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Infections in pediatric solid-organ transplant recipients

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ABSTRACT

Solid-organ transplantation in pediatrics can be a life-saving procedure, but it cannot be accomplished without risk of infection-related morbidity and mortality. Evaluation of the recipient during candidacy and donor during evaluation can assist with identification of risk. Further, risk of infection from the surgical procedure can be mitigated through careful planning and attention to infection prevention processes. Finally, early recognition of infection posttransplant can limit the impact of these events.

Solid-organ transplantation (SOT) is a life-saving therapy for those with end-stage organ dysfunction and is increasingly used for children. Despite advancements in diagnostics and development of new antimicrobials, infections remain an important cause of morbidity and mortality both prior to and following SOT. Better understanding the risk factors of both the recipient and donor pretransplant, surgical intervention, and posttransplant factors including immunosuppression allow improved prevention, recognition, and treatment of the infectious complications of SOT.

Pretransplant risk in the recipient

Pretransplant risk assessment supplies the opportunity to identify and mitigate risk associated with transplantation therefore decreasing risk for morbidity and mortality in the posttransplant period. Each assessment should provide actionable information that improves the transplant team's capacity to care for the patient.

Pretransplant infectious disease screening focuses on identification of events that would impact transplant eligibility and posttransplant risk. Serologic evaluation for undiagnosed infections that would require further assessment and management prior to candidacy approval including screening for HIV, hepatitis B, hepatitis C, and syphilis. While these are not absolute contraindications to transplantation, diagnosis of these infections would initiate additional interventions to optimize candidate potential.

Further, latent viruses that can reactivate with immunosuppression, including those potentially transmitted through a donor, should be evaluated in transplant candidates to identify risk and plan posttransplant monitoring and prophylaxis. Latent infection with cytomegalovirus, Epstein–Barr virus, and herpes simplex virus can be identified through serologic screening. Evidence of prior infection in recipient or donor confers risk that warrants further intervention in the posttransplant period.

Exposures at home and school can represent significant risk to transplant candidates and recipients.[1] Counseling on strategies for safer living including food and water safety, hand hygiene, animal exposures, and travel are recommended. Further, careful assessment of exposures including recent travel may prompt additional screening for pathogens including but not limited to toxoplasmosis, strongylodiasis, Chagas disease (*Typanosoma cruzi*), endemic mycoses (Coccidioidomycosis, Histoplasmosis, Blastomycosis), tuberculosis, West Nile virus, and Zika virus.

Screening transplant candidates for colonization with resistant pathogens is more controversial. Most studies reflect evaluations in adult liver transplantation with an increase in vancomycin-resistant enterococcus (VRE) colonization from 3–13% to 44% over the past decade although this may reflect individual center bias.[2–4] Both methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE colonization have been associated with increased risk for posttransplant infections in a meta-analysis.[5] More recently, screening for VRE in adult liver transplant recipients associated VRE colonization with increased duration of posttransplant hospitalization.[2] While MRSA risk appears to be declining secondary to infection prevention interventions, the utility of screening and decolonization are controversial.[6,7] Additionally, screening methodologies for resistant gram-negative organisms have not been

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optimized and the impact of screening and colonization is uncertain.

Past medical history and underlying disease also drive infectious risk prompting careful pretransplant assessment. For example, children with urinary tract malformations are predisposed to recurrent urinary tract infections, while patients with ascites or on peritoneal dialysis are at risk for peritonitis. Cystic fibrosis increases the risk for pulmonary and sinus disease with resistant organisms.[8] Additionally, ascending cholangitis is a common complication after Kasai portoenterostomy for biliary atresia, occurring in 50–80% of patients.[9,10] Functional or anatomic asplenia or splenectomy anticipated as part surgical plan increases risk for invasive infection with encapsulated organisms including pneumococcus and meningococcus further compounded by the increased risk for pneumococcal disease after liver transplantation.[11] Prior infection events including catheter-associated infections should be reviewed to identify individual risks for resistant bacterial, fungal infection, and viruses.

