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Prevention and Treatment of Infectious Complications in Pediatric Renal Transplant Recipients

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Introduction

Over the last few decades, significant advances have been made in the outcomes of pediatric kidney transplant recipients, with marked improvement in patient survival and early allograft survival. However, the more potent immunosuppressive therapy that successfully reduced the incidence of acute rejection has resulted in a higher incidence of infectious complications [1]. This increase has manifested as (1) an increase in the total frequency of infection [2]; (2) infection becoming the primary reason for post-transplant hospitalization [3]; and (3) the successive emergence of new viral infections in the past several decades. Specifically, cytomegalovirus (CMV) infections have been common in kidney transplant recipients since the 1980s, followed by Epstein Barr virus (EBV) related post-transplant lymphoproliferative disorder (PTLD) since the 1990s, and BK virus associated allograft nephropathy (BKVAN) in the last 15 years. Infections are not only a significant source of morbidity and hospitalization, but they also can lead to graft loss and patient death. Even when adjusting for death, infections represent an additional risk factor for worse graft survival [4–6], thus in part accounting for the less significant improvement in longer-term allograft survival [7]. Excessive PTLD resulted in the early termi-

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nation of a large multi-center immunosuppression trial in pediatric kidney transplantation in the US [8]. Hospitalizations due to infection occurred in 47% of children within the first 3 years after kidney transplant, higher than in adults with a kidney transplant or in children on dialysis [2]. Unlike adults, the total incidence of infections did not drop in children in more recent years. From 2019 onwards, the global SARS-COV-2 (COVID19) pandemic greatly affected organ transplant recipients.

Special Considerations in Pediatric Transplantation

Organ transplant recipients are at greater risk for infection than immunocompetent individuals. The immunosuppressive medications currently in use are non-selective in nature, suppressing immune responses to alloantigens, as well as to infectious organisms. An organ transplant is a major surgical procedure with the infection risks of any major surgery. Chronic kidney failure itself suppresses the immune system to some extent. Cytopenias are common post-transplant due to medication side-effects, and can raise the infection risk.

Further, children are exposed to some unique infection risks. Many of the main viral infections that occur post–transplant are associated with higher morbidity when they are primary infections. A primary viral infection is defined as infection in a recipient who is seronegative at the time of transplant, with no prior immunity. Reactivation infection occurs in the setting of a patient who is seropositive and has some prior immunity. Pediatric patients are at higher risk for primary infection due to higher rates of recipient seronegativity at the time of transplant. Recent US data demonstrated that approximately 50% of pediatric kidney transplant recipients were EBV seronegative and 65% were CMV seronegative at the time of transplant compared to 10% EBV and 40% CMV seronegativity among adults [9]. The grafts to children come most often from adult (therefore most likely seropositive) donors, thereby introducing the virus at transplant.

Viral Infections

Cytomegalovirus

CMV, now called human herpesvirus 5 (HHV5), a double-stranded DNA virus of the herpes virus family, is perhaps the single most important pathogen in solid organ transplantation [10]. CMV not only causes significant morbidity by direct infection, but its immunomodulatory effects also predispose to other infectious complications [10]. CMV infection and CMV disease are different from each other. CMV infection is defined as evidence of CMV replication regardless of symptoms (differs from latent CMV). CMV disease is defined as evidence of CMV infection with attributable symptoms. Three patterns of CMV infection may be seen post-transplantation: Primary infection, reactivation infection, and superinfection. Primary infection occurs in transplant patients who were CMV seronegative prior to transplant, most commonly via transmission from a graft from a seropositive donor [10–12]. Without preventative therapy, the incidence of CMV disease in such recipients is 50–65% [10]. Reactivation infection is due to activation of latent virus in seropositive recipients, while superinfection is activation of virus from a seropositive donor in a seropositive recipient. Infection with CMV usually presents in the first few months post-transplant and can manifest as CMV syndrome, characterized by fever, myalgias, malaise, leukopenia and thrombocytopenia, or CMV disease, in which there is clinical evidence of organ involvement by the infection [10, 13]. The transplanted kidney is at higher risk for CMV infection than are the native organs, but pulmonary, liver and gastrointestinal tract infection are common, regardless of the organ transplanted [14–16]. As stated above, in addition to causing direct infection, CMV has significant indirect effects,

including an increase in the overall state of immunosuppression leading to increased risk for opportunistic infection [10]. CMV infection has been demonstrated to increase the risk of EBV-associated PTLD [10, 16]. In addition, CMV and acute rejection are interrelated. CMV infection is a risk factor for acute rejection, while rejection leads to release of tumor necrosis factor, triggering the process that ultimately leads to CMV replication [17].

