Prevention and Management of Tuberculosis in Solid Organ Transplant Recipients

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KEYWORDS

• Solid organ transplantation • Tuberculosis • Latent tuberculosis infection
• Opportunistic infections • Donor derived infections

KEY POINTS

- Solid organ transplant recipients are at increased risk for tuberculosis reactivation owing to immunosuppression. Some candidates have risk factors for tuberculosis reactivation even pretransplantation.
- Screening for latent tuberculosis infection involves a detailed history, a tuberculin skin test or tuberculosis interferon-gamma release assay, and a chest radiograph.
- Isoniazid for 9 months is the preferred therapy for patients with rifamycin drug interactions. Rifamycins may be preferred for patients at risk of hepatotoxicity from isoniazid.
- Tuberculosis occurs months or years after transplantation. Patients can present with typical features of tuberculosis or with unusual or nonspecific manifestations.
- Tuberculosis treatment in solid organ transplant recipients may be complicated by drug interactions and adverse drug reactions and requires close monitoring.

INTRODUCTION

History and Importance

Because immune suppression to prevent allograft rejection is a cornerstone of solid organ transplantation (SOT), infections occur with relative frequency and often with increased severity. Given the ubiquity of tuberculosis (TB), it is not surprising that this infection has been reported in patients undergoing SOT since the 1960s and 1970s.[1,2]

SOT candidates and recipients contend with unique challenges in TB diagnosis and treatment. They are at high risk for TB reactivation after transplantation, and many enter transplantation with conditions such as end-stage renal disease, diabetes mellitus, or iatrogenic immunosuppression predisposing them to TB reactivation. The

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signs or symptoms of their underlying end-stage organ failure may overlap with the protean manifestations of TB, including weight loss, cough, and malaise. Given their comorbid conditions and medications, they may be at increased risk of adverse drug reactions (ADRs) from antituberculous therapy (ATT), including neuropathy, hepatotoxicity, and gout, and may contend with multiple drug interactions. Finally, posttransplant TB has been associated with allograft loss and increased mortality.[3,4]

Pathogenesis

The pathways through which SOT recipients may develop active TB are several, and can differ from those relevant to non-SOT recipients. SOT candidates may present with latent TB infection (LTBI; **Fig. 1**A) or active TB (**Fig. 1**D). After SOT, those with LTBI may or may not reactivate; those with active TB would be expected to have disease progression. Although difficult to prove, most SOT recipients who develop active TB presumably do so as a reactivation in the context of prior LTBI, especially in countries with low rates of TB endemicity where there is less likelihood of exposure after SOT. Previously uninfected SOT recipients may develop de novo infection through exposure to someone with infectious (typically pulmonary or laryngeal) TB (**Fig. 1**C), but, uniquely, may also contract TB as a donor-derived infection (**Fig. 1**B). TB bacilli may exist in transplanted organs in a spectrum of metabolic activity from quiescent infection in an otherwise healthy donor to florid infection that may have gone unrecognized.[5] Some of these donor-derived infections may be controlled by the recipient's immune system, but many of these recipients will likely develop clinically apparent TB disease.

The most obvious mechanism by which SOT recipients are at increased risk for TB reactivation involves intensive iatrogenic suppression of the immune system. In nearly all cases, SOT recipients are treated with combinations of corticosteroids, antimetabolites, calcineurin inhibitors (CNIs), and mammalian target of rapamycin inhibitors. Initial induction immunosuppression and treatment for rejection often involve administration of antibodies resulting in T-lymphocyte depletion or signaling impairment, including alemtuzumab, antithymocyte globulin, and basiliximab. Additionally, corticosteroids, CNIs, and mechanistic target of rapamycin inhibitors predispose to posttransplant diabetes mellitus, a known risk factor for TB reactivation. Patients can also develop other risk factors for TB reactivation posttransplant, such as end-stage renal disease owing to CNIs or significant weight loss.

Epidemiology

SOT has long been recognized as a strong risk factor for TB reactivation and testing and treating for LTBI has been recommended in these patients in guidelines dating back several decades.[6,7] Several recent studies have established that SOT recipients have a substantially increased risk of TB, with an incidence of at least 4 times that of the general population, and in some studies nearly 30 times that of the general population.[8–11] TB incidence is increased at least 2-fold, even when SOT recipients are matched closely with patients with end-organ disease who did do not ultimately undergo transplantation.[12] Some of these studies included patients who were screened and treated for LTBI, suggesting the incidence comparisons discussed may underestimate the natural history of the disease. Although high-quality data on the incidence of TB among SOT recipients in the United States are not available, the TB incidence among diverse SOT recipients in Spain, a country with a similar although slightly higher TB incidence, was found to be markedly elevated at more than 400 cases per 100,000 person-years.[8,13] Data are insufficient to address whether recipients of some organs are at greater risk than others, with the exception of lung transplantation, which confers a particularly high risk of TB.[8]