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REVIEW

Infectious disease risks in pediatric renal transplantation

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Abstract
Renal transplantation is a vital treatment option in children with ESRD with more than 10,000 pediatric kidney transplants and survival rates of greater than 80% at 10 years post-transplant in the USA alone. Despite these advances, infection remains a significant cause of morbidity in pediatric recipients. Screening potential organ donors and recipients is imperative to identify and mitigate infectious risks in the transplant patient. Despite the unique risks of each patient, the timing of many infections post-transplant is predictable. In early post-transplant infections (within 30 days), bacterial and fungal pathogens predominate with donor-derived events and nosocomial infections. In the intermediate period (31–180 days after transplant), latent infections from donor organs, such as EBV and CMV, develop. Late infections occurring > 180 days after the transplant can be due to latent pathogens or community-acquired organisms. Approaching an infectious evaluation in a pediatric kidney recipient requires finesse to diagnose and treat this vulnerable population in a timely manner. The following article highlights the most relevant and common infections including clinical manifestations, risk factors, diagnostic techniques, and treatment options.

Keywords Pediatric infections · Renal transplant · Post-transplant infections · Infection in immunocompromised child

Introduction

Renal transplantation is the first-line treatment in children with end-stage renal disease (ESRD) with more than 10,000 pediatric kidney transplants performed in the USA alone in the past 20 years [1]. Over time, the improved management of patients has led to survival rates of greater than 80% at 10 years post-transplant in the USA. Despite these advances, infection causes significant morbidity in pediatric recipients. Pediatric transplant patients are at risk for routine childhood illnesses in addition to infections related to their immunosuppressed state. Early in the post-transplant period, bacterial infections occur, such as urinary tract infections (UTIs) and bloodstream infections (BSIs). Children are at increased risk for viruses such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in the intermediate and late transplant periods, often due to lack of infection prior to transplant and receipt of an organ from a seropositive donor. BK polyomavirus (BKPyV) poses a unique challenge in the renal transplant population resulting in polyomavirus-associated nephropathy (PVAN) and allograft loss [2].

Approaching an infectious evaluation in a pediatric kidney recipient requires an appropriate index of suspicion to diagnose and treat children in a timely manner. The following article highlights the most relevant and common infections in this vulnerable population including clinical manifestations, risk factors, diagnostic techniques, and treatment options.

Pre-transplant evaluation

A thorough evaluation of the donor and recipient is essential to minimize infections prior to, during, and after transplantation. A detailed history can allow clinicians to identify potential exposures that may increase the risk for infections in the peri- and post-transplant period. Serologic assessment for both vaccination responses and infections that risk reactivation in immunosuppressed individuals are necessary to assess eligibility and timing of transplantation. Other risk factors for infection that can be evaluated in the pre-transplant assessment include chronic malnutrition, primary disease process, underlying anatomic defects, and young age at the time of transplantation.

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Screening

Screening of potential organ donors and recipients is imperative to evaluate for infectious risks in order to increase survival in the transplant patient. History, physical, and laboratory evaluation can reveal multiple pathogens that may be transmitted from the organ donor to the recipient through transplantation. In children, living donors are the most common source of renal allograft with parents comprising 80% of donors in the USA. Pre-transplant screening of a potential donor should identify treatable infections that should be addressed prior to donation including Hepatitis B and C. For the recipient, screening assists with prevention planning in addition to identification of infections that require therapy prior to transplantation such as latent tuberculosis [3]. Guidelines for screening have been developed by international transplant groups [4, 5]. Commonly, serologic testing for human immunodeficiency virus (HIV), herpes simplex (HSV), cytomegalovirus (CMV), the hepatitides (HBV, HCV), syphilis, Epstein-Barr virus (EBV), and varicella zoster virus (VZV) is performed [6]. Other testing for pathogens such as *Mycobacterium tuberculosis* via purified protein derivative (PPD) or interferon-release assay (IGRA), *Coccidioides* using antibody screening, and *Strongyloides* with antibody screening should be considered in patients from endemic areas or at epidemiologic high risk. However, in children < 18 months, serologic testing may not be reliable due to passive maternal antibodies and should be evaluated cautiously.

Vaccination

Pediatric patients with chronic kidney disease should receive standard immunizations as recommended by local and national authorities. Transplant recipients are at a higher risk with more severe courses of vaccine-preventable infections, and immunization of the patient and their close contacts is important pre-transplant. Literature suggests that up to 71% of children had not received age-appropriate vaccinations prior to solid organ transplantation although this includes heart and liver transplant recipients [7]. Serologic assessment for vaccine responses to measles, hepatitis B, hepatitis A, varicella, tetanus, and pneumococcus can guide pre-transplant immunization recommendations. While patients on dialysis may have lower seroconversion rates following vaccination with quickly declining antibodies compared to healthy peers, [8, 9] immunization responses pre-transplant are more robust than primary vaccinations initiated post-transplant. Further, pre-transplant immunization is associated with increased memory responses with post-transplant booster dosing. Therefore, pre-transplant immunization is strongly advised and, due to the availability of dialysis, transplantation may be delayed until the appropriate vaccinations are completed [10]. For additional vaccinations required post-transplant, most inactivated vaccines are considered safe. The data is limited on the ideal time for after transplant but it is suggested around 3–6 months when immunosuppression is tapered to maintenance levels.

