

The risk of tuberculosis in transplant candidates and recipients: A TBNET consensus statement

Running title: Tuberculosis in transplant recipients

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Abstract

Tuberculosis is a possible complication of solid organ and hematopoietic stem cell transplantation. Identification of candidates for preventive chemotherapy is an effective intervention to protect transplant recipients with latent infection with *Mycobacterium tuberculosis* from progression to active disease. The best available proxy for diagnosing latent infection with *M. tuberculosis* is the identification of an adaptive immune response by the tuberculin skin test or an interferon- γ -based *ex vivo* assay. Risk assessment in transplant recipients for the development of tuberculosis depends, among other factors, on the locally expected underlying prevalence of infection with *M. tuberculosis* in the target population. In areas of a high prevalence, preventive chemotherapy for all transplant recipients may be justified without immunodiagnostic testing while in areas of medium and low prevalence, preventive chemotherapy should only be offered to candidates with positive *M. tuberculosis*-specific immune responses. The diagnosis of tuberculosis in transplant recipients can be challenging. Treatment of tuberculosis is often difficult due to substantial interactions between anti-tuberculosis drugs and immunosuppressive medications. This management guideline summarises current knowledge on the prevention, diagnosis and treatment of tuberculosis related to solid organ and hematopoietic stem cell transplantation and provides an expert consensus on questions where scientific evidence is still lacking.

200 words

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Introduction

Tuberculosis is caused by the pathogenic species of the *Mycobacterium tuberculosis* complex. Only a minority of individuals who develop an adaptive immune response following infection with *M. tuberculosis* will ever develop tuberculosis, the actual risk depending on the extent to which the host immune system provides a successful or inadequate response [1, 2]. Individuals with impaired immune response such as solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients are therefore more prone to develop tuberculosis than immunocompetent persons.

Tuberculosis in transplant recipients is more frequent compared to the general population (estimates from the last decades state 20-74 times in SOT [3, 4] and two times in HSCT [5]), and more often fatal (up to 31% in SOT [6] and up to 50% in HSCT recipients [7]), thus adding effectiveness to interventions for its prevention, even in the face of difficulties with treatment related to adverse drug events and drug-drug interactions. Active tuberculosis in transplant recipients can result from latent infection with *M. tuberculosis* (LTBI) in the transplant candidate or in the donor tissue, or from *de novo* post-transplant infection. These various scenarios prompt for targeted pre-transplant screening of both recipient and, if possible, donors to allow focused management of recipients selected for preventive intervention in the pre- and/or post-transplant period. The term “preventive chemotherapy” is used to denote treatment of LTBI among individuals identified as having a positive immune response to *M. tuberculosis* antigens. “Chemoprophylaxis” is used here to denote primary chemoprophylaxis to prevent tuberculosis among individuals with risk factors (i.e. exposure to *M. tuberculosis*, living in or originating from highly endemic regions, etc) but without a positive immune response to *M. tuberculosis* antigens (either negative test or not tested).

Diagnosis and treatment of active tuberculosis in transplant recipients are challenging due to diverse pulmonary and non-pulmonary conditions mimicking tuberculosis, to more frequent adverse events from first-line antituberculous drugs, and to significant interactions with immunosuppressive drugs.

Direct evidence to support management of transplant recipients for prevention and treatment of tuberculosis is often lacking and decisions are largely based on expert opinion and extrapolation from immunocompetent and other immunocompromised populations. This document was elaborated by a TBNET consensus group and summarizes current evidence and clinical experience of the authors on tuberculosis prevention and treatment in SOT and HSCT recipients. It provides evidence-graded recommendations (evidence categories A-D, table 1) for screening and diagnosis of LTBI, preventive chemotherapy/chemoprophylaxis and treatment of active tuberculosis before and after transplantation.

Natural history of *M. tuberculosis* infection in transplant candidates and recipients

1.1 The natural history of *M. tuberculosis* infection

Infection with *M. tuberculosis* is almost exclusively acquired by inhalation of bacilli-containing droplet nuclei. Inhaled bacteria are engulfed by polymorphonuclear granulocytes and alveolar macrophages but have mechanisms to survive. In this early phase, there is potentially lympho- and hematogenic spread of *M. tuberculosis* to the lungs as well as to other organs and tissues until the specific immune response arrests further multiplication of bacilli, contains the infection, and ultimately eliminates bacilli in the majority of cases. Antigen-specific and -nonspecific signals from *M. tuberculosis*-infected macrophages stimulate T-cell immunity. The mechanisms of immune control of *M. tuberculosis* require a complicated collaboration between different cell

types that is only partly understood [8]. The role of a Th1 response, especially of CD4 and CD8 interferon (IFN)- γ producing T cells, is considered essential. Polyfunctional memory CD4 T cells that simultaneously produce IFN- γ , TNF- α and interleukin (IL)-2 appear to be mediators of long-lasting protection against tuberculosis reactivation [9-13].

Probably around 1% of putatively infected individuals other than infants and small children will have directly progressive active tuberculosis within the first year following primary infection. In most otherwise healthy individuals, specific cellular immune responses are sufficient to prevent the progress to tuberculosis. A clinically pragmatic definition of LTBI is the presence of a specific immune response detected by the tuberculin skin test (TST) or an IFN- γ release assay (IGRA), in the absence of tuberculosis [14]. Changes in gene expression of granuloma-encased bacilli are related to a state of low metabolic activity in which *M. tuberculosis* can survive for prolonged periods of time [15, 16]. The cumulative lifetime risk of reactivation tuberculosis is estimated at approximately 5-10% [17, 18], but varies depending on factors, notably age at infection and remaining lifetime and immune status. The risk is about 5% in the first five to seven years after infection decreasing to around 0.1% per year thereafter. The risk may persist for a lifetime as exemplified by a documented interval of more than 50 years [19, 20]. While there are recognized risk factors of reactivation, in most persons with reactivation tuberculosis there is no known risk factor. Age is relevant, as tuberculosis occurs more frequently among adolescents and young adults. The risk for disease might also be increased among very old persons, but apart from increasing age seemingly playing a role, little is known about the modifiers of age- and sex-specific risk. Except for rare inherited immunodeficiencies [21], the role of genetic factors as determinants of the risk of tuberculosis is probably limited compared to the level of exposure *per se* [22].

1.2 Pathogenesis of tuberculosis in the transplant setting

In addition to other recognized factors, the risk of active tuberculosis in a transplant recipient is related to infection and re-infection with *M. tuberculosis* and the net state of immunosuppression. When the cellular immune system is impaired due to disease or treatment, the risk is increased for all three contributory components of tuberculosis morbidity, namely primary tuberculosis resulting from progression of an infection acquired in the past five years, endogenous reactivation disease of a distant infection acquired more than five years in the past, and exogenous acquisition of a recent or distant infection, either of them leading to disease [23]. In general, active tuberculosis is associated with four different scenarios in transplant recipients (Figure 1):

Scenario A: Latent infection in the candidate. When a transplant candidate is latently infected with *M. tuberculosis*, this offers a window of opportunity for detection and preventive treatment (Figure 1A). Similar to immunocompetent individuals, where the risk of tuberculosis decreases with increasing time after infection, the risk of post-transplantation reactivation is probably inversely related to the interval between infection and transplantation, but this is hard to prove as the interval is rarely known.

Scenario B: Infection in the donor graft. The donor organ or tissue may be infected with *M. tuberculosis* that can be the source of donor-derived transmission (Figure 1B). Transmission via lung transplantation is most likely and best documented [24], since involvement and pathogen load may be higher; although LTBI may reactivate from other infected grafts [25, 26], risk estimates are less clear. Treatment of donors with recognized LTBI or risk factors for LTBI may reduce the risk of reactivation (see section 2 for details).

Both in scenarios A and B, the risk of reactivation is likely highest early post-transplant given enhanced immunosuppression; later onset may also occur with intensification of immunosuppression, such as during the treatment of rejection.

Scenario C: De novo infection post-transplant. Transplant recipients who are exposed to and become infected with *M. tuberculosis* post-transplantation have a very high risk of immediate progression. Unfortunately, exposure that may lead to infection is not always recognized, nor is a recently acquired infection, and even if it is recognized the available immunodiagnostic tests for screening are less reliable in immunosuppressed patients (see section 0).

Scenario D: Candidate with active tuberculosis requiring urgent transplantation. Rarely, a patient with active tuberculosis is in urgent need of transplantation, such as the result of drug-induced hepatotoxicity resulting in serious liver injury [27]. The special considerations regarding the treatment of active tuberculosis after transplantation are discussed further in section 0.

As most cases of post-transplantation tuberculosis originate from a focus of LTBI, a better understanding of latency is needed. One model supported by animal data is that latent infection is not a stationary phase, but rather a cyclic change between replication and immune containment, with a progressive increase in the length of the interval between successive episodes [28]. If correct, this model would explain the decreasing risk of reactivation over time and also why prolonged treatment is needed to eradicate just a small number of bacilli, isoniazid being an inhibitor of cell wall synthesis and therefore active only during rare episodes of heightened metabolic activity. Although it is possible that a substantial proportion of individuals may eliminate tubercle bacilli acquired in the past [29], all currently available tests measure a long-lasting immunologic response that is only partially dependent on the continued presence of live bacilli (exemplified by a persisting positive tuberculin skin test reaction remaining positive years after BCG vaccination). Therefore, it is not known how to specifically identify individuals where true LTBI has not yet died out. Such information would allow more targeted treatment of candidate transplant donors or recipients.

1.3 Summary

- Infection with *M. tuberculosis* in the transplant setting is relevant in four different scenarios, being (A) LTBI in the candidate recipient, (B) LTBI in a living or deceased donor, (C) *de novo* exposure post-transplantation and (D) when a patient with active tuberculosis urgently requires a transplant.
- The prevention of active tuberculosis is not always possible as it depends on reliable detection and treatment of true LTBI in recipients or donors and awareness of post-transplantation exposure.
- If the *a priori* risk of *M. tuberculosis* infection is high, therapeutic decisions may have to be made without evidence.

Risk of tuberculosis in solid organ transplant recipients

Tuberculosis remains a rare but clinically significant complication of SOT recipients [4]. The rates and risk of tuberculosis in transplant recipients are highly dependent upon the key features such as the frequency of tuberculosis in the recipient and donor population, the organ transplanted (highest in lung transplant recipients), the type and intensity of recipient screening for tuberculosis, and the use of prior or current anti-tuberculosis drug intake, preventively or curatively [4, 30, 31].

The rate of tuberculosis in transplant recipients is highly linked to endemicity of *M. tuberculosis* infection. In the United States and much of Western Europe, the general incidence of tuberculosis is currently low and ranges between 0-24 cases/100,000 population, whereas incidences may be as high or higher than 1% per annum in South Africa [32]. The overall frequency of tuberculosis in transplant populations has been estimated to be roughly between 20-74 times that of the general population [3, 4]. In areas with low endemicity of tuberculosis, the prevalence among SOT recipients is 0.5-6.4% while it has been reported to be as high as 15.2%

in highly endemic areas [3, 31]; as such, differential preventative strategies are needed for donors or recipients from regions with varying endemicity (see chapter 2).

Apart from general endemicity, the rate of tuberculosis is heavily dependent upon the organ transplanted and the level of immunosuppression involved [3]. There are no data to clearly associate an effect of a specific drug with risk for TB. This is mainly due to the fact that a minority of patients take single agents for immunosuppression. Although tuberculosis may affect any transplanted patient, recipients of lung transplants have the highest rate of tuberculosis relative to other transplanted organs (relative risk of 5.6) [33]. This is not surprising since the lung is the primary portal of entry for *M. tuberculosis*. Other factors that may affect the incidence of tuberculosis include the use of T-cell depleting antibodies, enhanced immunosuppression in the setting of rejection, chronic renal insufficiency or hemodialysis for kidney transplant recipients, diabetes mellitus, hepatitis C virus infection for kidney transplant recipients, chronic liver disease, or increased recipient age [3, 30, 33].

