Tuberculosis in the 19 Resources

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ABSTRACT: Physicians in the United States must maintain vigilance for the 25 000 annual new cases of tuberculosis, concentrated in the elderly, in immigrants, in migrant and minority populations, and in immunosuppressed patients. Tuberculosis rates in the South remain above the national average. Physicians diagnosing tuberculosis may also treat the disease, working with health departments, which can assist with drugs, follow-up tests, and contact investigation. Powerful short-course regimens have been standard treatments since 1986. The preferred combination is isoniazid, rifampin, and pyrazinamide daily for 2 months, followed by isoniazid and rifampin for 4 more months. A 9-month regimen of isoniazid and rifampin is equally effective. Supplementation or extension of these regimens is mandatory when drug resistance or immunosuppression, respectively, is likely. Isoniazid prophylaxis for 6 to 12 months continues to be a vital but often neglected preventive measure for those infected with *Mycobacterium tuberculosis*, but without active disease.

AFTER THREE DECADES of linear decline, the rate of new cases of active tuberculosis became level from 1985 through 1988 and rose 4.7% in 1989. The 25 701 new cases reported in the United States for 1990 (10.3 per 100 000 population) represents an annual increase of 9.4%—the largest recorded increase since national tuberculosis reporting began in 1953.[1,2]

While the largest *numbers* of new cases come from populous states such as New York and California, virtually all states in the South have *rates* remaining about the national average (Fig 1). This region is home to large immigrant,[3,4] migrant,[5] and minority[6,7] populations; each of these groups has high tuberculosis case rates. Likewise the southern United States has large numbers of the elderly, the age group that has the highest case rate in *all* ethnic groups in the US.[2]

What are the implications of this resurgence of tuberculosis for clinicians? Before detailing the new standard regimens for tuberculosis treatment and prophylaxis, I will review the demographic and clinical risk factors and the criteria for diagnosis. In concluding, I will emphasize educational, clinical, and public health resources now available to physicians and others caring for tuberculosis patients and their families.

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DEMOGRAPHIC AND CLINICAL RISK FACTORS

Reviewing the pathogenesis of tuberculosis from a population perspective reveals that any group—indeed the world's population—can be divided into three epidemiologic subsets, based on their experience with *Mycobacterium tuberculosis* (Fig 2). Among the 250 million persons in the United States, approximately 10 million (group 2 in Figure 2) are infected with *M tuberculosis*. The vast majority of them, now elderly, were infected when the prevalence of active tuberculosis (group 3) was much higher. However, 20 000 to 30 000 persons of all ages are newly infected in the US each year by those with active pulmonary tuberculosis (groups 3a and 3c), thus moving from group 1 to group 2.

Any recently infected person is at high risk for clinical tuberculosis, since half of the 10% lifetime risk of progressing from infection to active disease occurs in the first 2 years after the initial infection.[8,9] For persons infected with both the human immunodeficiency virus (HIV) and *M tuberculosis*, it appears that the risk of clinical tuberculosis doubles to 20% or more.[10,11] The public health challenge posed by these 10 million infected is to identify and successfully treat with isoniazid prophylaxis those who, if not treated, are most likely to progress to active tuberculosis (group 3). While chemotherapy for patients in each of the three subgroups (3a,3b,3c) with clinical tuberculosis is virtually identical, their epidemiologic and public health implications differ.

About 90% of the 25 701 new cases in 1990

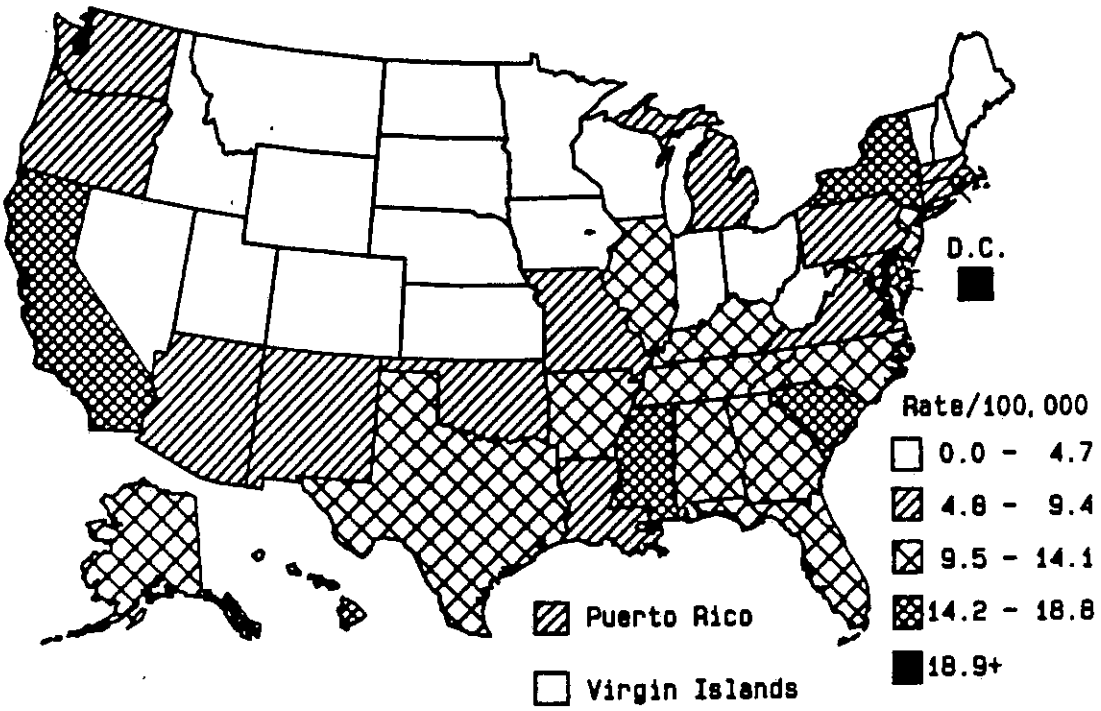

FIGURE 1. Rates of new tuberculosis cases in United States in 1989 by state. (Data from Snider.[1])

