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Tuberculosis and Non-tuberculous Mycobacterial Infections in Older Adults

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Tuberculosis

Epidemiology

Tuberculosis is one of the world's great public health crises. It is estimated by the World Health Organization that roughly one-third of the world's populations, or some 2 billion people, are infected with *Mycobacterium tuberculosis*, the causative agent. Over 8 million people every year will develop active tuberculosis disease, and 2 million will die as a result(1).

The vast majority of cases of tuberculosis occur in the 22 so-called high burden countries of the world. China and India contribute together nearly three million cases per year, and the remaining high burden countries are primarily poor nations with limited resources to devote to tuberculosis or health care in general. The annual incidence of active tuberculosis in these high burden countries ranges from 100 per 100,000 to as high as 1000 per 100,000(2). In contrast, rates of tuberculosis in most established market economy countries are in the range of 15-35 per 100,000, and in the United States in 2006, there were only 13,700 cases of active tuberculosis, for an incidence rate of 4.6 per 100,000. This rate is among the lowest of any country, and it represents a historical low for the United States.

In terms of sheer numbers, older patients (defined here completely arbitrarily as persons aged 65 and older) account for a significant number of TB cases in the world each year. According to the most recent statistical report from the World Health Organization, 9.8% of sputum smear positive cases of tuberculosis occur in this age group(2). Older patients account for over 234,000 cases of smear positive tuberculosis in the world. Although this is lower than for younger age groups (the mode of the age group distribution for prevalent cases is 25-34), the incident rate (cases of active, smear positive tuberculosis per 100,000 population) in the older than 65 age group is similar to most other age groups around the world.

In the United States, there is a more even distribution of tuberculosis among older age groups. In 2005, the most recent year for which data are available from the Centers for Disease Control and Prevention (CDC), 20% of all tuberculosis cases occurred in persons older than 65(3). Furthermore, incidence rates (cases per 100,000 persons) among persons in the older than 65 age group in the U.S. are the highest for any age group in this country. The incidence rate for TB among men older than 65 is just over 10/100,000 and the rate for women is just over 5/100,000. For males, this is considerably higher than the incidence rate in any other age group,

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and for females it is a slightly higher rate than observed in the 25-44 age group, which is the next highest. By way of comparison, the overall rate of tuberculosis in the United States is roughly 4.6/100,000.

Among members of all racial and ethnic minority groups, the trend toward a higher rate of tuberculosis is seen in older age groups, but the effect of age on tuberculosis incidence seems most pronounced in Asians, who in general have the highest rates of tuberculosis of all racial or ethnic groups in the U.S. There is nearly a four-fold increase in case rates in the over 65 age group (over 80 cases per 100,000 persons) as compared with the 15-25 year old cohort, for example. Even the 25-44 age group among Asians have only half the rate of tuberculosis as the over 65 group. The reasons for the much more pronounced effect of age on tuberculosis rates among Asians is not clear. Overall, the higher rate of TB in this group is probably due to the fact that many Asians have come to the U.S. from countries where TB is common, so that the rates of latent infection are quite high, but this does not explain the striking rise in rates among the older Asian population in the US.

Clinical presentation and diagnosis of tuberculosis in older adults

In general there has been an assumption that the vast majority of tuberculosis in older populations results from reactivation of latent infection. However, the determination as to whether a case is the result of reactivation of latent infection or of recently acquired infection is often inaccurate when made on clinical or radiographic grounds, as a recent molecular epidemiologic analysis of this issue has demonstrated(4). Certainly however, it is true that immune function, and in particular cellular immune function, declines with age, and there is every reason to think that older persons are in fact more susceptible to developing tuberculosis by whatever mechanism than younger persons(5,6).

The effect of age on the clinical presentation of tuberculosis has been examined in several studies, although most of these studies are several years old(7-12). Several points seem clear from these studies. Extrapulmonary tuberculosis, including miliary tuberculosis, appears to be more common in older patients. Features commonly identified in patients with tuberculosis, such as fever, cough, hemoptysis, and weight loss, appear to occur less frequently in older patients, and non-specific complaints such as fatigue, loss of appetite, or even worsening cognitive function may be presenting complaints, as is the case with many infectious syndromes among older individuals.

