



Tuberculosis in the elderly

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Although the last decade has been marked by a major decline in the incidence of tuberculosis (TB) in the United States, TB remains an important diagnosis to consider among older individuals. The clinical presentation is often insidious and non-specific, as is the radiological presentation. The elderly account for a large proportion of TB cases discovered at autopsy, illustrating the difficulty of clinical diagnosis in this age group.

The last decade has also seen changes in tuberculin skin testing (TST) strategies and in the treatment guidelines for latent TB. In the past, TST was recommended for almost all individuals as a part of routine health screening. TST is now targeted at persons who have risk factors for developing active TB, including nursing home residents.

Clarification of nomenclature has accompanied the most recent guidelines on TST. Those with reactive TSTs have latent TB infection (LTBI) and receive treatment for LTBI rather than “chemoprophylaxis.” Isoniazid continues to be the best method of preventing LTBI from becoming an active infection. In the past, nursing home residents or immigrants with a positive TST of unknown duration who were over age 35 were not given isoniazid unless certain comorbid conditions were present because of the risk of hepatotoxicity. Current guidelines no longer use age as an exclusionary condition, however.

Treatment of active disease in the elderly does not significantly differ from treatment of younger patients. Management dilemmas may arise when the diagnosis of active TB infection is suspected but not proven. In view of the poor outcome of untreated TB, empiric TB treatment should be more readily considered in the elderly.

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Epidemiology

The past decade has seen a peak and subsequent decline of the TB epidemic in the United States. The case rate decreased from 10.5/100,000 people in 1992 to 5.8/100,000 in 2000, a 45% decrease [1]. The incidence of tuberculosis decreased by 7% between 1999 and 2000, from 17,531 cases to 16,377 cases [1,2], continuing the 8-year downward trend. Although the case rate among those over age 65 has also decreased significantly, from 18.7/100,000 in 1992 to 11.7/100,000 in 1999, the elderly still have the highest case rate among all age groups (Fig. 1) [1].

The largest decline in number of TB cases by age group occurred in children under age 15 and among 25- to 44-year old adults, which had decreases of 43% and 46.5%, respectively, from 1992 to 2000. Among those over age 65, a similar decrease of 42% occurred, from 6025 cases in 1992 to 3534 cases in 2000 [1]. Despite these declines in absolute numbers, the proportion of cases among the elderly has remained stable, with the elderly accounting for 23% of all cases. More recently between 1999 and 2000, the proportion of cases occurring among the elderly decreased to 21.5% [1,2]. By contrast, the elderly account for 13% of the United States population [3]. The excess number of TB cases among the elderly may reflect the high frequency of exposure and infection that occurred in the first few decades of the twentieth century.

The case rate has been particularly high in nursing homes [4,5]. In a 29-state survey conducted by the Centers for Disease Control and Prevention (CDC) in 1984 and 1985, the incidence rate was 39.2 per 100,000 elderly nursing home residents, and 21.5 per 100,000 community-dwelling elderly patients compared with 9.1 per 100,000 nationally [4,6]. Thus, even before the TB epidemic of the early 1990s, the rate of TB disease among the elderly in nursing homes was twice as high compared with individuals in the community.

In a study by Stead et al of nearly all nursing home residents in Arkansas in 1985, the incidence of a positive skin test upon admission to a nursing home was 2400/100,000 [7]. The risk of TB infection and disease was increased among the nursing home residents compared with the elderly residing in the community,

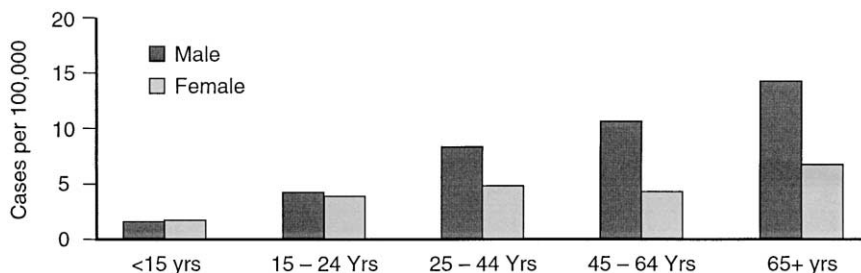


Fig. 1. Tuberculosis case rates by age group and sex, Unites States, 2000.

and length of stay in the nursing home was associated with an increasing likelihood of a positive TST. The rate of tuberculin reactivity was also higher in nursing homes with known recent infectious cases, indicating that the elderly were vulnerable to exogenous re-infection. In contrast, studies in Liverpool and Hong Kong nursing homes found no association between tuberculin reactivity and length of stay [8,9]. The risk for transmission may depend on features of communal living (eg, sitting together at meal times) and the general health and nutritional status of the residents.

