Tuberculosis Recommendations for Solid Organ Transplant Recipients and Donors

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EPIDEMIOLOGY

Epidemiology in Latin America

In the last 2 decades, the burden of tuberculosis (TB) has been considerably reduced in Latin America (LA) countries. The estimated absolute number of prevalent cases in the region declined from approximately 600 000 to 342 000 between years 1990 and 2014, with a parallel reduction in the number of TB-associated deaths from 43 000 to 22 000.[1] Nevertheless, TB remains a relevant public health problem in this region. Per World Health Organization estimates for 2014,[2] Brazil remains in the group of 22 countries with the highest TB burden in the world, with 110 000 prevalent cases and 7700 TB deaths. Besides, most countries in the region are still moderately to highly endemic, with incidence remaining over 100 cases per 100 000 in Haiti, Bolivia, and Peru (Figure 1). It is important to be aware that national average incidence estimates may mask wide variations within a country. In Brazil, for example, the estimated average national incidence in 2015, based on notification data, was 31 cases per 100 000, whereas among its largest cities these estimates ranged from as low as 11 cases per 100 000, and in the capital Brasilia, to figures between 60 and 100 cases per 100 000 in Rio de Janeiro, Porto Alegre, Manaus, and Recife. Marked variation may sometimes occur even within the same city. In Rio de Janeiro, for instance, the incidence in some underprivileged neighborhoods remains around 300 cases per 100 000.

Emergence of multidrug-resistant (MDR) TB, which is defined by the isolation of a causative strain of *Mycobacterium tuberculosis* resistant to rifampicin and isoniazid (INH), is a global challenge. Although the estimated proportion of MDR infection among new TB cases remains below 3% in most countries of the region, higher prevalence (between 3.0% and 6.0%) has been found in Ecuador, Guatemala, and Peru. Recent reports from the latter country provide evidence of ongoing community transmission of MDR infection with significant impact on mortality.[3] Moreover, the prevalence of MDR infection is expectedly higher among patients who were previously treated for TB. In those 3 countries, this prevalence has been estimated to range from 20% to 26%.

TB AFTER SOLID-ORGAN TRANSPLANTATION

The incidence rate of TB markedly increases after solid organ transplantation (SOT),[4,5] the risk being highest among lung recipients.[4] The proportion of patients affected by active TB infection also varies widely among transplant centers in correspondence with the local prevalence of the disease. In studies carried out in LA SOT centers in the last decade, TB was diagnosed in 0.9% to 5.9% of the recipients.[5-11]

Reactivation of foci of latent TB infection (LTBI) is probably the main cause of posttransplant TB. Primary infection acquired in the community, and less frequently in the nosocomial environment, may also account for a considerable proportion of the cases, especially among patients living in endemic areas. A minor proportion of primary infections result from donor-recipient transmission.[12] Most of these cases were documented in patients who received a graft from a deceased donor with active TB infection, a situation that has been associated with a risk of transmission of approximately 30%.[13,14] Although it is probable that donors with untreated LTBI may also be a source of TB transmission, the influence of donor LTBI on the risk of posttransplant TB is undetermined yet.[6]

International Travel and Posttransplant TB

Immigration, international travel to endemic countries, and transplant tourism may influence the risk of TB after SOT.[15] Transplant candidates originating from endemic areas have a higher prevalence of LTBI and are, hence, at

