Infections in Pediatric Solid Organ Transplant Recipients

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Infectious complications are an important cause of morbidity and mortality in children undergoing solid organ transplantation. Knowledge gained over the last 30 years provides a growing understanding of these infections. This review identifies risk factors for and timing of infections describes the common infectious syndromes and pathogens seen in children undergoing solid organ transplantation, and reviews preventive strategies.

Infectious complications remain an important cause of morbidity and mortality in children undergoing solid organ transplantation (SOT). Knowledge and experience accrued over the last 30 years provide a growing understanding of these infections. This review identifies the timing of and risk factors for infections, describes the common infectious syndromes and pathogens seen in children undergoing SOT, and reviews preventive strategies.

Two key principles inform our understanding of the infectious complications of SOT. The type of infection present in an SOT recipient can be predicted to some degree by the duration of time between transplantation and the child’s presentation with evidence of infection. In general, different types of infection occur within stereotypical time periods: during the early period (0–4 weeks), post-operative bacterial surgical infections predominate; during the middle period (generally 1–6 months) opportunistic infections are prominent and latent pathogens previously present in the recipient or derived from the donor reactivate; and during the late period (usually after 6 months), community-acquired viruses as well as infections associated with chronic graft dysfunction predominate [1, 2].

The second major principle is that there is a defined set of risk factors that predispose to infection in these children. The 3 major sets of risk factors—those present before SOT, those relating to the transplant procedure itself, and those occurring post-operation—are described.

RISK FACTORS FOR INFECTIONS

Pretransplant Factors

The age of the child at the time of SOT is an important factor that influences the types and severity of infections experienced after transplantation. Age impacts the chance of having had prior exposure to infectious agents. This can have both negative and positive effects on the transplant recipient. Younger patients are less likely to have encountered pathogens that establish lifelong latent infection (eg, cytomegalovirus [CMV] or tuberculosis) that may reactivate under the pressure of immune suppression. However, these young patients are also prone to the development of primary infections with pathogens such as CMV, respiratory syncytial virus (RSV), and influenza, which are associated with more severe infection compared with that faced by pediatric SOT recipients with prior immunologic experience with these same organisms [3–5]. Infection with Epstein–Barr virus (EBV) prior to transplant provides a high level of protection against the development of disease following SOT [6, 7]. Age also impacts the likelihood that children undergoing SOT will have received their full complement of immunizations [8–10]. Young children
undergoing transplant before receiving their routine primary vaccinations are at higher risk for vaccine-preventable infections.

A second pretransplant factor influencing the risk of infectious complications is the underlying cause of recipient organ dysfunction. Certain congenital anomalies and the surgical procedures undertaken to correct them may predispose to recurrent episodes of infection, increasing the risk of developing infection with multidrug-resistant bacteria both before and after SOT. Children undergoing heart transplant in the neonatal period are particularly vulnerable to bacterial infections [11]. Children undergoing intestinal transplantation frequently have had numerous bloodstream infections requiring treatment with multiple courses of antibiotics, predisposing them to colonization and subsequent infection with multidrug-resistant bacteria [12]. Finally, cystic fibrosis (CF) predisposes to pseudomonal and fungal infections after lung transplantation.

**Intra-operative Factors**

Pediatric SOT recipients often receive organs from adult donors, with a resultant discrepancy in organ size, which can lead to an increased risk for anastomotic complications, including leakage, thrombosis, or necrosis, as well as a prolonged period of time with an open body cavity (abdomen or chest), placing patients at increased risk for bacteria and yeast infections post-operatively [2, 12]. The use of older donors also increases the likelihood of children receiving mismatched organs (donor positive/recipient negative) for pathogens such as CMV and EBV, placing the recipients at higher risk for more severe disease following SOT [7, 12–16]. Finally, technical mishaps occurring during the operative procedure (eg, inadvertent nicking of the intestine) can lead to infectious sequelae following SOT.

