalised tissue, fluid collections
Metabolic conditions: uraemia, malnutrition, diabetes mellitus, liver disease
Infection with immunomodulating viruses: <i>Cytomegalovirus</i> , Epstein–Barr virus, hepatitis B and C viruses, human immunodeficiency virus

operative procedure. The effects of these infections are obviously more complex in RT [16].

The infection in the first month after transplantation can be transmitted from the donor (which may include the cause of death of deceased donors) or can be untreated infection in the recipient. Donor-derived infections can be active but not recognised at the time of donation. This group of infections

may include bacteria and fungi (staphylococci, *Streptococcus pneumoniae*, *Candida* species, *Salmonella*, *Escherichia coli*). Cultures from the donor, transport medium and recipient at the time of transplantation are necessary to guide antimicrobial therapy.

Patients waiting for transplantation may become colonised with nosocomial, antimicrobial-resistant organisms, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, antimicrobial resistant Gram-negative bacteria, fluconazole resistant *Candida* species, *Aspergillus* species and *Clostridium difficile*. The incidence is increased in those who have had procedures previously (e.g. bladder augmentation, gastrostomy and other catheter exit site colonisations and infections). After transplantation these organisms may infect wounds, catheters, haematomas and ascitic fluid or potentially cause pneumonia.

Infection 1–6 months after transplantation

The first 6 months post-transplantation is the critical period for RTR in terms of the greatest risk of life-threatening infections owing to high-dose immunosuppressive medications, the risk

