Review Article

Medical Progress

MANAGEMENT OF TUBERCULOSIS IN THE UNITED STATES

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IN the 1980s, after decades of steadily declining rates of tuberculosis, ambitious plans were made to eliminate the disease in the United States. Despite these plans, the control of tuberculosis was neglected, resulting in a resurgence of the disease.[1] This resurgence has reminded us that the overall goal of public health programs must be not merely the provision of health care for marginalized persons, but a systematic commitment to protect the health of the general public in a time of increasing globalization. Regrettably, these lessons have come at considerable costs, in terms of both individual health and health care budgets.

Fortunately, renewed attention to basic public health practices has reversed this trend, and the rate of tuberculosis is now at a historical low in the United States. A recent Institute of Medicine study concluded that we have been given another, perhaps final, chance to control and even eliminate tuberculosis in the United States.[2] The study further concluded that capitalizing on this opportunity will require continued attention to the treatment of cases of active tuberculosis, plus an expanded initiative to identify and treat persons with latent tuberculosis infection. In this article, we will review what health care providers must know and do as part of the effort to eliminate tuberculosis in the United States.

EPIDEMIOLOGIC FEATURES

Between the mid-1980s and the early 1990s, the synergistic combination of a deteriorating public health infrastructure, inadequate institutional control of infection, urban crowding, the epidemic of human immunodeficiency virus (HIV) infection, and immigration resulted in a resurgence of tuberculosis (Fig. 1), including infections with multidrug-resistant strains.[3] A conservative estimate is that this resurgence resulted in 67,000 more cases of tuberculosis than would have occurred had the strategy designed by the Centers for Disease Control and Prevention (CDC) and its Advisory Council for the Elimination of Tuberculosis been successfully implemented.[4]

Since its peak in 1992, the case rate for tuberculosis has decreased steadily. In 2000, 16,377 cases (5.8 cases per 100,000 population) were reported to the CDC, which represented a 45 percent decrease from the peak rate and was the lowest rate in U.S. history.[5] This improvement is largely attributable to a comprehensive strengthening of control activities and the resulting decrease in the transmission of *Mycobacterium tuberculosis* from persons with active disease. The financial costs of losing control of tuberculosis have been immense; in New York City alone, this cost has been estimated as approximately $1 billion.[6] As the rates of tuberculosis have declined, the distribution of cases has been limited to identifiable populations, primarily in urban and immigrant communities.[7-9]

However, the previous era of uncontrolled transmission of *M. tuberculosis* and continued immigration from areas with high rates of tuberculosis have resulted in a large number of cases of latent tuberculosis infection. The development of active disease in persons with latent infection poses a continual threat of transmission, the control of which will be particularly difficult in regions where low case rates have resulted in decreased expertise in the identification and control of outbreaks of tuberculosis.[10]

In contrast to the situation in the United States, it is not realistic even to contemplate the global elimination of tuberculosis with available interventions. Currently, more than one third of the world's population is infected with *M. tuberculosis;* 8 million new cases and approximately 2 million deaths are reported each year.[11] Although progress is being made in controlling the disease with the use of directly observed short-course treatment, this strategy may not be adequate in the many regions with high rates of HIV infection and drug-resistant tuberculosis.[12-14] The active participation of the United States in global programs to control tuberculosis is both a responsibility and an essential component of our efforts to eliminate the disease in this country.

CLINICAL CONSEQUENCES OF INFECTION

Virtually all *M. tuberculosis* is transmitted by airborne particles that are 1 to 5 μm in diameter (Fig. 2

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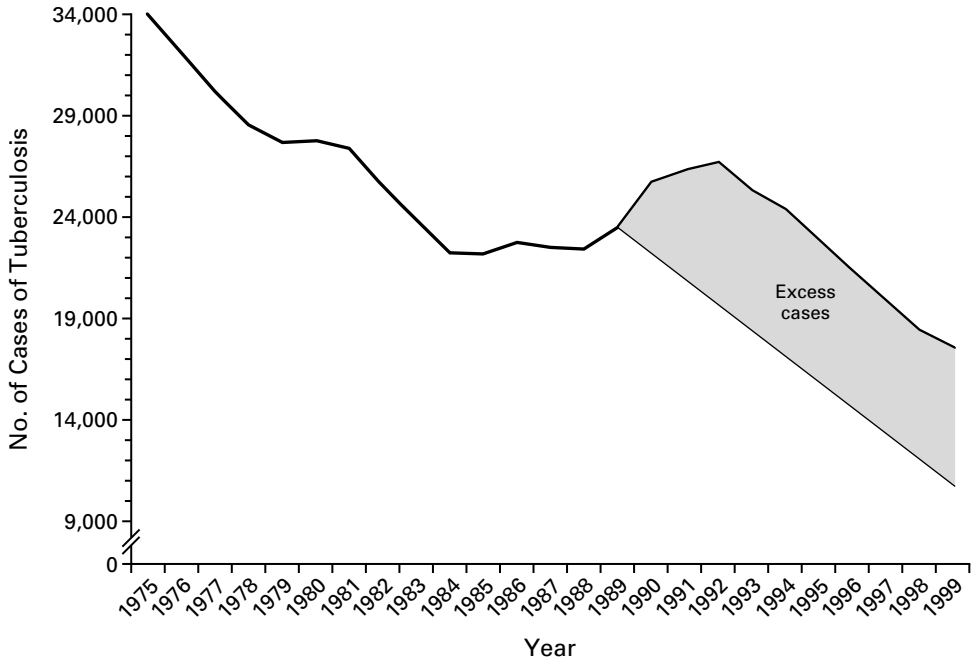

Figure 1. Reported Cases of Tuberculosis in the United States from 1975 to 1999.