In addition to accounting for a disproportionate share of all TB cases, the elderly account for a disproportionate share of TB-related mortality. In 1997, 748/1166 (64%) TB-related deaths in the United States occurred among those over age 65. Similarly, case–fatality rates increased by age: 0.8% for age 15 to 24; 1.6% for age 25 to 44; 5.0% for age 45 to 64; and 16.0% for those over age 65 [10]. These statistics clearly underscore the need to screen for and treat LTBI in the elderly.

Tuberculin skin testing

The general United States population currently has an estimated latent TB infection rate of 5% to 10%, based on TST [11]. Purified protein derivative (PPD) is used for TST despite being less than 100% sensitive and specific for detection of *Mycobacterium tuberculosis* infection. In October 2001 an advisory panel to the United States Food and Drug Administration (FDA) approved another method for identifying latent TB infection based on a whole-blood interferon γ assay called QuantiFERON-TB test (Cellestis, Ltd., Valencia, CA). Overall agreement between the assay and TST ranges from 83.1% [12] to 98.0% [13]. The ELISA-based assay has the advantage of being a one-step test, so patients do not have to return a second time for a reading, and results can be available within 24 hours. Sensitivity and specificity data are not yet available, however, and data on test performance in certain groups, including HIV-positive people, transplant patients, pregnant women, and children are also still lacking. For the time being, therefore, TST remains the standard method to detect latent TB infection .

For persons with LTBI and normal immune responsiveness, test sensitivity approaches 100%. False-positive TSTs occur in persons who have been infected with nontuberculous mycobacteria and in persons who have received Bacille Calmette-Guerin (BCG) vaccine, an attenuated mycobacterial strain derived from *M. bovis*. These false-positive reactions result in a lower specificity and a lower positive predictive value in persons who have a low probability of LTBI [11].

False-negative skin tests may occur in immunosuppressed persons, whose delayed-type hypersensitivity responses may decrease or disappear. This condition, known as anergy, occurs in the setting of severe or febrile illness, HIV and other viral infections, or the administration of corticosteroids or other immunosuppressive drugs [14]. TSTs may also be negative in patients who have active TB in up to 28% of individuals. Most false-negative test results in patients with

active TB are attributed to general illness and become positive 2 to 3 weeks after effective treatment is initiated [15].

Anergy rates in the general population have been difficult to quantify because of lack of a standardized anergy panel. Most authorities agree, however, that anergy is more common among the elderly. This increased prevalence has been attributed to a decline in cellular immunity with age, eradication of the dormant infecting organism from within the host, or a combination of both [8,16]. Several changes occur in the immune system of elderly individuals. For example, the number of circulating lymphocytes decreases by approximately 15%, primarily due to decreased number of T cells. Fewer interleukin-2 receptors in the lymphocyte cell membrane and decreased levels of adenosine triphosphate in the lymphocyte cytoplasm result in decreased lymphocyte proliferation in response to mitogen or antigen stimulation [17]. The absence of a reaction to TST in any individual does not rule out TB disease or infection; this is particularly true among the elderly.

Because anergy is more prevalent among the elderly, two-step TST is recommended for elderly persons at high risk (see below) who have not been skin tested for many years or who have never been tested. TST may stimulate or boost the immune system's ability to react to tuberculin, causing a positive reaction to subsequent tests. This boosted reaction may be misinterpreted as a new infection, and its frequency increases with age. Two-step testing is used to reduce the likelihood that a boosted reaction will be misinterpreted as evidence of a recent infection. If the reaction to the first test is classified as negative, a second test should be performed 1 to 3 weeks later. A positive reaction to the second test represents a boosted reaction and not a skin test conversion. If the second result is also negative, the person should be classified as uninfected. In these persons, a positive reaction to any subsequent test is likely to represent new infection with *M tuberculosis* [14].

The most recent guidelines from the American Thoracic Society (ATS) and the CDC were published in 2000 [11]. These guidelines emphasize targeted tuberculin testing among persons at high risk for recent LTBI or persons who have clinical conditions that increase the risk for development of TB, regardless of age (see Tables 1 and 2). Three cut points have been recommended for defining a positive tuberculin reaction: greater than or equal to 5 mm, greater than or equal to 10 mm, and greater than or equal to 15 mm of induration. These cut points are intended to improve the specificity of skin testing in different populations. For individuals at high risk of developing active TB disease, a cut point of greater than or equal to 5 mm of induration is recommended. High-risk groups include those who are immunosuppressed because of disease (eg, HIV infection) or medications (eg, corticosteroids), recent close contacts of infectious TB case patients, and those with abnormal chest radiographs suggestive of prior TB. The guidelines further define as high risk the use of corticosteroids such as prednisone (or its equivalent) at greater than 15 mg/day for 1 month or more. This dose suppresses tuberculin reactivity, whereas lower doses or those given intermittently are not associated with TB [11].