Prevention of CMV infection can be accomplished with either (1) universal prophylaxis: the administration of anti-CMV therapy to all patients except seronegative recipients of a seronegative organ; or (2) preemptive therapy: viral monitoring and initiation of the treatment dose of anti-viral medication when a certain positive threshold is reached. There is some controversy as to the optimal strategy, as both methods have advantages and disadvantages. Consensus guidelines from the American Society of Transplantation (AST), Kidney Disease: Improving Global Outcomes (KDIGO), and The Transplantation Society International CMV Consensus Group recommend universal prophylaxis for high risk patients (seronegative recipients of seropositive organs or seropositive recipients of seropositive organs in the setting of anti-T-cell antibody immunosuppression), based on the available data suggesting better graft survival and clinical outcomes [11, 12]. Preemptive therapy has not been well studied in pediatrics. Although several agents are available for prophylaxis, valganciclovir has revolutionized both CMV prevention and treatment [18]. It is a prodrug of ganciclovir and is approximately 60% bioavailable, which is tenfold more than ganciclovir [19]. While the dosing of valganciclovir is well established in adults, the dosing in pediatric patients is somewhat more complex due to the dependence on metabolic activation, renal clearance and variable absorption. Since 2009, the manufacturer recommends normalization of the adult dose for BSA and creatinine clearance. Other centers have employed a weight based approach. Due to the challenges, particularly in infants and young children, ganciclovir levels may be helpful to guide therapy. Leukopenia is a common side effect of valganciclovir therapy. The duration of prophylaxis is an area of debate. Consensus recommendations guide the duration of therapy based on the serostatus of the donor and recipient [11, 12] (Table 69.1). For CMV Donor (D)+/Recipient (R)- patients, 3–6 months of prophylaxis with oral ganciclovir or valganciclovir is recommended. For CMV R+ patients, 3 months is recommended but 6 months should be considered if anti-lymphocyte induction is used. No prophylaxis is recommended in the CMV D−/R- patient. In addition, treatment of rejection with antilymphocyte antibodies in at risk recipients (D+/R-) should prompt re-initiation of prophylaxis or preemptive therapy for 1–3 months [11, 12, 22]. For treatment of CMV disease in pediatric patients, IV ganciclovir is recommended [12]. Therapy should continue until the CMV is no longer detectable. Reduction of immunosuppression in life-threatening CMV disease is indicated in cases of persistent disease despite treatment.

Late onset CMV disease is defined as disease occurring after prophylaxis has been discontinued and has been reported in 25–40% of patients on universal prophylaxis [20, 23]. Late onset CMV is associated with significant morbidity and high mortality, underscoring the ability of anti-viral prophylaxis to delay but not prevent

Table 69.1 Recommendations for duration of CMV prophylaxis [20, 21]

CMVD+/R-	• 3–6 months of prophylaxis with oral ganciclovir or valganciclovir is recommended. • In addition, treatment of rejection with antilymphocyte antibodies in at risk recipients (D+/R-) should prompt re-initiation of prophylaxis or preemptive therapy for 1–3 months.
CMV D+/R+ CMV D−/R+	• 3 months is recommended but 6 months should be considered if anti-lymphocyte induction is used.
CMVD−/R-	• No prophylaxis is recommended.

Table 69.2 Expert recommendations regarding BK virus screening

	2003 Polyoma-virus associated nephropathy interdisciplinary group [24]	2009 AST infectious diseases group [25]	2009 KDIGO transplant work group [12]
Screening	Urine screening, various techniques, every 3 months till month 24 (grade A-II) and annually thereafter till fifth year post-transplant (grade B-III) or with allograft dysfunction Biopsy if urine BK DNA > 1×10^7, VP1 mRNA >6.5×10^5 or plasma DNA > 1×10^4	Urine screening every 3 months in first 2 years then annually until fifth year post-transplant (grade II-B). If plasma screening performed, then at monthly intervals Biopsy if urine BK DNA > 1×10^7, VP1 mRNA > 6.5×10^5 or plasma DNA > 1×10^4	Plasma BK nucleic acid testing monthly for first 3–6 months, then every 3 months till month 12, or if elevated serum creatinine or after treatment for acute rejection
Intervention	Various approaches discussed, none specifically endorsed	Reduce immunosuppression for presumptive BKVN (plasma BKV loads >1×10^4 for >3 weeks)	Reduce immunosuppression if plasma nucleic acid load persistently >1×10^4

Adapted from [139]

CMV. Thus, careful clinical follow-up and virologic monitoring is recommended after completion of prophylaxis.

Antiviral drug resistance should be suspected and tested for in the setting of a patient who has had cumulative ganciclovir exposure of more than 6 weeks and there are rising viral loads or progressive disease after 2 weeks at full dose [11]. Risk factors include prolonged antiviral drug exposure (median 5–6 months), ongoing active viral replication, lack of prior CMV immunity (D+/R-), and inadequate drug delivery. Currently, genotype testing includes the UL97 kinase and UL54 DNA polymerase, with the UL97 mutation appearing in 90% of cases.

The timing and frequency of screening for CMV is largely center-specific and influenced by donor and recipient CMV serostatus, as well as whether universal or preemptive therapy is employed. Published guidelines recommend regular monitoring using a quantitative viral load assay for the first year post-transplant; however, the duration and frequency may vary depending on the type of CMV prevention strategy [11, 12]. Table 69.2 summarizes the characteristics of many commonly used assays for the different viral infections. The recent development of an international standard for CMV is promising as it will permit determination of appropriate standardized trigger points for intervention and allow comparison among sites.