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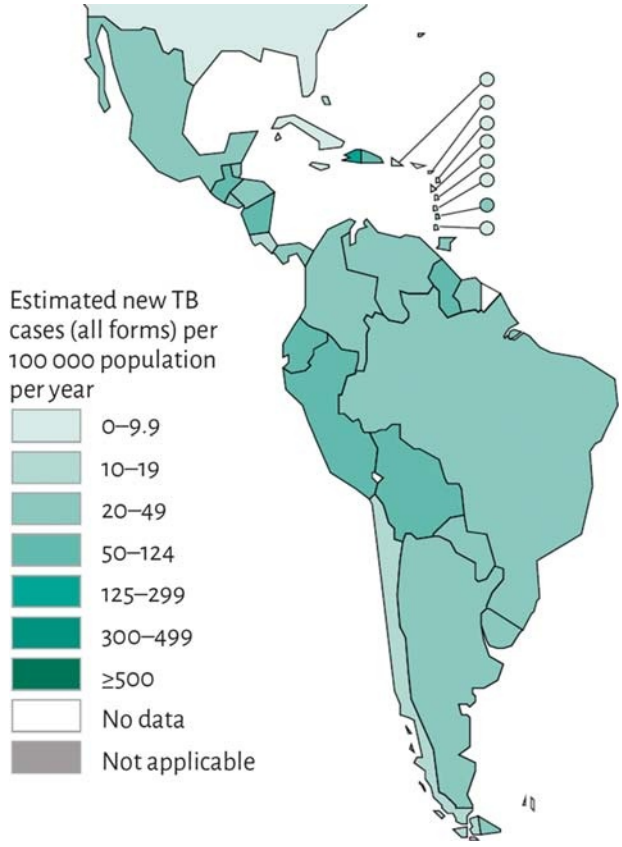

FIGURE 1. Estimated Incidence of TB in LA Countries in 2014. Source: World Health Organization, 2015.[2]

an increased risk of developing active TB infection after SOT. Recently, it has been reported that children born in the United States from parents that emigrated from endemic countries are also at an increased risk of developing TB,[16] a finding with clear implications for risk assessment of pediatric SOT candidates. Immigration may also impact the risk of donor transmission. In Spain, the prevalence of active TB infection was markedly increased in deceased donors who originated from a high-incidence country in eastern Europe.[14] In a few cases of donor-transmitted TB, the *M. tuberculosis* isolate causing infection in the recipient matched a genotype prevalent in the LA country of origin of the deceased donor.[17,18] The possibility of donor transmission of TB has also been associated with transplant tourism.[19]

Transplant recipients from low-incidence countries may be exposed to primary infection while traveling to an endemic area, but the actual impact of such exposure in this specific population has not been assessed. Among immunocompetent travelers returning from endemic countries, the estimated risk of acquisition of TB infection has generally ranged from 0.4% to 2.0%.[20-22] Higher rates (1.8% to 4.2%) were reported among travelers who were involved in Healthcare or academic medical exchange programs.[20,23,24] Although such figures are lower than those reported for other diseases, such as dengue fever and malaria, they are not negligible,[25] and it is possible that travel-related acquisition may account for a substantial proportion of new infections among people living in low-incidence countries.[20] Time spent in the endemic area influences the risk of TB infection. A cumulative history longer than 3 months of travel to high-incidence areas is associated with a significantly higher risk.[20] Humanitarian work with high-risk populations, such as prisoners and homeless people, may also be a significant risk factor. The impact of other possible types of exposure is not well defined. Although cases of transmission probably related to exposure in long-distance flights[26] have been reported, the actual risk related to such exposures is yet undetermined and, given the available evidence appears to be low. There is also evidence that transmission may occur in ground transportation.[27] In a recent report, the use of public transportation in a high-incidence area in Peru was an independent risk factor for active TB infection.[28] Visiting friends and relatives is a known risk factor for acute diseases, such as traveler's diarrhea, but the impact, if any, of such activity on the risk of acquiring TB has not been established.[29]