Pulmonary disease is still the most common manifestation of tuberculosis in older patients, but here too the clinical and radiographic presentation may be somewhat different from that typically seen in younger persons. Older patients with pulmonary tuberculosis may have relatively few symptoms, so clinicians need to have a high index of suspicion in order to make a diagnosis. In particular, for patients who have been in congregate settings such as nursing homes, clinicians should take care to obtain a history of sick contacts or other residents who have had similar respiratory illnesses.

Overall, one of the most thorough reviews of the clinical presentation of tuberculosis in older patients was a meta-analysis done by Perez-Guzmán and colleagues, in which they examined characteristics associated with tuberculosis in persons over age 60, as compared with all other age groups(13). After conducting a thorough search and review of the literature, they found that certain characteristics, including the prevalence of cough, sputum, weight loss, and fatigue or malaise were similar across all age groups. However, fever, night sweats and hemoptysis were all less common in persons over 60. Not surprisingly, co-morbid conditions such as cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease and history of gastrectomy, were all more common in older patients.

After a history and physical examination are completed, the first diagnostic examination to be performed will usually be a chest radiograph. The radiology of tuberculosis in older persons has been well-described. Certainly, upper lobe, cavitory disease is often seen in this age group, but somewhat more atypical manifestations can be seen as well. Again, Perez-Guzmán and colleagues have examined the range of radiographic findings across age groups. They found that upper lobe predominant disease was no more common in older patients than younger, but that cavities, at least as assessed by plain chest radiography, were less common.

Diagnostic evaluation

The approach to the diagnosis of tuberculosis has been extensively described and written about (14). In the United States and other resource rich countries, the diagnostic approach will generally include radiography and sputum examination by both smear and culture, whereas in resource-poor countries, radiography and sputum culture are often too expensive to be performed on a routine basis(15).

Tuberculin skin testing (TST) with purified protein derivative has a more limited role to play in the diagnosis of active tuberculosis than it does in identifying patients with latent tuberculosis infection, and this is particularly true in older individuals(16-19). In tuberculosis patients in general, TST can be negative about 20% of the time in the setting of active disease, and the skin test will be negative even more often in older patients(13). Thus, a negative TST should not be taken as strong evidence against the diagnosis of active tuberculosis in an older patient if epidemiologic, clinical and radiographic features support the diagnosis. The higher frequency of negative TST in older patients probably reflects a higher prevalence of anergy in this population due to impaired T-cell function.

More recently, interferon gamma release assays (IGRA) have been introduced as a diagnostic tool for the detection of tuberculosis(20). These tests rely on the *in vitro* production of interferon gamma by peripheral blood mononuclear cells after stimulation with *M. tuberculosis* specific antigens to identify persons who have been exposed to tuberculosis. Sensitivity of this test for active tuberculosis is also roughly 80%, although specificity for active disease (as opposed to latent infection) is considerably lower(21). As recent guidelines from the CDC point out however, IGRAs have not been evaluated thoroughly in patients at extremes of age, and at present, there seems to be little role for these assays in the diagnosis of active tuberculosis in older individuals(22).

Most studies suggest that sputum acid-fast smears are equally likely to be positive in older as well as younger patients with tuberculosis, and overall, roughly 50-60% of patients with pulmonary tuberculosis will have a positive smear. However, it is possible that older persons may be less able to produce an adequate sputum sample by spontaneous expectoration for examination. A substantial literature suggests that sputum induction is an extremely useful approach to obtaining sputum samples in patients who are unable to produce an expectorated sample, and this should be the next diagnostic maneuver in older patients with suspected tuberculosis(23,24). In general, bronchoscopy should be reserved for patients who are unable to produce a satisfactory sputum sample, even through induction, or for patients in whom substantial clinical uncertainty exists concerning the diagnosis(25). This may likely be the case in older patients in whom a diagnosis of primary or metastatic carcinoma is high on the differential list. If this is the case, a more aggressive evaluation is certainly warranted.

Treatment

The basic approach to treatment of tuberculosis in older persons is the same as in younger patients(26). Standard therapy of drug-susceptible disease consists of a two months' duration intensive phase of treatment with isoniazid (INH), rifampin, pyrazinamide and ethambutol

followed by a four month continuation phase of only isoniazid and rifampin. Vitamin B6 (pyridoxine) is usually given as a supplement to prevent the peripheral neuropathy that may occur from isoniazid-induced losses. This may be especially important in older persons, as there is evidence that dietary intake of B6 is lower in this patient group(27).