Invasive pneumococcal disease is a common cause of infection in the post-transplant period. In addition to the standard 13-valent conjugated pneumococcal vaccine series, the 23-valent polysaccharide vaccine is recommended for children ≥ 2 years of age who are immunocompromised for coverage of additional serotypes [11]. Currently, live vaccines (measles, mumps, rubella, and varicella) are not routinely offered after transplant and should be prioritized before transplantation. Interestingly, Zamora et al. found that of the 17 pediatric renal transplant recipients who received the varicella vaccine, 94% tolerated the vaccine without complications [12]. Only three children developed a mild case of varicella, and 76% maintained antibodies for > 2 years, indicating that post-transplant vaccination is potentially safe if necessary.

Routine vaccinations for influenza for the patient and family members should be offered. Adult renal recipients who received influenza vaccines had seroprotection rates of 78.7–92.7% depending on the strain although many had been immunized previously [13]. Children also demonstrate immunity to influenza after immunization with weaker serologic responses demonstrated in those receiving mycophenolate, suggesting that the immunosuppressive regimen impacts immune response to influenza vaccination [14]. Most patients have no adverse events, and although there is a hypothesized risk for acute rejection, this has not been demonstrated clinically in kidney transplant recipients [15]. Prior to travel abroad, other vaccines for diseases should be considered based on the diseases endemic to the region such as meningococcus, rabies, *Salmonella typhi* (injectable vaccine), and Japanese encephalitis; although live vaccinations including oral polio, oral formulation of *Salmonella typhi*, and yellow fever should be avoided.

Post-transplant infections

Despite the unique risks each patient may have, the timing of many infections post-transplant remains fairly predictable. Within the first 30 days of transplant, recovery of bacterial and fungal pathogens is most common and can be associated with underlying pre-transplant conditions, nosocomial exposures, or surgical complications. Up to 50% of all bacterial infections occur within the first month of transplant [16]. In the intermediate period (31–180 days after transplant), infections may involve activation of latent pathogens either acquired from the donor organ in a naive recipient or reactivation in a recipient with pre-transplant seropositivity. Common examples include Epstein-Barr virus (EBV) and cytomegalovirus (CMV). CMV may also occur late (> 180 days) after transplant, especially after antiviral prophylaxis is

discontinued. Both intermediate and late infections can have significant morbidity with the development of allograft dysfunction or other disease in other organ systems such as with CMV [17]. Return to home and school activities leads to exposures that increase the risk for community-acquired infections transmitted by family, friends, or healthcare providers. The most common and problematic infections in pediatric kidney recipients are highlighted below.

Urinary tract infection

Urinary tract infections (UTI) are a common infectious complication in the renal transplant population, accounting for 45–72% of all infections and 30% of hospitalizations for sepsis in adults [18]. Fernandes et al. reported that 28% of pediatric kidney transplant recipients developed a febrile UTI [19]. The highest risk for UTI is within the first 6 months post-transplant. UTIs represent a spectrum of disease ranging from uncomplicated cystitis to pyelonephritis and urosepsis with significant morbidity and mortality, leading to 16% of all deaths and contributing to 7.7% of deaths attributable to graft failure in adult populations [20]. However, consequences may differ in pediatric patients as an Austrian study of 47 pediatric patients who had received renal transplants > 6 months prior did not find a significant difference in long-term allograft function or risk factors in the 35 children who developed symptomatic cystitis [21].

Urinary tract infection diagnosis uses similar criteria as the general population, although controversy exists on the current methodology of bacterial colony counts as cut-offs for diagnostic criteria in urine cultures have not been standardized in transplant patients. Asymptomatic patients with two or more consecutive clean-catch specimens with $\geq 10^5$ cfu/mL of identical organisms collected 24 h apart are considered to have asymptomatic bacteriuria. A single sample obtained via urethral catheterization with $\geq 10^2$ cfu/mL also meets criteria. A symptomatic UTI is characterized by suprapubic pain, dysuria, and urinary frequency/urgency. Pain at the renal allograft site may be suggestive of upper urinary tract involvement or pyelonephritis. Patients are considered to have complicated UTIs if the infection is associated with structural or functional abnormalities.

Common risk factors for the development of post-transplant infection of the lower and/or upper urinary tract include female sex, young age, reflux prior to transplant, a deceased donor, and the presence of a bladder catheter or stent with extended duration or other instrumentation. Underlying lower urinary tract disease is not only a well-documented cause of end-stage renal disease but also increases risk for UTI and future graft loss [22] in pediatric patients. Neurogenic bladder is problematic as clean intermittent urethral catheterization is a known risk factor for bacteriuria and recurrent UTI, placing these children at higher risk for UTI. The immunosuppression regimen itself may also be a contributing factor. For example, antimetabolites such as azathioprine, mycophenolate mofetil, and cell-depleting antibodies are associated with increased genitourinary infection rates [18].

