Treatment of Tuberculosis

American Thoracic Society, CDC, and Infectious Diseases Society of America

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This Official Joint Statement of the American Thoracic Society, CDC, and the Infectious Diseases Society of America was approved by the ATS Board of Directors, by CDC, and by the Council of the IDSA in October 2002. This report appeared in the American Journal of Respiratory and Critical Care Medicine (2003;167:603–62) and is bc America, and the MMWR readership.

Purpose

The recommendations in this document are intended to guide the treatment of tuberculosis in settings where mycobacterial cultures, drug susceptibility testing, radiographic facilities, and second-line drugs are routinely available. In areas where these resources are not available, the recommendations provided by the World Health Organization be followed.

What’s New In This Document

- The responsibility for successful treatment is clearly assigned to the public health program or private provider, not the patient.
- It is strongly recommended that the initial treatment strategy utilize patient-centered case management with an adherence plan that emphasizes directly observed therapy.
- Recommended treatment regimens are rated according to the strength of the evidence supporting their use. Where possible, other interventions are also rated.
- Emphasis is placed on the importance of obtaining sputum cultures at the time of completion of the initial phase of therapy, and at the time of completion of the continuation phase of therapy.
- Extended treatment is recommended for patients with drug-susceptible pulmonary tuberculosis who have cavitation on the initial chest film and who have positive sputum cultures at the time 2 months of treatment.
- Treatment completion is defined by number of doses ingested, as well as the duration of treatment administration.
- The roles of rifabutin, rifapentine, and the fluoroquinolones are discussed and a regimen with rifapentine in a once-weekly dosage form is recommended.
- Special treatment situations, including human immunodeficiency virus infection, tuberculosis in children, extrapulmonary tuberculosis, and renal disease are discussed in detail.
- The management of tuberculosis caused by drug-resistant organisms is updated.
- These recommendations are compared with those of the WHO and the IUATLD and the DOTS strategy is described.
- The current status of research to improve treatment is reviewed.

Summary

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 M. tuberculosis among 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 must be responsible not only for prescribing an appropriate regimen but also for successful completion of therapy. Prescribing physicians must have a clear understanding of roles and responsibilities, oversight of treatment may be shared between a public health program and a private provider, not to the patient.

Organization and Supervision of Treatment

Treatment of patients with tuberculosis is most successful within a comprehensive framework that addresses both 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 (DOT), in which patients are observed to ingest each dose of antituberculosis medications, to maximize the likelihood that facilitate adherence to the drug regimen. Such measures may include, for example, social service support, treatment incentive and enabler programs, counseling, social workers, and antimicrobial medication adherence support teams.
coordination of tuberculosis services with those of other providers.

**Recommended Treatment Regimens**

The recommended treatment regimens are, in large part, based on evidence from clinical trials and are rated on the basis of a Diseases Society of America (IDSA). The rating system includes a letter (A, B, C, D, or E) that indicates the strength of the evidence supporting the recommendation (Table 1).

There are four recommended regimens for treating patients with tuberculosis caused by drug-susceptible organisms. Although 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 are, in large part, based on evidence from clinical trials and are rated on the basis of a Diseases Society of America (IDSA). The rating system includes a letter (A, B, C, D, or E) that indicates the strength of the evidence supporting the recommendation (Table 1).

The initial phases are denoted by a number plus a letter designation (a, b, or c). Drug doses are shown in Tables 3, 4, and 5.

The general approach to treatment is summarized in Figure 1. Because of the relatively high proportion of adult patients with initial phase for the 6-month regimen to be maximally effective. Thus, in most circumstances, the treatment regimen for all a (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (Table 2, Regimens 1–3). If (when) drug susceptibility children whose visual acuity cannot be monitored, EMB is usually not recommended except when there is an increased likely "adult-type" (upper lobe infiltration, cavity formation) tuberculosis. If PZA cannot be included in the initial phase of treatmen consist of INH, RIF, and EMB given daily for 2 months (Regimen 4). Examples of circumstances in which PZA may be with the initial phase of Regimen 4 until drug susceptibility is determined.

The initial phase may be given daily throughout (Regimens 1 and 4), daily for 2 weeks and then twice weekly for 6 weeks (R EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to INH suggests that EMB can be discontinued safely in less than 2 months (i.e., when susceptibility test results are known), but then

Although clinical trials have shown that the efficacy of streptomycin (SM) is approximately equal to that of EMB in the initi less useful. Thus, SM is not recommended as being interchangeable with EMB unless the organism is known to be susceptibility

The continuation phase (Table 2) of treatment is given for either 4 or 7 months. The 4-month continuation phase should be u three groups: patients with cavitary pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture phase of treatment did not include PZA; and patients being treated with once weekly INH and rifapentine and whose sputum may be given daily (Regimens 1a and 4a), two times weekly by DOT (Regimens 1b, 2a, and 4b), or three times weekly by D noncavitary pulmonary tuberculosis (as determined by standard chest radiography), and negative sputum smears at completion once weekly for 4 months by DOT (Regimens 1c and 2b) (Figure 1). If the culture at completion of the initial phase of treatm months. All of the 6-month regimens, except the INH–rifapentine once weekly continuation phase for persons with HIV inf patients. The once-weekly continuation phase is contraindicated (Rating EI) in patients with HIV infection because of an un twice weekly treatment, either as part of the initial phase (Regimen 2) or continuation phase (Regimens 1b and 2a), is not rec receive either daily (initial phase) or three times weekly (continuation phase) treatment. Regimen 4 (and 4a/4b), a 9-month treatment

**Deciding To Initiate Treatment**

The decision to initiate combination antituberculosis chemotherapy should be based on epidemiologic information; clinical, 1 bacilli (AFB)--stained sputum (smears) (as well as other appropriately collected diagnostic specimens) and cultures for mycob initial evaluation, but a negative PPD-tuberculin skin test does not exclude the diagnosis of active tuberculosis. However, a p tuberculosis, as well as latent tuberculosis infection in persons with stable abnormal chest radiographs consistent with inactiv If the suspicion of tuberculosis is high or the patient is seriously ill with a disorder, either pulmonary or extrapulmonary, that regimens should be initiated promptly, often before AFB smear results are known and usually before mycobacterial culture r diagnosis of tuberculosis. If the diagnosis is confirmed by isolation of *M. tuberculosis* or a positive nucleic acid amplification initial AFB smears and cultures are negative, a diagnosis other than tuberculosis should be considered and appropriate evalu (in this circumstance a reaction of 5 mm or greater induration is considered positive), empirical combination chemotherapy s therapy and no other diagnosis has been established, a diagnosis of culture-negative pulmonary tuberculosis can be made anc of treatment, an adequate regimen for culture-negative pulmonary tuberculosis (Figure 2). If there is no clinical or radiograph tuberculosis considered.

If AFB smears are negative and suspicion for active tuberculosis is low, treatment can be deferred until the results of mycob (months) (Figure 2). In low-suspicion patients not initially being treated, if cultures are negative, the PPD-tuberculin skin test one of the three regimens recommended for the treatment of latent tuberculosis infection could be used. These include (1) IN PZA for a total of 2 months. Because of reports of an increased rate of hepatotoxicity with the RIF--PZA regimen, it should 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 myc obtained. Sputum induction with hypertonic saline may be necessary to obtain specimens and bronchoscopy (both performe produce sputum, depending on the clinical circumstances. Susceptibility testing for INH, RIF, and EMB should be performed susceptibility testing should be done only in reference laboratories and be limited to specimens from patients who have had p demonstrated resistance to rifampin or to other first-line drugs, or who have positive cultures after more than 3 months of tre
It is recommended that all patients with tuberculosis have counseling and testing for HIV infection, at least by the time treatment is to 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), positive serum tests for hepatitis B and C, and the presence of symptoms should be tested for hepatitis B and C. Also, all patients should have measurement of serum amino transferase (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), bilirubin, a 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. More frequent AFB smears may be useful to assess the early response to treatment and to provide an indication of limited disease. Routine measurements of hepatic and renal function and platelet count are not necessary during treatment unless patients have infection, alcohol abuse). At each monthly visit patients taking EMB should be questioned regarding possible visual disturbances and should not be used.

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 drug regimen is started is a positive predictor of treatment failure. In the absence of symptoms, or more than five times the upper limit of normal in the presence of symptoms, or more than five times the upper limit of normal 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 INH, RIF, and PZA, all potential causes of hepatic injury, should be stopped immediately. Serologic testing for hepatitis B and C is recommended that, for patients who have cavitation on the initial film or a positive culture after completing the initial phase of treatment (i.e., at 2 months), the rate of relapse was significantly lower 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 chest radiograph or a positive culture after completing the initial phase of treatment, 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 the duration of treatment. In general, patients do not require follow-up after completion of therapy but should be instructed to seek care promptly if symptoms occur. Routine measurements of hepatic and renal function and platelet count are not necessary during treatment unless patients have infection, alcohol abuse). At each monthly visit patients taking EMB should be questioned regarding possible visual disturbances or other possible hepatotoxins, especially alcohol. Two or more antituberculosis medications without hepatotoxicity, such as INH, RIF, and PZA, all potential causes of hepatic injury, should be stopped immediately. Serologic testing for hepatitis B and C is recommended that, for patients who have cavitation on the initial film or a positive culture after completing the initial phase of treatment (i.e., at 2 months), the rate of relapse was significantly lower 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, the continuation phase should be made on an individual basis.

Practical Aspects of Patient Management During Treatment

The first-line antituberculosis medications should be administered together; split dosing should be avoided. Fixed-dose combinations may be used when DOT is given daily. It should be noted that for patients weighing more than 90 kg the dose of PZA in the three-drug combina 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 concomitant medications, the effects of which may be altered by the antituberculosis medications, especially the rifamycins. These interac Adverse effects, especially gastrointestinal upset, are relatively common in the first few weeks of antituberculosis therapy; havioral changes, especially alcohol, amikacin/kanamycin, capreomycin, or a fluoroquinolone (levofloxacin, moxifloxacin, or gatifloxacin), may be used until the limit of normal and symptoms have significantly improved, the first-line medications should be restarted in sequential fashio
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 non-HIV-infected patients. However, because of the effectiveness of these drugs, DOT and other adherence-promoting strategies are especially important for patients with HIV infection. Promoting strategies are especially important for patients with HIV infection. DOT and other adherence-promoting strategies are especially important for patients with HIV infection.

Management of HIV-related tuberculosis is complex and requires expertise in the management of both HIV disease and tuberculosis. DOT and other adherence-promoting strategies are especially important for patients with HIV infection.

On occasion, patients with HIV-related tuberculosis may experience a temporary exacerbation of symptoms, signs, or radiographic worsening (paradoxical reaction) occurs in HIV-infected patients with active tuberculosis and is thought to be due to immune reconstitution. Streptomycin and isoniazid are not used in children because of an unacceptably high rate of relapse, frequently rifampin resistance has also been noted among HIV-infected patients with advanced immunosuppression treated with twice weekly rifampin.

A diagnosis of tuberculosis can be strongly inferred from a positive tuberculin skin test in a person who has not been previously vaccinated. Unless previous radiographs are available showing that the patient was infected, treatment is usually begun. The diagnosis of tuberculosis is confirmed by isolation of the organism in culture. Failure to isolate the organism is not an indication for terminating therapy. All HIV-infected patients with active tuberculosis should be treated for a minimum of 6 months. 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 treatment regimens. Consequently, patients with CD4 cell counts below 200 cells/μl should always be treated with a 9-month regimen.

**Children**

Because of the high risk of disseminated tuberculosis in infants and children younger than 4 years of age, treatment should be initiated as soon as the diagnosis is suspected. Exceptions are disseminated tuberculosis and tuberculous meningitis, for which there are inadequate treatment regimens. Consequently, patients with CD4 cell counts below 200 cells/μl should always be treated with a 9-month regimen.

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

**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 or diagnostic studies undertaken in persons with a history of tuberculosis is strongly inferred from a positive tuberculin skin test in a person who has not been previously vaccinated. Unless previous radiographs are available showing that the abnormality is stable, it is essential to investigate the possibility of active tuberculosis being present. Also, if the patient has symptoms of tuberculosis related to an extrapulmonary focus (e.g., upper lobe fibronodular changes secondary to tuberculosis), the treatment regimen is those used for latent tuberculosis for 2 months (for patients who are unlikely to complete a longer course and who can be monitored closely) (Figure 2).

**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. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15. For patients with renal insufficiency and end-stage renal disease, dosing guidelines are provided in Table 15.
be used if at all possible, even in the presence of preexisting liver disease. If serum AST is more than three times normal before treatment, 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, Rif, and EMB. Although all of these drugs cross the placenta, they do not appear to have teratogenic effects. Streptomycin (congenital deafness) should not be used. Although detailed teratogenicity data are not available, PZA can probably be used in pregnant women when other regimens are not effective.

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, becomes culture positive again. In the latter situation, rigorous efforts should be made to determine the cause of drug resistance. Most relapses occur within the first 6–12 months after completion of therapy. In nearly all patients with drug-resistant tuberculosis, relapses occur with susceptible organisms. Conversely, drugs in breast milk should not be considered to serve as effective treatment for tuberculosis or for latent tuberculosis. To prevent relapse, treatment recommendations are based on the prior treatment scheme and severity of disease. For patients with tuberculosis that was caused by drug-resistant strains, the initial treatment regimen should consist of a fluoroquinolone, an injectable agent such as amikacin, kanamycin, or capreomycin, and an additional oral 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). 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 added to the failing regimen. If treatment failure occurs, early consultation with a specialty center is strongly advised. If treatment failure occurs, early consultation with a specialty center is strongly advised. If treatment failure occurs, early consultation with a specialty center is strongly advised.

Possible reasons for treatment failure in patients receiving appropriate regimens include nonadherence to the drug regimen, biological variation in response, and initial drug susceptibility testing. If treatment failure occurs, early consultation with a specialty center is strongly advised. If treatment failure occurs, early consultation with a specialty center is strongly advised. If treatment failure occurs, early consultation with a specialty center is strongly advised. If treatment failure occurs, early consultation with a specialty center is strongly advised.

Definitive randomized or controlled studies have not been performed to establish optimum regimens for treating patients with the various patterns of drug resistance. Most relapses occur within the first 6 months postoperatively, so 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 caused by strains resistant to at least INH and RIF, an additional two or three agents based on the probability of drug resistance 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 to have drug-resistant tuberculosis, the initial regimen should consist of 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). If treatment failure occurs, early consultation with a specialty center is strongly advised. If treatment failure occurs, early consultation with a specialty center is strongly advised. If treatment failure occurs, early consultation with a specialty center is strongly advised.

The role of resectional surgery in the management of patients with extensive pulmonary MDR tuberculosis has not been established. Surgeons with experience in these situations and only after the patient has received several months of intensive chemotherapy should consider the role of resectional surgery in the management of patients with extensive pulmonary MDR tuberculosis. Surveys of the literature suggest that the incidence of patients in low-income countries who were born in high-prevalence incidence countries is also important for persons managing these cases to be familiar with the approaches used in the countray. The major international recommendations and guidelines for treating tuberculosis are those of the WHO and of the IUATLD. A distillation of IUATLD practice, validated in the field.
The WHO and IUATLD documents target, in general, countries in which mycobacterial culture, drug susceptibility testing, r differences exist between these new ATS/CDC/IDSA recommendations, and the current tuberculosis treatment recommenda built around a national case management strategy called "DOTS," the acronym for "directly observed therapy, short course," components of DOTS are 1) government commitment to sustained tuberculosis control activities, 2) case detection by spu standardized treatment regimen of 6--8 months for at least all confirmed sputum smear--positive cases, with DOT for at least 5) a standardized recording and reporting system that enables assessment of treatment results for each patient and of the tube A number of other differences exist as well:

- The WHO and the IUATLD recommend diagnosis and classification of tuberculosis cases and assessment of respo recommended because of cost, limited applicability, and lack of facilities.
- Chest radiography is recommended by both the WHO and IUATLD only for patients with negative sputum smear.
- Both 6- and 8-month treatment regimens are recommended by the WHO. The IUATLD recommends an 8-month re suspected of having or known to have HIV infection, ethambutol is substituted for thiacetazone.
- The WHO and the IUATLD recommend a standardized 8-month regimen for patients who have relapsed, had inter considered "chronic" cases and are highly likely to have tuberculosis caused by MDR organisms. Susceptibility test the WHO, if testing and second-line drugs are available. The IUATLD recommendations do not address the issue.
- Neither baseline nor follow-up biochemical testing is recommended by the WHO and the IUATLD. It is recommend them promptly.