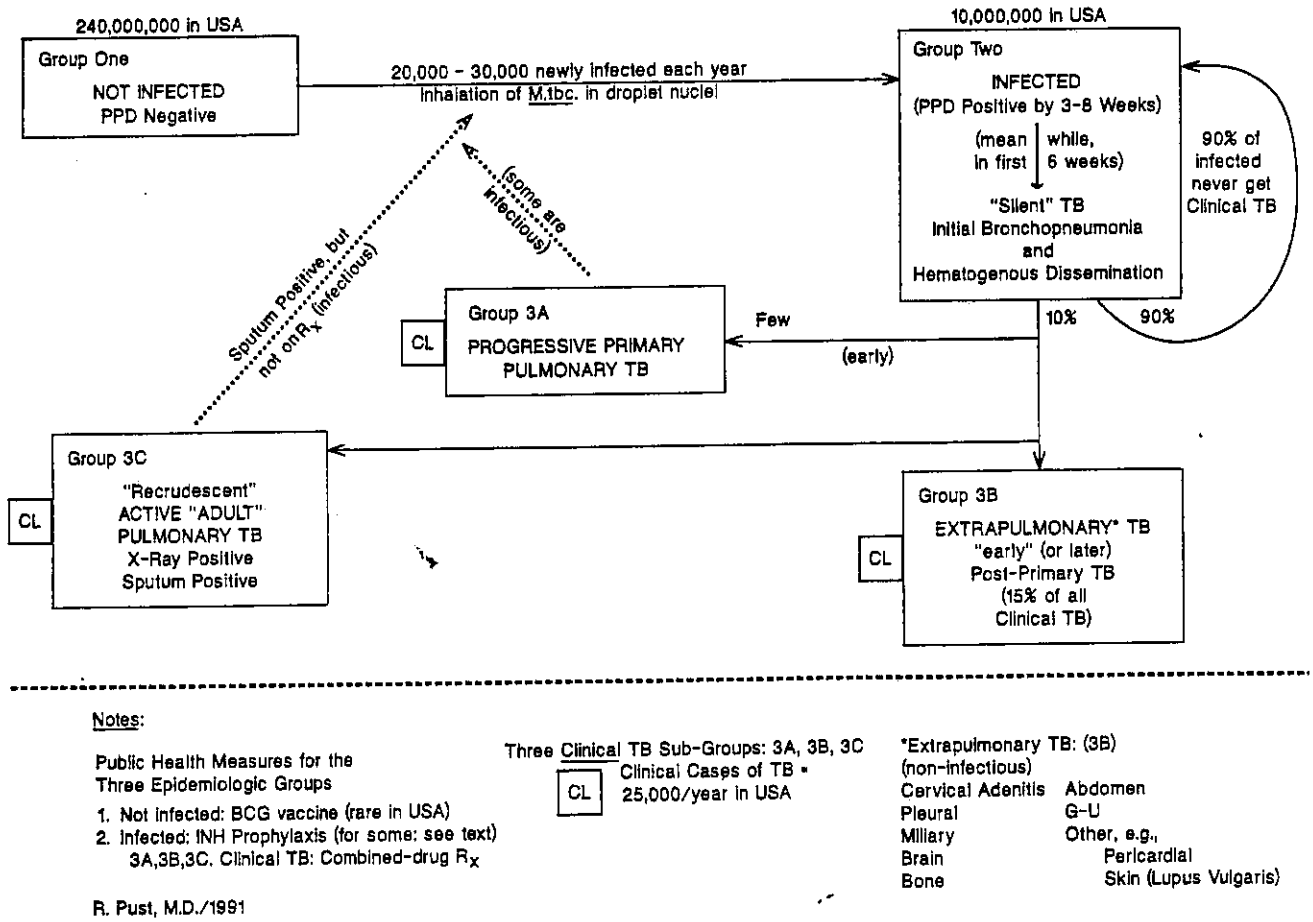

FIGURE 2. Epidemiology and pathogenesis of tuberculosis.

