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Infections in pediatric solid organ transplant recipients

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Despite the progress made in graft and patient survival in recent years, infectious complications remain a major source of morbidity and mortality in pediatric solid organ transplant recipients. The risk of infection after transplant is determined by the interaction of several factors, including age, type of organ transplanted, type and intensity of immunosuppression, environmental exposures, and the consequences of invasive procedures. Compared with adult transplant recipients, children are at higher risk of developing primary infection with various organisms after transplantation, as they often lack previous immunity from natural exposure to many microbes and often have not completed their primary immunization series at the time of transplantation. This article provides an overview of the risk factors, timing, and types of infectious complications associated with organ transplantation in children.

INDEX WORDS
Infection in transplant recipients; Opportunistic infection; Pediatric solid organ transplantation; Environmental exposure

Solid organ transplantation (SOT) is a major therapeutic option for many children with end-stage organ failure. In 2003, there were almost 2500 pediatric candidates and 1800 recipients of organ transplantation in the United States. With advances in immunosuppressive agents and surgical techniques, survival rates continue to improve. Despite the progress made in graft preservation and patient survival, infectious complications remain a major source of morbidity and mortality, particularly in pediatric transplant patients. Pediatric organ transplant recipients differ from their adult counterparts in several ways, including the underlying etiology of organ failure, the complexity of the surgical procedures, and the susceptibility to posttransplant complications, particularly infections. This article provides an overview of the infectious complications associated with organ transplantation in children.

Risk of infection in pediatric solid organ transplant recipients

The risk of infection in children after SOT is largely determined by the interaction of several factors including the type and intensity of immunosuppression (net state of immunosuppression), environmental exposures, and the consequences of invasive procedures. Factors predisposing to infection after transplantation can be further classified as those present before transplantation, those related to the transplant procedure, or those at the perioperative or posttransplant period (Table 1).

Age is an important determinant of susceptibility to certain pathogens and disease severity. Often young children will lack immunity to many pathogens before transplantation. This can occur if they have not completed their primary immunization series, rendering them susceptible to vaccine preventable illnesses or if they have not had exposure to common community pathogens. Accordingly, young children, compared with adult transplant recipients, are at higher risk of acquiring primary infection with many organisms after they are immunosuppressed, which can lead to increased severity.
The underlying disease processes and complications of end stage organ disease represent additional risks for infectious complications. The risk of urinary tract infection (UTI) after renal transplantation is increased in children who have underlying vesicoureteral reflux. Candidates for lung transplantation with cystic fibrosis (CF) are often colonized with fungi and highly resistant Gram-negative bacteria. Likewise prolonged hospitalization times before transplantation increase the risk of nosocomial colonization with resistant organisms. Disorders requiring palliative surgery can also lead to technical difficulties during subsequent transplantation increasing the risk of infection. Finally, children who were previously immunosuppressed from iatrogenic medications or chronic malnutrition are at enhanced risk of infection after transplantation.

The type of allograft and the technical factors unique to each organ transplant procedure are important determinants of both location and type of postoperative infections. For example, the risk of infection after liver transplantation has been associated with the type of biliary reconstruction used. Thrombosis of the hepatic artery has been shown to predispose to hepatic abscess and bacteremia following liver transplant. In thoracic transplant recipients, mediastinal bleeding requiring subsequent re-exploration increases the risk of mediastinitis and sepsis. Prolonged operative time has been associated with increased risk of infection and is likely a surrogate marker for the technical difficulty of the surgery. In addition, ischemic injury can reduce the viability of the allograft and increase the risk of infection.

Transplantation is a distinctively efficient mode of transmission of latent organisms including cell-associated viruses [CMV, EBV, human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV)], chronic bacteria (mycobacteria, syphilis), fungi (Histoplasma, Coccioidioides, Cryptococcus), and parasites (Toxoplasma gondii, Trypanosoma cruzi, Strongylodes stercoralis) with the graft. The adverse consequences of some of these microbes in the donor are so significant that they are often considered an absolute contraindication for transplantation (eg, HIV, HBV). For ubiquitous organisms, such as CMV and EBV, alternate strategies for prevention of disease post transplant can be instituted.