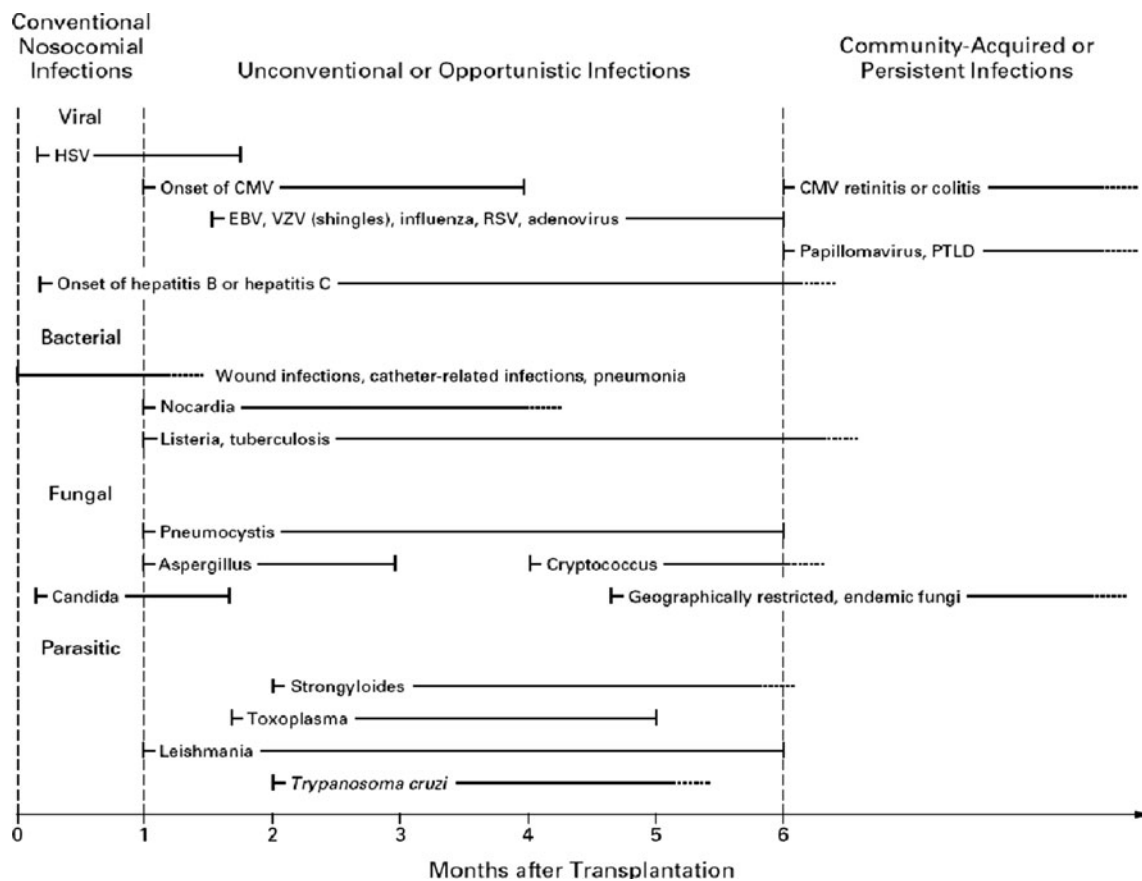


Fig. 2 Usual timing of infections after renal transplantation. Zero indicates the time of transplantation. Solid lines indicate the most common period for the onset of infection; dotted lines and arrows indicate periods of continued risk at reduced levels. HSV: herpes simplex

virus; CMV: *Cytomegalovirus*; EBV: Epstein–Barr virus; VZV: *Varicella zoster* virus; RSV: respiratory syncytial virus; PTLD: post-transplantation lymphoproliferative disease. Reproduced with permission from [15]

of CMV infections (which itself is immunosuppressing) and therefore increased risk of opportunistic infections. The combination of sustained immunosuppression and immunomodulating viruses increases the likelihood of opportunistic infections (including *Pneumocystis jiroveci*, *Aspergillus species*, *Listeria monocytogenes*) in the absence of an excessive epidemiological hazard.

Human CMV is generally considered to be the most frequently occurring opportunistic pathogen and the most important infectious agent in RT. Ganciclovir, a synthetic nucleoside analogue, is the medication currently most efficacious in both prophylaxis and treatment of CMV disease after RT and can provoke neutropaenia (depending on the duration of the therapy), thereby predisposing RTR to a higher risk of opportunistic infections.

Infection more than 6 months after transplantation

Patient and renal allograft survival rates have improved during the first year after transplantation [6–9]. RTR with good renal allograft function are maintained on reduced immunosuppressive therapy from 6 months after transplantation with lower infectious risks, although some patients continue to have increased susceptibility (e.g. hostile bladders) [15, 20]. In this period, excluding patients with chronic viral infections, there is an increased risk of opportunistic infections in patients who have had an increased immunosuppressive burden due to acute renal allograft rejection [15].

Common non-viral infections

Bacteraemia

It is well known that bacteraemic infections are a major cause of death among organ transplant recipients. Patients receiving deceased donor renal transplants are susceptible to various bacterial infections including bacteraemia and septicæmia and the results of antibiotic treatment are dependent on both the nature of the infecting organism and the presence of serious underlying complications [21]. The great majority of patients with bacteraemia have severe underlying disease or have undergone surgical procedures, and high incidences of bacteraemia have been described following urinary tract surgery or instrumentation, in severe skin infections and burns, and in patients with impaired body defence mechanisms (Table 2).

Fungal infections

There are two general categories of fungal infection that can occur in RTR: disseminated primary infection with one of the geographically restricted systemic mycoses (histoplasmosis,

Table 2 Risk factors for bacteraemia

Risk factors for bacteraemia

Aetiology of ESRF (autoimmune diseases with complement deficiencies (e.g. systemic lupus erythematosus and other glomerulonephritis with complement defects), glomerulonephritis with previous use of immunosuppressants)
Induction therapy with lymphocyte depletion
Early renal allograft rejection and use of pulsed-dose corticosteroids
Recurrence of primary disease and use of plasmapheresis, cyclophosphamide and rituximab
Active or latent infection in the donor or recipient
Technical complications: prolonged intubation, wound infection and poor healing, bleeding, anastomotic leak
Previous vascular line for haemodialysis, peritoneal dialysis (PD) catheter, urinary catheters
Previous major surgical procedures
Cardiac–respiratory tract diseases or abnormalities

ESRF, end stage renal failure

coccidioidomycosis, blastomycosis) and reactivation infection with fungal species that rarely cause invasive infection in the normal host (*Aspergillus* spp., *Candida* spp., *Cryptococcus*). Infection through intravenous cannulae with candida species is one of the most common in RTR [22]. Treatment of invasive fungal infections in RTR must be prolonged and given intravenously even if it is complicated by the fact that the administration of most antifungals (such as amphotericin and fluconazole) can affect the pharmacokinetics of calcineurin inhibitors. It is important to monitor renal function and calcineurin inhibitor levels during treatment.

