
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Seminars in Pediatric Surgery (2006) 15, 153-161

ELSEVIER

SEMINARS IN PEDIATRIC SURGERY

# Infections in pediatric solid organ transplant recipients

**Monica Fonseca-Aten, MD,[a] Marian G. Michaels, MD, MPH[b,c]**

[a]*From the Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas;*
[b]*Division of Allergy, Immunology and Infectious Diseases, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; and the*
[c]*Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.*

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

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.


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.[1] 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.[2] 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.

**Address reprint requests and correspondence:** Marian G. Michaels, MD, Children's Hospital of Pittsburgh, Division of Allergy, Immunology, and Infectious Diseases, 3705 Fifth Avenue, Pittsburgh, PA 15213.
E-mail: marian.michaels@chp.edu.

1055-8586/$ -see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1053/j.sempedsurg.2006.03.009

## 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.[3] 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[4] (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[5] 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.[6,7]

**Table 1** Factors determining the risk of infectious complications following transplantation[4]

| 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.[8] 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.[9] Finally, children who were previously immunosuppressed from iatrogenic medications or chronic malnutrition are at enhanced risk of infection after transplantation.[10,11]

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.[12] 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.[13] Prolonged operative time has been associated with increased risk of infection and is likely a surrogate marker for the technical difficulty of the surgery.[14] 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, Coccidioides, *Cryptococcus*), and parasites (*Toxoplasma gondii*, *Trypanosoma cruzi*, *Strongyloides 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.[3,15] 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.[16]

## 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.[3] 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.[17] Additional causes of infection in the early post transplant period in-

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 leukoreduction of packed red blood cells in many centers. Reactivation of endogenous CMV or superinfection with a new CMV strain are generally associated with lesser incidence and severity of disease due to the presence of CMV-specific humoral and cell-mediated immunity in the recipient. Antithymocyte globulin and CD3 monoclonal antibody increase the risk of CMV disease.[21]

CMV causes a wide range of clinical manifestations that vary according to the type of allograft and the nature and duration of immunosuppression. Definitions of CMV infection and disease have been developed for the purpose of consistent reporting 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 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-

related posttransplant lymphoproliferative disease (PTLD), as well as an increased risk of graft rejection.[3]

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%.[23,24] 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.[23,25] 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. Each strategy has advantages and disadvantages. Unfortunately, data from multicenter controlled randomized trials evaluating different prevention strategies in pediatric transplant recipients are lacking.[26]

Intravenous ganciclovir, a nucleoside analog, is the therapy of choice for established CMV disease. Myelotoxicity is the most limiting side effect. Foscarnet, a competitive inhibitor of viral DNA polymerase, and cidofovir, a nucleotide analog with broad antiviral activity, are therapeutic alternatives in cases of ganciclovir resistance, but both agents have significant nephrotoxicity. Oral agents, such as oral ganciclovir and most recently the ganciclovir prodrug 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.[27] 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.[28] 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.[29] 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.[30]

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).[6] 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.[6]

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.[31,32] 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.[33] 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.[34,35] 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.[36] The gamma-herpesvirus HHV-8 has been associated with Kaposi's sarcoma after transplantation, particularly in countries that have high seroprevalence rates.[37,38]

## 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.[39,40] 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.[41] 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.[18,40,42-45] 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.[44]

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.[46] 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.[47] 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.[48,49] 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.[50] The definitive diagnosis of BKV disease requires histopathological confirmation. The optimal management of BKV disease has not been established. Experience with antiviral therapy is only anecdotal, although 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.[51-53] During the outbreak of severe acute respiratory syndrome (SARS), transplant recipients with severe and rapidly progressive disease were reported.[54] 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).[55,56] 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.[57,58] 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.[59] 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, galactomanan, 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.[60]

*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 has been reported to occur in recipients of other organs.[61-63] Clinical symptoms usually develop within the intermediate posttransplant period.[63,64] Fever may be the only clinical manifestation. Dis-

**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.

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.