The majority of tuberculosis cases occur during the first 6 months post-transplant, except in renal transplant patients, where onset is typically later [3]. A history of a positive TST or radiographic evidence of past tuberculosis is associated with earlier onset of disease [3]. A greater proportion of patients who receive lymphocyte-depleting antibodies have an earlier onset of tuberculosis than those who receive other types of induction therapies [3]. Although most transplant patients present with pulmonary tuberculosis (51%), 16% have extrapulmonary disease of specific organs and 33% have disseminated tuberculosis [3]. Hallmark symptoms of tuberculosis, i.e. fever and constitutional symptoms, such as night sweats and weight loss, occur frequently but not universally in transplant patients. Fever, for example, was seen in 64% of transplant recipients with localized disease and in 91% with disseminated disease [3]. Atypical presentations may frequently occur, particularly in patients with disseminated tuberculosis; such presentations may be more common in donor-derived tuberculosis transmission [25]. In patients with pulmonary disease, a wide range of radiographic manifestations, including focal infiltrate, miliary pattern, nodules, pleural effusions, diffuse interstitial infiltrates, and cavitary disease have been described [3, 6, 30]. As a result, of the myriad of presentations, up to a third of patients may not have tuberculosis suspected initially and 3-5% may only be diagnosed after the death of the recipient [3, 6].

The risk of adverse outcomes following tuberculosis among SOT recipients is increased compared to non-immunocompromised patients. Mortality rates of 19-40% have been described which represents a 10-fold increase compared to the overall mortality of tuberculosis [3, 6, 30, 33, 34]. Most fatality (57-83%) in these patients is directly attributable to tuberculosis [3]. In addition, complex interactions between the agents used to treat tuberculosis and the agents typically used to prevent rejection may result in allograft loss in up to one third of cases [6, 35]. Additional features contributing to an increased morbidity and mortality include the difficulty in early diagnosis resulting in delay in initiation of therapy, and increased incidence of disseminated disease at the time of diagnosis.

Summary

- The prevalence of post-transplant tuberculosis is lower in low endemicity areas (0.5-6.4%) than in areas of higher endemicity for tuberculosis (up to 15.2%).
- The rate of post-transplant tuberculosis is heavily dependent upon the organ transplanted (highest for lung transplant recipients).
- Other risk factors for post-transplant tuberculosis include use of lymphocyte depleting antibodies, enhanced immunosuppression, chronic renal insufficiency or hemodialysis, diabetes mellitus, hepatitis C virus infection in kidney transplant recipients, chronic liver disease, increased recipient age, and positive TST or IGRA results pre-transplant.

- Although pulmonary disease may occur, other clinical presentations, including fever of unknown origin or septicemia, may occur post-transplant.
- Generally, transplant recipients have a higher rate of morbidity, mortality, and graft loss if tuberculosis complicates the post-transplant course.

Diagnosis of latent infection with *M. tuberculosis* in transplant candidates, donors and recipients

Detection of a cellular immune response against *M. tuberculosis*-specific antigens is the commonly accepted indirect measure of possible infection. This response is not *per se* indicative of the presence of viable bacilli and thus risk for future tuberculosis [14, 36]. The cellular immune response to *M. tuberculosis* may be analysed by the use of two test principles, the *in vivo* TST and the *ex vivo* IGRAs (figure 2). The TST elicits a delayed-type hypersensitivity (DTH) response after local intradermal application of purified protein derivative (PPD) [37]. The diameter of induration is quantified 48-72 hours after antigen injection [38] with specific cut-off values for positive test results that are defined to provide the putatively optimised value to balance deficiencies in sensitivity and specificity respectively. Preference is given to sensitivity at the cost of specificity if the expected risk is particularly high, such as in the case of immunodeficiency of an individual [39], but whether this trade-off is as efficient as postulated has been called into question, at least in HIV-associated immunodeficiency [40]. More recently, blood-based IGRAs have been developed and evaluated for the risk estimation of tuberculosis in clinical routine [41]. As with TST, IGRAs rely on specific stimulation of effector T cells that are activated to produce cytokines within hours after stimulation, and IFN- γ is most commonly used as readout for specific activation of T cells [42].

IFN- γ production may be analysed by a variety of experimental assays (figure 2). The amount of IFN- γ may either be analysed in the supernatants of stimulated whole blood cells using an enzyme-linked immunosorbent assay (ELISA) [43] or IFN- γ producing T cells may be quantified from isolated peripheral blood mononuclear cells (PBMC) using the enzyme-linked immunospot assay (ELISPOT) [44, 45]. Commercial tests are available for both formats (QuantiFERON TB® Gold in-tube by Cellestis, Australia, and T-SPOT.TB® by Oxford Immunotec, UK). More recently, flow cytometry has been used to quantify specifically activated T cells based on the intracellular accumulation of IFN- γ or other cytokines. Although this technique has so far largely been applied in experimental settings, its potential to perform multiparameter analyses may hold promise as an immune-based technique to distinguish LTBI from active disease [9, 11-13]. When compared to TST, IGRAs have some operational advantages that are particularly relevant in immunocompromised patients. Unlike the TST, antigen-specific stimulation *in vitro* is carried out along with negative and positive controls. As the positive control allows for assessment of general T-cell responsiveness, *in vitro* tests may be able to discriminate true negative responses from anergy and/or overt immunosuppression. Further advantages of IGRAs may result from an increase in specificity in the face of increased, or at least similar, sensitivity [46-48]. An increase in specificity is due to the use of antigens derived from *M. tuberculosis* that are absent in all strains of *M. bovis* BCG and most environmental mycobacteria including species from the *M. avium* complex [42, 49, 50]. These antigens, the early secretory antigenic target (ESAT)-6, culture filtrate protein (CFP)-10 (both RD1-derived), or TB7.7 (RD11-derived), elicit a T-cell response that is a more specific marker for *M. tuberculosis* infection than a TST-response towards PPD, especially in BCG-vaccinated individuals [48, 51]. *In vitro* assays may also hold promise as a more sensitive alternative to TST in immunocompromised patients, where skin-testing may frequently be falsely negative and thus of low negative predictive value for disease progression [52-54]. In the setting of transplantation, this is largely attributed to the combined action of various immunosuppressive drugs that interfere with T-cell function that may affect both TST and IGRAs (figure 2). Corticosteroids inhibit the function of both T cells and antigen-

presenting cells, anti-metabolite drugs interfere with proliferative capacities of T cells, calcineurin inhibitors directly inhibit induction of T-cell cytokines, and finally depleting antibodies used as induction or rejection therapy result in the elimination of T cells [55]. Likewise, the uraemia-associated immunodeficiency syndrome in transplant candidates with end-stage renal failure has been characterised by a defect in costimulatory activity to antigen-specific T cells that may directly contribute to a decrease in T-cell function [56, 57]. Studies on the use of IGRAs in transplant recipients are rare and frequently inconclusive. In theory, immunosuppressive drugs should equally interfere with T-cell reactivity in skin-testing and in IGRAs; yet evidence from experimental and clinical studies indicate that *in vitro* assays are less affected in patients with moderate immunosuppression [58]. If patients receive higher levels of immunosuppressive drugs and/or are severely T-cell depleted, however, caution is warranted with the use of IGRAs as they may yield falsely negative diagnoses or indeterminate results [58, 59]. As a consequence, the sensitivity of IGRAs varies between studies and is dependent on the overall level and mode of immunosuppression. Positive and negative predictive values of immunodiagnostic tests in the transplant population are influenced by the locality-specific prevalence of infection with *M tuberculosis* and they are likely to differ from respective estimates in other risk groups for tuberculosis or healthy contacts, a key determinant being age differences and thus accumulated risk of being infected with *M tuberculosis*.

In the setting of transplantation, screening for LTBI in both the recipient and the donor may allow assessment of the risk of developing tuberculosis after transplant; positive screening results in individuals from high-risk groups for the development of tuberculosis should prompt for a decision for preventive chemotherapy [60, 61]. While screening of living donors is achievable, testing of deceased donors is challenging, as TST is not feasible and the performance of *in vitro* assays have not yet been assessed. When screening recipients, the decrease in test sensitivity with increasing immunosuppression has important practical consequences, as screening should be carried out before administration of immunosuppressive drugs to ensure sensitivity and to allow sufficient time to initiate chemoprophylaxis. Studies in transplant candidates prior to liver [62, 63] or renal transplantation indicate that IGRAs may be applied, although agreement between TST and IGRAs in renal transplant candidates is only fair to moderate [64-68].

At present, the advantage of either test for risk assessment post transplant is not known, as the positive predictive value of a positive IGRA for the development of tuberculosis has not been sufficiently studied. The limited number of studies thus far indicate that its value may be higher in low prevalence countries [69-72] as compared to highly endemic regions [46, 73]. Up to now, recommendations that favour the use of IGRA over TST in immunocompromised patients are largely based on potential superiority in identifying individuals with LTBI. Notably, a recent prospective study in South Korea showed that 4 out of 272 TST negative renal transplant candidates developed tuberculosis post-transplant. All 4 individuals had a positive ELISPOT assay, whereas no tuberculosis developed in patients with negative or indeterminate results [74]. In addition, a recent retrospective analysis among 461 immunocompromised patients showed that 1/38 QFT positive and no QFT-negative patients developed active tuberculosis [75]. While this clearly indicates an improved identification of patients at risk for tuberculosis, more studies in both low and high prevalence regions are needed to comparatively assess the positive predictive values of different immunodiagnostic tests in the setting of transplantation.

1.4 Summary

- TST measures a cell-mediated immune response to tuberculin PPD and has poor specificity in patients with BCG vaccination given in the not too distant past.

- IGRAs are blood-based *ex vivo* tests that rely on the rapid induction of IFN- γ in response to antigens that are more specific for the detection of a latent *M. tuberculosis* infection than PPD.
- IGRA testing in living donors, transplant candidates, and transplant recipients is feasible, although sensitivity may decrease with increasing immunosuppression; knowledge of IGRA performance in deceased donors is lacking.
- Further longitudinal studies are needed to estimate the risk for progression to post-transplant tuberculosis after IGRA- and TST-based screening.

Prevention of tuberculosis in transplant recipients

Effective pre-transplant screening for LTBI may prevent significant morbidity and mortality post-transplant by identifying individuals at risk for reactivation disease. Apart from TST or IGRA positive individuals after targeted screening, treatment of SOT recipients may also be indicated due to a high-risk pre-transplant exposure history (even with negative TST or IGRA), residence in an endemic tuberculosis region during the early post-transplant period, specific *M. tuberculosis* exposure post-transplant, or with a donor history of untreated or incompletely treated LTBI or tuberculosis [31, 76]. In endemic areas, some centres administer isoniazid for a period of time after transplant [31, 77]. Recommendations for management of various clinical situations, including involvement of donors with tuberculosis, are described in chapter 10. Although treatment of LTBI in transplant candidates is complicated by the presence of organ failure, with careful monitoring it can generally be safely initiated before or early after transplantation.

