Tuberculosis in the elderly: Keep a high index of suspicion

July 01, 2006 | Geriatrics [1]
By Edward D. Chan, MD [2]

Abstract: Elderly persons with active tuberculosis may present with the classic features, such as cough, hemoptysis, and fever, but some patients present with less typical signs, such as hepatosplenomegaly, liver function abnormalities, and anemia. A high index of suspicion is required when a patient presents with cough or pneumonia unresponsive to conventional therapy. Acid-fast smear and mycobacterial culture of a sputum specimen are recommended for diagnosis. For an elderly patient who tests positive with purified protein derivative, 9 months of isoniazid prophylaxis is recommended. For patients who are intolerant of isoniazid or have been exposed to or infected by an isoniazid-resistant strain, rifampin single-agent preventive therapy may be an effective alternative. (J Respir Dis. 2006;27(7):307-315)

Several epidemiologic features differentiate tuberculosis (TB) in the elderly from TB in younger adults. First, case rates for active TB are higher in the elderly, despite the fact that reactivity to tuberculin decreases with increasing age. For example, in a study from Arkansas, 53% of persons with TB were older than 65 years, despite the fact that this age group represented 14% of the population.

The high rate of active TB in the elderly is explained in large part by the greater prevalence of latent infection with Mycobacterium tuberculosis in this population. Case rates of active TB are higher in the elderly because the reactivation rate is increased as a result of waning cell-mediated immunity from aging, cancer, and immunosuppressive drugs. Second, TB case rates are 4 times higher for residents of nursing homes than for elderly persons living at home (234 versus 60 cases per 100,000, respectively). The increased risk in nursing home residents is likely caused by associated illnesses that predispose them to reactivation TB and by increased transmission in the clustered environment. In fact, it has been estimated that for every case of active TB in a nursing home, 6 additional residents will be newly infected. However, since only a small minority of the geriatric population lives in nursing homes, most elderly patients with TB are not nursing home residents.

Finally, mortality rates from TB are highest in the elderly. Between 1979 and 1989, patients aged 65 years or older accounted for 60% of deaths from TB, a rate 10 times higher than that of young to middle-aged adults.

In this article, we review the presentation and diagnosis of TB in the elderly, and we delineate treatment options. Age-related changes in immunity

Elderly persons are at increased risk for infectious diseases as a result of senescent changes in the immune system. Although a decline in innate (neutrophil-mediated) immunity and specific (lymphocyte-mediated) immunity has been observed in the elderly, it is frequently not clear whether the defect is primary or secondary to an underlying systemic disorder or to the use of immunosuppressive drugs. Diet and exercise may also influence age-related changes in immune response.

In terms of innate immunity, macrophage function (including chemotaxis, adherence, and phagocytosis) appears to be largely unaffected by aging. Tests for natural killer (NK) cell function in humans show little if any age effects, although data from mouse studies are conflicting. In contrast, neutrophil chemotaxis and respiratory burst appear to be impaired with aging. The adaptive immune system, especially cell-mediated immunity, appears to be most vulnerable to the effects of aging, as evinced by:

- Reduced thrombopoietin and involution of the thymus.
- Diminished delayed-type hypersensitivity response caused by decreased T-cell proliferation.
- Loss of memory T-cell function.
- Decreased number of helper T cells and increased number of T suppressor cells.
- Reduced interleukin (IL)-2 production and IL-2 receptor numbers.
- Increased reactivation of TB and herpes zoster in elderly persons.

Success in controlling M tuberculosis infection depends on the ability of CD4+ T cells, and to a lesser
extent CD8+ T cells, to initiate an immune response by producing interferon-g (IFN-g), a cytokine that activates alveolar macrophages. Activated macrophages secrete additional cytokines IL-12 and tumor necrosis factor α, which slow the growth of the pathogen and help contain the bacilli within granulomas.

It is likely that this decline in CD4+ T cell-mediated response is the principal reason elderly patients are more susceptible to TB. Other factors that may predispose elderly persons to reactivation and primary TB include altered mucociliary clearance; malnutrition; increased risk of exposure for residents of group homes; and the greater prevalence of associated diseases, such as malignancies, that negatively affect immune surveillance.

