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Tuberculosis in Pediatric Solid Organ and Hematopoietic Stem Cell Recipients

Melanie M. Dubois, MD[1,2], Avika Dixit, MBBS, MPH, MBI[1,2], and Gabriella S. Lamb, MD, MPH[1,2]

Abstract

Children undergoing solid organ and hematopoietic stem cell transplantation are at high risk of morbidity and mortality from tuberculosis (TB) disease in the post-transplant period. Treatment of TB infection and disease in the post-transplant setting is complicated by immunosuppression and drug interactions. There are limited data that address the unique challenges for the management of TB in the pediatric transplant population. This review presents the current understanding of the epidemiology, clinical presentation, diagnosis, management, and prevention for pediatric transplant recipients with TB infection and disease. Further studies are needed to improve diagnosis of TB and optimize treatment outcomes for these patients.

Keywords

pediatric tuberculosis, solid organ transplant, hematopoietic stem cell transplant

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Introduction

Tuberculosis (TB) is the leading cause of death worldwide from a single infectious agent. There were 10 million new TB cases with 1.5 million deaths in 2018.[1] Though adults account for the majority of cases, TB remains a major health problem for children throughout the world. In 2018, 1.1 million children (<15 years old) developed TB disease, leading to more than 200 000 deaths.[1] This number is likely an underestimation due to reporting and diagnostic challenges.[2] Mathematical modeling studies estimate that up to 53 million children had TB infection in 2010.[3]

TB is caused by infection with the bacterium *Mycobacterium tuberculosis* (MTB). Children exposed to MTB can be classified into 3 main diagnostic categories: TB exposure, TB infection, and TB disease.[4] TB exposure refers to recent close contact with an adult or adolescent with infectious pulmonary TB, without evidence of TB infection or disease.[4] Children with TB infection have either a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA), without findings consistent with TB disease on physical exam or chest radiograph.[5] Both the TST and IGRA are tests that measure the cell-mediated immune response to MTB antigens.[6] Children with TB disease have symptoms, physical exam findings, or radiographic features suggestive of TB.[7] In addition to pulmonary disease, children can have hematogenous and lymphatic spread resulting in TB disease at extrapulmonary sites, including the lymph nodes, central nervous system, intra-abdominal organs, bones, joints, and disseminated TB, also known as miliary TB.[6-8]

Children with TB are considered less infectious than adults, largely due to the paucibacillary nature of TB in young children.[6] Hence, pediatric TB has historically been overlooked from a public health standpoint. Paucibacillary disease makes it difficult to detect mycobacteria in clinical specimens, often leading to delay in diagnosis or failure to diagnose TB.[6] Despite these challenges, it is important to identify and treat children with TB, as young children are more likely to progress from TB infection to TB disease and are more prone to extrapulmonary and life-threatening manifestations of TB than adults.[5] Children who are immunocompromised, such as those living with human immunodeficiency

[1]Boston Children's Hospital, Boston, MA, USA
[2]Harvard Medical School, Boston, MA, USA

Corresponding Author:
Melanie Dubois, Division of Infectious Diseases, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA.
Email: melanie.dubois@childrens.harvard.edu

virus (HIV), those with hematologic malignancies, or those who have received a solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) are at increased risk for development of TB disease and are more prone to life-threatening manifestations of TB.[7,9,10]

Pediatric transplant recipients are a particularly vulnerable subpopulation with a high risk of morbidity and mortality from TB. There are an increased number of transplants performed worldwide, both in countries with high and low TB incidence. There were 126 670 solid organs transplanted in 2015 worldwide, with kidney and liver as the most common organs.[11] In 2012, a total of 68 146 HSCT (36 220 autologous, 53%; 31 926 allogeneic, 47%) were reported worldwide; this was a relative increase of 46% total compared to 2006.[12] Pediatric-specific data is lacking for both SOT and HSCT transplants on a global level. Additionally, increased travel and migration globally contribute to an expanded donor pool and increase the risk of exposure to MTB in the transplant population.[13] Limited data indicate severe morbidity associated with post-transplant TB, particularly in the setting of delayed diagnosis, atypical presentations, medication interactions, and allograft rejection.[14] A mortality rate of 20% to 30% in both adults and children with post-transplant TB disease has been observed in the SOT population.[9] The mortality rate for post-transplant TB disease in HSCT patients is high, up to 50%, particularly in allogeneic recipients.[15]

There are limited data on the clinical presentation, diagnosis, management, and outcomes of TB infection and disease in pediatric SOT and HSCT recipients. This review serves to provide a summary of the literature on TB infection and disease in pediatric SOT and HSCT recipients. As data are limited, adult data have been extrapolated where no pediatric data exist.

Methods

Our review of the literature was conducted through a PubMed search from 1 November 2019 through 30 June 2020 using Medical Subject Headings for "tuberculosis," "pediatric," "solid organ transplant," and "hematopoietic stem cell transplant." We additionally sought out consensus statements, clinical practice guidelines, systematic reviews, case series, and case reports that are widely referenced by clinicians and pediatric infectious disease experts. The authors read individual articles and extracted information relevant to the review. Ethics approval was not required for this literature review.

Overview of TB Immunology

The immune response to MTB is complex and incompletely understood. This section serves as a brief overview of the immune mechanisms involved in the response to MTB infection and why immunocompromised hosts may be at greater risk for progression from TB infection to disease and to develop life-threatening manifestations of TB.