The risk of tuberculosis is highest in the first year post-transplant, during the time of maximal immunosuppression, with a median onset at 9 months [3]. Transplant recipients are at risk of other opportunistic infections at this time, and the diagnosis may therefore be overlooked, especially in areas of low tuberculosis endemicity, resulting in delayed treatment and poor outcomes [78]. Risk-adapted pre-transplant screening is therefore essential, not only to provide the opportunity for preventive chemotherapy in patients with LTBI, but also to raise the index of suspicion of active disease in those patients at high risk. In cases where the pre-transplant screening may be falsely negative, as with anergy to tuberculin skin testing or an indeterminate IGRA, specialized imaging may be employed in selected patients. Thoracic CT scanning may be superior to chest radiography in assessing the risk of post-transplant tuberculosis [79].

Genitourinary studies may also be helpful in higher risk recipients. Transplant candidates should not begin therapy for LTBI until they have been clinically evaluated for active tuberculosis, both pulmonary and extra-pulmonary [30]. It is strongly recommended that a physician with expertise in transplant infectious diseases be involved in this evaluation and subsequent therapy.

Treatment of LTBI in transplant candidates should be offered according to national guidelines, as these generally reflect regional drug availability and resistance patterns [39]. Potential regimens include alone or in combination isoniazid, rifampicin, and a fluoroquinolone. The combination of rifampicin and pyrazinamide has been associated with significant hepatotoxicity, and should no more be used with few exceptions that allow close monitoring [80-83]. Treatment should be initiated as early as possible pre-transplant, depending on the patient's medical condition and hepatic function. Careful monitoring for multiple potentially significant drug interactions is required, as well as close follow-up for adverse drug events, which may be significant in transplant candidates with end organ failure (table 2).

Timing of preventive chemotherapy/chemoprophylaxis in SOT recipients has not been well studied. Some clinicians prefer its administration in the pre-transplant period, as it lowers the risk of drug interactions. Others prefer to use it after transplant, once the immunosuppression has started and the risk of reactivation tuberculosis is higher. This can be problematic, as there is more potential for drug interactions, especially with the rifamycins (table 3). Transplant

recipients are generally monitored closely in the first year after transplant, which may improve safety through close therapeutic monitoring.

The choice of the agent(s) for preventive chemotherapy/chemoprophylaxis may depend on local rates of antituberculosis drug resistance of *M. tuberculosis* isolates, organ disease, drug or drug combination toxicity, drug interactions, likelihood of adherence, and other factors. Again, it is recommended that transplant programs follow the recommendations of local or governmental programs. Commonly used regimens include isoniazid for 9 months (often given with pyridoxine) or rifampicin for 4 months. When toxicity, resistance, or drug interactions preclude safe use of those drugs, preventive chemotherapy with a fluoroquinolone could be considered appropriate by some authorities. Clinicians caring for transplant recipients should be aware that administration of isoniazid or rifampicin significantly reduces the risk of development of tuberculosis depending on the duration the drugs are administered alone or in combination, but that preventive chemotherapy may not eliminate all viable *M. tuberculosis* bacilli. Reactivation of tuberculosis may have an atypical presentation in the immunosuppressed host, and may occur both in pulmonary and extra-pulmonary sites.

In patients awaiting heart transplantation, concomitant isoniazid and warfarin therapy may be initiated in cardiomyopathy patients, although it requires significant coordination with the cardiology team to ensure that appropriate monitoring of anticoagulation occurs. Alternative regimens such as rifamycins may decrease INR, increasing the risk of clotting. Fluoroquinolones may prolong the QT interval in patients at risk for arrhythmias.

The presence of hepatitis or end stage liver disease may significantly complicate the use of either isoniazid or rifampicin pre-transplant. Careful and frequent monitoring for signs and symptoms of drug-induced liver injury is strongly recommended in all patients being treated for LTBI, in conjunction with monthly liver enzyme testing throughout treatment [84]. More frequent monitoring may be indicated in high-risk patients, particularly older patients and those with the potential for significant drug-drug interactions. There are some data to suggest that hepatotoxicity may be less frequent with a shorter duration of the rifampicin regimen, a potentially important consideration for patients awaiting liver transplantation [85]. The optimal length of LTBI treatment has not been studied in this population. In general, it is recommended that transplant centers follow the recommendations of local or governmental programs. In some situations, treatment may be given for longer periods of time, especially in more intensely immunosuppressed transplant recipients, or where the risk of further acquisition of tuberculosis is higher (i.e. in endemic regions). Prolonging therapy of LTBI may be desired, but increases the risk of potential complications. Tuberculosis treatment decisions should be individualized with the assistance of transplant infectious disease expertise.

The optimal timing of LTBI treatment in transplant candidates cannot always be achieved, due to the complex drug interactions and organ dysfunction complicating the management of many patients with organ failure. It is not known what duration of treatment interruption is safe without incurring a substantial increased risk for active tuberculosis. Physicians must balance the risk of tuberculosis post-transplantation with the risk of deferring an organ offer in a seriously ill patient. It is usually possible to complete the course of LTBI therapy in most renal transplant recipients. Some practitioners prefer to defer treatment of liver transplant candidates and begin post-transplant, although others report successful treatment of patients with liver disease prior to surgery [86, 87]. If treatment is started pre-transplant and not completed by the time of transplant, reinitiation is recommended as soon as the patient can tolerate and absorb medications after surgery, providing that organ function is stable and with close attention to potential drug interactions. Prolonged treatment interruptions may require an extension of the total duration of LTBI post-transplant. If LTBI therapy is interrupted for more than 2 months, the organ recipient should be rechecked for evidence of active tuberculosis before single drug therapy is resumed [39, 88].

1.5 Summary

- Pre-transplant screening for LTBI may be performed with TST and/or IGRA, although some transplant candidates with LTBI may have false negative results despite a high-risk pre-transplant exposure history. Consider thoracic imaging and/or LTBI therapy for such candidates.
- Evaluate carefully to exclude active tuberculosis before initiating single drug therapy for LTBI.
- Consider treatment of LTBI pre-transplant, with careful monitoring for drug toxicity or interactions, particularly in patients with organ failure.
- Chemoprophylaxis/preventive therapy for LTBI need not be completed before transplant, and should be re-initiated as soon as the patient is stable after transplant; treatment interruptions may require a reassessment for development of active TB and an extended duration of LTBI therapy.

Treatment of active tuberculosis in transplant recipients

Prompt antituberculosis therapy should be initiated in patients with proven or probable tuberculosis, based on epidemiology, as well as on clinical, radiographic, microbiological, molecular biological and histopathological tests. Consequently, patients with clinical symptoms of weight loss, fever and sweats should receive immediate antituberculosis treatment unless contra-indicated. Tuberculosis treatment in transplant recipients differs from that in the general population in two ways. Firstly, as rifamycins interact with immunosuppressive drugs of the calcineurin inhibitor family (cyclosporine and tacrolimus), rapamycin and corticosteroids [113-116], rifamycin-sparing treatment regimens are preferred by many physicians. If a rifamycin is used, the risk of rejection may be increased due to lowered levels of calcineurin inhibitors; consequently, levels of cyclosporine or tacrolimus should be carefully monitored and doses should be adapted (3-5 fold increase) [89]. In cases of severe tuberculosis and/or if the organ is non-vital, any effort to reduce immunosuppression should be undertaken. Interactions between first-line antituberculosis drugs and immunosuppressive agents most commonly used in SOT recipients are summarised in table 3. Secondly, adverse antituberculosis drug events are more frequent. Consequently one or more first-line drugs cannot be used and thus the recommended duration of therapy is generally longer than in the general population [117, 118]. The length of treatment and the drugs used after the first 2 months are controversial areas, especially if rifampicin is not used in the first 2 months or must be suspended due to intolerance.

Recommendations given below are derived from studies in immunocompetent and other immunosuppressed individuals as direct evidence in transplant recipients is lacking. Daily dosage is recommended in all cases.

The standard short course antituberculosis drug regimen, i.e. a 2-month initiation phase with a four drug combination of isoniazid, rifampicin, ethambutol and pyrazinamide, followed by a 4-month continuation phase with isoniazid and rifampicin (2 RHZE/4 RH), is recommended for most cases in the transplant setting, and particularly for severe and/or disseminated forms of tuberculosis. Based on expert opinion, the continuation phase should be extended to 7 months in patients with pulmonary tuberculosis and cavitation on the initial chest radiograph or if sputum cultures remain positive at 2 months of treatment as these patients have a higher rate of relapse [90]. Some experts recommend a continuation phase of 7-10 months in CNS tuberculosis, mainly because of the increased risk of morbidity and mortality in these patients [90, 91].

Clinically stable patients with localized, non-severe forms of tuberculosis (excluding CNS, pericardial, osteoarticular and disseminated disease) and no suspicion or evidence of resistance to isoniazid may be treated with a rifamycin-free regimen, which will avoid drug interactions and may possibly reduce the risk of rejection [30]. However, results from a large case series of renal

transplant recipients with tuberculosis of whom more than 90% of cases were treated with rifampicin-based regimens indicate a similar rate of graft loss compared to the national mean [92]. Rifabutin interaction with immunosuppressive drugs is less important, and can be used instead of rifampicin with similar efficacy and possibly lower risk of graft loss. In rifamycin-free treatment regimens, combination therapy with isoniazid and ethambutol is recommended for 18 months with the addition of pyrazinamide for the first 2 months [91]. Irrespective of whether a rifamycin is part of an antituberculosis drug regimen, the risk of disease recurrence is low when treatment is extended beyond 12 months [119]. Isoniazid-free and pyrazinamide-free regimens similar to those used in immunocompetent individuals [90, 93, 94] should be used in case of resistance or intolerance.

Fluoroquinolones are an interesting drug class for antituberculosis treatment, given that one or more first-line drugs cannot be used in many SOT patients. Evidence from immunocompetent individuals suggests that later generation fluoroquinolones (i.e. gatifloxacin or moxifloxacin and probably to a lesser extent also levofloxacin, but not ciprofloxacin or ofloxacin) can probably be used as alternative drugs to oral first line agents [95]. Moxifloxacin has been shown to be equivalently effective to isoniazid in achieving culture conversion in the initial phase of treatment in one clinical trial [121]. There is also circumstantial evidence for the use of fluoroquinolones in SOT recipients. However the optimal duration of fluoroquinolone-containing regimens is unknown. Combined and prolonged use of levofloxacin and pyrazinamide has been associated with poor gastrointestinal tolerance [122, 123].

Special situations

In HIV infected transplant recipients, rifamycins may lead to greater hepatotoxicity and jeopardize antiretroviral therapy because of their interaction with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors. The recommended regimen in this population is isoniazid, pyrazinamide and ethambutol with moxifloxacin or levofloxacin [96].

In patients with significant hepatic disease and after liver transplantation, initial treatment with isoniazid, rifampicin and pyrazinamide in patients with tuberculosis has been associated with an increased risk of hepatotoxicity. Close monitoring of liver enzymes is necessary [97] and a pyrazinamide-free regimen is recommended in non-severe hepatic disease. In severe hepatic disease, an isoniazid- and pyrazinamide-free regimen (and even rifampicin-free) should be considered [126, 127]. In severe hepatic disease or early after hepatic transplantation, a combination of ethambutol with a later generation fluoroquinolone (e.g. moxifloxacin) might be a temporary solution until a more effective regimen can be administered.

Immune reconstitution inflammatory syndrome (IRIS) can occur in SOT recipients with tuberculosis under treatment [128]. A paradoxical worsening of symptoms with fever, cough, lymph node enlargement or roentgenographic abnormalities within the first 3 months of antituberculosis treatment initiation has been described [98]. High-dose systemic corticosteroids are the most commonly employed treatment [99].

Macrophage activation syndrome (or hematophagocytic syndrome) is a relatively rare association in transplant recipients with opportunistic infections including tuberculosis [100]. The clinical picture combines fever, hepatosplenomegaly, pancytopenia and liver dysfunction, and histologically consists of bone marrow and organ infiltration with non-malignant macrophages phagocytising erythrocytes. Fatality is high [131, 132] and optimal treatment is unknown.