A cut point of greater than or equal to 10 mm of induration is suggested for individuals who have normal or mildly impaired immunity and a high likelihood

Table 1
Criteria for tuberculin positivity, by risk group

Reaction >5 mm of induration	Reaction >10 mm of induration	Reaction >15 mm of induration
HIV-positive persons	Recent immigrants (ie, within the last 5 y) from high prevalence countries; injection drug users	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Residents and employees ^b of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with AIDS, homeless shelters	
Fibrotic changes on chest radiograph consistent with prior TB	Mycobacteriology laboratory personnel	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/d of prednisone for 1 mo or more) ^a	Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (eg, leukemias and lymphomas), other specific malignancies (eg, carcinoma of the head or neck and lung), weight loss of $\geq 10\%$ of ideal body weight, gastrectomy, jejunioileal bypass Children younger than age 4 y or infants, children, adolescents exposed to adults at high risk	

From Anonymous. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221.

^a Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

^b For persons who are otherwise at low risk and are tested at the start of employment, a reaction of >15 mm induration is considered positive.

of recent infection with *M tuberculosis*. This group includes recent immigrants from high-prevalence countries, residents and employees of high-risk congregate settings (such as nursing homes and other long-term facilities for the elderly), and persons who have certain medical conditions that place them at high risk such as diabetes, chronic renal failure, and weight loss of greater than 10% of ideal body weight. The inclusion of nursing home residence as a risk factor is supported by epidemiologic studies, such as those described above, which demonstrate increased incidence rates of TB among nursing residents.

Cancer is a risk factor, but not every cancer carries the same risk. Screening should focus on cancers that cause a significantly immunocompromised state,

Table 2

Changes from prior recommendations on tuberculin testing and treatment of latent tuberculosis infection

Tuberculin testing

Emphasis on targeted tuberculin testing among persons at high risk for recent LTBI or with clinical conditions that increase the risk for TB, regardless of age; testing is discouraged among persons at lower risk

For patients with organ transplants and other immunosuppressed patients (eg, persons receiving the equivalent of ≥ 15 mg/d of prednisone for 1 mo or more), 5 mm of induration rather than 10 mm of induration as a cut-off level for tuberculin positivity

A tuberculin skin test conversion is defined as an increase of ≥ 10 mm of induration within a 2-y period, regardless of age

Treatment of latent tuberculosis infection

For HIV-negative persons, isoniazid given for 9 mo is preferred over 6-mo regimens

For HIV-positive persons and those with fibrotic lesions on chest radiograph consistent with previous TB, isoniazid should be given for 9 mo instead of 12 mo

For HIV-negative and HIV-positive persons, rifampin and pyrazinamide should be given for 2 mo

For HIV-negative and HIV-positive persons, rifampin should be given for 4 mo

Clinical and laboratory monitoring

Routine baseline and follow-up laboratory monitoring can be eliminated in most persons with LTBI except for those with HIV infection, pregnant women (or those in the immediate postpartum period), and persons with chronic liver disease or those who use alcohol regularly

Emphasis on clinical monitoring for signs and symptoms of possible adverse effects, with prompt evaluation and changes in treatment as indicated

Abbreviations: LBTI, latent tuberculosis infection; TB, tuberculosis.

From Anonymous. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221.

significant weight loss, or are treated with chemotherapy. These include the lymphoreticular cancers and metastatic cancer. Lung, head and neck, and gastric cancers seem to pose special risks. Gastrectomy is a risk factor, but it is the weight loss and associated malabsorption, not the gastrectomy itself, that contributes most to the risk for TB [18,19]. Diabetes is a risk factor, but more so in individuals who have severe diabetes. An individual who has end-organ damage who has been on insulin for many years is at much higher risk than a person with diet-controlled diabetes with no end-organ damage.

Persons who are not likely to be infected with *M tuberculosis* should not be tested because the predictive value of a positive TST in low-prevalence populations is poor. Low risk individuals should be tested upon entry into a high-risk setting (eg, employment at a nursing home) and the higher cut point of greater than or equal to 15 mm should be used [14].

Clinical manifestations

The clinical presentation of TB might be atypical and subtle in the elderly. The diagnosis must be considered in a variety of clinical scenarios. Symptoms such as

unexplained weight loss, “failure to thrive,” fever, weakness, or a change in cognitive status may be the sole manifestation of the disease.

Although TB can develop in any organ, in adults it usually develops in the apex of one or both lungs as a fibrocaceous infiltrate. Hematogenous dissemination can occur at any stage of disease and produce miliary TB or meningitis. A granulomatous inflammation develops in infected tissues and the initial tuberculous lesions heal, although they contain small numbers of dormant, viable bacilli. These bacilli appear to mediate the host’s relative resistance to re-infection. If these healed lesions break down, re-activation of the infection occurs. Re-activation of a dormant infection is the predominant mechanism of disease in the elderly, with a lifetime risk of re-activation of 10%. As mentioned above, the elderly are also vulnerable to exogenous re-infection [7,20].