Both the innate and adaptive immune system play a role in defense against MTB. The innate response to MTB is primarily composed of macrophages and dendritic cells (antigen presenting cells, APCs) in the airway that play a role in phagocytosis of MTB. Within the phagosome, MTB is presented to T cells on major histocompatibility complex (MHC) class II molecules, triggering the adaptive immune response.[16] T-cell immunity, particularly CD4 T cells, is essential for protection against MTB. These MTB-specific CD4 T cells produce Th1 cytokines, including interferon-gamma (IFN-ɣ), interleukin-2 (IL-2), and tumor necrosis factor alpha (TNF-α).[17] IFN-ɣ activates macrophages and TNF-α facilitates mononuclear cell recruitment and activation.[6] Additionally, interleukin-12 (IL-12) is secreted by APCs and leads to CD4 cell proliferation and IFN-ɣ production.[17] This cell-mediated immune response is critical for granuloma formation and containment of MTB infection. Defects in the IFN-ɣ/IL-12 pathway have been identified in children with impaired granuloma formation and increased susceptibility to disseminated mycobacterial infections, known as "Mendelian Susceptibility to Mycobacterial Disease" (MSMD).[6,18]

Immunocompetent children under 5 and adolescents are at greater risk for progression from TB infection to disease.[19] Young children are at risk for primary pulmonary infection, which can progress to meningitis and disseminated TB around 1 to 3 months after primary infection.[6] One hypothesis for this phenomenon in young children is deficient macrophage phagocytosis in early childhood.[17] Infants and young children are more likely to develop Th2-type CD4 T cells in response to pathogens compared to adults, which may result in more severe and disseminated disease.[20] In addition to young children, adolescents are at higher risk to develop TB disease, often adult type cavitary lung disease.[6] While age plays an important role in the immune response, it remains unclear whether certain ages are at higher risk within the immunocompromised population.

MTB has developed a unique host-pathogen relationship that has allowed its survival throughout history.[21] MTB has a distinct pathogenic lifecycle within the host that involves granuloma formation, as well as certain virulence factors and differential mycobacterial load that can influence disease presentation.[6,21] Recent studies recognize a spectrum of TB infection and disease states in the host, related to the host immune response and bacterial load.[4,6,22] There are 3 main outcomes from infection with TB: spontaneous healing, containment, and disease, with the last outcome often occurring in the immunocompromised host.[16] Most

Table 1. Risk Factors for Development of Post-Transplant TB Disease.[10,24,25,27-48]

Solid organ transplant	Hematopoietic stem-cell transplant
Social factors	Social factors
Birth or residence in high-endemic area[27-29]	Birth or residence in high-endemic area[37]
Infectious Diseases History and Co-infections	Underlying indication for transplantation
Patient or donor history of TB infection or disease[27-29]	Hematologic malignancy[10]
HIV infection[28]	Conditioning Regimen
Other coinfections: Mycoses, CMV, PJP or Nocardia[24,27,30-31]	Busulfan[10]
Non-infectious co-morbidities	T-cell depleting agents[10,41]
Diabetes mellitus[24,27,28,30-32]	Total body irradiation[10,38,40,42,43]
Chronic liver disease[24,27,28,30-32]	Type of stem-cell transplant
Chronic renal insufficiency or hemodialysis[24,27]	Allogeneic transplant[10,38-40]
Organ Transplanted	Mismatched allograft[10]
Lung transplant[33]	Transplant complications
Non-renal transplant[34]	BOOP[10]
Immunosuppressive therapies	Chronic GVHD[10,25,38-41,43-48]
Cyclosporine[27,34]	Graft failure[48]
Intensification of immunosuppression for graft rejection[27,28]	Other risk factors
Mycophenolate mofetil[27]	Corticosteroid use[10,46,48]
OKT33 or anti-T lymphocyte antibodies[24,27,28,30,31,34-36]	
Tacrolimus[27]	
Transplant Complications	
Allograft rejection[30]	

Abbreviations: TB, Tuberculosis; HIV, Human Immunodeficiency virus; CMV, Cytomegalovirus; PJP, *Pneumocystic jiroveci* pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; GVHD, graft vs host disease.

patients undergoing transplant have impaired T-cell function due to their conditioning regimens and immunosuppressive therapies, placing them at risk for development of TB disease.[23]

Epidemiology and Clinical Presentation

Epidemiology of TB in Transplant Recipients

The World Health Organization (WHO) has defined 30 high TB burden countries, 30 high TB/HIV burden countries, and 30 high multidrug-resistant TB (MDR-TB) burden countries worldwide.[1] Given local epidemiology, pediatric transplant recipients in these countries are at increased risk for post-transplant TB. The incidence of TB disease in adult SOT recipients is estimated to be 20 to 74 times that of the general population.[24] This differs according to the organ transplanted, with greatest risk in lung transplant recipients.[9] Among HSCT recipients, the incidence of TB after HSCT is estimated to be 10 to 40 times higher than the general population.[25] In comparison to SOT recipients, TB occurs less commonly in HSCT recipients.[26] One hypothesis is that HSCT patients do not receive lifelong immunosuppression, allowing restoration of T-cell function over time.[26]

Risk factors for post-transplant TB in SOT recipients include social factors;[27-29] infectious disease history and co-infections;[24,27-31] underlying clinical conditions;[24,27,28,30-32] type of organ transplanted[33,34]; immunosuppressive therapies, particularly T-cell depleting antibodies[24,27,28,30,31,34-36]; and transplant complications[30] (Table 1).

Risk factors for post-transplant TB in HSCT recipients include social factors[37]; allogeneic transplantation[10,38-40]; underlying indication for transplantation[10]; pre-transplant conditioning therapies, particularly T-cell depleting agents[10,41] and total body irradiation[10,38,40,42,43]; and transplant complications, particularly chronic graft versus host disease[10,25,38-41,43-48] (Table 1).