Immunosuppression, prolonged use of indwelling cannulas, and environmental exposures are among the major determinants of the risk of infection following transplantation. Furthermore, the interaction of several factors, including the nature of the immunosuppressive regimen, treatment of rejection, neutropenia, metabolic abnormalities (ie, hypoalbuminemia, uremia, hyperglycemia), and infection with immunomodulating viruses (eg, CMV, EBV), will determine the overall state of immunosuppression for an individual transplant recipient and therefore his or her risk for other infections. As immunosuppressive regimens evolve, the specific nature of infectious complications may also change. Thus, it is important to monitor for new infectious complications when evaluating novel immunosuppressive agents.

### Timing of infection after transplantation

Infections after transplantation tend to follow a predictable temporal pattern in the absence of antimicrobial intervention, and can be grouped into three major time frames: early, intermediate, and late. This timetable has proved useful in the differential diagnosis of patients presenting with a possible infectious disease syndrome.

#### Early infections (0-30 days)

Most of the infections seen during the first month after transplantation are associated with technical problems and are similar to those complicating comparable major surgery. These include bacterial and candidal surgical wound infections, pneumonia, bacteremia, and UTI. Postoperative bacteremia is related predominantly to indwelling catheters, but can also be result from other foci of infection such as pneumonia, pyelonephritis, or mediastinitis. Additional causes of infection in the early post transplant period in-

### Table 1  Factors determining the risk of infectious complications following transplantation

| Pretransplantation factors | Perioperative factors | Post-transplant factors |
|----------------------------|----------------------|------------------------|
| **Young age**              | Type of organ transplanted | Net state of immunosuppression: |
| **Underlying disease**     | Transplant procedure:   | ● Dose, duration, and temporal sequence of immunosuppressive agents |
| **Duration and frequency of hospitalizations** | ● Ischemic injury | ● Augmented therapy for rejection |
| **Palliative surgery prior to transplant** | ● Prolonged operative time | ● Neutropenia |
| **Complications of end-stage organ disease** | ● Exposure to blood products | ● Metabolic abnormalities |
| **Malnutrition** | ● Technical problems | ● Viral infection |
| **Environmental exposures:** | ● Donor-transmitted pathogens | Environmental exposures: |
| ● Community | Indwelling cannulas (Endotracheal tube, urethral catheters, intravenous catheters) | ● Community |
| ● Hospital | | ● Hospital |
| **Travel** | | Indwelling cannulas |

The underlying disease processes and complications of end stage organ disease represent additional risks for infectious complications. The risk of urinary tract infection (UTI) after renal transplantation is increased in children who have underlying vesicoureteral reflux. Candidates for lung transplantation with cystic fibrosis (CF) are often colonized with fungi and highly resistant Gram-negative bacteria. Likewise prolonged hospitalization times before transplantation increase the risk of nosocomial colonization with resistant organisms. Disorders requiring palliative surgery can also lead to technical difficulties during subsequent transplantation increasing the risk of infection. Finally, children who were previously immunosuppressed from iatrogenic medications or chronic malnutrition are at enhanced risk of infection after transplantation.

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clude some pathogens present in the recipient before transplant, which may be exacerbated by the immunosuppressive therapy such as herpes simplex virus (HSV) and less commonly, acute infection transmitted with a contaminated allograft. Finally, nosocomial infection with respiratory viruses such as influenza, parainfluenza, and respiratory syncytial virus (RSV) are most severe in the early period after transplantation.18

**Intermediate (1-6 months)**

During the intermediate period, infections associated with postoperative complications or with augmented immunosuppression can develop. Reactivation of latent organisms within the host or graft associated with these same infectious agents such as CMV, EBV, or *T. gondii* comprise the major infections seen during this time period. The use of prophylaxis or preemptive therapy against CMV can modify the timing of disease to occur greater than 6 months after transplant. The overall state of immunosuppression also promotes a permissive environment for opportunistic infections with *Pneumocystis jiroveci*, and *Aspergillus* spp.