Parasitic infections

Some of the parasites that can cause opportunistic infections in RTR are geographically restricted like malaria, *Strongyloides*, *Leishmania*, schistosomiasis, *Trypanosoma cruzi*; others, like toxoplasmosis and *Cryptosporidium*, are more diffuse. *Strongyloides* is a disease caused by an intestinal nematode and has a prevalence of 0.4–4% in the USA and is transmitted by faecal–oral spread and possibly with the renal allograft [23]. The clinical presentation of strongyloidiasis in RTR is variable and often atypical, with the majority of cases presenting during the initial 4 months after transplantation with gastrointestinal and pulmonary symptoms. Leishmaniasis is a rare protozoal disease in the USA, but is endemic in Latin America, the Middle East and North Africa. Cutaneous leishmaniasis is almost the only one encountered, although visceral leishmaniasis occurs very rarely in recipients of solid organ transplants (SOT), but is associated with an elevated mortality rate despite treatment [24]. The use of donor and recipient screening for *Toxoplasma* in the era of universal co-trimoxazole

prophylaxis is controversial [25]. A Canadian study reviewed *Toxoplasma* serology in 1,006 adult SOT recipients. The seroprevalence was higher among the recipients (17.8%) than the donors (13.4%). Only 4 patients seroconverted, and the authors reported no clinical disease, so routine screening should not be offered, especially when prophylaxis is given. This may differ in paediatric RTR where mismatches (positive donor, negative recipient) may be more common, especially in regions where seroprevalence is high. There is a higher risk of severe, disseminated disease in children.

Potential sources of non-viral infections

Donor-derived infections

The transmission of infections from organ donors can be due to latent infection in transplanted tissues (CMV, tuberculosis), or to active donor infections like viraemia or bacteraemia (which may have been the cause of death in deceased donors). Pre-transplantation screening is essential in preventing serious post-transplant infection, either excluding a donor or defining the need for specific antimicrobial therapy after transplantation. Organs from donors with specified known infections may be considered for specific recipients, based on the urgency of the need for transplantation and the availability of effective antimicrobial therapies.

Transplant medium-derived infections

The perfusion fluid used to perfuse and preserve the kidneys prior to transplantation represents a potential medium in which organisms can grow. Contamination rates of 7–24% have been reported and both Gram-positive and Gram-negative organisms have been isolated [26–29]. The majority of organisms isolated are coagulase-negative staphylococci [26, 30], but also *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which can be associated with sepsis (local and general), anastomotic failure and renal allograft loss [31, 32]. The frequency with which contamination occurs justifies routine culturing of the perfusion fluid to ensure that potentially highly virulent organisms are not missed and treatment is instituted appropriately. The fact that culture results are invariably not available in time for transplantation further emphasises the importance of peri-operative antibiotic prophylaxis. In view of the variation in protocols and the possibility that virulent organisms requiring extended or modified antibiotic regimens may be necessary, alerting the recipient centre to the results of procurement perfusion fluid samples would be useful to ensure that potentially serious infective complications are prevented [33].

Peritoneal and haemodialysis catheters

As a foreign body, peritoneal dialysis (PD) and haemodialysis catheters represent a potential source of infection, particularly for immunosuppressed transplant patients. Early bacterial infections remain a significant problem during the first few post-operative months. Any catheter left in situ for a prolonged period can increase the risk of infection. Despite this increased risk, early primary non-function and delayed graft function remain a significant problem in deceased donor RTR, which can necessitate the use of a PD or haemodialysis catheter for dialysis. Published recommendations regarding the time of PD catheter removal have varied from as early as the time of transplantation to 4 months later [34, 35]. Two retrospective paediatric studies in 1994 and 2001 reported a higher use of PD catheter during the first month post-transplant (38–50% of deceased donor RTR) for acute rejection or primary allograft non-function. There have also been reported risks of infection by 3 months post-transplantation [35].

We advocate the removal of the peritoneal or haemodialysis catheter at the time of transplantation in living donor (LRDT) transplants if there are no surgical complications and at the same time as the removal of the transplant ureteric stent (TUS) in deceased donor RTR (which is up to 6 weeks post-transplantation), although it can be removed earlier if there is good renal allograft function to reduce the risk of infectious complications.