The most common causative pathogen for UTIs in renal transplant patients is *E. coli*, accounting for 70% of cases [23]. Other organisms include gram-negative and gram-positive bacteria such as *Pseudomonas*, *Enterococcus*, and coagulase-negative *Staphylococcus*. Rarely, *Salmonella species*, *Mycoplasma hominis*, and *Ureaplasma urealyticum* are reported.

The management of asymptomatic bacteriuria remains controversial, and older studies suggest that treatment may not improve outcomes in the renal transplant population. In pediatric patients, post-transplant asymptomatic bacteriuria is more common in those with pre-transplant bacteriuria and in those with underlying genitourinary abnormalities including neurogenic bladders [24]. Due to the uncertainty in association with rejection and graft failure in early post-transplant (< 3 months), many practitioners repeat the urine culture to evaluate for contamination and offer a short course of antimicrobials based on the susceptibilities of the isolated organism [25].

Approaching a symptomatic UTI includes controlling potential sources of infection with removal of infected foreign material and administration of antimicrobials based on pathogen susceptibility. An oral fluoroquinolone, amoxicillin/clavulanic acid, or a third generation cephalosporin such as cefixime can be used for many gram-negative pathogens causing cystitis. Fosfomycin administration for *Enterobacteriaceae* such as *E. coli* is growing in the context of antibiotic resistance but should be limited to cystitis as it concentrates in the urine only [6]. Parenteral antibiotics should be considered for systemically ill children or in those unable to tolerate enteral medications. Appropriate empiric options include beta-lactam antibiotics such as cefepime, piperacillin/tazobactam, or fluoroquinolones. A carbapenem may be indicated if there is a history of extended spectrum beta-lactamases (ESBLs). In cases of mild infection, a short course of 5–7 days may be considered although some adult literature recommend no shorter than 7–10 days within the first 6 months of transplant [23]. A 14–21-day course of antimicrobials may be required in the setting of severe illness such as pyelonephritis or urosepsis [26]. Further complications such as a perinephric abscess may require surgical intervention or extended antimicrobial therapy.

In children with recurrent UTIs, the question of antibiotic prophylaxis frequently arises. A meta-analysis in 2011 showed decreased risk of bacteremic sepsis by 87% in adult kidney transplant patients receiving prophylaxis [27]. The risk for developing asymptomatic bacteriuria also fell by 60% during the first 6 months of the post-transplant period; however, there was no reduction in mortality or allograft dysfunction [27]. Trimethoprim-sulfamethoxazole was commonly prescribed in the past as prophylaxis but increased antimicrobial resistance has led to higher rates of nitrofurantoin use [28]. A

study in which 100 kidney transplant patients received ofloxacin prophylaxis found a decrease in UTIs and pyelonephritis by 63 and 71% respectively with an associated increase in fluoroquinolone-resistant strains of *Pseudomonas aeruginosa* [29]. Overall, antimicrobial prophylaxis for UTI prevention is controversial, and, although biologically plausible, should be considered with caution due to the other risks of prolonged antibiotic use. Other preventive measures include addressing structural abnormalities and voiding dysfunction, minimizing prolonged use of urethral catheters, and basic infection prevention teaching.

Not only is bacteriuria a common predicament but candiduria in renal transplant patients is a frequent issue as well, occurring in up to 11% of adult patients, many of whom are asymptomatic [30]. *Candida albicans* has been isolated in up to 44% of cases although other species are emerging including *C. glabrata* (26%) and *C. tropicalis* (11%) [31]. The impact of asymptomatic candiduria on patient outcomes is unclear with limited literature. Progression to serious disease with ascending infection, candidemia, or obstruction of the urinary tract from fungal balls is a potential concern. Risk factors for infection include female gender, hospitalization in the intensive care unit, previous antibiotics, indwelling catheters, neurogenic bladder, malnutrition, and diabetes mellitus.

For symptomatic patients, fluconazole for 14 days can be considered based on susceptibilities. Echinocandins, voriconazole, and intravenous amphotericin B do not concentrate well in the urine but penetrate tissues well and may have a role in pyelonephritis although the data is limited [32]. The current recommendation is to avoid treatment in those who are asymptomatic unless a urologic procedure is imminent or the patient is neutropenic.

In summary, UTIs after pediatric kidney transplantation is a complex issue as risk factors may not be readily modifiable. The optimal approach to asymptomatic bacteriuria, candiduria, and recurrent UTIs remains controversial with a lack of data on the long-term benefits of antimicrobial prophylaxis and concern for the development of multidrug resistant organisms.