Transmission

Transmission of MTB is airborne and occurs via entry of the pathogen into the host by inhalation of bacilli into the lungs.[21] There are 3 mechanisms for developing TB in the post-transplant setting: progression from TB infection (also known as endogenous reactivation), donor-derived TB, and de novo infection.[49,50] A major risk factor for endogenous reactivation is residence in or previous travel to an endemic region.[28,29,51] Age impacts the risk of having TB infection at the time of transplant, which may progress to disease in the setting of immunosuppression;

young children are less likely to have been exposed to MTB than older children.[42,52] Donor-derived TB is another important mode of transmission, which can present early in the post-transplant period and should be considered in donors with residence in a TB-endemic area.[29] Among HSCT recipients, development of TB disease primarily occurs through progression of TB infection or de novo infection; approximately one-fourth of MTB infections in HSCT recipients are from endogenous reactivation.[10] The implementation of infection control measures in health care facilities is critical for prevention of de novo TB infection in transplant populations and health care workers.[53] Such measures include developing an infection control plan, ensuring safe sputum collection, improving room ventilation, and using personal protective equipment.[54]

Clinical Presentation of TB Disease

The clinical presentation of TB in the post-transplant setting is variable and can be different from immunocompetent hosts. The majority of SOT and HSCT recipients present with pulmonary TB, but remain at greater risk for extrapulmonary and disseminated disease than the immunocompetent host.[9,10] TB disease is generally defined as the following: pulmonary (involvement of pulmonary parenchyma), extrapulmonary (involvement of other organs), or disseminated (involvement of at least 2 noncontiguous organs).[33]

TB in SOT recipients can result in typical and atypical manifestations. In a literature review of TB in 476 SOT recipients (age 10-months-old to 71 years) between 1967 and 1997, 51% (244) had pulmonary TB, 33% (155) had disseminated TB, and 16% (77) had extrapulmonary TB (gastrointestinal (GI); skin, muscle, and osteoarticular TB; central nervous system (CNS); renal and genitourinary disease).[34] In a case series of mycobacterial infections after pediatric liver transplantation, 2 children (19-months-old and 9-years-old) developed disseminated TB over a 12 month period.[55] Atypical presentations have been reported in adults, including thyroid TB and TB mastitis post renal transplant,[56,57] and primary liver TB post liver transplant.[58] A case of hepatic graft TB was reported in a 10-month-old female with history of biliary atresia, likely transmitted from the living related donor; the transplant recipient died of pneumonia on day 273 after transplantation.[59] Increased mortality in SOT recipients is associated with delayed diagnosis, disseminated disease, prior organ rejection, and receipt of anti-T-cell antibodies.[14]

Clinical presentation of TB disease in HSCT recipients can be variable. In a case series of 10 adult HSCT recipients, all were found to have pulmonary TB.[38] Cases of pulmonary TB have been described in children with acute lymphoblastic leukemia (ALL) who received HSCT.[60,61] Additionally, extrapulmonary and disseminated TB can occur in this population. In a literature review of TB disease in HSCT recipients from 10 countries between 1966 and 2000, 80% (38 patients) had pulmonary TB, 18% (8 patients) extrapulmonary TB (CNS, musculoskeletal, kidney, and oral cavity), and 2% (1 patient) disseminated TB.[40] Atypical manifestations may also occur, including fever of unknown origin and non-specific clinical manifestations given immunological deficits.[10] Imaging and tissue biopsies may not show typical findings due to impaired T cell function.[10] Mortality in HSCT recipients is associated with multidrug-resistant strains, disseminated disease, and delayed initiation of therapy.[10]

Time to Diagnosis

Diagnosis of TB disease after transplantation requires a high index of suspicion, given atypical symptoms and other potential infectious and non-infectious causes of symptoms in the post-transplant setting. Diagnosis is often delayed, leading to increased morbidity and mortality.[9]

The majority of cases of TB disease in SOT recipients occur in the first year after transplant, with a median time for presentation of disease of 6 to 11 months.[9] In a retrospective review on clinical characteristics and management of 51 adult SOT recipients in Spain who developed post-transplant TB disease, the majority (61%) were diagnosed in the first year after transplantation.[62] In a review of 6 pediatric liver transplant recipients in the UK with TB disease, the median time to diagnosis was 8 months.[63] In a review of post-transplant associated pediatric TB disease in Spain, 7 children (6 SOT, 1 HSCT) developed TB disease over 26 years; the median time from transplantation to diagnosis was 2.5 years.[63] TB cases beyond 1 year post transplant have been described, which may be due to exposure to MTB in the community in countries with a high incidence of TB.[64]

Similar to SOT recipients, TB disease in HSCT recipients generally develops within the first year post-HSCT.[10] Post-HSCT infectious complications are divided into the pre-engraftment phase, post-engraftment phase (prior to day 100) and late phase (after day 100), with most cases of post-transplant TB presenting in the late phase.[26] In a retrospective review of mycobacterial infections following HSCT between 1974 and 1994 at University of Minnesota Hospital, 2 of 11 patients developed TB disease: 1 diagnosed before transplant, and one 70 days post-transplant.[65] In a literature review of TB disease in 47 adult HSCT recipients between 2010 and