**Late infections (more than 6 months)**

This period is less well defined. The types of infections seen will largely depend on the transplantation outcome and the degree of immunosuppression. Accordingly, the highest risk for life-threatening opportunistic infections occurs in the setting of poor allograft function, chronic viral infection, and greater exposure to immunosuppression. In contrast, the types and severity of infection seen in patients who have good allograft function and are on low-dose maintenance immunosuppression tend to be similar to those observed in otherwise healthy children such as community acquired respiratory viruses.3,19

There are some infections that can occur at any time and are more related to the patient’s clinical and immunosuppressive status rather than temporal events per se. For example, children with continued central intravenous access remain at risk for line associated infection regardless of the time post transplant, and hospitalized children are at risk for health care-associated infections.

**Viral infections**

Viral infections are a major cause of morbidity and mortality after pediatric organ transplantation. Their identification has been greatly aided by the availability of newer molecular diagnostic techniques. Herpesviruses [CMV, EBV, HSV, varicella zoster virus (VZV), and less frequently HHV-6, -7, and -8] are some of the most important viral infections after pediatric SOT. They share the ability to establish lifelong latency leading to intermittent reactivation, either spontaneously or as a result of various stimuli such as enhanced immunosuppression. Herpesviruses can arise as primary infection (community or graft associated), reactivation of the host virus, or re-infection with a new viral strain. In general, primary infection after SOT causes the most significant disease.

**Cytomegalovirus**

In the United States, primary CMV infection occurs during the first two decades of life as an asymptomatic infection or infectious mononucleosis-like syndrome in approximately 50% of the population. CMV is one of the most important infectious complications after SOT. Before widespread use of prophylaxis, CMV disease was reported to occur in 40% of pediatric liver recipients, 22% of kidney recipients, and 26% of thoracic organ recipients.4,20 During the last decade, the impact of CMV infection and disease on morbidity and mortality has been reduced by improvements in prevention and management strategies.

Several risk factors for the development of CMV infection and disease after organ transplantation are recognized. Primary CMV infection acquired from the donor allograft (ie, CMV donor-positive/recipient-negative) has been associated with the highest morbidity and mortality.7 Acquisition of CMV from blood products has significantly decreased since the era of screening blood and the institution of prophylaxis. CMV disease was reported to occur in 50% of the population. CMV is one of the most important infectious mononucleosis-like syndrome in approximately 50% of the population. CMV disease refers to the evidence of CMV in clinical trials.16 CMV infection is defined as having CMV replication in any body fluid or tissue specimen. CMV disease refers to the evidence of infection in the presence of attributable symptoms and typically presents 30 to 90 days after transplantation, but can be delayed in the setting of prophylaxis.22 Disease caused by CMV can be further classified as CMV syndrome, a clinical condition with fever, malaise, leukopenia, and/or thrombocytopenia in the absence of end organ involvement and CMV tissue invasive disease. CMV disease refers to the evidence of infection in the presence of attributable symptoms and typically presents 30 to 90 days after transplantation, but can be delayed in the setting of prophylaxis.22 Disease caused by CMV can be further classified as CMV syndrome, a clinical condition with fever, malaise, leukopenia, and/or thrombocytopenia in the absence of end organ involvement and CMV tissue invasive disease presenting as pneumonitis, hepatitis, gastrointestinal disease, myocarditis, and less frequently as encephalitis or retinitis. Histologic examination of involved organs is necessary to confirm the diagnosis of CMV invasive disease. There is a predilection for CMV to invade the allograft.

In addition to direct viral effects causing symptomatic disease, CMV has been associated with indirect immunomodulatory effects leading to an enhanced susceptibility to other opportunistic infections including aspergillus, EBV-
The diagnosis of CMV has evolved in recent years. CMV serology is useful for the determination of the donor and recipient pretransplant serostatus and posttransplant risk, but is of limited value after transplantation. CMV can be cultured from a variety of specimens including urine, tissues, and respiratory secretions. However, traditional culture is slow and less sensitive than detection by newer molecular techniques. Although rapid shell vial culture techniques for CMV improve the timeliness of detection, neither culture method is able to distinguish between viral shedding and true CMV disease. The pp65 antigenemia assay detects the late structural protein pp65 produced in leukocytes with a sensitivity of 89% and specificity of 100%. The need for both rapid processing and technical skill in interpretation limit its usefulness. Molecular diagnostic assays that detect and quantify CMV-DNA by polymerase chain reaction (PCR) have high sensitivity (95-100%) and are being increasingly recognized as the method of choice for diagnosis and therapeutic monitoring in CMV disease. Comparative studies between antigenemia detection and PCR have shown a more than 80% concordance. Both PCR and pp65 antigenemia can be used for early detection of viral replication according to local experience.