Epstein-Barr Virus

EBV is another herpes virus that causes significant morbidity post-transplantation. Distinctions are made between EBV infection and disease. Active, asymptomatic EBV infection is defined by the presence of a detectable EBV viral load as measured by a nucleic acid amplification assay. Uncommonly, asymptomatic infection may also be identified in lymphoid rich histopathologic specimens. EBV disease is defined by the presence of active EBV infection with symptoms or signs attributable to the virus. The spectrum of clinical manifestations of EBV in transplant recipients includes nonspecific viral syndrome, mononucleosis, lymphoproliferative disorders and malignant lymphomas.

Like CMV, EBV commonly infects immunocompetent people sometime in childhood and establishes a prolonged latency in reticuloendothelial cells. Thus, the patterns of infection are identical to CMV: primary infection (often from the graft of a seropositive donor), reactivation or superinfection. Again, like CMV, the primary infection in an immunosuppressed transplant recipient is more virulent. Unlike CMV, EBV infection does not seem to have many indirect effects except for the development of PTLD. PTLD is a major complication and is covered in detail in the next chapter. This section deals with EBV infection only.

Prospective viral surveillance studies revealed that subclinical EBV infection occurs in 35–40% of pediatric renal transplant recipients [6, 26]. In a recent cohort study of adult kidney transplant recipients, 40% had subclinical viremia [27]. EBV viremia often precedes the development of EBV disease and PTLD by 4–16 weeks [28, 29]. Thus, early identification of EBV viremia may allow for intervention that could prevent progression to EBV disease and PTLD. KDIGO recommends the following post-transplant EBV screening schedule for high risk D+/R- patients: once in the first week after transplant; at least monthly for the first 3–6 months; then at least every 3 months until the end of the first year with re-initiation of monitoring after treatment for acute rejection. While D−/R– patients might be at decreased risk of developing EBV disease compared to D+/R–, they are still at increased risk relative to R+ patients and therefore warrant close monitoring. Some centers may choose to measure EBV loads more frequently. Beyond the first year, selective monitoring, such as in those with persistently high viral loads or in those with higher than normal immunosuppression, may be performed based on center preferences. Some centers recommend continued monitoring for an indefinite period for all patients. For seropositive individuals, selective monitoring may be considered in the setting of increased immunosuppression or clinical concern.

The reader should note that PCR techniques to detect EBV DNA amplification vary greatly based on the type of sample and laboratory standards. Thus, PCR values from peripheral blood leukocytes and whole blood generally correlate with each other but not with PCR values from plasma [30, 31]. To date, there is no defined standard sample site for EBV. In practice, the most important strategy is to follow the viral load in the same lab using the same type of sample consistently over time and to be careful to not compare viral loads from one lab to another.

There is no universally accepted treatment for subclinical EBV infection post-transplant. Options include reduction of immunosuppression, antiviral therapy, intravenous immunoglobulin (IVIG), and monoclonal antibody therapy directed toward infected B lymphocytes [21, 29, 32–34]. Currently, the only consensus recommendation is for a reduction of immunosuppression in EBV seronegative patients with an increasing EBV viral load. The utility of antiviral therapy to prevent PTLD is controversial, with little evidence to support the role of acyclovir or ganciclovir in response to an elevated or rising EBV viral load without a concomitant reduction of immunosuppression. These agents seem to delay the onset of infection rather than reducing its incidence. Two studies suggest that anti-viral prophylaxis has an additional benefit of preventing the progression from EBV disease to PTLD [19, 35]. IVIG does not appear to be of added benefit [36]. Preemptive use of rituximab in response to subclinical EBV infection began in the hematopoietic stem cell population and has recently been reported in the adult kidney transplant population [37, 38]. It is important to remember, however, that children, in particular, can develop a chronic high load carrier state without ever progressing to PTLD [39–44]. Nevertheless, the majority of reports indicate that higher EBV PCR values are associated with a greater risk for subsequent PTLD [45–47]. An EBV vaccine, directed against an EBV-glycoprotein, was tested in the United Kingdom but failed [48]. Unlike with CMV, we are not aware of any cost-benefit analysis of EBV monitoring or preventative treatment strategies.

BK Virus and BKVAN

BK virus (BKV) was first isolated from the urine of a kidney transplant recipient in the 1970s [49], but it was not until the late 1990s that this virus emerged as a significant problem in kidney transplantation [50, 51]. BKV is a part of the polyoma group of viruses. Though this virus is not from the herpesvirus group, it shares the characteristics of herpesviruses of infecting most immunocompetent people during childhood and establishing a prolonged latency. Unlike the herpesviruses, the virus does not establish latency in reticuloendothelial cells but in the uroepithelium. This propensity for the uroepithelium is responsible for the clinical manifestations: hemorrhagic

cystitis in bone marrow transplant recipients and allograft nephropathy in kidney transplant recipients. The incidence of BKVAN in pediatric kidney transplantation appears to be the same as in adult kidney transplants at 3–8% [52–56]. Risk factors include the intensity of immunosuppression, recent treatment for acute rejection, and placement of a ureteral stent, though the data implicating specific immunosuppressive agents is conflicting [54, 57–59].

