



Complete Summary

GUIDELINE TITLE

Treatment of tuberculosis.

BIBLIOGRAPHIC SOURCE(S)

Neff M. ATS, CDC, and IDSA update recommendations on the treatment of tuberculosis. Am Fam Physician 2003 Nov 1;68(9):1854, 1857-8, 1861-2. [PubMed](#)

Treatment of tuberculosis. MMWR Recomm Rep 2003 Jun 20;52(RR-11):1-77. [534 references] [PubMed](#)

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Tuberculosis

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Pediatrics
Preventive Medicine
Pulmonary Medicine

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To guide the treatment of tuberculosis in settings where mycobacterial cultures, drug susceptibility testing, radiographic facilities, and second-line drugs are routinely available

TARGET POPULATION

Adults and children of all ages with tuberculosis who live in geographic settings where mycobacterial cultures, drug susceptibility testing, radiographic facilities, and second-line drugs are routinely available

INTERVENTIONS AND PRACTICES CONSIDERED

1. Patient-centered case-management with an adherence plan that emphasizes directly observed therapy (DOT)
2. Decision to initiate treatment based on: an evaluation of epidemiologic information; clinical, pathological, and radiographic findings; results of microscopic examination of acid-fast bacilli [AFB] – stained sputum (smears) and cultures for mycobacteria, purified protein derivative (PPD)-tuberculin skin test
3. Treatment with first-line antituberculosis drugs (isoniazid [INH]; rifampin [RIF], rifabutin, rifapentine, pyrazinamide [PZA], ethambutol [EMB])
4. Treatment with second-line antituberculosis drugs (cycloserine, ethionamide, streptomycin, amikacin/kanamycin, capreomycin, p-aminosalicylic acid [PAS], levofloxacin, moxifloxacin, gatifloxacin)
5. Treatment with combination antituberculosis drug therapy (INH and RIF [Rifamate®]; INH, RIF, and PZA [Rifater®])
6. Identification and management of patients at increased risk of treatment failure and relapse
7. Microbiological evaluation (sputum cultures) of response to treatment
8. Monitoring for and management of drug interactions and adverse effects of drug therapy
9. Treatment considerations in special situations (HIV infection; children; extrapulmonary tuberculosis; culture-negative pulmonary tuberculosis and radiographic evidence of prior pulmonary tuberculosis; renal insufficiency and end-stage renal disease; liver disease; pregnancy; and breastfeeding) and in low-income countries
10. Management of relapse, treatment failure, and drug resistance

MAJOR OUTCOMES CONSIDERED

- Effectiveness of treatment measures in rendering the patient noninfectious, preventing drug resistance, minimizing the risk of disability and death, and preventing relapse
- Safety, tolerability, and adverse effects of drugs

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

For this revision of the recommendations essentially all clinical trials of antituberculosis treatment in the English language were reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Infectious Diseases Society of America/United States Public Health Service Rating System

Quality of Evidence

- I. At least one properly randomized trial with clinical end points
- II. Clinical trials that either are not randomized or were conducted in other populations
- III. Expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The process by which this revision of the recommendations for treatment was developed was modified substantially from the previous versions. For the first time the Infectious Diseases Society of America (IDSA) has become a cosponsor of the statement, together with the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). The IDSA has had representation on prior statement committees but has not previously been a cosponsor of the document. Practice guidelines that serve to complement the current statement have been developed by the IDSA. In addition to the IDSA, representatives of the American Academy of Pediatrics (AAP), the (United States) National Tuberculosis Controllers Association (NTCA), the Canadian Thoracic Society (CTS), the International Union against Tuberculosis and Lung Disease (IUATLD), and the World Health Organization (WHO) participated in the revision. By virtue of their different perspectives these committee members served to provide broader input and to help ensure that the guidelines are placed in an appropriate context.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Infectious Diseases Society of America/United States Public Health Service Rating System

- A. Preferred; should generally be offered
- B. Alternative; acceptable to offer
- C. Offer when preferred or alternative regimens cannot be given
- D. Should generally not be offered
- E. Should never be offered

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These recommendations were compared with those of the World Health Organization (WHO) International Union Against Tuberculosis and Lung Disease (IUATLD).

This guideline was approved by the American Thoracic Society (ATS) Board of Directors, by the Centers for Disease Control and Prevention (CDC), and by the Council of the Infectious Disease Society of America (IDSA) in October 2002.

This guideline appeared in the American Journal of Respiratory and Critical Care Medicine (2003; 167: 603-62).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the ratings for the strength of the recommendations (A-E) and the quality of the evidence (I-III) are provided at the end of the "Major Recommendations."

Responsibility for Successful Treatment

The overall goals for treatment of tuberculosis are 1) to cure the individual patient, and 2) to minimize the transmission of *Mycobacterium tuberculosis* to other persons. Thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides. For this reason the prescribing physician, be he/she in the public or private sector, is carrying out a public health function with responsibility not only for prescribing an appropriate regimen but also for successful completion of therapy. Prescribing physician responsibility for treatment completion is a fundamental principle in tuberculosis control. However, given a clear understanding of roles and responsibilities, oversight of treatment may be shared between a public health program and a private physician.

Organization and Supervision of Treatment

Treatment of patients with tuberculosis is most successful within a comprehensive framework that addresses both clinical and social issues of relevance to the patient. It is essential that treatment be tailored and supervision be based on each patient's clinical and social circumstances (patient-centered care). Patients may be managed in the private sector, by public health departments, or jointly, but in all cases the health department is ultimately responsible for ensuring that adequate, appropriate diagnostic and treatment services are available, and for monitoring the results of therapy.

It is strongly recommended that patient-centered care be the initial management strategy, regardless of the source of supervision. This strategy should always include an adherence plan that emphasizes directly observed therapy (DOT), in which patients are observed to ingest each dose of antituberculosis medications, to maximize the likelihood of completion of therapy. Programs utilizing DOT as the central element in a comprehensive, patient-centered approach to case management (enhanced DOT) have higher rates of treatment completion than less intensive strategies. Each patient's management plan should be individualized to incorporate measures that facilitate adherence to the drug regimen. Such measures may include, for example, social service support, treatment incentives and enablers, housing assistance, referral for treatment of substance abuse, and coordination of tuberculosis services with those of other providers.