**Post-transplant Factors**

Immunosuppression is the major post-transplant risk factor for infection in children undergoing SOT. Children requiring higher levels of immune suppression due to rejection are at increased risk for the development of more severe infection. This is true not only for common transplant-associated pathogens (eg, CMV, EBV), but also for community-acquired viral pathogens such as RSV and influenza. Immunosuppression also results in decreased immunogenicity of vaccines that are provided following SOT [9, 10, 17–19]. This is even more of a concern when higher levels of immune suppression are required, likely placing these children at an even greater risk of developing vaccine-associated diseases. Live virus vaccines remain generally contraindicated after transplant [8–10, 20], placing young pediatric SOT recipients at increased risk for varicella as well as measles, mumps, or rubella should they be exposed to these viruses.

The presence of uncorrected technical complications after SOT (eg, bronchial stenosis following lung transplantation, vesicoureteral reflux following kidney transplantation) can predispose to recurrent bacterial infections. In general, the risk of recurrent infection persists until the underlying problem is corrected. Finally, the ongoing presence of indwelling catheters (eg, central venous catheters, endotracheal tubes, urethral stents, and urethral catheters) is associated with an increased risk of infection until the catheters are removed.

**COMMON INFECTIONS**

**Bacterial and Fungal Infections**

With the exception of infections related to the use of indwelling catheters, sites of bacterial infection tend to occur at or near the transplanted organ. The most common of these can be categorized as superficial wound or deep space infections. Deep space infections develop near the site of organ implantation. For liver and intestinal transplant recipients, these infections occur within the abdomen, involving the liver, biliary tree, or peritoneal space. For heart and lung transplant recipients, these infections occur within the chest or mediastinal space. Although the allograft kidney is placed within the peritoneum, urinary tract infection, especially pyelonephritis, is the most common bacterial infection occurring in kidney transplant recipients [21]. Although Gram-negative organisms are frequently associated with bacterial infections in pediatric SOT recipients, Gram-positive pathogens are frequently found when the chest and mediastinum are involved. The presence of multidrug resistance is frequently observed in pathogens recovered from children undergoing SOT.

A few special circumstances warrant additional comment. Children undergoing intestinal transplantation frequently develop bloodstream infections, likely due to disruption of the mucosal barrier associated with harvest injury, rejection, or viral infection.
Children undergoing heart transplantation at a young age are at increased risk for invasive infection due to *Streptococcus pneumonia* [23]. Children undergoing liver or lung transplantation for CF may develop infections with pathogens that colonize their respiratory tract prior to transplant, including *Pseudomonas aeruginosa*. Similarly, children developing bronchiolitis obliterans (chronic rejection) after lung transplant frequently develop colonization and pneumonia with *Ps aeruginosa*.

Fungal infections occur in children undergoing each type of SOT. In general, infections due to *Candida* spp predominate, with the most likely site of infection being nearest the site of surgery, although for kidney transplant recipients, the urinary tract is the most common site [24]. Pediatric SOT recipients are also at risk of infection with opportunistic fungi, such as *Aspergillus* spp [25, 26]. These episodes are generally uncommon but can be fatal [27]. However, children undergoing liver or lung transplantation for CF have an enhanced risk of developing infection due to *Aspergillus* spp [28]. *Aspergillus* spp and, to a lesser extent, other molds frequently complicate pediatric lung transplantation, even in recipients without CF. This is particularly true of patients with oblitative bronchiolitis. This has prompted many transplant centers to institute prophylaxis guidelines for patients at high risk for *Aspergillus* infections [29].

**Viral Infections**

Viruses are a major source of morbidity and mortality after SOT. Patterns of disease associated with individual viral pathogens are generally similar among all transplant recipients. However, frequency, mode of presentation, and relative severity can differ according to the type of organ transplanted and the pretransplant serologic status of the recipient.