Infections due to multidrug resistant organisms

The increasing prevalence of multidrug resistant (MDR) gram-negative infections globally has increased morbidity and mortality in transplant recipients. A multidrug resistant organism (MDRO) is defined as lack of susceptibility to one or more antibiotics in at least three classes of antimicrobials [33]. Unfortunately, pediatric studies in the transplant population are limited. Some MDR gram-negative infections reported in adult renal transplant patients include UTIs, pyelonephritis, bloodstream infections, and hospital-acquired pneumonias from *Enterobacteriaceae* and *Pseudomonas* species [34]. Suwantarat et al. reported that of children admitted to the pediatric intensive care unit, 1% of whom were solid organ transplant patients, 4% were colonized with a MDR *Enterobacteriaceae*, and an additional 4% became colonized with an MDRO during the hospitalization [35].

Risk factors for colonization and infection with resistant organisms are led by antibiotic exposure as with multiple antibiotic courses. Antibiotic prophylaxis against UTIs and treatment of asymptomatic bacteriuria are also contributing factors. For example, administration of TMP/SMX is associated with UTIs due to TMP/SMX-resistant pathogens in up to 62% of renal transplant patients [36]. Other risk factors include prolonged or previous stay in the intensive care unit, young age, combined pancreas-kidney transplant, post-transplant hemodialysis, and the presence of a central venous catheter.

In gram-negative organisms, ß-lactamase-mediated antibiotic resistance is common in both community- and hospital-acquired infections. One of the most frequently encountered patterns is characterized by extended spectrum ß-lactamases (ESBLs) where resistance genes lead to resistance to penicillins, cephalosporins, and monobactams. Carbapenem resistant *Enterobacteriaceae* (CRE) occurs phenotypically through ß-lactamases that hydrolyze all ß-lactam antimicrobials except for monobactams. Both ESBLs and CREs are growing in pediatric populations and are endemic in the developing world although specific impact after pediatric kidney transplant is unreported to date. A study in adult renal recipients found increased mortality in carbapenem-resistant *Klebsiella pneumoniae* bacteriuria when compared to those with carbapenem-susceptible *K. pneumoniae* bacteriuria (30 vs 10% with increased risk of recurrence at 50%) [37].

Similar to treatment for other bacterial infections, removal of infected hardware and drainage of fluid collections are important for bacteriologic cure and improved patient outcomes. In patients with ESBL-producing *Enterobacteriaceae*, carbapenems are an appropriate first-line option. Cefepime and piperacillin/tazobactam can be considered based on documented susceptibilities and infections with a likely low bacterial inoculum such as a UTI. CRE is more problematic and often requires combinations of colistin, fosfomycin, tigecycline, aminoglycosides, or high-dose and prolonged infusions of carbapenems [38]. It is important to note that tigecycline is not considered adequate as monotherapy for either UTIs due to inadequate concentration in the urine or bloodstream infections because of concern for poor outcomes such as mortality and lack of microbiologic cure [39]. Additionally, fosfomycin concentrates only in the urine and cannot be used for pyelonephritis or bacteremia. The survival benefits of combination regimens are unclear although some small retrospective studies suggest decreased mortality in CRE bloodstream infections of non-transplant adults [40]. For MDR *Pseudomonas* species, regimens of two or more drugs may be used including the extended spectrum beta-lactams such as ceftazidime/avibactam, aminoglycosides, or ciprofloxacin based on susceptibilities [41]. In pan-resistant pseudomonal infections,

individualized treatments with three or more antimicrobials are often employed with colistin, anti-pseudomonal carbapenem doripenem at high doses and with prolonged infusions, aminoglycosides, fosfomycin, and rifampicin [42].

There are multiple other MDR pathogens contributing to the morbidity and mortality of the renal transplant population. In addition to MDR gram-negative organisms, resistant gram-positive bacteria have significant consequences in renal allograft recipients. A case-control study of 1499 adult kidney transplants found that pre-operative methicillin-resistant *Staphylococcus aureus* (MRSA) was associated with increased incidence of allograft failure with 5-year graft survival rates of 78% when compared to 93% in controls [43]. Up to 3.4% of post-transplant infections can be due to MRSA in the adult renal transplant population [34]. Fecal colonization with vancomycin-resistant *Enterococcus* prevalence is reported at 4.2% in adults receiving hemodialysis and 12.4% in the first 6 months post-transplant in the adult population [44, 45]. Up to 69% of children with ESRD who were receiving dialysis were colonized with VRE, 51.8% were E faecalis and 40% were E faecium. Rates of VRE were higher in patients who had received vancomycin in the past [46]. Other studies cite previous hemodialysis, tacrolimus use in infants, and steroids or anti-lymphocyte courses for anti-rejection therapies as risk factors for VRE. A study of hospitalized children reported that VRE colonization was associated with an increased risk for infection with VRE that was nine times higher than those who were not colonized [47].

Overall, MDROs are increasing in prevalence globally, and, although the literature is limited in the pediatric renal transplant population, the available data on other pediatric and adult populations is concerning. Infections from pathogens such as VRE and MRSA are not specifically reported in pediatric kidney transplant recipients although these patients have risk factors associated with VRE and MRSA. Clinicians should be vigilant in their assessment for the emergence of these serious pathogens.