It has recently been suggested that pulmonary TB in the elderly might differ from the disease presenting in younger patients and that it should be classified as a separate entity [21,22]. It has also been suggested that these differences might account for a delay in the diagnosis, which in turn leads to increased morbidity and mortality in this age group [21]. Although several published works have looked for differences between younger and older tuberculous patients, they usually provide quite discordant findings [21,23–28]. Perez-Guzman et al [26] performed a meta-analysis of published studies comparing pulmonary TB in older and younger patients to clarify this issue. Several clinical manifestations differed between the younger and older patients. Fever was less frequently observed in older subjects; sweating was also less frequent among the older patients, most likely related to the lower frequency of fever. Dyspnea was more frequent among older patients, which can be explained by the expected decrease in pulmonary function with aging. Hemoptysis was less common among the elderly, correlating with the lower prevalence of cavitory disease in older populations. Older TB patients had higher rates of comorbid conditions such as cardiovascular disorders, chronic obstructive pulmonary disease, diabetes, gastrectomy, and malignancies. The differences in the presentation of pulmonary TB among the elderly can therefore be explained by the already known physiologic changes that occur with aging, and they must be kept in mind during the diagnostic evaluation.

In the United States, extrapulmonary TB represented 19.7% of the total number of TB cases in the year 2000. Lymphatic and pleural TB were more prevalent than osteoarticular, genito–urinary, meningeal, or peritoneal disease [1]. Extrapulmonary TB usually presents more of a diagnostic problem than pulmonary TB. It is less familiar to most clinicians because it is less common. In addition, extrapulmonary TB involves relatively inaccessible sites, and because of the nature of the sites involved, fewer bacilli can cause much greater damage. The combination of small numbers of bacilli and inaccessible sites makes bacteriologic confirmation of the diagnosis more difficult, and invasive procedures are frequently required to establish a diagnosis.

Disseminated TB occurs because of the inadequacy of host defenses in containing TB infection. This failure of containment can occur in either re-

activation of the disease or in recently acquired infection. Multiorgan involvement is probably much more common than is recognized, because once *M tuberculosis* is identified in any specimen, other sites are not generally evaluated. The presenting symptoms and signs are generally nonspecific and are dominated by systemic effects, particularly fever, weight loss, night sweats, anorexia, and weakness [29]. Most patients with disseminated disease also have pulmonary involvement; therefore, the chest film is often abnormal. Radiographic findings range from a typical miliary pattern to upper lobe infiltrates with or without cavitation, and evidence of pleural or pericardial effusions [29].

Tuberculous lymphadenitis usually presents as painless swelling of one or more lymph nodes. Systemic symptoms are not common unless there is concomitant TB elsewhere. The nodes usually involved are those of the posterior or anterior cervical chain or those in the supraclavicular fossa. Rupture of the node can result in formation of a sinus tract, which may be slow to heal. A sinus tract may also form after an excisional biopsy of the tuberculous node. It is therefore best to begin the diagnostic evaluation with a fine needle aspiration of the enlarged node. If the smear or culture confirms the presence of acid-fast bacilli (AFB), then an excisional biopsy is not needed and the node will heal more rapidly.

Pleural TB can present as acute pleurisy with effusion or as empyema. Early in the course of a tuberculous infection a few organisms may gain access to the pleural space. In an immunocompetent host, a hypersensitivity response leads to the effusion. Usually this form of tuberculous effusion resolves spontaneously, but some patients develop an acute illness with fever and pleuritic pain. Parenchymal disease is nearly always present. In contrast, if a large number of organisms spill into the pleural space from rupture of a cavity or an adjacent parenchymal focus, a tuberculous empyema will develop. Thoracentesis reveals lymphocytic exudative fluid and the Gram stain and bacterial cultures are negative. The fluid is often hemorrhagic but usually has too few AFB to be detected on smear or culture. Because pleural tissue is more likely to have either detectable levels of AFB or granulomas, a second thoracentesis with a pleural biopsy is usually required. A pleural biopsy that shows granulomas, with or without AFB, from a patient with constitutional symptoms is usually sufficient to make the diagnosis.

The clinical manifestations of tuberculous meningitis—headache, confusion, and dizziness—are similar in elderly and young patients. Due to the high prevalence of neurologic disease in the elderly, however, the diagnosis may not be apparent at first. Hyponatremia due to the syndrome of inappropriate antidiuretic hormone may develop and contribute to confusional states. In a study of tuberculous meningitis, typical cerebrospinal fluid findings included lymphocytosis and an elevated protein level. A low glucose level was found in only 17% of patients [30]. In contrast, pyogenic meningitis is more consistently associated with low cerebrospinal fluid glucose.

TB of the skeleton usually involves the weight-bearing bones, particularly the vertebrae (Pott's disease) and joints such as the hip, knee, ankle, elbow, or wrist.

Paraspinal abscesses are common. Infection usually begins in the anterior part of a vertebral body. Collapse of two adjacent infected vertebrae leads to anterior wedging with a loss of the intervertebral space. Thus, the typical finding on radiograph is of a posterior prominence, or gibbus, of the thoracic or lumbar spine. In contrast, pyogenic infection of the spine produces sclerotic changes rather than collapse in the vertebral body and is also marked by a more rapid destruction of the disc [31]. Monoarticular pain and loss of motion is typical of joint involvement, and a history of previous trauma is common. Systemic manifestations are infrequent. As a result, complaints of joint pain may be inappropriately attributed to osteoarthritis in the elderly. The diagnosis of skeletal TB is made by joint aspiration or bone biopsy.