Recommended Treatment Regimens

There are four recommended regimens for treating patients with tuberculosis caused by drug-susceptible organisms. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances, described subsequently. Each regimen has an initial phase of 2 months followed by a choice of several options for the continuation phase of either 4 or 7 months. The recommended regimens together with the number of doses specified by the regimen are described in the table below titled "Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms." The initial phases are denoted by a number (1, 2, 3, or 4) and the continuation phases that relate to the initial phase are denoted by the number plus a letter designation (a, b, or c). Drug doses are shown in Tables 3, 4 and 5 of the original guideline document.

Table: Drug Regimens for Culture-positive Pulmonary Tuberculosis Caused by Drug-susceptible Organisms

Regimen 1 (Initial Phase)

Drugs: Isoniazid (INH); Rifampin (RIF); Pyrazinamid (PZA); Ethambutol (EMB)

Interval and doses [@] (minimal duration): Seven days per week (wk) for 56 doses (8 wk) or 5 days/week (d/wk) for 40 doses (8 wk) [&]

Regimen 1a (Continuation Phase)

Drugs: INH/RIF

Interval and doses ^{@\$} (minimal duration): Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk) [&]

Ranges of total doses (minimal duration): 182-130 (26 wk)

Rating (evidence): HIV-: A (I); HIV+: A (II)

Regimen 1b (Continuation Phase)

Drugs: INH/RIF

Interval and doses ^{@\$} (minimal duration): Twice weekly for 36 doses (18 wk)

Ranges of total doses (minimal duration): 92-76 (26 wk)

Rating (evidence): HIV-: A (I); HIV+: A (II) [#]

Regimen 1c ^{**} (Continuation Phase)

Drugs: INH/RPT

Interval and doses ^{@\$} (minimal duration): Once weekly for 18 doses (18 wk)

Ranges of total doses (minimal duration): 74-58 (26 wk)

Rating (evidence): HIV-: B (I); HIV+: E (I)

Regimen 2 (Initial Phase)

Drugs: INH, RIF, PZA, EMB

Interval and doses [@] (minimal duration): Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk), [&] then twice weekly for 12 doses (6 wk)

Regimen 2a (Continuation Phase)

Drugs: INH/RIF

Interval and doses ^{@\$} (minimal duration)) Twice weekly for 36 doses (18 wk)

Ranges of total doses (minimal duration): 62-58 (26 wk)

Rating (evidence): HIV-: A (II); HIV+: B (II) [#]

Regimen 2b** (Continuation Phase)

Drugs: INH/RPT

Interval and doses ^{@\$} (minimal duration): Once weekly for 18 doses (18 wk)

Ranges of total doses (minimal duration): 44-40 (26 wk)

Rating (evidence): HIV-: B (I); HIV+: E (I)

Regimen 3 (Initial Phase)

Drugs: INH, RIF, PZA, EMB

Interval and doses [@] (minimal duration): Three times weekly for 24 doses (8 wk)

Regimen 3a (Continuation Phase)

Drugs: INH/RIF

Interval and doses ^{@\$} (minimal duration): Three times weekly for 54 doses (18 wk)

Ranges of total doses (minimal duration): 78 (26 wk)

Rating (evidence): HIV-: B (I); HIV+: B (II)

Regimen 4 (Initial Phase)

Drugs: INH, RIF, EMB

Interval and doses [@] (minimal duration): Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk) [&]

Regimen 4a (Continuation Phase)

Drugs: INH/RIF

Interval and doses ^{@\$} (minimal duration): Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk) [&]

Ranges of total doses (minimal duration): 273-195 (39 wk)

Rating (evidence): HIV-: C (I); HIV+: C (II)

Regimen 4b (Continuation Phase)

Drugs: INH/RIF

Interval and doses @\$ (minimal duration): Twice weekly for 62 doses (31 wk)

Ranges of total doses (minimal duration): 118-102 (39 wk)

Rating (evidence): HIV-: C (I); HIV+: C (II)

@ When direct observation of therapy (DOT) is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

\$ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

& Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is AIII.

Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/microliter

** Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

The general approach to treatment is summarized in Figure 1 of the original guideline document. Because of the relatively high proportion of adult patients with tuberculosis caused by organisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the 6-month regimen to be maximally effective. Thus, in most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of a 2-month initial phase of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (see Table above titled "Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms," Regimens 1--3). If (when) drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included. For children whose visual acuity cannot be monitored, EMB is usually not recommended except when there is an increased likelihood of the disease being caused by INH-resistant organisms (see Table below titled "Epidemiological circumstances in which an exposed person is at increased risk of infection with drug-resistant Mycobacterium tuberculosis) or when the child has "adult-type" (upper lobe infiltration, cavity formation) tuberculosis. If PZA cannot be included in the initial phase of treatment, or if the isolate is resistant to PZA alone (an unusual circumstance), the initial phase should consist of INH, RIF, and EMB given daily for 2 months (Regimen 4). Examples of circumstances in which PZA may be withheld include severe liver disease, gout, and, perhaps, pregnancy. EMB should be included in the initial phase of Regimen 4 until drug susceptibility is determined.

Table: Epidemiological Circumstances in which an Exposed Person is at Increased Risk of Infection with Drug-resistant Mycobacterium tuberculosis*

- Exposure to a person who has known drug-resistant tuberculosis
- Exposure to a person with active tuberculosis who has had prior treatment for tuberculosis (treatment failure or relapse) and whose susceptibility test results are not known
- Exposure to persons with active tuberculosis from areas in which there is a high prevalence of drug resistance
- Exposure to persons who continue to have positive sputum smears after 2 months of combination chemotherapy
- Travel in an area of high prevalence of drug resistance

*Note: This information is to be used in deciding whether or not to add a fourth drug (usually EMB) for children with active tuberculosis, not to infer the empiric need for a second-line regimen.

The initial phase may be given daily throughout (Regimens 1 and 4), daily for 2 weeks and then twice weekly for 6 weeks (Regimen 2), or three times weekly throughout (Regimen 3). For patients receiving daily therapy, EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to INH and RIF. When the patient is receiving less than daily drug administration, expert opinion suggests that EMB can be discontinued safely in less than 2 months (i.e., when susceptibility test results are known), but there is no evidence to support this approach.

Although clinical trials have shown that the efficacy of streptomycin (SM) is approximately equal to that of EMB in the initial phase of treatment, the increasing frequency of resistance to SM globally has made the drug less useful. Thus, SM is not recommended as being interchangeable with EMB unless the organism is known to be susceptible to the drug or the patient is from a population in which SM resistance is unlikely.