A Research Agenda for Tuberculosis Treatment

New antituberculosis drugs are needed for three main reasons: 1) to shorten or otherwise simplify treatment of tuberculosis c 3) to provide more efficient and effective treatment of latent tuberculosis infection. No truly novel compounds that are likely further work to optimize the effectiveness of once-a-week rifapentine regimens using higher doses of the drug and using rif New categories of drugs that have shown promise for use in treating tuberculosis include the nitroimidazopyrans and the ox thought to be necessary for maintaining the latent state, might be useful for treatment of latent tuberculosis infection. A number of other interventions that might lead to improved treatment outcome have been suggested, although none has und administration of "protective" cytokines such as interferon-γ and interleukin-2, and nutritional supplements, especially vitam Research is also needed to identify factors that are predictive of a greater or lesser risk of relapse to determine optimal length supervise treatment. In addition, identification of behavioral factors that identify patients at greater or lesser likelihood of bei

1. Introduction and Background

Since 1971 the American Thoracic Society (ATS) and CDC have regularly collaborated to develop joint guidelines for the di intended to guide both public health programs and health care providers in all aspects of the clinical and public health manag The most recent version of guidelines for the treatment of tuberculosis was published in 1994 (2). The current document differs from its predecessor in a number of important areas that are summarized above. The process by substantially from the previous versions. For the first time the Infectious Diseases Society of America (IDSA) has become a prior statement committees but has not previously been a cosponsor of the document. Practice guidelines that serve to compl representatives of the American Academy of Pediatrics (AAP), the (United States) National Tuberculosis Controllers Associ the revision. By virtue of their different perspectives these committee members served to provide broader input and to help e current guidelines are intended for areas in which mycobacterial cultures, drug susceptibility tests, radiographic facilities, an For this revision of the recommendations essentially all clinical trials of antituberculosis treatment in the English language li IDSA/USPHS rating scale (4). This revision of the recommendations for treatment of tuberculosis presents a significant philosophic departure from previou primarily on the provider or program initiating therapy rather than on the patient. It is well established that appropriate treat the risk of disability or death from tuberculosis, and nearly eliminates the possibility of relapse. For these reasons, antituberc the treatment of, for example, hypertension or diabetes mellitus, wherein the benefits largely accrue to the patient. Provider r of their care. All reasonable attempts should be made to accommodate the patient so that a successful outcome is achieved. F nonadherent.

The recommendations in this statement are not applicable under all epidemiologic circumstances or across all levels of resou of therapy described in this document apply regardless of conditions, the diagnostic approach, methods of patient supervisi recommended, are quite different in high-incidence, low-income areas compared with low-incidence, high-income areas of t document and those of the IUATLD and the WHO is found in Section 10, Treatment of Tuberculosis in Low-Income Countr In the United States there has been a call for the elimination of tuberculosis, and a committee constituted by the Institute of N had two main recommendations related to treatment of tuberculosis: first, that all U.S jurisdictions have health regulations th treatment be administered in the context of patient-centered programs that are based on individual patient characteristics and treatment services, as well as the drugs that are used, to treat patients effectively. This philosophy is the core of the DOTS st Recommendations of the WHO and the IUATLD), developed by the IUATLD and implemented globally by the WHO. Thus.

high- and low-incidence countries, the fundamental concern, regardless of where treatment is given, is ensuring patient adhe
References

2. Organization and Supervision of Treatment
Successful treatment of tuberculosis depends on more than the science of chemotherapy. To have the highest likelihood of an individual patient’s circumstances. Optimal organization of treatment programs requires an effective network of public health departments and community outreach programs, and between the private and public sectors of medical care. This section describes the approaches to organization of treatment that serve to ensure that treatment has a high likelihood of being successful.

As noted previously, antituberculosis chemotherapy is both a personal health measure intended to cure the sick patient and a public health measure intended to control the spread of tuberculosis. Typically, tuberculosis treatment is provided by public health departments, often working in collaboration with other organizations, such as hospitals, hospices, long-term care facilities, and homeless shelters. Private providers and public health departments may work together to ensure that the patient completes therapy.

2.1. Role of the Health Department
The responsibility of the health department in the control of tuberculosis is to ensure that all persons who are suspected of having tuberculosis are identified and evaluated promptly and that an appropriate course of treatment is prescribed and completed successfully (1,2). A critical component of the evaluation scheme is access to proficiency testing. The responsibilities of the health department may be accomplished indirectly by epidemiologic surveillance and monitoring, more directly by provision of diagnostic and treatment services, as well as by conducting epidemiologic investigations. Give mechanisms by which health care is delivered, the means by which the goals of the health department are accomplished may vary. In dealing with individual patients, approaches that focus on each person’s needs and characteristics should be used to determine the most effective treatment plans. The patient is an active participant in the process, working closely with the physician and/ or nurse, outreach workers, and other community resources. The success of tuberculosis control in the United States is due to the efforts of health departments working in collaboration with other organizations.
ensure his/her participation in developing the treatment plan. Ideally, a specific case manager is assigned individual responsibilities and revised as needed. These reviews may be accomplished in meetings between the patient and the assigned provider, as we principle of using the least restrictive measures that are likely to achieve success. The full spectrum of measures that may be outpatient setting to legally mandated hospitalization (4). Directly observed therapy (DOT) is the preferred initial means to a stepwise fashion. Any approach must be balanced, ensuring that the needs and rights of the patient, as well as those of the provider, are met. Care plans for patients being managed in the private sector should be developed jointly by the health department and the private provider, and must address identified and anticipated barriers to adherence.

2.2. Promoting Adherence

Louis Pasteur once said, "The microbe is nothing...the terrain everything" (5). Assuming appropriate drugs are prescribed, the treatment becomes the most important consideration in completion of tuberculosis treatment. Many factors may be part of the linguistic barriers to cooperation, lifestyle differences, homelessness, substance abuse, and a large number of other condition tuberculosis (6). Barriers may be patient related, such as conflicting health beliefs, alcohol or drug dependence, or mental illness (7). Effective tuberculosis case management identifies and characterizes the terrain and determines an approach that is, by increasing communication with the patient, it provides opportunities for further education con.

To maximize completion of therapy, patient-centered programs identify and utilize a broad range of approaches based on the initial strategy and deserves special emphasis. Although DOT itself has not been subjected to controlled trials in low-incidence areas, strongly suggest that DOT, coupled with individualized case management, leads to the best treatment results (8–10). To date, showed no benefit and one (11) in which there was a significant advantage for DOT. What is clear from these studies is that aggressive interventions when patients miss doses. Using DOT in this manner can only improve results.

DOT can be provided daily or intermittently in the office, clinic, or in the "field" (patient's home, place of employment, scho personnel. DOT should be used for all patients residing in institutional settings such as hospitals, nursing homes, or correctional facilities. Nonetheless, even in such supervised settings careful attention must be paid to ensuring that ingest preparations that use intermittent drug administration have all doses administered under DOT because of the potentially serious drug reactions, and clinical worsening of tuberculosis. DOT provides a close connection to the health care system for a group.

The use of DOT does not guarantee ingestion of all doses of every medication (15). Patients may miss appointments, may not patients, including those who are being treated by DOT, should continue to be monitored for signs of treatment failure. DOT incentives and enablers described subsequently (16–20). Patients who are more likely to present a transmission risk to others when resources are limited. When DOT is not being used, fixed-dose combination preparations (see Section 6.2, Fixed-Dose patient taking only one drug and may help prevent the development of drug resistance. Combination formulations are easier to administer if adherence is a problem. Depending on the identified obstacles to completion of therapy, the treatment plan may also include enablers and incentives: utilizes DOT in addition to other adherence-promoting tools (9,21,22). These studies demonstrate, as shown in Figure 3, that completion rates (in excess of 90% across a range of geographic and socioeconomic settings), and reinforces the importance of intensive educational efforts should be initiated as soon as the patient is suspected of having tuberculosis. The instruction should be tailored to tuberculosis, expected outcomes of treatment, the benefits and possible adverse effects of the drug regimen, methods of sup透视 medication regimen must be explained in clear, understandable language and the verbal explanation followed with written in same language. Materials should be appropriate for the culture, language, age, and reading level of the patient. Relevant info.

The patient's clinical progress and the treatment plan must be reviewed at least monthly to evaluate the response to therapy and a discussion of infectiousness and infection control. The health department and the private provider, and must address identified and anticipated barriers to adherence.

3. References

3. Drugs in Current Use

Currently, there are 10 drugs approved by the United States Food and Drug Administration (FDA) for treating tuberculosis (Table 9). In addition, the fluoroquinolones, although not approved by the FDA for tuberculosis, are used relatively commonly to treat tuberculosis caused by drug-resistant organisms or for patients who are intolerant of some of the first-line drugs. Rifabutin, approved for use in preventing *Mycobacterium avium* complex disease in patients with HIV infection but not approved for tuberculosis, is useful for treating tuberculosis in patients concurrently taking drugs that have unacceptable interactions with other rifamycins. Amikacin and kanamycin, nearly identical aminoglycoside drugs used in treating patients with tuberculosis caused by drug-resistant organisms, are not approved by the FDA for tuberculosis.

Of the approved drugs isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) are considered first-line antituberculosis agents and form the core of initial treatment regimens. Rifabutin and rifapentine may also be considered first-line agents under the specific situations described below. Streptomycin (SM) was formerly considered to be a first-line agent and, in some instances, is still used in initial treatment; however, an increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. The remaining drugs are reserved for special situations such as drug intolerance or resistance. The drug preparations available currently and the recommended doses are shown in Tables 3, 4, and 5.

3.1. First-Line Drugs

3.1.1. Isoniazid

**Role in treatment regimen.** Isoniazid (INH) is a first-line agent for treatment of all forms of tuberculosis caused by organisms known or presumed to be susceptible to the drug. It has profound early bactericidal activity against rapidly dividing cells (1,2).

**Dose.** See Table 3.

*Adults (maximum):* 5 mg/kg (300 mg) daily; 15 mg/kg (900 mg) once, twice, or three times weekly.

*Children (maximum):* 10--15 mg/kg (300 mg) daily; 20--30 mg/kg (900 mg) twice weekly (3).

**Preparations.** Tablets (50 mg, 100 mg, 300 mg); syrup (50 mg/5 ml); aqueous solution (100 mg/ml) for intravenous or intra

**Adverse effects.**

*Asymptomatic elevation of aminotransferases:* Aminotransferase elevations up to five times the upper limit of normal occur in some patients; enzyme levels usually return to normal even with continued administration of the drug.
Clinical hepatitis: (see Table 10.) Data indicate that the incidence of clinical hepatitis is lower than was previously thought. A latent tuberculosis infection in an urban tuberculosis control program (5). Prior studies suggested a higher rate, and a meta-analysis (6–8). In the meta-analysis the rate of clinical hepatitis was 1.6% when INH was given with other agents, not including RIF. For INH alone the risk increases with increasing age; it is uncommon in persons less than 20 years of age but is nearly 2% in disease, in those with a history of heavy alcohol consumption, and, data suggest, in the postpartum period, particularly among women. Fatal hepatitis: A large scale study estimated the rate of fatal hepatitis to be 0.023%, but more recent studies suggest the rate is slightly lower. Clotting abnormalities (including hypoprothrombinemia) and continued administration of INH despite onset of symptoms of hepatitis (12).

Peripheral neurotoxicity (13,14): This adverse effect is dose related and is uncommon (less than 0.2%) at conventional doses. Neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as for pregnant and elderly patients, are at increased risk. CNS penetration. Penetration is excellent. Cerebrospinal fluid (CSF) concentrations are similar to concentrations achieved in serum.

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) INH can be used safely without dose adjustments. Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The risk of drug accumulation and drug-induced hepatitis may be increased in patients with liver disease. Laboratory and clinical monitoring should be more frequent in such situations.

Monitoring. Routine monitoring is not necessary. However, for patients who have preexisting liver disease or who develop symptoms of hepatitis, serum concentrations of phenytoin and carbamazepine may be increased. Serum concentrations of the anticonvulsants are limited by the decrease caused by RIF. Thus, it is important to measure serum phenytoin concentrations to ensure adequate blood levels.

3.1.2. Rifampin

Role in treatment regimen. Rifampin (RIF) is a first-line agent for treatment of all forms of tuberculosis caused by organisms dividing rapidly (early bactericidal activity) (1) and against semidormant bacterial populations, thus accounting for its sterilizing effect.

Dose. See Table 3.

Adults (maximum): 10 mg/kg (600 mg) once daily, twice weekly, or three times weekly.

Children (maximum): 10–20 mg/kg (600 mg) once daily or twice weekly.

Preparations. Capsules (150 mg, 300 mg); contents of capsule may also be mixed in an appropriate diluent to prepare an oral suspension.

Adverse effects (28).

Cutaneous reactions (29): Pruritis with or without rash may occur in as many as 6% of patients but is generally self-limited. More severe, true hypersensitivity reactions are uncommon, occurring in 0.07–0.3% of patients (17,31,32).

Gastrointestinal reactions (nausea, anorexia, abdominal pain): The incidence is variable, but symptoms are rarely severe enough to require chronic hemodialysis (26).

Flulike syndrome: This may occur in 0.4–0.7% of patients receiving 600 mg twice weekly but not with daily administration of a higher dose (29,35).

Hepatotoxicity: Transient asymptomatic hyperbilirubinemia may occur in as many as 0.6% of patients receiving the drug. M Hepatitis is more common when the drug is given in combination with INH (2.7%) than when given alone (nearly 0%) or in combination with other antituberculosis drugs such as oral contraceptives, metformin, and antiretroviral agents. Because information regarding rifamycin drug interactions is evolving rapidly, readers should consider these effects.

Use in pregnancy. RIF is considered safe in pregnancy (38).

CNS penetration. Concentrations in the CSF are generally sufficient for clinical efficacy. Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) RIF can be used safely without dose reductions.

Use in hepatic disease. (see Section 8.8: Hepatic Disease.) Clearance of the drug may be impaired in the presence of liver disease, particularly in patients with underlying liver disease, such as oral contraceptives, methadone, and warfarin. In addition there are important bidirectional interactions between RIF and INH (2.7%) than when given alone (nearly 0%) or in combination with drugs other than INH (1.1%) (16,17).

Table 3

<table>
<thead>
<tr>
<th>Rifampin Dose</th>
<th>Adults (maximum)</th>
<th>Children (maximum)</th>
<th>Preparations</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg (600 mg)</td>
<td>10–20 mg/kg (600 mg)</td>
<td>Capsules (150 mg, 300 mg)</td>
<td>Cutaneous reactions (29): Pruritis with or without rash may occur in as many as 6% of patients but is generally self-limited. More severe, true hypersensitivity reactions are uncommon, occurring in 0.07–0.3% of patients (17,31,32). Gastrointestinal reactions (nausea, anorexia, abdominal pain): The incidence is variable, but symptoms are rarely severe enough to require chronic hemodialysis (26). Flulike syndrome: This may occur in 0.4–0.7% of patients receiving 600 mg twice weekly but not with daily administration of a higher dose (29,35). Hepatotoxicity: Transient asymptomatic hyperbilirubinemia may occur in as many as 0.6% of patients receiving the drug. M Hepatitis is more common when the drug is given in combination with INH (2.7%) than when given alone (nearly 0%) or in combination with other antituberculosis drugs such as oral contraceptives, metformin, and antiretroviral agents. Because information regarding rifamycin drug interactions is evolving rapidly, readers should consider these effects. Use in pregnancy. RIF is considered safe in pregnancy (38). CNS penetration. Concentrations in the CSF are generally sufficient for clinical efficacy. Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) RIF can be used safely without dose reductions. Use in hepatic disease. (see Section 8.8: Hepatic Disease.) Clearance of the drug may be impaired in the presence of liver disease, particularly in patients with underlying liver disease, such as oral contraceptives, methadone, and warfarin. In addition there are important bidirectional interactions between RIF and INH (2.7%) than when given alone (nearly 0%) or in combination with drugs other than INH (1.1%) (16,17).</td>
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</table>
Monitoring. No routine monitoring tests are required. However, rifampin causes many drug interactions described in Section 7, the drugs in question.