BKVAN and BKV infection are two separate entities. BKVAN is defined as the presence of virus in the renal parenchyma, with accompanying evidence of either tubulointerstitial nephritis or elevated serum creatinine, as defined by a working group of the AST [2]. BKVAN is more prevalent in the medulla of the kidney, so at least one core should be deep enough to include medulla. A negative biopsy result does not rule out BKVAN due to the possibility of sampling error and the focal nature of the infection, so sensitivity is not 100%. In cases where the biopsy is negative, but there is high clinical suspicion for BKVAN, a repeat biopsy may be indicated. The histologic patterns of BKVAN have been divided into three types, as reviewed by Liptak et al. and the AST Transplant Infectious Diseases Group [25, 60]: Type A has intranuclear viral inclusions only, Type B has additional acute inflammation but very little chronic fibrosis, and Type C has significant chronic fibrosis and atrophy. The value of this classification lies in its prognostic value of clinical outcomes: the incidence of progression to end-stage kidney disease (ESKD) was only 13% with Type A, 55% with Type B and 100% with Type C [61]. BKVAN represents a diagnostic challenge because the condition may resemble acute rejection. Symptoms are often minimal or absent. Serum creatinine elevations are found on clinical lab monitoring. Since the treatment of acute rejection (intensifying immunosuppression) is the opposite of the treatment of BKVAN (reduction in immunosuppression), making the correct diagnosis is critical.

Early identification of BKV infection (detectable viral load in blood or urine) may permit intervention that may prevent BKVAN. Data suggest that the BK viremia precedes BKVAN by a median of 8 weeks [24]. BKV viral load >10,000 copies/L has a high positive predictive value for BKVAN [59]. Indications for biopsy vary among centers but many include viral load >10,000 copies/L with or without an elevated creatinine.

Routine screening is the most important tool used to identify patients at risk for BKVAN. Various schedules of surveillance are shown in Table 69.3. Intervention options include reduction of immunosuppression and use of other agents such as cidofovir, leflunomide, or IVIG. Stepwise immunosuppression reduction is recommended for kidney transplant recipients with plasma BKV-DNAemia of >1000 copies/ml sustained for 3 weeks or increasing to >10,000 copies/ml, reflecting probable and presumptive BKVAN, respectively [64]. The approach to immunosuppression reduction varies among centers, with varying levels of supporting evidence, and includes the following: (1) switching from tacrolimus to cyclosporine (CSA) or sirolimus; (2) mycophenolate mofetil (MMF) to azathioprine or sirolimus or leflunomide; (3) decreasing tacrolimus (trough levels <6 ng/ml), MMF (dosing ≤1 g/day), and CSA (trough levels 100–150 ng/ml); or (4) decreasing tacrolimus or MMF (maintain or switch to dual therapy with calcineurin inhibitor (CNI) and prednisone, sirolimus/prednisone, MMF/prednisone) [12]. While the reduction of immunosuppression raises concerns about the unintended consequence of rejection, several studies have reported successful preemptive intervention with no increase in rejection [65, 66].

There are virtually no randomized controlled trials to test any of these strategies head to head for any of the viral infections. Anti-viral therapy against BKV is more complicated than for CMV or EBV, since acyclovir, ganciclovir or their analogues are not active against BKV. Cidofovir is one anti-viral drug that has been tried with some success [67, 68]. Higher doses of cidofovir can be very nephrotoxic. Probenecid in combination with the higher dose cidofovir or intermediate dose cidofovir prevents the nephrotoxicity [69]. Fluoroquinolones are not recommended for either prophylaxis or treatment [64].

Table 69.3 Recommended vaccinations for pediatric transplant candidates and recipients [62, 63]

Vaccine	Inactivated/live attenuated (I/LA)	Recommended before transplant[a]/ strength of recommendation	Recommended after transplant/ strength of recommendation	Monitor vaccine titers?	Quality of evidence
Influenza, injected	I	Yes/A	Yes/A	No	II
Hepatitis B	I	Yes/A	Yes[b]/B	Yes[b]	II
Hepatitis A	I	Yes/A	Yes/A	Yes	II
Pertussis	I	Yes/A	Yes/A	No	III
Diphtheria	I	Yes/A	Yes/A	No	II
Tetanus	I	Yes/A	Yes/A	No	II
Polio, inactivated	I	Yes/A	Yes/A	No	III
Hemophilus influenzae	I	Yes/A	Yes/A	Yes[c]	II
Streptococcus pneumoniae[d] (conjugated/ polysaccharide)	I/I	Yes/A	Yes/A	Yes[c]	III
Neisseria meningitidis[e]	I	Yes/A	Yes/A	No	III
Rabies[f]	I	Yes/A	Yes/B	No	III
Varicella	LA	Yes/A	No/D	Yes	II
Measles	LA	Yes/A	No/D	Yes	II
Mumps	LA	Yes/A	No/D	Yes	III
Rubella	LA	Yes/A	No/D	Yes	II
Bacille Calmette-Guérin [g]	LA	Yes/B	No/D	No	III
Smallpox[h]	LA	No/C	No/D	No	III
Anthrax	I	No/C	No/C	No	III