Experimental studies in mice have corroborated that the aging immune system is less able to defend against *M tuberculosis*.15 Old mice are less able than young mice to mount an antigen-specific CD4+ T cell-mediated response against *M tuberculosis*. Orme16 found that old mice were unable to control the growth of *M tuberculosis* administered intravenously and were more susceptible to disseminated disease, especially in the lung, spleen, and liver. This may be partly the result of slower kinetics in the recruitment of CD4+ T cells to the site of infection.17,18

Poor T-cell migration may be the result of the failure of CD4+ T cells to alter the expression of adhesion molecules (particularly the integrin α chain) on their cell surfaces in response to *M tuberculosis*. Antigen-specific CD4+ T cell responses are also significantly reduced in old mice.15 In addition, old mice synthesize less IL-2 in response to infection, which results in diminished CD4+ T cell proliferation in the lungs during *M tuberculosis* infection.17,19

In contrast, old mice challenged with low-dose *M tuberculosis* via the respiratory route were able to control mycobacterial growth in the first 21 days after infection. In fact, the early effective response by old mice surpassed that of young mice.17,20 This early response is dependent on resident CD8+ T cells. In old mice, these cells are found in greater numbers both before and during infection with *M tuberculosis*, and they play a different role in the lungs. Because the response of CD4+ T cells is delayed, old mice rely on CD8+ T cells to control bacterial loads in the early stages of infection.21-23

CD8+ T cells secrete IFN-g much earlier in infection in old mice than in young mice. Old mice that had impaired ability to produce IFN-g were unable to express early resistance to *M tuberculosis* in the first weeks of infection.24 Thus, CD8+ T cells allow old mice to rapidly respond to infection; however, this response is not antigen-specific.

CD8+ T cells in the lungs of old mice had increased expression of several NK-associated molecules, allowing them to mount what is probably an antigen-independent response against *M tuberculosis*-infected cells; over time, however, the bacterial loads increased, surpassing those seen in young mice.20 The old mice have early resistance to respiratory infection with *M tuberculosis* but cannot sustain this resistance, resulting in increased susceptibility over time. This increased susceptibility is the result of the differences in the inherent properties of the cells in the lungs of old and young mice.Purified protein derivative testing

In men, reactivity to purified protein derivative (PPD) drops from 50% at age 65 to 74 years to 10% at 95 years or older; the corresponding decline in women is from 40% to about 5%.4 PPD reactivity rates are higher in nursing home residents. This appears to be the result of more than simply the reactivation of disease.25 Potential explanations include unrecognized nosocomial spread of TB in a clustered environment, earlier demise of anergic patients, improvement in nutrition and general health after admission, and a delayed or booster effect.2

The rate of PPD reactivity for patients at the time of admission to a nursing home (including a booster, if necessary) is only 10% to 15%. However, general screens of residents find higher rates, ranging from 20% to 51%,25-27 and when serial testing is performed, annual PPD conversion rates are high. For example, PPD conversion occurred in nearly 5% of 642 nursing home residents over 1 year in the absence of an outbreak of disease.26 In a study of 9937 PPD-negative patients, annual conversion rates were 5% in residents of nursing homes with recognized infectious cases and 3.5% in residents of nursing homes without recognized cases.2

The unrecognized nosocomial spread of disease is thought to be the major reason for skin test conversion. However, investigators in Belgium demonstrated a progressive booster response with 4-stage testing, suggesting that delayed-type hypersensitivity may be recalled.28 Because of the high rate of conversion in the absence of symptoms, a 2-step approach is recommended on admission to a nursing home; if the initial result is negative or equivocal, the tuberculin test should be repeated 1 to 2 weeks later.29,30

A "positive booster effect" is defined as an increase of 6 mm or more for an induration of less than 10 mm on the first test to 10 mm or more on the second test. This information at baseline helps
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Pulmonary TB is the most common form of TB in the elderly. The clinical presentation is similar to that seen in younger persons and includes cough, weight loss, hemoptysis, and fever. However, atypical clinical presentations can delay the diagnosis. In one series, patients aged 65 years or older were significantly less likely to have the cardinal symptoms of hemoptysis, fever, and night sweats. Some elderly patients may present with weight loss, hepatosplenomegaly, liver function test abnormalities, or anemia.