The shaded area represents the 67,000 cases that would not have occurred if earlier plans for the elimination of the disease had been successfully implemented.

and 3).[15] Transmission is greatly influenced by characteristics of the source case (such as the number of bacteria excreted) and the nature of the encounter (such as the duration and closeness of exposure). However, regardless of these factors, it is thought that infection results when as few as one to five bacteria are deposited in a terminal alveolus. Primary tuberculosis, a self-limited, mild pneumonic illness that generally goes undiagnosed, may develop in a subgroup of infected persons. During this illness, bacillemia and seeding of other organs may occur, setting the stage for subsequent reactivation in extrapulmonary sites.

A precarious balance is subsequently struck between the host and the pathogen. In about 5 percent of persons, the infection progresses from a latent form to active disease within two years after infection, and an additional 5 percent have active disease at some later point in their lives. Although the majority of cases of active tuberculosis are thought to arise from a reactivation of latent infection, exogenous reinfection with a second strain of *M. tuberculosis* can occur, particularly in profoundly immunocompromised persons and in those heavily exposed to new bacilli.[16-18]

The symptoms of tuberculosis are protean and nonspecific and can be classified as either systemic or organ-specific. Classic systemic symptoms include fever, night sweats, anorexia, weight loss, and weakness. However, since tuberculosis is associated with other illnesses that have similar symptoms, this lack of specificity can result in a delayed diagnosis or even a misdiagnosis.

Organ-specific symptoms of pulmonary tuberculosis include cough, pleuritic pain, and hemoptysis. In patients with primary tuberculosis, chest radiographs often show infiltrates in the middle or lower lung zones, with ipsilateral hilar adenopathy. In patients with reactivation tuberculosis, the classic radiographic findings include upper-lobe infiltrates, frequently with cavitation.[19] The clinical signs of pulmonary tuberculosis are more varied and less specific in persons with HIV infection.[20]

Although the lung is the primary site of disease in 80 to 84 percent of cases of tuberculosis in the United States,[7] extrapulmonary tuberculosis has become more common with the advent of HIV infection, and the risk of tuberculosis increases as immunosuppression progresses.[21-23] The most commonly reported extrapulmonary sites of disease are the lymph nodes, pleura, and bones or joints.[7] Other sites include the genitourinary system, the central nervous system, the abdomen and pericardium, and in rare cases, virtually any other organ.[19]

TREATMENT OF DISEASE

Comprehensive treatment of tuberculosis requires a complex interaction between clinical care and public health. All states require that cases of tuberculosis be reported to public health authorities. Such reports

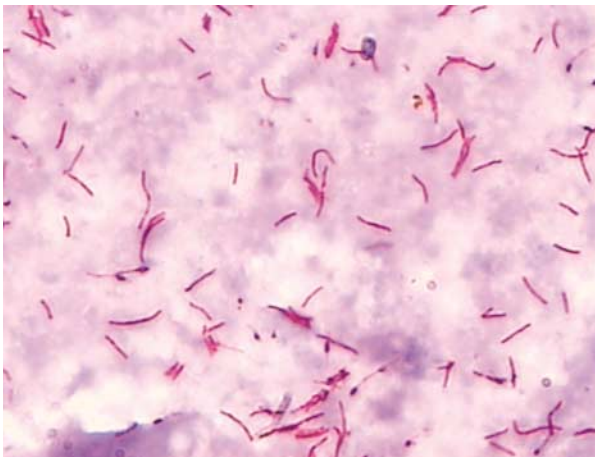

Figure 2. Photomicrograph of an Acid-Fast Smear of *Mycobacterium tuberculosis.*

The pathogen is likely to kill more than 20 million persons in the coming decade. Photograph provided courtesy of Alfredo Ponce de Leon.

set in motion a range of activities designed not only to treat the individual patient but also to protect the health of other persons in the community. Even when care is provided by the private medical sector, the treatment of patients with tuberculosis should be monitored by public health officials to ensure compliance, prevent the emergence of drug-resistant organisms, coordinate the evaluation of contacts, monitor patterns of drug resistance in the community, provide patient education, and identify possible outbreaks.

Antituberculosis Drugs

Five first-line antimicrobial agents (Table 1) form the basis of currently recommended antituberculosis therapy. Extensive studies of these drugs have shown that they have favorable therapeutic ratios.[30,31] An additional drug, rifabutin, can be substituted effectively for rifampin in order to minimize interactions with protease inhibitors and nonnucleoside reverse-transcriptase inhibitors used to treat HIV infection.[32] The second-line medications (Table 1) either have been shown to be less effective and more toxic than the first-line agents or have not been studied as extensively. Because these medications have not been proved to be equivalent to the first-line agents, they should be used only in patients who cannot tolerate the first-line drugs or who are infected with organisms that are resistant to them.

Current Recommendations

According to the current recommendations, whenever possible, isoniazid should be used (in conjunction with other drugs) for the duration of therapy because of its efficacy, low cost, and tolerability.[33] If rifampin is not used, 18 months is the minimal duration of therapy associated with acceptable rates of cure. In the absence of drug resistance, a regimen of isoniazid and rifampin administered for nine months is curative. The addition of pyrazinamide for the first two months of treatment allows the regimen to be shortened to six months and is associated with improved compliance and cure rates. No regimen administered for less than six months has acceptable cure rates for cases of culture-confirmed tuberculosis.[33]

Of equal importance for successful therapy is the administration of medications according to a schedule conducive to adherence. An important advance in this respect has been the use of six-month regimens, with an initial period of daily drug administration, followed by administration two or three times a week under direct observation. The currently recommended regimens include initial treatment with three or four antituberculosis agents, followed by a four-month continuation phase in which two drugs are administered. In selecting a regimen for an individual patient, the clinician should consider the local rates of drug resistance and the schedule of administration that is most likely to ensure adherence.