Transplant ureteric stent

Major urological complications (e.g. urinary leak, obstruction) after RT contribute to patient morbidity and compromised renal allograft function. The majority arise from the vesico-ureteric anastomosis and present early after transplantation. TUS have been successfully used to treat such complications. A recent Cochrane review of seven studies (1,154 patients) reports that the incidence of major urological complications is significantly reduced by the use of prophylactic stenting and that urinary tract infections (UTI) are more common in patients with TUS. The addition of antibiotic prophylaxis (with co-trimoxazole) does not alter the incidence of UTI [36]. However, there can be more complications with TUS rather than UTI, like migration, macroscopic haematuria and pain. These complications may be related to how long the TUS remains in situ. In our experience we reviewed retrospectively 180 RTR from 2002 to 2008 with cystoscopic TUS removal performed in 151 patients at 8–90 (median 42) days with TUS complications in 20% (16 UTI, 9 macroscopic haematuria, 4 migration, 1 blocked stent) [37]. These resulted in early TUS removal in 64% of patients, with ureteric complications found in 5% of patients (two leaks and five stenoses). Six

patients had TUS sutured with the catheter, although no patients in this group developed stent or ureteric complications. Suturing the TUS to the catheter facilitates early removal and may reduce the incidence of stent complications [37].

Urinary tract infection

Urinary tract infections (UTI) are the most common form of bacterial infection in RTR and an important clinical problem encountered in 15–33% of paediatric RTR [38–41]. Meticulous surveillance, diagnosis and treatment of UTI are necessary to minimise acute morbidity and compromise of long-term renal allograft function from transplant pyelonephritis and scarring. It is important to distinguish asymptomatic bacteriuria, lower UTI (cystitis) and febrile UTI (transplant pyelonephritis) as the latter can cause organ damage and can promote the development of chronic allograft dysfunction with biopsy-confirmed chronic changes with interstitial fibrosis and tubular atrophy (IF/TA). Many children with ESRF who receive renal transplants have lower urinary tract abnormalities, bladder pathology with abnormal urodynamic assessment and a significant post-micturition residual requiring urinary catheterisation. It is common for these patients to have asymptomatic bacteriuria and develop UTI. Febrile UTI may cause significant morbidity and is usually associated with acute renal allograft dysfunction. The acute deterioration of renal function during UTI is a well-known feature [37, 40], which, together with the significant inflammatory parenchymal response, emphasises the potential risk of tissue damage in the transplanted kidney in acute and long-term follow-up, despite normalisation of renal function after UTI. In addition, acute rejection episodes may be triggered by febrile UTI [42].

Although *Escherichia coli* remains the most frequently isolated microorganism [43–45], it is isolated less frequently than in the general paediatric population. This may be due to underlying immunosuppression, colonisation, antibiotic prophylaxis and mainly the higher risk of bladder malformations in this population. Risk factors for developing febrile UTI include anatomical, functional and demographic factors, as well as baseline immunosuppression and foreign bodies, such as catheters and stents. Underlying urological abnormalities have to be regarded as risk factors for UTI even before transplantation, such as hydronephrosis, vesico-ureteric reflux (VUR), and/or neurogenic bladder, often in combination. Bladder augmentation has been found to be the most significant predisposing factor for bacteriuria in RTR, which may result in scarring of the transplant [44].

99-Tc-Dimercaptosuccinic acid (DMSA) scintigraphy is regarded as the gold standard in the diagnosis of acute

pyelonephritis as well as in the documentation of residual scarring in repeat scans performed 6 months after UTI. Long-term data suggest that febrile UTI might lead to focal defects on DMSA scanning [46, 47], but other events, such as vascular complications and renal biopsy, may also do so, and need to be considered in the interpretation of the images [48]. We perform a baseline DMSA scan within the first 3 weeks post-transplantation in all patients at risk of developing UTI (such as those with hostile bladders and at risk of pyelonephritis in the future).