Cytomegalovirus (CMV)

Although bacteria and fungi have an important role in morbidity in the solid organ transplant population, ubiquitous viruses can have both direct invasive effects as well as an indirect impact on both short- and long-term graft function. Cytomegalovirus (CMV) is a herpesvirus with a seroprevalence of 30–97% in the general population [48]. After primary infection, life-long latency develops in a variety of cells which serve as reservoirs for reactivation in immunosuppressed individuals. Multiple studies have associated CMV infection with increased mortality as well as increased risk for acute rejection and graft loss. CMV may also have an indirect effect contributing to the risk for post-transplant lymphoproliferative disorder (PTLD).

Cytomegalovirus presents with a spectrum of issues from asymptomatic replication to tissue-invasive disease. Up to 20% of adult kidney transplant recipients who do not receive prophylaxis develop symptomatic CMV infection, and 50% of recipients have asymptomatic viral replication [49]. In children, 50–65% develop symptomatic disease without preventive therapy [50]. Most recently, Höcker et al. reported that CMV replication was seen in 14.5% of pediatric kidney recipients on prophylaxis in the first year after transplant with 4.1% of children developing a CMV syndrome [51]. The risk CMV disease is greatest in donor-seropositive and recipient-seronegative (D+/R-) patients. Other reported risk factors include absolute neutrophil count (ANC) of < 1000 and younger age. While high-dose mycophenolate is associated with increased CMV risk, everolimus-based regimens are associated with an 83% lower risk than other immunosuppressive options, perhaps decreasing the risk of disease [52].

A variety of methods exist for the diagnosis of CMV infection include histopathology, quantification of CMV nucleic acid with molecular assays, antigenemia, and culture. Molecular tests that detect DNA or RNA are preferred for CMV testing after transplant due to rapid turnaround time and increased sensitivity and specificity compared to older testing methods. In general, higher CMV viral loads are suggestive of increased risk for tissue-invasive disease whereas lower values are seen in asymptomatic CMV infection; however, overlap of clinical syndromes is reported including tissue-invasive disease in the absence of circulating DNA in the blood [53]. Histopathology is useful to diagnose tissue-invasive CMV disease, especially when coinfection or graft rejection is suspected.

In patients who are considered high-risk for CMV infection, antiviral prophylaxis is recommended for 6 months after kidney transplantation [48]. Weekly monitoring with initiation of antivirals if CMV is detected to prevent progression from asymptomatic DNAemia to disease is an alternative known as preemptive therapy. The advantages of prophylaxis include efficacy, ease of coordination, improved graft survival, and decreased rates of reactivation of other herpesviruses while disadvantages comprise increased risk of late onset disease, higher drug costs, and more drug toxicity including the potential development of antiviral resistance when compared to preemptive therapy. CMV antiviral resistance is reported with both strategies but is more often linked to prophylaxis regimens [54]. Cameron et al. described CMV viremia in 71% of pediatric renal recipients within the first 6 months of completing prophylaxis and that shorter prophylaxis courses were associated with a higher incidence of CMV infection [55]. Of note, a recent study by Erdbrüegger et al. of 594 adult kidney recipients did not show that CMV viremia was a significant risk factor for long-term graft loss in the antiviral prophylaxis era [56]. Further, a study of pediatric kidney recipients reported better allograft function 3 years post-

transplant in those received prophylaxis when compared to those who received preemptive therapy [51].

CMV treatment includes reduction of immunosuppression if possible and treatment with antivirals. First-line therapy with parenteral ganciclovir until demonstrating both clinical and virologic responses has been traditionally recommended for severe cases of tissue-invasive disease. In mild to moderate cases, valganciclovir may be used as its efficacy in resolution of DNAemia as part of pre-emptive therapy has been shown [57]. Risk of CMV relapse is lower in patients with undetectable CMV DNA at the end of therapy. Foscarnet and cidofivir are offered in patients unable to tolerate ganciclovir or if the virus has developed resistance via mutations at the genes UL97 or UL54 [58]. Unfortunately, both options have significant nephrotoxicity. Brincidofivir, an oral prodrug of cidofivir with significantly fewer renal effects, has activity against CMV and is being studied in clinical trials but is not yet commercially available for children.

An active area of research in CMV is focusing on unique options to better approach prevention and treatment of the disease. Maribavir is being studied for CMV infections resistant or refractory to ganciclovir and/or foscarnet with some success in older adolescents and adults with stem cell or solid organ transplant [59]. Letermovir has been approved for prophylaxis in adult stem cell transplant patients with a favorable decrease in subsequent CMV infection when compared to placebo [60]. Cytotoxic T cells (CTLs) have been studied in the stem cell transplant population for resistant or refractory CMV disease [61]. Factors that complicate CTL use in the solid organ transplant population include the need for lifelong viral suppression, for which CTLs are not designed to achieve and would require repeated administration. Calcineurin inhibitors can prevent activation of the cytokine genes in T cells as well. Research is ongoing on genetic modifications to the CTLs to evade the blocking effects of the calcineurin inhibitors and the utility of immunosuppression reduction before administering CTLs [62]. Finally, issues related to choosing the correct HLA-match for CTLs to promote control of the virus without activating the allograft need to be addressed.

