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Management and diagnosis of tuberculosis in solid organ transplant candidates and recipients: Expert survey and updated review☆,☆☆

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ABSTRACT

Background: Optimal screening and management of latent tuberculosis infection (LTBI) and active tuberculosis (TB) in solid organ transplant (SOT) candidates and recipients is necessary to prevent morbidity and mortality.

Methods: We conducted a cross-sectional survey of TB and transplant experts across the United States reviewing the clinical practice preferences on key management issues related to LTBI and TB in SOT candidates and recipients.

Results: Thirty TB and 13 SOT experts were surveyed (response rate = 53.8%). Both groups agreed that tuberculin skin test (TST) and chest x-ray screening in SOT candidates was useful (78.6% and 84.6%, respectively). TST after SOT was not useful for most transplant experts and TB experts (0% vs. 32.1%, respectively), but both groups were split on usefulness of interferon gamma release assays (IGRA) in SOT recipients (42.9% TB experts vs. 46.2% SOT experts). Most experts recommend LTBI treatment prior to SOT if close monitoring is assured (82.1% TB experts vs. 76.9% transplant experts). LTBI treatment with isoniazid was preferred for patients on calcineurin inhibitors. Evaluation for suspected TB in SOT recipients varied, but most TB experts favored sputum testing (88.9%) whereas most transplant experts favored bronchoscopic testing (69.2%). Preferred TB treatment regimens in SOT recipients were similar to regimens recommended for immunocompetent patients.

Conclusions: Most TB and transplant experts recommend evaluation and treatment for LTBI in SOT candidates. Liver transplant candidates, however, should only be treated if close monitoring can be assured and after consulting with a hepatologist. Practice preferences varied regarding the initial diagnostic approach for suspected TB in SOT recipients; however, most experts agreed that SOT recipients should receive similar treatments as immunocompetent patients.

Introduction

Tuberculosis (TB) incidence in solid organ transplant (SOT) recipients is reported between 0.25 to 13.7%, and occurs more often in countries and settings with high prevalence of TB [1–5]. Moreover, TB in SOT recipients carries high TB-related and SOT-related morbidity and mortality. The most recent TB consensus guidelines in the United States addressed the diagnosis in immunosuppressed individuals and some aspects of TB treatment in SOT recipients, such as drug-to-drug interactions with anti-TB medications. They do not, however, provide a dedicated section with recommendations for the diagnosis and management of LTBI and TB in various types of SOT candidates and recipients [6–9]. The Spanish Society of Infectious Diseases and Clinical Microbiology previously put together a consensus statement to provide

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clinical guidelines specifically for the management of SOT recipients in 2009 [10]. Several of those recommendations are based on expert opinion and retrospective data [11]. However, it is unclear if consensus between TB and SOT experts exists, if there are TB management practice variations between Spain and the US, and some key clinical issues remain unaddressed.

Important considerations in SOT candidates are clinical evaluation of latent tuberculosis infection (LTBI) with the tuberculin skin testing (TST) and/or interferon gamma release assays (IGRAs), the utility of routine screening chest x-rays (CXR), and LTBI treatment regimens (especially in liver transplant candidates). In SOT recipients, important considerations are diagnostic accuracy of testing for LTBI, diagnostic approach for suspected active TB, and treatment regimens for LTBI and active TB.

Anti-TB medications, specifically rifamycins (rifampicin, rifabutin, or rifapentine) interact with calcineurin inhibitors (i.e. cyclosporine and tacrolimus), mammalian target of rapamycin (mTOR) inhibitors (i.e. sirolimus and everolimus), and corticosteroids by reducing serum levels of these medications potentially precipitating graft rejection and dysfunction [6,12,13]. For these reasons, the use of rifamycin-based regimens for the treatment of LTBI and active TB in SOT recipients is controversial [14]. Moreover, common LTBI regimens have associated risk of hepatotoxicity. Isoniazid and rifamycins can cause drug-induced hepatitis, and the previously used combination of rifampicin/pyrazinamide can cause severe liver toxicity [6,10]. This raises the issue of how to best treat liver transplant candidates with LTBI or liver transplant recipients with LTBI or active TB.