Transplantation in a patient with lower urinary tract dysfunction (LUTD) is associated with a high incidence of urological and infectious complications. However, despite this, several studies have found no differences in patient survival or transplant outcome between RTR with and without LUTD [49–52]. Surgery of the urinary tract before listing for transplantation is often necessary and should decrease the risk of infections. There is a higher incidence of UTI in RTR with neurogenic bladder, with associated morbidity and poorer renal allograft function [53]. There are no controlled data available demonstrating that bladder augmentation procedures prevent or decrease the rate of UTI after transplantation. However, it seems mandatory that evaluation and treatment of neurogenic bladders are very important, should be performed before renal transplantation and require specific follow-up after transplantation. Because of the high urological complication rates, careful surveillance of lower urinary tract function by urodynamic evaluation is essential before transplantation. A review of 25 articles on transplantation in patients with urinary tract dysfunction has suggested that bladder reconstruction should be performed before transplantation when clinically indicated [51], although one study suggests that there is no adverse outcome with regard to long-term renal allograft survival or function from transplantation into the unaugmented valve bladder [54]. There is still considerable controversy over the best way to manage RTR with LUTD, with no established guidelines defining criteria for reconstructive surgery, the optimal surgical procedure; or when, in relation to renal transplantation, surgery should be carried out. Treatment options for LUTD are divided into conservative measures, including bladder training with or without pharmacological agents or clean intermittent catheterisation or both, and reconstructive surgery procedures (drainage, augmentation, urinary diversion). Our current approach is for accurate urodynamic assessment before transplantation in paediatric patients with ESRF and LUTD. If the cystometric bladder capacity is lower than that expected and/or in presence of high changes in detrusor pressure with or without VUR, we consider a trial of bladder cycling and repeat urodynamics. We perform bladder surgery prior to renal transplant if the urodynamics continue to show signs of reduced bladder capacity [55].

Vesico-ureteric reflux (VUR) is present in many patients as an underlying diagnosis, and UTI could affect the native and the transplanted kidney (or both). Some authors recommend native nephrectomies with VUR to decrease the risk of native-kidney UTI after transplantation, although no controlled studies are available [56]. Pre-transplant anti-reflux surgery does not reduce the risk of febrile UTI after transplantation. In a recent study, Basiri et al. compared 36 patients without VUR, 12 children with VUR who underwent reimplantation and 17 children who did not. The frequency of febrile UTI after surgical correction of VUR before transplantation remained higher than in RTR without VUR [57]. VUR does not need to be corrected before transplantation, unless it is causing symptoms or infection [58–60]. Parenteral antibiotics are usually indicated for RTR with transplant pyelonephritis, although controlled data are not available [61].

Prevention of infection

Vaccinations

Pre-transplantation immunisation is one of the best means of preventing serious infections. RTR have an advantage compared with recipients of other solid organs as they have time before transplantation to be fully immunised. RTR should be protected against tuberculosis (TB), pneumococcus, meningococcal group C, diphtheria, tetanus, pertussis, inactivated poliomyelitis, *Haemophilus influenzae* B, measles, mumps, rubella, hepatitis B, varicella and influenza. All these vaccines are safe and efficacious in patients with CKD and ESRF on dialysis, although vaccine responses may be reduced because of proteinuria (from nephrotic syndrome) or in inherently immunocompromised children (such as systemic lupus erythematosus) or those on immunosuppressive medications for their underlying condition [62–64]. The incidence of TB in RTR varies in different groups of patients from around the world with rates of 0.5–1% in North America, 1–4% in Europe and the Middle East, and 10–13% in India [65]. In the USA, the minimal annual incidence of TB in RTR has been reported to be 37 times higher than in the general population. Uraemia, with its immunosuppressive effects, and high-dose corticosteroids and other immunosuppressive medications may promote reactivation of latent TB. There can be a good response to treatment of TB in RTR, but there are interactions between antituberculous medications and immunosuppressive agents. It is advocated to vaccinate all patients younger than 6 years of age against TB and to vaccinate older patients if the tuberculin skin test is negative. The tuberculin skin test is required before vaccination in children who were born or lived for more than 1 month in countries where the TB incidence is high. Varicella is a common disease in childhood

and it is very contagious, although usually it is a very mild infection, but in the immunocompromised host could be very serious with complications like hepatitis, pneumonia, encephalitis and even death. All patients who are seronegative must be vaccinated before transplantation. The live-attenuated vaccine is safe and gives persisting immunity to chickenpox, even if cases of disease are described in immunocompromised patients that had received the vaccine [66].

