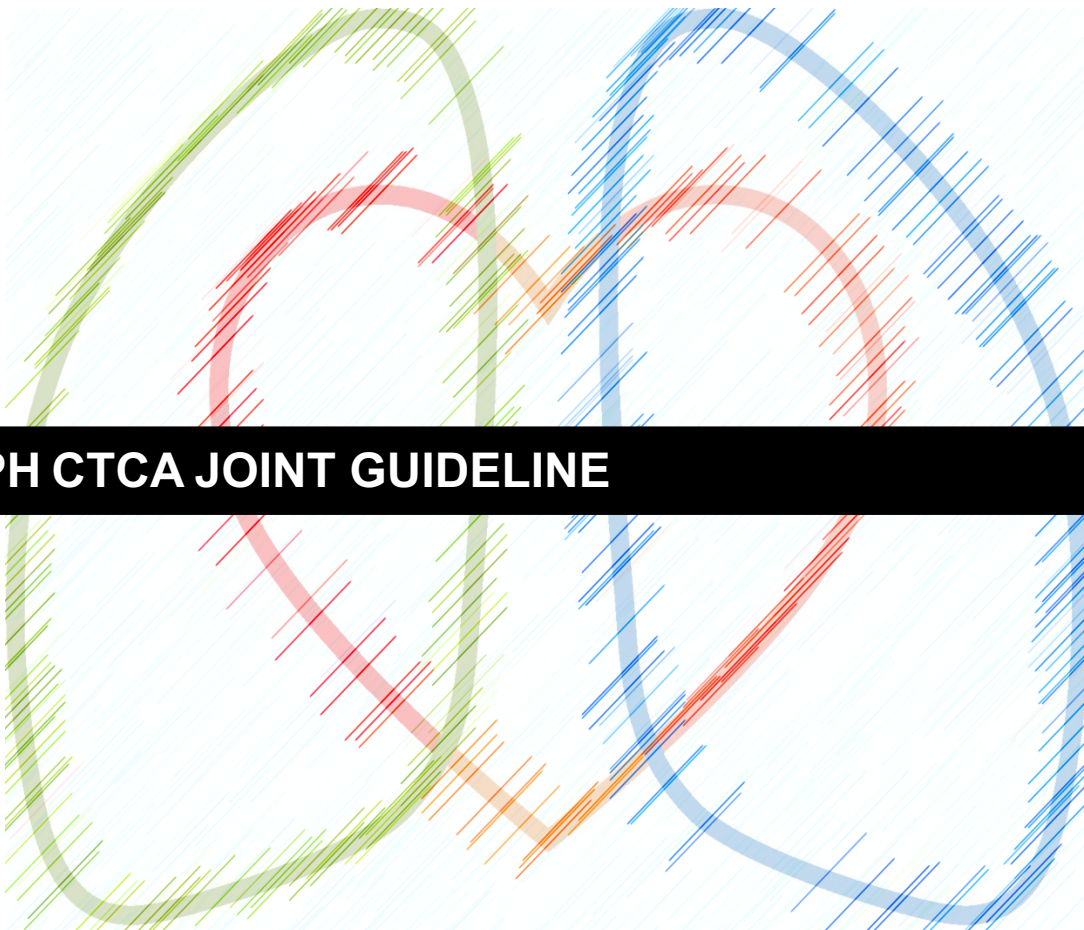


Supplement to the ATS/CDC/IDSA 2016 Guidelines on the Treatment of Drug Susceptible Tuberculosis



CDPH CTCA JOINT GUIDELINE

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Purpose

This document is a supplement to the 2016 national ATS/CDC/IDSA tuberculosis (TB) guidelines¹ written to address issues specific to TB epidemiology and clinical practice patterns among TB clinicians in California. Previous CTCA/CDPH TB Treatment Guidelines (2000) differed from national guidelines with regard to the treatment of culture negative TB. After review of the 2016 national guidelines in the context of current California TB epidemiology, CTCA/CDPH recommend that clinicians in California follow the national guidelines and that they consider the additional, California-specific, information below.

Introduction

CTCA 2003 tuberculosis treatment guidelines ²

The California TB treatment guidelines recommended the use of three or four drugs in the continuation phase (i.e., continue ethambutol and/or pyrazinamide) of culture negative TB. The rationale for this recommendation was a concern that unidentified isoniazid resistance in these culture negative cases without the benefit of drug susceptibility results could lead to acquired MDR TB during the standard continuation phase of rifampin and isoniazid.

ATS/IDSA/CDC 2016 tuberculosis treatment guidelines

The 2016 national guidelines reviewed data on the treatment of smear negative, culture negative pulmonary TB and, on the basis of that review, recommended that a regimen of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 2 more months of rifampin and isoniazid be used in HIV uninfected adults. Radiographic response to treatment at 4 months is then used to determine extension of treatment to 6 months. If there is concern about the adequacy or accuracy of microbiologic evaluation, the 6 month regimen should be used. This shorter duration of treatment recommendation does not apply to extrapulmonary TB.

California Epidemiology

During 2014-2018, there were an average of 161 cases (per year) (n=806 total) of culture negative pulmonary TB (without extrapulmonary involvement) reported in California. The duration of completed treatment for 32% of these cases was less than 6 months, while 68% received 6 months or more of treatment.