Adapted from (a) Advisory Committee for Immunization Practices 2013; (b) The American Society of Transplantation (AST) Handbook of Transplant Infections, 2011

[a]Whenever possible, the complete complement of vaccines should be administered before transplantation. Vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic after transplantation. Some vaccines, such as Pneumovax, should be repeated regularly (every 3–5 years) after transplantation

[b]Routine vaccine schedule recommended prior to transplant and as early in the course of disease as possible; vaccine poorly immunogenic after transplantation, and accelerated schedules may be less immunogenic. Serial hepatitis B surface antibody titers should be assessed both before and after transplantation to assess ongoing immunity

[c]Serologic assessment recommended if available

[d]Children older than 5 years should receive 23-valent pneumococcal polysaccharide vaccine. Children less than 2 years should receive conjugated pneumococcal vaccine. Those 2 years–5 years of age should receive vaccination based on age and number of previous immunizations with conjugated pneumococcal vaccine

[e]Vaccination with conjugated meningococcal vaccine recommended in United States for all children aged 11–12 years of age and adolescents at high school entry or 15 years of age, whichever comes first

[f]Not routinely administered. Recommended for exposures, or potential exposures due to vocation or avocation

[g]The indications for Bacille Calmette-Guérin administration in the United States are limited to instances in which exposure to tuberculosis is unavoidable and where the measures to prevent its spread have failed or are not possible

[h]Transplant recipients who are face-to-face contacts of a patient with smallpox should be vaccinated; vaccinia immune globulin may be administered concurrently if available. Those who are less intimate contacts should not be vaccinated

Varicella

Varicella-zoster virus (VZV) is the most infectious of the human herpesviruses. Primary infection with VZV results in chickenpox. Following primary infection, the virus remains in the body in a latent state from which it may be reactivated, resulting in cutaneous herpes zoster, or shingles. Most adult kidney transplant recipients have experienced primary infection in childhood and, therefore, are at risk for reactivation and the development of herpes zoster with the introduction of immunosuppressive medication post-transplant [70]. Historically many children were VZV naive at the time of transplantation and primary infection was a significant cause of morbidity and mortality [71, 72]. With the development of a safe and effective VZV vaccine, routine immunization of pediatric kidney transplant candidates has been documented to reduce the incidence of primary VZV infection post-transplantation [73]. Given these findings, it is recommended that all transplant candidates over 9–12 months of age receive immunization with the VZV vaccine [74]. Studies in children with chronic kidney disease and on dialysis suggest that two doses, rather than one, may be necessary to elicit protective antibody levels, so it is recommended that antibody levels be obtained at least 4 weeks following immunization, and a second dose given if necessary [74–76]. Although some studies have evaluated the use of this vaccine in post-transplant patients, both the American Academy of Pediatrics Committee on Infectious Diseases and the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) advise against the use of this live viral vaccine in immunocompromised patients [77, 78]. Thus, it is imperative that immunization be provided and protective antibody levels documented prior to transplant whenever possible.

Patients who are varicella-naive at the time of transplant, i.e. no history of chicken pox or VZV immunization, or fail to develop protective antibody after immunization, and who are exposed to varicella should receive prophylactic therapy. Previous recommendations included the delivery of varicella zoster immune globulin (VZIG); however, this product is no longer being manufactured [79]. In North America, an investigational VZIG product, VariZIG (Cangene Corporation, Winnipeg, Canada) has become available under an investigational new drug application and the ACIP recommends that use of this product be requested if an immunocompromised patient is exposed to varicella infection [79]. If this product is not available, IVIG, which contains some anti-varicella antibody, may be given. Any prophylactic therapy should be given as soon as possible, up to 96 hours after exposure. Patients who develop infection, either primary or secondary, should receive treatment with intravenous or oral acyclovir, with consideration of reduction of immunosuppression [12, 80, 81].

COVID-19

The coronavirus disease 2019 (COVID-19), characterized by significant respiratory and multiorgan disease, is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS–COV–2). This virus first emerged in December 2019 in Wuhan, China [82]. Droplets expelled during talking, coughing, sneezing, or eating are the most common mode of transmission. Transmission may also occur through aerosol; however, it is unclear if this is a significant mode of transmission outside of laboratory settings. Common symptoms of COVID-19 infection include fever, dry cough, shortness of breath, fatigue, myalgias, nausea and vomiting, diarrhea, headaches, weakness and rhinorrhea. Common complications include pneumonia, acute respiratory distress syndrome, liver injury characterized by elevation of liver enzymes, cardiac injury marked by troponin elevation, acute heart failure, myocarditis, prothrombotic coagulopathy, acute kidney injury, and acute cerebral vascular disease. Rare complications include cytokine storm and macrophage activating syndrome. Patients become contagious about 2–3 days prior to the onset of symptoms until about 8 days after symptom onset [82]. Nearly 80% of patients with COVID-19 have mild manifestations, 15% develop severe illness and 5% become critical.