Genitourinary TB can involve the kidneys, ureters, bladder, prostate, epididymis, and seminal vesicles. The typical manifestations are dysuria, frequency, hematuria, and urgency, although some patients may be asymptomatic. Pyuria with or without hematuria or proteinuria is found on urinalysis. Routine bacterial cultures are persistently sterile. An intravenous pyelogram can assist in delineating the infection, although mycobacterial culture results are necessary to define the infection as tuberculosis. At least three morning urine specimens are recommended for detection of genitourinary *M tuberculosis* [32].

Diagnosis

Because the diagnosis of TB can be difficult and elusive, the diagnosis may unfortunately be recognized only at autopsy. Rieder et al [33] found that between 1985 and 1988 5.1% of TB cases reported in the United States were diagnosed at death. The proportion of cases diagnosed at death increases with age, from 0.7% in patients less than 5 years old to 18.6% among patients aged 85 years and older. Only 26% of cases diagnosed alive were among those 65 years and older, but 60.3% of those diagnosed at autopsy were over 65 years. These data indicate that TB too often remains unrecognized and that a high index of suspicion of TB remains important, particularly among the elderly.

A complete medical evaluation for TB includes a complete history and physical examination, TST, chest radiograph, and any appropriate bacteriologic or histologic examinations. A positive skin test indicates previous or current infection, but as noted above, a negative test does not exclude the diagnosis. The chest radiograph may reveal typical upper lobe lesions; however, several studies have described atypical lower lung field lesions in elderly patients [21,26,28]. TB in an older tuberculin-negative individual may cause a nonspecific, nonresolving pneumonitis in the lower or middle lobes, similar to primary infection in childhood except with much less hilar and mediastinal adenopathy [34].

Old healed TB usually presents a different radiographic appearance from active TB. Dense pulmonary nodules with or without visible calcification can be seen in the hilar area or upper lobes. Alternatively, small nodules with or without fibrotic scars may be seen in the upper lobes. Upper-lobe volume loss often

accompanies these scars. Nodules and fibrotic scars contain slowly multiplying tubercle bacilli with the potential for future progression to active TB. Conversely, calcified nodular lesions (calcified granuloma) pose a low risk for future progression to active TB. It is important to consider these differences, especially in the evaluation of a person who has a positive reaction to the TST and no symptoms of disease [5].

Detection of AFB in stained smears can provide the first bacteriologic clue of active TB. Various specimens can be submitted, including blood, bone marrow, sputum, bronchial washings, gastric lavage, stool, tissue biopsy, and urine. Fluorochrome staining with auramine–rhodamine is the preferred staining method because it is faster than the traditional methods in which Ziehl-Neelsen or Kinyoun stains are used [5]. Several quantitative studies have shown that there must be 5000 to 10,000 bacilli per milliliter of specimen to allow the detection of bacteria in stained smears. In contrast, 10 to 100 organisms are needed for a positive culture. Smear examination permits only the presumptive diagnosis of TB because the AFB in a smear might be mycobacteria other than *M tuberculosis*. Furthermore, many TB patients have negative AFB smears. A single smear of a respiratory specimen has a sensitivity of 22% to 43%. When multiple specimens are examined, the detection rate improves to 96%. Specimens from other sources are associated with a lower sensitivity. Factors influencing the sensitivity of smears include staining technique, centrifugation speed, reader experience, and the prevalence of TB disease in the population being tested [14].

The isolation of *M tuberculosis* by culture, the “gold standard” for the diagnosis of TB, can take up to 6 weeks. The need for more rapid diagnostic tests has largely been met by molecular biology methods that allow direct detection of *M tuberculosis* complex in clinical specimens. Two direct amplification tests (DATs) have been approved by the FDA, the *M tuberculosis* Direct Test (MTD; Gen-Probe, San Diego, CA) and the Amplicor *M tuberculosis* Test (AMPLICOR MTB Test; Roche Diagnostic Systems, Branchburg, NJ). Both tests amplify and detect *M tuberculosis* 16S ribosomal RNA [35] and can confirm the presence of *M tuberculosis* within 1 to 3 days. In addition, these tests may detect *M tuberculosis* DNA in tissue samples that have been preserved in formalin or other preservatives that preclude the possibility of culture. The MTD test is more widely used because it is FDA-approved for both smear-positive and smear-negative specimens and it is technically easier to perform.

