Management of Latent Tuberculosis Infection

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In the US, approximately 13 million people have latent tuberculosis infection (LTBI), defined as people who are infected with Mycobacterium tuberculosis who do not have symptoms and do not transmit the disease. Without treatment, approximately 5% to 10% of immunocompetent persons with LTBI develop active TB disease in their lifetimes.1

In June 2020, the US Preventive Services Task Force recommended screening all at-risk adults older than 18 years for LTBI with a blood test (interferon-gamma release assay) or a tuberculin skin test. At-risk individuals include those from TB-endemic regions and those who are immunocompromised or are starting an immunosuppressive medication, such as tumor necrosis factor antagonists or systemic corticosteroids at a dose of at least 15 mg of prednisone per day, or take immunosuppressive drugs after organ transplant.2 Evaluation for LTBI should include a medical history, physical examination, and chest radiographic imaging to rule out active TB disease. After confirmation that active TB is not present, LTBI treatment can be initiated. This article reviews the 2020 Centers for Disease Control and Prevention and National Tuberculosis Controllers Association LTBI treatment recommendations.3

LTBI Treatment Regimens

According to the Morbidity and Mortality Weekly Report, “preferred” medications for managing LTBI have excellent tolerability and efficacy and shorter treatment duration and higher completion rates than longer regimens. “Alternative” medications have excellent efficacy but longer treatment duration, which may lower completion rates. A “strong” recommendation is one for which a panel of experts has confidence that the benefits of adherence to a recommendation outweigh the undesirable effects; a “conditional” recommendation indicates one for which the benefits of adherence outweigh undesirable effects, but the panel is not confident. Treatment regimens were ranked on level of evidence available (high, moderate, low, or very low).4 Recommended preferred and alternative regimens that have at least moderate evidence are summarized below.

Strongly Recommended Preferred Regimens

Four Months of Daily Rifampin
Rifamycin-based regimens are preferred therapy because they are effective, safe, and associated with higher adherence rates than longer isoniazid regimens. Compared with 9 months of isoniazid, 4 months of daily rifampin had higher treatment completion (63.2% vs 78.8% [P < .001]), defined as receipt of more than 80% of doses within the study-defined time of 12 months for rifampin and 18 months for isoniazid, and lower rates of adverse effects (2.6% vs 1.5% for all events [P = .003]; 1.5% vs 0.3% for hepatotoxic events [P < .001]).5 Rifamycin-based regimens interact with many commonly prescribed drugs, including warfarin, azole antifungals, hormonal contraceptives, and HIV antiretroviral medications.

Three Months of Weekly Isoniazid and Rifapentine
Three months of weekly isoniazid and rifapentine is strongly recommended in all adults with LTBI. Compared with 9 months of isoniazid, weekly isoniazid and rifapentine for 3 months had higher completion rates (82% vs 69% [P < .001]), fewer serious adverse events (1.6% vs 2.9% [P < .001]), and less hepatotoxicity (0.4% vs 2.7% [P < .001]) when administered via directly observed therapy, which occurs when a health care worker directly observes an individual taking their prescribed medication.6

Although fewer individuals discontinued 3 months of weekly isoniazid and rifapentine treatment compared with 9 months of daily isoniazid, a greater proportion of treatment discontinuations among those receiving isoniazid and rifapentine was related to adverse effects compared with discontinuations among those receiving 9 months of daily isoniazid (4.9% vs 3.7% [P = .009]).7 Although this regimen was associated with more nonhepatotoxic adverse effects, such as possible hypersensitivity (0.5% vs 3.8%), compared with 9 months of isoniazid, these adverse effects were less severe than those from isoniazid.

Recommended Alternative Regimens With Moderate Evidence

Isoniazid for either 6 or 9 months is an alternative to rifamycin regimens for individuals at risk for drug interactions or those experiencing adverse effects with the aforementioned regimens. Nine months of isoniazid is conditionally recommended. Six months of isoniazid is strongly recommended for HIV-negative patients and conditionally recommended for patients with HIV. This recommendation was based on results from the International Union Against Tuberculosis trial, which demonstrated that the 5-year risk of developing TB was associated with reduced risk by 21% with the 3-month treatment duration, 65% with the 6-month duration, and 75% with the 12-month duration.5

Because no clinical trial data have directly compared 9 months of isoniazid with placebo, or with 6 or 9 months of isoniazid, conditional recommendations were made. Because isoniazid can cause peripheral neuropathy, pyridoxine (25-50 mg/d) should be administered with isoniazid to individuals who have risk factors for neuropathy.

Selecting an LTBI Treatment Regimen

Although rifamycin-based regimens are preferred, clinicians should consider patient characteristics and preferences when making decisions about LTBI treatment regimens. Although isoniazid costs less than rifamycin-based regimens per dose, the total cost of treatment when considering clinic visits, supplies, and time can exceed that of rifamycin-based treatments.6 Isoniazid is an alternative when drug interactions preclude use of rifamycins. For a patient with preexisting liver disease, rifampin is associated with less hepatotoxicity than isoniazid. For pregnant individuals at low risk for TB disease progression, LTBI treatment should be deferred until 2 to 3 months after delivery.2

Nitrosamine Contamination of Rifamycins

In June 2020, the US Food and Drug Administration announced that increased levels of potentially carcinogenic nitrosamines were detected in rifampin and rifapentine.7 Although daily use of a nitrosamine-containing drug for 70 years incurs an estimated 1:100 000 cancer risk,
LTBI treatment involves a considerably shorter treatment duration.8 Because shorter rifamycin-based regimens are efficacious, well tolerated, and result in increased rates of treatment completion, the Centers for Disease Control and Prevention recommends that clinicians prescribe rifamycins after explaining the negligible risk of nitrosamine impurities and the risks and benefits of isoniazid.7

**Summary of Findings**
Current guidelines recommend shorter rifamycin-based regimens over isoniazid treatment. Isoniazid remains an effective, strongly recommended alternative for patients who are unable to complete rifamycin-based treatment. The algorithm in the Figure, based on the latest evidence and expert recommendations, has not been validated but may be helpful for clinicians in the US. Shared decision-making, which takes into account patient characteristics, preferences, and potential risks, is key to successful LTBI treatment.

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