3.1.3. Rifabutin

Role in treatment regimen. Rifabutin is used as a substitute for RIF in the treatment of all forms of tuberculosis caused by HIV or for patients who are receiving any medication having unacceptable interactions with rifampin (44) or have experience with rifabutin.

Dose. See Table 3.

Adults (maximum): 5 mg/kg (300 mg) daily, twice, or three times weekly. The dose may need to be adjusted when there is a possible increase in the dose of rifabutin should be increased to 450–600 mg either daily or intermittently. Bacterial infection may be treated with the CDC web site, http://www.cdc.gov/nchstp/tb/, to obtain the most up-to-date information.

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The drug should be used in patients with underlying liver disease. Dose reduction may be necessary in patients with severe liver dysfunction (42, 43–47).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Rifabutin may be used without dosage adjustment in patients with renal insufficiency and end-stage renal disease (50).

Monitoring. Monitoring is similar to that recommended for rifampin. Although drug interactions are less problematic with rifabutin, they still occur and close monitoring is required.

3.1.4. Rifapentine

Role in treatment regimen. Rifapentine may be used once weekly with INH in the continuation phase of treatment for HIV infection. The dose may need to be increased to 450–600 mg either daily or intermittently. Bacterial infection may be treated with the CDC web site, http://www.cdc.gov/nchstp/tb/, to obtain the most up-to-date information.

Dose. See Table 3.

Adults (maximum): 10 mg/kg (600 mg), once weekly during the continuation phase of treatment. Data have suggested that a dose of 900 mg is well tolerated but the clinical efficacy of this dose has not been established.

Children: The drug is not approved for use in children.

Preparation. Tablet (150 mg) for oral administration.

Adverse effects.

Hematologic toxicity: In a placebo-controlled, double-blind trial involving patients with advanced acquired immunodeficiency syndrome (AIDS), the drug was tested at dosages of 10 mg/kg (600 mg), once weekly during the continuation phase of treatment. Data have suggested that a dose of 900 mg is well tolerated but the clinical efficacy of this dose has not been established.

Use in pregnancy. There is insufficient data to recommend the use of rifabutin in pregnant women; thus, the drug should be reserved for patients who are receiving any medication having unacceptable interactions with rifampin (44) or have experience with rifabutin.

CNS penetration. The drug penetrates inflamed meninges (50).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Rifabutin may be used without dosage adjustment in patients with renal insufficiency and end-stage renal disease (50).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The drug should be used in patients with and without HIV infection, with increased clinical and laboratory monitoring (50).

Monitoring. Monitoring is similar to that recommended for rifampin. Although drug interactions are less problematic with rifapentine, they still occur and close monitoring is required.

3.1.5. Pyrazinamide

Role in treatment regimen. Pyrazinamide (PZA) is a first-line agent for the treatment of all forms of tuberculosis caused by
greatest activity against the population of dormant or semidormant organisms contained within macrophages or the acidic environment of caseous foci (73, 74). The agent penetrates the meninges in the presence of inflammation but does not have demonstrated efficacy in patients with reactivation meningitis (72). EMB should be administered at a dose of 15--20 mg/kg three times a week after dialysis in patients with end-stage renal disease (72).

**Use in pregnancy.** There is little information about the safety of PZA in pregnancy. However, when there are sound reasons for administering PZA to a pregnant woman (e.g., concern with INH or RIF resistance), EMB should be used if there is concern with resistance to INH or RIF, because the risk of optic toxicity is lower in patients receiving PZA compared to INH or RIF.

### 3.1.6. Ethambutol

**Role in treatment regimens.** Ethambutol (EMB) is a first-line drug for treating all forms of tuberculosis. It is included in in treatment regimens for INH and RIF. However, EMB is generally not recommended for routine use in children whose visual acuity cannot be monitored. Ethambutol is a rare adverse effect that may occur in up to 40% of patients receiving daily doses of PZA. This rarely requires discontinuation of treatment (65). The drug can be used safely in older children but should be used with caution in children less than 5 years of age, generally a contraindication to the use of EMB in patients with renal insufficiency.

**Dose.** See Table 3 and 5.

**Adults:** 20--25 mg/kg per day. Recommended adult dosages by weight, using whole tablets, are listed in Table 4.

**Children (maximum):** 15--30 mg/kg (2.0 g) daily; 50 mg/kg twice weekly (2.0 g).

**Preparations.** Tablets (500 mg, scored).

**Adverse effects.**

**Hepatotoxicity:** Early studies (55, 56) using doses of 40--70 mg/kg per day reported high rates of hepatotoxicity. However, in one study, however, hepatotoxicity attributable to PZA used in standard doses occurred at a rate of about 1% (55, 56). In younger children EMB can be used if there is concern with resistance to INH or RIF (66). In younger children EMB can be used if there is concern with resistance to INH or RIF.

**Use in hepatic disease.** (See Section 8.8: Hepatic Disease.) Although the frequency is slightly lower than with INH or RIF, the drug can cause liver injury that may be severe and prolonged. If the drug is used in patients with underlying liver disease, laboratory and clinical monitoring should be increased.

**Monitoring.** Serum uric acid measurements are not recommended as a routine but may serve as a surrogate marker for comorbid underlying liver disease or when it is used with rifampin in treating latent tuberculosis infection.

**CNS penetration.** The drug passes freely into the CSF, achieving concentrations equivalent to those in serum (64).

**Use in renal disease.** (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) EMB is cleared primarily by the kidney (65). However, in patients with renal insufficiency, the drug may be administered at a dose of 25 mg/kg per day or less (15, 34, 57). The risk of hyperuricemia caused by PZA is increased in patients with renal insufficiency. The drug can be used safely in older children but should be used with caution in children less than 5 years of age, generally a contraindication to the use of EMB in patients with renal insufficiency.

**Dose.** See Table 3 and 5.

**Adults:** 15--20 mg/kg per day; Table 5 lists recommended dosages for adults, using whole tablets.

**Children (maximum):** 15--20 mg/kg per day (2.5 g); 50 mg/kg twice weekly (2.5 g). The drug can be used safely in older children but should be used with caution in children less than 5 years of age (66). In younger children EMB can be used if there is concern with resistance to INH or RIF.

**Preparations.** Tablets (100 mg, 400 mg) for oral administration.

**Adverse effects.**

**Peripheral neuritis:** This is a rare adverse effect (69).

**Cutaneous reactions:** Skin reactions requiring discontinuation of the drug occur in 0.2--0.7% of patients (68).

**Use in pregnancy.** EMB is considered safe for use in pregnancy (70--72).

**CNS penetration.** The agent penetrates the meninges in the presence of inflammation but does not have demonstrated efficacy in patients with reactivation meningitis (72).

**Use in renal disease.** (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) EMB is cleared primarily by the kidney (65). However, in patients with renal insufficiency, the drug may be administered at a dose of 15--20 mg/kg three times a week after dialysis in patients with renal insufficiency. Higher doses can be given safely twice or three times weekly.

**Use in hepatic disease.** (See Section 8.8: Hepatic Disease.) EMB can be used safely in patients with hepatic disease.

**Monitoring.** Patients should have baseline visual acuity testing (Snellen chart) and testing of color discrimination (Ishihara tests). At each monthly visit patients should be questioned regarding possible visual disturbances.

**Contraindications.** The drug can be used safely in patients with hepatic disease. Patients should be instructed to contact their physician or public health clinic immediately permanently if there are any signs of visual toxicity.

**3.1.7. Fixed-dose combination preparations**

**Preparations.** Two combined preparations, INH and RIF (Rifamate®) and INH, RIF, and PZA (Rifater®), are available in the United States. These formulations are a means of minimizing inadvertent errors in the administration of these drugs. Formulations for intermittent administration are not available in the United States.

**Contraindications.** The drug can be used safely in patients with hepatic disease. Patients should be instructed to contact their physician or public health clinic immediately if there are any signs of visual toxicity.

**Preparations and dose.**

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*Preparations and dose.* Constituent drugs are combined in proportions compatible with daily treatment regimens. Formulations for intermittent administration are not available in the United States.
**Rifamate®**: As sold in North America, each capsule contains RIF (300 mg) and INH (150 mg); thus, the daily dose is two capsules of INH are used by some programs for intermittent therapy given twice weekly as DOT.

**Rifater®**: Each tablet contains RIF (120 mg), INH (50 mg), and PZA (300 mg). The daily dose is based on weight as follows: for children (maximum) 10–15 mg/kg per day, usually 500–750 mg/day given in two doses. Clinicians with experience with cycloserine indicate that toxicity is more common at doses over 500 mg/day. Serum concentrations should be measured. cycloserine may cause peripheral neuropathy.

**Adverse effects**. See comments under individual drugs above.

**Use in pregnancy**. Rifamate® may be used in daily treatment of pregnant women. Rifater® should not be used because it contains PZA.

**Use in renal disease**. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Rifamate® may be used in persons with renal insufficiency if the dose of PZA is reduced and serum concentrations measured. Cycloserine should not be used in patients having a creatinine clearance of less than 50 ml/minute unless the patient is receiving hemodialysis. For patients being treated with ethionamide, serum concentrations of phenytoin should be measured.

**3.2. Second-Line Drugs**

**3.2.1. Cycloserine**

**Role in treatment regimen**. Cycloserine (76,77) is a second-line drug that is used for treating patients with drug-resistant tuberculosis disease. It may also be used on a temporary basis for patients with acute hepatitis in combination with other nonhepatotoxic drugs.

**Dose**. See [Table 3](#).

**Adults (maximum)**: 10–15 mg/kg per day (1,000 mg), usually 500–750 mg/day given in two doses. Clinicians with experience with cycloserine indicate that toxicity is more common at doses over 500 mg/day. Serum concentrations should be measured. Cycloserine should not be used in patients having a creatinine clearance of less than 50 ml/minute unless the patient is receiving hemodialysis. For patients being treated with ethionamide, serum concentrations of phenytoin should be measured.

**Children (maximum)**: 10–15 mg/kg per day (1.0 g/day).

**Preparations**. Capsules (250 mg).

**Adverse effects**.

**Central nervous system effects**: The central nervous system effects range from mild reactions, such as headache or restlessness, to severe reactions, such as seizures or mental illness. Seizures have been reported to occur in up to 16% of patients receiving 500 mg twice daily. Neurotoxic side effects and is usually given in a dosage of 100–200 mg/day (79). Rarely, cycloserine may cause peripheral neuropathy.

**Use in pregnancy**. Cycloserine crosses the placenta. There are limited data on safety in pregnancy; thus, it should be used with caution.

**CNS penetration**. Concentrations in CSF approach those in serum (77).

**Use in renal disease**. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) The drug can accumulate in patients with renal insufficiency measured. Cycloserine should not be used in patients having a creatinine clearance of less than 50 ml/minute unless the patient is receiving hemodialysis. For patients being treated with ethionamide, serum concentrations of phenytoin should be measured.

**Use in hepatic disease**. (See Section 8.8: Hepatic Disease.) There are no precautions except for patients with alcohol-related liver disease. Neuropsychiatric status should be assessed at least at monthly intervals and more frequently if symptoms develop.

**Monitoring**. Liver function tests should be obtained at baseline and, if there is underlying liver disease, at monthly intervals measured at baseline and at monthly intervals.

**3.2.2. Ethionamide**

**Role in treatment**. Ethionamide (76,77) is a second-line drug that is used for treating patients with drug-resistant tuberculosis disease.

**Dose**. See [Table 3](#).

**Adults (maximum)**: 15–20 mg/kg per day (1.0 g/day), usually 500–750 mg/day in a single daily dose or two divided doses. The drug may also be used on a temporary basis for patients with acute hepatitis in combination with other nonhepatotoxic drugs.

**Children (maximum)**: 15–20 mg/kg per day (1.0 g/day).

**Preparations**. Tablets (250 mg).

**Adverse reactions**.

**Gastrointestinal effects**: Ethionamide commonly causes profound gastrointestinal side effects, including a metallic taste, nausea, and vomiting if doses are taken with food or at bedtime.

**Hepatotoxicity**: Ethionamide is similar in structure to INH and may cause similar side effects. Hepatotoxicity occurs in about 1% of patients receiving 500 mg twice daily. Neurotoxic side effects and is usually given in a dosage of 100–200 mg/day (79). Rarely, ethionamide may cause peripheral neuropathy.

**Endocrine effects**: Ethionamide crosses the placenta and is teratogenic in laboratory animals. It should not be used in pregnant women. Ethionamide should be used with caution in patients with underlying liver disease. Liver function tests should be obtained at baseline and, if there is underlying liver disease, at monthly intervals measured at baseline and at monthly intervals.

**Use in renal disease**. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Ethionamide should be used with caution in patients with renal insufficiency.

**Monitoring**. Liver function tests should be obtained at baseline and, if there is underlying liver disease, at monthly intervals.

**3.2.3. Streptomycin**

**Role in treatment regimen**. Streptomycin (SM) (76,77,87–89) and EMB have been shown to be approximately equivalent to streptomycin (SM) [Table 15](#). Each tablet contains RIF (120 mg), INH (50 mg), and PZA (300 mg). The daily dose is based on weight as follows: for children (maximum) 10–15 mg/kg per day, usually 500–750 mg/day given in two doses. Clinicians with experience with cycloserine indicate that toxicity is more common at doses over 500 mg/day. Serum concentrations should be measured.
likely to have acquired *M. tuberculosis* in a high-incidence country, the relatively high rate of resistance to SM limits its use.

**Dose.** See Table 3.

*Adults (maximum):* 15 mg/kg per day (1 g/day) parenterally, usually given as a single daily dose (5–7 days/week) initially, a conversion, depending on the efficacy of the other drugs in the regimen (90). For persons over 59 years of age, the dose should be reduced (i.e., 12–15 mg/kg per dose, two or three times per week) in persons with renal insufficiency (see below: Use in Renal Disease) (91,92). *Children (maximum):* 20–40 mg/kg per day (1 g/day).

**Preparations.** Aqueous solution in vials of 1 g (93).

**Adverse effects.**

*Ototoxicity:* The most important adverse reaction caused by SM is ototoxicity, including vestibular and hearing disturbances (ethacrynic acid). The risk of ototoxicity increases with increasing single doses and with the cumulative dose, especially abov

*Neurotoxicity:* SM relatively commonly causes circumoral parasthesias immediately after injection. Rarely, it may interact with SM. Nephrotoxicity occurs less commonly with SM than with amikacin, kanamycin, or capreomycin (95). Renal impairment was seen in 8.7% of patients receiving amikacin, with a higher frequency in patients with initially increased creatinine levels, patients receiving larger total doses, and patients receiving other nephrotoxic agents. A frequency of 3.4% was reported in persons with renal insufficiency (see below: Use in Renal Disease) (91,92).

**Use in pregnancy.** SM is contraindicated in pregnancy because of the risk of fetal hearing loss (77,97,98).

**CNS penetration.** There is only slight diffusion of SM into CSF, even in patients with meningitis (77,99).

**Use in renal disease.** See Section 8.7: Renal Insufficiency and End-Stage Renal Disease. SM should be used with caution in patients with renal insufficiency. Because clearance is almost exclusively by the kidney, dosing adjustments are essential in patients with underlying renal insufficiency, including patients with renal syndrome. For persons greater than 59 years of age the dose should be reduced to 10 mg/kg per day (750 mg). The dosing frequency should be reduced to two or three times per week, but the milligram dose should be maintained (Table 15) (91,92). Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate drug concentration measurements to avoid toxicity (91).

**Use in hepatic disease.** See Section 8.8: Hepatic Disease. No precautions are necessary.

**Monitoring.** An audiogram, vestibular testing, Romberg testing, and serum creatinine measurement should be performed at baseline. Assessments of renal function, and questioning regarding auditory or vestibular symptoms, should be performed monthly. An audiogram and vestibular testing should be repeated if there are symptoms of toxicity.

**3.2.4. Amikacin and kanamycin**

**Role in treatment regimen.** Amikacin and kanamycin (76,77,101) are two closely related injectable second-line drugs that may substitute for the agents. There is nearly always complete cross-resistance between the two drugs, but most SM-resistant strains are susceptible to both (102–104). Resistance between the two drugs, but most SM-resistant strains are susceptible to both.