Approaches for the prevention of CMV include the use of CMV seronegative or leukocyte-reduced blood products, antiviral agents, and immunoglobulin therapy. Specific prevention strategies vary widely among centers with the two approaches most commonly used being universal prophylaxis of all patients at risk for CMV and preemptive therapy. Appropriate dosing for valganciclovir, have been used most often for prophylaxis or preemptive therapy. Appropriate dosing for valganciclovir in children is still not known but should benefit from an ongoing multi-center, international study of the pharmacology of a liquid formulation in pediatric transplant recipients. The benefit of adding CMV hyperimmune globulin in treating CMV disease remains uncertain. Judicious reduction of immunosuppression is an important component in the treatment of CMV disease. Despite successful treatment, CMV infection recurs in one-third of solid organ recipients. The incidence of resistance in SOT patients receiving prophylaxis is estimated at 0% to 13%.

Epstein–Barr virus

EBV is a ubiquitous human herpesvirus that has the ability to transform and immortalize B lymphocytes resulting in life-long latent infection. In the normal host, the proliferation of immortalized B cells is limited by a cytotoxic T lymphocyte (CTL) response. In transplant recipients, however, immunosuppressive therapy impairs this response, creating the potential for uncontrolled lymphoproliferation. This is particularly true for recipients who undergo primary infection after transplantation. EBV infection has been associated with a wide spectrum of disease in pediatric transplant patients, including asymptomatic seroconversion, nonspecific viral illness, mononucleosis, PTLD, and lymphoma. The term EBV-associated PTLD is generally used to describe a heterogeneous group of clinical syndromes associated with EBV driven lymphoproliferation ranging from a benign self-limited form of polyclonal proliferation to true malignancies containing clonal chromosomal abnormalities. The disease may be nodal or extranodal, localized or disseminated. PTLD has been identified as the most common post transplant malignancy in pediatric SOT patients.

Primary EBV infection, often donor-associated (EBV seropositive donor/seronegative recipient), is the most clearly defined risk factor for the development of early PTLD (<12 months after transplant). Children are therefore at considerably higher risk of developing PTLD than adults as they are often EBV naïve at the time of transplantation. The incidence of PTLD is also dependent on the type of organ transplanted, with small intestinal transplant recipients being at highest risk (up to 32%), pancreas, heart, lung, and liver transplant recipients are at moderate risk (3-12%), and recipients of kidney transplants are at relatively low risk.

A high index of suspicion and clinical vigilance must be maintained to allow for timely evaluation for EBV disease or PTLD. An increasing body of evidence supports the measurement of quantitative EBV viral load using PCR in peripheral blood as an adjunct for early diagnosis of EBV/PTLD, particularly in those at highest risk. Ongoing research will assist with developing recommendations for an optimal monitoring protocol.

EBV disease/PTLD should be considered in SOT recipients who present with fever, mononucleosis, gastrointestinal disturbances, lymphadenopathy, or organomegaly. Less often, PTLD presents with focal neurologic symptoms, or allograft dysfunction. Diagnostic evaluation should include a thorough history and physical examination, quantitative EBV assays, and radiological evaluation with CT scans of the chest, abdomen, and pelvis. Additional evaluation in selected patients with gastrointestinal endoscopy, brain imaging, or bone marrow biopsy should be included when clinically indicated. Pathology remains the gold standard for the diagnosis and classification of PTLD. Therefore, it is important to pursue biopsy of suspicious lesions or nodes. Most, but not all cases of PTLD are associated with EBV infection; in general, EBV-negative cases have a worse prog-
nosis than cases of EBV-related PTLD. EBV-negative PTLD are more common late after transplantation (greater than a year).