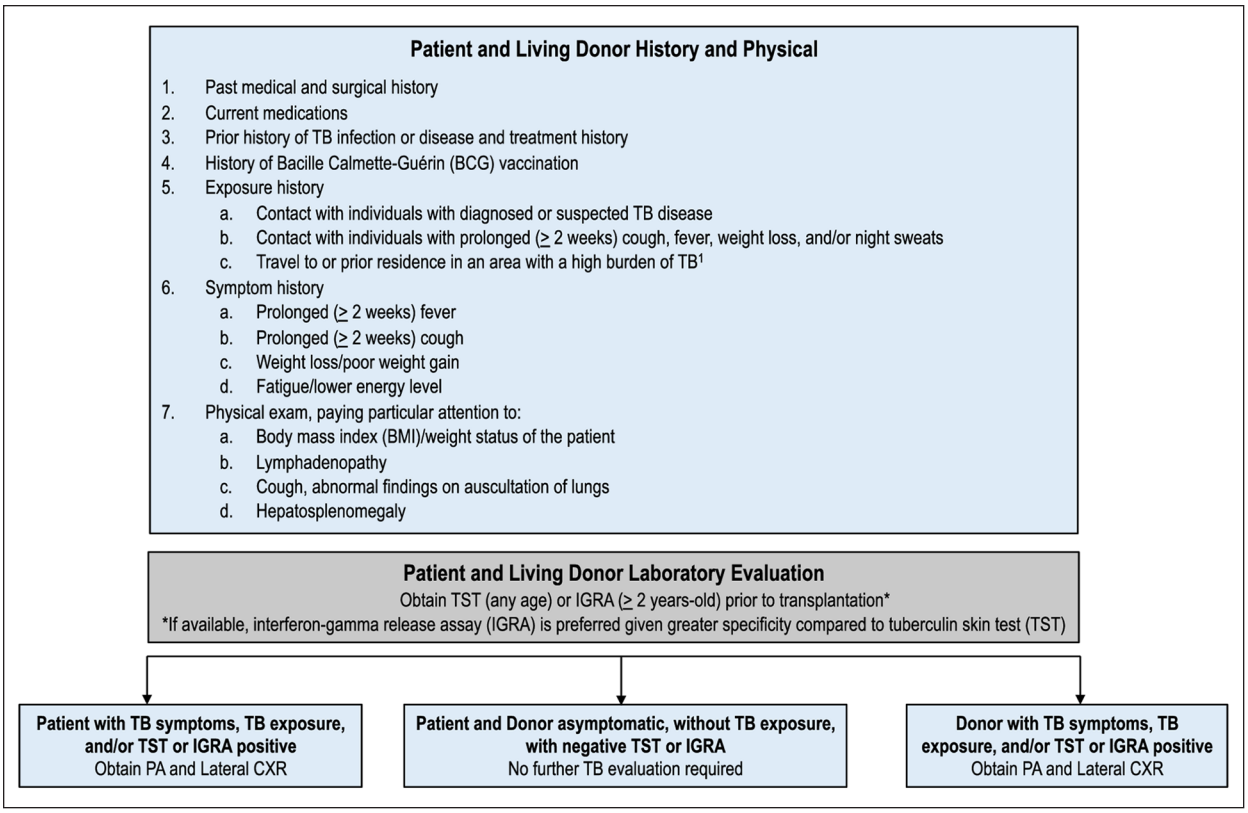

Figure 1. Pre-transplant evaluation for TB for pediatric solid organ and hematopoietic stem-cell transplant candidates and living donors. (World Health Organization 2019)[1](American Academy of Pediatrics)[7](Subramanian and Theodoropoulos, 2019)[9](Tomblyn, Chiller and Einsele, 2009)[26]

2018, the median time to clinical presentation was 4.6 months based on cohort data and 2.4 months based on individual case reports.[44] Given variable clinical presentation and diagnostic delays, it is important to maintain a high index of suspicion for TB among HSCT recipients from endemic areas.[10]

Pre-transplant Evaluation

History and Exam

Children often undergo a rigorous pre-transplant evaluation to determine risk factors for development of infectious diseases prior to SOT and HSCT. Based on literature review and clinical experience, we recommend the following key steps in the pre-transplant evaluation to determine risk factors and prevent the development of TB disease. We additionally recommend that all providers consult their national TB guidelines for information regarding country-specific practices.

We recommend starting the evaluation by obtaining a detailed history about the patient: past medical history, current medications, prior history of TB infection or disease (details about prior TST/IGRA results if available), history of BCG vaccination, and exposure history (Figure 1). (World Health Organization 2019)[1,7,9,26] In children, it is particularly important to inquire about contact with infectious TB source case, as children with TB infection and disease often have recent exposure to an adult with infectious pulmonary TB.[66] Next, we recommend obtaining a symptom history for TB from the patient and/or caregiver, including a fever and/or cough for more than 2 weeks, weight loss, night sweats, or fatigue.[53] Vital signs should be measured, with attention to temperature and weight. Lastly, a thorough physical exam should be performed, with particular attention to the respiratory exam and evaluation for lymphadenopathy and hepatosplenomegaly (Figure 1).

Diagnosis

All transplant candidates should then undergo evaluation for TB infection with TST or an IGRA test prior to transplantation.[7] TST results should be interpreted based

on diameter of induration in millimeters per local guidelines. The American Society of Transplantation uses the cutoff for a positive result as ≥5 mm of induration at 48 to 72 hours.[9] The TST is the preferred method for evaluation of TB infection in children under 2-years-old primarily due to paucity of data for use of IGRAs in this age-group.[7] However, studies have shown that there is a lower number of indeterminate IGRAs in children under 2-years-old than previously expected, which may allow its future use in this young population.[67,68]

There are 2 types of IGRAs: QuantiFERON-TB Gold In-Tube or the newer Gold Plus (QFT-GIT and QFT-Plus; Qiagen, Hilden, Germany) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK). Both are approved by the Food and Drug Administration in the United States as blood tests that measure the cell-mediated immune response to MTB antigens.[7] The T-SPOT.TB measures the percentage of lymphocytes releasing IFN-ɣ; the QFT measures the total quantity of IFN-ɣ released into the plasma.[69] IGRAs are preferred over TST in patients with history of BCG vaccination because the antigens used in IGRAs are not found in the BCG vaccine, reducing the frequency of false-positive results.[9] Both these tests, however, must be interpreted with caution, especially in immunocompromised patients. As patients undergoing HSCT or SOT are often on immunosuppressive drugs, there can be falsely negative or indeterminate results. T-SPOT.TB may be preferred in immunocompromised patients as it appears to have slightly higher sensitivity for detecting MTB infection compared to QFT.[6,10,70] The test used varies by institution. It is important to note that a negative result from either the TST or IGRA test does not exclude TB infection or disease.[7]