The continuation phase (see Table above titled "Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms") of treatment is given for either 4 or 7 months. The 4-month continuation phase should be used in the large majority of patients. The 7-month continuation phase is recommended only for three groups: patients with cavitory pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive; patients whose initial phase of treatment did not include PZA; and patients being treated with once weekly INH and rifapentine and whose sputum culture obtained at the time of completion of the initial phase is positive. The continuation phase may be given daily (Regimens 1a and 4a), two times weekly by direct observation of therapy (DOT) (Regimens 1b, 2a, and 4b), or three times weekly by DOT (Regimen 3a). For human immunodeficiency virus (HIV)-seronegative patients with noncavitory pulmonary tuberculosis (as determined by standard chest radiography), and negative sputum smears at completion of 2 months of treatment, the continuation phase may consist of rifapentine and INH given once weekly for 4 months by DOT (Regimens 1c and 2b) (See Figure 1 titled "Treatment algorithm for tuberculosis" in the original guideline document"). If the culture at completion of the initial phase of treatment is positive, the once weekly INH and rifapentine continuation phase

should be extended to 7 months. All of the 6-month regimens, except the INH--rifapentine once weekly continuation phase for persons with HIV infection (Rating E1), are rated as A1 or A11, or B1 or B11, in both HIV-infected and uninfected patients. The once-weekly continuation phase is contraindicated (Rating E1) in patients with HIV infection because of an unacceptable rate of failure/relapse, often with rifamycin-resistant organisms. For the same reason twice weekly treatment, either as part of the initial phase (Regimen 2) or continuation phase (Regimens 1b and 2a), is not recommended for HIV-infected patients with CD4⁺ cell counts <100 cells/microliters. These patients should receive either daily (initial phase) or three times weekly (continuation phase) treatment. Regimen 4 (and 4a/4b), a 9-month regimen, is rated C1 for patients without HIV infection and C11 for those with HIV infection.

Deciding To Initiate Treatment

The decision to initiate combination antituberculosis chemotherapy should be based on epidemiologic information; clinical, pathological, and radiographic findings; and the results of microscopic examination of acid-fast bacilli (AFB)--stained sputum (smears) (as well as other appropriately collected diagnostic specimens) and cultures for mycobacteria. A purified protein derivative (PPD)-tuberculin skin test may be done at the time of initial evaluation, but a negative PPD-tuberculin skin test does not exclude the diagnosis of active tuberculosis. However, a positive PPD-tuberculin skin test supports the diagnosis of culture-negative pulmonary tuberculosis, as well as latent tuberculosis infection in persons with stable abnormal chest radiographs consistent with inactive tuberculosis (see below).

If the suspicion of tuberculosis is high or the patient is seriously ill with a disorder, either pulmonary or extrapulmonary, that is thought possibly to be tuberculosis, combination chemotherapy using one of the recommended regimens should be initiated promptly, often before AFB smear results are known and usually before mycobacterial culture results have been obtained. A positive AFB smear provides strong inferential evidence for the diagnosis of tuberculosis. If the diagnosis is confirmed by isolation of *M. tuberculosis* or a positive nucleic acid amplification test, treatment can be continued to complete a standard course of therapy (see Figure 1 titled "Treatment algorithm for tuberculosis" in the original guideline document). When the initial AFB smears and cultures are negative, a diagnosis other than tuberculosis should be considered and appropriate evaluations undertaken. If no other diagnosis is established and the PPD-tuberculin skin test is positive (in this circumstance a reaction of 5 mm or greater induration is considered positive), empirical combination chemotherapy should be initiated. If there is a clinical or radiographic response within 2 months of initiation of therapy and no other diagnosis has been established, a diagnosis of culture-negative pulmonary tuberculosis can be made and treatment continued with an additional 2 months of INH and RIF to complete a total of 4 months of treatment, an adequate regimen for culture-negative pulmonary tuberculosis (see Figure 2 titled "Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis" in the original guideline document). If there is no clinical or radiographic response by 2 months, treatment can be stopped and other diagnoses including inactive tuberculosis considered.

If AFB smears are negative and suspicion for active tuberculosis is low, treatment can be deferred until the results of mycobacterial cultures are known and a comparison chest radiograph is available (usually within 2 months) (see Figure 2 titled "Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis" in the original guideline document). In low-suspicion patients not initially being treated, if cultures are negative, the PPD-tuberculin skin test is positive (5 mm or greater induration), and the chest radiograph is unchanged after 2 months, one of the three regimens recommended for the treatment of latent tuberculosis infection could be used. These include (1) INH for a total of 9 months, (2) RIF with or without INH for a total of 4 months, or (3) RIF and PZA for a total of 2 months. Because of reports of an increased rate of hepatotoxicity with the RIF--PZA regimen, it should be reserved for patients who are not likely to complete a longer course of treatment, can be monitored closely, and do not have contraindications to the use of this regimen.

Baseline and Follow-Up Evaluations

Patients suspected of having tuberculosis should have appropriate specimens collected for microscopic examination and mycobacterial culture. When the lung is the site of disease, three sputum specimens should be obtained. Sputum induction with hypertonic saline may be necessary to obtain specimens and bronchoscopy (both performed under appropriate infection control measures) may be considered for patients who are unable to produce sputum, depending on the clinical circumstances. Susceptibility testing for INH, RIF, and EMB should be performed on a positive initial culture, regardless of the source of the specimen. Second-line drug susceptibility testing should be done only in reference laboratories and be limited to specimens from patients who have had prior therapy, who are contacts of patients with drug-resistant tuberculosis, who have demonstrated resistance to rifampin or to other first-line drugs, or who have positive cultures after more than 3 months of treatment.

It is recommended that all patients with tuberculosis have counseling and testing for HIV infection, at least by the time treatment is initiated, if not earlier. For patients with HIV infection, a CD4⁺ lymphocyte count should be obtained. Patients with risk factors for hepatitis B or C viruses (e.g., injection drug use, foreign birth in Asia or Africa, HIV infection) should have serologic tests for these viruses. For all adult patients baseline measurements of serum amino transferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count should be obtained. Testing of visual acuity and red-green color discrimination should be obtained when EMB is to be used.