The most commonly used regimen consists of isoniazid, rifampin, and pyrazinamide administered daily for 8 weeks, followed by isoniazid and rifampin given daily, twice a week, or three times a week for 16 weeks. Unless the rate of resistance to isoniazid is documented to be less than 4 percent in the community, ethambutol or streptomycin should also be used until the organism is known to be fully susceptible to all drugs used. An alternative approach is to use the same initial drugs but to administer them daily for 2 weeks, then twice a week for 6 weeks, followed by the administration of isoniazid and rifampin daily, twice a week, or three times a week for 16 weeks. Alternatively, isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin can be administered three times a week for the entire six-month period. Finally, for patients with cultures that remain negative for *M. tuberculosis,* therapy can be discontinued after only two months of the continuation phase of treatment with isoniazid and rifampin.[33]

In the late 1980s, it became clear that a substantial number of patients were not completing treatment[34] and that noncompliance was unrelated to the level of education, race or ethnic group, income, or other demographic or social factors. To address this problem, the American Thoracic Society and the CDC recommended that direct observation of therapy (often referred to as DOT) by a trained health care worker be considered for all patients as part of a comprehensive patient-centered program with features that encourage patients to complete therapy (e.g., incentives such as meals, food coupons, or cash, as well as expanded clinic hours, child care, and transportation

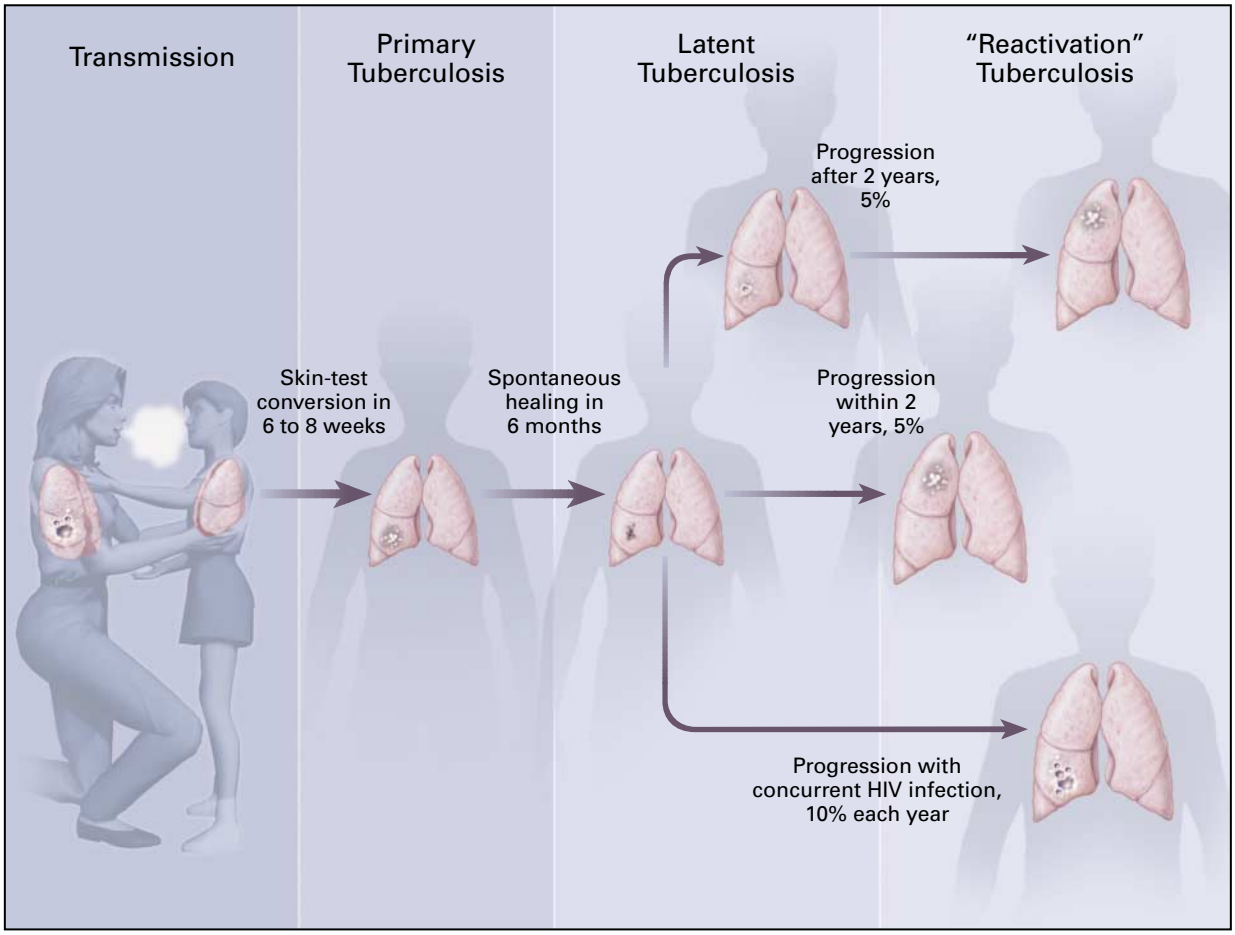

Figure 3. Transmission of Tuberculosis and Progression from Latent Infection to Reactivated Disease.