When DATs are performed on AFB smear-positive respiratory specimens, each DAT has a sensitivity of greater than 95% and a specificity of essentially 100% for detecting *M tuberculosis* complex. When AFB smear-negative respiratory specimens are tested, however, the specificity remains greater than 95%, but the sensitivity ranges from 40% to 77%. As with all diagnostic tests, the positive and negative predictive values of DATs vary with the pretest probability of the disease. If the clinical suspicion is high for TB, the positive predictive value is 98% but the negative predictive value is only 37%. In cases in which there is low

clinical suspicion, the positive predictive value of the test is 39% but the negative predictive value is 98% [36]. Rapid diagnostic tests for TB are therefore most likely to influence decisions regarding antituberculosis therapy when the likelihood of TB is neither high nor low. This includes patients with positive AFB smears in whom the clinical suspicion of TB is intermediate or low and patients who have negative AFB smears in whom the clinical suspicion of TB is high or intermediate [35].

The ATS developed a consensus statement on the status of direct amplification tests for the rapid diagnosis of TB [36]. DATs should be performed in conjunction with microscopy and AFB culture, and each test result should be interpreted within the overall clinical setting. When the AFB smear and DAT are both negative, it is unlikely the specimen will be culture-positive for *M tuberculosis*. When there is discordance between the AFB smear and DAT results, additional consideration must be given to the overall clinical picture, and repeat testing is indicated.

Treatment

Latent tuberculosis infection

Although the terms “preventive therapy” and “chemoprophylaxis” have been used for decades, they are somewhat misleading. “Preventive therapy” or “chemoprophylaxis” for PPD-positive individuals is not true primary prevention (ie, prevention of infection). Instead, these terms have referred to the use of a simple regimen to prevent the development of active TB disease in persons known or likely to be infected with *M tuberculosis*. The ATS and the CDC therefore recently changed the nomenclature to “treatment of LTBI” to promote greater understanding of the concept for both patients and providers [11].

For more than three decades, treatment of persons who have LTBI to prevent the development of active disease has been an essential component of TB control in the United States. In 1965, isoniazid treatment of LTBI was recommended for persons with evidence of previously untreated TB and persons with recent TST conversions. In 1967, the recommendations were broadened to include all persons who had had a TST reaction of greater than 10 mm.

In 1970, among several thousand persons who began isoniazid treatment, 19 developed clinical signs of liver disease and two died of hepatic failure attributed to isoniazid. The frequency of hepatotoxicity was age-related: 0.3% for ages 20 to 34; 1.2% for ages 35 to 49, and 2.3% for those over age 50 [37]. When the guidelines for treatment of LTBI were updated in 1974, low-risk persons older than age 35 were therefore no longer considered candidates for treatment. Those over the age of 35 who had certain high-risk conditions such as diabetes, chronic steroid use, or silicosis were still considered candidates for treatment of LTBI. Other conditions, however, such as nursing home residence, history of incarceration, homelessness, or recent immigration from a high-prevalence country,

were not officially recognized as risk factors and therefore did not warrant isoniazid (INH) “chemoprophylaxis.”

Subsequent controversy over the appropriate cut-off age centered around low-risk, tuberculin-positive persons. The debate over whether to prescribe or withhold isoniazid for tuberculin-positive persons older than age 35 involved a trade-off between the risk of developing active TB versus the risk of developing isoniazid-induced hepatitis. Salpeter et al [38] developed a decision analysis model to evaluate the use of monitored isoniazid prophylaxis in low-risk tuberculin reactors older than age 35. They found that isoniazid prophylaxis increased life expectancy for 35-, 50-, and 70-year-olds by 4.9 days, 4.7 days, and 3.1 days, respectively, and concluded that the public health benefits of providing prophylaxis for tuberculin reactors of all ages, with no contraindications, would be substantial. Despite the publication of many analyses [39–41], the decision to treat older, tuberculin-positive persons at low risk for developing active TB remained controversial.

The guidelines published by the ATS and the CDC in 2000 address this age controversy. The new guidelines recommend targeted tuberculin testing among persons at high risk for recent LTBI, regardless of age, and discourage testing among persons at low risk, regardless of age. In addition, the guidelines have expanded the list of high-risk conditions (see Table 1) to include, for example, nursing home residence and recent immigration from a high-prevalence country.

The guidelines also address treatment issues (Table 2). Treatment of LTBI with isoniazid for 9 months is preferred to the 6- or 12-month regimen regardless of HIV status. Previous cost-effectiveness analyses were responsible for the widespread adoption of the 6-month regimen of isoniazid for the treatment of LTBI in HIV-seronegative persons who had normal chest radiographs [42]. More recent prospective, randomized trials of up to 12 months of isoniazid therapy in HIV-uninfected persons demonstrate that the maximal benefit is achieved by 9 months [11,43]. A 9-month regimen of isoniazid is also recommended for HIV-infected persons; however, this is based on extrapolation from available data. The updated recommendation therefore represents a lengthening of the previously recommended 6-month regimen for HIV-uninfected persons and a shortening of the previous 12-month regimen recommended for HIV-infected persons (see Table 2).