*Cytomegalovirus*. Cytomegalovirus is one of the most common and important viral pathogens in SOT recipients [1, 2]. Infection can be asymptomatic or symptomatic and can be due to primary or secondary infection (reactivation of latent infection or superinfection with a different strain in a previously seropositive individual). The use of preventive strategies and ganciclovir treatment has resulted in decreased rates and severity of CMV disease. Primary CMV infection, typically acquired from an infected organ donor, is associated with the highest morbidity and mortality rates. Secondary infection tends to result in milder illness [30]. Patients treated with unusually high doses of immunosuppressive agents, especially antilymphocyte products, have increased rates of CMV disease, regardless of previous immunity [1, 2]. Symptomatic CMV disease typically manifests during the intermediate time period after SOT. However, the time of onset can be later if antiviral chemoprophylaxis is used [31]. A characteristic constellation of fever and hematologic abnormalities (including leukopenia, atypical lymphocytosis, and thrombocytopenia) is frequently seen. Disseminated CMV disease is manifest by visceral organ involvement; common sites include the gastrointestinal tract, liver, and lungs. The site of involvement varies according to the type of transplant. Before the availability of ganciclovir, fatal CMV disease occurred relatively frequently in pediatric SOT recipients [32, 33]. More recently, fatal CMV disease has become rare, although CMV viremia is still associated with an increased rate of death and retransplantation in pediatric lung transplant recipients [34].

Diagnosis of CMV disease is confirmed in a patient with a compatible clinical syndrome by means of quantitative nucleic acid based or CMV pp65 antigenemia viral load assays, histopathology, or culture [35]. Of note, results of viral cultures of the urine and respiratory secretions (including bronchoalveolar lavage specimens) can be difficult to interpret because patients frequently shed CMV asymptomatically in these secretions. Histologic examination of involved organs to confirm the presence of CMV remains the gold standard when invasive CMV disease is suspected.

The use of effective antiviral therapy has dramatically improved the outcome of CMV disease. Initial therapy of CMV disease consists of intravenous ganciclovir in conjunction with reduction of immunosuppression, unless there is evidence of concurrent rejection. Initial clinical response is usually observed in 5–7 days. Duration of therapy is based on clearance of CMV viral load, as demonstrated by performance of serial quantitative assays [35]. The role of CMV hyperimmune globulin in combination with ganciclovir in the treatment of CMV disease is controversial, although there is some evidence to support use for CMV pneumonia [35, 36]. Studies of oral valganciclovir in adults have shown it to be comparable with intravenous ganciclovir for adults with mild to moderate CMV disease [35, 37]. However, data on use of valganciclovir for treatment of CMV disease in pediatric SOT recipients are limited [35]. Use of foscarnet or cidofovir should be restricted to patients with
suspicuous (pending appropriate testing) or proven resistance to ganciclovir.

**Epstein–Barr Virus.** Epstein–Barr virus is an important cause of morbidity and mortality in pediatric SOT recipients [13, 14]. Epstein–Barr virus disease ranges from a nonspecific viral illness to post-transplant lymphoproliferative disease (PTLD) including lymphoma. Variation in severity of disease is related to the degree of immunosuppression and adequacy of the host immune response. Symptomatic EBV infection in general and PTLD in particular are more common after primary EBV infection [38]. Onset of EBV/PTLD occurs most frequently within the first year, although lymphoma often presents later.

The diagnosis of EBV/PTLD should be suspected in patients with protracted fever, diarrhea, exudative tonsillitis, lymphadenopathy, organomegaly, leukopenia, and/or atypical lymphocytosis [13, 14]. Serologic evaluation should be avoided due to frequent confounding presence of passive antibody. Quantitative EBV polymerase chain reaction assays to predict risk for or presence of EBV/PTLD are widely used [39, 40]. Although very sensitive, these assays lack specificity; viral load is often elevated in asymptomatic patients [40]. Accordingly, every effort should be made to obtain histologic confirmation of EBV/PTLD. Occult sites of PTLD are assessed by imaging of the neck, chest, and abdomen. Palpable nodes or suspect lesions (or both) should be biopsied. Endoscopic evaluation should be performed in patients with an elevated viral load and diarrheal illnesses. Histologic evaluation can be augmented through the use of the Epstein–Barr encoded RNA (EBER) probe [41].

