Tuberculosis (TB) reactivation after solid-organ transplant carries significant morbidity and confers high mortality (up to 30%) [1]. Incidences among transplant recipients vary—the variation depends primarily on geographic location, and incidences range from <1% in Europe and North America to 2%–15% in Africa, the Middle East, and Asia—but are generally greater than those in the general population. Rates also vary depending on the type of organ transplant performed as well as on local screening practices and immunosuppression protocols. In this issue of Clinical Infectious Diseases, Torre-Cisneros et al. [2] review a large Spanish database of information on organ transplant recipients (the RESITRA [Spanish Network of Infection in Transplantation] cohort) and describe an incidence of posttransplant TB of 512 cases per 10^5 patients per year in their cohort. This was significantly greater than the incidence for the general population of the country, among whom the incidence was 18.9 cases per 10^5 inhabitants per year, resulting in 26.6-fold greater relative risk.

Perhaps the most comprehensive analysis conducted to date of the epidemiology of TB after transplant was published in 1998 by Singh and Paterson [1], who reviewed the published literature on TB and transplantation. Their analysis found that approximately two-thirds of TB cases occurred during the first year after transplant. Risk factors for early posttransplant TB included nonrenal transplant, allograft rejection occurring <6 months before the onset of TB, and primary immunosuppression with muromonab-CD3 or other T cell–depleting agents. The majority of reactivation cases were pulmonary, although at least one-third of cases were disseminated. It is clear from published series that the diagnosis of active TB is often delayed because of atypical presentations and should be suspected in transplant recipients presenting with fever of unknown origin, pulmonary mass lesions, or meningoencephalitis. A broad range of opportunistic infections are included in the differential diagnosis of such presentations.

In the RESITRA cohort, the greatest incidence of posttransplant TB was observed among lung transplant recipients. Lung transplant recipients are at greater risk for pulmonary infection in general, because they are more immunosuppressed and the allograft is in direct contact with the environment. It is difficult to discern from Torre-Cisneros et al.’s study whether the TB in the lung transplant recipients represented reactivation of latent TB, new infection after transplant, or donor-derived infection. Donor-derived TB is thought to represent ~4% of TB cases described in the literature [1]. A determination of donor transmission can be made by restriction fragment–length polymorphism analysis of donor and recipient TB strains, as was done for the recently documented multiorgan transmission of TB in the United States [3]. However, this is not generally possible in most cases of potential transmission, because mycobacterial infection is present only in a latent form in donor organs. Ultimately, the incidence of donor-derived TB is likely underestimated, because donors (at least deceased donors) do not undergo formal screening for latent infection. Although information on history of travel and prior exposure to TB is sought and chest radiography and lower respiratory tract cultures for acid-fast bacilli are commonly performed, it is generally not possible to screen cadaveric donors by a tuberculin purified protein derivative (PPD) skin test. The practical issues of screening deceased donors may be overcome by interferon-γ release assays, such as the QuantiFERON-TB Gold assay (Cellestis). No studies are published evaluating this assay in organ donors, and this would be a good area for further investigation. Results would not necessarily be available before organ procurement and transplant and would likely not change the decision to accept the organ, but they could guide appropriate prophylaxis for the recipient after transplant.

Screening of living donors (as is the case...
for renal, liver, or lobar lung donation) is recommended [4]. If latent TB is detected in a living donor, the options are to provide prophylaxis either to the donor before transplant or to the recipient after transplant. This decision often depends on a number of concurrent factors, including the urgency of the transplant.