When 9 months of isoniazid cannot be taken, there are several alternative regimens. A 6-month regimen of isoniazid has been demonstrated to be superior to placebo in both HIV-infected and HIV-uninfected persons [42,44]. The 6-month regimen is not advised for those who have fibrotic lesions on chest radiographs or those who are HIV-infected. Rifampin and pyrazinamide daily for 2 months had previously been shown to be safe and effective in HIV-infected persons. This regimen was therefore presumed to be effective in HIV-uninfected persons. Recent reports of severe liver injury [45] have led to revised recommendations regarding the use of rifampin and pyrazinamide for LTBI. This regimen is now limited to patients who do not have a history of underlying liver disease or INH-associated liver injury. The regimen should be used with caution in patients

concurrently taking other medications associated with liver injury and those with alcoholism. Serum transaminases should be measured at baseline and at 2, 4, and 6 weeks of treatment in patients taking rifampin and pyrazinamide.

When patients cannot tolerate isoniazid or pyrazinamide, rifampin given daily for 4 months is an acceptable alternative treatment for both HIV-infected and HIV-uninfected persons. Some patients might not be candidates for treatment of LTBI at all. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI, especially if the likelihood of TB transmission to vulnerable contacts is low. In addition, low-risk individuals of any age who are incidentally found to be tuberculin-positive are not necessarily candidates for treatment of LTBI [11].

Since 1983, routine clinical and laboratory monitoring for persons older than age 35 and other persons at risk for hepatotoxicity was standard. The 2000 guidelines have also revised the recommendations in this area. Baseline and follow-up laboratory monitoring can be eliminated in most persons who have LTBI, including the elderly, except for those who have specific associated conditions (Table 2). Baseline laboratory tests of liver function are still indicated for those who have a history of liver disease, who use alcohol regularly, or are at risk for chronic liver diseases, regardless of age.

The elimination of routine laboratory monitoring is based on some recent studies demonstrating the efficacy of clinical monitoring. For example, a public health TB clinic that used clinical monitoring exclusively reported 11 cases of clinical hepatotoxicity (0.1%) and no deaths among more than 11,000 persons using isoniazid for LTBI over a 7-year period [46]. The 2000 guidelines therefore give particular emphasis to clinical monitoring for all patients in a monthly basis. Patients should be questioned and educated monthly about the signs of hepatitis and instructed to discontinue medications immediately if they note the onset of symptoms such as anorexia, nausea, or vomiting. The continuation of medications despite clinical symptoms has been associated with the more severe cases of hepatotoxicity.

Treatment of tuberculosis disease

The recommendations for treatment of TB disease do not differ for the elderly. The major challenge in the elderly is to select a therapeutic regimen that produces minimal adverse reactions, is easily administered, and is acceptable to the patient.

Although there has been much concern over the emergence of multi-drug-resistant (MDR) isolates of *M tuberculosis* and the complex issue of TB in HIV-infected persons, the vast majority of TB cases among United States elderly are caused by drug-sensitive strains of *M tuberculosis*; this has been explained by the fact that TB in the elderly usually results from re-activation of a latent infection and that these individuals presumably acquired the infecting organism during the time prior to the availability of effective antituberculous chemotherapy. Hence, unless the older patient is from a country with a high

prevalence of drug-resistant *M tuberculosis*, had previously been inadequately treated, or had acquired the infection from a known MDR TB contact, the overwhelming majority of TB cases in the elderly will be highly susceptible to isoniazid and rifampin [47].

The ATS, in conjunction with the CDC, modified the recommendations for treatment of TB in 1994 due to the rise of MDR TB cases [48]. Initial empiric treatment should consist of the four-drug regimen: isoniazid (300 mg/day), rifampin (600 mg/day), ethambutol (15–25 mg/day) and pyrazinamide (15–30 mg/day) for 4 months, followed by isoniazid and rifampin for an additional 4 months (Tables 3 and 4). Ethambutol can be omitted if the frequency of isoniazid resistance is 4% or less in a given community or if the population in question has a low risk for drug resistance. This 6-month regimen is sufficient for disease at any site, with the exception of tuberculosis meningitis, for which treatment with isoniazid and rifampin should be continued for 12 months. Some authorities also recommend that miliary and bone disease be treated for 12 months.

As mentioned above, a definite diagnosis of pulmonary TB is based on the isolation of *M tuberculosis* in culture specimens from the lung. In elderly patients,

Table 3

Regimen options for the preferred initial treatment of children and adults

Option 1	Option 2	Option 3
Administer daily isoniazid, rifampin, and pyrazinamide for 8 wk followed by 16 wk of isoniazid and rifampin daily or 2–3 \times /wk ^a . In areas where the isoniazid resistance rate is not documented to less than 4%, ethambutol or streptomycin should be added to the initial regimen until susceptibility to isoniazid and rifampin is demonstrated. Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.	Administer daily isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol for 2 wk followed by 2 \times /wk ^a administration of the same drugs for 6 wk (by DOT), and subsequently with 2 \times /wk administration of isoniazid and rifampin for 16 wk (by DOT). Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.	Treat by DOT 3 \times /wk ^a with isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin for 6 mo. ^b Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.