Reduction of immunosuppression is widely accepted as the initial strategy in the management of most categories of EBV disease. The optimal role and timing of additional therapy, such as antiviral agents, intravenous immunoglobulin, monoclonal antibodies, interferon, and chemotherapy, remain controversial. In general, the goal of therapy is to promote regression of disease with minimal patient morbidity while preserving graft function. Clinical recurrence of PTLD has been estimated to occur in approximately 5% of cases.

Other herpes viruses

Typically, HSV reactivation occurs early after SOT in previously seropositive subjects who are not on antiviral prophylaxis. Primary infection transmitted from the allograft has been described but is rare. Children who are seronegative may acquire the virus from close contacts. Whereas the HSV infections commonly present as orolabial disease, disseminated disease in the form of pneumonitis, esophagitis, and hepatitis may occur. Antiviral prophylaxis of patients that are HSV seropositive for the first 1 to 3 months after transplantation has generally prevented serious HSV disease. Young children who are not fully immunized are at risk for primary VZV infection after SOT. They are at an increased risk of developing more severe skin disease and visceral involvement, such as encephalitis, pneumonitis, or hepatitis. It is strongly recommended that children be immunized against VZV before transplantation. It has been recommended that susceptible children who are exposed to VZV receive prophylaxis with varicella zoster immune globulin within 72 to 96 hours of the exposure. However, its limited availability leads to recommendations for intravenous immunoglobulin or oral acyclovir starting at 7 days post exposure. These strategies have yet to be fully studied. Severe disease with HSV or VZV should be treated with intravenous acyclovir.

More recently, recognized herpesviruses such as the beta herpesviruses HHV-6 and HHV-7 have been associated with disease after transplantation. In particular, HHV-6 has been linked to a variety of clinical manifestations in transplant recipients, including pneumonitis, fever, encephalitis, and myelosuppression. Similar to CMV, HHV-6 is thought to have an immunomodulatory effect. It has been postulated that coinfection with HHV-6 or HHV-7 and CMV promotes development of CMV disease. The gamma-herpesvirus HHV-8 has been associated with Kaposi’s sarcoma after transplantation, particularly in countries that have high seroprevalence rates.

Community acquired viral infections

Infections with community acquired respiratory viruses are increasingly recognized as a cause of morbidity, graft failure, and mortality in transplant recipients. Influenza, parainfluenza, and RSV infections are common causes of upper respiratory tract infection in children, but in transplant recipients they are associated with an increased risk of progression to pneumonia. It is also well recognized that respiratory viral infection can predispose patients to coinfections, particularly bacterial pneumonia. In addition, immunocompromised patients tend to have prolonged viral shedding after resolution of symptoms. In lung transplant recipients, respiratory viral infections have been associated with rejection. The diagnosis of respiratory viral infections can be established by culture, rapid antigen detection, PCR, or monoclonal antibody testing of nasopharyngeal aspirates or bronchoalveolar lavage specimens.

Risk factors for more severe disease with these common childhood viral infections after SOT include onset of infection early after transplantation, augmented immunosuppression for rejection, and a younger age. Prevention of respiratory viral infection is predominately through infection control measures. Immunization against influenza should be administered yearly to the child and close contacts (household contacts and health care workers). Prophylaxis with the RSV-specific monoclonal antibody palivizumab has been recommended in high-risk infants younger than 24 months. No randomized trials have been conducted to evaluate the use of palivizumab after SOT; however, some experts support the use of immunoprophylaxis for infants less than 1 year of age who receive their transplant during the RSV season. Adenovirus infection, although frequently asymptomatic, can cause a wide variety of infectious syndromes, especially in transplant recipients. Clinical manifestations are often related to the type of transplant and range from self-limited fever, gastroenteritis, hemorrhagic cystitis, to necrotizing hepatitis or pneumonia with the potential to cause life-threatening infection. Adenovirus was the third most important viral infection following pediatric liver transplantation under cyclosporine in one series. Its epidemiology is less well characterized after other SOT types but can be particularly severe early after lung transplantation, where it may be associated with fatal pneumonitis. Adenovirus infection has been identified in up to 50% of pediatric intestinal transplant recipients, but many of these patients are thought to be experiencing asymptomatic shedding of adenovirus in their stools. The frequency of symptomatic and invasive disease remains to be determined in this population.