During treatment of patients with pulmonary tuberculosis, a sputum specimen for microscopic examination and culture should be obtained at a minimum of monthly intervals until two consecutive specimens are negative on culture. More frequent AFB smears may be useful to assess the early response to treatment and to provide an indication of infectiousness. For patients with extrapulmonary tuberculosis the frequency and kinds of evaluations will depend on the site involved. In addition, it is critical that patients have clinical evaluations at least monthly to identify possible adverse effects of the antituberculosis medications and to assess adherence. Generally, patients do not require follow-up after

completion of therapy but should be instructed to seek care promptly if signs or symptoms recur.

Routine measurements of hepatic and renal function and platelet count are not necessary during treatment unless patients have baseline abnormalities or are at increased risk of hepatotoxicity (e.g., hepatitis B or C virus infection, alcohol abuse). At each monthly visit patients taking EMB should be questioned regarding possible visual disturbances including blurred vision or scotomata; monthly testing of visual acuity and color discrimination is recommended for patients taking doses that on a milligram per kilogram basis are greater than those listed in the original guideline document (see Table 5 titled "Suggested ethambutol doses, using whole tablets, for adults weighing 40-90 kilograms" in the original guideline document) and for patients receiving the drug for longer than 2 months.

Identification and Management of Patients at Increased Risk of Treatment Failure and Relapse

The presence of cavitation on the initial chest radiograph combined with having a positive sputum culture at the time the initial phase of treatment is completed has been shown in clinical trials to identify patients at high risk for adverse outcomes (treatment failure, usually defined by positive cultures after 4 months of treatment, or relapse, defined by recurrent tuberculosis at any time after completion of treatment and apparent cure). For this reason it is particularly important to conduct a microbiological evaluation 2 months after initiation of treatment (See Figure 1 titled "Treatment algorithm for tuberculosis" in the original guideline document). Approximately 80% of patients with pulmonary tuberculosis caused by drug-susceptible organisms who are started on standard four-drug therapy will have negative sputum cultures at this time. Patients with positive cultures after 2 months of treatment should undergo careful evaluation to determine the cause. For patients who have positive cultures after 2 months of treatment and have not been receiving DOT, the most common reason is nonadherence to the regimen. Other possibilities, especially for patients receiving DOT, include extensive cavitary disease at the time of diagnosis, drug resistance, malabsorption of drugs, laboratory error, and biological variation in response.

In the United States Public Health Service (USPHS) Study 22, nearly 21% of patients in the control arm of the study (a continuation phase of twice weekly INH and RIF) who had both cavitation on the initial chest radiograph and a positive culture at the 2-month juncture relapsed. Patients who had only one of these factors (either cavitation or a positive 2-month culture) had relapse rates of 5--6% compared with 2% for patients who had neither risk factor. In view of this evidence, it is recommended that, for patients who have cavitation on the initial chest radiograph and whose 2-month culture is positive, the minimum duration of treatment should be 9 months (a total of 84--273 doses depending on whether the drugs are given daily or intermittently) (see Figure 1 titled "Treatment algorithm for tuberculosis" in the original guideline document and Table above titled "Drug regimes for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms"). The recommendation to lengthen the continuation phase of treatment is based on expert opinion and on the results of a study of the optimal treatment duration for patients with silicotuberculosis showing that extending treatment from 6 to 8 months greatly reduced the rate of relapse (Rating AII). The recommendation is also supported by the results of a trial in

which the once weekly INH--rifapentine continuation phase was extended to 7 months for patients at high risk of relapse. The rate of relapse was reduced significantly compared with historical control subjects from another trial in which the continuation phase was 4 months.

For patients who have either cavitation on the initial film or a positive culture after completing the initial phase of treatment (i.e., at 2 months), the rates of relapse were 5--6%. In this group decisions to prolong the continuation phase should be made on an individual basis.

Completion of Treatment

A full course of therapy (completion of treatment) is determined more accurately by the total number of doses taken, not solely by the duration of therapy. For example, the "6-month" daily regimen (given 7 days/week; see below) should consist of at least 182 doses of INH and RIF, and 56 doses of PZA. Thus, 6 months is the minimum duration of treatment and accurately indicates the amount of time the drugs are given only if there are no interruptions in drug administration. In some cases, either because of drug toxicity or nonadherence to the treatment regimen, the specified number of doses cannot be administered within the targeted period. In such cases the goal is to deliver the specified number of doses within a recommended maximum time. For example, for a 6-month daily regimen the 182 doses should be administered within 9 months of beginning treatment. If treatment is not completed within this period, the patient should be assessed to determine the appropriate action to take---continuing treatment for a longer duration or restarting treatment from the beginning, either of which may require more restrictive measures to be used to ensure completion.

Clinical experience suggests that patients being managed by DOT administered 5 days/week have a rate of successful therapy equivalent to those being given drugs 7 days/week. Thus, "daily therapy" may be interpreted to mean DOT given 5 days/week and the required number of doses adjusted accordingly. For example, for the 6-month "daily" regimen given 5 days/week the planned total number of doses is 130. (Direct observation of treatment given 5 days/week has been used in a number of clinical trials, including USPHS Study 22, but has not been evaluated in a controlled trial; thus, this modification should be rated AIII.) As an option, patients might be given the medications to take without DOT on weekends.

Interruptions in treatment may have a significant effect on the duration of therapy. Reinstitution of treatment must take into account the bacillary load of the patient, the point in time when the interruption occurred, and the duration of the interruption. In general, the earlier in treatment and the longer the duration of the interruption, the more serious the effect and the greater the need to restart therapy from the beginning.

Practical Aspects of Patient Management During Treatment

The first-line antituberculosis medications should be administered together; split dosing should be avoided. Fixed-dose combination preparations may be administered more easily than single drug tablets and may decrease the risk of acquired drug resistance and medication errors. Fixed-dose combinations may be

used when DOT is given daily and are especially useful when DOT is not possible, but they are not formulated for use with intermittent dosing. It should be noted that for patients weighing more than 90 kg the dose of PZA in the three-drug combination is insufficient and additional PZA tablets are necessary. There are two combination formulations approved for use in the United States: INH and RIF (Rifamate®) and INH, RIF, and PZA (Rifater®).

Providers treating patients with tuberculosis must be especially vigilant for drug interactions. Given the frequency of comorbid conditions, it is quite common for patients with tuberculosis to be taking a variety of other medications, the effects of which may be altered by the antituberculosis medications, especially the rifamycins. These interactions are described in Section 7 of the original guideline document, titled "Drug Interactions."