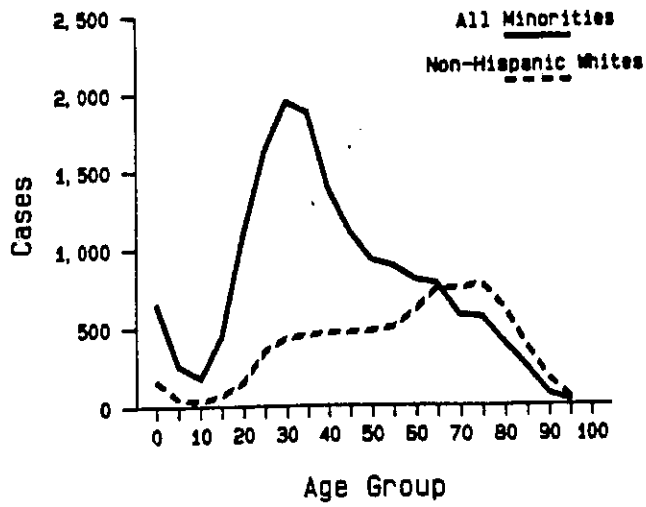

FIGURE 3. Numbers of new tuberculosis cases in United States in 1989, by age and race/ethnicity. (Data from Snider.[1])

arose from persons infected several to many years ago. These remotely infected persons make up nearly 99% of the 10 million harboring *M tuberculosis* (group 2). This is reflected in the high case *rates* in the elderly of all ethnic groups. However, when the *numbers* of new cases are separated by ethnic origin (Fig 3), two distinct age distributions emerge, with a far larger—and growing—number of cases among minorities arising in younger persons.[6] The Centers for Disease Control (CDC) estimates that 28 000 "excess" cases occurred from 1985 to 1990, virtually all due to tuberculosis in the HIV-positive population.[1] In Miami, for example, 99 (24%) of 422 consecutive new cases of tuberculosis occurred in patients who were HIV infected; in Seattle, there were 7 of 30 (23%).[11] With the increasing percentage of new tuberculosis cases that now come from the immunocompromised HIV-positive population the proportion of all active tuberculosis that is progressive primary (group 3a) is also increasing. Since radiologic and clinical recognition of these cases is more difficult,[12-17] the index of suspicion should obviously be high in patients who may be HIV positive, particularly in populations with high tuberculosis prevalence.

Extrapulmonary tuberculosis (group 3b), which now makes up about 15% of all clinical cases, poses no public health threat, because it is rarely if ever infectious. However, its protean manifestations (listed in approximate order of frequency in Figure 2) and unpredictable incubation period pose diagnostic challenges beyond the scope of this overview. The majority of patients with active tuberculosis—and the infectious source for most newly acquired infections—continues to be those with so-called adult pulmonary tuberculosis, who have positive sputum culture and often also have smears positive for acid-fast bacilli (AFB), especially if the disease is cavitary.

Tuberculosis risk, like that of any other public health problem, can be analyzed with reference to the classic epidemiologic triad of environment, host, and agent. The risk for *initial infection,* which is by airborne droplet nuclei, depends mainly upon the environment and thus differs by population. The identification of high-risk populations for tuberculosis control programs is thus given priority by the CDC.[8,9,18] *Once infected,* the risk of active disease largely depends on host factors, especially cell-mediated immunocompetence as manifested by delayed type hypersensitivity. The agent discussed in this article is *M tuberculosis,* since, except for *M leprae,* there is no solid evidence that nontuberculous mycobacteria are transmitted between humans.[19] However, *Mycobacterium avium-intracellulare* complex (MAC) is of increasing concern, since it is extremely common in AIDS—indeed is a "marker" for AIDS.[12,19]

DIAGNOSIS OF TUBERCULOSIS

Clinical Suspicion

The diagnosis of tuberculosis, though usually straightforward, may nonetheless be difficult in cases without classic findings. Since clinical signs are frequently absent, and symptoms, even when present, are often nonspecific, the key to the diagnosis of tuberculosis is a high index of suspicion in patients from high-risk groups. Recalling both demographic and individual risk factors already enumerated will assure that the clinician evaluates the likelihood of tuberculosis.

Patients who *are* symptomatic from active tuberculosis may present systemic, pulmonary, or extrapulmonary symptoms, or any combination of these.[20,21] Among the early symptoms, low-grade fever and weight loss persisting over weeks or months are the most objective and verifiable findings. While these are nonspecific, they clearly are serious and should alert the physician to the need for a thorough organic investigation. Malaise and anorexia are even less specific, but may accompany the more objective systemic findings. If the tuberculosis is pulmonary, and particularly if it is the "recrudescent/adult" type (group 3c) with fibrosis and caseation necrosis, cough will gradually develop and progress in nearly all cases. The onset of persistent cough is strongly associated with cavitation and infectiousness, as the tubercle bacilli liberated by caseation necrosis are effectively aerosolized by cough. Insidious cough is far more common than hemoptysis and chest pain at this stage, but is often overlooked by patients and