Despite advances to decrease CMV events in pediatric kidney transplant recipients, the virus remains a significant cause of morbidity with a spectrum of symptoms from asymptomatic replication to allograft dysfunction. Recent studies suggest that prophylaxis especially in high-risk D+/R- patients is preferred and research on new treatment options is ongoing.

Epstein-Barr virus (EBV) and post-transplant lymphoproliferative disorder (PTLD)

Epstein-Barr virus (EBV) is another herpesvirus widespread in humans with a seroprevalence of up to 90% by age 5 in the developing world and 50% in affluent countries [63]. EBV establishes lifelong latency and has transformative properties that are associated with the development of post-transplant lymphoproliferative disorder (PTLD) with 50–80% of PTLD biopsies demonstrating EBV within tumor cells [64]. PTLD itself has a broad spectrum of disease from indolent lymphoproliferation to malignant, disseminated lymphomas. Renal transplant recipients have a lower incidence of PTLD at 1–2% when compared to other solid organ transplants in pediatric and adult patients [65]. Children present a unique challenge as they are disproportionately affected compared to adults. In the 1990s, a retrospective study of pediatric kidney transplant recipients found a 48% mortality rate among PTLD cases although contemporary literature reports mortality of 13% in a recent single-center study [66, 67]. Other manifestations of EBV include mononucleosis, hematologic changes (thrombocytopenia, anemia), and organ-specific disease (hepatitis, pneumonitis).

Risk factors for the development of PTLD are complex and interrelated. A well-described risk in most studies is primary EBV infection, making pediatric renal transplant recipients more vulnerable to the disease as they are often seronegative at the time of transplant and may receive a seropositive donor organ (D+/R-). Early PTLD (< 12 months after transplant) risks include D+/R- status, polyclonal antilymphocyte antibodies, young age, and CMV mismatch or CMV disease. Late PTLD (> 12 months after transplant) was associated with prolonged immunosuppression, Caucasian race, and male gender in one study. In general, PTLD incidence has a bimodal distribution, peaking within the first year post-transplantation followed by a second peak in the third year post-transplant [68]. However, children present with PTLD earlier in the post-transplant course (5.5–25 months) relative to adults (25–72 months) [66].

Although serologies may be useful in immunocompetent patients, they are less reliable for PTLD or primary EBV infection diagnosis in the transplant population. Similar to CMV testing, molecular tests are preferred for rapid results and high sensitivity and specificity. Viral load assays for EBV surveillance and disease monitoring are used although universal monitoring for EBV DNAemia but is not routinely recommended as PTLD screening due to the lack of predictive capacity. Further work-up is typically directed based on the clinical presentation of the individual patient such as imaging, other laboratory testing, or gastrointestinal endoscopy. Pathology remains the gold standard for PTLD diagnosis with immunophenotyping and molecular genetic markers of antigen receptor genes.

Reduction of immunosuppression to allow immune reconstitution is the primary treatment of PTLD but the response rates are variable. In the past, acyclovir and ganciclovir were administered to treat early PTLD but efficacy has not been established in prospective trials. Surgical resection, radiation, chemotherapy, and immunomodulators including the anti-

CD20 antibody rituximab are more often used. Poor prognostic factors for response to therapy include elevated lactate dehydrogenase (LDH) levels, multifocal disease, neurologic disease, and negative tumor staining for CD20 [66].

The role of antiviral prophylaxis for PTLD prevention is controversial. Ganciclovir or valganciclovir have been administered due to their higher in vitro activity, especially in patients with CMV risk and/or infection as part of a CMV prevention strategy. A recent systematic review of the literature reported that antiviral prophylaxis or preemptive therapy had no effect on EBV-associated PTLD incidence in adult and pediatric solid organ transplant patients who are considered high-risk [69]. Anti-CMV immunoglobulin may decrease lymphoma in adult kidney transplant recipients within the first year according to one study but was not supported in a small randomized control trial of pediatric liver transplant recipients with no significant differences in the 2-year PTLD-free rates (91% for CMV-IVIG and 84% for placebo) [70, 71].

Limited data exists in adult populations on the use of adoptive immunotherapy in adult solid organ transplantation. Research is ongoing on the use of CTLs for EBV infection as well with promising early data. Haque et al. conducted a phase II multicenter trial in pediatric and adult solid organ and stem cell transplant recipients with refractory EBV-associated PTLD with response rates of 52% at 6 months after tapering of immunosuppression [62].

In summary, EBV has a complex role in the development of infection and PTLD in the renal transplant population. Strategies for prevention and treatment are varied and the need for continued research to understand the mechanism of progression to PTLD as well develop new treatment remains high in an effort to decrease this life-threatening process in the vulnerable pediatric population.