DIAGNOSIS

Diagnosis of LTBI

There is no diagnostic reference standard for LTBI. The tuberculin skin test (TST) remains the best studied test and, therefore, most current guidelines still recommend its use for the screening of LTBI in solid organ candidates/recipients and living donors.[12,30-32] IFN-γ release assays (IGRAs) have emerged as new diagnostic tools in the last decade. They offer some advantages as compared with TST: avoid interpreting bias, reduce false-positive results related to previous exposure to nontuberculous mycobacteria or BCG vaccination, and are probably more sensitive in candidates with chronic renal failure and advanced cirrhosis, because they show a higher yield and a better correlation with clinical risk factors for LTBI in these patients.[30,33-36] However, despite their better yield, the negative predictive value of IGRAs is not optimal to rule out infection in patients considered to be at high risk for LTBI,[37] which includes those who were born to or lived in endemic countries, household contacts of a case of active TB infection, and those who work or live in high-risk settings, such as correctional facilities and homeless shelters. Other limitations of these assays include their higher cost and the frequent occurrence of conversions and reversions of test results when serial screening is performed, which may complicate the interpretation of their results among SOT candidates.[38,39] As a probable result of the limitations of TST and IGRAs, there is marked variation across transplant centers regarding the approach for screening LTBI in candidates. Per a recent European survey, TST alone was used in 48% of the participating centers, IGRA alone in 30%, TST and IGRA simultaneously in 16% and TST followed by IGRA in 6%.[40] Some specialists suggest adapting the diagnostic approach per the estimated risk of being infected, because predictive values of both tests are influenced by the estimated prevalence of LTBI. Thus, in low-risk patients, IGRAs could be considered as the sole approach, because the use of a more specific test might reduce the rate of false-positive results and, consequently, the number of patients who will unnecessarily be exposed to LTBI therapy. On the other hand, in high-risk patients, both tests could be performed, and any positive result should be considered evidence of LTBI, to maximize the sensitivity of screening.[12,30]

Diagnosis of Active TB Infection

The diagnosis of active TB infection relies on the detection of *M. tuberculosis* bacilli by direct observation, by culture,

and nucleic acid testing. Neither TST nor IGRAs are recommended for diagnosing active infection.[41,42]

Probably the most challenging situation lies on the clinical suspicion of active infection. SOT recipients may present unusual manifestations, with a greater proportion of extrapulmonary involvement. TB should be considered in the differential diagnosis of patients presenting with fever of unknown origin. Invasive diagnostic procedures are more frequently required in this population, resulting in a delay of the proper diagnosis and higher mortality.[43] In this regard, the availability of a rapid molecular test, such as the Xpert MTB/RIF assay, may have a major impact in the management of these patients. This test is highly specific and has an estimated sensitivity in smear positive and smear negative respiratory samples of 98% and 67%, respectively.[44] A similar performance has been observed when testing nonrespiratory samples, such as tissue biopsies and cerebrospinal fluid, indicating that Xpert MTB/RIF assay is a useful rule-in diagnostic test for extrapulmonary TB.[45] It also allows the simultaneous detection of rifampicin resistance, which is highly predictive of MDR-TB. Thus, it may have a critical role for providing the timely start of MDR-TB treatment while results of conventional culture and drug susceptibility tests are pending.[44] One limitation of this assay is that false-positive results have been observed among patients who had been successfully treated for TB.[46] It is also noteworthy that it cannot fully replace the execution of conventional drug susceptibility tests.

PREVENTION

Risk Assessment of the Transplant Candidate

A history of clinical or radiological TB and the treatment received should be assessed in all recipients. If there is no history of past TB or treatment for LTBI, candidates should undergo evaluation for LTBI with either TST or IGRA. If TST is selected as the screening test, an induration of 5 mm or greater at 48 to 72 hours should be considered a positive reaction. In addition, a second TST should be performed 7 to 10 days after the first TST to evaluate a boosted-related skin conversion. As explained in section 3.1, the screening strategy may be adapted per the patient's characteristics. Candidates who have low risk for LTBI should preferably be tested solely with IGRA. In high-risk candidates (ie, patients originated from endemic countries, household contacts of active TB infection, and those who work or live in correctional facilities or homeless shelters), both tests could be performed and any positive reaction considered an evidence of LTBI. Whenever this dual-test approach is used, IGRA should be performed before or concurrently with TST placement to avoid TST-mediated boosting of subsequent IGRA responses.[47]

Active TB infection must be excluded in all candidates with a positive result in any of these tests before LTBI treatment is started. This evaluation includes checking the presence of symptoms and signs suggestive of TB, performing a chest radiograph and, in cases with extrapulmonary manifestations, imaging of other body sites. If any evidence of active infection is found in this workup, appropriate clinical specimens should be collected for microbiological confirmation of the diagnosis. Once active TB infection is diagnosed, transplantation should be postponed until the disease is well controlled with adequate treatment and smears are negative. Nevertheless, active infection may not be considered an absolute contraindication to transplantation for candidates who urgently need it.[48]

Risk Assessment of Deceased and Living Donors

Living donors should undergo the same evaluation as candidates, with the exception that the cutoff for TST should be 10 mm or greater.

