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Treatment of latent TB: first do no harm

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"While the Hippocratic Oath compels us to first do no harm, using a regimen that is ineffective would make any harm excessive. It is prudent to demand more evidence before changing the guideline-preferred regimen for latent TB infection."

Treatment of latent TB infection (LTBI) prevents active disease and is an essential component of TB control in low-incidence countries. Because only a minority of latently infected individuals go on to develop active disease, the decision to treat latent TB requires careful consideration of the long-term benefits of prevention versus the immediate risk of therapy-associated adverse events. This article will summarize the current state of latent TB management, highlighting recent advances and future directions.

Treatment of LTBI can reduce morbidity, mortality and healthcare costs [1,2]. People with LTBI are neither symptomatic nor contagious, and the majority will never develop active disease. Recommended treatment is lengthy and has the potential for serious adverse effects. Hence, the risk should be weighed carefully against the potential benefit of preventing active disease.

Current guidelines recommend treating people with LTBI that are at increased risk of development of active disease [1,3,101]. Risk factors for reactivation include recent TB infection, comorbid conditions and medications that impair host immune responses (e.g., HIV infection, solid organ transplant, diabetes mellitus, chronic hemodialysis, certain cancers, smoking, glucocorticoids and TNF-α inhibitors), low bodyweight (BMI ≤20) and radiographic abnormalities typical of prior TB infection [1,3,101]. Among latently infected persons that are at low risk of adverse events from treatment, if they have any risk factor that confers an increased risk of reactivation, then treatment is warranted. The decision to treat is more difficult when patients with LTBI possess risk factors for reactivation and also for therapy-associated adverse events. A thorough understanding of LTBI treatment options and their side-effect profiles will guide clinicians in the management of such cases.

"…accumulating evidence highlighting poor compliance and toxicity make it time to reconsider the preferred latent TB infection regimen."

Self-administered isoniazid (INH) monotherapy for 9 months (9INH) is currently the preferred regimen for LTBI in most authoritative guidelines [1,3,101]. Several randomized trials have demonstrated that rates of active TB are reduced by 60–90% with INH depending on the number of doses taken [2]. While INH is an inexpensive drug, the lengthy therapy and need for close follow-up to enhance safety and compliance substantially increases cost [4–7]. Approximately half of all patients beginning 9INH complete therapy [5]. Factors associated with failure to complete treatment include use of 9INH (in contrast to shorter regimens) and therapy-related side effects [5]. Adverse events associated with this drug are generally mild such as nausea or headache, but can include rash, hepatitis, peripheral neuropathy and drug interactions. The most serious complication is INH-induced hepatitis, which can progress to fulminant hepatic failure and death [8]. This usually occurs within the first 3 months of therapy [8]. Risk factors

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include pre-existing liver disease (e.g., viral hepatitis), daily alcohol consumption and older age [8]. In several large-scale observational studies from the last two decades, overall INH hepatitis risk was less than 1% [8–12]. However, patients over 50 years of age and, in particular, those over 65 of age years experienced higher rates of INH hepatitis. In a population aged 65 years and older, when compared with an untreated population, an excess of two hospitalizations for suspected INH hepatitis was observed for every 100 patients treated [12]. Fortunately, death from INH hepatitis is rare [8]. Treatment of LTBI with 9INH is supported with evidence from multiple randomized trials and decades of experience. However, accumulating evidence highlighting poor compliance and toxicity make it time to reconsider the preferred LTBI regimen.

> "People with latent TB infection are neither symptomatic nor contagious … hence, the risk should be weighed carefully against the potential benefit of preventing active disease."

An alternative regimen recommended for the treatment of LTBI is 4 months of rifampin (4RIF) [1,3,101]. Clinical data supporting the effectiveness of 4RIF in treatment of LTBI is sparse [13–15]. The only randomized double-blind trial of RIF monotherapy was conducted among patients in Hong Kong with silicosis, a known risk factor for LTBI activation. This study demonstrated that 3 months of RIF was somewhat superior (albeit not significantly) to 6 months of INH [13]. Two case series have demonstrated high rates of acceptability and completion, with low rates of adverse events and no prevention failures among homeless individuals in Boston (MA, USA) and high school students in California (CA, USA) [15]. Adverse events associated with 4RIF include gastrointestinal upset, skin rash, headache and hematologic reactions. Because RIF interacts with the cytochrome P450 isoenzymes, drug interactions are an important consideration prior to initiating therapy. Liver injury in association with RIF has been reported and is thought to be due to a hypersensitivity-type reaction [8]. While large randomized studies comparing efficacy of 4RIF and 9INH have not yet been completed, several studies have evaluated safety, adherence and cost [4,16–18]. These have been summarized in a recent systematic review, which found that the 4RIF regimen was superior to 9INH with respect to adverse event rates, treatment completion and costs [18].

A brief discussion follows on combination regimens for the treatment of LTBI. The 2-month combination of RIF and pyrazinamide is no longer recommended owing to an unacceptably high risk of hospitalization and death due to liver injury [19]. INH and RIF are recommended as an alternative regimen for LTBI in some national guidelines [3,101]. In several small trials, the effectiveness of this regimen was similar to that of 6 months of INH or 3 months of RIF alone [13,14]. Adverse events were similar to those seen with the longer regimens of INH. Hence, this regimen cannot be considered a major improvement compared with INH, and we believe the combined risk of adverse events and increased cost does not justify the routine use of this regimen in LTBI management. A large-scale multicenter trial comparing 9INH with 12 weeks of directly observed once-weekly INH and rifapentine (a rifamycin with much a longer half-life) has recently been completed. Results of this trial are expected soon.

Why is 4RIF not the preferred treatment for LTBI? The main reason is a lack of effectiveness data from randomized trials [6,13,18]. The only randomized trial evaluating RIF for LTBI was conducted in men in Hong Kong with silicosis [13]. Other studies have evaluated the safety, tolerability and completion rates, and estimated efficacy based on comparison with concurrent or historical controls [6,18]. While the Hippocratic Oath compels us to first do no harm, using a regimen that is ineffective would make any harm excessive. It is prudent to demand more evidence before changing the guideline-preferred regimen for LTBI.

In summary, 9INH remains the preferred regimen for treatment of LTBI. Its efficacy is supported by decades of research and the risk of therapy-associated adverse events is well characterized. However, the prevalence of risk factors for activation and for therapy-associated adverse events is changing in the population with LTBI. These changes have brought into focus the poor completion rates and adverse events of 9INH. 4RIF is a well-tolerated alternate regimen that could replace 9INH as the guideline-preferred approach to treating LTBI. The evidence supporting 4RIF is building, with multiple studies showing improved compliance, safety and cost savings with 4RIF over 9INH. What we lack is the keystone: data on effectiveness from a randomized trial in a general population with latent infection. Such a trial is ongoing, with expected completion in 2016. This will contribute to an evidence based re-evaluation of the safest, most acceptable, least expensive and most effective regimen for treatment of LTBI.

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