Resistance Multidrug-resistant (MDR) tuberculosis (i.e. resistance to isoniazid and rifampicin) has rarely been reported in SOT [133-135] or HSCT recipients [101]. Despite limitations in drug susceptibility testing (DST) MDR tuberculosis should be treated according to the results of DST with at least 4 drugs that are active against *M. tuberculosis in vitro*. The selection of drugs for the treatment of MDR tuberculosis should be performed in a hierarchical order.

Extensively drug-resistant (XDR) tuberculosis (i.e. MDR tuberculosis plus *in vitro* drug resistance against any fluoroquinolone and one of the injectable aminoglycosides/polypeptides) has not yet been reported in transplant recipients and should, in case of occurrence, be treated following the same principles as for MDR tuberculosis.

The WHO suggests a total duration of treatment of 18 months following *M. tuberculosis* culture conversion in M/XDR tuberculosis [102]. Validated biomarkers to guide physicians in the decision for treatment discontinuation are lacking. Adjunctive surgery may be required in selected patients [103]. When M/XDR tuberculosis is suspected, the decision for treatment initiation and the choice of anti-tuberculosis drugs should be made on an individual basis involving a physician with experience in the treatment of M/XDR tuberculosis.

Other

Adjunctive therapy and treatment monitoring for efficacy and adverse effects are similar as in immunocompetent individuals. In pulmonary tuberculosis, sputum smear and culture should be performed as a minimum at 2 and 4 months of treatment, at the end of treatment and on two more occasions until the end of a year. Extrapulmonary tuberculosis should be followed clinically.

Doses should be adjusted according to creatinine clearance. In case of hepatic disease, or elevated risk of drug-induced liver injury, frequent monitoring of serum aminotransferases and bilirubin should be performed and treatment regimens changed in case of a significant hepatotoxic reaction. At the beginning of a rifamycin-based regimen the dose of cyclosporine, tacrolimus or sirolimus should first be increased three times when the rifamycin is introduced and then adjusted according to regularly measured serum levels. Similarly, when rifamycin is stopped, the dose of either immunosuppressive drug should be reduced to the pre-rifamycin dosage, and again adjusted by frequent serum level measurements. Oral corticosteroid dose should be increased by 50% during treatment with a rifamycin.

Isolation is particularly important in transplant recipients as they might come in contact with other transplant recipients in medical facilities. Pulmonary tuberculosis suspects should be isolated until active tuberculosis has been excluded. Pulmonary tuberculosis patients should be isolated for at least 2 weeks if *M. tuberculosis* strains are sensitive; many centres advocate isolation until they have three consecutive negative sputum smear results. Continuous isolation until *M. tuberculosis* cultures are negative may be advocated if patients are in contact with other immunocompromised individuals although the risk of transmission is low in patients with sputum conversion on treatment.

Summary

- In general, the same short course treatment regimen (2 HRZE/4 RH) is recommended for transplant recipients as for other patients with tuberculosis.
- Tuberculosis treatment in transplant recipients is often complicated by interactions between rifamycins and immunosuppressive drugs and the increased frequency of adverse antituberculosis drug events.
- A rifamycin-free antituberculosis treatment regimen is an important option in non-severe cases in order to avoid drug interaction with immunosuppressive drugs and thus reduce the risk of graft rejection.
- Fluoroquinolones are promising drugs in the treatment of tuberculosis in transplant recipients although clinical evidence for the treatment efficacy are still lacking.
- Length of continuation phase is dependent on the drugs used in the initial phase and in the continuation phase; except for the standard regimen, many recommendations are extrapolated from immunocompetent individuals or are opinion-based.

Special considerations in stem cell transplant recipients

As with SOT patients, the frequency of tuberculosis in HSCT recipients expectedly correlates with the local notification rates of incident tuberculosis. Areas where tuberculosis is highly incident report a tuberculosis frequency of 1 to 16% during follow-up [104-107]. In developed regions, the reported proportions range from 0.4 to 2.2% [108-110]. Published cases from developed nations commonly include immigrants from countries where tuberculosis is endemic, other groups with increased risk and thus prevalence of infection, prisoners, or contacts with a history of exposure [110]. In the USA, the frequency of tuberculosis in HSCT is approximately double that in the general population, underscoring the effects of immunosuppression [5]. Nevertheless, tuberculosis is more frequently diagnosed in SOT than in HSCT recipients [111]. This disparity may reflect the immune reconstitution in HSCT, notably of cellular immunity, and/or the impact of the use of fluoroquinolones in antibacterial prophylaxis during neutropenia with incidental anti-mycobacterial efficacy [106, 111].

Tuberculosis has generally been observed as a delayed complication of HSCT occurring beyond day 100. Early presentations have been reported, often as a cryptic source of fever after HSCT [112]. Cases are predominantly pulmonary with variable radiographic features, and dissemination is documented infrequently. Experience in Hong Kong and Taiwan document upper lobe-predominant disease, suggestive of reactivation tuberculosis [106, 113]. In a South Korean series, nodular or multilobar airspace disease was more common without zonal predominance, consistent with primary tuberculosis [114].

Prospective donors with symptoms of tuberculosis should be evaluated for active disease and should not donate until tuberculosis has been adequately treated. Routine screening for active tuberculosis of potential donors from endemic regions for tuberculosis has not been studied, but appears to be unnecessary.

Risk factors

Recipients of allogeneic stem cell grafts, particularly matched unrelated grafts, appear to be at higher risk for *M. tuberculosis* infection than recipients of autologous stem cell grafts [111-113]. In autologous transplantation, risk factors for mycobacteriosis due to environmental mycobacteria include conditioning regimens affecting T-cell function such as fludarabine, ATG, or alemtuzumab [115]. In some series, development of tuberculosis was found to be related to receipt of T-cell depleted allografts [116]. Administration of corticosteroids was significantly associated with development of tuberculosis in one case series [111]. Conditioning with total body irradiation has also been cited as another risk factor [104, 106, 111]. In multiple series, acute or chronic graft versus host disease (GvHD) with associated depression of phagocytic and cellular immune functions is the most strongly associated risk factor for the development of tuberculosis [106, 112, 113, 116]. Following *M. bovis* BCG vaccination, transfer of PPD-reactive memory T cells from donor to recipients is not protective in individuals suffering GvHD [117]. No correlation has been found between specific conditioning chemotherapeutic regimens or GvHD prophylactic regimens and the risk for tuberculosis. Reactivation of cytomegalovirus has been unreliably reported in HSCT who contract tuberculosis, precluding analysis of correlation. New biologic agents (TNF antagonist therapies, T- and B-lymphocyte depletion, or co-stimulatory blockade) are additional risk factors for tuberculosis. These agents can be used either as a part of the conditioning before HSCT or as a treatment for GvHD, a condition associated with increased risk for tuberculosis. There are case reports of tuberculosis in patients given alemtuzumab as part of the conditioning therapy [118], and one suspected but unproven case of tuberculosis associated with rituximab given for chronic GvHD [119]. Although there are few data in HSCT, most of these agents have been associated with an increased risk for tuberculosis

in other patient populations and may pose an increased risk in the HSCT population as well [120, 121].

Prevention, diagnosis and therapy

Evaluation for LTBI or tuberculosis should be performed in candidates for HSCT who have a history of prior exposure to tuberculosis [122]. Screening should be performed in recipients from endemic regions using TST or IGRA. Prior chemotherapy may reduce TST responses [123]. IGRAs may be useful in screening patients with prior *M. bovis* BCG vaccination [123, 124]. Use of IGRAs for LTBI in HSCT patients is under investigation. Available data suggest a high percentage of indeterminate test results, especially in the first year after transplantation [59]. Any individual with a positive *M. tuberculosis*-specific immunodiagnostic test should be evaluated for active disease.

When identified and treated before HSCT, tuberculosis rarely recurs [104, 111]. No standardized screening protocol exists for LTBI prior to HSCT. A multicenter study of 351 allogeneic stem cell recipients screened by chest radiograph prior to HSCT from Turkey examined pre-HSCT screening strategies: chest radiography only; use of PPD with isoniazid therapy for TST size >15 mm; or universal use of INH prophylaxis immediately prior to, and for six months following receipt of HSCT [105]. No tuberculosis occurred after HSCT in patients given isoniazid either by mandatory protocol or for a positive PPD. None of 7 patients who had a positive PPD pre-HSCT with a negative chest radiograph developed tuberculosis. In the series, 5 of 274 untreated patients developed pulmonary tuberculosis. Among these 5 patients, all had clear chest radiographs, two had not been tested by PPD and three had a TST <10 mm prior to HSCT.

In general, it is reasonable in endemic regions to provide empiric prophylaxis based on either exposures or screening test positivity. The interpretation of TST results may be difficult, as the underlying disease or prior chemotherapy may lead to skin test anergy. Such individuals merit careful follow up. This also underscores the need for more accurate diagnostics in this population. Live *M. bovis* BCG vaccination is contraindicated in HSCT recipients [125, 126]. As with SOT patients, diagnosis of tuberculosis is often delayed in HSCT recipients given the non-specific signs and symptoms of tuberculosis, often compounded by a low index of suspicion in low-incidence countries. The diagnosis of all forms of tuberculosis should be based on microbiologic evaluation, including antimicrobial susceptibility data on the isolates, whenever possible. Initial therapy may be empiric and based on microscopic demonstration of AFB, clinical suspicion, radiographically suggestive presentation or histology; therapy should not be delayed until culture results are available if other evidence is sufficiently strong to warrant intervention [113]. The use of nucleic acid amplification or hybridization techniques has been incompletely evaluated in this population.

The mortality of patients with tuberculosis after HSCT is reported to range between 0-50% [7]. Tuberculosis following autologous transplantation generally responds well to treatment [111, 112]. To date, few cases of MDR-TB have been reported in the HSCT population [106, 107].

Summary

- The magnitude of the tuberculosis risk in HSCT recipients is strongly associated with the epidemiology of tuberculosis in the general population to which the patients belong. Recipients of allogeneic HSCT, particularly matched unrelated grafts, are at higher risk of tuberculosis than recipients of autologous HSCT.
- The risk of death from or with tuberculosis after HSCT is high (up to 50%).
- Evaluation for LTBI or tuberculosis should be performed in candidates for HSCT with possible increased exposure risk. Screening should be performed in recipients from endemic regions using TST or IGRA. Prior chemotherapy may reduce TST responses.

- Tuberculosis after HSCT is predominantly pulmonary with a wide spectrum of radiographic features. Tuberculosis is generally a late complication of HSCT occurring beyond day 100. Earlier disease manifestations often include presentations as cryptic febrile illnesses.
- Acute or chronic graft versus host disease (GvHD) is an independent risk factor for the development of tuberculosis in addition to the intensity of immunosuppression.

Special considerations in children

Epidemiology of tuberculosis in paediatric transplant recipients

Data regarding tuberculosis in paediatric transplant recipients are scarce; many studies do not include children or results are not reported separately from adult data. However, published reports of small numbers of cases from single institutions suggest that rates of tuberculosis following liver transplantation in children range from 2.4-3.6% in non-endemic and highly endemic areas, respectively [94, 127] whilst rates following renal transplantation of 8-9.7% have been reported from highly endemic areas [93, 128]. In agreement with reports in adults, the incidence of tuberculosis following bone marrow transplantation is lower than that observed with SOT, with rates of 1.7% reported in a retrospective study in India [129]. Whilst published estimates of the incidence of tuberculosis are lacking, these data suggest that rates of tuberculosis in paediatric transplant recipients are significantly higher than in the general population, in common with the increased risk observed in adult recipients [54]. Incidence of tuberculosis varies with the type of organ transplanted and population prevalence of tuberculosis.