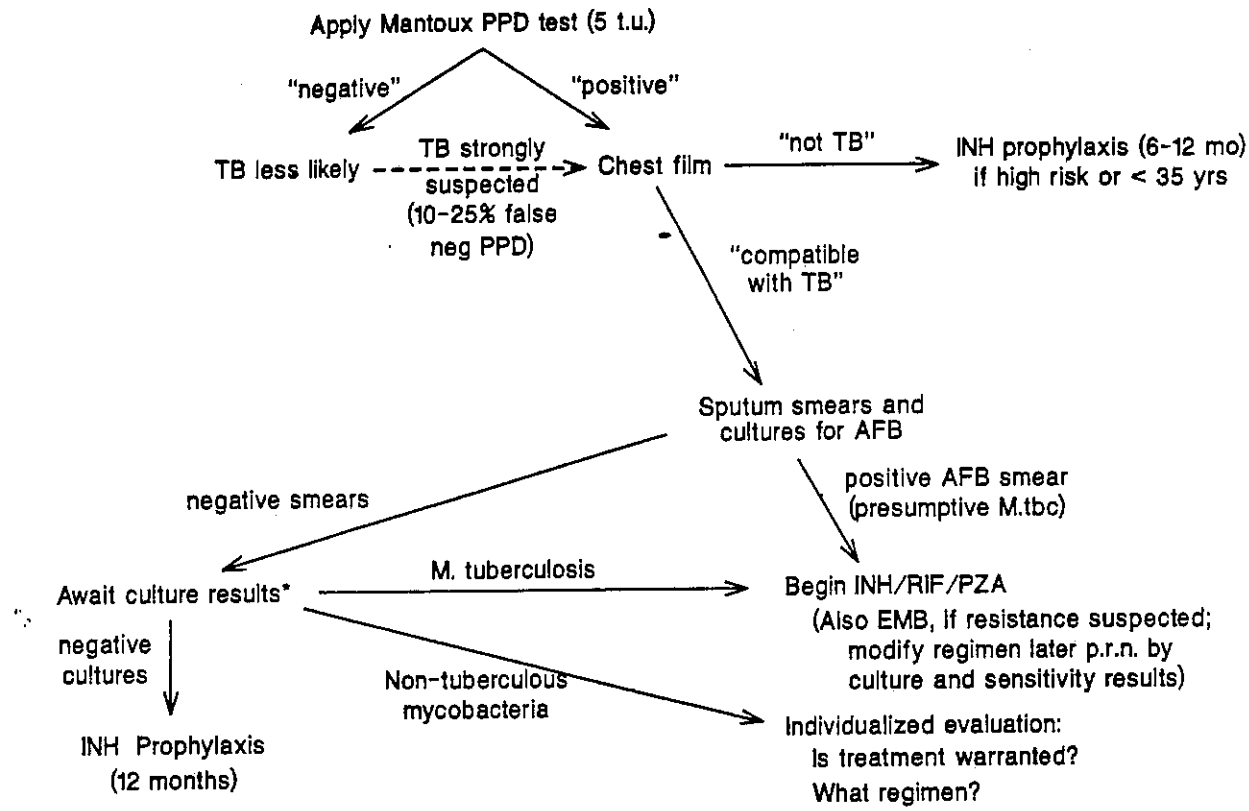

FIGURE 4. Algorithm for diagnosis, drug prophylaxis, and active-case treatment of tuberculosis.

their doctors, who are more likely to respond to more dramatic conditions. Sputum is usually produced in small but increasing amounts as the disease progresses, but it is also often ignored by smokers or other patients who habitually produce sputum.

Though active tuberculosis is clearly recognized as a sequel of HIV infection,[14,15,17] its diagnosis in persons with AIDS is often delayed.[16] The tuberculin test may be negative.[17] In AIDS, the presentation of tuberculosis often resembles primary tuberculosis, eg, endobronchial infection and hilar node enlargement, in which sputum smears are less likely to reveal acid-fast bacilli. Since the most ubiquitous and recurrent signs in AIDS, fever and weight loss, may in fact be due to newly active tuberculosis, chest films and the search for nonpulmonary tuberculosis must be regularly repeated.

When tuberculosis is confined to extrapulmonary sites, the obvious findings are usually referable to those sites,[21-23] but are often nonspecific for tuberculosis. When the patient is from a high-risk group, however, tuberculosis should be considered, particularly if there are systemic as well as localized signs. Since 15% of clinical cases are manifested in the extrapulmonary form, frequently without overt pulmonary manifestations, diagnosis again depends on a high index of suspicion based on risk factors. Finally, of course, any combination of systemic, pulmonary, and extrapulmonary signs and symptoms may coexist.

Confirmatory Tests

Once tuberculosis is suspected, the three classic tests for tuberculosis should enable the clinician to make a definitive diagnosis clinically and, with reference to Figure 2, epidemiologically. The algorithm in Figure 4 depicts the sequential diagnostic use of the Mantoux tuberculin test, the chest roentgenogram (when thoracic tuberculosis is suspected), and mycobacteriology of sputum or biopsy specimens. When the disease is not pulmonary, appropriate imaging and alternative bacteriologic specimens will replace the chest film and sputum study, respectively. Further details may be found in recent standard references.[20-24] At the time the diagnosis of tuberculosis is considered, all suspects should have an intermediate strength (5 tuberculin unit) Mantoux test (Connaught or Park-Davis) intradermally. The test can be read at any time between 48 and 96 hours. Because

10% to 25% of all patients with active tuberculosis will have a false-negative test result at the time of diagnosis, the clinician may elect to obtain a chest film at the first visit as well, if tuberculosis is even moderately likely. If the chest film is not compatible with active tuberculosis and if extrapulmonary tuberculosis is not present, the patient is likely to be a candidate for isoniazid (INH) prophylaxis, according to well-established criteria. Since the reaction to the standard Mantoux test in groups of patients with culture-proven *M tuberculosis* disease is distributed in a normal, bell-shaped curve with a mean of 16 to 18 mm and a standard deviation of 4 to 6 mm, any cutoff point for a "positive" test in a tuberculosis suspect is statistically arbitrary. In practice, however, cutoff points of 5, 10, and 15 mm of induration have been defined for various epidemiologic groups.[8] The lowest (5 mm) cutoff point is applied to those with the highest risk of progression from infection to active tuberculosis, thus minimizing the chances that a high-risk individual would not receive appropriate intervention.