Diagnosis of adenovirus includes culture, antigen detection, and more recently PCR assays. Histologic evaluation remains the gold standard for diagnosis of invasive disease. At this time, there is no definitive treatment for adenovirus infection. Decrease in immunosuppression remains an important component of therapy. The role of antiviral agents remains to be elucidated. Anecdotal reports and small case series in bone marrow or stem cell recipients suggest a benefit with cidofovir. However, a variety of dosing
regimens have been employed and no controlled trial has been conducted.

Polyoma viruses

Infection with *Polyomavirus hominis* type 1, better known as BK virus (BKV) typically occurs during childhood, with latency occurring in renal and urogenital cells. Serological evidence of exposure to BKV has been found in more than 70% of the general population worldwide. Asymptomatic reactivation and low-level replication with viruria occurs in 5% of healthy individuals. In renal transplant recipients, persistent high-level BKV replication has been associated with tubulointerstitial nephritis and ureteral stenosis. In pediatric renal transplant recipients, pretransplant BKV seronegative status has been associated with increased risk of primary infection with subsequent BKV nephropathy. The definitive diagnosis of BKV disease requires histopathological confirmation. The optimal management of BKV disease has not been established. Experience with antiviral therapy has not been documented. Trials with low dose cidofovir are underway. Judicious reduction of immune suppression and active surveillance for rejection usually result in improvement.

Emerging transplant viral infections

Donor-derived infection with West Nile virus, lymphocytic choriomeningitis virus (LCMV), and rabies has been recently described. During the outbreak of severe acute respiratory syndrome (SARS), transplant recipients with severe and rapidly progressive disease were reported. Higher viral burdens appeared to be present in transplant patients and may have had implications for the increased infectivity of these patients. These reports emphasize the challenges of preventing and detecting transmission of unusual pathogens through transplantation or in the posttransplant period.

Bacterial and fungal infections

Bacterial and fungal infections can be problematic after transplantation. Prophylactic strategies have decreased their risk early after transplantation but in recent years, multidrug-resistant (MDR) bacteria have emerged in many transplant centers. These include Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, as well as Gram-negative bacteria (eg, MDR *Pseudomonas aeruginosa*, and extended-spectrum β-lactamase [ESBL]-producing Enterobacteriaceae). Complicated surgical and invasive diagnostic procedures, indwelling catheters, prolonged hospital stays, and high antimicrobial use contribute to nosocomial infection with MDR bacteria after SOT. Aggressive infection control measures and judicious use of antimicrobials are critical for protecting highly susceptible transplant recipients. Transplant recipients are also at risk for infections caused by unusual organisms, such as nontuberculous mycobacteria, *Legionella*, and *Nocardia* species. Donor-derived bacterial infections can result from local colonization or unrecognized bacteremia predisposing the recipient for metastatic bacteremia and/or mycotic aneurysm at the site of vascular anastomosis. Surveillance cultures and knowledge of local antimicrobial resistance patterns can be useful in guiding empirical antibiotic therapy.

Opportunistic fungal infections have long been recognized as a significant complication in SOT recipients. A majority of fungal infections early after transplantation are caused by Candida; with *Aspergillus* species being more common early after lung transplantation. Invasive candidiasis is primarily related to technical aspects of the surgery (eg, in liver transplant recipients) or recipient and donor allograft colonization (eg, in lung transplant recipients). Pulmonary aspergillosis can disseminate to the CNS. Likewise aspergillosis is the most common cause of brain abscess in organ transplant recipients. CMV infection is a risk factor for subsequent aspergillus infection. Fungal infections that develop late after transplantation may be due to reactivation of organisms that are able to establish latency (endemic fungi: *Histoplasma*, *Coccidioides*), or Cryptococcus but are less frequent in children than in adults. Aspergillus may be associated with chronic lung rejection. The value of screening assays for invasive fungal infection (eg, galactomannan, β-glucan, or PCR) is yet to be determined.