Adverse effects, especially gastrointestinal upset, are relatively common in the first few weeks of antituberculosis therapy; however, first-line antituberculosis drugs, particularly RIF, must not be discontinued because of minor side effects. Although ingestion with food delays or moderately decreases the absorption of antituberculosis drugs, the effects of food are of little clinical significance. Thus, if patients have epigastric distress or nausea with the first-line drugs, dosing with meals or changing the hour of dosing is recommended. Administration with food is preferable to splitting a dose or changing to a second-line drug.

Drug-induced hepatitis, the most serious common adverse effect, is defined as a serum AST level more than three times the upper limit of normal in the presence of symptoms, or more than five times the upper limit of normal in the absence of symptoms. If hepatitis occurs INH, RIF, and PZA, all potential causes of hepatic injury, should be stopped immediately. Serologic testing for hepatitis viruses A, B, and C (if not done at baseline) should be performed and the patient questioned carefully regarding exposure to other possible hepatotoxins, especially alcohol. Two or more antituberculosis medications without hepatotoxicity, such as EMB, SM, amikacin/kanamycin, capreomycin, or a fluoroquinolone (levofloxacin, moxifloxacin, or gatifloxacin), may be used until the cause of the hepatitis is identified. Once the AST level decreases to less than two times the upper limit of normal and symptoms have significantly improved, the first-line medications should be restarted in sequential fashion. Close monitoring, with repeat measurements of serum AST and bilirubin and symptom review, is essential in managing these patients.

Treatment in Special Situations

HIV Infection

Recommendations for the treatment of tuberculosis in HIV-infected adults are, with a few exceptions, the same as those for HIV-uninfected adults (see table above titled "Drug regimes for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms"). The INH--rifapentine once weekly continuation phase (Regimens 1c and 2b) is contraindicated in HIV-infected patients because of an unacceptably high rate of relapse, frequently with organisms that have acquired resistance to rifamycins. The development of acquired rifampin resistance has also been noted among HIV-infected patients with advanced immunosuppression treated with twice weekly rifampin- or rifabutin-based

regimens. Consequently, patients with CD4⁺ cell counts <100/microliters should receive daily or three times weekly treatment (Regimen 1/1a or Regimen 3/3a). DOT and other adherence-promoting strategies are especially important for patients with HIV-related tuberculosis.

Management of HIV-related tuberculosis is complex and requires expertise in the management of both HIV disease and tuberculosis. Because HIV-infected patients are often taking numerous medications, some of which interact with antituberculosis medications, it is strongly encouraged that experts in the treatment of HIV-related tuberculosis be consulted. A particular concern is the interaction of rifamycins with antiretroviral agents and other anti-infective drugs. Rifampin can be used for the treatment of tuberculosis with certain combinations of antiretroviral agents. Rifabutin, which has fewer problematic drug interactions, may also be used in place of rifampin and appears to be equally effective although the doses of rifabutin and antiretroviral agents may require adjustment. As new antiretroviral agents and more pharmacokinetic data become available, these recommendations are likely to be modified.

On occasion, patients with HIV-related tuberculosis may experience a temporary exacerbation of symptoms, signs, or radiographic manifestations of tuberculosis while receiving antituberculosis treatment. This clinical or radiographic worsening (paradoxical reaction) occurs in HIV-infected patients with active tuberculosis and is thought to be the result of immune reconstitution as a consequence of effective antiretroviral therapy. Symptoms and signs may include high fevers, lymphadenopathy, expanding central nervous system lesions, and worsening of chest radiographic findings. The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other etiologies, particularly tuberculosis treatment failure. Nonsteroidal anti-inflammatory agents may be useful for symptomatic relief. For severe paradoxical reactions, prednisone (1--2 mg/kg per day for 1--2 weeks, then in gradually decreasing doses) may be used, although there are no data from controlled trials to support this approach (Rating CIII).

Children

Because of the high risk of disseminated tuberculosis in infants and children younger than 4 years of age, treatment should be started as soon as the diagnosis of tuberculosis is suspected. In general, the regimens recommended for adults are also the regimens of choice for infants, children, and adolescents with tuberculosis, with the exception that ethambutol is not used routinely in children. Because there is a lower bacillary burden in childhood-type tuberculosis there is less concern with the development of acquired drug resistance. However, children and adolescents may develop "adult-type" tuberculosis with upper lobe infiltration, cavitation, and sputum production. In such situations an initial phase of four drugs should be given until susceptibility is proven. When clinical or epidemiologic circumstances (see Table above titled "Epidemiological circumstances in which an exposed person is at increased risk of infection with drug-resistant *Mycobacterium tuberculosis*") suggest an increased probability of INH resistance, EMB can be used safely at a dose of 15--20 mg/kg per day, even in children too young for routine eye testing. Streptomycin, kanamycin, or amikacin also can be used as the fourth drug, when necessary.

Most studies of treatment in children have used 6 months of INH and RIF supplemented during the first 2 months with PZA. This three-drug combination has a success rate of greater than 95% and an adverse drug reaction rate of less than 2%. Most treatment studies of intermittent dosing in children have used daily drug administration for the first 2 weeks to 2 months. DOT should always be used in treating children.

Because it is difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis, it is frequently necessary to rely on the results of drug susceptibility tests of the organisms isolated from the presumed source case to guide the choice of drugs for the child. In cases of suspected drug-resistant tuberculosis in a child or when a source case isolate is not available, specimens for microbiological evaluation should be obtained via early morning gastric aspiration, bronchoalveolar lavage, or biopsy.

In general, extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. Exceptions are disseminated tuberculosis and tuberculous meningitis, for which there are inadequate data to support 6-month therapy; thus 9--12 months of treatment is recommended.

The optimal treatment of pulmonary tuberculosis in children and adolescents with HIV infection is unknown. The American Academy of Pediatrics recommends that initial therapy should always include at least three drugs, and the total duration of therapy should be at least 9 months, although there are no data to support this recommendation.

Extrapulmonary Tuberculosis

The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease. Although relatively few studies have examined treatment of extrapulmonary tuberculosis, increasing evidence suggests that 6- to 9-month regimens that include INH and RIF are effective. Thus, a 6-month course of therapy is recommended for treating tuberculosis involving any site with the exception of the meninges, for which a 9- 12-month regimen is recommended. Prolongation of therapy also should be considered for patients with tuberculosis in any site that is slow to respond. The addition of corticosteroids is recommended for patients with tuberculous pericarditis and tuberculous meningitis.