Human BK polyomavirus virus (BKPyV)

Human BK polyomavirus (BKPyV) is common in the general population with a seroprevalence of up to 90% by adulthood [72]. The urinary tract is a frequent site of latent infection. In immunocompromised patients, asymptomatic urinary BKPyV replication can be seen with > 7 $\log_{10}$ cp/mL on urine cytology with up to one third of renal transplant patients developing BKPyV viremia [73]. Approximately 1–10% of kidney transplant patients will develop polyomavirus-associated nephropathy (PVAN) related to BKPyV infection increasing the risk of graft loss to 90% in the adult population [74]. A retrospective analysis of pediatric kidney recipients showed that the five patients who developed BKPyV viremia had significantly higher serum creatinine than those who had BKPyV viruria alone and 60% developed graft dysfunction [2]. BK nephropathy in the pediatric kidney recipients was associated with acute rejection (32%) and graft failure (40%) at 24 months after diagnosis [75]. A possible association with BKPyV viruria and acute T-cell-mediated rejection has been described in adults. Extrarenal complications have also reported such as encephalitis, pneumonia, hepatitis, capillary-leak syndrome, and malignancy in adults.

Risk factors include donor and recipient determinants as well as post-transplant complications. Donor issues such as HLA-mismatch or receipt of a deceased donor, high BKPyV antibody titers suggestive of recent BKPyV infection have been associated with increased risk of BKPyV infection in the recipient. Recipient determinants include low BKPyV antibody titers which are common in children. Post-transplant stents, previous acute rejection episodes, and previous graft loss due to PVAN also increase the risk for PVAN. High level immunosuppression and the use of tacrolimus, mycophenolic acid, and steroids are also associated with BKPyV.

Current guidelines recommend screening for BKPyV in the urine every 3 months for the first 2 years after renal transplantation and then yearly for another 3 years to identify 80–90% of patients at risk for PVAN before graft failure occurs [76]. Tests include urine cytology, urine electron microscopy, and urine BKPyV load. If positive, quantitative plasma BKPyV load should be obtained. Patients who have persistently elevated BKPyV levels > 10,000 copies/mL, an allograft biopsy should be considered to evaluate for PVAN [74].

Similar to other latent viral infections, reduction of immunosuppression is an important aspect of treatment for patients diagnosed with PVAN; specific recommendations are based on histologic pattern of disease, graft function, and risk of graft loss. In patients with persistent high-level plasma BKPyV load despite decreased immunosuppression, clinicians may consider adjunctive antivirals, although the efficacy data is limited. Cidofivir has been used with conflicting results, and cidofovir administration must be balanced with the risk of nephrotoxicity. Brincidofivir is being investigated as an alternative therapy in clinical trials. Administration of leflunomide to three pediatric renal transplant patients for approximately 2 years has been reported with a significant decrease in BKPyV viral loads without side effects. However, adult studies of leflunomide have reported significant toxic effects, and efficacy in this cohort were confounded by concurrent immunosuppression reduction in most patients [77]. Fluoroquinolones have been given with a limited effect as prophylaxis and treatment for BKPyV and are not routinely recommended. Intravenous immunoglobulin coupled with reduced immunosuppression and other therapies resulted in more rapid and prolonged clearance of viremia in adults with PVAN although graft survival was not significantly different from patients treated with standard therapies alone [78].

Human BKPyV is a significant concern in the renal transplant population. Close monitoring is recommend in the early post-transplant period and treatment includes reduction of immunosuppression and antiviral therapy.

Infectious diarrhea

Gastrointestinal issues are common in kidney recipients with diarrhea occurring in up to 22% of kidney recipients in the first 3 years post-transplant [79]. Typically, diarrhea is defined as three or more liquid bowel movements per day and can be considered acute (1–2-week duration) or chronic (2- or more week duration). In the renal transplant population, severe symptoms may lead to weight loss, dehydration, increased serum creatinine, and variable immunosuppressive drug levels. The differential diagnosis is broad and includes infections due to bacteria, viruses, and parasites. Drug-induced diarrhea is also an important consideration and may be due to the immunosuppressive regimen such as with mycophenolate, especially if combined with tacrolimus. The DIDACT study in adult patients with diarrhea found that 39% of kidney transplants had symptoms for < 14 days with > 50% of individuals developing diarrhea 2 or more years after the transplant [80]. Of the 50% of patients who underwent adjustments to their immunosuppressive therapies, 67% of cases had resolution of their gastrointestinal symptoms [80].

An infection increasing in incidence is *Clostridium difficile*, occurring in 3.5–16% of adult patients with kidney transplant alone and in 1.5–7.8% of pancreas-kidney recipients. At a single center in the USA, up to 12% of pediatric solid organ transplant patients developed *C. difficile* infection (CDI) with 4.7% of kidney recipients developing CDI [81]. Infection causes a spectrum of illness from mild diarrhea to fulminant colitis [82, 83]. Antimicrobial exposure is a significant risk factor for the development of CDI with ampicillin, clindamycin, cephalosporins, and fluoroquinolones being most commonly associated with the development of disease. Treatment is based on severity of illness and national guidelines. In severe cases, fidaxomicin or fecal transplant are implemented with continued research on the utility and safety in the immunocompromised population [84]. Probiotics may be offered as adjunctive therapy. Other commonly reported bacterial pathogens include nontyphoidal *Salmonella* species and *Campylobacter jejuni* as well as other enteric pathogen such as *Shigella*, *Yersinia*, and *Escherichia coli*.