**Dose.** See Table 3.

*Adults (maximum):* 15 mg/kg per day (1.0 g/day), intramuscular or intravenous, usually given as a single daily dose (5–7 days/week) after culture conversion, depending on the efficacy of the other drugs in the regimen (90). For persons greater than 59 years of age the dose should be reduced (i.e., 12–15 mg/kg per dose, two or three times per week) in persons with renal insufficiency (see below: Use in Renal Disease) (91,92). *Children (maximum):* 15–30 mg/kg per day (1 g/day) intramuscular or intravenous as a single daily dose.

**Preparations.** Aqueous solution for intramuscular or intravenous injection in vials of 500 mg and 1 g.

**Adverse effects.**

*Ototoxicity:* Amikacin and kanamycin may cause deafness, but they cause less vestibular dysfunction than SM (103,104). Ototoxicity is seen in 24% of patients receiving amikacin, with higher rates occurring among those receiving longer treatment and nephrotoxicity. Amikacin and kanamycin are contraindicated in pregnant women because of risk of fetal nephrotoxicity (96). CNS penetration. Only low concentrations of the drugs are found in CSF, although slightly higher concentrations have been reported.

**Use in renal disease.** See Section 8.7: Renal Insufficiency and End-Stage Renal Disease. Amikacin and kanamycin should both be used at lower dosages in patients with renal insufficiency to avoid toxicity (91).

**Use in hepatic disease.** See Section 8.8: Hepatic Disease. No precautions are necessary.

**Monitoring.** Monitoring should be performed as described for SM. An advantage of amikacin is that serum concentration monitoring is not necessary.

**3.2.5. Capreomycin**

**Role in treatment regimen.** Capreomycin is a second-line injectable drug that is used for patients with drug-resistant tuberculosis (91,92).

**Dose.** See Table 3.

*Adults (maximum):* 15 mg/kg per day (1.0 g/day), usually given as a single daily dose five to seven times a week, and reduce on the efficacy of the other drugs in the regimen (90). For persons greater than 59 years of age the dose should be reduced to three times per week in persons with renal insufficiency (see below: Use In Renal Disease) (91,92).

*Children (maximum):* 15–30 mg/kg per day (1 g/day) as a single daily or twice weekly dose.

**Preparations.** Capreomycin is available in vials of 1 g for both intramuscular and intravenous administration.
Adverse effects.

Nephrotoxicity: Nephrotoxic effects may result in reduced creatinine clearance or potassium and magnesium depletion. Protr reported to occur in 20–25% of patients (110,111).

Otosotoxicity: Vestibular disturbances, tinnitus, and deafness appear to occur more often in elderly persons or those with prex Use in pregnancy. Capreomycin should be avoided in pregnancy because of risk of fetal nephrotoxicity and congenital hear

CNS penetration. Capreomycin does not penetrate into the CSF (77).

Use in renal disease. Capreomycin should be used with ototoxicity and nephrotoxicity (112). Because capreomycin is nearly entirely cleared by the kidneys, dosing adjustments are patients undergoing hemodialysis. In such patients, the dosing frequency should be reduced to two or three times weekly, bu concentration-dependent bactericidal effect (Table 15) (91,92). Smaller doses may reduce the efficacy of this drug. The drug (100,113). Serum drug concentrations should be monitored to avoid toxicity (91).

Use in hepatic disease. No precautions are necessary.

Monitoring. Monitoring should be performed as described for SM. In addition, serum potassium and magnesium concentra

3.2.6. p-Aminosalicylic acid

Role in treatment. p-Aminosalicylic acid (PAS) is an oral agent used in treatment of drug-resistant tuberculosis caused by o

Dose. See Table 3.

Adults: 8–12 g/day in two or three doses. For PAS granules, 4 g three times daily has been the usual dosage (114,115). How serum concentration (116).

Children: 200–300 mg/kg per day in two to four divided doses (117).

Preparations. The only available formulation in the United States is granules in 4-g packets (Paser Granules®) (118). It was recent data suggest that this is not necessary (C. Peloquin, personal communication). Tablets (500 mg) are still available in s-

Adverse effects.

Hepatotoxicity: In a review of 7,492 patients being treated for tuberculosis, 38 (0.5%) developed hepatitis, of which 28 cases Gastrointestinal distress: This is the most common side effect of PAS (122). In a large study of INH and PAS 11% of patien gastrointestinal side effects is less with lower d (8 g daily) and with the granular formulation of the drug.

Malabsorption syndrome: This is characterized by steatorrhea and low serum folate levels (123).

Hypothyroidism: This is a common side effect, especially with prolonged administration or concomitant use of ethionamide. Thyroid function returns to normal after discontinuation of the drug (124).

Coagulopathy: A doubling of the prothrombin time that seemed to be lessened by coadministration of streptomycin has been

Use in pregnancy. No studies have been done in humans; however, PAS has been used safely in pregnancy. The drug should resistent tuberculosis.

CNS penetration. In the presence of inflamed meninges, PAS concentrations are between 10–50% of those achieved in serum.

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Approximately 80% of the drug i insufficiency because of the accumulation of the acetylated form (123,126,127). Because both PAS and acetyl-PAS are remc removal of the drug (126).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The clearance of PAS is not substantially altered in liver disease monitoring (127).

Monitoring. Hepatic enzymes and thyroid function should be measured at baseline. With prolonged therapy (i.e., more than

3.2.7. Fluoroquinolones

Role in treatment regimen. Of the fluoroquinolones (128–131), levofloxacin, moxifloxacin, and gatifloxacin have the mos profile with long-term use of levofloxacin, this drug is the preferred oral agent for treating drug-resistant tuberculosis caused cannot be used because of intolerance. Data on long-term safety and tolerability of moxifloxacin and gatifloxacin, especially ciprofloxacin, ofloxacin, and levofloxacin and presumably is a class effect (132). Fluoroquinolones should not be considered intolerant of first-line drugs.

Dose. (See Table 3.) The doses given are for levofloxacin.

Adults: 500–1,000 mg daily.

Children: The long-term (more than several weeks) use of fluoroquinolones in children and adolescents has not been approv that the drug should be considered for children with MDR tuberculosis. The optimal dose is not known.

Preparations (Levofloxacin). Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500 mg) for intravenous administration

Adverse effects. The adverse effects (133) cited are for levofloxacin.

Gastrointestinal disturbance: Nausea and bloating occur in 0.5–1.8% of patients taking the drug.

Neurologic effects: Dizziness, insomnia, tremulousness, and headache occur in 0.5% of patients.

Cutaneous reactions: Rash, pruritus, and photosensitivity occur in 0.2–0.4% of patients.

Use in pregnancy. This class of drugs should be avoided in pregnancy because of teratogenic effects (119,134).

CNS penetration. The concentration in CSF after administration of a standard dose of levofloxacin is 16–20% of that in ser
**Interference with absorption.** Because antacids and other medications containing divalent cations markedly decrease absorp
tion of such medications (see Section 7.1: Interactions Affecting Antituberculosis Drugs).

**Use in renal disease.** (See Section 8.7: Renal Insufficiency and End Stage Renal Disease.) The drug is cleared primarily (80%
if creatinine clearance is less than 50 ml/minute (Table 15) (136). It is not cleared by hemodialysis; supplemental doses after

**Use in hepatic disease.** Drug levels are not affected by hepatic disease (135). It is presumed to be safe for use in the setting of severe liver disease, but a reduction in dosage should be made in patients with severe hepatic disease.

**References**

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4. Principles of Antituberculosis Chemotherapy

4.1. Combination Chemotherapy
The primary goals of antituberculosis chemotherapy are to kill tubercle bacilli rapidly, prevent the emergence of drug resistance, and eliminate persistent bacilli from the host’s tissues to prevent relapse (1). To accomplish these goals, multiple antituberculosis drugs must be taken for a sufficiently long time. The theoretical model of chemotherapy for tuberculosis is found on current understanding of the biology of M. tuberculosis in the host and on the specific activities of antituberculosis drugs. This model is supported by data from numerous in vivo and in vitro studies.

It is theorized that there are three separate subpopulations of M. tuberculosis within the host. These populations are defined by their growth characteristics and the milieu in which they are located (1). The largest of the subpopulations consists of rapidly growing extracellular bacilli that reside mainly in cavities. This subpopulation, because of its size, is most likely to harbor organisms with random mutations that confer drug resistance. The frequency of these mutations that confer resistance is about $10^{-6}$ for INH and SM, $10^{-8}$ for RIF, and $10^{-5}$ for EMB; thus, the frequency of concurrent mutations to both INH and RIF, for example, would be $10^{-14}$, making simultaneous resistance to both drugs in an untreated patient a highly unlikely event (2).

INH has been shown to possess the most potent ability to kill rapidly multiplying M. tuberculosis during the initial part of therapy (early bactericidal activity), thereby rapidly decreasing infectiousness (3–5). It is followed in this regard by EMB, RIF, and SM. PZA has weak early bactericidal activity during the first 2 weeks of treatment (3,6). Drugs that have potent early bactericidal activity reduce the chance of resistance developing within the bacillary population.

Early experience in clinical trials demonstrated that multiple agents are necessary to prevent the emergence of a drug-resistant population as a consequence of the selection pressure from administration of a single agent. Shortly after the discovery of SM, it was demonstrated that treatment with this agent alone resulted in treatment failure and drug resistance (7). Subsequently, it was shown that the combination of PAS and SM substantially lessened the likelihood of acquired resistance and treatment failure (8). In modern regimens both INH and RIF have considerate ability to prevent the emergence of drug resistance when given with another drug. EMB and SM are also effective in preventing the emergence of drug resistance, whereas the activity of PZA in this regard is poor (9,10). For this reason PZA should not be used with only one other agent when treating active tuberculosis.

The rapidly dividing population of bacilli is eliminated early in effective therapy as shown by the early clinical responses and...
subpopulations of *M. tuberculosis* account for treatment failures and relapses, especially when the duration of therapy is inad
acidity environment provided by areas of necrosis, and a group that is characterized by having spurts of growth interspersed
mainly in these two subpopulations that persist beyond the early months of therapy, thus decreasing the risk of relapse (1). T
rifampin (RIF) and pyrazinamide (PZA) have the greatest sterilizing activity followed by isoniazid (INH) and streptomycin (SM) (11,12). The sterilizing activity of RIF persists throughout the initial 2 months of therapy. The sterilizing activity of INH for MDR tuberculosis may include PZA for the full course of treatment if the isolate is susceptible to this agent.

### 4.2. Optimum Duration of Treatment

Truly effective chemotherapy for tuberculosis became available with the introduction of INH in the early 1950s. Adding INH
for 2 months (13). Eventually, EMB replaced PAS as the companion agent for INH (14). Subsequent investigations of combinato
intermittently.

The British Medical Research Council (BMRC) in East Africa (15) conducted the first large-scale multicenter study of short
regimen of daily SM and INH increased the proportion of patients whose sputum cultures were negative by 2 months after th
short-course regimens was no greater than that of the standard 18-month regimen containing SM, INH, and thiacetazone
month regimen of SM, INH, and PZA daily, twice weekly, or three times weekly was associated with a relapse rate of only 5
supervised therapy and SM had to be used for the entire 9 months. Subsequent investigations conducted by the British Thora
achieve excellent results with a 9-month treatment duration, using INH and RIF throughout (17,18). The BMRC conducted s"therapy, thereby demonstrating that an all-or-none regimen was effective (19).

The addition of PZA to a regimen containing INH and RIF enabled further shortening of the duration of therapy to 6 months
supplemented during the first 2 months with PZA and either EMB or SM, was as effective as a 9-month regimen of INH and an
rifampin-containing regimen had no additional benefit. The efficacy of the treatment regimens was similar regardless of whe
Subsequent studies of 6-month regimens have served to refine the approach used currently. USPHS Trial 21 compared self-a
RIF for 9 months (21). EMB was added only if INH resistance was suspected. Patients taking the 6-month PZA-containing r
months without PZA and relapse rates were similar for the two regimens (3.5 versus 2.8%).

In the laboratory it was noted that in vitro exposure of tubercle bacilli to drugs was followed by a lag period of several days l
maintaining continuous inhibitory drug concentrations was not necessary to kill or inhibit growth of *M. tuberculosis*. Studies efficacy; however, there was a significant decrease in activity with an 8-day dosing interval (30,31).

The concept of intermittent drug administration continues to evolve. Studies have demonstrated that the frequency of drug ac
INH and rifampicin for certain highly selected patients (32–34). Because of the newness of these findings the data are prese
The results from these open-label, randomized clinical trials indicate that rifampicin given with INH once a week is safe and tuberculosis. In a study performed in Hong Kong, patients with pulmonary tuberculosis were allocated at random to receive rifampicin for 4 months after completion of a standard 2-month initial phase (32). Overall, about 11% of patients in the two rifampicin who received three times weekly INH–RIF (control arm) in the continuation phase of treatment. Omitting every third dose of INH may have a negligible effect. Multivariate analyses showed that the significant prognostic factors were treatment men. The frequency of failures and relapses was also greater in all three arms if the second culture was positive. The pivotal study for drug registration was conducted in North America and South Africa among HIV-negative patients with weekly rifampicin together with daily self-administered INH, PZA, and EMB in the initial 2 months, followed by 4 months of standard four-drug initial phase, followed by twice weekly INH–RIF. Relapse rates during 2 years of follow-up were similar (standard control arm), and cavitary disease, sputum culture positivity at the end of the initial phase, and nonadherence with INH, EMB relapse.

The third study was conducted by the CDC Tuberculosis Trials Consortium, and employed a design similar to the Hong Kon
standard 2-month initial phase therapy (34). Again, results, as measured by rates of failure/relapse, were remarkably similar to
interruption between two dosing intervals (35). Thus, intermittent dosing of antituberculosis medications in all of these studies, intermittent regimens were demonstrated
with 5.6% in the control (INH–RIF twice weekly) arm. However, as in the South Africa study, relapse was significantly assosciated with cavitary disease and had negative sputum cultures at 2 months were low in both treatment arms. However, rifapentine arm was 22% and in the twice weekly INH–RIF arm was 21% (Table 11). In all of the cited studies, rifapentine \ A small number of HIV--positive patients were enrolled in the CDC study, but this arm was closed after the development of

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5. Recommended Treatment Regimens

5.1. Evidence-based Rating System
To assist in making informed treatment decisions based on the most credible research results, evidence-based ratings have been used in the recommendations for treating latent tuberculosis infection, in which a letter indicating the strength of the recommendation, are assigned to each regimen (1). Thus, clinicians can use the ratings to differentiate among recommendation-relevant clinical practice and scientific rationale for such practice when clinical trial data are not available.

5.2. Recommended Regimens
There are four basic regimens recommended for treating adults with tuberculosis caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB. 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. In Table 2 the initial phase is denoted by a number (1, 2, 3, or 4) and a letter (a, b, or c). DOT is the preferred initial management strategy for all regimens and should be used whenever feasible.

5.2.1. Six-month regimens
The current minimal acceptable duration of treatment for all children and adults with culture-positive tuberculosis is 6 month-period of INH, RIF, PZA, and EMB given daily throughout (Regimen 1), daily for 2 weeks followed by two times weekly for 6 weeks (Regimen 2), or three times a week (Regimen 3). The minimum number of doses is specified in Table 2. On the basis of substantial clinical experience, 5 day-a-week drug administration by DOT is considered although administration of antituberculosis drugs by DOT at 5 days/week, rather than 7 days, has been reported in a large number of studies it has not been compared with 7 day administration; thus, either may be considered “daily.”

The recommendation that a four-drug regimen be used initially for all patients is based on the current proportion of new tuberculosis cases caused by organisms that are resistant to INH. However, if therapy is being initiated after drug susceptibility test results are discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to the first-line agents The continuation phase of treatment should consist of INH and RIF given for a minimum of 4 months (18 weeks). Patients in regimen (Table 2). The continuation phase can be given daily (Regimen 1a), twice weekly (Regimens 1b and 2a), or three times weekly (Regimen 3a). The continuation phase of treatment is 4 months (Regimen 4) followed by INH and RIF for 7 months given either daily or twice weekly (Regimens 4a and 4b).