The major concerns related to treatment of tuberculosis in older age groups are those of adverse effects of drugs, as treatment efficacy should not be greatly different in tuberculosis patients as a function of age. Isoniazid is a well-known cause of drug-induced hepatitis. As many as 10-20% of patients who take INH will develop a transient rise in liver function tests (predominantly transaminases), but fortunately in most cases this rise will be transient and asymptomatic and will not require an alteration of therapy. However, serious and even life-threatening liver injury may occur as a result of INH treatment. The incidence of this is difficult to determine with precision, but may be as high as 0.1%-2.0%. Patients at higher risk for INH-induced liver damage include those with prior liver disease, and importantly, persons older than 50 years of age(28,29). In such patients, prudent practice is to obtain baseline and monthly liver function tests. Patients should also be educated about the signs and symptoms of liver damage, and should be encouraged to report promptly to their physician any of these complaints. Rifampin and pyrazinamide also may be associated with liver injury, and the same caveats apply.

Ethambutol is in general a safe and well-tolerated drug. The major adverse effect of this drug is ocular toxicity, with optic neuritis, and impairment of visual acuity and color vision. This is generally quite uncommon at dose ranges in current clinical use (generally 15-25 mg/kg). In general, it is felt that much of the ocular toxicity caused by ethambutol is reversible. However, some reports indicate that ocular changes caused by ethambutol may be more frequent, and less reversible, in older patients(30). As most patients with tuberculosis will receive ethambutol for only 1-2 months, the risk of serious injury is probably still quite low, but visual acuity and color vision should be monitored monthly in patients on prolonged ethambutol-containing regimens. The problem of ethambutol ocular toxicity may be much greater in patients treated for non-tuberculous mycobacterial infections, as treatment in these cases is prolonged(31).

Non-tuberculous mycobacteria

A discussion of syndromes caused by infection with all the numerous species of non-tuberculosis mycobacteria (NTM) is beyond the scope of this chapter. Instead, the discussion will largely focus on disease caused by *M. avium* complex, as this is the most frequently encountered of the NTM in clinical practice.

Epidemiology

The epidemiology of infection and disease caused by NTM in general, and *M. avium* complex organisms in particular, is difficult to describe with the same precision as that of tuberculosis, for several reasons. First and most significant is the fact that NTM infections are not reportable in the U.S., as they are generally not felt to be communicable diseases whose severity warrants a major public health response. Secondly, there has often been confusion (and undoubtedly, a great deal of this confusion persists today) regarding issues of colonization, infection and disease in patients from whom NTM have been isolated. There has been a lack of consensus regarding the definition of clinical syndromes due to NTM, and there is great heterogeneity among reports and case series of these conditions. As a result, there is considerable uncertainty regarding the true epidemiology of disease caused by NTM. A recent statement by the American Thoracic Society notes that in industrialized countries the rate of disease due to NTM is felt to be in the range of 1.0-1.8/100,000, but the statement also notes that in most mycobacteriology laboratories, isolation of NTM is now more common than isolation of *M. tuberculosis*(32). In the U.S. the rate of TB is 4.6/100,000, so there appears to be a discrepancy

between the number of positive NTM cultures and the number of patients diagnosed with disease. A very recent survey based on skin testing with NTM antigens suggests however that 1 in every 6 Americans is now exposed to NTM, as opposed to 1 in 9 about 30 years ago(33).

NTM appear to be widely distributed in the environment, and soil and water represent natural reservoirs for these organisms(34-37). It is generally felt that there is little if any human-to-human transmission of NTM. In recent years, it appears that there may be an increase in the number of persons with NTM infection, and there may be several reasons for this. First, better culture methods, primarily using broth-based systems, have been employed in more and more laboratories, and there is evidence that these systems are more sensitive than solid media-based systems for recovering NTM(38). Thus to a certain extent, the increase in cases of disease due to NTM may be partially an artifact of better detection. However, there are also reasons to think that exposure to NTM may in fact be higher and that the increase in cases may be real. Cultural shifts from bathtubs to showers, and more time spent in hot tubs and Jacuzzis may be associated with a true increase in infection, as these warm water sources are well-known to be reservoirs of NTM and persons using them are exposed to fine aerosols which may aid in transmission of mycobacteria.