Among persons who are seronegative for the human immunodeficiency virus (HIV), approximately 30 percent of heavily exposed persons will become infected. In 5 percent of persons with latent infection, active disease will develop within two years, and in an additional 5 percent, progression to active disease will occur later. The rate of progression to active disease is dramatically increased among persons who are coinfected with HIV.

vouchers), as well as staff members who can communicate in the patient's native language and who are sensitive to cultural issues and a mechanism to ensure immediate follow-up of patients who do not adhere to the treatment regimen.[35,36] The value of directly observed therapy is supported by a comprehensive review of 27 studies of adherence to treatment regimens for pulmonary tuberculosis, which showed that the rate of adherence increased with the intensity of the program of directly observed therapy.[37] A regimen that includes the use of rifapentine, a long-acting rifamycin, once a week in the continuation phase of treatment is being studied in a further effort to increase adherence.[38,39]

Because treatment differs for persons infected with drug-resistant strains, every effort should be made to obtain adequate specimens for culture and susceptibility testing before treatment is initiated. In adults, base-line measurements of hepatic enzymes, bilirubin, and creatinine and a complete blood count with a platelet count should be performed. If pyrazinamide is used, uric acid levels should be measured, and if ethambutol is given, visual acuity and red–green color perception should be tested. In general, only visual acuity and color-perception tests are necessary in children. During treatment, all patients should be asked about symptoms, and monitored for adverse effects on a monthly basis.

A chest radiograph should be obtained at the beginning of treatment to help establish the diagnosis. For culture-negative cases of tuberculosis, the response to therapy is monitored by reviewing symptoms and obtaining a chest radiograph at three months. A chest radiograph should also be obtained at the end of treatment as a base line for future reference.

The rapidity of the resolution of symptoms, al-

though helpful in assessing an individual patient's response to therapy, can be highly variable.[40] Thus, in persons with positive sputum cultures, the conversion to negative cultures provides the only objective measure of successful treatment, and cultures should be obtained monthly until conversion is documented. More than 85 percent of patients who receive both isoniazid and rifampin have negative sputum cultures within two months after the initiation of treatment. If cultures remain positive for more than three months, nonadherence, malabsorption of drugs, drug resistance, or some combination of these factors should be suspected. Adherence to the treatment regimen can be assessed by pill counts, as well as by evaluation of urine for discoloration in patients taking rifampin and testing for elevated uric acid levels in those taking pyrazinamide. Although blood levels of antituberculosis medications are usually not monitored, such monitoring may be prudent if therapy is ineffective. A sputum sample should be cultured at the completion of treatment to document a cure.

TREATMENT IN SPECIAL SITUATIONS

HIV-Infected Patients

HIV-infected persons who adhere to standard regimens of treatment for tuberculosis do not have an increased risk of treatment failure or relapse. Thus, in general, the duration of treatment with antituberculosis drugs in such persons is six months. Treatment should be prolonged, however, if the bacteriologic or clinical response is slow or suboptimal.[32,41]

The use of protease inhibitors and nonnucleoside reverse-transcriptase inhibitors for the treatment of HIV infection has complicated the treatment of tuberculosis in HIV-infected persons. The administration of these drugs with rifampin can result in subtherapeutic blood levels of antiretroviral agents and toxic levels of rifampin. Rifabutin has fewer interactions with protease inhibitors and nonnucleoside reverse-transcriptase inhibitors. The protease inhibitors indinavir and nelfinavir, the nonnucleoside reverse-transcriptase inhibitor nevirapine, and all the other currently available nonnucleoside reverse-transcriptase inhibitors can be used with rifabutin; the protease inhibitors saquinavir and amprenavir and the nonnucleoside reverse-transcriptase inhibitor efavirenz can probably be used with rifabutin. However, the protease inhibitor ritonavir and the nonnucleoside reverse-transcriptase inhibitor delavirdine should not be used with rifabutin.[32]

Extrapulmonary Tuberculosis

Given the excellent tissue penetration of antituberculosis agents and the relative paucity of organisms at extrapulmonary sites of infection, as compared with the numbers of organisms in the lung, the treatment of extrapulmonary disease should be no more difficult than that of pulmonary disease. Thus, the six-month regimens outlined above should suffice. However, there have been few controlled trials of treatment in patients with extrapulmonary disease, and the use of 12-month regimens is still recommended for meningitis in infants and children, and for miliary tuberculosis and bone or joint involvement in patients of all ages, with the extra months added to the continuation phase of treatment.[33]

Drug-Resistant Tuberculosis

Drug-resistant tuberculosis can sometimes be anticipated on epidemiologic grounds but is more commonly recognized on the basis of the results of cultures and susceptibility tests. Isolated isoniazid-resistant tuberculosis should be treated with rifampin, pyrazinamide, and ethambutol for six months.[33] For cases of tuberculosis in which the strains are resistant solely to rifampin, an alternative regimen is the administration of isoniazid and ethambutol for 18 months or isoniazid, pyrazinamide, and streptomycin for 9 months.[42] Multidrug-resistant tuberculosis (defined as resistance to at least isoniazid and rifampin) is curable even in low-income countries, but the necessary therapy is complex and should be administered in collaboration with a clinician who has expertise in treating such cases.[43-45]

MANAGEMENT OF LATENT TUBERCULOSIS INFECTION

As the number of reported cases of tuberculosis in the United States continues to decline and the disease retreats into specific populations, general internists may not diagnose or treat a case of active tuberculosis for decades. However, most health care providers will frequently see patients who should be screened or treated for latent tuberculosis infection. In a recently released statement, the American Thoracic Society and the CDC recommended that the more precise phrase "treatment of latent tuberculosis infection" replace the ambiguous terms "preventive therapy" and "chemoprophylaxis."[46] Treatment of latent tuberculosis infection is both a basic component of preventive health care for individual patients and an increasingly important public health intervention. An emphasis on the diagnosis and treatment of latent tuberculosis infection represents a substantial shift in the approach to tuberculosis control.[47]

Candidates for Tuberculin Skin Testing

Testing for tuberculosis infection should be performed only in persons who are at high risk for infection and who would benefit from treatment. Because of the limited specificity of screening procedures, their widespread application to low-risk populations is likely to generate false positive results in most cases. A decision to test a patient should reflect a commitment to treat the patient if the test is positive. Groups that are at high risk for tuberculosis infection and should be