If the chest film or other clinical investigation is compatible with active tuberculosis, bacteriologic specimens should be obtained.[20] Therapy for active disease can be begun if AFB are found in the specimen, although definitive culture diagnosis confirming *M tuberculosis* and its drug sensitivities may later alter treatment decisions or regimens. Again at this phase (Fig 4), if there is neither bacteriologic evidence nor strong clinical suspicion of *active* tuberculosis, the patient is likely a candidate for INH preventive therapy. Despite some prospect of newer technologies for the more accurate and rapid diagnosis of active tuberculosis,[20,25] these three classic diagnostic modalities remain the current standard.

TREATMENT REGIMENS

Once it is decided that treatment is needed, either prophylactically or for active tuberculosis, several principles from the basic sciences of mycobacteriology and pharmacology form the foundation for standard drug regimens. Once these principles are understood and the rationale for standard regimens is clear, the physician must assess each patient individually, applying the classic epidemiologic triad of environment, host, and agent factors. With regard to the mycobacterial agent, the relevant factors are the bacterial load, generation time, and subpopulations of bacilli.

The mycobacterial load, or total number of viable *M tuberculosis* bacilli in the host, determines the mathematical likelihood of spontaneous drug resistance through mutation, and thus the number of drugs that must be used to circumvent the development of resistance.[26] About one in 10^5 to 10^6 *M tuberculosis* organisms are mutants resistant to isoniazid. Resistance to other antituberculous drugs occurs at about the same frequency. Since these spontaneous events apparently are independent, the chance of a single organism being resistant to two of these drugs is the product of their independent probabilities, ie, about one in 10.[12] The number of organisms in a tuberculosis infection that is in its earliest preclinical stages or that has been well controlled by host defenses is considerably less than 10^6; thus one drug alone, eg, INH, is sufficient for *prophylactic* treatment. In ongoing active *disease,* however, populations grow well beyond 10^6, the wall of a single cavity commonly containing 10^8 to 10^9 organisms. Thus in clinically active tuberculosis, a minimum of two bactericidal drugs to which the infecting organisms are primarily sensitive must be used. This also means that when a drug regimen is failing because of presumed resistance, not one but two or more new drugs to which the organisms are assumed to be sensitive must be added to prevent resistance to each drug were it to be added singly.[26-28]

Finally, because the generation time of *M tuberculosis* is about 20 hours, rather than the 20 minutes common to other bacteria, therapy must be prolonged for a matter of months, rather than days. Likewise the growth of mycobacteria occurs at varying rates and sites in various subpopulations, of which at least three are identified.[26,29] Extracellular organisms in the active growth phase have the highest potential for resistant mutants. Two smaller populations—those inside macrophages at an acid pH and those at a neutral pH in caseating material—grow intermittently. These more indolent populations would persist were it not for the activity of the newer bactericidal agents. Rifampin is bactericidal against each of these three subpopulations, and isoniazid against the active growth population and those inside macrophages. Pyrazinamide is bactericidal against only the latter. Streptomycin and other antituberculous aminoglycosides are bactericidal against only the actively growing extracellular population.

Based on these principles, INH and rifampin (RIF) are the cornerstones of all current treatment regimens for active tuberculosis. One or two of the other first-line drugs—pyrazinamide (PZA), ethambutol (EMB), and streptomycin (SM)—may be added to further shorten the duration of treatment or to prevent the emergence of multiply-resistant organisms when it is possible that there may be resistance at the outset to one or more of

TABLE 1. Criteria for Determining Need for Preventive Therapy for Persons With Positive Tuberculin Reactions, by Category and Age Group (From Reference 8)

Category	Age Group (years)	
	<35	≥35
With risk factor*	Treat at all ages if reaction to 5 TU purified protein derivative (PPD) is ≥10 mm (or ≥5 mm and patient has had recent exposure, has HIV infection, or has radiographic evidence of old TB)	
No risk factor	Treat if PPD ≥10 mm	Do not treat
High-incidence group†		
No risk factor	Treat if PPD ≥15 mm**	Do not treat
Low-incidence group		

*Risk factors include HIV infection, recent contact with infectious person, recent skin-test conversion, abnormal chest radiograph, intravenous drug abuse, and certain medical risk factors.

†High-incidence groups include foreign-born persons, medically underserved low-income populations, and residents of long-term-care facilities.

**Lower or higher cut off points may be used for identifying positive reactions, depending upon the relative prevalence of *Myobacterium tuberculosis* infection and nonspecific cross-reactivity in the population.

the drugs in the usual standard regimens.

Host factors that must be considered in formulating regimens include the patient's age and, where relevant, pregnancy. Patients who are severely immunocompromised (eg, those with AIDS, lymphoreticular malignancies, etc) need to be treated longer. Finally, if the patient fails or is likely to fail to take the drugs regularly as prescribed, directly administered therapy (DAT) is highly advisable and can be accomplished through special programs without hospitalization. Environmental factors are important if they inhibit the patient's compliance with the regimen, but are even more important epidemiologically. Untreated patients who have active pulmonary disease, especially if cavitary, and who cough in a closed environment, repeatedly exposing those in the same living quarters, are the chief sources of transmission and thus of the continuation of the tuberculosis problem in the United States and throughout the world.