Culture-negative Pulmonary Tuberculosis and Radiographic Evidence of Prior Pulmonary Tuberculosis

Failure to isolate *M. tuberculosis* from persons suspected of having pulmonary tuberculosis on the basis of clinical features and chest radiographic examination does not exclude a diagnosis of active tuberculosis. Alternative diagnoses should be considered carefully and further appropriate diagnostic studies undertaken in persons with apparent culture-negative tuberculosis. The general approach to management is shown in Figure 2, titled "Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis" in the original guideline. A diagnosis of tuberculosis can be strongly inferred by the clinical and radiographic response to antituberculosis treatment. Careful reevaluation should be performed after 2 months of therapy to determine whether there has been a

response attributable to antituberculosis treatment. If either clinical or radiographic improvement is noted and no other etiology is identified, treatment should be continued for active tuberculosis. Treatment regimens in this circumstance include one of the standard 6-month chemotherapy regimens or INH, RIF, PZA, and EMB for 2 months followed by INH and RIF for an additional 2 months (4 months total). However, HIV-infected patients with culture-negative pulmonary tuberculosis should be treated for a minimum of 6 months.

Persons with a positive tuberculin skin test who have radiographic evidence of prior tuberculosis (e.g., upper lobe fibronodular infiltrations) but who have not received adequate therapy are at increased risk for the subsequent development of tuberculosis. Unless previous radiographs are available showing that the abnormality is stable, it is recommended that sputum examination (using sputum induction if necessary) be performed to assess the possibility of active tuberculosis being present. Also, if the patient has symptoms of tuberculosis related to an extrapulmonary site, an appropriate evaluation should be undertaken. Once active tuberculosis has been excluded (i.e., by negative cultures and a stable chest radiograph), the treatment regimens are those used for latent tuberculosis infection: INH for 9 months, RIF (with or without INH) for 4 months, or RIF and PZA for 2 months (for patients who are unlikely to complete a longer course and who can be monitored closely) see Figure 2 titled "Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis" in the original guideline document).

Renal Insufficiency and End-stage Renal Disease

Specific dosing guidelines for patients with renal insufficiency and end-stage renal disease are provided in Table 15 titled "Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis" in the original guideline document. For patients undergoing hemodialysis, administration of all drugs after dialysis is preferred to facilitate DOT and to avoid premature removal of drugs such as PZA and cycloserine. To avoid toxicity it is important to monitor serum drug concentrations in persons with renal failure who are taking cycloserine or EMB. There is little information concerning the effects of peritoneal dialysis on clearance of antituberculosis drugs.

Liver Disease

INH, RIF, and PZA all can cause hepatitis that may result in additional liver damage in patients with preexisting liver disease. However, because of the effectiveness of these drugs (particularly INH and RIF), they should be used if at all possible, even in the presence of preexisting liver disease. If serum AST is more than three times normal before the initiation of treatment (and the abnormalities are not thought to be caused by tuberculosis), several treatment options exist. One option is to treat with RIF, EMB, and PZA for 6 months, avoiding INH. A second option is to treat with INH and RIF for 9 months, supplemented by EMB until INH and RIF susceptibility are demonstrated, thereby avoiding PZA. For patients with severe liver disease a regimen with only one hepatotoxic agent, generally RIF plus EMB, could be given for 12 months, preferably with another agent, such as a fluoroquinolone, for the first 2 months; however, there are no data to support this recommendation.

In all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury.

Pregnancy and Breastfeeding

Because of the risk of tuberculosis to the fetus, treatment of tuberculosis in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. Although all of these drugs cross the placenta, they do not appear to have teratogenic effects. Streptomycin is the only antituberculosis drug documented to have harmful effects on the human fetus (congenital deafness) and should not be used. Although detailed teratogenicity data are not available, PZA can probably be used safely during pregnancy and is recommended by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD). If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

Breastfeeding should not be discouraged for women being treated with the first-line antituberculosis agents because the small concentrations of these drugs in breast milk do not produce toxicity in the nursing newborn. Conversely, drugs in breast milk should not be considered to serve as effective treatment for tuberculosis or for latent tuberculosis infection in a nursing infant. Pyridoxine supplementation (25 mg/day) is recommended for all women taking INH who are either pregnant or breastfeeding. The amount of pyridoxine in multivitamins is variable but generally less than the needed amount.

Management of Relapse, Treatment Failure, and Drug Resistance

Relapse refers to the circumstance in which a patient becomes and remains culture negative while receiving therapy but, at some point after completion of therapy, either becomes culture positive again or has clinical or radiographic deterioration that is consistent with active tuberculosis. In the latter situation rigorous efforts should be made to establish a diagnosis and to obtain microbiological confirmation of the relapse to enable testing for drug resistance. Most relapses occur within the first 6--12 months after completion of therapy. In nearly all patients with tuberculosis caused by drug-susceptible organisms and who were treated with rifamycin-containing regimens using DOT, relapses occur with susceptible organisms. However, in patients who received self-administered therapy or a nonrifamycin regimen and who have a relapse, the risk of acquired drug resistance is substantial. In addition, if initial drug susceptibility testing was not performed and the patient fails or relapses with a rifamycin-containing regimen given by DOT, there is a high likelihood that the organisms were resistant from the outset.

The selection of empirical treatment for patients with relapse should be based on the prior treatment scheme and severity of disease. For patients with tuberculosis that was caused by drug-susceptible organisms and who were treated under DOT, initiation of the standard four-drug regimen is appropriate until the results of drug susceptibility tests are available. However, for patients who have life-threatening forms of tuberculosis, at least three additional agents to which the organisms are likely to be susceptible should be included.

For patients with relapse who did not receive DOT, who were not treated with a rifamycin-based regimen, or who are known or presumed to have had irregular treatment, it is prudent to infer that drug resistance is present and to begin an expanded regimen with INH, RIF, and PZA plus an additional two or three agents based on the probability of in vitro susceptibility. Usual agents to be employed would include a fluoroquinolone (levofloxacin, moxifloxacin, or gatifloxacin), an injectable agent such as SM (if not used previously and susceptibility to SM had been established), amikacin, kanamycin, or capreomycin, with or without an additional oral drug.