Miliary TB is more common in elderly than younger persons and frequently is not detected until autopsy. Older patients with miliary TB may present with a protracted illness characterized by a nonspecific decline. As in younger patients, the absence of upper lobe cavitary disease may falsely lower the suspicion of TB. However, a retrospective study and a meta-analysis of 12 studies revealed no significant delay in diagnosis in the elderly. The latter study did indicate that elderly patients have a lower frequency of fever, night sweats, hemoptysis, and cavitary disease; lower serum albumin levels; and lower white blood cell counts.

In nursing home residents, the clinical presentation may be subtle and the risk of transmission is high. Therefore, for any patient who presents with cough or pneumonia that is unresponsive to conventional therapy, it is important to suspect TB and to send a sputum specimen for acid-fast smear and mycobacterial culture. Patel and associates reported that TB is more likely to be diagnosed by fiberoptic bronchoscopy in geriatric patients than in younger adults; up to 20% of cases were missed on sputum examination but were diagnosed by examination of smear and culture specimens obtained by bronchoscopy. This may reflect the belief that the elderly have more difficulty in expectorating sputum.

Prophylaxis and treatment

In an elderly patient with a positive PPD test result, the annual risk of active TB is 2% to 3%; in known recent converters, the risk is significantly higher—7.6% for women and 11.7% for men. Isoniazid prophylaxis is recommended for these patients (5 mg/kg/d [maximum, 300 mg] or 15 mg/kg [maximum, 900 mg] twice weekly).

In a study of 1935 nursing home residents who had risk factors for TB, isoniazid prophylaxis offered 85% protection against infection. When isoniazid was given specifically for skin test conversion, it offered 98.4% protection and improved survival. In this cohort, 7% to 12% had drug toxicity, defined as an aspartate aminotransferase (AST) level greater than 500 U/L, or intolerance.

PPD conversion is defined as an increase in induration of 10 mm or more within a 2-year period, regardless of age. In addition to recommending isoniazid preventive therapy for PPD-converters, the American Thoracic Society recommends isoniazid based on the following PPD reactions:
- An induration of 5 mm or more for those infected with HIV, those in close contact with an infected person, and persons with fibrotic lesions (consistent with prior TB) on a chest radiograph.
- An induration of 10 mm or more for injection drug users who are HIV-seronegative and persons with a condition that increases their risk of active disease. These conditions include diabetes mellitus; prolonged treatment with corticosteroids or immunosuppressive therapy; Hodgkin disease or leukemia; end-stage renal disease; and conditions associated with chronic malnutrition, including intestinal bypass surgery, the postgastrectomy state, chronic peptic ulcers, malabsorption syndromes, chronic alcoholism, and cancers of the oropharynx and upper GI tract.

Nine months of isoniazid prophylaxis is recommended. It is important to monitor for the risk of isoniazid-associated hepatitis, defined as symptoms consistent with hepatitis; AST levels 5 times greater than normal levels; and resolution of signs and symptoms of hepatotoxicity after withdrawal of isoniazid. This risk is 0.1% in persons younger than 35 years and about 0.2% to 0.3% in persons aged 35 years or older. Risk increases with age, current alcohol use, ingestion of other hepatotoxic drugs, and chronic hepatitis B or C.

For the standard isoniazid regimen for latent TB infection, baseline and follow-up liver function tests are not routinely indicated, except for persons who are HIV-positive, are pregnant, have a history of chronic liver disease, or regularly imbibe alcohol. Patients should be evaluated monthly to determine their adherence to the regimen and uncover any symptoms suggestive of hepatitis. Patients should abstain from consuming alcohol and other potential hepatotoxins.

Patients should be monitored for clinical signs of hepatitis, such as fever, fatigue, nausea, vomiting, and jaundice. Mild elevations of hepatic transaminase levels are common; in the absence of symptoms, patients do not necessarily require interruption of medication. Fulminant, life-threatening hepatitis may rarely occur. If AST and alanine aminotransferase levels are 5 times greater than the upper limit of normal or 3 times greater than normal with compatible symptoms, then isoniazid...
Experience suggests that rifampin single-agent preventive therapy (600 mg once daily for 4 months) may provide an alternative for persons intolerant to isoniazid or those exposed to or infected by an isoniazid-resistant strain. Treatment of latent TB infection resulting from a presumed multidrug-resistant strain of M. tuberculosis has not been prospectively studied and is thus controversial. An unacceptably high risk of hepatitis (about 25% to 32%) was documented in high school students and teachers in Orange County, California, and in health care workers in the Bronx, New York, who were treated with ofloxacin and pyrazinamide after being exposed to multidrug-resistant TB (MDRTB).