Current guidelines for the management of EBV/PTLD recommend a stepwise approach to therapy, starting with reduced immunosuppression, with further escalation of treatment primarily based on the clinical response of the patient and the histopathology of the PTLD lesion [42]. Although antiviral agents and intravenous immunoglobulin are frequently used as part of this initial strategy, their efficacy has not been established and the benefit of their use is controversial. Reduction of immunosuppression, alone or in combination with antiviral agents, results in ~67% cure rate of EBV/PTLD. For patients failing this initial approach, 2 alternative treatment strategies have been proposed. Rituximab, an anti-CD20 antibody, has been increasingly used for the treatment of EBV disease [42]. Experience to date suggests that up to two-thirds of patients who fail initial withdrawal of immunosuppression will respond to a 4-week course of this agent [43, 44]. However, relapse of EBV disease occurs in ~25% of treated patients 6–8 months following completion of therapy. The second alternative uses modified doses of cyclophosphamide and prednisone and has achieved success in approximately two-thirds of treated patients [45]. Unfortunately, relapse of PTLD has been seen in 22% of treated patients, and outright treatment failures have occurred in patients presenting with fulminant disease. Comparative studies are needed to define the optimal treatment for children who fail initial therapeutic modification of immunosuppression. Finally, the use of cytotoxic chemotherapy should be considered for those patients failing to respond to this stepwise approach and can be used as first-line therapy in the setting of monomorphic PTLD occurring late after transplant and in patients with T-cell or central nervous system PTLD [42].

**Other Viruses.** The incidence of adenovirus infection varies among the different types of organ recipients, as do the clinical manifestations of infection. In general, gastrointestinal illness and/or hepatitis are more common among liver and/or intestinal transplant recipients, whereas pneumonia (which can be life-threatening) has been the most important manifestation in lung transplant recipients [37, 46]. Of note, although adenovirus has been observed frequently in pediatric intestinal transplant recipients, many children are asymptomatic, and identification of this virus in these patients may be due to frequent surveillance sampling of their intestines to look for rejection [47]. Because adenovirus can be latent and can reactivate asymptomatically, ascribing a causative role in the pathologic process can be difficult.

Many children undergo SOT before developing immunity against varicella-zoster virus (VZV). Early experience in pediatric SOT recipients identified a significant risk for severe and potentially fatal disease in children developing varicella [48, 49]. However, more recent reports are encouraging, with few or no patients developing any complications of VZV [50]. In general, these results were achieved in children treated with intravenous acyclovir, although some were only treated with oral therapy. Current recommendations still favor an aggressive response to varicella exposure and disease.

Although poorly documented, most pediatric SOT recipients experience the usual childhood respiratory and gastrointestinal tract illnesses without significant
PREVENTIVE STRATEGIES