Clinical syndromes

This and remaining sections will focus exclusively on *M. avium* complex (MAC). There are several clinical syndromes associated with MAC infection(39,40). These include hypersensitivity pneumonitis, the Lady Windermere syndrome, and bronchiectasis, and pulmonary nodules with the well-described “tree-in-bud” appearance.

Hypersensitivity pneumonitis (HP) due to MAC (occasionally called “hot tub lung”) is usually a disease of younger persons, and it will not be discussed at length here. Cases have been described in persons exposed to MAC in the settings of showers, saunas, Jacuzzis and hot tubs (41-45). The presentation is similar to other HP syndromes, and patients usually improve when they are no longer in contact with the offending antigen, in this case MAC. Treatment therefore is generally avoidance of the source of the hypersensitivity, and occasionally prednisone is added. There is some controversy about the utility of antibiotic treatment for MAC in patients with hot tub lung, but it appears that most patients will improve without this.

More important in older patients are the syndromes of bronchiectasis and pulmonary nodules (often in the “tree-in-bud” pattern noted above) which are well-known to pulmonary physicians but which also pose great challenges of diagnosis and treatment. The term “Lady Windermere syndrome” was first used in 1992 by Reich and Johnson to describe 6 older women who presented with right middle lobe or lingular infiltrates and evidence of infection with MAC (46). The name they assigned to the syndrome was drawn from a play by Oscar Wilde, and was chosen to reflect the authors' contention that the patients in their series had voluntary suppression of cough, a behavior they ascribed to Wilde's character. Since that initial description, the entire spectrum of MAC pulmonary disease in apparently immunocompetent hosts has been increasingly recognized.

The symptoms of pulmonary disease cause by MAC in immunocompetent patients are exceedingly non-specific. Cough, dry or productive of sputum, is the predominant complaint, but patients also often note fatigue and malaise, weight loss, non-specific chest pain, and fever.

Plain chest radiographs may mimic tuberculosis quite closely, and TB must be excluded as a diagnostic possibility. Computerized tomography (CT), particularly using the high-resolution technique (HRCT), has dramatically altered the understanding of pulmonary disease caused by MAC, and this is an extremely helpful tool in the evaluation of patients with *M. avium* complex in respiratory secretions. HRCT studies demonstrate that disease is generally more

diffuse than generally appreciated on the basis of plain chest radiographs(47-49). In addition, HRCT studies often demonstrate what have come to be viewed as characteristic findings of MAC infection, namely, multiple small nodules and associated bronchiectasis(48,50,51). The nodules are usually numerous and smaller than 1 cm in diameter. However, they occasionally can be larger and in older patients with a history of tobacco use, there is often a question of whether one nodule among many could represent a malignancy.

Diagnosis of *Mycobacterium Avium* Complex

The diagnosis of pulmonary disease in patients with MAC has been the source of some controversy, which has mainly focused on the issue of differentiating infection (or colonization) from disease. The recently revised ATS statement on NTM requires both clinical and microbiologic criteria to be met(32). The criteria are as follows:

1. Clinical:
 - a. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a HRCT scan that shows multifocal bronchiectasis with multiple nodules

AND

 - b. Appropriate exclusion of other diagnoses (particularly TB and malignancy)
2. Microbiologic
 - a. Positive culture results from at least two separate expectorated sputum samples

OR

 - b. Positive culture result from at least one bronchial wash or lavage

OR

 - c. Transbronchial or other lung biopsy with granulomatous inflammation or AFB and positive culture from bronchoscopy or sputum

However, the most important aspect of the new ATS guidelines is the following statement: "Making the diagnosis of NTM lung disease does not, *per se*, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients." In fact, it is the feeling of the author that diagnosis has been somewhat overemphasized until recently, when the most difficult issues center around treatment.

Treatment of *MAC* pulmonary disease in older patients

The decision to initiate therapy for MAC disease, particularly in older patients, can be an extremely difficult one. The beneficial effects of therapy are uncertain, and there are considerable adverse effects associated with the drugs commonly used to treat these infections.

The most commonly used regimen in the treatment of pulmonary MAC disease in the immunocompetent host consists of a rifamycin (usually rifampin or rifabutin), a macrolide (clarithromycin or azithromycin) and ethambutol. There have been efforts to rely on regimens that substitute agents such as clofazimine for rifamycins in an effort to reduce toxicity of treatment, but the published experience with these approaches is limited(52). Unlike treatment of tuberculosis, reliance on drug susceptibility testing is of much less certain value in developing a treatment regimen for MAC, with the possible exception of testing for macrolide susceptibility.