Paediatric tuberculosis

Paediatric tuberculosis is most commonly a result of primary infection and therefore a previous history of tuberculosis is infrequently found in children who develop the disease following transplant [127, 130]. Tuberculosis arising from the donated organ would be expected to be uncommon [76].

Children have an age-dependent increased risk of progression from LTBI to disease; those less than five years, adolescents and young adults have the highest risk of disease and the school-aged children have the lowest risk [131]. Immunosuppression further increases the risk.

Children, particularly of very young age, who develop tuberculosis are more prone to present with extrapulmonary and disseminated forms compared to adults, a risk that is also reflected in the presence of immunosuppression [132]. Whilst the majority of reported cases of tuberculosis in paediatric transplant recipients are pulmonary, some case series report frequencies of disseminated disease and extrapulmonary disease in excess of 50% [93, 127-129, 133].

Compared to the adult population, children who develop tuberculosis have an increased risk of death. One case series reports mortality of over 30% in paediatric transplant patients who develop tuberculosis [127].

Diagnosis of infection with *M. tuberculosis*

Depending on the age of the child, the source of infection is commonly an infectious adult living in the same household, making screening of family members for active disease important in paediatric transplant candidates [131]. In one study, 80% of children who developed tuberculosis following liver transplantation had a family member identified as having tuberculosis or *M. tuberculosis* infection.

Screening of children for infection with *M. tuberculosis* relies on history of exposure, tuberculin skin testing and the exclusion of clinical and radiological signs and symptoms of tuberculosis. IGRAs have recently been included in national guidelines in some parts of Europe [134-136]. Tuberculin skin testing can be influenced by recent *M. bovis* BCG vaccination and

environmental mycobacteria and it may be falsely negative in young children and those who are immunosuppressed. In support of this, in one UK case series the TST was unreactive in 5 out of 6 children who developed tuberculosis following liver transplantation [127]. IGRAs were not used in this study. Whilst neither *M. bovis* BCG nor most environmental mycobacteria influence the result of IGRAs, data regarding their value in immunosuppressed children and young children are lacking. Studies evaluating IGRAs in transplant candidates to date have excluded children [62, 63].

The diagnosis of active tuberculosis is similarly challenging in children due to the difficulties collecting specimens, the paucibacillary nature of disease and the increased possibility of non-specific symptoms and signs. Diagnosis in paediatric transplant recipients may be even more challenging as these difficulties may be compounded by immunosuppression and necessitate invasive sampling methods [127, 133]. Recent advances in tuberculosis diagnostics may assist in the diagnosis in this vulnerable population, however they urgently require evaluation in children [137].

Prevention of TB in paediatric transplant recipients

Identification and treatment of household members with active disease is important in the prevention of tuberculosis in paediatric transplant candidates and recipients. Although immunosuppressive therapy might impair performance of both TST and IGRA, it would be prudent to screen children prior to transplantation with these tests. If they are positive, active tuberculosis needs to be excluded and if they are negative this might indicate genuine absence of *M. tuberculosis* sensitization or false-negative results. In children identified as having LTBI, one should consider preventive therapy with 9 months of isoniazid, commencing prior to transplantation. However, there are concerns regarding the liver toxicity of isoniazid preventive therapy in paediatric transplant candidates and recipients; Verma *et al.* report that 2 out of 6 children treated for tuberculosis with isoniazid developed isoniazid-induced hepatitis, although this was resolved with dose reduction [127]. The lack of data makes recommendations difficult; some institutions recommend use of isoniazid preventive chemotherapy, whilst others withhold it or reserve preventive treatment for children at highest risk only [93, 94, 127].

1.6 Summary

- Few studies report the incidence of tuberculosis in paediatric transplant recipients and the numbers of children in such studies are very small, however data available are consistent with that reported in adult transplant recipients.
- There are a number of features unique to paediatric tuberculosis which are likely to be amplified in children who are immunosuppressed following transplantation, namely an increased risk of progression from infection to disease, extrapulmonary, including disseminated disease, and higher risk of death from or with tuberculosis.
- Screening of paediatric transplant candidates for *M. tuberculosis* infection and screening of family members for active disease is important and careful consideration must be given to the

provision of isoniazid preventive therapy to those identified as having LTBI to decrease the tuberculosis risk following transplantation.

- Whether TST or IGRA or both are the preferred approach remains unresolved, and which strategy is being used will also depend on resource availability.

Published national guidelines

Guidance on assessing and managing both LTBI and tuberculosis in SOT or HSCT recipients has been produced in several countries. Considering only English language publications, seven national guidelines have been identified [4, 30, 126, 138-141], six of which relate to SOT and one to HSCT. Some offer guidance on screening of living and deceased donors in addition to screening and management of LTBI and tuberculosis in the recipients. These publications are from the following countries or geographic areas Canada [138], Europe [139], Spain [30], UK [140], USA [4, 141] or global [126]. Four deal specifically with renal transplantation [4, 138-140], two with SOT in general [4, 30], including some specific information on liver and lung transplants, and one with HSCT [126]. In addition, there are four further statements relating to tuberculosis and transplantation. One on general testing and treatment of LTBI [142], a conference update briefly covering cardiac transplantation [143], one general statement [144] and one review of the evidence for preventive chemotherapy/chemoprophylaxis [31]. The guidelines and statements are hitherto referred to as “guidelines” and are discussed and compared on screening for LTBI and tuberculosis, recommendations for preventive chemotherapy/chemoprophylaxis and regimens, and therapy for tuberculosis and its duration.

Points of Agreement

There is general consistency in most of the recommendations made across all the publications. Some are more comprehensive than others. Where mentioned, all guidelines recommend screening for evidence of LTBI and tuberculosis, including taking a full clinical history and making a physical examination as part of the initial assessment, with the exception of the HSCT guidelines [126] which recommend screening only for demonstrable risk. The breadth of recommended history taking varies but includes details on ethnicity, country of birth, history of recent contact with tuberculosis, previous disease and treatment, together with evaluation for any additional risk, such as diabetes or travel to countries of high background incidence. A chest radiograph is recommended, to be supplemented by a TST and/or an IGRA by all guidelines. The more recent guidelines [4, 126, 140-142] include IGRA testing, with or without TST. All suggest screening pre-transplant, preventive therapy for LTBI with isoniazid plus pyridoxine (vitamin B6), monitoring of liver enzymes and full treatment for active tuberculosis.

Areas of Difference

The UK and HSCT guidelines do not give a cut-off point for a positive TST as they make the point that the TST is unreliable in patients with advanced chronic kidney disease or who receive immunosuppressive treatment. A positive test is being judged to be useful but a negative test not because of too frequent false negative results. The UK guidelines [140] recommend using an IGRA with or without a TST. The HSCT guidelines [126] consider an IGRA to be more useful in the immunocompromised but note that a negative test does not exclude LTBI, a point also made by the US renal guidelines [141]. Most of the other guidelines recommend a TST cut-off of ≥ 5 mm as a positive result, but the European guidelines draw a distinction between transplant

recipients ($\geq 5\text{mm}$) and dialysis patients ($\geq 10\text{mm}$). The Spanish [30] and US [4] guidelines recommend repeating the TST to increase sensitivity by provoking a “booster effect”.

In general, all include isoniazid as single agent, most recommending nine months of treatment, with the exception of the UK [140] where 6 months is recommended as “regimens longer than 6 months isoniazid have only very minimal additional advantage at the cost of an increase in the risk of hepatitis” [145]. The European and US SOT guidelines [4, 139] recommend 9 months of isoniazid but include a caveat that this can be shortened to 6 months. Other regimens suggested by different guidelines include 3 months isoniazid plus rifampicin; 4-6 months rifampicin alone, and 2 months rifampicin plus pyrazinamide (see **table 4**).

The UK guidelines [140] are unique in attempting to quantify the relative risk of reactivating tuberculosis compared with the risk of developing significant hepatitis resulting from various regimens. As neither the TST nor the IGRAs are wholly reliable indicators of LTBI, this can aid the clinical decision on which patients should receive preventive chemotherapy/chemoprophylaxis.

Most guidelines recommend standard quadruple therapy for active tuberculosis for a total of 6 months for non-CNS tuberculosis that is fully drug susceptible. Although all raise the issue of drug interactions between rifampicin and immunosuppressive drugs (see table 3), the Spanish guidelines [30] are alone in recommending avoiding rifamycins, except in disseminated disease and where isoniazid resistance is a possibility. All recommend dose monitoring of immunosuppressive drug levels and the UK guidelines [140] recommend doubling the dose of corticosteroids in patients taking rifampicin. Rifabutin is frequently suggested as an alternative to rifampicin as it is a less potent inducer of cytochrome P450. A summary of the main recommendations made in the different publications can be found in **table 4**.

Summary

- There is overall agreement in most recommendations found in seven national, regional, and global guidelines together with three further relevant short statements relating to screening for LTBI and active tuberculosis.
- Preventive therapy with isoniazid, isoniazid plus rifampicin or rifampicin alone is generally recommended pre-transplant if there is evidence of LTBI or chemoprophylaxis if there is a significant risk.
- Standard treatment is recommended for active tuberculosis with some guidelines recommending prolonged treatment.
- Attention should be paid to serum levels of immunosuppressive drugs when rifampicin is used.

2 Consensus recommendations

Current evidence regarding optimal management for the prevention and treatment of tuberculosis in transplant recipients is limited. Recommendations made in this consensus statement largely rest on expert opinion and inference derived from tuberculosis prevention and treatment in the non-transplant setting (for evidence levels, see table 1). These consensus recommendations aim to guide physicians responsible for the care of transplant recipients until better clinical evidence becomes available.

1. Is screening for latent infection with *M. tuberculosis* recommended for all transplant candidates?

The indication for screening should be guided by locally established frequency of tuberculosis in transplant recipients. Preventive chemotherapy against tuberculosis without prior screening for LTBI may be appropriate for all transplant recipients in regions of high tuberculosis incidence ($\geq 100/100.000$) (Evidence level D). In regions of medium tuberculosis incidence ($\geq 20/100.000$)

or in regions with medium local tuberculosis burden), all candidates should be screened for the presence of *M. tuberculosis* specific immune responses (the best available proxy for LTBI) (Evidence level C). In regions of low tuberculosis incidence, a decision for screening of transplant recipients for the presence of *M. tuberculosis* specific immune responses should include an individual risk assessment for LTBI. In centers where LTBI screening is not performed for all transplant recipients candidates as a routine procedure, screening should be performed in candidates with at least one additional risk factor for infection with *M. tuberculosis*, e.g. a recent contact to an infectious patient with tuberculosis, immigration from a high incidence country of tuberculosis, a medical history of previous untreated or insufficiently treated tuberculosis or fibrotic/calcified lesions on chest radiography compatible with a past history of tuberculosis in previously untreated patients (Evidence level D). All children should be screened (Evidence level D).

In general, all transplant candidates should be questioned about a history of prior tuberculosis or tuberculosis contact (including a past TST or IGRA) and should have a chest radiograph to search for evidence of prior or current tuberculosis. In case of abnormal radiographic findings compatible with past (such as fibrotic lesions, calcified granulomas or lymph nodes, pleural thickening with or without calcification) or active tuberculosis (fibronodular or cavitating lesions), an additional CT-scan may provide more specific information (Evidence level B).