TABLE 1. DRUGS USED FOR THE TREATMENT OF TUBERCULOSIS.*

DRUG	DOSE			ADVERSE EFFECTS†	RECOMMENDED REGULAR MONITORING	COMMENTS
	DAILY	TWICE WEEKLY	THRICE WEEKLY			
First-line medications						
Isoniazid, oral or intramuscular‡	Children, 10 mg/kg Adults, 300 mg (maximum, 300 mg)	Children, 20–70 mg/kg Adults, 15 mg/kg (maximum, 900 mg)	Adults, 15 mg/kg (maximum, 900 mg)	Elevated hepatic enzymes, peripheral neuropathy, hepatitis, CNS effects, increased phenytoin levels, interaction with disulfiram	Measure hepatic enzymes (if baseline values are abnormal)	Overdose may be fatal; aluminum-containing antacids reduce absorption; pyridoxine hydrochloride (vitamin B_6) may decrease peripheral neuritis and CNS effects
Rifampin, oral or intravenous‡	Children 10–20 mg/kg Adults, 600 mg (maximum, 600 mg)	Children, 10–20 mg/kg Adults, 600 mg (maximum, 600 mg)	Adults, 600 mg	Hepatitis, fever, thrombocytopenia, and flulike syndrome; reduces blood levels of many drugs, including methadone, warfarin, birth-control pills, theophylline, dapsone, ketoconazole, protease inhibitors, and nonnucleoside reverse-transcriptase inhibitors	Measure hepatic enzymes (if baseline values are abnormal)	Causes orange discoloration of secretions, urine, tears, and contact lenses; single doses should be taken on an empty stomach (2 hours before or after meals); patients receiving methadone need an increased dose of methadone (average increase, 50%) to prevent opiate withdrawal; interaction with many drugs leads to decreased levels of rifampin, the other drug, or both; may make glucose control more difficult in patients with diabetes
Pyrazinamide, oral‡	Children, 20–30 mg/kg Adults, 1.5 g (<50 kg), 2.0 g (51–74 kg), 2.5 g (≥75 kg)	Children, 40–50 mg/kg Adults, 2.5 g (<50 kg), 3.0 g (51–74 kg), 3.5 g (≥75 kg)	Adults, 2.0 g (<50 kg), 2.5 g (51–74 kg), 3.0 g (≥75 kg)	GI disturbance, hepatic effects, hyperuricemia, arthralgias, rash	Measure hepatic enzymes (if baseline values are abnormal)	May complicate management of diabetes; hyperuricemia can be used as indicator of compliance; treat increased uric acid only if symptomatic
Ethambutol, oral‡	Children and adults, 15–25 mg/kg (maximum, 2.5 g)	Children, 30–50 mg/kg Adults, 50 mg/kg	Adults, 30 mg/kg	Decreased red–green discrimination, decreased visual acuity, rash	Check color vision and visual acuity monthly	Optic toxicity may be unilateral; check each eye separately; if possible, avoid use in children too young to undergo vision testing
Streptomycin, intramuscular or intravenous§	Children, 20–30 mg/kg Adults, 15 mg/kg	—	—	Auditory, vestibular, and renal effects; hypokalemia; hypomagnesemia	Audiometry, renal function, and electrolytes	Ultrasound and warm compresses at injection site may reduce pain and induration
Second-line medications						
Capreomycin, intramuscular or intravenous§	Children, 15–30 mg/kg Adults, 15 mg/kg	—	—	Auditory, vestibular, and renal effects; eosinophilia; hypokalemia; hypomagnesemia	Audiometry, renal function, and electrolytes	Ultrasound and warm compresses at injection site may reduce pain and induration
Ciprofloxacin, oral or intravenous¶‖	Adults, 750–1500 mg	—	—	Abdominal cramps, GI disturbance, tremulousness, insomnia, headache, photosensitivity, interactions with warfarin and theophylline	—	Variable absorption; check serum levels if possible; antacids and sucralfate reduce absorption; effects of caffeine may be increased
Clofazimine, oral¶	Children, 50–200 mg Adults, 100–300 mg	—	—	GI symptoms that can mimic appendicitis, visual disturbances in rare cases	—	Efficacy unproved; causes orange–brown discoloration of skin
Cycloserine, oral	Children, 15–20 mg/kg Adults, 500–1000 mg (divided doses)	—	—	Psychosis, seizures, headache, depression, and other CNS effects, rash; increased phenytoin levels	Assessment of mental status	Increase dose gradually, checking serum levels; 50 mg of pyridoxine hydrochloride (vitamin B_6), given with each 250 mg, may decrease CNS effects; monitor blood levels weekly until stable, if possible