If PZA cannot be included in the initial regimen, or if the isolate is determined to be resistant to PZA (an unusual circumstance, exc...
5.2.3. Alternative regimens

In some cases, either because of intolerance or drug resistance, the above-described regimens cannot be used. In these instances, clinical trials conducted by the BMRC it was concluded that, in the presence of initial resistance to INH, if a four-drug regimen is used throughout (5). On the basis of these data, when INH cannot be used or the organism is an INH-containing regimen (Rating BII) (5). Alternatively, RIF and EMB for 12 months may be used, preferably with PZA/INH should be given for a minimum of 12–18 months complemented with PZA during at least the initial 2 months (Rating BIII). To treat extensive disease or to shorten the duration (e.g., to 12 months), (7,8).

Levofloxacin, moxifloxacin, or gatifloxacin may be useful in alternative regimens, but the potential role of a fluoroquinolone as first-line agents cannot be used because of intolerance, regimens based on the principles described for treating multiple drug-resistant organisms should be used.

5.3. Deciding to Initiate Treatment

The decision to initiate combination chemotherapy for tuberculosis should be based on epidemiologic information, clinical a (preferably three) and, subsequently, cultures for mycobacteria. Rapid amplification tests, if used, can also confirm the diagnosis of active tuberculosis. A chest radiograph should be considered highly likely to have tuberculosis. In such situations combination drug therapy should be initiated promptly when a patient is seriously ill with a disorder that is thought possibly to be tuberculosis. The patient will have completed 2 months of combination treatment that is positive (5 mm or greater induration), and there is no response to treatment (Figure 2, top). Even when the suspicion of active tuberculosis is low, treatment for latent tuberculosis infection is indicated in the limited circumstances described (11). The preferred options are INH for 9 months or RIF, with or without INH, for 4 months. RIF and EMB for 12 months may be used, preferably with PZA during at least the initial 2 months (Rating BII) (5,6). On the basis of these data, when INH cannot be used or the organism is an INH-containing regimen (Rating BII) (5). Alternatively, RIF and EMB for 12 months may be used, preferably with PZA/InH should be given for a minimum of 12–18 months complemented with PZA during at least the initial 2 months (Rating BIII). To treat extensive disease or to shorten the duration (e.g., to 12 months), (7,8).

A positive AFB smear provides strong inferential evidence for the diagnosis of tuberculosis. If the diagnosis is confirmed by culture or radiographic improvement consistent with a response to treatment, the regimen can be continued to complete the initial evaluation, but a negative test does not exclude the diagnosis of active tuberculosis. However, a positive skin test suggests chest radiographs consistent with inactive tuberculosis, a diagnosis of latent tuberculosis infection (see below).

If the cultures are negative, the PPD-tuberculin skin test is positive (5 mm or greater induration), and there is no response to treatment. If clinical suspicion for active tuberculosis is low, the options are to begin treatment with combination chemotherapy or to defer treatment until additional data have been obtained to clarify the situation (usually within 2 weeks). The preferred options are INH for 9 months or RIF, with or without INH, for 4 months. RIF and EMB for 12 months may be used, preferably with PZA during at least the initial 2 months (Rating BII) (5,6). On the basis of these data, when INH cannot be used or the organism is an INH-containing regimen (Rating BII) (5). Alternatively, RIF and EMB for 12 months may be used, preferably with PZA/INH should be given for a minimum of 12–18 months complemented with PZA during at least the initial 2 months (Rating BIII). To treat extensive disease or to shorten the duration (e.g., to 12 months), (7,8).

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which subsequent examinations can be compared, but, as with the 2-month examination, it is not essential. When the initial s is noted, generally by the time 2 months of treatment has been completed. Thus, in patients with negative initial cultures, a cl treatment is desirable. Generally, follow-up after completion of therapy is not necessary.

As a routine, it is not necessary to monitor liver or renal function or platelet count for patients being treated with first-line drn measurements. Patients who have stable abnormalities of hepatic or renal function at baseline should have repeat measureme worsening. Patients receiving EMB should be questioned regarding visual disturbances at monthly intervals; monthly repeat exceeding 15--20 mg/kg (the recommended range) and for patients receiving the drug for more than 2 months. Monitoring te

5.5. Identification and Management of Patients at Increased Risk of Relapse

The result of a sputum culture at the conclusion of the initial phase of treatment (2 months) has been shown to correlate with clinical trials performed by the BMRC, the regimens that had the highest proportion of patients with a positive sputum cultu within 2 years (17). Of greater relevance to the current recommendations, data from USPHS Trial 22 comparing once weekly patients who had a positive culture at 2 months in both study arms (18). Cavitation on the initial chest radiograph was also ar presence of both cavitation and a positive culture at completion of 2 months of therapy was associated with a 21% rate of rel reported in a retrospective analysis of data from BMRC trials (17) and from a USPHS trial conducted in Poland (19).

The most effective means of decreasing the likelihood of relapse for patients at increased risk has not yet been determined by prolongation of the continuation phase from 4 to 6 months decreased the rate of relapse from 22 to 7% (p <0.025) (20). Also month initial phase did not improve the efficacy of RIF-containing regimens (21). It has been reported that for patients at big 7 months resulted in significantly better results compared with patients in an earlier trial (4).

In view of this evidence and on the basis of expert opinion, it is recommended that treatment for patients who have cavitation of therapy should be extended with INH and RIF for an additional 3 months for a total of 9 months (Rating AIII).

In USPHS Study 22 patients treated with INH and RIF twice weekly in the continuation phase who had either cavitation on t relapse (Table 11) (18). This rate of adverse outcomes is not deemed to be sufficient to recommend prolongation of the conti more closely and consideration given to lengthening treatment if there are suggestions of a poor response. Additional factors culture at 2 months (but not both) might include being more than 10% underweight at diagnosis, having HIV infection, or ha Patients with noncavitary pulmonary tuberculosis and a negative AFB smear at 2 months who are started on the once weekly months should have treatment extended by an additional 3 months for a total of 9 months.

5.6. Definition of Completion of Therapy

Treatment for a defined duration without accounting for the number of doses taken can result in undertreatment. Therefore, t doses taken—not solely on the duration of therapy (Table 2). For example, the 6-month daily (given 7 days/week) regimen s administered by DOT at 5 days/week, the minimum number of doses is 130. A similar reduction in the target number of dose In some cases, either because of drug toxicity or nonadherence to the regimen, the specified number of doses cannot be adm number of doses for the initial phase be delivered within 3 months and those for the 4-month continuation phase be delivertargets are not met the patient must be considered to have interrupted therapy and be managed as described below.

5.7. Interruptions in Therapy

Interruptions in therapy are common in the treatment of tuberculosis. When interruptions occur, the person responsible for st intended originally. This decision depends in part on whether the interruption occurred during the initial or the continuation 4 serious the effect and the greater the need to restart the treatment from the beginning. Continuous treatment is more impor developing drug resistance is greatest. During the continuation phase, the number of bacilli is much smaller and the goal of t status of the patient before and after the interruption are also important considerations.

There is no evidence on which to base detailed recommendations for managing interruptions in treatment, and no recomm Figure 5, modified from the New York City Bureau of Tuberculosis Control Clinical Policies and Protocols (22), is presents 14 days or more in duration, treatment should be restarted from the beginning. However, if the lapse is less than 14 days, the the initial phase should be given. If the interruption in treatment occurs during the continuation phase after the patient has re treatment may not be necessary if the patient’s sputum was AFB smear negative on initial presentation. However, for patient doses is warranted. If the patient has received less than 80% of the planned total doses and the lapse is 3 months or more in d duration, treatment should be continued to complete a full course.

At the time the patient is returned to treatment sputum cultures should be obtained and repeat drug susceptibility testing perfcultures are negative the patient could be treated as having culture-negative tuberculosis and given an additional 4 months of should be used. If the patient was already being managed with DOT, additional measures will be necessary to ensure comp Consultation with an expert is recommended to assist in managing treatment interruptions.

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6. Practical Aspects of Treatment

6.1. Drug Administration

The first-line antituberculosis medications should be administered together as single dose rather than in divided doses. A sin; Administering a single daily dose also facilitates using DOT. Ingestion with food delays or moderately decreases the absorb agents, the effects of food are of little clinical significance. Thus, if patients have epigastric distress or nausea with the first-l dose or changing to a second-line drug. The absorption of INH can be substantially decreased when the drug is ingested with for flavor, rather than glucose or lactose. However, sorbitol can cause diarrhea, limiting the acceptability of the commercial L glucose, such as applesauce, has not been formally evaluated, but has been used successfully by many providers. Antacids have minimal effects on the absorption of the first-line antituberculosis drugs. With the exception of fluoroquinolor antituberculosis drugs. In the absence of data, it is preferable to administer the drugs on an empty stomach if they are tolerate absorption of the fluoroquinolones, an interaction that has been associated with failure of antibiotic therapy (2,3). Therefore,
Because the schedule for restarting antituberculosis medications is slower with hepatitis than for rash or drug fever, it is generally questioned carefully regarding symptoms suggestive of biliary tract disease and exposures to other potential hepatotoxins, particularly alcohol and hepatotoxic medications. However, if AST levels are more than five times the upper limit of normal (with or without symptoms) or more than three times normal in the presence of symptoms, hepatotoxicity should be considered.

It is important to note that an asymptomatic increase in AST concentration occurs occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with rifampin hepatotoxicity, because of modest asymptomatic elevations of AST, but the frequency of clinical and laboratory monitoring should be increased. Asymptomatic aminotransferase elevations resolve spontaneously. In most patients, asymptomatic aminotransferase elevations resolve spontaneously.

### 6.3.2. Rash

All drugs used in treating tuberculosis can cause a rash. The response to a patient with a rash depends on its severity. The rash is usually minor and does not require further treatment. The initial approach to gastrointestinal intolerance, not associated with hepatic toxicity, is to change the hour of drug administration and/or to administer the drugs with food. If patients are taking daily DOT, the timing of administration can be altered to bedtime. If gastrointestinal intolerance persists it may be best to administer therapy can take the medications at bedtime. If gastrointestinal intolerance persists it may be best to administer therapy can take the medications at bedtime. If gastrointestinal intolerance persists it may be best to administer therapy can take the medications at bedtime.

### 6.3.3. Drug fever

Recurrence of fever in a patient who has been receiving therapy for several weeks should suggest drug fever, especially if the fever from tuberculosis may persist for as long as 2 months after therapy has been initiated. Fever may also be a marker of HIV Infection. The clinical hallmark of drug fever is that the patient looks and feels well despite having a high fever (often present. The first step in management of a possible drug fever is to ensure that there is no superinfection or worsening of tuberculosis will resolve within 24 hours. Patients with severe tuberculosis should be given at least three new drugs in the interim. Once the fever has subsided, the fourth drug should be restarted unless the rash was relatively mild and the fourth drug is considered essential for therapy.

### 6.3.4. Hepatitis

(Management of patients with baseline abnormal liver function is described in Section 8.8: Hepatic Disease.) Three of the first level three or more times the upper limit of normal in the presence of symptoms, or five or more times the upper limit of normal, toxicity can be considered mild, an AST level 5–10 times normal defines moderate toxicity, and an AST level greater than 10 times normal defines severe toxicity. Occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with rifampin hepatotoxicity. It is important to note that an asymptomatic increase in AST concentration occurs in nearly 20% of patients treated with rifampin because of modest asymptomatic elevations of AST, but the frequency of clinical and laboratory monitoring should be increased. However, if AST levels are more than five times the upper limit of normal (with or without symptoms) or more than three times the upper limit of normal, the potential for reducing medication errors make them preferable to individual medications in many instances. When prescribing the trade names of Rifin (Rifadin®) and the fixed-dose combinations Rifamate®, Rifater®).
of hepatotoxicity can be determined and an appropriate longer term regimen begun. The suspect antituberculosis medication: upper limit of normal. (In patients with elevated baseline AST from preexisting liver disease, drugs should be restarted when than is INH or PZA (Table 10) and is the most effective agent, it should be restarted first. If there is no increase in AST increase. If symptoms recur or AST increases the last drug added should be stopped. If RIF and INH are tolerated, and hepat circumstance, depending on the number of doses of PZA taken, severity of disease, and bacteriological status, therapy might

6.4. Serum Drug Concentration Measurements

The first-line drugs (INH, RIF, PZA, and EMB) have relatively predictable pharmacokinetics (11,12) and are highly efficacious. Altered metabolism of the first-line drugs, resulting in failure of therapy (15,16) Second-line agents have a much narrower therapeutic index (rarely causing toxicity) than the first-line drugs, and the consequences of treatment failure of drug-resistant tuberculosis may be helpful: 1) patients with treatment failure that is not explained by nonadherence or drug failure, 2) the management of multidrug-resistant tuberculosis with second-line drugs. Be aware, however, of treatment. An important limitation is the lack of sufficient data to formulate clinically validated therapeutic ranges for antituberculosis drugs. It is to use the distribution of concentrations achieved in healthy volunteers as the therapeutic range. However, in short line drugs among HIV-infected patients with active tuberculosis are frequently lower than those in healthy volunteers (17,18). The disadvantages of therapeutic drug monitoring are as follows: 1) the time necessary, from both patients and providers, to concentrations. Until more data are available, it seems prudent to restrict therapeutic drug monitoring for the first-line drugs to patients who evidence of severe gastrointestinal or metabolic abnormalities. Examples of such circumstances include severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption, and renal insufficiency. As a result in abnormal pharmacokinetics of antituberculosis drugs may have an increased incidence of malabsorption of antituberculosis drugs; much more often the antituberculosis drugs cause clinically relevant changes in the concentrations of other drugs. The exceptions to this general rule are rifabutin and the rifamycins is to use the distribution of concentrations achieved in healthy volunteers as the therapeutic range. However, in short line drugs among HIV-infected patients with active tuberculosis are frequently lower than those in healthy volunteers (17,18). The disadvantages of therapeutic drug monitoring are as follows: 1) the time necessary, from both patients and providers, to concentrations.

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References

fluoroquinolones.
Rifabutin is partially metabolized by cytochrome P450 (CYP) 3A. Inhibitors of CYP3A increase serum concentrations of rifabutin. For example, administration of ritonavir, a potent CYP3A inhibitor, with the standard daily dose of rifabutin (300 mg) increases rifabutin (7) and is associated with increased rates of leukopenia, arthralgias, skin discoloration, and uveitis (2), all recognizing rifabutin with a CYP3A inducer decreases its concentrations, perhaps to ineffective levels. For example, efavirenz, a potent CYP3A inhibitor, for making dose adjustments of rifabutin when it is given with commonly used CYP3A inhibitors and in the context of antiretroviral therapy strongly suggest that the management of cases of HIV-related tuberculosis should involve a physician with experience in this field.

Absorption of the fluoroquinolones is markedly decreased by ingestion with medications containing divalent cations (calcium (10), sucralfate (11); and the chewable tablet formulation of didanosine (12). These drug interactions can be avoided by assuring that medications containing divalent cations are ingested at least 2 hours apart from doses of fluoroquinolones (13).

7.2. Effects of Antituberculosis Drugs on Other Drugs
7.2.1. 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 (interact with the clinically relevant drug) or drug interactions involving the antituberculosis drugs are due to the effect of the rifamycins (rifampicin) on the metabolism of a variety of metabolic pathways, particularly those involving the various isozymes of the cytochrome P450 system. A decrease in the serum concentrations of many drugs, sometimes to levels that are subtherapeutic. The rifamycins differ in their relative potency as inducers, and rifabutin is the least potent enzyme inducer (19).

The well-described, clinically relevant drug interactions involving the rifamycins are presented in Table 12 (1,5,15,20-21). These interactions can be avoided by assuring that medications containing divalent cations are ingested at least 2 hours apart from doses of fluoroquinolones. Some of these drug interactions can be managed with close clinical or laboratory monitoring and dose increases of the decrease in concentrations of a concomitant medication may be such that serum concentrations cannot be restored by a dose increase to remember that the dose of this drug will probably need to be decreased within the 2 weeks after the rifamycin is discontinued. In some situations, rifabutin can sometimes be used in place of rifampin, if there is an unacceptable drug interaction with rifampin. If the dose of a medication is increased to compensate for the effect of a rifamycin, it is important to check all concomitant medications for possible drug interactions.