The prevalence of isoniazid resistance in California during 2014-2018 was 10.4%. This is somewhat higher than the national prevalence of 9.4% (2013-2017). INH resistance prevalence varies by country of birth. Among TB cases in California reported during 2014-2018, patients born in Peru (11 of 38), Laos (29 of 120), Taiwan (12 of 67), Vietnam (152 of 914), and Burma (10 of 61) had $\geq 15\%$ INH resistance. Countries with lower rates of INH resistance include U.S. (6.9%; 98 of 1413) and Mexico (6.3%; 113 of 1784).³

Acquired resistance is rare in California and is only possible to document for patients with positive cultures at diagnosis. During 2009-2018 there were 7 pulmonary cases that acquired MDR TB in California. All of these patients had either a cavity on chest radiograph or smear positive sputum at the time of initial diagnosis with pansusceptible (n=2) or INH resistant disease (n=5). No cases of documented acquired pulmonary MDR TB started with smear negative noncavitary disease, forms of pulmonary TB that typically have fewer numbers of *M. tuberculosis* bacilli present.

California-specific recommendations – Treatment of smear negative, culture negative pulmonary tuberculosis

In accordance with national guidelines, CTCA/CDPH recommends treating culture negative pulmonary TB in adults with an initial regimen of at least INH, rifampin, pyrazinamide, and ethambutol for 2 months followed by a continuation phase of at least isoniazid and rifampin. In consultation with the local TB control program, continuing pyrazinamide or ethambutol beyond the initial 2 months can be done based on risk factors for drug resistance, adequacy of initial microbiologic investigations and response to treatment.

The duration of the continuation phase should be at least 2 months, but should be extended to at least 4 months based on response to treatment, adequacy of initial microbiologic investigations, patient comorbidities, and provision of directly observed treatment.

Regimen Composition

Clinicians in California should treat most cases of culture negative pulmonary TB with a regimen consistent with the national guidelines. Clinicians in California may choose to include additional drugs in the continuation phase of treatment of culture negative TB cases when there is concern that inadequate microbiologic investigations were conducted at the time of initial diagnosis or when there is specific concern for drug resistance. Concern for drug resistance includes known contact with an infectious drug resistant case of TB. This recommendation could be extended to a person with TB exposure in a country with elevated rates of INH resistance at the judgement of the clinician and local TB controller.

Standard adequate microbiologic investigations for attempting to culture *M. tuberculosis* includes smear and culture on at least 2, but preferably 3, good quality sputum specimens (>3mL) collected at least 8 hours apart. At least one of these specimens should be collected in the early morning or should be induced. Molecular diagnosis with Xpert MTB/RIF or equivalent molecular assay should be performed on at least one sputum specimen.⁴

The rationale for this recommendation is that when adequate specimens are collected and are culture negative, the bacillary load of culture negative disease is likely to be low. In that situation, the likelihood of acquiring resistance from isoniazid mono resistance after 2 months of isoniazid, rifampin, ethambutol, and pyrazinamide is probably low even during subsequent treatment with only rifampin as an effective drug in the continuation phase. Some patients with a diagnosis of culture negative TB may not, in fact, have TB. Use of pyrazinamide and ethambutol for durations longer than necessary puts patients at risk for additional side effects including hepatotoxicity and vision loss.

Duration

Duration of treatment of culture negative pulmonary TB should be determined by response to treatment, consideration of national guidelines, extent of disease as well as presence of comorbidities such as diabetes, end-stage renal disease, immunosuppression, and the inability to provide directly observed therapy or otherwise ensure near 100% adherence to treatment. Extending total treatment duration from a minimum of 4 months to 6 or 9 months is acceptable practice, particularly when any of the above conditions are present.

Decisions on treatment of all TB including culture negative TB should be made in consultation with the local public health TB control program.

The recommendation for setting continuation phase duration of two months in national guidelines is based on results of an observational study and two clinical trials comparing 4 month and 6 month regimens for adult patients with smear negative paucibacillary pulmonary TB. These studies showed no difference in rates of relapse, which was very low overall (1.2%).^{1,5-7}

The rationale for extending treatment beyond the minimum of 2 months of the continuation phase (4 months total) is that characteristics of the host, the treatment, or the extent of disease may make shorter durations less likely to be successful. Examples of these characteristics proposed in other states include TB in young children, immunosuppressing conditions (e.g., HIV infection, organ transplantation), extensive pulmonary disease, inadequate adherence to treatment, other conditions that could predispose to poor treatment outcomes (e.g., diabetes, malignancy, end-stage renal disease on dialysis).⁸ Clinicians should consult with their local TB control program regarding these or other characteristics such as pyrazinamide intolerance in determining an appropriate duration of treatment.

California-specific recommendations – Treatment of smear negative, culture negative extrapulmonary tuberculosis

Extrapulmonary culture negative TB should be treated according to national guidelines (2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of rifampin and isoniazid for known or presumed pansusceptible TB). In consultation with the local TB control program, continuing pyrazinamide or ethambutol beyond the initial 2 months can be done based on risk factors for drug resistance, adequacy of initial microbiologic investigations and response to treatment.

Similar to culture negative pulmonary TB, clinicians should treat culture-negative extrapulmonary TB according to national guidelines and can consider continuing ethambutol and pyrazinamide in the continuation phase in certain situations. These situations include concern that adequate microbiologic investigations have not been performed or when there is specific concern for drug resistance. However, extrapulmonary TB can be more difficult to confirm with culture because of lack of sensitivity of culture for some tissue or fluid specimens or because of difficulty obtaining tissue or fluid for culture. Pathologic examination of tissue without culture is not considered adequate investigation because culture-based drug susceptibility testing cannot be performed on fixed tissue. Risks and benefits of diagnostic procedures should be considered on a case by case basis. Additional considerations for extrapulmonary disease include severity and bacillary burden associated with the disease site. Consultation with the local TB control program to determine the optimal composition and duration of treatment is recommended.

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