Ethionamide	Children, 15–20 mg/kg Adults, 500–1000 mg (divided doses)	—	—	GI disturbance, bloating, hepatotoxic effects, hypothyroidism (especially in combination with aminosalicylic acid), metallic taste	Hepatic enzymes (if base-line values are abnormal) and thyroid function	Antacids or antiemetics and lying flat for 20 minutes after doses may increase tolerance; start with 250 mg daily and increase as tolerated
Kanamycin§ and amikacin,¶ intramuscular or intravenous	Children, 15–30 mg/kg Adults, 15 mg/kg	—	—	Auditory and renal toxic effects, vestibular effects in rare cases, hypokalemia, hypomagnesemia	Audiometry, renal function, and electrolytes	Ultrasound and warm compresses at injection site may reduce pain and induration
Levofloxacin, oral or intravenous¶‖	Adults, 500–1000 mg	—	—	Similar to effects of ciprofloxacin but fewer	—	Variable absorption; check serum levels if possible; antacids and sucralfate reduce absorption; effects of caffeine may be increased
Ofloxacin, oral or intravenous¶‖	Adults, 600–800 mg	—	—	Probably similar to effects of ciprofloxacin, possibly with fewer drug interactions	—	Variable absorption; check serum levels if possible; antacids and sucralfate reduce absorption; effects of caffeine may be increased
Aminosalicylic acid, oral	Children, 150 mg/kg Adults, 4 g every 12 hr	—	—	GI disturbance, hypersensitivity, hepatotoxic effects, hypothyroidism, decreases digoxin levels, increases phenytoin levels; levels decreased by diphenhydramine	Thyroid function	Increase dose gradually as tolerated; may cause hemolytic anemia in patients with G6PD deficiency
Rifabutin, oral¶	Children, 10–20 mg/kg Adults, 5 mg/kg (maximum, 300 mg)	Children, 10–20 mg/kg Adults, 5 mg/kg (maximum, 300 mg)	ND	Rash, hepatitis, fever, neutropenia, and thrombocytopenia; reduces levels of many drugs, including protease inhibitors, nonnucleoside reverse-transcriptase inhibitors, dapsone, ketoconazole, and birth-control pills; uveitis with high doses	Complete blood count with platelet count monthly and hepatic enzymes (if base-line values are abnormal)	Causes orange discoloration of body fluids; adjust daily dose and monitor for decreased antiretroviral activity and for toxic effects if rifabutin is taken concurrently with protease inhibitors or nonnucleoside reverse-transcriptase inhibitors
Rifapentine	ND	Adults, 600 mg once or twice a week	—	Nausea, vomiting, dizziness, rash, elevated values on liver-function tests, hyperuricemia	Liver-function tests, bilirubin, complete blood count with platelet count	Cross-resistance with rifampin; half-life approximately 4 times longer than that of rifampin; causes orange–red discoloration of body fluids; induces cytochrome P-450 system: rifampin > rifapentine > rifabutin

*Ideally, every patient with active tuberculosis should receive every dose of antituberculosis medication in a program of directly observed therapy. Intermittent therapy, which should always be directly observed, can be used only in some clinical situations. Intermittent doses of oral second-line medications are not recommended. Drug information is from the Bureau of Tuberculosis Control,[24] Temple and Nahata,[25] the American Society of Health-System Pharmacists,[26] Peloquin et al.,[27] Pharmacia & Upjohn,[28] and *Drug Facts and Comparisons*.[29] CNS denotes central nervous system, GI gastrointestinal, G6PD glucose-6-phosphate dehydrogenase, and ND not determined.

†Not all toxic effects are listed. Check package insert or pharmacology reference for further information.

‡A combination tablet containing 150 mg of isoniazid and 300 mg of rifampin and a combination containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide are available and should be used whenever patients are not in a program of directly observed therapy.

§In persons over the age of 60 years, the daily dose should be limited to 10 mg per kilogram; for patients with drug-resistant isolates, injectable medications are generally given five days per week for several months, then two or three times per week, preferably after sputum cultures have become negative.

¶The drug has not been approved by the Food and Drug Administration for the treatment of tuberculosis.

‖The drug should not be used for treatment of children.

targeted for tuberculin testing include HIV-infected persons, immigrants from countries with high rates of tuberculosis, homeless persons, health care professionals, and persons living or working in long-term care facilities.

Persons who are at high risk for the progression from latent infection to active disease and who should therefore be specifically targeted for testing include those with immunosuppressive conditions and those who have recently been exposed to infectious tuberculosis. Persons coinfected with HIV and *M. tuberculosis* have the highest rates of progression to active disease, with an annual rate of progression ranging from 3.5 to 16.2 percent. Other conditions that confer a predisposition to the progression from latent infection to active disease include diabetes mellitus (relative risk as compared with that in the general population, 2 to 4), chronic renal failure (relative risk, 10 to 25), head or neck cancer (relative risk, 16), and organ transplantation (relative risk, 20 to 74). Injection-drug use is a strong risk factor, even in the absence of HIV infection. Silicosis, the presence of radiographic manifestations suggestive of untreated tuberculosis, and a body weight that is 5 to 15 percent less than the ideal weight are also indications for testing.[46] In addition, close contacts of patients with infectious tuberculosis and persons who have immigrated to the United States within the previous five years from areas with a high incidence of tuberculosis should be tested.[48,49]

Interpreting Tuberculin Skin Test Results

Although it is imperfect, the gold standard for diagnosing latent tuberculosis infection remains the intradermal injection of purified protein derivative (5 TU) into the volar or dorsal surface of the forearm (Mantoux method). Multipronged devices should not be used, because it is difficult to quantify accurately the amount of antigen being applied. The diameter of induration (not erythema) should be measured in millimeters 48 to 72 hours after injection, although positive reactions usually persist for at least seven days.[19,50]

Because the tuberculin skin test is imperfect, three different diameters of induration have been defined as indicative of latent tuberculosis infection in order to increase the predictive value of the test.[51] The lowest cutoff value (5 mm) is used for persons who may not have a strong immunologic response, including persons who are infected with HIV or are being treated with immunosuppressive drugs such as corticosteroids. A cutoff value of 5 mm is also used for those with recent exposure to persons with infectious tuberculosis, who may not yet have mounted a full immunologic response. The same cutoff value is used for persons with a high pretest probability of infection, as evidenced by abnormalities on a chest radiograph. A cutoff value of 15 mm is used for persons at low risk for tuberculosis. For all other persons, the cutoff value is 10 mm. A person with a negative initial tuberculin test and a subsequent test performed within two years that shows an increase of at least 10 mm in the diameter of induration is considered to have had a conversion to a positive skin test, indicating recent infection and a high risk of progression to active disease.