7.2.2. Drug interactions due to isoniazid

Isoniazid is a relatively potent inhibitor of several cytochrome P450 isozymes (CYP2C9, CYP2C19, and CYP2E1) (92), but these potential interactions have not been investigated fully and additional clinically relevant interactions undoubtedly will be described. Therefore, it is necessary to be familiar with the effects of isoniazid on drug metabolism.

Isoniazid may increase toxicity of other drugs such as delavirdine (58), valproate (59), and diazepam (60). These drug interactions can be avoided by assuring that medications containing divalent cations are ingested at least 2 hours apart from doses of fluoroquinolones. These drug interactions can be avoided by assuring that medications containing divalent cations are ingested at least 2 hours apart from doses of fluoroquinolones.

7.2.3. Drug interactions due to fluoroquinolones

Ciprofloxacin (104) inhibits the metabolism of theophylline and can cause clinical theophylline toxicity (105). However, levofloxacin inhibits the metabolism of theophylline and can cause clinical theophylline toxicity (105).

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continuation phase should not be used in patients with CD4 cell counts <100/µl, it is recommended that patients with advanced HIV disease be treated with daily or three times
EMB given for 2 months followed by INH and RIF for 4

Recommendation

Investigators in Uganda have reported a higher mortality rate among HIV
infected patients treated with regimens that did not contain R

but has le

M. tuberculosis

Table 1

and described in Secti

8.1. HIV Infection

Treatment of tuberculosis in patients with HIV infection follows the same principles as treatment of HIV-uninfected patients infection. These differences include the potential for drug interactions, especially between the rifamycins and antiretroviral a
the development of acquired resistance to rifamycins when treated with highly intermittent therapy.

8.1.1. Clinical trials of treatment for tuberculosis in HIV-infected patients

There have been seven prospective studies of 6-month regimens for the treatment of pulmonary tuberculosis in patients with controlled trials (1–4), and three were observational in nature (5,6). These studies differed somewhat in design, patient popu therefore, it is difficult to provide meaningful cross-study comparisons. All of the studies reported a good early clinical resp

treatment failure rates were similar to these indices of treatment efficacy in patients without HIV infection.

Recurrence rates have varied among studies, with most reporting rates of 5% or less (2,3,5,6). In one study from the Democr compared with 3% in the 12-month arm, nonadherence in the continuation phase and/or exogenous reinfection may have cor versus twice weekly INH--RIF in the continuation phase of therapy, 5 of 30 (17%) HIV-infected patients receiving treatment -RIF arm (4). Four of the five relapsed patients in the once weekly group had resistance to rifampin alone compared with not it is difficult to interpret the relapse rate of 10%.

In an observational study of twice weekly INH--rifabutin among HIV-infected tuberculosis patients also receiving antiretov failure/relapse was low (4.6%), M. tuberculosis isolated from all five of these patients was resistant to RIF alone. The pheno RIF therapy, albeit at a lower rate (3). In all of these studies, acquired RIF resistance occurred only among patients with CD-
was given daily.

A consistent finding in the treatment studies has been a high mortality rate among HIV-seropositive patients. In most studies tuberculosis, but deaths during the continuation phase of therapy are usually due to other AIDS-related conditions. Mortality advanced HIV disease (1,3,6,8). However, the use of effective antiretroviral therapy during the treatment of tuberculosis in p described subsequently (9).

A major concern in treating tuberculosis in the setting of HIV infection is the interaction of RIF with antiretroviral agents (se against M. tuberculosis but has less of an effect in inducing hepatic microsomal enzymes than RIF. Data from clinical trials s colleagues (10) reported the first randomized clinical trial comparing rifabutin (150 and 300 mg) with RIF in a 6-month regi there were few adverse reactions.

Investigators from South Africa reported a randomized, open-label trial comparing rifabutin with RIF in a standard four-drug the HIV seroprevalence was reportedly low at the time of the study. In the continuation phase, the medications were given tw of those given rifabutin had negative sputum cultures. The relapse rate was 3.8% in the RIF group versus 5.1% in the rifabut

Only one study examining the effectiveness of rifabutin included HIV-infected patients (12). A single blind randomized stud rifabutin together with INH, EMB, and PZA. Time to sputum conversion was similar between groups when controlling for b Investigators in Uganda have reported a higher mortality rate among HIV-infected patients treated with regimens that did no associated with shortened survival compared with an RIF-based regimen. In addition to the higher mortality associated with the setting of HIV infection (14,15). Thus, every effort should be made to use a rifamycin-based regimen for the entire cours

8.1.2. Treatment recommendations

Recommendations for the treatment of tuberculosis in HIV-infected adults are, with two exceptions, identical to those for HI EMB given for 2 months followed by INH and RIF for 4 months when the disease is caused by organisms that are known or intermittent administration as listed in Table 1 and described in Section 5.2: Recommended Regimens. However, on the basi cell counts <100/µl, it is recommended that patients with advanced HIV disease be treated with daily or three times weekly t

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Six months should be considered the minimum duration of treatment for adults, even for patients with culture-negative tuber 2 months of therapy), prolongation of the continuation phase to 7 months (a total of 9 months treatment) should be strongly c

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8. Treatment in Special Situations

8.1. HIV Infection

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Six months should be considered the minimum duration of treatment for adults, even for patients with culture-negative tuber 2 months of therapy), prolongation of the continuation phase to 7 months (a total of 9 months treatment) should be strongly c
HIV-related tuberculosis. Although there are no data on which to base recommendations, the American Academy of Pediatrics recommends that all patients with tuberculosis should be advised to undergo voluntary counseling and HIV testing. Efforts should be made to screen patients for tuberculosis. Ideally, patients should be managed by physicians who are expert in the treatment of tuberculosis/HIV coinfection. Communication between them is essential and should occur frequently throughout the course of treatment.

8.1.3. Safety and tolerability
The frequency of antituberculosis drug-related toxicity in patients with HIV infection has varied from study to study. In a recent study of regimen-based adverse drug reactions, RIF was the drug implicated most commonly, producing an adverse reaction in 1 in 25 patients developed a rash but in none of the cases was the reaction interrupted. Paresthesia was reported in 21% of the cases, suggesting that other patients may have had low rates of significant adverse reactions. In three of the cases studied, the adverse reaction was due to the antituberculosis drug used. Because of the difficulties in diagnosing a drug reaction and in determining the responsible agent, the finding of strong evidence that the antituberculosis drug was the cause of the reaction is important. In such situations, consultation with an expert is recommended. In a study reported by Ungo and associates, it was demonstrated that the relative risk of developing drug-induced hepatitis was greater in patients with hepatitis C virus and HIV infections. This finding was extended to greater in patients with HIV and hepatitis C virus who were given INH. Current IDSA and USPHS guidelines recommend that for HIV-infected patients, antituberculosis drug-related toxicity should be managed by physicians who are expert in the treatment of tuberculosis/HIV infection. If the HIV care provider and tuberculosis care provider are not the same, communication between them is essential and should occur frequently throughout the course of treatment.

8.1.4. Concurrent administration of antiretroviral agents and rifamycins
Most patients with tuberculosis have relatively advanced HIV disease and, thus, antiretroviral therapy is indicated. Antituberculosis therapy in the setting of tuberculosis therapy is complex. In those patients who are not already receiving antiretroviral therapy, the choice of new drugs with interactions and overlapping toxicities that would be difficult to evaluate. Although there are few data on which to base recommendations, expert opinion suggests that treatment for tuberculosis should be initiated at any time after tuberculosis treatment was begun, based on current recommendations. Patients who are already receiving an antiretroviral regimen, treatment should generally be continued, although the type of regimen may need to be modified on the basis of the risk of drug-drug interactions, as described in Section 7: Drug Interactions. Even though drug interactions are common, a rifamycin should not be excluded from the tuberculosis treatment regimen for fear of interactions. Although antiretroviral therapy has a dramatic effect in decreasing progression of HIV disease (decreasing CD4+ cell counts), antiretroviral therapy in the setting of tuberculosis therapy is complex. In those patients who already receive antiretroviral therapy, the incidence of side effects and paradoxical reactions, some severe enough to warrant discontinuation of treatment, may present a tremendous adherence challenge for patients adjusting to the diagnoses of both tuberculosis and HIV infection. Tuberculosis therapy has potential advantages of being better able to ascribe a specific cause for a drug side effect, the patient. Until there have been controlled studies evaluating the optimal time for starting antiretroviral therapy in patients with initial response to treatment for tuberculosis, occurrence of side effects, and ready availability of multidrug antiretroviral therapy, the initiation of antiretroviral therapy should be delayed until after tuberculosis treatment was begun, based on current recommendations. For patients who are at high risk of developing drug-induced hepatitis, the use of rifamycins is contraindicated. Rifabutin is a rifamycin that is metabolized by the liver and is recommended for use in patients with HIV infection. When rifabutin is combined with antiretroviral agents, its dose and the dose of the antiretroviral agents may require adjustment. When starting NNRTIs of PIs for tuberculosis patients receiving RIF, a 2-week "washout" period is generally recommended. When starting NNRTIs or PIs for tuberculosis patients receiving RIF, a 2-week "washout" period is generally recommended. When starting NNRTIs or PIs for tuberculosis patients receiving RIF, a 2-week "washout" period is generally recommended. When starting NNRTIs or PIs for tuberculosis patients receiving RIF, a 2-week "washout" period is generally recommended. When starting NNRTIs or PIs for tuberculosis patients receiving RIF, a 2-week "washout" period is generally recommended. When starting NNRTIs or PIs for tuberculosis patients receiving RIF, a 2-week "washout" period is generally recommended.
The paradoxical worsening after beginning treatment for tuberculosis compared with 7% of those who were not taking antiretroviral therapy with tuberculosis developed paradoxical worsening and the reactions were not associated with antiretroviral therapy. Signs of a paradoxical reaction may include high fevers, increased size and inflammation of involved lymph nodes, new lymphadenopathy, expanding central nervous system lesions, worsening of pulmonary parenchymal infiltrates, and airway compromise from enlarging lymph nodes, enlarging serosal fluid collections, and sepsis syndrome, have not been seen in 1 mg/kg and gradually reduced after 1 to 2 weeks.

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8.2. Children and Adolescents

Children most commonly develop tuberculosis as a complication of the initial infection with *M. tuberculosis* (primary tuberculosis) caused by the absence of cavitation. However, children, occasionally, and adolescents, more frequently, develop adult-type tuberculosis (upper lobe infiltration and cavitation associated with sputum production). The lesions of primary tuberculosis have a smaller number of *M. tuberculosis* organisms than those of adult-type pulmonary tuberculosis; thus, treatment failure, relapse, and development of secondary resistance are rare phenomena among children.

Because it is more difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis than from an adult, it is frequently necessary to rely on the results of culture and susceptibility tests of specimens from the person presumed to be the source of the infection in the child to guide the choice of drugs for the child. In children in whom drug resistance is suspected or for whom no source case isolate is available, attempts to isolate or cultivate organisms via three early morning gastric aspirations (optimally during hospitalization), bronchoalveolar lavage, or tissue biopsy must be considered.

Because tuberculosis in infants and children younger than 4 years of age is more likely to disseminate, treatment should be started as soon as the diagnosis is suspected. Asymptomatic children with a positive PPD-tuberculin skin test and an abnormal chest radiograph (atelectasis, parenchymal infiltrate, or hilar adenopathy) should receive combination chemotherapy, usually with INH, RIF, and PZA as initial therapy.

Several controlled and observational trials of 6-month therapy in children with pulmonary tuberculosis caused by organisms known or presumed to be susceptible to the first-line drugs have been published (1--9). Six months of therapy with INH and RIF has been shown to be effective for hilar adenopathy and pulmonary disease caused by drug-susceptible organisms (5,6). However, most studies used 6 months of daily treatment with INH and RIF, supplemented during the first 2 weeks to 2 months with PZA. This three-drug combination has a success rate of greater than 95% and a rate of adverse effects of less than 2%. Two studies used twice or three times weekly therapy from the beginning with good results (1,7).

Many experts prefer to treat children with three (rather than four) drugs in the initial phase because the bacillary population is low, many infants and children cannot tolerate the pill burden required with four oral drugs, and because of the difficulty in performing visual acuity tests in young children who are being treated with EMB. In children with three-drug therapy, the initial phase should consist of INH, RIF, and PZA. If the susceptibility of the presumed infecting strain is not known, some experts prefer the three-drug regimen. However, children and adolescents with adult-type pulmonary tuberculosis, as defined above, should be treated for (10). When epidemiologic circumstances (Table 6) suggest an increased risk of drug-resistant organisms being present, EMB
routine eye testing. Older children should have monthly evaluations of visual acuity and color discrimination while taking EIs. The usual doses for daily and twice weekly treatment in children are listed in Section 3, Drugs in Current Use, and shown in Table 2. Recommended treatment regimens for children are listed in Table 3, including those for tuberculosis of the Spine. Tuberculosis of the Spine, among other indications, is recommended for infants, children, and adolescents who are being treated with INH and who have nutritional deficiencies, so DOT should be used for all children with tuberculosis. The lack of pediatric dosage forms of most antituberculosis medicaments makes the use of adult formulations difficult. However, in some cases, it may be necessary to use adult formulations. The medications must be monitored closely. Tolerance of the medications must be monitored closely. Parents should not be relied on to supervise DOT. Because of the difficulties in isolating *M. tuberculosis* from children, bacteriological examinations are less useful in evaluating progress. However, hilar adenopathy and resultant atelectasis may require 2–3 years to resolve. Thus, a persistent abnormal finding is not necessarily indicative of treatment failure or relapse in a child. A decision to modify the drug regimen should not be made lightly, but often must be made on clinical grounds only. In general, extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. Exceptions may be disseminated disease, meningitis, and **Table 13** extrapulmonary tuberculosis, specifically meningitis and pericarditis caused by drug-resistant *M. tuberculosis*. 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 with low toxicities and high bactericidal activity. **Table 13** The usual doses for daily and twice weekly treatment in children are listed in Section 3, Drugs in Current Use, and shown in Table 3. Recommended treatment regimens for children are listed in Table 3, including those for tuberculosis of the Spine. Tuberculosis of the Spine, among other indications, is recommended for infants, children, and adolescents who are being treated with INH and who have nutritional deficiencies, so DOT should be used for all children with tuberculosis. The lack of pediatric dosage forms of most antituberculosis medicaments makes the use of adult formulations difficult. However, in some cases, it may be necessary to use adult formulations. The medications must be monitored closely. Parents should not be relied on to supervise DOT. Because of the difficulties in isolating *M. tuberculosis* from children, bacteriological examinations are less useful in evaluating progress. However, hilar adenopathy and resultant atelectasis may require 2–3 years to resolve. Thus, a persistent abnormal finding is not necessarily indicative of treatment failure or relapse in a child. A decision to modify the drug regimen should not be made lightly, but often must be made on clinical grounds only. In general, extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. Exceptions may be disseminated disease, meningitis, and **Table 13** extrapulmonary tuberculosis, specifically meningitis and pericarditis caused by drug-resistant *M. tuberculosis*. 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 with low toxicities and high bactericidal activity. **Table 13**
8.3.3. Pericardial tuberculosis
For patients with pericardial tuberculosis, a 6-month regimen is recommended. Corticosteroids are recommended as adjuncts randomized, double-blind, controlled trial, patients in the later effusive–constrictive phase who received prednisolone had a treated patients also had a lower mortality (2 of 53 [4%] versus 7 of 61 [11%]) and needed pericardiectomy less frequently ((8). Prednisolone did not reduce the risk of constrictive pericarditis. In a second prospective, double-blind, randomized trial (disease), prednisolone reduced the need for repeated pericardiocenteses (7 of 76 [9%] versus 17 of 74 [23%]; p < 0.05) and w. prednisolone compared with 10 of 74 [14%] among those not given prednisolone; p < 0.05) (9). As before, there was no statis additional small randomized trial by Hakim and associates (20) performed in HIV-infected patients with tuberculous pericarditis. On the basis of these studies, it is recommended that daily adjunctive prednisolone or prednisone treatment be given to adults for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks, and finally their weight, beginning with about 1 mg/kg body weight and decreasing the dose as described for adults.