2. Is there a difference in the recommendations for screening of recipients of solid organs or hematopoietic stem cells?

The same recommendations apply (Evidence level D). However, the risk of false-negative immune responses is considerable in persons already using immunosuppressive medication or following recent chemotherapy for hematological malignancy, or in chronic renal failure.

3. Should screening for latent infection with *M. tuberculosis* be performed by skin testing, IGRA, or both?

The best choice for a screening test to detect LTBI in candidates awaiting SOT or HSCT is unclear, as the positive predictive value for the development of tuberculosis in this setting is largely unknown and varies with tuberculosis prevalence. In general, neither IGRAs nor the TST have high accuracy for the prediction of active tuberculosis (Evidence level B). Until more data on the predictive ability are available, the choice of the test should be based on the relative specificity in different prevalence regions, logistics, and cost. IGRAs have some operational advantages as mitogen controls may allow differentiation between anergic and non-sensitized individuals. Tuberculin skin testing should be interpreted carefully in individuals with a known history of *M. bovis* BCG vaccination, although the effect of such vaccination wanes after 1-2 decades; IGRAs can help distinguish responses due to BCG vaccination from infection with *M. tuberculosis*. Given the discordant results between IGRAs and TST in several studies in immunocompromised hosts, a combination of both assays may result in a higher sensitivity if false negativity is a concern. This approach may be particularly useful in children. It is currently unclear, however, whether the combination will result in a better risk estimation for the development of tuberculosis after transplantation. For the diagnosis of latent infection with *M. tuberculosis* in low prevalence settings, experts suggest using the QuantiFERON® TB Gold in-tube test or the T-SPOT.TB® test (Evidence level D). If IGRAs are not available, tuberculin skin testing should be used for screening for LTBI. A higher risk of false negative immunological test results in patients with recent chemotherapy or T-cell depleting agents should be taken into account.

4. If IGRAs are used for the diagnosis of latent infection with *M. tuberculosis*, is there a preference for QuantiFERON® TB Gold in-tube or T-SPOT.TB® test?

There is no evidence available to favour either test for diagnosing LTBI in transplant candidates. There is some evidence of increased sensitivity of the T-SPOT.TB® test over QuantiFERON® TB Gold In-Tube test in HIV-infected individuals with low CD4 counts (Evidence level C).

5. Which cut-offs should be used for the tuberculin skin test and IGRAs for the diagnosis of latent infection with *M. tuberculosis* in transplant candidates?

Pending further evidence, the cut-offs for IGRAs for the diagnosis of LTBI in candidate recipients of SOT or HSCT should be used as recommended by the manufacturers for Europe (Evidence level D). A tuberculin skin test result of ≥ 10 mm is commonly used as being indicative of LTBI in the non-BCG vaccinated individual and should not generally need confirmation by an IGRA. A TST result of ≥ 5 and < 10 mm in a person using immunosuppression may be considered as probable LTBI in the absence of BCG vaccination, but specificity at such low cut-off points is often poor due to the possibility of sensitization with environmental mycobacteria, while the gain in sensitivity might be marginal [40]. In children, a cut off of ≥ 5 mm is recommended as it is assumed that accumulated non-specific cross-reactions are less frequent (however, the influence of BCG, where given at birth, might be considerable). TST and IGRA should both be performed at the same time. If the result of the IGRA is positive, the child should be treated for LTBI once active tuberculosis is excluded. If the result of the IGRA is negative and the TST induration is ≥ 10 mm in an immunocompetent child or ≥ 5 mm in an immunocompromised child, a diagnosis of LTBI should be assumed (Evidence level D).

6. What decision should be taken when testing for latent infection with *M. tuberculosis* provides a positive test result?

All candidates with a positive TST or IGRA test result after targeted screening should receive preventive chemotherapy to reduce the risk for the development of tuberculosis (“intention to test is intention to treat”) (Evidence level A).

7. What decision should be taken when testing for latent infection yields discordant results (e.g. positive tuberculin skin test and negative IGRA test result)?

If results from both tests are available and are discordant, then the positive result, be it IGRA or TST, should be used for clinical decision making regarding preventive chemotherapy (Evidence level D). This should also be the approach taken in children, whether BCG-vaccinated or not. The reason for accepting a positive test as a basis of therapy is that false-negative results for either test are common; moreover, it is not possible to disprove that a positive test result is truly positive. In individuals with a history of *M. bovis* BCG vaccination in the last 10 years and a positive TST result with a value of less than 15 mm (less than 10 mm if BCG vaccination was performed > 10 years ago), with a normal chest radiograph, and in the absence of additional risk factors, TST may be regarded as a false-positive. The risks of withholding preventive therapy should be discussed with the patient and the final decision should be agreed upon by all parties involved. Post-transplantation vigilance should be high in this situation with a low threshold for further diagnostics.

8. Under which circumstances should preventive chemotherapy against tuberculosis be offered to transplant candidates in the absence of immunodiagnostic testing or in the presence of a negative results of immunodiagnostic testing?

In the absence of immunodiagnostic testing or in the presence of a negative result of immunodiagnostic testing, treatment for the prevention of tuberculosis should be offered to all individuals with fibrotic or calcified lesions on chest imaging as putative radiographic evidence of previous tuberculosis who did not receive adequate antituberculosis chemotherapy, in individuals with a strong history of exposure or even documentation of a positive TST or IGRA result in the past, in individuals originating from a country with a very high incidence (e.g. $\geq 100/100.000$ per year), and to any child with recent documented exposure to bacteriologically confirmed tuberculosis (Evidence level C).

9. When should infection with *M. tuberculosis* be expected in a donor graft?

Infection with *M. tuberculosis* of the donor graft is likely to be related to the risk of *M. tuberculosis* infection of the donor and the type of graft. All organs of donors with active or inadequately treated tuberculosis should be considered infectious for the immunocompromised

recipient. In lung transplantation, lungs from donors with evidence for LTBI (based on a prior positive TST or prior/actual IGRA result in the absence of active tuberculosis) should be considered as potentially infectious. To what extent transplantation of organs other than lungs from donors with LTBI increases the risk for tuberculosis in the immunocompromised recipient is unknown. However, organs derived from individuals with likely *M. tuberculosis* exposure in endemic regions may potentially contain live *M. tuberculosis* (Evidence level D).

10. Should all transplant candidates from a donor who is/was thought to be infected with *M. tuberculosis* be offered prophylactic treatment against tuberculosis?

Active tuberculosis in an SOT donor should be assessed and if positive excluded from donation (Evidence level C). Hematopoietic stem cells are highly unlikely to harbour live *M. tuberculosis* except perhaps in a person with disseminated tuberculosis at the time of harvest (Evidence level D). Solid organs from donors with LTBI may contain live *M. tuberculosis*, especially the lungs, but transmission via other organs has been described in rare instances only. For living donors, the benefit of prophylactic chemotherapy to reduce the risk of *M. tuberculosis* transmission is uncertain. If LTBI is thought to be present in a deceased donor, the recipient of the lung transplant should be treated for LTBI while the benefit in recipients of other organs may be outweighed by potential toxicities (Evidence level D). Clinical monitoring and constant vigilance is mandatory in the post-transplantation period.

11. Which regimen for preventive chemotherapy/chemoprophylaxis is most effective in reducing the risk of developing tuberculosis in recipients who either have positive *M. tuberculosis* specific immune responses or receive a graft from an individual that is thought to be infected with *M. tuberculosis*?

Few data exist to use in the selection of specific regimens based on factors other than drug toxicity and interactions. In endemic regions, treatment of individuals with preventive chemotherapy/chemoprophylaxis with positive screening assays prior to immunosuppression results in a reduced rate of clinical tuberculosis. However, the effectiveness of various chemotherapeutic regimens to prevent tuberculosis has not been studied in this setting. The best clinical evidence of efficacy in other populations supports a choice of a preventive chemotherapy regimen of 9-12 months of isoniazid (Evidence level A). The efficacy of that regimen exceeds 90% and the effectiveness exceeds 60%. An alternative choice of 4 months of rifampicin or a combination of 3 months isoniazid plus rifampicin or rifapentine cannot be routinely recommended for the transplant setting due to interactions of immunosuppressive drugs with rifamycins, but can be considered if pre-transplant treatment is possible (Evidence level B). The interaction between rifampicin and anticoagulant or other drugs such as beta-blocking agents can often be managed with dose adjustments and close supervision (Evidence level C).

12. When should transplantation be performed in relation to the initiation of preventive treatment of latent tuberculosis infection?

If treatment of LTBI cannot be completed before transplantation, it should be completed after transplantation as scheduled if possible (Evidence level D). Given interactions with calcineurin inhibitors, rifampicin-free regimens may be preferred. Transplant patients are monitored closely during the first year, which will allow timely detection of tuberculosis reactivation. No specific additional diagnostic tests can be advised routinely, but new unexplained symptoms or signs should be analysed without delay. In this setting, the diagnostic approach must be aimed at direct detection of bacilli, and immunodiagnostic tests are not useful (Evidence level C).

13. Which is the optimal treatment for active tuberculosis in transplant recipients?

All treatments of active TB should be based on susceptibility testing of mycobacterial isolates. While awaiting such data, a standard daily regimen with a 2-month initiation phase with a four-drug combination HRZE followed by a 4-month continuation phase with H and R is recommended for recipients of SOT or HSCT (Evidence level B). The continuation phase should be extended to 7 months in patients with pulmonary tuberculosis and both cavitation on the initial chest radiograph and/or positive sputum cultures at 2 months of treatment as these patients

have a higher risk of relapse (Evidence level D). Some experts recommend a continuation phase of 7-10 months in CNS tuberculosis mainly because rifampicin and ethambutol have reduced CNS penetration. If a rifamycin is used, the risk of rejection may be increased due to lowered levels of prednisone or calcineurin inhibitors; consequently, steroid dosage should be increased by around 50%, and levels of cyclosporine, tacrolimus and rapamycin should be carefully monitored and dosage increased accordingly. A rifamycin-free regimen (H, Z, E, fluoroquinolone) is an option in non-severe TB cases in order to avoid interaction with immunosuppressive drugs (Evidence level C).

14. How should patients who started preventive chemotherapy for LTBI be followed in relation to the timing of solid organ or hematopoietic stem cell transplantation?

Patients undergoing treatment for LTBI should be followed with weekly assessment initially for liver enzyme testing and, if appropriate, immunosuppressive drug levels. If stable for one month, monthly assessments are likely to be adequate, including questioning about adverse effects of therapy and liver function testing. In case of symptoms, patients should be seen without delay to allow timely detection of adverse drug events or breakthrough tuberculosis (Evidence level D).

15. How should patients who started treatment of active tuberculosis be followed in relation to the timing of solid organ or hematopoietic stem cell transplantation?

Active tuberculosis under treatment is regarded as a relative contraindication for transplantation in many centres other than emergency heart, lung, or liver transplantation. Individuals developing severe antituberculosis drug-induced liver injury may also require emergency transplantation. In general, patients should have at least completed the induction period (2 months) and it is preferred, although not always possible, to complete the full treatment against tuberculosis prior to transplantation (Evidence level D).

The treatment of tuberculosis in transplant patients is complex and requires a multidisciplinary approach. Frequent monitoring is required for early diagnosis of adverse events (including liver function tests) and for adjustment of immunosuppressive drug dosage. When potentially hepatotoxic drugs such as H, R or Z must be avoided, MDR-TB treatment regimens may be an alternative. However, although evidence is lacking, recommended treatment durations for these regimens are up to 2 years following *M. tuberculosis* culture conversion (Evidence level D).

Future research directions

Research directions should address both diagnosis and therapy of tuberculosis to improve tuberculosis management in transplant recipients.