For patients with evidence of TB exposure or TB infection, it is critical to further evaluate for TB disease prior to starting therapy. Initiation of treatment for TB infection when the child has TB disease can lead to under-treatment and development of resistance. If the patient has symptoms concerning for TB, TB exposure, and/or the TST or IGRA is positive, the child should be evaluated with a chest radiograph (Figure 1). Radiographic findings of TB in children include hilar or mediastinal lymphadenopathy, large airway compression, parenchymal infiltrates, Ghon complexes/foci, miliary picture, and cavitations.[71] Apical cavitation as is seen in reactivation TB in adults is uncommon, though can be seen in adolescents who often develop adult type TB disease.[7] For detailed evaluation of children with TST/IGRA results that are negative or indeterminate with epidemiologic risk for TB infection or disease, chest computed tomography (CT) scan can be considered to further evaluate lung pathology, which can show consolidations, nodules, cavitary lesions, and lymphadenopathy.[9,72] Further evaluation is recommended for children under 12-months-old with suspected TB given their risk for TB meningitis and disseminated disease. For children this age, most experts recommend obtaining CSF for indices, acid fast bacilli (AFB) stain and culture, and MTB PCR given the risk of meningitis.[7]

When there is concern for TB disease, it is important to obtain a microbiological diagnosis to provide susceptibility data prior to initiation of treatment. Samples for laboratory isolation of MTB can be obtained by various methods, via sputum sample in older children (10 years of age or older), gastric aspirate for younger children (particularly those under age 5), and induced sputum samples for all ages as long as proper training and equipment are available.[53] Laboratory testing for MTB is performed via smear microscopy for AFB, nucleic acid amplification test via Xpert® MTB/Rif assay (GeneXpert) if available, and mycobacterial culture, which remains the gold standard. At times, histological confirmation by biopsy is helpful, which can demonstrate the presence of AFB and histologic findings ranging from typical caseous necrosis with granulomas to poorly organized granulomas, depending on the degree of immune suppression.[58] Though microbiological confirmation from a patient source is optimal, this is not often achievable in children. In these circumstances, the susceptibility pattern of the index case, if known, should be used to guide treatment of the child.[7]

Additional Considerations

Recommendations for pre-transplant evaluation for TB for transplant candidates and donors are based on limited data, largely consensus statements and expert opinion. If screening is negative for TB infection or disease, transplant candidates may proceed to transplant if there are no other contraindications. In endemic regions, empiric treatment for TB infection may be given with negative screening results due to high suspicion.[73] If screening is positive for TB infection with negative evaluation for TB disease, the ideal approach is to treat for TB infection prior to transplantation, but this is not possible in every case.[27] In liver transplant patients, it may be reasonable to delay initiation of therapy until liver function stabilization after transplantation in order to prevent further liver dysfunction from anti-tuberculosis therapy (ATT) or alternatively treat with an agent that is less hepatotoxic, such as a fluoroquinolone.[27,28]

If screening is positive for TB disease, transplant candidates should start treatment prior to transplant when possible, given challenges of treatment in the post-transplant setting. Some experts regard TB disease in the recipient as a relative contraindication to transplant,

except when a transplant is deemed urgent and life-saving.[73,74] Patients with pulmonary TB can be considered as candidates for non-pulmonary SOT if the patient is receiving TB treatment and if sputum is AFB smear negative prior to transplant.[27] HSCT should be delayed until TB disease is deemed controlled based on clinical judgment.[26]

In addition to transplant candidates, living donors should undergo a similar pre-transplant evaluation for TB infection and disease by obtaining exposure and symptom history as well as TST or IGRA testing (Figure 1). For deceased donors, we recommend obtaining contact and exposure history as feasible. There are limited data on the performance of IGRAs in the deceased donor population.[69] If a living or deceased donor is found to have TB disease, it is recommended that the organ not be used.[9]

In most countries, children receive the live Bacille Calmette-Guérin (BCG) vaccine at birth, which offers protection to infants and young children from meningitis and disseminated TB disease.[7,75] We recommend consultation with national guidelines regarding recommendations for BCG vaccination at birth. In high endemic TB settings, the WHO recommends BCG vaccination for all infants. (World Health Organization) BCG vaccination can have a rare complication of disseminated BCG disease and should not be used in children with impaired immunity.[6,53] Children with history of BCG vaccination and underlying immunodeficiency are at risk for disseminated BCG disease after transplant, as seen in the case report of a 23-month-old girl with Bare Lymphocyte Syndrome type II who underwent allogeneic HSCT with development of disseminated BCG infection.[76]

Management

Treatment of TB infection and disease in children is similar to adults, but there are several differences to highlight for children. Children in general are able to tolerate TB medications for infection and disease better than adults, and are less likely to have hepatotoxicity, although such side effects do occur in certain high risk groups, including children undergoing transplant. Children also have different psychosocial needs; it is important to provide education appropriate to the child's age and encourage adherence to medications.[6] Treatment decisions are guided by the drug susceptibility pattern. MDR-TB, defined as MTB resistant to isoniazid and rifampin, presents treatment challenges for children, but new data is emerging regarding safety and pharmacokinetic studies in children along with child-friendly formulations.[77,78] (World Health Organization) Additionally, TB treatment varies by region based on national TB guidelines.