The evaluation of the deceased donor for TB relies on:

- Medical history. The history of untreated or insufficiently treated TB should be investigated, as well as previous reactive IGRA or TST.
- Endemic exposures. Travel to or residence in endemic areas, exposure to active TB infection in the household or workplace within the last 2 years, homeless or refugee status, incarceration and alcoholism may be associated with LTBI. In this regard, it is important to notice that, given the declining trend of TB incidence in LA, current estimates of TB prevalence may not accurately reflect the actual risk of past exposure in these countries.
- Radiographic findings, such as apical fibronodular lesions, calcified solitary nodules, calcified lymph nodes, or pleural thickening.

Time does not allow for a TST and IGRAs have not been validated in deceased donors. Active TB infection should be ruled out in donors at increased risk by obtaining samples, for example, sputum or bronchoalveolar lavage, to test for the presence of *M. tuberculosis*. Because the results of microbiological investigation will more often be available after procurement, it must be ensured that all data will be forwarded to transplant teams as soon as possible to enable appropriate actions.

Organs from donors with known active TB infection should be discarded. If the microbiologic diagnosis of TB in the donor becomes available only after organ transplantation, therapy for active infection should be immediately started in the recipient per local guidelines. Drug susceptibility tests should be performed on any *M. tuberculosis* specimen isolated from the donor, since the detection of drug resistance may be of critical importance for guiding therapy in the recipients. Organs from donors with a history of TB successfully treated for at least 6 months can be transplanted. Lungs with residual tuberculous lesions should not be used for transplantation. A history of untreated LTBI without evidence of active infection is not a contraindication to donation, but administration of preventive therapy to all recipients should be considered, especially for lung recipients. The risk of transmission is estimated to be low if therapy for LTBI was completed before organ donation and, therefore, transplant recipients from such donors can be clinically monitored without receiving LTBI therapy.

TREATMENT

Treatment of LTBI in Transplant Candidates and Recipients

Criteria to Start Treatment

Therapy for LTBI is an effective strategy for the prevention of active TB infection in transplant recipients.[49,50] LTBI therapy is recommended for transplant candidates with positive TST or IGRA who have not been previously treated.[11,29,30] Those with high-risk pretransplant TB exposure should be

considered for therapy even if the TST or IGRA is not positive, as should those with history of active TB infection that was inadequately treated. Chest imaging suggestive of previous untreated TB should prompt consideration for therapy, especially in areas where endemic mycoses are uncommon.[12,31,32] Therapy is recommended for transplant recipients whose donor has a history of untreated or incompletely treated LTBI or TB, or if the recipient is exposed to TB after transplantation.[12,31,32] In considering treatment for LTBI, it is imperative to first rule out active TB infection (see Risk Assessment of the Transplant Candidate).

Therapeutic Regimens

For treatment of LTBI, the preferred regimen is oral INH 300 mg/d for 9 months, along with oral pyridoxine 25 to 50 mg daily.[12,31,32] Nine months of therapy is preferred over 6 months because of better protection. Transplant candidates and recipients on INH should be monitored for hepatotoxicity with at least serum alanine aminotransferase checked every 2 weeks for 6 weeks, then monthly thereafter. Alternative regimens containing rifamycins can be considered pretransplant, but should be avoided posttransplant because of immunosuppressive drug interactions. These regimens include RIF 600 mg daily for 4 months or INH and rifapentine weekly for 12 weeks.[51,52] Fluoroquinolones (± ethambutol) have been suggested for LTBI therapy. However, a recent randomized study of pretransplant levofloxacin versus posttransplant INH in liver transplant recipients was stopped early because of excessive adverse events in the levofloxacin arm.[53]

Timing of Treatment

The timing of LTBI treatment requires balancing risks and benefits for each patient. When possible, treatment for LTBI should be started before transplant, and can often be completed while the patient is on the waitlist. If urgent transplant is indicated, the treatment can be held perioperatively and resumed when medically possible until completion of the originally planned course, with the caveat that rifamycins are usually avoided after transplant. It can be particularly challenging to treat liver transplant candidates before transplant. Although in several small studies, INH has been shown to be safe in those with compensated cirrhosis awaiting transplant with careful monitoring,[54-56] some experts do prefer waiting until after transplant to begin INH once liver function has been normalized.