Improvements in the diagnosis of active tuberculosis

Novel generations of automated nucleic acid amplification tests, e.g. the Xpert MTB/RIF test (Cepheid, Sunnyvale, CA, USA) could potentially improve the rapid diagnosis of tuberculosis in transplant patients. In immunocompetent patients the Xpert MTB/RIF test has a very high diagnostic accuracy, especially in patients with acid-fast bacilli sputum smear positive pulmonary tuberculosis [146, 147]. However, the diagnostic sensitivity for pulmonary tuberculosis is substantially reduced in immunocompromised patients with HIV-infection and acid-fast bacilli sputum smear negative pulmonary tuberculosis [148] and the value of this method for the rapid diagnosis of tuberculosis in transplant patients still needs to be established.

Improvements in the diagnosis of LTBI in transplant candidates and donors

Although the predictive value of IGRAs and the TST for progression to active disease have been studied in immunocompetent subjects [46, 69, 70] its value to predict active tuberculosis after transplantation, the impact of various immune suppression regimens and pathogen prevalence have not been assessed [149]. Current generations of immunodiagnostic tests are poor predictors of future tuberculosis risk because of relative low specificity for live bacilli in immunocompetent individuals, e.g. donors. In the immunocompromised host such as transplant recipients, the concern is less with test specificity, but the recognized deficiency in test sensitivity. Unlike TST, IGRAs may have potential to be used for LTBI screening of deceased donors to improve donor-derived risk assessment, but this has not been formally tested. New diagnostic approaches are needed that allow for a more targeted identification of patients at risk to develop tuberculosis. This may involve modifications of in vitro immunodiagnostic assays such as the use of novel stimulatory antigens [15, 150, 151], alternative biomarkers other than IFN- γ [152-158], variations in incubation time [159, 160], the readout system [9, 12, 13, 161, 162] or the clinical specimen instead of blood [163-165]. In addition, both for the detection of LTBI with a risk of reactivation and for suspected active tuberculosis, a novel approach based on a whole blood transcriptional signature could provide a biomarker system with high discriminative potential [166]. While the results of this research may lead to an improvement of the current immunodiagnostic assays in general, it may be of particular value in immunocompromised patients including transplant recipients.

Improvements on therapy

Future clinical trials should separately address therapies in transplant candidates and in post-transplant recipients who are receiving immunosuppressive therapy. Potential improvement could be obtained by new drug combinations including novel drugs such as the diarylquinoline TMC207 [167], or combinations with immunopotentiators [168, 169]. The availability of treatment regimens with equal or better effectiveness that require shorter treatment durations and have fewer interactions with immunosuppressive drugs compared to current antituberculosis therapies are desirable for both active disease and LTBI. In both situations, the optimal choice of a rifamycin is unclear, as it needs to be established which regimens without rifamycins are most effective. Recently, a three-month regimen including isoniazid and rifapentine once weekly has been shown to be equally effective to 9 months daily isoniazid therapy in the prevention of tuberculosis in healthy contacts [170]. This drug regimen needs to be evaluated in the transplant

setting. Special attention should be given to liver transplant recipients that may suffer from increased drug-mediated liver toxicity.

2.1 Summary

Research needs comprise the following areas:

- The use of rapid nucleic acid amplification tests in the diagnosis of active tuberculosis in immunocompromised patients
- The use of IGRAs in deceased donors and need for new diagnostic approaches for a more targeted identification of transplant candidates and recipients at risk to develop tuberculosis
- Treatment regimens that require shorter treatment durations and have fewer interactions with immunosuppressive drugs

Conclusions

Post-transplant tuberculosis is a rare complication after solid organ or hematopoietic stem cell transplantation. However, it has a high morbidity and mortality and its treatment is complicated by several interactions between immunosuppressive and anti-bacterial drugs. Although tuberculosis occurs more frequently in transplant recipients as compared to the general population, the management of post-transplant tuberculosis and widespread adherence to uniform guidelines is complicated by the fact that its overall prevalence varies considerably and largely depends on the local tuberculosis prevalence of a given geographic region. Hence, careful risk-adapted screening and preventive chemotherapy as well as constant vigilance for early signs or symptoms of disease including prompt treatment are currently the most effective modalities for prevention and management of tuberculosis post-transplant.

In this statement by the TBNET we have summarized the current knowledge of the risk of tuberculosis after solid organ and hematopoietic stem cell transplantation and we have provided detailed consensus recommendations for the most important clinical questions related to its management in adults and children. Targeted tuberculosis screening adapted to the local or individual risk of latent *M. tuberculosis* infection and preventive chemotherapy for all individuals with evidence for latent infection with *M. tuberculosis* should become the standard of care for all individuals undergoing transplantation. Following the guidelines of this document will lead to a significant reduction in the number of cases of active tuberculosis after transplantation.

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Figure legends

Figure 1. The four different scenarios for infection with *M. tuberculosis* in the transplant setting, (A) endogenous reactivation due to latent infection with *M. tuberculosis* (LTBI) in the candidate recipient, (B) donor-derived reactivation due to LTBI in a living or deceased donor, (C) *de novo* exposure and infection post-transplantation and (D) when a patient with active tuberculosis urgently requires a transplant (i.e. urgent liver transplantation); TB – tuberculosis.

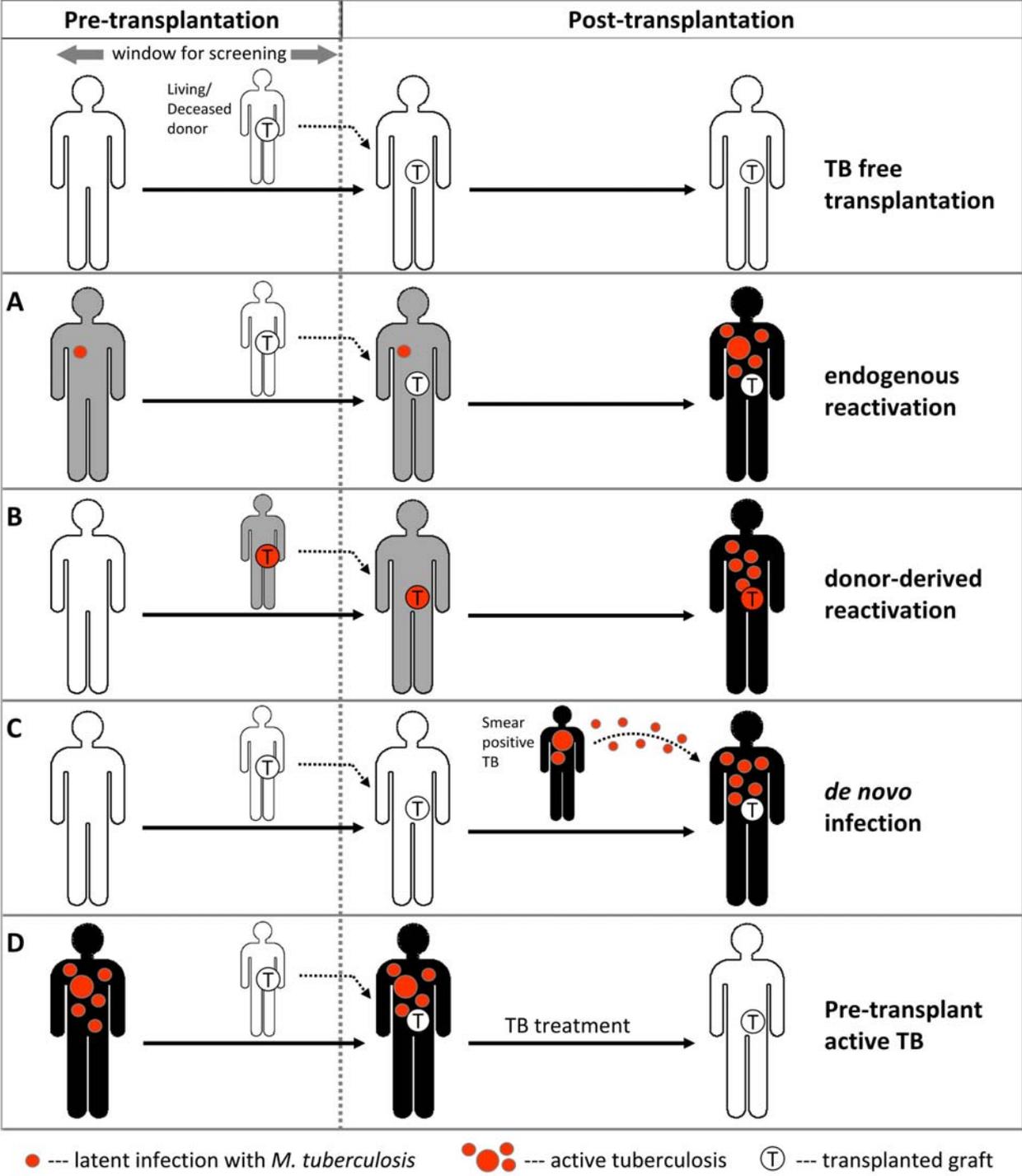
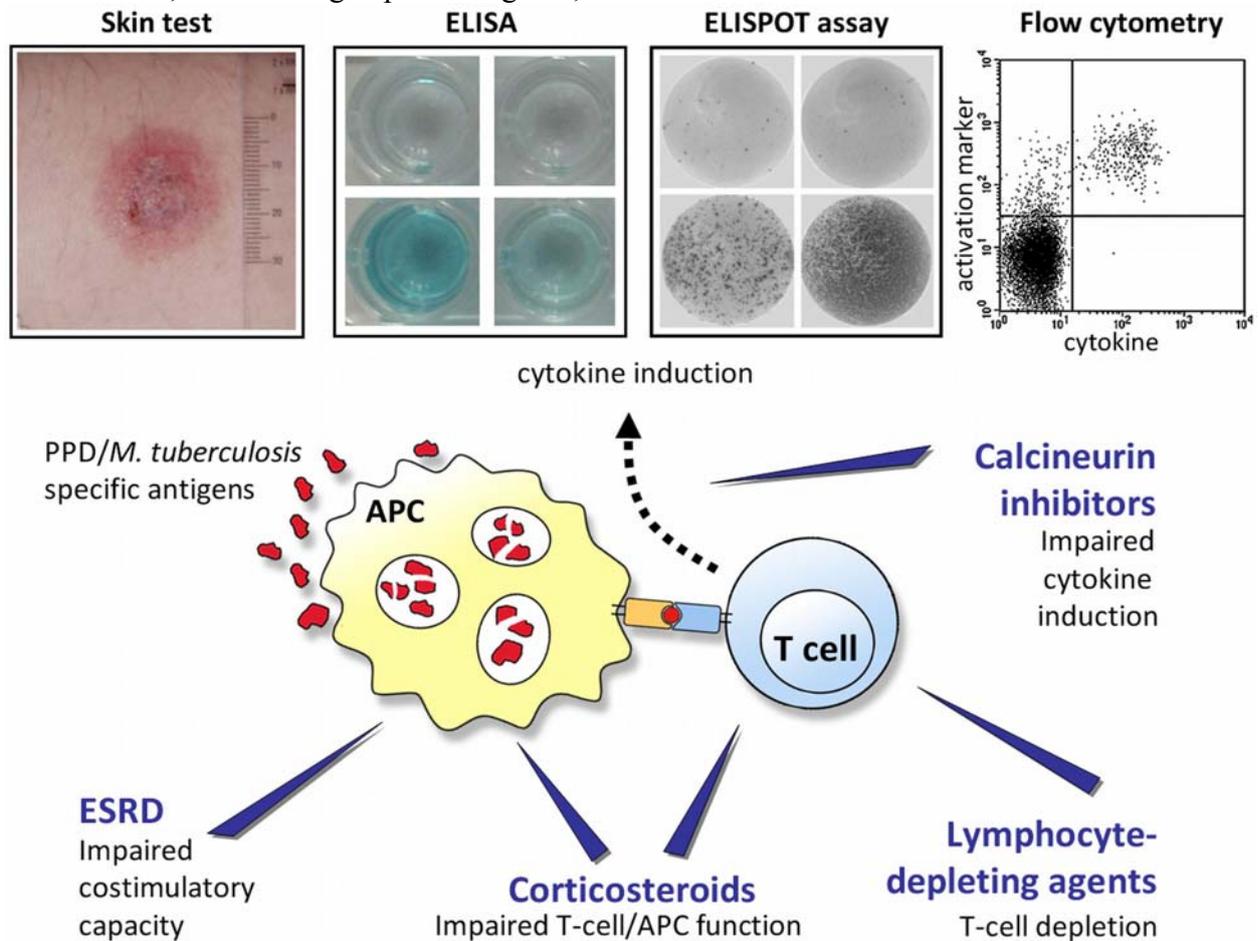


Figure 2. Immune-based T-cell assays for the diagnosis of a latent infection with *M. tuberculosis*. All tests rely on stimulation with either PPD or *M. tuberculosis* specific antigens that elicit a cytokine induction in specific T cells. Cytokines may be detected *in vivo* by skin-testing or *in vitro* by IFN- γ release assays (ELISPOT-assay, ELISA, or flow-cytometry). ESRD as well as currently used immunosuppressive drugs or lymphocyte-depleting agents applied in SOT or HSCT have various mechanisms to interfere with T-cell reactivity; ESRD – end stage renal disease; APC – antigen presenting cell; PPD – tuberculin.