In contrast, persons infected with *M. tuberculosis* in the distant past may lose the ability to react to tuberculin and initially have a false negative tuberculin skin test. Immunologic stimulation from the initial skin test may reinvigorate the immune response so that a subsequent test will induce a stronger reaction (the booster phenomenon). This result actually reflects long-standing infection, but clinically, it mimics a tuberculin conversion. To prevent confusion in interpreting this result, persons who need to undergo serial testing and who have negative results initially should be retested in approximately two weeks (two-step testing). An increase in the diameter of induration during this period is interpreted as indicative of long-standing infection. Even with frequent tuberculin skin testing, it is not possible to induce induration in an uninfected person with serial testing.[51,52]

Although bacille Calmette–Guérin (BCG) vaccine has never been recommended for the control of tuberculosis in the United States, it is the most widely used vaccine in the world and causes confusion in diagnosing latent tuberculosis infection. The size and persistence of the tuberculin reaction after BCG vaccination vary according to the dose, the manufacturer, and the method and timing of administration.[52] Thus, it is impossible to distinguish with certainty induration induced by BCG vaccination from that caused by *M. tuberculosis* infection. However, because BCG vaccine is frequently used in areas with high rates of transmission of tuberculosis and because it does not provide protection against most forms of the disease, the CDC recommends that a history of BCG vaccination be ignored when administering and interpreting a tuberculin skin test.[46,52,53]

Because persons dually infected with HIV and *M. tuberculosis* are at extremely high risk for progression from latent infection to active disease, treatment of their latent infection is critical. The defect in cell-mediated immunity can cause HIV-infected persons to have false negative tuberculin skin tests. However, skin testing with nontuberculous antigens (anergy testing) has not been standardized, the results have not been shown to be reproducible,[54] and tuberculosis has not been prevented when isoniazid has been given to anergic HIV-infected persons.[55,56] Thus, anergy testing is no longer recommended for the evaluation of tuberculosis infection in HIV-infected persons.

Choosing a Treatment Regimen

The American Thoracic Society and the CDC have recently published revised recommendations that include new therapeutic regimens for treating latent tuberculosis infection. The key points are summarized

here, and the treatment options are outlined in Table 2. Readers are encouraged to consult the final document for a more detailed discussion of the data underlying this intervention.[46]

Before therapy for latent tuberculosis is initiated, a history should be taken to document any previous treatment for active disease or latent infection, other medical conditions (such as HIV infection), and current medications that may interact with antituberculosis drugs. In addition, a chest radiograph should always be obtained to ensure that active pulmonary tuberculosis is not present.[46,57]

Since the 1950s, isoniazid has been the mainstay of therapy for latent tuberculosis infection,[48] though there have been recent changes in the recommended duration of therapy. The one study designed to test the efficacy of various durations of treatment showed that among persons with fibrotic lung lesions that were consistent with the presence of inactive disease, the incidence of tuberculosis over 5 years was lower among those who received isoniazid for 12 months (0.36 percent) than among those who received the drug for 6 months (0.50 percent) or 3 months (1.13 percent).[58] Among patients who took more than 80 percent of the prescribed doses, the 6-month regimen decreased the incidence of active tuberculosis by 69 percent and the 12-month regimen reduced the incidence by 93 percent, as compared with the 3-month regimen.

In 1986, however, on the basis of the fact that the cost of the 6-month regimen was half that of the 12-month regimen[59] and because of the difficulty of ensuring prolonged compliance, the 6-month regimen was recommended, and it subsequently became the standard treatment in HIV-seronegative persons with no abnormalities on chest radiographs. A recent reanalysis of data from an outbreak of tuberculosis in the 1960s showed that treatment with isoniazid for 9 or 10 months provided optimal protection against the development of active tuberculosis and that treatment for more than 12 months did not provide additional protection.[60]

Nine months of treatment with isoniazid is the new standard for both HIV-seronegative and HIV-seropositive persons and for those with fibrotic lung lesions (findings consistent with previous untreated tuberculosis), and it is the only acceptable regimen for persons under 18 years of age.[46,61] Six months of isoniazid is an acceptable, but inferior, alternative regimen for HIV-seronegative persons.

Combinations of drugs have been studied in an effort to shorten the duration of treatment for latent infection. A regimen of rifampin and pyrazinamide administered for two months has been studied most extensively.[56,62-64] Although the results have varied, one study showed that the protective effect of this regimen was similar to that of a 6-month regimen of isoniazid alone, and another study showed therapeutic equivalence to a 12-month regimen of isoniazid in HIV-infected persons.[55,62] However, case reports and rates of adverse drug reactions in some of these studies suggest that the combination of drugs may not be as well tolerated as isoniazid alone.[65] According to the current guidelines, two months of daily treatment with rifampin and pyrazinamide is an effective alternative regimen.[46] Although the trials included only HIV-seropositive persons, the efficacy of this regimen is assumed to be similar in HIV-seronegative persons.

TABLE 2. RECOMMENDED REGIMENS FOR THE TREATMENT OF ADULTS WITH LATENT TUBERCULOSIS INFECTION.*

DRUG	DURATION OF TREATMENT	DOSE		COMMENTS
		DAILY	TWICE WEEKLY	
	mo			
Isoniazid	9	5 mg/kg (maximum, 300 mg)	15 mg/kg (maximum, 900 mg)	Preferred regimen for all adults
Isoniazid	6	5 mg/kg (maximum, 300 mg)	15 mg/kg (maximum, 900 mg)	Acceptable for HIV-negative adults and may be more cost effective than a 9-month regimen of isoniazid; not recommended for HIV-positive persons, those <18 years of age, or those with fibrotic lesions on chest films
Rifampin and pyrazinamide	2	10 mg/kg (maximum, 600 mg) and 15–20 mg/kg (maximum, 2 g)	10 mg/kg (maximum, 600 mg) and 2.5 g (<50 kg), 3.0 g (51–74 kg), 3.5 g (≥75 kg)	Also appropriate for contacts of patients with isoniazid-resistant tuberculosis; rifampin should generally not be coadministered with protease inhibitors or nonnucleoside reverse-transcriptase inhibitors in HIV-positive persons; in some cases rifabutin may be substituted; in general, pyrazinamide should not be used to treat pregnant women
Rifampin	4	10 mg/kg (maximum, 600 mg)	—	For persons who cannot tolerate pyrazinamide

*HIV denotes human immunodeficiency virus.