## References


1. Harmon WE, McDonald RA, Reyes JD, et al. Pediatric transplantation, 1994-2003. Am J Transplant 2005;5:887-903.
2. Dharnidharka VR, Stablein DM, Harmon WE. Post-transplant infections now exceed acute rejection as cause for hospitalization: a report of the NAPRTCS. Am J Transplant 2004;4:384-9.
3. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998;338:1741-51.
4. Green M, Michaels MG. Infections in solid organ transplant recipients. In: Long SS, Pickering LK, Prober CG, eds. Principles and Practice of Pediatric Infectious Diseases (ed 2). Philadelphia, PA: Churchill Livingstone, 2003:554-61.
5. Campbell AL, Herold BC. Immunization of pediatric solid-organ transplantation candidates: immunizations in transplant candidates. Pediatr Transplant 2005;9:652-61.
6. Cockfield SM. Identifying the patient at risk for post-transplant lymphoproliferative disorder. Transpl Infect Dis 2001;3:70-8.
7. Rubin RH. Cytomegalovirus in solid organ transplantation. Transpl Infect Dis 2001;3:1-5 (suppl 2).
8. Casale P, Grady RW, Mitchell ME, et al. Recurrent urinary tract infection in the post-transplant reflux nephropathy patient: is reflux in the native ureter the culprit? Pediatr Transplant 2005;9:324-7.
9. Cuervas-Mons V, Rimola A, Van Thiel DH, et al. Does previous abdominal surgery alter the outcome of pediatric patients subjected to orthotopic liver transplantation? Gastroenterology 1986;90:853-7.
10. Moukarzel AA, Najm I, Vargas J, et al. Effect of nutritional status on outcome of orthotopic liver transplantation in pediatric patients. Transplant Proc 1990;22:1560-3.
11. Avery RK. Recipient screening prior to solid-organ transplantation. Clin Infect Dis 2002;35:1513-9.
12. Kusne S, Dummer JS, Singh N, et al. Infections after liver transplantation. An analysis of 101 consecutive cases. Medicine (Baltimore) 1988;67:132-43.
13. Schowengerdt KO, Naftel DC, Seib PM, et al. Infection after pediatric heart transplantation: results of a multiinstitutional study. The Pediatric Heart Transplant Study Group. J Heart Lung Transplant 1997;16:1207-16.
14. George DL, Arnow PM, Fox AS, et al. Bacterial infection as a complication of liver transplantation: epidemiology and risk factors. Rev Infect Dis 1991;13:387-96.
15. Introduction to the guidelines. Am J Transplant 2004;10:6-9 (suppl 4).
16. Humar A, Michaels MG. American Society of Transplantation Recommendations for Screening, Monitoring and Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation. Am J Transplant 2006;6:262-74.