Immunosuppressed children are at increased risk for gastrointestinal infection with CMV. Adenovirus may present with gastrointestinal symptoms but is more likely to cause hemorrhagic cystitis or respiratory issues. Other common viral pathogens that cause typical childhood illnesses may be seen as well such as norovirus and rotavirus. Up to 81% of adult renal transplant patients hospitalized with norovirus/sapovirus-related diarrhea experienced acute renal failure during the admission [85].

Diarrhea from intestinal parasites is uncommon in solid organ transplant patients in the developed world. A study in Iran, however, found up to 33% of the renal transplant population evaluated had intestinal parasites, although not all have clinical significance [86]. Infections from *Microsporidium*, I*sopsora belli*, *Strongyloides stercoralis*, and *Giardia lamblia* have been reported. In a single-center study of pediatric renal transplant patients, 18% had infectious diarrhea due to cryptosporidiosis and all presented with profuse watery diarrhea and acute renal failure [87].

The evaluation of diarrhea is based on risk factors but often includes a stool culture or molecular panel, microscopic stool evaluation for ova and parasites, and viral PCR studies. Differentiating drug-induced diarrhea from an infectious cause requires a careful medication history.

Supportive care including intravenous fluids for rehydration and electrolyte repletion may be necessary if moderate to severe dehydration is present or the patient is systemically ill. Antimotility agents such as loperamide and opioids are typically discouraged if a toxin-mediated process is suspected. Specific antimicrobial regimens should be based on the identified infection. A third-generation cephalosporin, fluoroquinolone, or azithromycin may be offered depending on the bacterial etiology including assessment of clinical picture and appreciating the risk for prolonged colonization or shedding with antibacterial therapy. As previously discussed, CMV is treated with ganciclovir or valganciclovir. Nitazoxanide is approved to treat cryptosporidium infection [87]. Giardiasis may be treated with metronidazole or nitazoxanide.

Overall, the differential diagnosis for diarrhea in pediatric renal recipients is broad. Assessment for common bacterial and viral pathogens is strongly suggested prior to categorizing diarrhea as medication-associated. Parasitic infections should be addressed with exposures consistent with epidemiologic risk, including ingestion of well water and travel to or residence in endemic areas.

Emerging infections

New or re-emerging pathogens may impact the renal transplantation population at any time. Infections from atypical Mycobacterium species are more common in the immunocompromised patients [88]. Cerebral toxoplasmosis has been reported in the adult kidney recipients with up to 50% mortality [89].

In the past few years, arboviral illnesses such as chikungunya, dengue, and Zika virus that are transmitted via the bite an infected *Aedes aegypti* mosquito have become a concern in transplant patients. For example, the flavivirus Zika virus, may be transmitted through sexual contact, blood products, or the donated organ. In immunocompetent individuals, 80% of individuals are asymptomatic although neurologic effects such as Guillain Barre syndrome have been described [90]. The transplant population may also manifest differently than the classic fever, conjunctivitis, joint pain, and rash as typically seen. A brief report in which four solid organ transplant patients (two of which were kidney recipients) were diagnosed with Zika virus, 75% of which developed

a secondary bacterial infection with no deaths [91]. Reverse transcriptase-polymerase chain reaction (RT-PCR) is offered at many centers and may be positive within the first week of symptoms although the optimal test is not yet known. Serologies may cross-react with other flaviviruses such as dengue or yellow fever. Currently, there are no international guidelines on Zika virus and transplantation although the Organ Procurement and Transplantation Network suggests that previous Zika infection should not preclude donors from transplantation [92]. Adult solid organ transplant recipients who received organs from Zika immunoglobulin G (IgG) positive donors had no difference in outcomes compared to seronegative donors although the sample size was small [93]. Treatment for Zika virus infection is supportive.

Infection with Zika virus illustrates many of the issues surrounding emerging infections where the data may be limited and the risks to organ recipients is unknown. Reporting of unusual infections and communication among practitioners is essential to collaborate as other infections emerge in the pediatric renal population.

Conclusions

Renal transplantation is the treatment of choice for ESRD and has become increasingly successful. Guidelines provide a framework on screening, work-up, and management for many infections encountered in the post-transplant period although much of the literature is based on adult populations. Infections commonly seen in children include UTIs, CMV, EBV, BKPyV, and infectious diarrhea. Other infections are emerging as well, such as Zika virus and MDROs. Approaching an infectious evaluation in a pediatric kidney recipient requires practitioners to be up-to-date on the literature and willing to collaborate with other experts in the field to best manage this complex population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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