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NEW TB TREATMENT GUIDELINES

In 1943 Albert Schatz and Selman Waksman discovered streptomycin—the first antibiotic effective against tuberculosis. Ever since that monumental achievement, experts have been crafting and revising TB treatment recommendations in an effort to get rid of the disease. This issue of the *CD Summary* commemorates the 60th anniversary of streptomycin's discovery by reviewing the latest of these recommendations, issued jointly by the American Thoracic Society, the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention.

LTBI TREATMENT ALERT

Stop using the 2-month rifampin + pyrazinamide regimen for treatment of latent TB infection.

This recommendation was made after evaluation of reports of severe and fatal hepatitis associated with the use of this regimen. Instead, the regimens shown in the table below should be employed.[1] Those who are on a rifampin+ pyrazinamide regimen should be switched to rifampin alone to complete a 4-month course of that drug.[2]

N.B. This recommendation does not pertain to the use of rifampin and pyrazinamide in multidrug regimens for the treatment of persons with active tuberculosis.

LTBI treatment history

For more than 30 years, isoniazid (INH) for 6–12 months was the standard treatment for LTBI in the United States. However, due to the length of treatment and fears of INH-associated hepatitis, adherence to INH regimens was poor. Therefore, CDC undertook a series of studies of "short-course" treatment for LTBI. The analysis of those and prior INH studies resulted in the recommendation that a "short-course" 2-month rifampin + pyrazinamide regimen be added to the guidelines for the treatment of LTBI.[3] Additionally, it was recommended only to test and treat infected persons who were at higher risk of developing active TB disease than the general public.

Afterwards, cases of severe and fatal hepatitis were reported in patients receiving this regimen. CDC retrospectively collected data from cohorts of patients in the United States who had received rifampin + pyrazinamide for LTBI between January 2000 and June 2002. A standardized case definition and case-report forms were developed.[1] They found 48 cases of severe liver injury, 11 of which were fatal, including two in persons with HIV infection. To estimate the incidence of severe liver injury and death associated with this regimen, in September 2002 CDC mailed a questionnaire to all public providers known to be prescribing rifampin + pyrazinamide for LTBI. As of June 2003, a total of 109 providers (78%) had responded. Of 7,737 persons who had begun to take this regimen, 30 (0.4%) had been hospitalized, 7 of whom died. This corresponded to a hospitalization rate of 3.0 per 1,000 and a mortality rate of 0.9 per 1,000.

In May, June, and July 2003, CDC presented the results from the surveillance system, the survey, and recently published studies of rifampin+pyrazinamide-associated liver injury and hospitalization to experts from the Infectious Diseases Society of America, the American College of Chest Physicians, and the Food and Drug Administration. After the experts reviewed the data, ATS and CDC recommended against the use of rifampin + pyrazinamide for treatment of LTBI.[4, 5]

Currently recommended regimens for treatment of LTBI are shown in the table below. CDC's "Treatment of Latent Tuberculosis Infection" and other fact sheets regarding tuberculosis may be found at *http://www.dhs.state.or.us/publichealth/tb/*. More complete recommendations regarding treatment of LTBI have been published previously.[3]

ACTIVE TUBERCULOSIS

The "Treatment of Tuberculosis" statement also has been revised. These new recommendations are available with continuing education credits through CDC in a recent issue of MMWR.[6] (*N.B.* The version of these guidelines published in the American Journal of Respiratory and Critical Care Medicine had a few errors that were not corrected before publication.[7] MMWR has the corrected version.)

What's new and what's updated—we asked for it and we got it!

The new guidelines, though lengthy, are much more comprehensive and address many troublesome scenarios that occur among persons with active tuberculosis. Our own TB Controller, Evelyn Lancaster, was a member of the Ad Hoc Panel that reviewed the document and provided comments and feedback. (Thank you to everyone who provided feedback on previous guidelines and made requests for future guidelines. Your input was taken into consideration and changes were made based on your feedback.)

Recommended treatment for latent TB infection

Drug	Duration	Interval	Minimum no. doses
Isoniazid	9 months	Daily	270
		Twice weekly (via DOT only)*	76
Isoniazid	6 months	Daily	180
		Twice weekly (via DOT only)*	52
Rifampin	4 months	Daily	120
Rifampin+Pyrazinamide		Generally should not be offered	

- DOT: directly observed therapy, i.e., a healthcare worker observes every dose being ingested. Twice-weekly regimens must always be given via DOT.

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New Stuff

- The responsibility for successful treatment is entrusted to the private provider and public-health program, rather than to the patient.
- Directly observed therapy (DOT) and patient-centered case management are now considered the standard of care.
- Regimens are rated according to the strength of the evidence supporting their use.
- Completion of treatment is defined by the number of doses ingested as well as by duration of treatment.
- Practical aspects of care are now addressed—such as the decision to initiate treatment, clarification regarding baseline and follow-up evaluations, monitoring and management of common side effects and drug interactions, and various gnarly treatment situations (e.g., what to do if therapy is interrupted).
- *Note*: Due to the high rates of relapse, treatment failure, and relapse with rifampin-resistant disease, the Oregon TB Program is discouraging the use of Regimen-1C, which is the continuation phase containing once- weekly rifapentine, until the current recommendation has proved safe and effective in the outpatient setting.[1–4]
- Streptomycin was demoted to a second-line drug.*

Revisions or Increased Emphasis

- Sputum should be collected monthly for AFB stain and culture to monitor response to treatment, especially at the end of the initial phase of treatment, to document culture conversion and to identify patients at increased risk for relapse who will need extended therapy.
- Extended treatment is recommended for patients with cavitation and positive sputum cultures 2 months into therapy. Additionally, strong consideration should be given to extend treatment for all patients with drug-susceptible strains whose sputum remains culture-positive after 2 months of treatment. The recommendation is to extend the continuation phase to 7 months—for a total of 9 months of treatment. (The old guideline did not indicate how long to extend.)
- The roles and doses of TB drugs are discussed in more detail.

A WORD ABOUT REPORTING

Latent TB infection, i.e., a positive TB skin test but no disease, is not reportable.

Active tuberculosis—whether suspected or confirmed—is reportable. When you suspect or confirm a case of active TB and plan to start treatment, call the local health department for the jurisdiction in which the patient resides to report the case and to arrange for DOT with the public-health nurse. A list of health departments and contact information is available at h*ttp://www.dhs.state.or.us/acd/isrpt.cfm#where*.

In general, cases should be reported even before confirmatory laboratory evidence is available—i.e., as "suspect" cases. Confirmation requires a positive culture for *Mycobacterium tuberculosis* or a clinical response to treatment. Waiting to report until a case is confirmed could delay appropriate public-health intervention for several weeks.

At the time of the report, the public-health nurse will ask about any pertinent medical and TB exposure history, symptoms, TB skin test results, chest x-ray findings (even for extra-pulmonary disease), and available microbiologic results (on sputum, bronchoscopic specimens or extra-pulmonary specimens). The local health department staff will co-monitor the treatment of the case with you. At this time, agreement should be reached regarding which of you will assume the lead responsibility for the various steps that monitor compliance, response to treatment (symptoms, monthly sputum collections until culture is negative, etc.), and side effects. Remember that DOT for all cases of active TB is now considered the standard of care.

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7 American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of Tuberculosis. Am J Respir Crit Care Med 2003;167:603–62.

* So much for nostalgia.