Treatment failure is defined as continued or recurrently positive cultures during the course of antituberculosis therapy. After 3 months of multidrug therapy for pulmonary tuberculosis caused by drug-susceptible organisms, 90--95% of patients will have negative cultures and show clinical improvement. Thus, patients with positive cultures after 3 months of what should be effective treatment must be evaluated carefully to identify the cause of the delayed conversion. Patients whose sputum cultures remain positive after 4 months of treatment should be deemed treatment failures.

Possible reasons for treatment failure in patients receiving appropriate regimens include nonadherence to the drug regimen (the most common reason), drug resistance, malabsorption of drugs, laboratory error, and extreme biological variation in response. If treatment failure occurs, early consultation with a specialty center is strongly advised. If failure is likely due to drug resistance and the patient is not seriously ill, an empirical retreatment regimen could be started or administration of an altered regimen could be deferred until results of drug susceptibility testing from a recent isolate are available. If the patient is seriously ill or sputum AFB smears are positive, an empirical regimen should be started immediately and continued until susceptibility tests are available. For patients who have treatment failure, *M. tuberculosis* isolates should be sent promptly to a reference laboratory for drug susceptibility testing to both first- and second-line agents.

A fundamental principle in managing patients with treatment failure is never to add a single drug to a failing regimen; so doing leads to acquired resistance to the new drug. Instead, at least two, and preferably three, new drugs to which susceptibility could logically be inferred should be added to lessen the probability of further acquired resistance. Empirical retreatment regimens might include a fluoroquinolone, an injectable agent such as SM (if not used previously and the patient is not from an area of the world having high rates of SM resistance), amikacin, kanamycin, or capreomycin, and an additional oral agent such as p-aminosalicylic acid (PAS), cycloserine, or ethionamide. Once drug-susceptibility test results are available, the regimen should be adjusted according to the results.

Patients having tuberculosis caused by strains of *M. tuberculosis* resistant to at least INH and RIF (multidrug-resistant [MDR]) are at high risk for treatment failure and further acquired drug resistance. Such patients should be referred to or consultation obtained from specialized treatment centers as identified by the local or state health departments or CDC. Although patients with strains resistant to RIF alone have a better prognosis than patients with MDR strains, they are also at increased risk for treatment failure and additional resistance and should be managed in consultation with an expert.

Definitive randomized or controlled studies have not been performed to establish optimum regimens for treating patients with the various patterns of drug-resistant tuberculosis; thus, treatment recommendations are based on expert opinion, guided by a set of general principles specified in Section 9, titled "Management of Relapse, Treatment Failure, and Drug Resistance" in the original guideline document. Table 16 titled "Potential regimens for the management of patients with drug-resistant pulmonary tuberculosis" in the original guideline document contains treatment regimens suggested for use in patients with various patterns of drug-resistant tuberculosis (all are rated AIII).

The role of resectional surgery in the management of patients with extensive pulmonary MDR tuberculosis has not been established in randomized studies and results have been mixed. Surgery should be performed by surgeons with experience in these situations and only after the patient has received several months of intensive chemotherapy. Expert opinion suggests that chemotherapy should be continued for 1--2 years postoperatively to prevent relapse.

Treatment of Tuberculosis in Low-Income Countries: Recommendations of the WHO and Guidelines from the IUATLD

A summary of the important differences between the recommendations in this document and those of the IUATLD and the WHO is found in Section 10, titled "Treatment of Tuberculosis in Low-Income Countries: Recommendations of the WHO and the IUTLD" of the original guideline document.

Definitions:

Infectious Diseases Society of America/United States Public Health Service Rating System for Strength of Recommendations:

- A. Preferred; should generally be offered
- B. Alternative; acceptable to offer
- C. Offer when preferred or alternative regimens cannot be given
- D. Should generally not be offered
- E. Should never be offered

Infectious Diseases Society of America/United States Public Health Service Rating System for Quality of Evidence:

- I. At least one properly randomized trial with clinical end points
- II. Clinical trials that either are not randomized or were conducted in other populations
- III. Expert opinion

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for:

- The Treatment for Tuberculosis
- The Treatment for Active, Culture-negative Pulmonary Tuberculosis and Inactive Tuberculosis

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- The overall goals for treatment of tuberculosis are 1) to cure the individual patient, and 2) to minimize the transmission of Mycobacterium tuberculosis to other persons. Thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides.
- It is well established that appropriate treatment of tuberculosis rapidly renders the patient noninfectious, prevents drug resistance, minimizes the risk of disability or death from tuberculosis, and nearly eliminates the possibility of relapse.

POTENTIAL HARMS

Overall Potential Harms

- Adverse effects of medications
- Drug interactions

Specific Adverse Effects of First-Line Drugs

- Isoniazid. Asymptomatic elevation of aminotransferases; clinical hepatitis; fatal hepatitis; peripheral neurotoxicity; central nervous system effects; lupus-like syndrome; hypersensitivity reactions; monoamine (histamine/tyramine) poisoning; diarrhea
- Rifampin. Cutaneous reactions; gastrointestinal reactions (nausea, anorexia, abdominal pain); flulike syndrome; hepatotoxicity; severe immunologic reactions; orange discoloration of bodily fluids (sputum, urine, sweat, tears); drug interactions due to induction of hepatic microsomal enzymes
- Rifabutin. Hematologic toxicity; uveitis; gastrointestinal symptoms; polyarthralgias; hepatotoxicity; pseudojaundice (skin discoloration with normal bilirubin); rash; flulike syndrome; orange discoloration of bodily fluids (sputum, urine, sweat, tears)
- Rifapentine. Similar to those associated with RIF; may increase metabolism of coadministered drugs that are metabolized by these enzymes
- Pyrazinamide. Hepatotoxicity; gastrointestinal symptoms (nausea, vomiting); nongouty polyarthralgia; asymptomatic hyperuricemia; acute gouty arthritis; transient morbilliform rash; dermatitis
- Ethambutol: Retrobulbar neuritis; peripheral neuritis; cutaneous reactions

Specific Adverse Effects of Second-Line Drugs

- Cycloserine. Central nervous system effects
- Ethionamide. Gastrointestinal effects; hepatotoxicity; neurotoxicity; endocrine effects
- Streptomycin. Ototoxicity; neurotoxicity; nephrotoxicity
- Amikacin and kanamycin. Ototoxicity; nephrotoxicity
- Capreomycin. Nephrotoxicity; ototoxicity
- p-Aminosalicylic acid. Hepatotoxicity; gastrointestinal distress; malabsorption syndrome; hypothyroidism; coagulopathy
- Levofloxacin. Gastrointestinal disturbance; neurologic effects; cutaneous reactions

Note: Refer to the original guideline document for details about the adverse effects listed above.