17. Eppes SC, Troutman JL, Gutman LT. Outcome of treatment of candidemia in children whose central catheters were removed or retained. Pediatr Infect Dis J 1989;8:99-104.
18. Apalsch AM, Green M, Ledesma-Medina J, et al. Parainfluenza and influenza virus infections in pediatric organ transplant recipients. Clin Infect Dis 1995;20:394-9.
19. Their M, Holmberg C, Lautenschlager I, et al. Infections in pediatric kidney and liver transplant patients after perioperative hospitalization. Transplantation 2000;69:1617-23.
20. Green M, Wald ER, Fricker FJ, et al. Infections in pediatric orthotopic heart transplant recipients. Pediatr Infect Dis J 1989;8:87-93.
21. Humar A, Uknis M, Carlone-Jambor C, et al. Cytomegalovirus disease recurrence after ganciclovir treatment in kidney and kidney-pancreas transplant recipients. Transplantation 1999;67:94-7.
22. Cytomegalovirus. Am J Transplant 2004;10:51-8 (suppl 4).
23. Tanabe K, Tokumoto T, Ishikawa N, et al. Comparative study of cytomegalovirus (CMV) antigenemia assay, polymerase chain reaction, serology, and shell vial assay in the early diagnosis and monitoring of CMV infection after renal transplantation. Transplantation 1997;64:1721-5.
24. Murray BM, Amsterdam D, Gray V, et al. Monitoring and diagnosis of cytomegalovirus infection in renal transplantation. J Am Soc Nephrol 1997;8:1448-57.
25. Schmidt CA, Oettle H, Peng R, et al. Comparison of polymerase chain reaction from plasma and buffy coat with antigen detection and occurrence of immunoglobulin M for the demonstration of cytomegalovirus infection after liver transplantation. Transplantation 1995;59: 1133-8.
26. Campbell AL, Herold BC. Strategies for the prevention of cytomegalovirus infection and disease in pediatric liver transplantation recipients. Pediatr Transplant 2004;8:619-27.
27. Preiksaitis JK, Brennan DC, Fishman J, et al. Canadian society of transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. Am J Transplant 2005;5: 218-27.
28. Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. N Engl J Med 2004;350: 1328-37.
29. Epstein-Barr virus and lymphoproliferative disorders after transplantation. Am J Transplant 2004;10:59-65, (suppl 4).
30. Smets F, Sokal EM. Epstein-Barr virus-related lymphoproliferation in children after liver transplant: role of immunity, diagnosis, and management. Pediatr Transplant 2002;6:280-7.
31. Lee TC, Savoldo B, Rooney CM, et al. Quantitative EBV viral loads and immunosuppression alterations can decrease PTLD incidence in pediatric liver transplant recipients. Am J Transplant 2005;5:2222-8.
32. Rowe DT, Webber S, Schauer EM, et al. Epstein-Barr virus load monitoring: its role in the prevention and management of post-transplant lymphoproliferative disease. Transpl Infect Dis 2001;3:79-87.
33. Green M, Webber S. Posttransplantation lymphoproliferative disorders. Pediatr Clin North Am 2003;50:1471-91.
34. Singh N, Dummer JS, Kusne S, et al. Infections with cytomegalovirus and other herpesviruses in 121 liver transplant recipients: transmission by donated organ and the effect of OKT3 antibodies. J Infect Dis 1988;158:124-31.
35. Smyth RL, Higenbottam TW, Scott JP, et al. Herpes simplex virus infection in heart-lung transplant recipients. Transplantation 1990;49: 735-9.
36. Mendez JC, Dockrell DH, Espy MJ, et al. Human beta-herpesvirus interactions in solid organ transplant recipients. J Infect Dis 2001;183: 179-84.
37. Qunibi W, Akhtar M, Sheth K, et al. Kaposi's sarcoma: the most common tumor after renal transplantation in Saudi Arabia. Am J Med 1988;84:225-32.
38. Michaels MG, Jenkins FJ. Human herpesvirus 8: Is it time for routine surveillance in pediatric solid organ transplant recipients to prevent the development of Kaposi's sarcoma? Pediatr Transplant 2003;7:1-3.
39. Ison MG, Hayden FG. Viral infections in immunocompromised patients: what's new with respiratory viruses? Curr Opin Infect Dis 2002;15:355-67.
40. Englund JE, Whimbey EE. Community-acquired respiratory viruses after hemopoietic stem cell or solid organ transplantation. In: Bowden RA, Ljungman P, Paya CV, eds. Transplant Infections (ed 2). Baltimore, MD: Lippincott Williams & Wilkins, 2003:367-98.
