CLINICAL VIGNETTE

An Update on the Diagnosis and Treatment of Latent TB

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A 44-year-old homeless man with a past medical history of alcohol abuse presented to the emergency room for evaluation of multiple skin abscesses. He was admitted after incision and drainage of two skin abscesses in the emergency room. During his hospitalization, he was treated with vancomycin for the associated cellulitis and diagnosed with poorly controlled type 2 diabetes mellitus. The patient was tested for tuberculosis (TB) given his risk factors of homelessness and recent immigration from Cuba. His quanti-FERON-TB Gold (QFT) was positive but subsequent negative sputum cultures were negative. The patient was started on daily isoniazid (INH) 300 mg and pyridoxine 50 mg for treatment of latent tuberculosis infection (LTBI). However, due to concern about compliance and duration of therapy, his regimen was changed to rifampin 600 mg/day for four months.

LTBI is an important public health problem in the US affecting over 20 million people[1]. Over 80% of cases of active TB occur due to reactivation of latent TB[2]. Latent TB can develop into active TB with a 5-10% lifetime risk[1]. However, 50% of this risk occurs in the first 2 years after conversion. Worldwide, rates of TB have increased from 8 million cases in 1997 to 8.4 million in 1999[3]. Screening for latent TB remains the key to prevent the development of active TB in high-risk groups.

Screening for latent TB should be performed in high-risk groups including recent immigrants from high prevalence countries, close contacts of patients with TB, the homeless, intravenous drug abusers and prisoners. 59% of all TB cases in the US result from reactivation of latent TB in foreign-born individuals[4]. Other important populations to screen include patients with HIV infection and patients on immunosuppressive drugs like TNF-alpha inhibitors[1]. Increased risk of reactivation also exists in patients with poorly controlled type 2 diabetes mellitus and end-stage renal disease[1].

Screening can be performed through the tuberculin skin test (TST) or interferon-gamma releasing assays (IGRAs). PPD testing detects induration that is caused by memory T cells[2]. A positive reading on a PPD skin test incorporates the clinical suspicion of latent TB and the degree of induration recorded. IGRAs are a newer test for LTBI that work by detecting gamma interferon, a part of the cellular immune system response to TB infection. There are two types of IGRAs, quantiFERON-TB Gold (Cellestis) and T-SPOT.TB (Oxford Immunotec)[2]. Quanti-FERON-TB Gold (QFT) testing evaluates inter-feron gamma release by enzyme-linked im-muneosorbant assay while TSPOT. TB quan-titates the cells producing interferon-gamma[1].

IGRAs have several benefits over PPD testing including fewer false positives, no booster effect and no follow-up required. IGRA testing avoids potential pitfalls in populations previously vac-cinated with the Bacillus Calmette-Guerin vaccine (BCG). Recent TB exposure is best detected by IGRA testing rather than PPD[1]. However, IGRAs do require lab testing and increased costs over traditional PPD skin testing.

The sensitivity and specificity of IGRAs is superior to the PPD[5]. QFT has a reported sensitivity of 71% and specificity of 97% while the newest generation test has a 85% sensitivity and 97% specificity[1]. T-SPOT.TB is 90% sensitive and 90% specific[1]. Results of IGRA testing are recorded as positive, negative or indeterminate. Borderline or indeterminate test-ing occurs 2-4%[1]. However, more indeter-minate results occur in the HIV+ population. CDC guidelines recommend IGRA testing in all clinical scenarios where the TST is performed[1].

One area of uncertainty is the use of IGRAs in serial testing of health care workers. Variation exists with repeat testing of .32-.36 IU/mm[31]. Serial testing can result in reversion and conversion without clinical significance. In countries like the US with a low incidence of TB, patients with an initial borderline result of

.2-.7 IU/ml may have inconsistent results on subsequent testing[6]. Current guidelines recommend retesting prior to treatment in patients with borderline results of .2-.7 IU/ml [6].

Prior to treatment for possible LTBI, it is essential to rule out active tuberculosis. Treatment for latent TB has traditionally included 9 months of INH. In cases of INH resistance, rifampin may be used for 4 months. Recently, an additional regimen has been added to TB treatment protocols: INH in combination with rifapentine weekly for 12 weeks as directly observed therapy. 3 randomized controlled trials indicate that this alternative is as effective as INH. Moreover, the combination INH plus rifapentine has a higher completion rate as compared with standard INH therapy[7]. Compliance with LTBI regimens has been historically low. 9 months of INH typically has a 60% completion rate while 4 months of rifampin has a 78% completion rate[2].

During treatment for LTBI, it is important to monitor for possible medication side effects. Peripheral neuropathy may be caused by INH as it interrupts the metabolism of pyridoxine. This problem is mitigated by providing patients with daily pyridoxine[2]. INH therapy can cause hepatitis although severe symptomatic hepatitis is uncommon. During therapy with INH, patients must avoid alcohol. Adverse drug events with rifampin are uncommon but drug-drug interactions are important to monitor. Prior regimens including rifampin and pyrazinamide have been abandoned due to higher rates of hepatotoxicity as compared with INH mono-therapy.

INH plus rifapentine may be particularly helpful in correctional facilities, immigrant clinics and homeless shelters as it is administered weekly as directly observed therapy. This combination is contraindicated in pregnancy, cases of isoniazid resistance and in HIV patients on antiretroviral therapy. In initial studies, rifapentine caused rare neutropenia, hypersensitivity reactions and elevated liver function tests[7]. Combination therapy had significantly more drug discontinuation from adverse effects as compared with INH (4.9 vs. 3.7%, $p < .01$)[7]. As rifapentine induces the cytochrome p450 system, significant drug interactions may occur with warfarin, oral contraceptives and methadone[7]. Combination therapy with INH and rifapentine had lower rates of serious hepatotoxicity than INH (0.3 vs. 2%, $p < .01$)[7].

Monitoring during therapy should include baseline liver function tests especially for patients with chronic liver disease, HIV, alcohol users or patients on hepatotoxic medications. Monthly clinical evaluation is recommended. Patients with baseline abnormalities in liver function should have serial laboratory evaluation. Cessation of therapy should occur if liver function enzymes exceed 3-5x the upper limit of normal[2].

In summary, latent TB remains a highly prevalent health problem with serious implications. Control of reactivation TB remains a goal of public health by targeting high-risk populations and treating latent TB infections. IGRAs are a relatively new means of detecting latent TB infection. These tests are particularly helpful in the foreign-born population and patients with recent exposure. More data are needed to clarify the role of IGRAs in serial testing of health care workers. A new treatment regimen, INH plus rifapentine, serves as a viable alternative to standard INH therapy. Combination therapy with this regimen offers higher completion rates and a shorter duration of treatment, however, clinical experience with this regimen is limited.

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