Vaccine-preventable diseases confer significant risk that is potentially avoidable through routine vaccination. Several studies have shown suboptimal vaccination status in transplant candidates including liver and heart candidates.[12–14] As vaccine responses after transplant are attenuated by immunosuppression,[15] pretransplant vaccination is a priority. Guidelines outline the suggested vaccinations in pediatric and adult transplant candidates,[16,17] and improvement efforts can substantially improve pretransplant vaccination status.[13] Serology can identify patients who have failed to respond to vaccination and is recommended.[16,17] Additional vaccination may be necessary, especially for patients with chronic kidney and liver disease that fail to respond to hepatitis B vaccination. Careful medical history is necessary to identify risk for vaccine-preventable diseases that are not part of the routine childhood vaccination schedule or require acceleration of vaccination. For example, patients with functional or anatomic asplenia or splenomegaly can receive additional pneumococcal vaccination and accelerated meningococcal vaccination, including the newly introduced meningococcal B vaccination, while acceleration of varicella and MMR can be considered in infants.[16,17]

Donor evaluation and donor-derived infections

Infections originating from the organ donor, or donor-derived infections (DDI), are a significant cause of morbidity and mortality. Bacterial, viral, fungal, parasitic, and prion infections can all originate from allografts.[18] New diagnostic testing has increased the ability to diagnose many infections prior to transplant, potentially allowing for therapeutic intervention to prevent disease in the recipient. However, the clinical significance of some newly described pathogens in SOT is sometimes unknown, as is optimal management and whether they represent contraindication to donation. Efforts to expand the donor pool, including accepting allografts with known or increased risk of infection, are currently being explored and utilized by some centers.

Bacterial infections

Bacteremia and other serious bacterial infections in the donor can pose significant risk to the recipient, but the degree of risk is dependent upon multiple factors, including site of infection, virulence and antibiotic susceptibility of the bacteria, and treatment prior to procurement and after transplantation. Sepsis syndrome and meningitis/encephalitis of uncertain etiology and focal bacterial infection in the organ to be transplanted in the donor are contraindications to transplant.[19] Donor bacteremia can cause sepsis in the recipient with formation of mycotic aneurysms at the anastomotic sites.[20] However, some studies suggest that graft and patient outcomes are similar from donors with bacteremia as compared to nonbacteremic donors permitting the use of donors with treated bactermia.[21–23] The increasing prevalence of multidrug resistant (MDR) bacteria with more limited therapeutic options, especially in children, require additional consideration. Such MDR bacteria include MRSA, VRE, and MDR gram-negative bacteria (including carbapenem-resistant Enterobacteriaceae, MDR *Pseudomonas* species and extended spectrum beta lactamase producing organisms). Availability of viable therapeutic antibacterial options should be evaluated if a donor has a bacterial infection with an MDR organism before an organ is accepted.

In general, active bacterial infections should be adequately treated and ideally resolved prior to organ harvest. However, official recommendations on duration of antibiotic treatment in the donor or recipient do not exist and the decision of whether to proceed with the transplant depends upon individual circumstances and appropriate informed consent of the recipient.[24] One author suggests that bacteremic donors should receive a minimum of 24 hours of adequate antibiotic therapy (and ≥48 hours for MDR organisms) prior to organ harvest and that recipients should receive a minimum of 7 days of targeted antibiotic therapy posttransplant, with longer durations (≥2 weeks) for MDR bacteria and other more virulent organisms depending upon the infection type.[19] Infectious diseases consultation is strongly recommended in this situation.

While transplant-related tuberculosis (TB) is most often due to reactivation of latent TB in the recipient, donor-transmitted TB is well-described and is responsible for approximately 5% of posttransplant TB.[25] While TB is not endemic to the United States, the number of TB cases in the US is increasing and donors may originate TB endemic countries even if they arrived decades prior to donation. Potential living donors should be screened for TB infection with either a tuberculin skin test (TST; two-stage test if from an endemic area) or interferon gamma release assay (IGRA) and if positive, active disease must be ruled out. If transplantation is nonurgent, the donor can be treated first, but if this is not feasible, then treatment of the recipient is generally recommended,[26] but published guidelines differ on their recommendations, as some recommend treatment of the donor and others recommend preventive therapy to the recipient.[27] In deceased donors, exposure and epidemiologic history can be challenging to obtain, but clinical evidence of active TB is a contraindication to transplantation. Clinical history and laboratory testing for latent TB is even more challenging in deceased donors, but a recent study suggests that IGRA testing may be promising.[28]

Viral respiratory infections

Viral respiratory infections are some of the most common infections affecting both adults and children. Most of these viral infections are self-limited in immunocompetent patients, but can cause life-threatening disease in immunosuppressed children. Newer multiplex PCR-based testing for respiratory pathogens has increased the sensitivity of detection of certain viral pathogens compared to conventional methods.[29] Unfortunately, the majority of these viral infections have no targeted antiviral therapy making the acceptance of donor organs complicated. Generally, avoidance of lung donors with acute respiratory viral infections is suggested while acceptance of any organ in a donor with adenovirus is cautioned due to the risk of dissemination in immunocompromised patients.[19]

However with the availability of effective antiviral therapy, donor infection with influenza presents an opportunity for potential use of donor organs in some cases. In general, potential donors