TB Infection

There are several regimens, each with different toxicities, available for treatment of TB infection (Table 2).[7,79-81] Three preferred regimens include 3 months of once-weekly isoniazid and rifapentine for children above 2 years of age; 4 months of daily rifampin monotherapy; and 3 months of daily isoniazid plus rifampin therapy.[81-83] Given shorter treatment duration and higher completion rates, these 3 regimens are preferred for patients who are able to tolerate it.[81] Alternative regimens include 6 or 9 months of isoniazid monotherapy. Other regimens can be used in select circumstances, including fluoroquinolones as a treatment regimen for TB infection in liver transplant patients and in patients with MDR-TB contacts.[28,78] Preventative therapy for TB is recommended for exposed contacts with impaired immunity, particularly immunosuppressed children and children younger than 5-years-old.[7]

TB Disease

Treatment recommendations for TB disease depend on whether the organism is drug-susceptible or drug-resistant (Table 3).[6,7,78,84-87] The treatment of drug-susceptible TB (DS-TB) disease is typically 6 to 9 months of therapy for pulmonary and extrapulmonary TB, with 2 months of a 4-drug regimen (rifampin, isoniazid, pyrazinamide, and ethambutol) followed by 4 to 7 months of a 2-drug regimen (rifampin and isoniazid). If there is low concern for isoniazid-resistant TB in the community, some experts recommend an initial regimen of rifampin, isoniazid, and pyrazinamide, without ethambutol.[7] Given risk of peripheral neuropathy with isoniazid, pyridoxine (vitamin B6) supplementation is recommended for children in certain circumstances, particularly those with nutritional deficiencies.[7] This duration of therapy depends on immunocompromised status and location of disease; for example, patients with TB meningitis or osteoarticular disease are typically treated with 9 to 12 months of anti-TB therapy.[6]

MDR-TB is typically treated with at least 4 to 5 drugs based on the susceptibility pattern of the patient's isolate. The WHO has classified the second-line TB treatment drugs into 3 groups: Group A (include all 3 drugs, unless they cannot be used), Group B (add both drugs, unless they cannot be used), and Group C (add to complete regimen and when drugs from Groups A and B cannot be used).[78,86] In children, it is recommended that all-oral regimens be used.[78] More recently, newer medications have been recommended in children and adults, including bedaquiline (children aged 6 years and above) and delamanid (children aged 3 years and above); however,

Table 2. Medications for TB Infection in Children.[7,80-82]

Medication	Dose range (mg/kg)	Duration/frequency
A) Isoniazid-susceptible[a]		
Isoniazid (INH) and Rifapentine (RPT)[80]	**1) Isoniazid:** Children age 2-11 year: 25 mg/kg Children age 12 and older: 15 mg/kg Max dose: 900 mg **2) Rifapentine:** 10-14 kg: 300 mg 14.1-25 kg: 450 mg 25.1-32 kg: 600 mg 32.1-49.9 kg: 750 mg >50 kg: 900 mg Max dose 900 mg	3 months/once weekly
Rifampin (RIF)[7]	15-20 mg/kg[b] Max dose: 600mg	4 months/daily
Isoniazid (INH) and Rifampin (RIF)[80]	**1) Isoniazid:** 10 mg/kg Max 300 mg **2) Rifampin** 15 mg/kg Max dose: 600 mg	3 months/daily
Isoniazid (INH)[79]	10 mg/kg Max 300 mg 20-30 mg/kg Max 900 mg	9 months/daily[c] 9 months/twice weekly[d]
B) Isoniazid-rifampin resistant		
Recommend consultation with an ID specialist. Recommend regimen based on drug resistance profile of source case if available. Consider use of fluoroquinolone (levofloxacin or moxifloxacin).[80]		

[a]Isoniazid (INH) and rifapentine (RPT), rifampin (RIF), and isoniazid (INH) and rifampin (RIF) are preferred regimens. Isoniazid monotherapy is an alternative regimen.[81]
[b]A daily rifampin dose of 20-30 mg/kg/day is recommended for infants and toddlers.[7]
[c]WHO recommends 6 or 9 months daily of isoniazid.[80]
[d]The INH twice weekly regimen must be provided via directly observed therapy (DOT).[79]

dosing and safety data remain unknown in younger children.[86,88] Historically, drug-resistant TB has been treated with long regimens lasting about 12 to 24 months.[6] Shorter regimens are available in adults, for example the 9 to 12 month "Bangladesh regimen," which consists of an initial 4 to 6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol.[89,90] Another regimen, the BPaL regimen, is now being used for adults with extensively drug-resistant TB (XDR-TB), which consists of oral bedaquiline, pretomanid, and linezolid for 6 to 9 months.[91] While these shorter regimens are promising, there are limited data in children and immunocompromised patients to date; hence their utility in the pediatric transplant population remains uncertain.

In immunocompromised patients, the treatment duration can be variable, often prolonged, and tailored to the individual's condition and complications.[63] The American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) recommend extending the total duration of DS-TB treatment to at least 9 months for SOT recipients.[93] In a retrospective review of MTB in pediatric liver transplant recipients from the UK between 1991 and 1998, TB treatment duration ranged between 9 and 18 months.[63] In a case series of 10 adult HSCT patients with pulmonary TB, five patients received treatment with the standard 4-drug regimen in Hong Kong for 6 months and 2 or 3 drugs for another 6 months, which was well-tolerated.[38] There remains scarce data on treatment duration in cases of drug-resistant TB in pediatric transplant recipients; one case series

Table 3. Medications for Treatment of Drug Susceptible and Drug Resistant TB in Children.[7,79,87,88]