From Bass JBJ, Farer LS, Hopewell PC, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. Am J Respir Crit Care Med 1994;149:1359–74.

^a All regimens administered 2 \times /wk or 3 \times lwk should be monitored by directly observed therapy (DOT) for the duration of therapy.

^b The strongest evidence from clinical trials is the effectiveness of all four drugs administered for the full 6 mo. There is weaker evidence that streptomycin can be discontinued after 4 mo if the isolate is susceptible to all drugs. The evidence for stopping pyrazinamide before the end of 6 mo is equivocal for the 3 \times /wk regimen, and there is no evidence on the effectiveness of this regimen with ethambutol for less than the full 6 mo.

Table 4

Dosage recommendation for the initial treatment of tuberculosis in children^a and adults

Drugs	Dosage					
	Daily dose		Twice-weekly dose		Thrice-weekly dose	
	Children	Adults	Children	Adults	Children	Adults
Isoniazid, mg/kg	10–20	5	20–40	Max 15	20–40	Max 15
	Max	Max	Max	Max	Max	Max
Rifampin, mg/kg	300 mg	300 mg	900 mg	900 mg	900 mg	900 mg
	10–20	10	10–20	10	10–20	10
	Max	Max	Max	Max	Max	Max
Pyrazinamide, mg/kg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg
	15–30	15–30	50–70	50–70	50–70	50–70
	Max 2 g	Max 2g	Max4g	Max 4 g	Max 3 g	Max 3 g
Ethambutol, mg/kg ^b	15–25	15–25	50	50	25–30	25–30
	20–40	15	25–30	25–30	25–30	25–30
Streptomycin, mg/kg	Max 1.0 g	Max	Max 1.5 g	Max 1.5 g	Max 1.5 g	Max 1.5 g
		1.0 g				

Data From Bass JBJ, Farer LS, Hopewell PC, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. Am J Respir Crit Care Med 1994;149:1359–74.

^a Children <12 y of age

^b Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (<8 y of age). Ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or susceptibility is likely.

however, it is often difficult to obtain adequate material for microbiologic diagnosis, which results in postponement of therapy and increased mortality. Some experts suggest that empiric therapy should be instituted less reluctantly in elderly patients with suspected but not proven active TB despite the fear of increased hepatic toxicity in this age group [49].

The largest and most comprehensive study of isoniazid-related hepatitis was conducted by the US Public Health Service between 1971 and 1972 [37]. In this survey, nearly 14,000 persons who received isoniazid were monitored for the development of hepatitis. The overall rate of probable isoniazid-related hepatitis was 1%, but it was age related, with no cases occurring among persons younger than age 20 and the highest rate (2.3%) occurring among persons older than age 50. An association of hepatitis also was found with alcohol consumption, with rates being four-fold higher among persons who consumed alcohol daily than among those who did not consume alcohol.

Studies of isoniazid-related fatal hepatitis have estimated that the overall death rate among patients on single-drug isoniazid chemoprophylaxis is 4.2 to 7 per 100,000 persons [50]. For those over age 35, the overall death rate is 1/43,334 or 0.002% [51]. Studies on hepatotoxicity caused by three-drug regimens in elderly patients have also been performed. Van Den Brande et al [49] studied 131 patients receiving treatment for pulmonary TB with isoniazid, rifampicin, and ethambutol; subjects who had apparent hepatic disease were

excluded. Increased transaminases occurred in 38% of the patients older than age 60 ($n = 64$) versus 18% among younger patients ($n = 67$). One patient, who was over age 65, died of hepatotoxicity for a fatality rate of 1.5% among those over age 65.

Current guidelines state that adults receiving treatment for TB should have baseline measurements of liver enzymes and be monitored clinically for adverse reactions during the treatment period. All patients with abnormal baseline tests should have follow-up of these findings. Routine laboratory monitoring for toxicity in people with normal baseline tests is generally not necessary; however, if symptoms suggesting drug toxicity occur, appropriate laboratory testing should be performed to confirm or exclude such toxicity [48].

Summary

As the result of the strengthening of TB-control programs nationwide, a decline in the overall number of reported TB cases in the United States has been observed within the last 10 years. Despite these declines in absolute numbers, the elderly continue to account for a disproportionate share of the cases. The high number of cases diagnosed at autopsy among the elderly suggests that this condition often remains unrecognized, possibly due to the subtle clinical manifestations in this age group. Evidence suggests that, compared with their community-dwelling counterparts, the institutionalized elderly are at a greater risk for re-activation of latent TB and for the acquisition of new TB infection. More studies are needed to make final conclusions. New guidelines for the treatment of LTBI emphasize targeted TST among persons at high risk for development of active TB and no longer use age as an exclusionary condition. All nursing home residents must therefore be regularly screened for LTBI and treated if necessary. Even though elderly persons are at greater risk for hepatic toxicity from TB treatment, the poor outcome of untreated TB in this age group warrants more aggressive treatment of this condition.

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