Peri-operative antibiotic prophylaxis

In our centre, we advocate antibiotic therapy with ciprofloxacin as part of the operative and postoperative management of RTR with intravenous ciprofloxacin 5 mg/kg over 30–60 min, to be given with pre-medication and continued on a once daily basis until a negative culture has been obtained from the transplant medium fluid. Other broad-spectrum antibiotics can be used as perioperative prophylaxis. Cephalosporins such as ceftriaxone can be administered intravenously on a once-daily basis.

Antimicrobial prophylaxis has significantly altered the severity and incidence of infections post-transplantation. By far the most effective prophylactic therapy is co-trimoxazole (trimethoprim and sulfamethoxazole) for the first 6 months after transplantation. The incidence of *Pneumocystis jiroveci* pneumonia (PJP) among RTR not receiving co-trimoxazole prophylaxis has been reported to be 5–10% [22]. Their routine use has eliminated *Pneumocystis jiroveci* and UTI. The major side-effect of co-trimoxazole are rashes and haematological effects including leucopaenia and thrombocytopaenia.

A recent report described 33 RTR who developed PJP without prophylaxis in Japan [67]. PJP prophylaxis has been abandoned in Japan because of the nephrotoxicity of co-trimoxazole. The European Renal Transplant Guidelines recommends PJP prophylaxis for at least 4 months post-transplantation [68], whereas another report recommended the use of PJP prophylaxis for 6–12 months. However, in this decade, large outbreaks of PJP after an index case have been reported in RTR in France (2004), Germany (2005 and 2008) and the Netherlands (2007) [69–72]. We recommend PJP prophylaxis for 6 months post-transplantation (upper limit of incubation period) in all RTR.

Antibiotic prophylaxis with co-trimoxazole is also useful in view of the high prevalence of UTI and transplant vesico-ureteric reflux. Most paediatric renal transplant centres prescribe prophylactic antibiotics with co-trimoxazole for the first 3–6 months post-transplantation, which also covers against PJP [33, 73]. Several studies have shown how co-trimoxazole is effective in preventing UTI and Gram-negative sepsis of urinary tract origin [74, 75]. However, not all studies confirmed a beneficial effect and even demonstrated a high bacterial resistance rate [44]. If prophylactic

antibiotics are used, it seems that they should be administered for prolonged periods, as UTI may occur late, especially in girls. The rate of UTI in adolescent girls has been reported to be twice as high as in male RTR for anatomical reasons such as a shorter urethra and predisposing immunological factors [61].

Role of immunosuppression

Immunosuppression has an important impact on defence mechanisms and risk of infections after renal transplantation. There have been considerable changes in the use of immunosuppression over the years. A recent report of the NAPRTCS shows that the use of cyclosporin has decreased from 82.3% in 1996 to 20.7% in 2003. In contrast, use of tacrolimus has increased from 5.5% to 67.1% over the same period. There has also been a move away from azathioprine (AZA), from 56.4% to 1.9%, towards mycophenolate mofetil (MMF), the use of which has now reached approximately 57.4%. Antibody induction has also moved away from antithymocyte globulin (ATG) and OKT3 monoclonal antibody to anti-IL2 receptor blockers. The use of steroid-sparing regimens is also becoming common [76]. Several studies have analysed the possible association between immunosuppression regimens (induction and maintenance therapy) and viral, bacterial or fungal infections.

Induction therapy

Almost 70% of RTR receive induction therapy with either rabbit ATG or non-lymphocyte-depleting monoclonal antibodies that target interleukin-2 receptor (basiliximab). Their impact on infections has been analysed in several studies. While the use of induction agents has been associated with a lower incidence of acute rejection [77, 78], their role in renal allograft survival is more controversial and there is a higher incidence of infections in patients receiving antibody induction therapy with both monoclonal and polyclonal antibodies [79, 80].

In a recent analysis of the NAPRTCS database, 3,106 children undergoing a transplant between 1996 and 2002 with 2-year follow-up were analysed [79]. This NAPRTCS report showed that in comparison to those receiving no induction therapy, patients receiving monoclonal antibody were more likely to have infections (42% vs 34%), both bacterial (24% vs 21%) and viral (29% vs 21%). The hospitalisation rates for infections were similarly higher in patients receiving polyclonal antibodies in comparison to those with no induction therapy (45% vs 34%), both bacterial (28% vs 21.2%) and viral (30% vs 21%). At 2 years post-transplant there was no difference in the risk of having

one acute rejection or in the percentage of graft failure comparing patients who had received polyclonal or monoclonal antibodies and patients who did not receive induction therapy [79].