Pretransplant screening for latent TB in potential organ recipients may be problematic. Pretransplant screening by means of a PPD test and a chest radiograph is widely recommended [4]. In Torre-Cisneros et al.’s study, among patients with TB, only 3 of 6 had a positive PPD test result. Although the numbers are small, this finding is consistent with the literature, which suggests that many cases of reactivation occur in those with a negative PPD test result. This finding also suggests that the sensitivity and specificity of the PPD test in this population are poor, which is also consistent with published findings [5]. Many patients with chronic end-stage organ failure may experience anergy (up to 70%) [1, 5]. Use of anergy testing is no longer recommended by guidelines for the general population or by transplant guidelines [4, 6]. Interferon-γ release assays have been evaluated in patients awaiting liver transplant [7]. Although there is no criterion standard for the diagnosis of latent TB, the Quantiferon-TB Gold assay had sensitivity and specificity similar to those of the PPD test. Data on the utility of these assays in the posttransplant population are limited. It is important to note that accurate results from interferon-γ release assays depend on adequate numbers of lymphocytes as well as adequate stimulation of T cells by the TB-specific antigens, both of which may be diminished after transplant.

In Torre-Cisneros et al.’s study, pretransplant screening was performed for 40.5% of patients, and approximately half of those with a positive PPD test result received chemoprophylaxis. A relatively low rate of chemoprophylaxis use for patients with a positive PPD test result is often observed in transplant populations, the reason for which may be multifactorial. For example, there may not be sufficient time to commence prophylaxis because of the urgent nature of some transplants. There also is a significant reluctance to administer prophylaxis to patients with end-stage liver disease, because of the risk of precipitating further hepatic decompensation. Two small studies have now assessed the safety of isoniazid for patients with compensated liver disease [8, 9]. Jahng et al. [9] also demonstrated the safety of rifampin monotherapy in this population, although only 5 patients were analyzed. However, it is common practice to wait until after the liver transplant to begin prophylaxis. For nonliver transplant recipients, it is reasonable to begin prophylaxis before transplant and to continue it after transplant until a total of 9 months of prophylaxis are completed; this would not be considered a contraindication to proceed with a transplant by most programs. To our knowledge, no cases of reactivation during receipt of prophylaxis have been reported in the posttransplant setting, although multidrug-resistant TB in transplant recipients has been reported [10].

There is no standard time to begin TB prophylaxis after transplant, although it should be initiated as early as possible given that the majority of reactivations occur during the first year. Isoniazid is recommended and does not have clinically significant interactions with immunosuppressive medications. Data on isoniazid hepatotoxicity after transplant are limited. However, in the review by Singh and Paterson [1], isoniazid hepatotoxicity requiring discontinuation of drug occurred in 41% of liver transplant recipients, in 2.5% of renal transplant recipients, and in 10% of heart transplant recipients [1]. Given the relatively low risk of toxicity in nonliver transplant recipients, isoniazid is a reasonable option. However, special consideration should be given to alternatives in the liver transplant population, for whom a rise in transaminase levels may result from multiple etiologies, such as acute rejection, recurrent hepatitis C, or opportunistic infection (e.g., cytomegalovirus infection). A liver biopsy is often required for diagnosis. In liver transplant recipients, a nonhepatotoxic alternative for prophylaxis would be ideal. Rifampin is generally unsuitable, because of the risk of hepatotoxicity and significant drug interactions with immunosuppressive medications. Rifampin is a potent inducer of cytochrome P3A4 and decreases calcineurin-inhibitor levels (thereby potentially triggering acute rejection) as well as levels of azole antifungals, which are commonly used after transplant. Rifabutin has an efficacy equal to that of rifampin but has less effect on cytochrome P3A4 and fewer interactions with immunosuppressive medications. An alternative would be quinolone prophylaxis, although no studies have evaluated it in the transplant population. Although quinolones are recommended as second-line therapy in the American Thoracic Society’s guidelines for the treatment of TB, some investigators have suggested that this class be considered part of the first-line regimen in the treatment of posttransplant TB [11, 12].

Torre-Cisneros et al. have highlighted the increased risk of posttransplant TB. However, improved methods for screening organ donors and recipients need to be identified, and alternative therapies that have lower toxicity profiles are needed for transplant recipients.

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