8.3.4. Pleural tuberculosis
A 6-month regimen is also recommended for treating pleural tuberculosis. A number of studies have examined the role of co double blind, and randomized (7,22). In both of these studies, prednisone (or prednisolone) administration did not reduce the pleural tuberculosis who received prednisone had a significantly more rapid resolution of symptoms such as fever, chest pain radiographic resolution of the effusions. In the study by Wyser and colleagues (7), all patients had complete drainage of the to receive adjunctive oral prednisone or placebo for 6 weeks. The complete drainage led to a rapid resolution of symptoms, a Tuberculous empyema, a chronic, active infection of the pleural space containing a large number of tubercle bacilli, usually requiring a surgical procedure) and antituberculous chemotherapy. Surgery, when needed, should be undertaken by experien tuberculosis has not been established.

8.3.5. Tuberculous meningitis
Before the advent of effective antituberculosis chemotherapy, tuberculous meningitis was uniformly fatal. Tuberculous menin mortality, despite prompt initiation of adequate chemotherapy (24–29). HIV-infected patients appear to be at increased risk 1 similar to those in patients without HIV infection (24–26,29). Patients presenting with more severe neurologic impairment or mortality. Chemotherapy should be initiated with INH, RIF, PZA, and EMB in an initial 2-month phase. INH and RIF, as well forms for patients with altered mental status who may not be able to take oral medications.

After 2 months of four-drug therapy for meningitis caused by susceptible strains, PZA and EMB may be discontinued, and II chemotherapy is not defined, and there are no data from randomized, controlled trials to serve as the basis of recommendatio glucose, and protein, especially in the early course of therapy.

Differences in regimens among patient groups and in the use of corticosteroid therapy have made meta-analysis of published years (28,31), whereas others have suggested that short-course RIF-based regimens for 6 to 9 months may be adequate ther develop tuberculomas during therapy, perhaps as a form of paradoxical reaction; however, this does not necessarily indicate A number of investigators have examined the role of adjunctive corticosteroid therapy in the treatment of tuberculous menin not include RIF. There are no large, prospective, randomized, controlled trials of adjunctive corticosteroid use for tubercul benefit of corticosteroid therapy in terms of survival, frequency of sequelae, or both. In the study conducted by Girgis and cc presentation (4 of 27 [15%] of those who received dexamethasone died versus 14 of 35 [40%] in the control group; p < 0.02). between those who received dexamethasone and control patients (28 of 44 [64%] mortality for the dexamethasone group ver finding an effect. Likewise, there were too few patients with Stage 1 disease (alert) on entry to determine the effectiveness of On the basis of the available data, albeit limited, adjunctive corticosteroid therapy with dexamethasone is recommended for meningitis. The recommended regimen is dexamethasone in an initial dose of 8 mg/day for children weighing less than 25 kg 3 weeks and then decreased gradually during the following 3 weeks.

8.3.6. Disseminated tuberculosis
A 6-month regimen is recommended for tuberculosis at multiple sites and for miliary tuberculosis, although there are limited treatment for children with disseminated tuberculosis.) Expert opinion suggests that corticosteroid therapy may be useful for its use.

8.3.7. Genitourinary tuberculosis
Renal tuberculosis is treated primarily with medical therapy (12,42–46), and a 6-month regimen is recommended. If ureteral hydrenephrosis and progressive renal insufficiency due to obstruction, renal drainage by stenting or nephrostomy is recomm discussed in the urologic literature but the efficacy of steroids in this setting is unclear. Nephrectomy is not usually indic nonfunctioning or poorly functioning kidney, particularly if hypertension or continuous flank pain is present. Tuberculosis o need only for residual large tubo-ovarian abscesses.

A positive urine culture for M. tuberculosis occurs relatively commonly as an incidental finding among patients with pulmor in the absence of any abnormalities on urinalysis and does not necessarily represent genitourinary tract involvement.

8.3.8. Abdominal tuberculosis
A 6-month regimen is recommended for patients with peritoneal or intestinal tuberculosis (47,48). There are insufficient da
In a small study of peritoneal tuberculosis alternate patients received adjunctive corticosteroid therapy for 4 months (total of in none of those in the steroid group (23 patients), but the difference was not statistically significant.

### 8.3.9. Other sites of involvement

As noted above, tuberculosis can involve any organ or tissue. In treating tuberculosis in sites other than those mentioned, the basic principles of therapy apply, but experts should be consulted for specific advice concerning

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**References**

Instances of severe and fatal liver disease have been reported in patients taking RIF and PZA for treatment of latent tuberculosis infection (without INH) for 4 months, and RIF and PZA for 2 months (for persons who are unlikely to complete a longer course and who can be monitored carefully) (showed that the efficacy of INH decreased significantly if less than 9 months of the drug was taken, but that further protection was not conferred if the duration given for 12 months was significantly better than 6 months (89 versus 67% reduction). A reanalysis of data from a commun

The optimum

Patients should not be classified as having radiographic evidence of prior tuberculosis if another disease is found to account for the subsequent

Persons with a positive tuberculin PPD skin test who have radiographic findings consistent with prior pulmonary tuberculosis (ATS/CDC Class 4) (using one of the recommended regimens.

Failure to isolate M. tuberculosis from appropriately collected specimens in persons who, because of clinical or radiographic tuberculosis. For the United States as a whole, about 17% of the reported new cases of pulmonary tuberculosis have negative expelled, and errors in specimen processing all may result in failure to isolate organisms from patients who have active tuberculous disease. Thus, it is imperative that all patients with a positive test for M. tuberculosis have three sputum specimens

8.4. Culture-Negative Pulmonary Tuberculosis in Adults

Failure to isolate M. tuberculosis from appropriately collected specimens in persons who, because of clinical or radiographic tuberculosis. For the United States as a whole, about 17% of the reported new cases of pulmonary tuberculosis have negative expelled, and errors in specimen processing all may result in failure to isolate organisms from patients who have active tuberculous disease. Thus, it is imperative that all patients with a positive test for M. tuberculosis have three sputum specimens

8.5. Radiographic Evidence of Prior Tuberculosis: Inactive Tuberculosis

Persons with a positive tuberculin PPD skin test who have radiographic findings consistent with prior pulmonary tuberculosis development of active tuberculosis (2-4). The radiographic findings that constitute evidence of prior tuberculosis are apical pulmona...
8. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection. MMWR 2000;49:735.

8.6. Pregnancy and Breastfeeding

Untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does treatment of the disease. I to women without tuberculosis and, rarely, the infant may acquire congenital tuberculosis (11,12,13). Thus, treatment of a pregnant woman represents a moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. SM should not be substituted for EM. IUATLD (5), the drug has not been recommended for general use in pregnant women in the United States because of insufficient data. However, some public health jurisdictions in the United States have used PZA in pregnant women without reported adverse events (1). If PZA is not included in the initial treatment regimen for pregnant women who are receiving INH, RIF, EMB cross the placenta, but none has been shown to have teratogenic effects (6). SM, the only antituberculosis agent that may cause congenital deafness. In 40 pregnancies among women being treated with SM, 17% of the babies had e Kanamycin, amikacin, and capreomycin presumably share this toxic potential; however, there is little specific information on or was no indication of teratogenicity among babies whose mothers had received these two drugs (2). There are not enough data to confirm these effects attributed to ethionamide (8). The fluoroquinolones have been associated with arthropathies in young anir. In general, administration of antituberculosis drugs is not an indication for termination of pregnancy (2). However, in women should be provided because of the known and unknown risks of the second-line agents. Breastfeeding should not be discouraged for women being treated with first-line agents, because the small concentrations of INH in breast milk should not be considered to serve as effective treatment for active tuberculosis or latent tuberculosis infection: INH. The administration of the fluoroquinolones during breastfeeding is not recommended, although, as of 1998, there have

References

8.7. Renal Insufficiency and End-stage Renal Disease

Renal insufficiency complicates the management of tuberculosis because some antituberculosis medications are cleared by the kidney. Thus, some alteration in dosing antituberculosis medications is commonly necessary in patients with decreasing the dose of selected antituberculosis drugs may not be the best method of treating tuberculosis because, although decreasing the dose of the antituberculosis agent, increasing the dosing interval is recommended (1). The general approach is to clear the drugs by the kidneys to patients having a creatinine clearance of less than 30 ml/minute and those receiving hemodialysis. There are insufficient data to guide dosing recommendations for patients having a reduced creatinine clearance but not less than 30 ml/minute. In such patients standard doses should be administered and to facilitate DOT. Doses of streptomycin, kanamycin, amikacin, and capreomycin must be adjusted in patients with renal failure because the kidneys
hemodialysis when these drugs are given just before hemodialysis (8). Far less drug is likely to be removed once the drugs have been anticipated. As with EMB and PZA, the dosing interval should be increased. In general, the dose should not be reduced because of reduced drug efficacy. Ethionamide is not cleared by the kidneys, nor is the drug removed with hemodialysis, so no dose adjustment is necessary. Acetylation-PAS, is substantially removed by hemodialysis; twice daily dosing (4 g) should be adequate if the granule formulation is used (56%). Thus, an increase in the dosing interval is necessary to avoid accumulation between hemodialysis sessions. Fluoroquinolones undergo some degree of renal clearance that varies from drug to drug. For example, levofloxacin undergoes multiple dosing recommendations for end-stage renal disease provided by the manufacturers were developed for treating pyogenic bacteria in patients with end-stage renal disease.

As noted above, administration of all antituberculosis drugs immediately after hemodialysis will facilitate DOT (three times per week) and avoid premature drug elimination. The hepatic abnormalities caused by tuberculosis will improve with effective treatment. Careful use of the antituberculosis drugs is mandatory in treating such patients. It should be noted that tuberculosis itself may involve the liver, causing abnormal liver function tests noted at baseline should be attributed to the disease confound monitoring for drug-induced hepatitis. Thus, clinicians may consider regimens with fewer potentially hepatotoxic agents for patients with end-stage renal disease, provided that the recommended doses are still adequate for effective treatment.

8.8. Hepatic Disease
The treatment of tuberculosis in patients with unstable or advanced liver disease is problematic for several reasons. First, the hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening. Finally, fluctuations in the disease course may complicate the treatment plan. Possible treatment regimens in the setting of liver disease include the following.

8.8.1. Treatment without INH
As described in Section 5.2, Alternative Regimens, analysis of data from several studies conducted by the BMRC in patients with advanced liver disease suggests that the initial phase contained four drugs and RIF was used throughout the 6 months (2). Thus, it is reasonable to employ an initial phase regimen containing ethambutol, pyrazinamide, isoniazid, and rifampin. Although this regimen has two potentially hepatotoxic medications, it has the advantage of retaining the 6-month regimen.

8.8.2. Treatment without PZA
Although the frequency of PZA-induced hepatitis is slightly less than occurs with INH or RIF, the liver injury induced by the initial phase of INH, RIF, and EMB for 2 months followed by a continuation phase of INH and RIF for 7 months, for a total of 24 months (Rating BII). Although this regimen has two potentially hepatotoxic medications, it has the advantage of retaining the 6-month regimen.

8.8.3. Regimens with only one potentially hepatotoxic drug
For patients with advanced liver disease, a regimen with only one potentially hepatotoxic drug might be selected. Generally, RIF, cycloserine, and injectable agents. The duration of treatment with such regimens should be 12–18 months, depending on the regimen.

8.8.4. Regimens with no potentially hepatotoxic drugs
In the setting of severe unstable liver disease, a regimen with no hepatotoxic agents might be necessary. Such a regimen might provide guidance as to the choice of agents or the duration of treatment or that indicate the effectiveness of such a regimen. (CIII). Consultation should always be obtained before embarking on such a treatment plan.

References
8.9. Other Associated Disorders
Tuberculosis commonly occurs in association with other diseases or conditions. An associated disorder may alter immune response and the level of drug susceptibility. Examples of the former class of disorders include HIV infection, chronic renal failure, poorly controlled, insulin-dependent diabetes mellitus, and malnutrition. Silicosis, by impairing pulmonary function, is a unique example of an associated disorder. The latter group of disorders includes chronic alcoholism and its secondary effects, other substance abuse, and psychiatric illness. The response of immunocompromised patients to treatment is not impaired. Nevertheless, therapeutic decision making is more complex, and the severity of tuberculosis in the response to treatment. When possible, steps should be taken to correct the immune deficiency. If the continuation phase is extended for at least 2 months (12, 26).

References

9. Management of Relapse, Treatment Failure, and Drug Resistance
9.1. Relapse
Relapse refers to the circumstance in which a patient becomes and remains culture-negative while receiving antituberculosis treatment. Relapses may be due to failure of therapy to sterilize the host tissue, thereby enabling exogenous reinfection with a new strain of Mycobacterium tuberculosis. Patients who are most likely to have true relapses are those with extensive tuberculosis whose sputum cultures remain positive for at least 2 months (12, 26). Patients who also fall into this category are those with tuberculosis caused by drug-susceptible organisms who were treated with rifampin or who received self-administered therapy for 6 months or less. However, in patients who received self-administered therapy or a nonrifamycin regimen and who have a relapse, the risk of being infected with a rifampicin-resistant strain is high. Among patients who received self-administered therapy, the risk of erratic drug administration leading to relapse with resistant strains for patients with relapses should be based on the prior treatment scheme. For patients with tuberculosis that was successfully treated with the standard four-drug initial phase regimen, relapses are more likely to occur and may be responsible for the apparent relapse (12, 26).

For the relatively few patients in whom epidemiologic circumstances provide a strong suspicion of exogenous reinfection as a pattern of the presumed source case. If the presumed source case is known to have tuberculosis caused by drug-susceptible or drug-resistant organisms, an empirically expanded regimen based on the resistance profile should be used. The choice of agents to include in expanded empirical regimens for presumed drug-resistant pulmonary tuberculosis should be based on the probability of in vitro susceptibility to the drug, the clinical presentation, and the probability of acquiring a higher risk of acquired drug resistance and benefit from an expanded regimen (see below).

9.2. Treatment Failure
Treatment failure is defined as continued or recurrently positive cultures in a patient receiving appropriate chemotherapy. Ar 90--95% of patients will be culture-negative after 3 months of treatment with a regimen that contains INH and RIF. During this time the patient gains weight and has no increase in the number of positive cultures after 3 months of chemotherapy. However, patients whose sputum cultures remain positive after 4 months of treatment are considered to have failed treatment. There are multiple potential reasons for treatment failure. If the patient is not receiving DOT, the most likely explanation for DOT failure is either nonadherence or the presence of drug-resistant organisms, who were treated by DOT, and who have relapses, or DOT failure due to erratic drug administration, thereby enabling endogenous recrudescence of the original infection. In some hyperendemic settings, however, there are multiple potential reasons for treatment failure. If the patient is not receiving DOT, the most likely explanation for DOT failure is either nonadherence or the presence of drug-resistant organisms, who were treated by DOT, and who have relapses, or DOT failure due to erratic drug administration, thereby enabling endogenous recrudescence of the original infection. In some hyperendemic settings, however, most patients relapse within the first 6 months after treatment (12--14).

Clinicians should be alert, as well, to the possibility of transient clinical or radiographic worsening (paradoxical reactions), inflammation at sites of lymphadenitis, worsened abnormalities on chest radiographs after several months of treatment, or the paradoxical worsening during treatment occurs more commonly but not exclusively in persons with HIV infection (12--14). For patients who meet criteria for treatment failure, the possible reasons listed above should be addressed promptly. If clinicians consult with a specialty center is indicated. If treatment failure is presumed to be due to drug resistance and the patient is waiting for drug susceptibility results from a recent isolate. If the patient is seriously ill or has a positive sputum AFB smear, an empirical retreatment regimen is indicated. For patients who have failed treatment, mycobacterial isolates are often second-line drugs.

A fundamental principle in managing patients who have failed treatment is that a single new drug should never be added to a regimen containing INH, RIF, and PZA plus an additional three agents, based on the probability of in vitro susceptibility to the drug, the clinical presentation, and the probability of acquiring a higher risk of acquired drug resistance and benefit from an expanded regimen (see below).
generally prudent to add at least three new drugs to which susceptibility could logically be inferred to lessen the probability of an empirical regimen; however, expert opinion indicates that empirical retreatment regimens might include a fluoroquinolone (if susceptible initially), amikacin, kanamycin, or capreomycin, and an oral agent such as PAS, cycloserine, or ethionamide according to the results.