Data are emerging on the impact of COVID-19 on kidney transplant recipients. The incidence of COVID-19 in solid organ transplant (SOT) recipients is 10- to 15-fold higher than in the general immunocompetent population and adult SOT patients with COVID-19 appear to be at higher risk of poor outcomes on the basis of their chronically immunosuppressed state and underlying medical comorbidities [67, 68]. Initial reports in pediatric kidney transplant recipients demonstrate a decreased risk for infection and less severe disease when compared to adult kidney transplant recipients [83, 84].

Transplant Candidate Considerations

Vaccination is recommended to occur prior to transplantation, ideally completing the vaccine series a minimum of 2 weeks prior to transplant. Living donor candidates should self-quarantine or follow strict social distancing for a 14 day period prior to the transplant. All candidates should also have a negative nucleic acid amplification test (NAT) documented prior to surgery.

Post-Transplant Vaccination

The AST recommends vaccination against SARS CoV-2 using the locally approved vaccines for pediatric kidney transplant recipients [85]. Information about COVID-19 vaccine responses in transplantation is rapidly evolving. However, antibody responses to COVID-19 vaccines in transplant recipients are diminished compared with the general population [86–97]. Data suggest that providing a third dose of mRNA vaccine to SOT recipients that have previously received two doses of mRNA vaccine can increase antibody titers to SARS-CoV-2 [98–100]. In a recent, double-blind, randomized placebo-controlled trial, a third dose mRNA vaccine provided 2 months after the second dose significantly increased antibody titers, neutralizing antibody, and cellular immune response to SARS-CoV-2 compared to a third dose placebo [94]. Based on this, a third dose of mRNA vaccine is recommended for SOT recipients who have previously completed a 2-dose mRNA vaccine series. The use of a third dose should, until further evidence is available, be based on individual patient's unique situation and must depend on local availability of vaccines and local regulations. In addition, vaccination is recommended for all eligible household and close contacts. Routine antibody testing following vaccination is not recommended by the FDA.

COVID-19 and Donor Considerations

The AST published guidelines for organ donor screening for COVID-19. All deceased donors should be tested for SARS-CoV-2 infection using RT-PCR from the upper respiratory tract within 72 hours, but ideally as close to organ recovery as possible. For donors previously known to have had COVID-19, organ acceptance can be considered if the following circumstances are met: negative SARS-CoV-2 RT-PCR testing from the respiratory tract, symptoms of COVID-19 have resolved, AND at least 21 days have transpired since the date of disease onset. Data regarding the safety of organ donation from donors with previous COVID-19 are limited at this time and consultation with transplant infectious disease experts is recommended. Living donors should be advised to follow universal masking precautions and strict social distancing for 14 days prior to donation. All living donors should undergo respiratory tract SARS-CoV-2 RT- PCR testing within 3 days of donation. Donors should be encouraged to self-quarantine after the preoperative COVID-19 test [101].

Bacterial Infections

Urinary Tract Infection

Urinary tract infection (UTI) is the most common bacterial infection in kidney transplant recipients, in both adults [102, 103] and children [104].

UTIs develop in 20–60% in the first year post-transplant and 40–80% by 3 years post-transplant [2, 102–105]. UTI is not only a cause of morbidity but is also associated with higher rates of graft loss and patient death [106, 107]. Early UTI (within 6 months of transplant) elevated the risk for graft loss in children, while late UTI did not [108]. The urogenital tract is the most common entry point for systemic sepsis [109]. Numerous risk factors have been identified for UTIs post-transplant. Urologic anomalies such as neurogenic bladder, urinary tract obstruction, vesicoureteral reflux, bladder augmentation, ureteral stents and intermittent catheterization have all been associated with an increased risk of UTI post-transplant [105, 110–112]. UTI risk is highest in the first 3–6 months post-transplant but some risk remains at later time points. While the organisms implicated are usually the same as in immunocompetent individuals, such as Enterobacter species (e.g., *Escherichia coli* and *Klebsiella)*, a higher percentage of UTIs in transplant patients are due to unusual organisms such as *Pseudomonas* species [113]. Clinical symptoms may include fever, dysuria, graft tenderness and foul-smelling or cloudy urine. In some patients, symptoms may be masked due to immunosuppression. A rise in serum creatinine may occur and can mimic acute rejection. UTIs can also precipitate acute rejection.