Isoniazid (INH) Prophylaxis

The recent increase in the incidence of active tuberculosis in the United States begs the question of why it is not prevented.[30] Despite its proven ability to prevent 60% to 80% of cases otherwise expected, there has been a hesitancy to apply isoniazid chemoprophylaxis, primarily because of fear of INH-induced hepatitis and divergent analyses of risks versus benefits. While the basic recommendations for INH prophylaxis, which included assessment of the hepatitis risk, have not changed in principle since 1974, the Advisory Committee for the Elimination of Tuberculosis (ACET) has recently published through CDC a clarification of these principles and the priority groups among those infected who should receive INH prophylaxis.[8] Table 1 summarizes these priorities by the risk category and age group into which the infected individual falls. The size of the tuberculin reaction that dictates chemoprophylaxis varies with risk category and patient age, ie, the higher the risk category and the lower the age, the lower the minimum size of the tuberculin reaction indicating the need for INH preventive therapy. The most important and neglected recommendation is that preventive treatment is indicated "at *all ages* if the patient has a risk factor," as defined at the bottom of Table 1. Thus the risk of progression to active tuberculosis in patients with any of these risk factors far outweighs the risk of INH hepatitis at *all ages*. The principles underlying Table 1 translate into the following list (in approximate order of priority) of those who should be given INH prophylaxis.[8] Groups 1, 2, and 3 are all high priority.

1. Recent tuberculin converters who meet the criterion for conversion: a ≥10 mm increase in PPD reaction within the previous 2 years for those <35 years old, or a 15 mm increase for those >35 years of age.
2. Persons with proven or suspected HIV infection (≥5 mm). In addition, any person who has proven anergy (no response to candidal, mumps, or tetanus toxoid antigens) and who is from a population subgroup with ≥10% prevalence of tuberculosis should be considered for INH therapy even if there is no response to PPD.[17]
3. Close contacts of persons with newly diagnosed infectious tuberculosis (≥5 mm). Those less than 20 years old should be treated even if the reaction is <5 mm, or until a repeat PPD 12 weeks after the contact ceases remains <5 mm.
4. Persons who have not previously had adequate drug treatment and whose chest films show fibrotic lesions consistent with old healed tuberculosis (≥5 mm). A calcified Ghon complex on the roentgenogram does not meet this criterion for priority.
5. Intravenous drug users (IVDU) known to be HIV negative (≥10 mm). (If HIV status of IVDU is unknown, give INH if PPD reaction is ≥5 mm.)
6. Persons with medical conditions considered to increase the risk of active tuberculosis (≥10 mm). These medical risk factors include silicosis, diabetes, chronic renal failure, gastrectomy or jejunoileal bypass, weight <90% of ideal, prolonged treatment with steroids or other immunosuppressive drugs, and leukemia, lymphoma, and certain other malignancies.

While persons in those six risk groups should be treated *regardless of age*, there is a second echelon of groups at risk.[8] Even in the absence of individual risk factors, all individuals from the following three groups should be treated if they are <35 years of age and their PPD reaction is 10 mm or more: (1) foreign-born persons from countries with a high prevalence of TB; (2) medically underserved low-income populations, including

TABLE 2. Standard Six-Month Tuberculosis Chemotherapy

*Intensive Phase**
Two months of daily single-dose:
Isoniazid (INH) 300 mg
Rifampin (RIF) 600 mg
Pyrazinamide (PZA) 1.5 - 2.0 (15-30 mg/kg/day)

Continuation Phase
Four months:

Daily	*[or]*	*Twice-Weekly, Supervised*
INH 300 mg		INH 15 mg/kg (900 mg for most adults)
RIF 600 mg		RIF 600 mg (same as daily dose)

*If there is potential for initial drug resistance: Add ethambutol (EMB), 25 mg/kg, pending drug susceptibility studies on culture.
All doses are for adults; children can be given same regimens in reduced doses (see Table 3).

ethnic minorities; and (3) residents of such facilities as prisons, nursing homes, and mental health hospitals. Persons with neither individual nor group risk factors should be treated only if they are <35 years old and the Mantoux test reaction is 15 mm or more.

In addition to this recent rational refinement of criteria for INH prophylaxis, the other important recent change in recommendations is that the duration of *preventive INH may be shortened to as little as 6 continuous months of daily therapy.*[8,31] The two major exceptions to this shortened course are persons with HIV infection and those with abnormal findings on chest films consistent with past tuberculosis; these two groups should continue to receive a full 12 months of INH therapy.[8,9] The usual adult prophylactic dose remains 300 mg of INH daily. If compliance is unlikely, however, directly observed chemoprophylaxis can be given twice weekly in a dose of 15 mg/kg (up to 900 mg).[8]

This recent clarification of risk-benefit priorities should dispel the controversy about isoniazid prophylaxis that has arisen because of the more rigid application of these principles since 1974.[32,33] It is hoped that this will lead to prophylaxis for increased numbers of the 10 million infected in the United States—especially if they are in the high-risk categories now more clearly elucidated.