Drug Interactions

- Drug interactions due to rifamycins. The drugs used to treat tuberculosis affect the metabolism of many other drugs, and can result in a lack of efficacy (interactions with the rifamycins) or toxicity (interactions with isoniazid and the fluoroquinolones). Most of the clinically relevant drug--drug interactions involving the antituberculosis drugs are due to the effect of the rifamycins (rifampin, rifabutin, and rifapentine) on the metabolism of other drugs. All of the rifamycins are inducers of a variety of metabolic pathways, particularly those involving the various isozymes of the cytochrome P450 system. By inducing the activity of metabolic enzymes, rifamycin therapy results in a decrease in the serum concentrations of many drugs, sometimes to levels that are subtherapeutic. The rifamycins differ substantially in their potency as enzyme inducers; rifampin is the most potent, rifapentine is intermediate, and rifabutin is the least potent enzyme inducer. The well-described, clinically relevant drug-drug interactions involving the rifamycins are presented in Table 12 of the original guideline document.
- Drug interactions due to isoniazid. Isoniazid is a relatively potent inhibitor of several cytochrome P450 isozymes (CYP2C9, CYP2C19, and CYP2E1), but has minimal effect on CYP3A. As an inhibitor, isoniazid can increase concentrations of some drugs to the point of toxicity. The clearest examples of toxicity due to the inhibitory activity of isoniazid are the anticonvulsants, phenytoin and carbamazepine. Isoniazid also increases concentrations of benzodiazepines metabolized by oxidation, such as diazepam and triazolam, but not those metabolized by conjugation, such as oxazepam. It is worth noting that rifampin has the opposite effect on the serum concentrations of many of these drugs. The available data demonstrate that the inductive effect of rifampin outweighs the inhibitory effect of isoniazid, so that the overall effect of combined therapy with rifampin and isoniazid is a decrease in the concentrations of drugs such as phenytoin and diazepam. Isoniazid may increase toxicity of other drugs---acetaminophen, valproate, serotonergic antidepressants, disulfiram, warfarin, and theophylline---but these potential interactions have not been well studied.
- Drug interactions due to fluoroquinolones. Ciprofloxacin inhibits the metabolism of theophylline and can cause clinical theophylline toxicity. However, levofloxacin, gatifloxacin, and moxifloxacin do not affect theophylline metabolism.

CONTRAINDICATIONS

CONTRAINDICATIONS

- The once-weekly continuation phase is contraindicated in patients with HIV infection because of an unacceptable rate of failure/relapse, often with rifamycin-resistant organisms.
- Preexisting gout is generally a contraindication to the use of pyrazinamide.
- Streptomycin is contraindicated in pregnancy.
- Both amikacin and kanamycin are contraindicated in pregnant women because of risk of fetal nephrotoxicity and congenital hearing loss.
- P-Aminosalicylic acid (PAS) is contraindicated in severe renal insufficiency because of the accumulation of the acetylated form.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The recommendations in this statement are not applicable under all epidemiologic circumstances or across all levels of resources that are available to tuberculosis control programs worldwide. Although the basic principles of therapy described in this document apply regardless of conditions, the diagnostic approach, methods of patient supervision, and monitoring for response and for adverse drug effects, and in some instances the regimens recommended, are quite different in high-incidence, low-income areas compared with low-incidence, high-income areas of the world. A summary of the important differences between the recommendations in this document and those of the International Union Against Tuberculosis and Lung Disease (IUATLD) and the World Health Organization (WHO) is found in the original guideline document.
- Many possible interactions involving the rifamycins have not been investigated fully and additional clinically relevant interactions undoubtedly will be described. Therefore, it is important to check all concomitant medications for possible, as well as confirmed, drug--drug interactions with rifamycins.
- The following drugs, which are suggested for use in selected cases, are not approved by the Food and Drug Administration for treatment of tuberculosis: rifabutin, amikacin, kanamycin, moxifloxacin, gatifloxacin, and levofloxacin.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Successful treatment of tuberculosis depends on more than the science of chemotherapy. To have the highest likelihood of success, chemotherapy must be provided within a clinical and social framework based on an individual patient's circumstances. Optimal organization of treatment programs requires an effective network of primary and referral services and cooperation between clinicians and public health officials, between health care facilities and community outreach programs, and between the private and public sectors of medical care. Section 2

of the original guideline describes the approaches to organization of treatment that serve to ensure that treatment has a high likelihood of being successful.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Neff M. ATS, CDC, and IDSA update recommendations on the treatment of tuberculosis. Am Fam Physician 2003 Nov 1;68(9):1854, 1857-8, 1861-2. [PubMed](#)

Treatment of tuberculosis. MMWR Recomm Rep 2003 Jun 20;52(RR-11):1-77. [534 references] [PubMed](#)

ADAPTATION

Not applicable: Guideline was not adapted from another source.

DATE RELEASED

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GUIDELINE DEVELOPER(S)

American Thoracic Society - Medical Specialty Society
Centers for Disease Control and Prevention - Federal Government Agency [U.S.]
Infectious Diseases Society of America - Medical Specialty Society

GUIDELINE DEVELOPER COMMENT

The current revision of this guideline was cosponsored by the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA).

Representatives of the American Academy of Pediatrics (AAP), the (United States) National Tuberculosis Controllers Association (NTCA), the Canadian Thoracic

Society (CTS), the Union Against Tuberculosis and Lung Disease (IUATLD), and the World Health Organization (WHO) also participated in the revision.

SOURCE(S) OF FUNDING

American Thoracic Society
Centers for Disease Control and Prevention (CDC)
Infectious Diseases Society of America

GUIDELINE COMMITTEE

Joint Committee of the American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), and the Centers for Disease Control and Prevention (CDC)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Michael Iseman, M.D., has indicated that he has a financial relationship with Ortho-McNeil, which manufactures Levaquin®. The remaining preparers have signed a conflict of interest disclosure form that verifies no conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

- [HTML Format](#)
- [Portable Document Format \(PDF\)](#)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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