The diagnosis of UTI is usually made by urine culture, though patients on trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jiroveci* may not demonstrate positive cultures. Treatment is with antimicrobial therapy. Initially, the antimicrobial prescribed should cover the common gram negative organisms, such as the beta-lactams or the quinolones [114]. Once the organism is known, the most specific and cost-effective antimicrobial can be prescribed. Treatment route and total duration are determined by the severity of infection, recipient age, and other risk factors. Kidney allograft pyelonephritis can be associated with bacteremia and significant morbidity. If allograft pyelonephritis is suspected, hospitalization and treatment with intravenous antibiotics for up to 14 days is recommended [12]. Shorter 5–7 day oral courses, as are used in immunocompetent individuals, can be used for milder cystitis episodes in older children [92]. KDIGO suggests that all kidney transplant recipients receive UTI prophylaxis with daily trimethoprim-sulfamethoxazole for at least 6 months post-transplant based on data showing a decrease in the frequency of UTIs [115]. For patients who are allergic to trimethoprim-sulfamethoxazole, the recommended alternative is nitrofurantoin. Currently, the available evidence does not support routine treatment of asymptomatic bacteriuria [114].

Other Bacterial Infections

Other bacterial infections, such as wound infections, line sepsis and pneumonia are seen with significant frequency in kidney transplant recipients. Wound infections and line sepsis are commonly due to gram-positive *staphylococcus* and *streptococcus*.

Pneumonia can be due to multiple etiologies (bacterial, viral or fungal), but bacterial pathogens are responsible for approximately 44% of cases [116]. In adult transplant recipients, cellulitis and bacterial abscesses are frequent problems, largely due to co-morbid diabetes mellitus. In general, these complications are less common in the pediatric population. The treatment of these infections is generally no different than standard treatment in immunocompetent hosts, though duration of therapy may be longer.

Bartonella henselae infection (also known as cat-scratch disease) has been reported in pediatric organ transplant recipients, including kidney transplants [117].This infection typically presents as fever and lymphadenopathy, and thus must be included in the differential diagnosis for PTLD. However, unlike PTLD, this infection is treated with antimicrobial therapy.

The incidence of *Mycobacterium tuberculosis* infection in kidney transplant recipients varies geographically, occurring in less than 2% of kidney transplant recipients in North America and Europe, but 5–15% in Asia and Africa [118–120]. This infection may present at any time post-transplant, but is most common in the first post-

transplant year [119]. *M. tuberculosis* infection presents with a myriad of symptoms, including weight loss, cough, fever and lymphadenopathy, again mimicking PTLD. The diagnosis of tuberculosis in the transplant recipient is similar to that in other populations, although the tuberculin skin test may be positive in only a third of kidney transplant recipients with tuberculosis [120]. Early diagnosis is best achieved by staining for acid-fast bacilli or using PCR from sputum, bronchoalveolar lavage or gastric aspirates. Interferon-gamma release assays such as QuantiFERON and T-SPOT.TB are alternative methods used to detect latent infection. Management of tuberculosis is complex and evolving and has long been directed by recommendations developed, updated and disseminated by expert panels [12, 120–122]. A four-drug regimen, similar to the regimen recommended in the general population, should be used in case of active tuberculosis after transplantation [123]. Rifampin is associated with numerous drug interactions through its activation of the CYP3A4 pathway which can impact levels of CNIs and mTOR inhibitors, sometimes necessitating higher CNI doses. Alternatively, rifabutin could be used instead of rifampicin given its milder interactions [123].

Other Infections

Pneumocystis Jiroveci Pneumonia

Pneumocystis jiroveci was previously known as *Pneumocystis carinii* and classified as a protozoal disease. The classification has evolved based on DNA sequence analysis such that *P. jirovecii* is now classified as a fungus. Human pneumocystis is now called jirovecii as *Pneumocystis carinii* only infects rats. *P. jirovecii* pneumonia (PJP) is an important opportunistic infection that has fortunately decreased in frequency due to the widespread use of sulfamethoxazole/trimethoprim prophylaxis in the immediate post-transplant period. Patients typically present with fever, dyspnea and nonproductive cough, interstitial infiltrate on chest x-ray and hypoxemia. Elevated lactate dehydrogenase and hypercalcemia are characteristic biochemical findings supporting the diagnosis. The diagnosis is established by demonstration of pneumocystis in lung secretions obtained from bronchoalveolar lavage or in tissue from lung [124]. Gomori stain or toluidine blue staining will demonstrate the cysts and Giemsa staining will identify the sporozoites. CMV infection is the major differential diagnosis. Many children may have dual infection, in which CMV infection predisposed to superinfection with *P. jirovecii*. Treatment recommendations include high dose intravenous trimethoprim-sulfamethoxazole, corticosteroids and a reduction in immunosuppression. Chemoprophylaxis with three times a week oral sulfamethoxazole/trimethoprim (5 mg/kg trimethoprim component/dose) has reduced the incidence of PJP from 3.7% to 0% [125]. Daily dosing may be easier for patient adherence and is recommended by KDIGO [12]. Prophylaxis is recommended in all transplant recipients for 3–6 months post-transplant. Some also advocate its use after anti-rejection therapy, particularly with anti-T cell antibodies.