9.3. Management of Tuberculosis Caused by Drug-Resistant Organisms

Tubercle bacilli are continually undergoing spontaneous mutations that create resistance to individual antituberculosis drugs. Combination chemotherapy that is reliably ingested, clinically significant resistance will not develop (see Section 4.1: Combination Chemotherapy). If there is a large bacillary population, such as in pulmonary cavities, when an inadequate drug regimen is prescribed (i.e., the provider to ensure that an adequate regimen is taken (16)). Rarely, malabsorption of one or more antituberculosis drugs may be caused by the immense number of rapidly multiplying bacilli in the cavity(ies) (17). During extensive resistance may transmit their strains to others who, if they develop tuberculosis, will have primary drug resistance. Drug resistance in a patient with newly diagnosed tuberculosis may be suspected on the basis of historical (previous treatment region in which drug resistance is common) (18,19). In such situations it is prudent to employ an empirically expanded regimen can be proven only by drug-susceptibility testing performed in a competent laboratory (Table 16). A step taken when resistance to both INH and RIF (MDR) are at high risk for treatment failure and further acquired resistance; they centers. Patients with strains resistant to RIF alone have a better prognosis than MDR cases, but also are at increased risk for scrutiny.

Definitive randomized or controlled studies have not been performed among patients with the various patterns of drug resistant to rifampin. The WHO and IUATLD have formulated standard algorithmic regimens listed below, as well as on expert opinion (20,21). This approach is best suited to regions without in vitro susceptibility test results are available. However, the clinical significance and effectiveness of the use of INH in the setting of low-level INH better survival rates in patients with the strain-W variety of MDR M. tuberculosis that was susceptible to higher costs

Resistance to RIF is associated in nearly all instances with cross-resistance to rifabutin and rifapentine (28). Rare sti nfections involving the RNA-polymerase locus in the bacillus (29). However, unless in vitro susceptibility to rifabutin is d between RIF and rifapentine appears almost universal (28).

There is no cross-resistance between SM and the other injectable agents: amikacin, kanamycin, and capreomycin (a amikacin and kanamycin is universal (24). Simultaneous use of two injectable agents is not recommended due to th

Determination of resistance to PZA is technically problematic and, thus, is not made in many laboratories. However, mono resistance to PZA is observed, consideration must be given to the possibility that the etiologic agent is M. bovis M. tuberculosis by nucleic acid hybridization--probe assays that are commonly used for identification). Table 16 contains regimens suggested for use in patients with various patterns of drug-resistant tuberculosis.

9.4. Role of Surgery in MDR Tuberculosis

The role of resectional surgery in the management of patients with extensive pulmonary MDR tuberculosis has not been esta having resistance to more than 5 drugs) appeared to benefit from the resection of cavitary or badly damaged lung tissue when drug resistance having similar cure rates without surgery (25,32). The disparity in these reports may be due to long-standing performed by an experienced surgeon after the patient has received several months of intensive chemotherapy. Even with su demonstrated susceptibility, should be given.

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9.5 Laboratory Considerations in Determining Drug Resistance

Susceptibility testing of *M. tuberculosis* is critical for appropriate patient management and should be performed on an initial isolate. Routinely, all laboratories will perform susceptibility testing on initial isolates, but, often, private laboratories do not perform such testing unless specifically requested to do so by the physician. As noted previously, susceptibility testing should be repeated if the patient still has a positive culture result after 3 months of therapy or again develops positive cultures after a period of negative cultures. Antimicrobial susceptibility testing should be performed using a standard methodology, such as that recommended by the National Committee for Clinical Laboratory Standards (3). The second edition of a tentative standard (M24-T2) for susceptibility testing of mycobacteria was published by the National Committee for Clinical Laboratory Standards in 2000 (3).

Susceptibility of *M. tuberculosis* is determined by evaluating the ability of an isolate to grow on agar or in broth containing a single "critical" concentration of a drug (2). The agar proportion method has been proposed as the reference method for all antituberculosis drugs except pyrazinamide, in which case the BACTEC broth-based methodology is the reference method (3). With the agar proportion method, resistance is defined as growth on the drug-containing plate that is more than 1% of the growth on the non-drug-containing plate (4). Because the agar method requires up to 6 weeks to yield results, it is recommended that initial susceptibility testing of *M. tuberculosis* isolates to first-line antituberculosis drugs be performed using more rapid broth-based methods (e.g., BACTEC) available within 28 days of receipt of a clinical specimen (5). The critical concentrations recommended by the National Committee for Clinical Laboratory Standards for the agar proportion method and "equivalent" broth methods are provided in Table 4. As noted, the agar method is the reference method for first-line drugs, while the BACTEC method is the reference method for pyrazinamide.
concentrations for broth-based testing methods are shown in Table 17 (2,3).
The National Committee for Clinical Laboratory Standards recommends that susceptibility testing be performed for INH (tw initial M. tuberculosis isolates. Pyrazinamide testing may be done if there is a sufficiently high prevalence of PZA resistance there is resistance to RIF alone or to two or more drugs. Testing of second-line drugs is performed using the agar proportion are capreomycin, ethionamide, kanamycin (which also predicts amikacin susceptibility), ofloxacin (used to assess fluoroquin of EMB is also recommended. Susceptibility testing for cycloserine is not recommended because of the technical problems a

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10. Treatment Of Tuberculosis in Low-Income Countries: Recommendations and Guidelines of th
This brief summary of the differences between the recommendations for treatment of tuberculosis in high-income, low-incid context for the ATS/CDC/IDSA guidelines. As tuberculosis in low-incidence countries, such as the United States, becomes r care providers in low-incidence countries have an understanding of the differences in the approaches used and the reasons fo high-incidence countries (I). As noted at the outset of this document, the ATS/CDC/IDSA recommendations cannot be assur tuberculosis and the resources with which to confront it to an important extent determine the approaches used.
A number of differences exist between these new ATS/CDC/IDSA recommendations, and the current tuberculosis treatment Rather than being recommendations per se, the IUATLD document presents a distillation of IUATLD practice, validated in t mycobacterial culture and susceptibility testing and radiographic examinations are not widely available. These organizations Course) in which direct observation of therapy ("DOT" in the current statement) is only one of five key elements (4). The bo Selected important differences among the recommendations are summarized below. Some of the differences arise from varia weekly regimens, arise from different interpretations of common elements, for example, whether DOT is used throughout the

10.1. Microbiological Tests for Diagnosis and Evaluation of Response
The WHO and the IUATLD recommend diagnosis and classification of cases and assessment of response based on sputum A in many countries. In addition, the AFB smear identifies patients who are most likely to transmit the organism. Susceptibility facilities. However, susceptibility testing is recommended by the WHO for patients who fail (sputum smear--positive in mon
those who fail a supervised retreatment regimen. Regarding follow-up, it is recommended by the WHO and the IUATLD that at completion of treatment (either 6 or 8 months). The IUATLD recommends that for patients who have positive smears 10.2. Use of Chest Radiographs in Diagnosis and Follow-Up of Patients Being Treated

In many parts of the world radiographs are not readily available. Moreover, because the highest priority for treatment is the interpretation of radiographic findings alone is an inefficient use of resources. Thus, chest radiography is recommended by both the WHO and the IUATLD for follow-up.

10.3. Initial Treatment Regimens

The WHO recommends a single initial phase of daily INH, RIF, PZA, and EMB (or SM) for 2 months followed by a continu- ous daily INH and EMB for 6 months (self-administered). The WHO specifically discourages programs from using twice weekly doses of INH, RIF, and EMB. The IUATLD recommends a 2-month initial phase of INH, RIF, PZA, and EMB given by DOT, followed by a 6-month continued phase of daily INH and EMB. The IUATLD also recommends a 12-month regimen with a 2-month initial phase of INH and thioacetazone. This regimen is intended to be used for patients who have negative smears or when the 8-month regimen is less efficacious in patients with drug-susceptible tuberculosis, but use of this regimen will cost about 27% less than a 4-month continuation phase of daily INH. The IUATLD also recommends EMB in place of thiaacetazone.

10.4. Approach to Previously Treated Patients

The WHO and the IUATLD recommend a standardized regimen for patients who have relapsed, interrupted treatment, or treatment failure. The regimen consists of an initial phase of INH, RIF, PZA, EMB, and SM given daily for 2 months and then 1 month of daily INH, RIF, and EMB.

Patients who have failed supervised retreatment are considered "chronic" cases and are highly likely to have tuberculosis caused by M. tuberculosis that is drug-resistant. The issue of chronic cases is an area of considerable controversy (6). In countries with sufficient resources, such as the United States, Management of Relapse, Treatment Failure, and Drug Resistance, are recommended. However, in countries with limited resources, at least one group has demonstrated that in a high-incidence, low-income country (Peru) treatment with individualized regimens is feasible and effective (6).

10.5. Monitoring of Outcomes of Therapy

Both the WHO and the IUATLD recommend a formal system for monitoring outcomes of treatment that classifies all cases into one of six categories (cured, not cured, treatment failure, death, lost to follow-up, and transfer out). The assessment of cure is based on clinical response and on sputum AFB smear (or culture when available) identification of programmatic shortcomings.

10.6. Recommended Doses of Antituberculosis Drugs

The WHO recommends 10 mg/kg as the dose for three times weekly INH, whereas the ATS/CDC/IDSA recommend 15 mg/kg to a maximum of 300 mg/day, but the ATS/CDC/IDSA recommend a higher dose for children (10–15 mg/kg per day), based on the number of pills required for three weight ranges resulting in a dose of about 5 mg/kg up to 300 mg/day.

The clinical trials of the BMRC that established the efficacy of three times weekly regimen all used an INH dose of 15 mg/kg, which is an area of considerable controversy (6). The IUATLD recommends an INH dose of 15 mg/kg per day, based on the number of pills required for three weight ranges resulting in a dose of about 5 mg/kg up to 300 mg/day.

10.7. Drugs/Preparations Not Available in the United States

Thioacetazone, which formerly was commonly used, is still available in many parts of the world, but is used less frequently. Thioacetazone is used in the recommended IUATLD first-line regimen. Combination preparations not available in the United States but thioacetazone (50 mg); and INH (75 mg), RIF (150 mg), PZA (400 mg), and EMB (275 mg). The IUATLD recommends using a combination of INH and RIF or INH and thiacetazone.

10.8. Treating Pregnant Women

Both the WHO and the IUATLD include PZA in the regimen for treating pregnant women, in the absence of data indicating resistance to PZA.

10.9. Management of Common Adverse Reactions

Neither baseline nor follow-up testing is recommended by the WHO and the IUATLD. It is recommended that patients be monitored for adverse reactions.

References

11. Research Agenda for Tuberculosis Treatment

11.1. New Antituberculosis Drugs

New antituberculosis drugs are needed for three reasons: to shorten or otherwise simplify treatment of tuberculosis caused by drug-susceptible organisms, to improve the treatment of patients with MDR tuberculosis, and to provide more effective and efficient treatment of latent tuberculosis infection (LTBI) (1). Although treatment regimens for drug-susceptible tuberculosis are effective, they must be administered for a minimum of 6 months to achieve optimal results. Nonadherence to this relatively lengthy course of treatment remains a major problem. To address this, DOT (as a component of the DOTS strategy) is recommended as a standard of care worldwide. However, the administrative and financial burden of providing DOT for all patients is considerable. Thus, new drugs that would permit significant shortening of treatment are urgently needed, as are drugs that could enable effective treatment to be given at dosing intervals of 1 week or more.

Rates of multidrug-resistant tuberculosis are alarmingly high in several countries (2), and even in countries, such as the United States, where the rates are low and decreasing, the occasional case presents an often extremely difficult treatment problem (see Section 9: Management of Relapse, Treatment Failure, and Drug Resistance). Current treatment regimens for drug-resistant tuberculosis utilize drugs that are less effective, more toxic, and more expensive than those used for standard treatment. Moreover, these treatment regimens often have to be given for 18–24 months. Although new drugs that are effective against resistant organisms would alone not solve the problem of drug resistance, their judicious use would greatly improve the treatment for many patients.

Finally, the United States and several other low-incidence countries have embarked on plans to eliminate tuberculosis. An important component of an elimination strategy is the identification and treatment of persons with LTBI who are at high risk of developing tuberculosis (3). In the United States the most commonly used LTBI treatment regimen is INH given for 9 months; however, poor adherence to this regimen imposes a major limitation on its effectiveness. A shorter LTBI treatment regimen with RIF and PZA appears to be effective, but reports have indicated that toxicity may be unacceptably high (4). Thus, new drugs to provide safe and effective "short-course" LTBI treatment are a major need.

No truly novel compounds that are likely to have a significant impact on tuberculosis treatment are presently available for clinical study. However, further work to optimize the effectiveness of once weekly rifapentine regimens and investigate the role of newer fluoroquinolones in the treatment of drug-susceptible tuberculosis is warranted. As noted above, once weekly rifapentine--INH is recommended only in the continuation phase for HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum smears at completion of 2 months of treatment. Two approaches to improve intermittent rifapentine regimens have been suggested by experimental studies: increasing the rifapentine dosage (5), and adding moxifloxacin as a companion drug to provide better protection against the development of drug resistance and enhance the sterilizing activity of the regimen (6). Other data from a clinical trial of ofloxacin suggest that fluoroquinolones have the potential to significantly shorten treatment (7). Of the newer fluoroquinolones with more potent activity against M. tuberculosis, moxifloxacin appears to be the most promising.

Other compounds that might become available for clinical evaluation in the future include the nitroimidazopyrans that are chemically related to metronidazole, for which activity against dormant M. tuberculosis has been suggested; oxazolidinones such as linezolid; and drugs that target isocitrate lyase, an enzyme that may be necessary for the establishment of latent tuberculosis infection (8). The nitroimidazopyran compound PA-824 has bactericidal activity comparable to that of INH and appears to act as well on bacilli maintained in an anaerobic environment (9). However, additional preclinical evaluation of PA-824 is needed before clinical studies could begin. Although linezolid, a drug that is marketed for the treatment of selected acute bacterial infections, does have demonstrated...
treatment of tuberculosis (10).

11.2. Other Interventions To Improve the Efficacy of Treatment

A number of other approaches have been suggested that might lead to improved treatment outcome, including alternative drug regimens. Experimental studies have demonstrated that effective serum concentrations of INH and PZA can be provided through incorporation into slow-release formulations. Moreover, some studies have shown promise and deserve further evaluation (11). However, there has been little apparent commercial interest in pursuing this approach. Liposomal encapsulation of antimicrobial agents, for example, has been shown to provide a more effective and better tolerated therapy, as well as for more widely spaced treatment. Similarly, incorporation of drug into inhalable microparticles may reduce dose requirements, minimize toxicity, and deliver drug to infected alveolar macrophages. Although experimental studies have suggested potential benefits, little clinical work has been done in these areas (11,12).

Because of possible detrimental effects of the cytokine, tumor necrosis factor-a, in HIV-associated tuberculosis, there has been limited work on the role of cytokine and chemokine therapy. Studies have shown that administration of thalidomide improves weight gain in both HIV-infected and HIV-uninfected patients with tuberculosis (14). However, the potential side effects of these drugs include infertility and anemia, among other complications (15). Other cytokines, such as aerosolized interferon-g and subcutaneous interleukin-2, that have shown activity as adjuncts to anti-tuberculosis therapy, the use of heat-killed preparations of Mycobacterium vaccae as a therapeutic vaccine, has not shown clinical efficacy in early trials (16). A recent study suggested that the administration of Vitamin A and zinc to patients with pulmonary tuberculosis may be indicated (17).

11.2.1. Better methods to identify and manage high- and low-risk patients

As noted above, sputum culture positivity at 2 months appears to be a marker for an increased risk of relapse for patients with IDUs. Whether or not low-risk patients can be managed with shorter regimens using currently available drugs is a topic of ongoing research.

11.2.2. Health services research to facilitate treatment administration and improve treatment outcome

Although DOT (as a component of DOTS) is widely advocated as a universal standard of care for tuberculosis treatment, many programs do not have the resources to provide DOT for all patients. DOT continues to be interest in this approach, especially for patients with advanced drug-resistant tuberculosis. Other vaccines that have been shown to lead to expression of protective cytokines have shown more promise in clinical trials than previous vaccines (18). Finally, although limited work has been done in the area of behavioral tuberculosis studies of patients and providers, an ambulatory care setting has been revisited (19).

References


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Joint Committee of the American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), and CDC

Membership List*

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Table 1

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Figure 1