Medication	Dose range (mg/kg)	Maximum daily dose (mg)	Adverse reactions
Drug susceptible TB			
Rifampin[7]	15-20 mg/kg daily	600	Orange discoloration of secretions, hepatitis, drug-drug interactions
Isoniazid[7]	10-15 mg/kg daily	300	Hepatitis, peripheral neuropathy
Pyrazinamide[7]	30-40 mg/kg daily	2000	Hepatitis, GI upset, arthralgia, pruritus
Ethambutol[7]	15-25 mg/kg daily	1000	Optic neuritis, decreased red-green color discrimination
Drug resistant TB[a]			
Group A Drugs			
Levofloxacin/Moxifloxacin[87]	15-20 mg/kg daily	1500	Tendonitis, QTc prolongation, GI upset
	10-15 mg/kg daily	800	Tendonitis, QTc prolongation, GI upset
Bedaquiline[87]	>6 years: 200 mg/day for 2 weeks, then 100 mg 3 times/week for 22 weeks[b] >12 years: 400 mg/day for 2 weeks, then 200 mg 3 times/week for 22 weeks	400	Hepatitis, possible QTC prolongation
Linezolid[86]	<16 kg: 15 mg/kg daily >16 kg: 10-12 mg/kg daily	1200	Bone marrow suppression, peripheral neuropathy, optic neuritis
Group B Drugs			
Clofazimine[87]	2-5 mg/kg/day	100	Hepatitis, possible QTC prolongation
Cycloserine/terizidone[87]	15-20 mg/kg daily	1000	Neurologic/psychiatric effects
Group C Drugs[c]			
Delamanid[87]	>3-5 years and 10-20 kg: 25 mg twice daily 6-11 years and 20-34 kg: 50 mg/dose twice daily 12-17 years: 100 mg/dose twice daily	200	Hepatitis, Possible QTC prolongation
Imipenem-cilastatin[87]	15-25 mg/kg/dose IV 4 times daily (imipenem component)	—	GI upset, rash, nephrotoxicity, seizures
Meropenem[87]	20-40 mg/kg/dose IV 3 times daily	—	GI upset, rash, nephrotoxicity
Amoxicillin-clavulanate[86,d]	40 mg/kg given twice daily based on amoxicillin component	—	GI upset, rash
Amikacin/Streptomycin[87]	15-20 mg/kg daily	1000	Auditory and vestibular toxic effects, nephrotoxic effects
Ethionamide/Prothionamide[87]	15-20 mg/kg daily (divided into 2 daily doses)	1000	GI upset, hepatitis, thyroid dysfunction
P-aminosalicylic acid (PAS)[78]	8-12 g/day (in 2-3 divided doses)	12 000	Electrolyte monitoring, hepatitis, thyroid dysfunction

Abbreviations: mg/kg, milligram/kilogram; GI, gastrointestinal; QTc, Corrected QT interval.

[a]Classification adapted from *WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment*[78] and *ATS/CDC/ERS/IDSA Clinical Practice Guideline on Treatment of Drug-Resistant Tuberculosis*.[87]

[b]Dose is based on expert opinion. Studies are ongoing in lower age groups and weights.[87]

[c]Pyrazinamide and Ethambutol are included in group C drugs.[78]

[d]Amoxicillin-clavulanate should be co-administered with carbapenems. It should be given 30 minutes prior to IV infusion of imipenem or meropenem.[86]

Table 4. Treatment Challenges during TB Treatment in Pediatric Transplant Patients.[9,85,87,93]

Adverse effects	Medications	Management considerations
Drug-drug Interactions with Rifampin[9,93,a]	**Antiretroviral agents:**	
	HIV-1 protease inhibitors, NNRTIs, INSTIs	Rifabutin is preferred with protease inhibitors, as it is a less strong inducer of cytochrome p450 activity. Dose adjustments may be necessary when using rifampin with NNRTIs and INSTIs.[93]
	Anti-microbials:	
	1) Macrolide antibiotics (azithromycin, clarithromycin, erythromycin)	1) Azithromycin has no interaction with. Clarithromycin and erythromycin have interactions with rifampin; recommend use of alternative agents.
	2) Azole antifungal agents (fluconazole, voriconazole, itraconazole)	2) Dosing of azoles may be sub-therapeutic with rifampin. Recommend laboratory monitoring and considering increase in azole dose with co-administration of rifampin.
	3) Doxycycline	3) Rifampin may decrease serum concentration of doxycycline; consider alternative agent.
	4) Atovaquone	4) Use alternate drug for PJP prophylaxis.
	Immunosuppressive agents:	
	1) Calcineurin inhibitors (cyclosporine, tacrolimus)	1) Monitoring of calcineurin inhibitor serum concentrations may assist with dosing. Consider replacing rifampin with rifabutin to help maintain immunosuppressant levels.
	2) mTOR inhibitors (sirolimus)	2) Monitoring of mTOR inhibitor serum concentrations may assist with dosing.
	3) Corticosteroids	3) Recommend clinical monitoring, as may require 2-3 fold increase in corticosteroid dose.
	Hormone therapy: Ethinylestradiol, norethindrone	Women on oral contraceptives should use a barrier method of contraception while on rifampin.
	Cardiovascular agents:[90] Propanolol, metroprolol	Clinical monitoring recommended; may require alternate cardiovascular drug.
	Anticoagulants: Warfarin	Monitor prothrombin time; may require 2-3 fold warfarin dose increase.
	Anticonvulsants: Phenytoin, lamotrigine	TDM recommended; may require dose increase in anticonvulsant dose.
Hepatoxicity[84,86]	Rifampin, Pyrazinamide, Ethionamide/ Prothionamide, Bedaquiline, Clofazimine, Delamanid, PAS	Stop all drugs if ALT/AST >5 times upper limit of normal. Allow liver enzymes to normalize. Re-introduce drugs one-by-one, starting with least hepatotoxic drugs. If symptoms recur or ALT increases, the last drug added should be stopped.