Opportunistic infections

*Pneumocystis jiroveci* is an important cause of pneumonia in immunocompromised patients (PCP). Most cases occur between 1 and 6 months after transplantation, but it is infrequent with the widespread use of prophylaxis. Trimethoprim-sulfamethoxazole is considered the prophylactic agent of choice. Alternative agents available include pentamidine, dapsone, atovaquone, and combination therapy with clindamycin and pyrimethamine. Notably, breakthrough PCP infections in patients receiving alternative prophylactic regimens have been reported and are often atypical.

*Toxoplasma gondii* is also an opportunistic pathogen in immunocompromised individuals. Toxoplasmosis after SOT may result from primary infection or from reactivation of latent infection with the greatest risk for acquisition of *T. gondii* infection occurring in seronegative heart transplant recipients from a seropositive donor. Although post transplant toxoplasmosis has been most frequently found after cardiac transplantation, it has also been reported to occur in recipients of other organs. Clinical symptoms usually develop within the intermediate posttransplant period. Fever may be the only clinical manifestation. Dis-
semination of the parasite to the CNS may lead to signs and symptoms of meningoencephalitis. A sepsis-like picture, pneumonia, or cutaneous lesions are unusual manifestations. Prophylactic administration of pyrimethamine to seronegative recipients of hearts from seropositive donors has prevented disease. Alternatively, prophylaxis with trimethoprim-sulfamethoxazole appears to be protective in adult cardiac transplant recipients.65

Although uncommon, infection with *Mycobacterium tuberculosis* (MTB) after transplantation is associated with substantial morbidity and mortality. The frequency of posttransplant MTB is 1.2% to 6.4% in most developed countries, but it may reach 15% among SOT recipients living in endemic areas. Most commonly, MTB results from reactivation of latent infection with disease onset during the intermediate period.66,67 Compared with normal hosts, clinical presentation after SOT has a higher incidence of disseminated disease and extrapulmonary involvement. Manifestations include fever of unknown origin and allograft dysfunction. Coinfection with other pathogens is not uncommon. Treatment of MTB after SOT poses special challenges because of potential interactions between anti-MTB drugs and immunosuppressive medications and potential hepatotoxicity. Prophylaxis with isoniazid is indicated in patients with evidence of latent MTB infection.68 Most experts recommend screening candidates and administering prophylaxis to those that are positive before undergoing transplantation.

**Pre-transplantation evaluation**

The pretransplant evaluation of potential pediatric recipients and donors is an important component of the transplantation process. Its purpose includes identification of conditions that may disqualify either donor or recipient, and the recognition of any latent or active infections that may require therapy before transplantation. The infectious disease screening of donor and recipient may influence the type of monitoring and prophylaxis the recipient receives for preventing infection after transplantation. Finally, the pretransplant evaluation is an opportunity to provide cohesive education about infections and their prevention to both the child and their family (Table 2). Additional screening of potential donors and recipients should be guided by clinical suspicion of infection. Since vaccinations are likely to be less effective after transplant, the pretransplant evaluation provides an important opportunity to update immunizations. Live vaccines should be given at least 4 weeks before the date of transplant.

### Table 2 Pretransplant evaluation

| History and Physical Examination |  |
|---------------------------------|--|
| Epidemiologic exposures (pets, travel, geography) |  |
| Past infections |  |
| Drug allergies |  |
| Immunization history |  |
| Serologic screen |  |
| HIV-1, HIV-2 |  |
| HSV |  |
| CMV |  |
| EBV |  |
| VZV |  |
| Hepatitis A,B,C |  |
| RPR |  |
| Measles, Mumps, Rubella* |  |
| Toxoplasma (in heart recipients) |  |
| Tuberculin skin test |  |
| Cultures in appropriate cases (e.g. respiratory culture in CF patients) |  |
| Chest radiograph |  |
| Update vaccinations |  |
| Education and counseling |  |

*Some centers do measles titer to assess immunity to MMR vaccine.

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