Treatment of Active Tuberculosis

Regimens for patients with active clinical tuberculosis (groups 3a, 3b, and 3c in Figure 1) are likewise based upon the basic science principles enumerated. Since the introduction of RIF, which is rapidly bactericidal, successive controlled trials of various combinations of antituberculous drugs have allowed the progressive shortening of the period of chemotherapy.[34-37] Because mutational resistance develops to all tuberculosis drugs, however, the need for combinations continues. The most recent reduction in recommended duration of therapy—to 6 months—has been made possible by the addition of the older drug pyrazinamide (PZA) to INH and RIF. The standard regimens recommended jointly by the Centers for Disease Control (CDC) and the American Thoracic Society (ATS) since 1986 are summarized in Table 2.[38] These regimens, which are standard for first-time treatment of pulmonary or extrapulmonary[39] tuberculosis *in immunocompetent patients,* consist of a short *intensive phase* (usually 2 months) of drugs given once daily, followed by a longer *continuation phase* consisting of at least two of the intensive phase drugs given either daily or twice weekly. The standard regimen of INH, RIF, and PZA for a 2-month intensive phase, followed by INH and RIF for 4 months is now considered preferable to the 9-month regimen of INH and RIF.[35] Although both regimens are equally effective in ultimate outcome under ideal conditions, curing more than 95% of patients infected by susceptible organisms, the shorter regimen is often better in practice because patients are more likely to complete 6 than 9 months of therapy and because smears and cultures become negative somewhat more rapidly with the addition of PZA in the intensive phase.

The principles of chemotherapy dictate three types of modification of the standard regimens, corresponding to three special clinical situations. First, the *duration* of standard therapy should be extended in immunocompromised hosts, particularly patients with clinical AIDS. While the same intensive-phase regimen of INH, RIF, and PZA is used (supplemented by EMB or SM if there is CNS or disseminated tuberculosis), the continuation phase of INH/RIF must be longer. The minimum total duration for HIV-positive patients should be 9 months or at least 6 months after cultures are negative, whichever is *longer.*[11,24] This does not mean that the tuberculosis of persons with AIDS is more infectious than that of HIV-negative patients. In fact, there is some evidence (CDC, unpublished data) that it may be somewhat less infectious, probably because it is usually not cavitary. However, its airborne spread necessitates precautions to prevent tuberculosis transmission in all health-care settings.[40]

Extending the length of therapy is also sometimes considered in extrapulmonary tuberculosis. Because extrapulmonary tuberculosis represents a broad and varied spectrum of clinical disease,[21] no comprehensive trials have been carried out to confirm the efficacy of the newer standard regimens on all forms of extrapulmonary tuberculo-

TABLE 3. "First Line" Drugs Recommended for Initial Treatment of Tuberculosis*

Drug	Dosage Form	Daily Dose		Maximum Daily Dose	Twice-Weekly Dose		Monthly Cost (1986)		Major Adverse Reactions	How to Monitor
		Children	Adults		Children	Adults	Daily	Biweekly		
Isoniazid (INH)	Tablets: 100 mg 300 mg Syrup: 50 mg/5 mL Vials: 1 g	10-20 mg/kg PO or IM	5 mg/kg PO or IM	300 mg	20-40 mg/kg Max. 900 mg	15 mg/kg Max. 900 mg	Under $1	Under $1	Liver enzyme elevation, hepatitis, neuropathy, hypersensitivity	Clinical; liver enzymes
Rifampin (RIF)	Capsules: 150 mg 300 mg Syrup: 10 mg/mL Vials: 600 mg	10-20 mg/kg PO or IV	10 mg/kg PO or IV	600 mg	10-20 mg/kg Max. 600 mg	10 mg/kg Max. 600 mg.	$13-$21	$4-$6	Orange color to secretions and urine; hepatitis, fever, purpura; oral contraceptives, other drugs less effective	Clinical; liver enzymes
Pyrazinamide (PZA)	Tablets: 500 mg	15-30 mg/kg PO	15-30 mg/kg PO	2 g	50-70 mg/kg	50-70 mg/kg	$19-$48	$17-$32	Hepatotoxicity, hyperuricemia, arthralgias, skin rash, gastrointestinal upset	Clinical; liver enzymes, uric acid
Streptomycin (SM)	Vials: 1 g, 4 g	20-40 mg/kg IM	15 mg/kg IM	750 mg-1 g	25-30 mg/kg IM	25-30 mg/kg IM	$23-$27	$16-$20	Ototoxicity, nephrotoxicity	Audiogram; creatinine; BUN
Ethambutol (EMB)	Tablets: 100 mg 400 mg	15-25 mg/kg PO	15-25 mg/kg PO	2.5 g	50 mg/kg	50 mg/kg	$27-$72	$23-$36	Optic neuritis (decreased red-green discrimination and visual acuity), skin rash	Ishihara and Snellen tests

*Adapted and updated from CDC/American Thoracic Society.[38]

sis.[39] However, since bacterial loads are virtually always smaller (and probably never larger) in extrapulmonary disease than in adult recrudescent cavitary cases, the standard regimen for pulmonary tuberculosis should, in principle, be fully effective.[9,26]

The second special clinical situation arises when it is suspected that the patient's *M tuberculosis* organisms may be initially resistant to one or more of the drugs in the standard regimen.[27,28] Drug resistance should be considered when a patient has been treated previously, but inadequately. In some patients, the source case for infection is known to be excreting drug-resistant organisms; it is thus prudent to assume that the new patient's organisms will be primarily resistant to the same drugs. Patients who have immigrated from countries where tuberculosis control programs are not fully developed often fall into one or both of these categories.[4] Thus most experts recommend that when one or more of these adverse conditions prevails, an additional drug, nearly always ethambutol, be added to the intensive-phase regimen until drug sensitivity tests are returned after 3 to 6 weeks of therapy. At that point, the patient can be reassessed and, should the organisms in fact be sensitive to all three drugs in the standard regimen, the EMB can be stopped. Since primary resistance to more than two drugs is unusual, the prospective use of four drugs in the intensive phase virtually assures that the requisite minimum of two effective drugs will be present from the outset. If resistance to one or more of the four drugs is documented on initial cultures, an effective, but not standard, regimen can still be constructed. Experts in tuberculosis chemotherapy, either locally or through the Centers for Disease Control, should be consulted.