Table adapted from *ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis.*[93]
Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; TDM, therapeutic drug monitoring; PJP, *Pneumocystis jiroveci* pneumonia.
[a]Not all available drug-drug interactions with rifampin are listed here.

in adult transplant recipients with MDR-TB showed a treatment duration ranging between 18 and 24 months.[94]

Treatment Challenges

There are numerous treatment challenges when treating TB in pediatric transplant recipients, including medication adverse effects that can be difficult to monitor in children and interactions with other treatment medications. Rifampin and isoniazid, along with other agents used for ATT, can cause hepatotoxicity, which can be particularly concerning in liver transplant patients.[30]

Two significant treatment challenges include drug-drug interactions, particularly with rifampin, and hepatotoxicity (Table 4). Rifampin is a strong inducer of microsomal enzymes that metabolize immunosuppressive agents, including calcineurin inhibitors, mTOR

inhibitors, and corticosteroids.[9] Therefore, doses of these medications often need to be increased at least 2 to 5 fold when used concurrently with rifampin.[63] Rifampin also interacts with other drug classes, including antiretroviral agents, other anti-infectives, hormone therapy, cardiovascular agents, anticoagulants, and anti-convulsants.[93] Rifabutin can be substituted for rifampin in some circumstances, particularly for those on antiretroviral therapy for HIV, as it is a less strong inducer of cytochrome p450 activity.[7,95] If available, measurement of drug concentrations for medications that interact with rifampin may be a helpful monitoring strategy to ensure therapeutic levels and prevent toxicity, particularly for children.[93] An additional treatment challenge is hepatotoxicity, which is associated with rifampin, isoniazid, pyrazinamide, and other TB medications (Table 4). Use of hepatotoxic drugs should be suspended if ALT or AST increase 3-fold in symptomatic patients and 5-fold in asymptomatic patients.[27,93] Once liver enzymes normalize, it is then possible to reintroduce medications one-by-one, starting with the least hepatotoxic drugs, or consider using alternative agents that are not hepatotoxic.[86] For patients with prolonged or severe hepatotoxicity, treatment with isoniazid and rifampin without pyrazinamide with treatment extension to 9 months may be considered.[96] It is important to exclude other causes of abnormal liver function tests, such as viral hepatitis, biliary tract disease, and other hepatotoxic drugs, prior to attributing drug-induced hepatotoxicity to ATT.[93]

Immunocompromised patients are at risk for complications of TB and increased mortality, secondary to their immunosuppression and underlying disease. SOT recipients can develop immune reconstitution syndrome, similar to patients living with HIV.[27,36,95,97] After HSCT, children may be at risk for opportunistic infections that require concurrent treatment, such as fungal disease. A case series from Korea reports 2 children with ALL who developed co-infections with pulmonary TB and invasive pulmonary fungal infection after allogeneic HSCT.[61] It was difficult to determine patient response to ATT in these patients given presence of co-infection.[61] Drug interactions have also been reported with ATT and antifungals, particularly the azole class. Isoniazid (INH) is well tolerated post-HSCT with fluconazole, but itraconazole is not recommended and the safety of concurrent use of voriconazole or posaconazole is not known.[26] Transplant recipients are additionally at risk for graft rejection and failure in the setting of drug-drug interactions between ATT and immunosuppressants (Table 4).[30,48]

Another treatment challenge is the delay in obtaining drug susceptibility testing, beyond the rapid rifampin resistance testing provided by the Xpert-MTB/RIF. It is important to diagnose drug-resistant TB presumptively if the known TB source case has drug-resistant TB. Drug-resistant TB should be considered if a patient is clinically worsening on appropriate therapy in a setting where MDR-TB is endemic.[41] Patients on therapy for drug-resistant TB may require additional monitoring, as medications used to treat MDR-TB are often associated with toxicities (Table 3).

Discussion

Children undergoing SOT and HSCT have unique vulnerabilities and challenges in the post-transplant setting. Their immune response is impaired, due to decreased T-cell function from conditioning regimens and immunosuppressive regimens. Pediatric transplant recipients are at greatest risk for pulmonary TB, but can additionally have extrapulmonary and disseminated disease with atypical presentations. It is important to maintain a high degree of suspicion for TB in children with relevant medical and social risk factors, particularly those residing in or traveling to an endemic region. Children should undergo comprehensive pre-transplant evaluation to screen for TB infection and disease in order to reduce the risk of post-transplant TB. Patient characteristics and drug susceptibility patterns should be considered when choosing a treatment regimen. Treatment challenges, particularly due to medication interactions and toxicity, can lead to morbidity and mortality in this immunocompromised population. There remains limited data on TB in pediatric transplant recipients, with a need for further research related to diagnosis, treatment, and prevention.

There are limitations on the sensitivity of current diagnostic modalities to diagnose TB infection and disease. Young children remain vulnerable, as it is difficult to obtain a microbiological diagnosis in this age group. Since immunosuppression may alter TST and IGRA responses, it is important to develop diagnostic tests for TB infection that do not rely on an intact T-cell response.[6] Further, a test that distinguishes TB infection and disease is needed.[6] Given increased risk of extrapulmonary and disseminated disease in this population, further research to develop diagnostic testing for MTB using other clinical specimens (in addition to sputum) is vital.[51]

There is also a need for medications with less toxicities, child-friendly formulations, and shortened regimens. Given the hepatotoxicity from ATT, many liver transplant recipients are at risk for interruptions in therapy and graft rejection. Shorter regimens for TB infection and disease are key to preventing these complications and improving completion rates. MDR-TB treatment remains a particular challenge in many settings worldwide, with a need for clinical trials in children and treatment availability in low-resource settings worldwide.

Finally, there is a need for further implementation of therapy for TB infection in vulnerable populations worldwide to prevent progression to TB disease. Screening of TB in deceased donors with IGRAs is another area of research that will be helpful to prevent TB transmission to SOT recipients. Infection control to prevent transmission of TB remains critical in all settings, both in the clinic and hospital setting.

Conclusion

This review serves to provide a summary of the literature to date on TB infection and disease in pediatric SOT and HSCT recipients. There are many challenges related to diagnosis, treatment and prevention of TB in this population. Further research is needed to improve diagnosis and treatment in order to reduce morbidity and mortality of this disease.

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Author Contributions

Melanie M. Dubois: Contributed to conception and design; contributed to analysis; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
Avika Dixit: Contributed to conception and design; contributed to analysis; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
Gabriella S. Lamb: Contributed to conception and design; contributed to analysis; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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ORCID iD

Melanie Dubois https://orcid.org/0000-0001-9972-8533

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