Parasitic Infections

Although several parasitic infections have been reported in pediatric recipients of solid organ or bone marrow transplantation, there are few reports of such infections in pediatric kidney recipients. Several parasitic infections deserve mention, however, as they have been reported as transmitted by the transplanted graft in adult kidney transplant recipients. *Strongyloides stercoralis* is an intestinal nematode that infects tens of millions of people worldwide. It is endemic in tropical and sub-tropical regions. The highest rate of infection in the US is in the Southeast [126]. *S. stercoralis* may remain in the human intestinal tract without symptoms for decades, and then cause disseminated infection with the introduction of immunosuppressive medication post-transplant [126]. In addition, there are case reports of transmission of strongyloidiasis by kidney transplantation in an adult recipient [127]. Interestingly, CSA but not tacrolimus has effects

against *S. stercoralis* and may reduce the risk for disseminated strongyloidiasis [128, 129]. Active infection typically presents with cutaneous, gastrointestinal and pulmonary symptoms as well as eosinophilia [130]. With disseminated disease, fever, hypotension, and central nervous system symptoms may be present [130]. In uncomplicated infections, diagnosis is made by detection of larvae in stool, although 25% of infected patients may have negative stool examinations [131]. In disseminated disease, larvae may be found in stool, sputum, bronchoalveolar lavage fluid, and peritoneal and pleural fluid [126, 132]. Serologic testing using ELISA may also be of value, but may be falsely negative in immunocompromised hosts [132, 133]. Thiabendazole, previously the treatment of choice for *S. stercoralis,* has been replaced by ivermectin, with albendazole as an alternative [134].

Other parasitic infections reported in kidney transplant recipients as transmitted by the transplanted graft include Chagas' disease and malaria [126, 135, 136]. Chagas' disease is caused by *Trypanosoma cruzi* and is found only in the southern US, Mexico and Central and South America. The manifestations of Chagas' disease classically include megaesophagus, megacolon, and cardiac disease, although CNS involvement has been reported in kidney transplant recipients [135]. The diagnosis is routinely made serologically and treatment typically consists of benznidazole or nifurtimox. Post-transplant malaria, transmitted from donors living in high-risk areas, is a frequent occurrence [136]. The discussion of these infections is meant to illustrate the potential problem of parasitic infections post-transplant. Policies to screen potential recipients and donors for these and other parasitic infections should be based on the presence of risk factors, including residence in or travel to an endemic area.

Fungal Infections

In general, serious invasive fungal infections such as aspergillosis are less common in pediatric kidney transplant recipients than thoracic organ recipients. Candida is the most common organism affecting kidney transplant recipients, either as oral and esophageal thrush, vaginitis, nail infection or UTI. The diagnosis of thrush is by clinical examination or demonstration of hyphae on a smear. Candidal UTI is diagnosed by urine culture. Treatment for topical candida is by topical nystatin or clotrimazole. Prophylactic measures include oral clotrimazole lozenges, nystatin, or fluconazole for 1–3 months post-transplant and for 1 month after treatment with an anti-lymphocyte antibody [12]. Treatment of invasive disease typically requires amphotericin. Fluconazole may be used for treatment of less severe disease, or for infections that have stabilized after initial therapy with amphotericin. Dose adjustment and close monitoring of the levels of CNIs are necessary when fluconazole is used due to the drug-drug interactions. In addition, there are potential drug-drug interactions between CNIs and clotrimazole [137].

Immunizations

One of the cornerstones of preventative care in pediatrics is the delivery of routine childhood immunizations. Unfortunately, the complicated medical care required by many children with chronic kidney disease may result in only sporadic delivery of routine well-child care, including immunizations. Complete immunization is especially important in children with ESKD as they approach transplantation given the increased risk for vaccine preventable disease post-transplant. In general, children with chronic kidney disease should receive immunizations according to the recommendations for healthy children in the region. Because they may also be more susceptible to or at risk for more serious infection from pathogens that are not typically problematic in healthy children, candidates for or recipients of kidney transplantation may also benefit from supplemental or additional vaccinations [76]. Table 69.3 provides a list of vaccinations recommended specifically for pediatric transplant candidates and recipients. Because children with chronic kidney disease and on dial-

ysis may have sub-optimal response to many immunizations, or lose immunity prior to transplantation, it is important not only to ensure timely delivery of routine childhood immunizations, but also to monitor antibody titers or levels and revaccinate when indicated [138]. This is especially true of the live viral vaccines, including measles, mumps, rubella and varicella zoster vaccine, which are contraindicated in the immunosuppressed patient post-transplant.

In the post-transplant period, immunizations may be given after immunosuppressive medications have reached a baseline level, typically 6 to 12 months post-transplant. Again, live viral vaccines are generally contraindicated in the post-transplant period. Because the presence of immunosuppressive medications may impair response to vaccines, maximal protection requires universal immunization of health care workers, family members and household contacts [74]. In particular, annual immunization with injectable influenza vaccine is required [74].

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