HIV-negative persons can be treated with at least 2 drugs to which the isolated strain is susceptible, or they can be observed for the development of active TB. HIV-positive persons should be treated with at least 2 drugs to which the strain is susceptible, because the risk of progression to active TB in this population is so high. Alternatively, fluoroquinolone monotherapy can be considered, with the caveat that long-term efficacy data are lacking. Other recommended options include pyrazinamide and ethambutol (pyrazinamide, 25 to 30 mg/kg/d orally; ethambutol, 15 to 25 mg/kg/d orally) or a regimen containing a fluoroquinolone and ethambutol. Close monitoring of liver function is highly recommended, especially for patients receiving pyrazinamide and ethambutol.

Treatment for active TB in older patients should not be significantly altered. For patients infected with sensitive strains of M. tuberculosis, the standard regimen is still recommended: 2 months of isoniazid, rifampin, and pyrazinamide followed by 4 months of isoniazid and rifampin. For empiric treatment of infection with more resistant strains, ethambutol is added to the initial 2-month induction regimen.

Twice-weekly directly observed therapy has been advocated as an important measure to increase compliance and avoid the emergence of drug resistance. Currently, MDRTB is uncommon in elderly Americans. However, the number of cases of MDRTB will probably increase as a result of immigration from areas with high rates of MDRTB, such as Southeast Asia, China, India, Eastern Europe, Russia, and Africa.

Two pharmacologic issues, while applicable to both young and elderly patients, are particularly relevant in the elderly population:

- The prevalence of drug-drug interactions is increased in the elderly, since these persons tend to take more medications.
- The incidence of drug toxicities is higher in the elderly. This may, in part, be the result of the decreased glomerular filtration rate (GFR) that occurs with aging.

Patients who are taking multiple medications are at increased risk for drug-drug interactions. Rifampin is a potent inducer of the hepatic and intestinal cytochrome P-450 enzyme system and the P-glycoprotein transport system. Among the anti-TB drugs, therefore, rifampin has the greatest potential to affect the metabolism of other drugs (Table).

Among the first-line anti-TB drugs, rifampin is associated with an increased risk of toxicity. Although some researchers have found an increased incidence of hepatotoxicity in elderly patients receiving anti-TB drugs, others have not. For medications that are renally cleared, drug accumulation can predictably occur if age-related decreases in GFR are not considered.

Elderly patients are also more susceptible to drug nephrotoxicity because of a decreased reserve of renal function and the potential for concomitant use of other nephrotoxic drugs. Isoniazid and rifampin are metabolized mainly by the liver; their doses, therefore, must be reduced in patients with hepatic dysfunction but generally not in those patients with decreased creatinine clearance.

Pyrazinamide is hydrolyzed by liver enzymes to pyrazinoic acid, the purported antimicrobial moiety of pyrazinamide. Pyrazinoic acid is excreted primarily by glomerular filtration; therefore, pyrazinamide doses must be modified in patients with hepatic or renal dysfunction. Ethambutol is excreted mainly (about 80%) unchanged by the kidneys; therefore, the dose must be reduced for patients who have renal insufficiency.

Among the second-line agents, the aminoglycosides (streptomycin, kanamycin, and amikacin) and capreomycin are not only nephrotoxic but must be dose-adjusted for age-related decreases in GFR. The Cockcroft-Gault equation can be used to estimate creatinine clearance, a surrogate marker of GFR. The equation is calculated as creatinine clearance = (140 2 age)(weight in kg)(0.85 [for female patients])/ (72 3 plasma creatinine in mg/dL). Often, the creatinine clearance overestimates GFR by about 10% because of tubular secretion of creatinine. Serum drug levels should therefore be measured to definitively tailor correct drug dosages and prevent further nephrotoxicity.
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