To help address these key clinical issues, the American College of Chest Physicians (ACCP) sponsored a project to conduct a national survey that invited United States experts in TB and SOT to compare medical preferences for common TB diagnostic and management questions in SOT candidates and recipients. After reviewing the recently released American Thoracic Society(ATS), Centers for Disease Control and Prevention(CDC), and Infectious Disease Society of America(IDSA) diagnostic and treatment guidelines, we decided to publish this original work and discuss our findings in comparison with the most recent published data [7,9].

Material and methods

The study was reviewed and approved by the Mayo Clinic Institutional Review Board and was research exempt.

We conducted a web-based survey amongst TB and transplant experts from August 18, 2009 to June 21, 2010.

Development of survey questionnaire

No validated questionnaire regarding TB practices in SOT existed. Therefore, a seven-member steering committee representing pulmonary and infectious diseases TB experts and transplant experts reviewed the literature and developed potential survey questions utilizing the Delphi method. The survey questions were focused on the following clinical themes: (1) diagnostic utility of TST and IGRAs, before and after SOT, (2) usefulness of routine CXR in assessment of candidates undergoing SOT evaluations, (3) LTBI treatment alternatives for patients taking calcineurin and/or mTOR inhibitors, (4) management of LTBI, before or after liver transplantation, (5) diagnostic work-up and treatment alternatives for active TB after SOT. Responses were formatted on a 5-point Likert scale or for priority ranking, and comments were allowed. The proposed questionnaire and survey instructions were reviewed by non-TB experts and non-transplant experts from the ACCP Chest Infection Network for clarity and comments. The questionnaire was revised accordingly. One question, in which consensus guidelines exists for the treatment of patients with active TB in general, was included for internal validation. The final questionnaire had 11 questions (see Appendix A).

Selection of study participants

We sought a representative sample from the sampling frame of TB and SOT experts of varied institutions and geographic regions from the United States to avoid bias based on regional practice variation and differences in TB prevalence. TB and SOT experts were identified in three ways: (1) nomination by the study's steering committee based on known contributions in the field of TB or SOT; (2) through a PubMed publication search using terms “tuberculosis” and “solid organ transplantation” and/or; (3) practitioner in a TB or SOT referral center in the United States obtained from the ACCP and other professional organizations databases. Inclusion criteria for TB experts included physicians who care for TB patients in a referral practice and/or have published one or more research articles on TB. TB experts were comprised of the following specialties: Pulmonary Medicine, Infectious Diseases, and Internal Medicine. Transplant experts included physicians who manage SOT patients in referral centers and/or published one or more research articles related to SOT. SOT experts were comprised of Pulmonary Medicine and Infectious Diseases specialists. Experts were sorted by their contributions to the respective fields (SOT or TB) and current practice setting, not by specialty training.

Survey procedure

Need for consent was waived by the IRB. The self-administered, web-based questionnaire was sent to participants via an email invitation. The email included survey instructions, voluntary nature of the study, a statement regarding the purpose of the study, identification of the study sponsor and principal investigator, and an option to accept or decline participation as previously described [14]. If no response was received within 2 weeks, a subsequent e-mail invitation was sent. If there was no response by four weeks, the e-mail address was reconfirmed and a follow-up invitation was sent at 6 weeks and if necessary 8 weeks. On failure to obtain response after the fourth invitation, experts were deemed non-participators. No incentive or remuneration was offered.

Measurable outcomes

The measurable outcomes were level of agreement amongst experts and order of preference on priority ranking.

Definitions

Agreement was defined as responding either “agree” or “strongly agree”, and disagreement was defined as responding “disagree” or “strongly disagree”. Neutral responses were counted in the denominator. Consensus level was defined when 80% of respondents in a category were in agreement or disagreement.