Recommendations for Transplanted Patients Who Travel to Endemic Areas

If recently transplanted patients are planning to move to a highly endemic area (ie, those with prevalence ≥100/100 000), INH preventive therapy should be considered during the first posttransplant year, especially for those planning to take part in medical or humanitarian care, given the higher risk of primary TB acquisition. There is no indication for BCG vaccine before travel, and it is contraindicated in transplant recipients.[57] Transplant recipients who are traveling to TB endemic areas to provide medical or humanitarian care should follow standard precautions to prevent nosocomial acquisition of infection. Those with possible TB exposure should be evaluated on return, and anyone with symptoms of infection should seek medical evaluation immediately.

Treatment of Active TB Infection

Treatment should follow local guidelines for the general population. The number of drugs used in the intensive phase regimen should be defined per the prevalence of drug resistance in each population. Nevertheless, in most cases, a 4-drug regimen is recommended. INH and rifampicin are the most powerful first-line drugs against TB. In the context of SOT, many factors should be carefully considered, such as the risk of hepatotoxicity related to the antituberculous treatment and drug interactions of rifampicin.

The optimal length of treatment of TB in transplant recipients is not defined. Many specialists recommend that treatment duration should be at least 9 months, based on the results of a few studies that have suggested an association between shorter regimens and greater recurrence and mortality.[58,59]

Monitoring of Adverse Events Related to Therapy

Due to the increased risk of adverse events and potential drug interactions, close monitoring is highly recommended, mainly during the first 2 months of treatment when it should be performed biweekly. Concomitant use of INH, rifampicin, and pyrazinamide is associated with an increased risk of hepatotoxicity, especially in liver recipients.[60] Low-grade elevation of aminotransferases can be observed during the first 2 months of treatment, but a 3-fold increase accompanied by any symptom or a 5-fold increase regardless of symptomatology requires discontinuation.

Drug Interactions

Rifamycins have an induction effect on different drug-metabolizing enzyme systems, most notably the cytochrome P450 (CYP) 3A4, which lead to a reduction in the blood levels of most immunosuppressive drugs used after SOT (tacrolimus, cyclosporine, sirolimus, everolimus, and even corticosteroids). A lower blood level of these drugs is associated with higher risk of graft rejection. Therefore, close monitoring and continuous dose adjustment are highly recommended.[61,62] Rifampin has the most potent enzyme induction effect. Two- to 5-fold increments in the daily dose of cyclosporine, tacrolimus, and mammalian target of rapamycin inhibitors are generally necessary to maintain trough levels of the drug in the therapeutic range. Although enzyme induction start within hours after the first dose of rifampin, maximum effect is reached in about 1 to 2 weeks and slowly declines over 2 weeks after stopping its use.[63] Thus, therapeutic drug monitoring of immunosuppressive drugs should be more frequent in the beginning of rifampin treatment and in the first 2 weeks after its interruption. Despite these drug interactions, rifampicin is not contraindicated in SOT recipients. Regimens containing this drug have a stronger sterilizing activity. Besides, provided that adequate monitoring is implemented, rejection and mortality rates are not influenced by treatment with rifampicin-based regimens.[64] Rifabutin, a rifamycin with weaker and more limited spectrum of enzyme induction, is an alternative for rifampin. It has been demonstrated to be as effective as rifampin for the treatment of TB in trials conducted in nontransplant patients. Its weaker effect on CYP3A4 makes it easier to maintain therapeutic blood levels of calcineurin and mammalian target of rapamycin inhibitors during TB treatment.[65] Nonetheless, the same recommendation for

close therapeutic drug monitorings of these immunosuppressive drugs apply when rifabutin is used.[66]

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