41. Khalifah AP, Hachem RR, Chakinala MM, et al. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med 2004;170:181-7.
42. Wendt CH, Fox JM, Hertz MI. Paramyxovirus infection in lung transplant recipients. J Heart Lung Transplant 1995;14:479-85.
43. Pohl C, Green M, Wald ER, et al. Respiratory syncytial virus infections in pediatric liver transplant recipients. J Infect Dis 1992;165: 166-9.
44. Community-acquired respiratory viruses. Am J Transplant 2004;10: 105-9 (suppl 4).
45. Mauch TJ, Bratton S, Myers T, et al. Influenza B virus infection in pediatric solid organ transplant recipients. Pediatrics 1994;94:225-9.
46. Michaels MG, Green M, Wald ER, et al. Adenovirus infection in pediatric liver transplant recipients. J Infect Dis 1992;165:170-4.
47. Bridges ND, Spray TL, Collins MH, et al. Adenovirus infection in the lung results in graft failure after lung transplantation. J Thorac Cardiovasc Surg 1998;116:617-23.
48. Carter BA, Karpen SJ, Quiros-Tejeira RE, et al. Intravenous Cidofovir therapy for disseminated adenovirus in a pediatric liver transplant recipient. Transplantation 2002;74:1050-2.
49. Hoffman JA, Shah AJ, Ross LA, et al. Adenoviral infections and a prospective trial of cidofovir in pediatric hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2001;7:388-94.
50. Smith JM, McDonald RA, Finn LS, et al. Polyomavirus nephropathy in pediatric kidney transplant recipients. Am J Transplant 2004;4: 2109-17.
51. Srinivasan A, Burton EC, Kuehnert MJ, et al. Transmission of rabies virus from an organ donor to four transplant recipients. N Engl J Med 2005;352:1103-11.
52. Lymphocytic choriomeningitis virus infection in organ transplant recipients–Massachusetts, Rhode Island, 2005. MMWR Morb Mortal Wkly Rep 2005;54:537-9.
53. West Nile virus infections in organ transplant recipients–New York and Pennsylvania, August-September, 2005. MMWR Morb Mortal Wkly Rep 2005;54:1021-3.
54. Chui AK, Rao AR, Chan HL, et al. Impact of severe acute respiratory syndrome on liver transplantation service. Transplant Proc 2004;36: 2302-3.
55. Rebuck JA, Olsen KM, Fey PD, et al. Characterization of an outbreak due to extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in a pediatric intensive care unit transplant population. Clin Infect Dis 2000;31:1368-72.
56. Singh N, Gayowski T, Rihs JD, et al. Evolving trends in multiple-antibiotic-resistant bacteria in liver transplant recipients: a longitudinal study of antimicrobial susceptibility patterns. Liver Transpl 2001;7: 22-6.
57. Singh N. Fungal infections in the recipients of solid organ transplantation. Infect Dis Clin North Am 2003;17:113-34.
58. Gladdy RA, Richardson SE, Davies HD, et al. Candida infection in pediatric liver transplant recipients. Liver Transpl Surg 1999;5:16-24.
59. Montero CG, Martinez AJ. Neuropathology of heart transplantation: 23 cases. Neurology 1986;36:1149-54.
60. Pneumocystis jiroveci (formerly Pneumocystis carinii). Am J Transplant 2004;10:135-41 (suppl 4).
61. Barcan LA, Dallurzo ML, Clara LO, et al. Toxoplasma gondii pneumonia in liver transplantation: survival after a severe case of reactivation. Transpl Infect Dis 2002;4:93-6.

62. Wulf MW, van Crevel R, Portier R, et al. Toxoplasmosis after renal transplantation: implications of a missed diagnosis. J Clin Microbiol 2005;43:3544-7.
63. Michaels MG, Wald ER, Fricker FJ, et al. Toxoplasmosis in pediatric recipients of heart transplants. Clin Infect Dis 1992;14:847-51.
64. Hall WA, Martinez AJ, Dummer JS, et al. Central nervous system infections in heart and heart-lung transplant recipients. Arch Neurol 1989;46:173-7.
65. Montoya JG, Giraldo LF, Efron B, et al. Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. Clin Infect Dis 2001;33:629-40.
66. Munoz P, Rodriguez C, Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. Clin Infect Dis 2005;40: 581-7.
67. Verma A, Dhawan A, Wade JJ, et al. Mycobacterium tuberculosis infection in pediatric liver transplant recipients. Pediatr Infect Dis J 2000;19:625-30.
68. Mycobacterium tuberculosis. Am J Transplant 2004;10:37-41 (suppl 4).