Strategies aimed at the prevention of infectious complications in pediatric organ transplant recipients have resulted in improved outcomes in these children. Immunization status should be assessed as part of the pretransplant evaluation, and immunizations should be updated using expedited vaccination regimens where necessary. Perioperative prophylaxis against common post-operative infections typically includes the use of antibacterial agents for 1–3 days. The choice and duration of prophylactic agents can be modified in response to recipient factors, including a history of colonization with multidrug-resistant bacteria or the development of intraoperative complications. However children undergoing lung transplantation for underlying CF are routinely given a course of antibiotics to cover their own colonizing flora; in addition a course of treatment may be required if bacteria are recovered from the donor lungs. Although the duration of therapy may vary, we currently recommend 2 weeks at our institution. These strategies originally were implemented to prevent bacteremia, which was found in the early era of lung transplantation [52]. Trimethoprim sulfamethoxasole (TMP-SMX) dosed 3 times per week is used against the development of Pneumocystis jirovecii [53]. Although some centers will discontinue PCP prophylaxis when the SOT recipient is out 1–2 years from their transplants, the risk for PCP always remains above that of the general population. Accordingly, we and other experts often continue PCP prophylaxis indefinitely, as long as the recipients are tolerating the medication. Use of daily TMP-SMX after renal transplantation also affords prophylaxis against urinary tract infections that are common in young children, especially if they occur soon after transplant and during periods of maximal immunosuppression [34]. Finally, the development of any respiratory virus infection in lung transplant recipients may have significant impact regardless of the timing post-transplant.

Topical nystatin preparations are commonly used in infant transplant recipients regardless of organ to decrease colonization with yeast species. In addition, antifungal prophylaxis is commonly employed for children undergoing lung transplantation. Because of the small number of pediatric lung transplants compared with adult transplants, strategies are often based on studies performed in adult recipients. Voriconazole, itraconazole, or aerosolized amphotericin are most commonly employed for 1–3 months after lung transplantation [54].

Preventive strategies against CMV have evolved over time and are most commonly individualized based on the serologic status of both the donor and the recipient. Variation in type and duration of preventive strategy exists between centers. The 2 key strategies include either prophylaxis, in which case antiviral agents are given post-transplant to all patients at risk for CMV disease, or preemptive monitoring, in which case patients are monitored for the presence of subclinical infection with CMV by serial measurement of CMV load in the blood by nucleotide amplification test or pp65 antigenemia assay. In preemptive therapy, antiviral therapy is initiated when a specific cutoff is exceeded [15, 16]. It is worth noting that these cutoffs will vary between centers based upon the use of local viral load assays. Intravenous ganciclovir and its oral bioavailable ester form valganciclovir are the most widely used drugs for prophylaxis and preemptive therapy. For the highest risk mismatched pediatric recipients (donor seropositive against CMV and recipient seronegative), prophylaxis is usually recommended over preemptive monitoring. Adult studies have increasingly prolonged the duration of prophylaxis [35, 37], but these studies have not been replicated in pediatric recipients, and many centers, including our own, use a combination of prophylaxis initially followed by monitoring with quantitative viral loads [55]. Most of the quantitative assays against CMV are developed and standardized within individual laboratories. Interlaboratory variability has been substantial; for this reason, monitoring should be done with the same laboratory, even once the patient has been discharged [56].

Controversy exists regarding whether or not antiviral therapy affords effective prophylaxis against EBV [6, 42]. Studies that show benefit have been dominated by recipients who have prior EBV immunity, despite the fact that these recipients are at very low risk of developing EBV disease. In addition, EBV viremia has been well documented in children on ganciclovir or valganciclovir for CMV prophylaxis. Accordingly, any role of antiviral agents is likely to be limited to the EBV seronegative host, and even here benefit has not been demonstrated. Regardless of whether or not antiviral therapy
offers any therapeutic benefits, evidence suggests that serial quantitative measurement of the EBV load in the peripheral blood from patients at risk for EBV/PTLD is useful. Serial measurement permits judicious reduction of immunosuppression when levels are found to increase, often avoiding disease. Similar to CMV, the diagnostic assays against EBV have been developed by individual centers with great interlaboratory variability; accordingly, samples should be assayed by the same laboratory for accurate evaluation [57].

CONCLUSION

Infectious complications remain an important problem in children undergoing SOT. Increased understanding and use of newer diagnostic tests, antiviral therapy, and preventative strategies have led to marked improvements in the prevention and management of many of these complications. The conduct of prospective collaborative studies would likely further improve outcomes and should be a goal of those caring for children undergoing SOT.

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