There is a paucity of data on rifampin monotherapy for latent infection. A small, randomized trial of rifampin given for three months to HIV-seronegative persons with silicosis showed that the efficacy of this regimen was similar to that of a six-month regimen of isoniazid.[66] Largely on the basis of this finding, a four-month regimen of rifampin has been deemed an acceptable alternative for persons who cannot tolerate isoniazid or pyrazinamide. The duration of treatment has been extended one month beyond that of the study because of the relatively high rate of active tuberculosis in that study (4 percent).[66] There are no data that support the use of fluoroquinolones, either singly or in combinations, for treating latent infection. There are also no data demonstrating the efficacy of alternative regimens for persons thought to be infected with *M. tuberculosis* strains that are resistant to both isoniazid and rifampin. On the basis of expert opinion, however, a regimen of pyrazinamide and ethambutol or a fluoroquinolone and ethambutol has been suggested for such persons with a high risk of progression to active disease.[67]

A periodic review of symptoms and physical examination are imperative for all patients taking medications. Regardless of age, laboratory tests at base line and during treatment are indicated only for persons with HIV infection, women who are pregnant or who have given birth within the past three months, persons with heavy alcohol use, and patients with chronic liver disease.[46] If a regimen of six months or longer is interrupted, the patient should be given isoniazid for an additional three months. Two-month regimens should be completed within three months. If the lapse in treatment is longer than three months, the regimen should be restarted. In a previously treated person who is reexposed to a person with infectious tuberculosis, repeated treatment is generally not recommended, but repeated treatment is prudent in contacts coinfected with HIV.

NEW RESEARCH

There have been great gains in our understanding of the basic biology of tuberculosis, although they are not likely to contribute to the control of the disease in the immediate future.[68] The combination of a fully sequenced genome, efficient methods for genetic manipulation, and a variety of in vitro and in vivo models is providing insight into such fundamental issues as virulence and latency.[69-71] Post-genomic approaches are detailing the precise mechanism of action of current drugs and may suggest bacterial targets for new drugs.[72] Genome-wide linkage analysis may identify regions of the human genome that contain genes that confer susceptibility to tuberculosis.[73] The steps for developing an improved tuberculosis vaccine have been outlined,[74] and as of June 2001, more than 190 candidate vaccines have been screened in animal models (Ginsberg A: personal communication). The nature of the protective immunologic response has been partially elucidated, and there is hope that with this knowledge, correlates of protection will be identified that will facilitate trials of new vaccines.[75]

There has also been progress in many aspects of applied research. Molecular studies have clarified the current epidemiology of tuberculosis and have shown that targeted control measures are associated with decreased rates of tuberculosis.[76] Bacterial genotyping performed in an area with a high prevalence of tuberculosis has shown that exogenous reinfection is a cause of recurrent tuberculosis after curative therapy.[17] Alternatives to tuberculin skin testing have had promising preliminary results in clinical trials.[77] Comparative genomic and proteomic analyses of *M. tuberculosis* and BCG have identified genes that may ultimately make it possible to distinguish between latent infection and immunity induced by BCG.[78-80]

Insight into the molecular mechanisms of drug resistance has already led to the development of rapid, nucleic acid–based methods of susceptibility testing.[81] A new, longer-acting rifamycin, rifapentine, has been evaluated in clinical trials and approved by the Food and Drug Administration for the treatment of tuberculosis.[82] Preliminary clinical trials of adjunctive therapy with immunomodulators, such as cytokines, have had promising results.[83] Additional, rigorous trials will be required, however, before these advances can be incorporated into clinical practice.[84]

CONCLUSIONS

Despite the resurgence of tuberculosis in the late 1980s and early 1990s, we have been given a second, perhaps final, chance to eliminate the disease in the United States. The levels of public awareness and political support for this goal are high, but with recent declines in rates of tuberculosis, there is a renewed risk of complacency. The recent report on tuberculosis by the Institute of Medicine is a wake-up call to maintain our national commitment to this goal.[2] Currently available interventions will continue to reduce tuberculosis if they are correctly implemented, but elimination of the disease will require both an investment in research and use of the fruits of that research to develop effective new diagnostic tests, medications, and vaccines.

Most important, the lessons from the recent increase in cases of tuberculosis must be heeded if the goal of eliminating the disease is to be accomplished. In the coming decades, the public health infrastructure must be maintained to ensure continued progress toward that goal. Local health departments must continue to provide all the components of a comprehensive tuberculosis-control program, including education and training of health care providers, case finding, surveillance, and laboratory monitoring, as well as direct observation of treatment and the use of incentives and other measures to improve adherence.[85] The role of cli-

nicians in this endeavor will be to remain vigilant for cases of active disease, relying on updated laboratory methods to establish a prompt diagnosis and to identify drug-resistant strains and following updated guidelines for treatment. In addition, clinicians need to intensify their efforts to identify and treat latent tuberculosis infection. Failure to do so is likely to result in another resurgence of disease and loss of hard-won progress toward the elimination of tuberculosis in the United States.

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