Tables

Table 1: Description of levels of evidence.

Evidence category	Sources of Evidence	Definition
A	Randomized controlled trials (RCT), rich body of data.	Evidence is from endpoints of well-designed RCT that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	RCT, limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of RCT, or meta-analysis of RCT. In general, category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials, observational studies.	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgement.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

Table 2. Monitoring of LTBI treatment in SOT candidates/recipients [39, 171]

Timing of intervention	Physical exam	Laboratory testing
Prior to onset of LTBI treatment	Rule out active TB through careful history, physical exam, testing	Rule out active TB by thoracic imaging using CXR, consider CT thorax if high suspicion of LTBI Evaluate sputum AFB smear & culture and PCR if appropriate Evaluate urine AFB and genitourinary (GU) imaging if high suspicion of GU TB infection AST, ALT, Bilirubin
Monthly during therapy (may begin follow-up 2 weeks after initiation of therapy in high-risk liver patients)	Physical exam	AST, ALT, Bilirubin Drug levels of medications with high risk for drug interaction
With signs or symptoms of hepatotoxicity	Emergent evaluation with physical exam	AST, ALT, Bilirubin Drug levels of medications with high risk for drug interaction Strongly consider holding medication while awaiting results
Discontinue medication	Signs or symptoms of hepatotoxicity (severe anorexia, rash, nausea, vomiting, jaundice, dark urine, right upper quadrant pain) or new symptoms of peripheral neuropathy, more than 3 days of unexplained fever and weakness	AST or ALT > 3 times the upper limit of normal with symptoms
Discontinue medication	No signs or symptoms	AST or ALT > 5 times the upper limit of normal without symptoms

Table 3. Consequences of interactions between common tuberculosis chemoprophylaxis agents/first line antituberculous drugs and immunosuppressive agents most commonly used in SOT and HCST recipients

	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol	Streptomycin	Moxifloxacin/ levofloxacin
Corticosteroids	Combination may increase corticosteroid levels, risk of adverse effects (hepatic metabolism inhibited)	Combination may decrease corticosteroid levels and efficacy (hepatic metabolism induced)	None	None	None	Risk of tendon-related side effects may be enhanced
Cyclosporine A (CyA)	None	Use alternative or monitor levels of CyA. Combination may decrease CyA levels and efficacy (hepatic metabolism induced)	None	None	Avoid combination or monitor renal function. Combination may increase risk of nephrotoxicity (additive toxicity)	Combination may increase CyA levels (levofloxacin only)
Tacrolimus	None	Use alternative or monitor levels of tacrolimus. Combination may decrease tacrolimus levels and efficacy (hepatic metabolism induced)	None	None	Avoid combination or monitor renal function. Combination may increase risk of nephrotoxicity (additive toxicity)	None
Rapamycin/ sirolimus	None	Use alternative or monitor levels of rapamycin/sirolimus. Combination may decrease rapamycin/sirolimus levels and efficacy (hepatic metabolism induced)	None	None	None	None
Mycophenolate mofetil	None	Use alternative or monitor MMF levels. Combination may decrease MMF levels and efficacy (enterohepatic recirculation decrease)	None	None	None	Combination may decrease MMF levels

Source: Lexi-Comp Online™ Interaction Monograph

Table 4: Summary of the main recommendations made in guidelines and statements on screening and treatment of latent TB infection (LTBI) and active tuberculosis in transplant recipients.

National Guidelines/Year	Screening Recommendations	Prophylaxis Recommendations	Active TB
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Transplant Specificity	Who should be screened?	History of previous TB or exposure	CXR	TST	IGRA	Who should get prophylaxis?	LTBI Treatment	Interactions of Drugs	Treatment
Canada 2005 [138] Renal General Screening	All recipients before Tx	Exposure Previous TB not addressed	Yes	All recipients One step	Not addressed	TST + (not induced by BCG); CXR changes with no history of treatment	Not addressed Complete before Tx	Not addressed	Complete before Tx Drugs + doses not specified
Europe 2002 [139] Renal General Screening	All donors & recipients	Previous TB inadequately treated; Exposure	Yes Donor – residual lesions contraindicate lung Tx	All recipients One step	Not addressed	TST+ (ignore previous BCG): ≥5mm post Tx ≥10mm in dialysis patients; CXR changes with no history of treatment; Close contact	9H 300mg daily or 9H15mg/kg 2x/week; Can shorten to 6H; or 4R or 2RZ – monitor for hepatotoxicity; Stop treatment only if liver enzymes 3-5x normal in asymptomatic	Monitor calcineurin inhibitors & rapamycin; Rb may replace R	Standard No E if local H resistance <4%
Spain 2009 [30] SOT Specific TB-related guideline	All donors & recipients; Deceased donors – well founded suspicion of active TB contraindicates donation; Residual pulmonary lesions contraindicate lung Tx; For lung Tx – check donated lung	Previous TB inadequately treated; Exposure	Yes	All recipients 2 step at 7-10 days; All donors	Mentioned No specific recommendation	TST+ ≥5mm Contact CXR changes with no history of treatment	9H + vit B6 4RH + B6 Delay in liver recipients until after Tx	Monitor levels of calcineurin inhibitors; increase dose 3-5 fold if use R	Localised non-severe TB: H+E (or Z) 12-18 months – avoid rifamycins; Severe disseminated – add R or Rb; continuation phase min 9HR or HRb
UK 2010 [140] Renal Specific TB-related guideline	All recipients before Tx	Details length & type previous TB treatment; Exposure	Yes	Possibly with IGRA One step	All recipients	+ve IGRA (TST may be -ve). -Generally all Africans, Asians & others born outside UK. -CXR old TB no previous treatment -Contacts -Risk assess for prophylaxis -Ethnicity, place of birth versus hepatitis risk with	6H + vit B6 or 3RH + vit B6 or 4-6R Before Tx	Drug levels MMF, tacrolimus, ciclosporin & adjust dose appropriately; double dose corticosteroids	2RHZE or moxi then 4RH except in CNS disease – treat for 1 year. Appendix of 2 nd line therapy; All cases to be managed by TB specialist.

National Guidelines/Year Transplant Specificity	Screening Recommendations					Prophylaxis Recommendations		Active TB	
	Who should be screened?	History of previous TB or exposure	CXR	TST	IGRA	Who should get prophylaxis?	LTBI Treatment	Interactions of Drugs	Treatment
						prophylaxis			
USA 2009 [4] SOT Specific TB-related guideline	All donors & recipients; active TB contraindicates donation; Residual lung lesions contraindicate lung Tx; Deceased donors – history previous TB & treatment	Details length & type previous TB treatment; History of previous treatment for LTBI; Exposure	Yes	All recipients Living donors – interpret as per CDC guidelines; If reliable history treated LTBI – no TST; Two step at 2 weeks	For those not highly immuno-suppressed	TST+ TST- if CXR changes old TB inadequately treated, organ from TST+ donor or close prolonged contact	adults: 9H 300mg daily; children: 9H 10-15mg/kg (max 300mg) daily; or 9H 2x/week – adults: 15mg/kg (max 900mg/dose), children: 20-25 mg/kg (max 900mg/dose) 2x/week; 6H (daily dose) 4R – avoid after Tx; Timing – balance risks & benefits; Check for hepatotoxicity especially liver Tx	Monitor levels of immuno-suppressive drugs; increase dose 2-5 fold if use R	Standard Discontinue E if H sensitive; Can replace R with Rb
USA 2009 [141] Renal General Tx guideline	All recipients	History previous TB & treatment	Yes	All recipients Ignore previous BCG	Can use but data suggests limited detection of LTBI in CKD stage 5	CXR suggestive of past TB inadequately treated; Exposure or reasonable suspicion even if –ve TST or IGRA; Donor with +ve history or TST	9H	Not addressed	Standard Alternative 2HEZ+ fluoroquinolone then 10-12H+ fluoroquinolone

National Guidelines/Year Transplant Specificity	Screening Recommendations					Prophylaxis Recommendations		Active TB	
	Who should be screened?	History of previous TB or exposure	CXR	TST	IGRA	Who should get prophylaxis?	LTBI Treatment	Interactions of Drugs	Treatment
Global 2009 [126] SCT General guideline	All recipients; Screening donors with TST unnecessary	All patients	Yes	Not routine Include if risks; Ignore previous BCG	More useful in iimmuno-suppression; Negative does not exclude LTBI	Exposure to smear +ve laryngeal or pulmonary TB, regardless of TST or IGRA status; TST+ or IGRA+ without previous treatment & no evidence of active TB	Minimum 9H + vit B6 & until immuno-suppressive drug doses reduced to prednisolone <0.5mg.kg (children) or <20mg/kg (adults); Or 4R 2RZ not recommended.	Drug-drug interactions – avoid R	Not addressed Donors with active TB – treat before donation; Marrow from untreated TST+ donor without active TB poses no known risk.
Saudi 2010 [142] General LTBI screening & treatment only	All recipients	Not addressed	Not stated	All recipients	For: - BCG vaccinated; - To confirm +ve TST; - If –ve TST thought to be false	TST+	9H or 4R Before Tx	Not addressed	Not addressed
Canada 2009 [143] Cardiac Specific cardiac Tx guidelines	All recipients before Tx	Not addressed “risk factor assessment”	Not addressed	All recipients	Not addressed	TST+ or risk factors	H no time given TB physician supervision	Not addressed	Not addressed
Europe 2009 [144] Kidney General urology guidelines	All recipients	History of previous TB	Yes	Not addressed	Not addressed	Not addressed	“Adequate preventative measures, eg H”	Not addressed	Not addressed

TST, tuberculin skin test; IGRA, IFN- γ release assay; CXR, chest radiograph; Tx, transplant; BCG, Bacille Calmette Guérin vaccination; H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; moxi, moxifloxacin; Rb, rifabutin; the numbers before these drugs denote the number of months eg 9H = 9 months of isoniazid; vit B6, vitamin B6 (also known as pyridoxine); CKD, chronic kidney disease.