Finally, the age or sex of the patient with active tuberculosis may dictate modification of these standard regimens. Tuberculosis in children is safely and effectively treated with the same regimens used in adults with the appropriate doses listed in Table 3. Ethambutol cannot be used in children[23,26,38,41,42] unless they are old enough to be tested for toxicity by color vision charts.[43] Bacteriologic confirmation of active tuberculosis may be more difficult in children because they are more likely to have extrapulmonary or primary pulmonary disease and, even in the rare instance in which sputum is present, are usually unable to cooperate in producing specimens. This leads to two relevant recommendations. First, children with a significant tuberculin test reaction and clinical or radiologic evidence highly consistent with active tuberculosis should be treated with standard two- or three-drug regimens even in the absence of strict bacteriologic confirmation. Second, when the source of a childhood case of tuberculosis—usually within the household—can be identified, clinicians should initially assume that the drug sensitivity pattern of the child's tuberculosis mirrors that of the adult source case.[38]

In pregnant women with active tuberculosis, the

9-month INH and RIF regimen (Table 2) is safe and effective.[9,44,45] Because of insufficient data on teratogenicity, PZA should not be used. Streptomycin is ototoxic to the fetus. Isoniazid prophylaxis, though safe, is usually withheld until the third trimester or after delivery.[8,46] Treatment with INH or RIF is not a contraindication to breast-feeding.[47]

Since a large proportion of the active tuberculosis cases developing in the United States are in the elderly, special attention should be paid to appropriate dose reduction and potential toxicity, especially of SM and EMB, when elderly patients are being treated. However, since neither of these two drugs is in the current standard regimen, these issues will not arise frequently.

Toxicity, Side Effects, and Interactions

Details on the five "first-line" drugs used in initial treatment of tuberculosis are found in Table 3. There remain five other drugs that are active against tuberculosis, but because of suboptimal efficacy or toxicity, those are reserved for the rare situations in which drug resistance limits the application of the standard and alternative regimens containing the five first-line drugs.[48] These five "second-line" drugs—capreomycin, kanamycin, ethionamide, para-aminosalicylic acid (PAS), and cycloserine—are discussed in accessible references.[22,24,26,27,38]

Table 3 lists the major precautions, but a few additional caveats should be mentioned. Although each of the standard three—INH, RIF, and PZA—has potential hepatic toxicity, the risk of such toxicity incurred by giving more than one of these drugs concurrently apparently is not additive.[35] Baseline liver (and renal) function tests should be obtained in all patients. Caution should be observed when using any of these drugs in patients with active liver disease, especially those who consume alcohol daily,[26,38] though the mere history of alcoholism per se may pose only minimal risk. This potential problem rarely should limit the initial use of these three drugs, unless the liver disease is serious and progressive. Risk-benefit considerations dictate that isoniazid should be used more cautiously in the prophylactic than in the treatment situation. In general, potential liver or other toxicity can be monitored by monthly clinical history and directed physical examination without repeat laboratory tests unless there is clinical suspicion of adverse reaction.[38] Some clinicians may prefer to repeat liver function tests at set intervals.

RESOURCES

Most local and state health departments are eager to collaborate with clinicians in caring for patients with tuberculosis, since the two crucial elements in tuberculosis control are the effective treatment of infectious clinical cases and prophylactic isoniazid. Health departments often supply or reimburse for the drugs and for bacteriologic and other diagnostic tests, while the physician manages the patient clinically. Tuberculosis programs prioritize their contact investigations according to the infectiousness of the source case.[49] Primary care physicians familiar with the household should supply pertinent information. By completing a standard case report, the diagnosing physician will activate this partnership and fulfill a medicolegal responsibility. Laboratories licensed for mycobacteriology are also mandated to report positive cultures for *M tuberculosis,* thus providing a supplementary check on case reporting. In the voluntary sector, chapters of the American Lung Association disseminate information and provide selected pertinent patient services.

Nationally, a fortunate partnership has been forged between the American Thoracic Society (ATS), which is the professional affiliate of the American Lung Association, and the USPHS Centers for Disease Control (CDC). The most recent and important ATS/CDC consensus statements are among the references. Telephone numbers are (212) 315-8808 for ATS and (404) 639-2508 for the CDC Division of Tuberculosis Control. The National Tuberculosis Training Initiative (NTTI)[50] and its *Core Curriculum on Tuberculosis*[9] have grown out of "A Strategic Plan for the Elimination of Tuberculosis in the United States,"[51] endorsed by the ATS, CDC, American Medical Association, and American Public Health Association. This is a consensus rationale of the clinical, public health, and research actions needed to achieve the elimination of tuberculosis from the United States (defined as an annual incidence of less than one case per million population) by the year 2010. This is indeed a daunting challenge, given the recent national *increase.* The estimated 7 million new active cases worldwide *each year,*[25,52] a number likely to increase in the wake of the AIDS pandemic, presents an even larger global task in view of scarce resources.[3,53,54] However, because of the centrality of case diagnosis and chemotherapy in tuberculosis control, it is a challenge thrown squarely to the clinicians of this nation and of the world.

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