Several small studies have been published which describe outcomes, mostly microbiologic, in patients treated with macrolide-containing regimens, which are generally felt to be the most potent for treating these infections(53-58). These studies, taken together, establish that drug susceptibility testing results have meaning for use of macrolides, but probably not for other agents. They also suggest that sputum culture conversion can be achieved in a majority of patients whose isolates are in fact susceptible to macrolides, but little in the way of meaningful long-term clinical response and outcomes can be gleaned from these reports.

Recently, a larger experience was reported on the outcomes of MAC patients treated with the three drug regimen of a macrolide, rifamycin and ethambutol. Lam and colleagues described results of patients with pulmonary MAC who were treated as the control arm of a study designed to examine the role of adjunctive immunotherapy with interferon gamma(59). In this study, 91 patients with pulmonary MAC (diagnosed according to the ATS guidelines) were treated with a thrice weekly regimen of clarithromycin (or azithromycin), ethambutol, and rifampin (or rifabutin). Patients with HIV infection were excluded from the study, as were patients with cystic fibrosis, sarcoidosis, or malignancy. Patients underwent rigorous clinical, radiographic and bacteriologic assessments, and sputum samples were collected frequently throughout the study.

The mean age of patients enrolled in the study was 60.9 years for those with cavitary disease and 67.8 years old for those without. Most patients had a history of prior bronchiectasis and COPD, and bronchiectasis and nodules were common findings on HRCT. Patients had evidence of moderate airflow limitation on pulmonary function testing, with a mean FEV₁/FVC of 61% in the cavitary group and 66% in the non-cavitary group. Dyspnea was reported by most patients, and a quarter to one half reported consistent sputum production. Overall, this patient group was representative of sicker patients with MAC, and most clinicians would agree with treatment.

Results from this study were revealing. Overall, with culture conversion defined as going from a positive to a negative culture, only 13% of patients with baseline positive cultures overall had a satisfactory response (4% in the cavitary group and 24% in the non-cavitary group). Overall, the study reported that 60.4% of patients had improvement in HRCT findings of disease, and 52.5% had symptomatic improvement. These benefits were not immediate however. Mean time for HRCT improvement was between 164 and 340 days, depending on the presence of cavities, and the mean time for symptom improvement was 252 days. Adverse events were very common in the study. Over 90% of patients reported at least one side effect, with nearly a third of subjects reporting nausea.

What can this and other studies teach us about the treatment of MAC pulmonary disease in this relatively older (and certainly representative) cohort of patients with more severe disease? On the whole, bacteriologic response rates were low, and radiographic and clinical improvement was modest and often took a long time to achieve. Side effects were common. These data are helpful in framing expectations about treatment responses in patients with pulmonary MAC, but they also raise further questions. The study was limited by the lack of an untreated control group. Is it possible that symptomatic therapy alone (chest physiotherapy, drainage maneuvers and assists, bronchodilators) would have achieved similar results, without the antibiotic therapy. Also, what about patients who have less advanced disease? Would results be better or worse? It is not uncommon for pulmonary physicians to encounter patients well into their 70s who have cough and sputum cultures positive for MAC, but fairly localized bronchiectasis or a few nodules on HRCT, and normal or near normal pulmonary function. My own approach to such patients is generally not to institute triple antibiotic therapy with the attendant side effects, but rather to follow them closely and only to implement drug treatment if there is a marked change in clinical or radiographic status. In general, rifampin-containing regimens are

better tolerated in older patients than rifabutin-containing regimens, and intermittent (thrice-weekly) therapy also seems better tolerated, and perhaps no less efficacious, than daily therapy (60).

Conclusion

Mycobacterial infections remain extraordinarily common around the world, and older persons are particularly vulnerable. Tuberculosis can be diagnosed and treated in a straightforward way in the majority of instances, but infections with non-tuberculous mycobacteria pose greater challenges. Treatment of these latter infections is often associated with significant adverse effects and uncertain clinical outcomes. Physicians' judgment has an important role to play in selecting patients for treatment and in choosing an optimal drug regimen.

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