Many studies reported a lower risk of infections and of CMV disease with basiliximab compared with ATG [81–83]. One recent prospective, randomised, international study comparing the use of ATG and basiliximab in 278 patients reported a higher incidence of non-viral infections, particularly UTI, in the ATG-treated group (86% vs 75%, $p=0.03$), but a lower incidence of CMV disease (8% vs 18%, $p=0.02$) [84].

It may be prudent to select patients for antibody induction therapy for those RTR undergoing second or subsequent renal transplant, patients with cytotoxic antibodies and those in whom there is a need to minimise other immunosuppressive agents such as utilising steroid minimisation protocols. The use of ATG is reserved for patients with corticosteroid-resistant acute rejection.

Maintenance therapy

A large prospective study with intention-to-treat analysis has evaluated 1,398 adult transplant recipients of the RESISTRA Transplant Network. With the exception of sirolimus there was no association between the immunosuppression regimens and the development of specific infection. The probability of developing CMV infection in patients not receiving sirolimus was significantly higher than in patients who did receive sirolimus. Sirolimus was associated with a higher risk of surgical site infection [85].

Sirolimus inhibits growth factor production in response to tissue injury and it has been associated with a higher number of bacterial infections [86–88] and pneumonia [89–91]. Different studies have confirmed a decreased rate of CMV infection in patients receiving sirolimus [92–94] or everolimus [95, 96].

Mycophenolate mofetil has been associated with a higher risk of CMV infection in some studies [97, 98] and a decrease in *Pneumocystis jiroveci* infections in others [99]. Different studies confirmed that in maintenance therapy, no differences in infection rates have been observed among patients receiving cyclosporin or tacrolimus [100–102]. A recent study reviewed the incidence of infections in RTR who have received intravenous rituximab. They were at a significantly lower risk of viral infections, a higher risk of fungal infections and there was a high percentage of deaths related to infections, mostly in patients who had also received ATG [103].

Summary

Renal transplantation is the gold standard treatment for children with ESRF. There has been a significant improvement in

patient and renal allograft survival in the last few decades with newer potent immunosuppressive agents and the use of antimicrobial prophylaxis. However, non-viral infections continue to be a serious complication for RTR. Most of the opportunistic infections occur in the first 6 months post-transplantation and can be related to catheters or lines left in situ post-transplantation. UTI are the most frequent infections that can provoke renal allograft damage and occur more frequently in patients with LUTD. Therefore, it is mandatory to perform an accurate urodynamic assessment pre-transplantation and have multi-disciplinary discussion of the best surgical approach. The use of potent immunosuppressive agents with monoclonal or polyclonal antibodies increases the risk of infection. Our current opinion is that the optimal approach to preserving renal allograft function is to minimise the immunosuppressive burden, thereby achieving a balance between the risk of rejection and infectious complications.

Questions (answers are provided following the reference list)

1. What proportion of the mortality rate is due to infections after renal transplantation ?
 - a. 5–15%
 - b. 15–25%
 - c. 25–55%
 - d. 55–75%
 - e. 75–80%
2. What is the most frequent infection in the first month after renal transplantation ?
 - a. Fungal infections
 - b. Parasitic infections
 - c. TB
 - d. UTI
 - e. Viral infections
3. Which is the current statement regarding prophylaxis with co-trimoxazole after renal transplantation:
 - a. Must be given for 1 year post-transplant
 - b. Not currently advocated
 - c. Significant side-effects
 - d. Useful in preventing PJP
 - e. Useful in preventing PJP and UTI
4. What is the optimal time for the removal of PD catheters in children who receive a successful living, related renal transplant?
 - a. At the time of the transplant
 - b. In the first month post-transplantation
 - c. Within 2 months post-transplantation
 - d. Within 3 months post-transplantation
 - e. Within 6 months post-transplantation
5. Which immunosuppressive treatment is most associated with a higher risk of non-viral infections?
 - a. ATG
 - b. Everolimus
 - c. MMF
 - d. Sirolimus
 - e. Tacrolimus

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Answers

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2. d
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4. a
5. a