Review Article

Update on Pulmonary Tuberculosis

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Introduction:

Tuberculosis (TB), which is caused by a complex of organisms, Mycobacterium tuberculosis, Mycobacterium bovis, and Mycobacterium africanum, is an ancient human disease, evidence of TB can be found in human remains dating back to Neolithic times.[1]

Tuberculosis remains a pressing global public health problem. Millions die of TB annually in spite of the availability of highly effective therapy, a trend toward increasing tuberculosis morbidity worldwide, particularly in association with AIDS, this trend is especially prevalent in developing countries.

TB bacilli are a small, rod-shaped, aerobic bacillus that does not form spores. Globally, TB remains a leading infectious cause of morbidity and mortality. The incidence of TB increased worldwide in 2003 but it remained stable or decreased in several regions, including Latin America and Central Europe, incidence remains high in Eastern Europe and eastern and southern Africa, where rates of HIV infection are also high.[2] TB rates in some Asian and sub-Saharan African nations have increased to more than 300 cases per 100,000 people, in some of these areas, nearly 50% of the HIV-infected population is co-infected with M. Tuberculosis.[3]

Pathophysiology:

The development of TB begins with inhalation of the M. tuberculosis organism within airborne droplets expelled by an infected individual during coughing, sneezing, or talking. If the organism bypasses the nasal turbinates and bronchial mucociliary defenses and reaches the alveoli, it can replicate locally and spread throughout the body through the blood and lymphatic systems.

In the majority of people with healthy immune systems, alveolar macrophages engulf the tubercle bacillus and release a substance that attracts T lymphocytes. Prior to this point, the bacillus has the potential to disseminate to the kidneys, bones, meninges, and other sites where there is a possibility of reactivation year's later.[4]

Latent TB infection occurs when an individual becomes infected with the TB bacillus, but does not become acutely ill. For any number of reasons, the individual may not be able to eliminate the infection without taking anti-TB medications. A person with latent TB is asymptomatic and cannot spread the infection to others, but will demonstrate a positive Mantoux intracutaneous test using purified protein derivative (PPD). The risk of reactivation of active disease is greatest among those with HIV disease or other immunosuppressive illnesses or conditions, the elderly, and organ transplant recipients. TB may,

In fact, be one of the most common HIV-related opportunistic infections.[5]

A single cough can generate 3000 infective droplets. Fewer than 10 mycobacterial bacilli may initiate a pulmonary infection.[6]

Roughly 80% of TB cases involve pulmonary disease, though TB can involve any organ system. In patients who are severely immunocompromised, extrapulmonary disease and atypical presentations are common.

Treatment markedly reduces infectivity. The first dose of medication reduces the bacillary load 10-fold. Therapy for 2 weeks reduces the bacillary load by a 100-fold factor.[7] Patients require 3 negative sputum samples to be considered noninfectious, which usually necessitates treatment for 4 weeks.

Clinical Presentation:

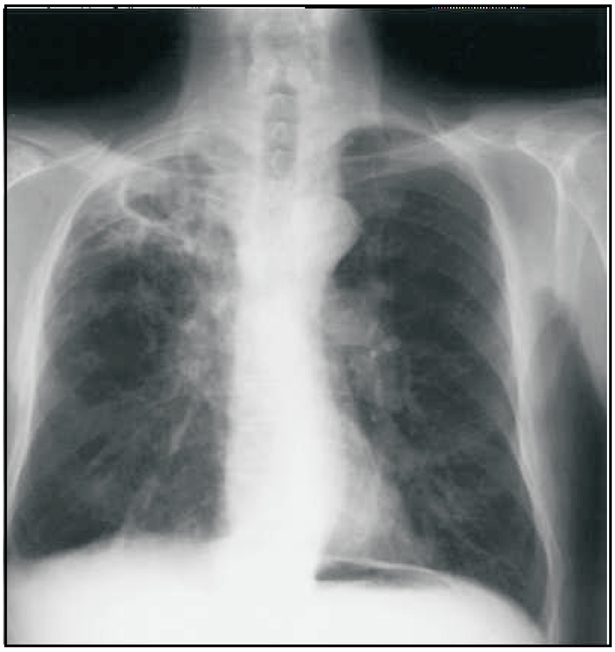
Generalized symptoms, including fever, night sweats, malaise, and weakness, anorexia, and weight loss accompany TB infection. Fever is seen in 40% to 80% of patients with pulmonary TB but is less common in elderly patients.[8] Anorexia and weight loss are equally common in all age groups but are often overlooked or attributed to another cause in geriatric patients .[9]

Active pulmonary TB may begin with isolated constitutional symptoms; however, cough eventually develops in most patients. Initially mild and nonproductive, cough from active pulmonary TB can become continuous and productive without treatment. In this later stage, cough may be associated with hemoptysis that is usually mild but, rarely, can be massive as a result of ecstatic blood vessel rupture in the wall of a TB cavity (Rasmussen aneurysm). Dyspnea is uncommon without extensive parenchymal involvement or preexisting lung disease.[8] Pleuritis is also uncommon but suggests extension of the inflammatory process to the pleura and may be associated with pleural effusion and, rarely, empyema.

Other than localized auscultatory changes over the involved areas of the lung, the physical examination findings and routine laboratory test results are nondiagnostic with rare exception. Immunologic phenomena, such as clubbing, erythema nodosum, and erythema induratum, may occur infrequently as a result of active pulmonary infection.

Hyponatremia related to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), an elevated sedimentation rate, and hypoalbuminemia are other nonspecific laboratory findings that may be seen.[1]

In the early stages of disease, the clinical manifestations of TB in people infected with HIV may be indistinguishable from those in people with competent immune systems. As the T-lymphocyte population declines in HIV-infected individuals, however, TB follows a predictable and devastating course. Extrapulmonary involvement occurs in the majority of HIV-infected individuals, and it may take on an exotic form such as diffuse lymphadenitis or



Chest radiographs (TB cavity)

recommended cutoff level of skin induration indicating tuberculin positivity is 10 mm.

Low-risk people are those with no risk factors for TB; in this group, the recommended cutoff level of skin induration that indicates tuberculin positivity is 15 mm, A tuberculin skin test conversion is now defined as an increase of 10 mm or more of induration within a 2-year period, regardless of age.[11] Even when clinical TB is present, the tuberculin skin test will be falsely negative in up to 25% of cases.[10]

New tests for latent TB infection, however, are being established.[14] Knowledge about the important role of T lymphocytes and interferon gamma (IFN-γ) in TB has led to the development of in-vitro diagnostic assays to detect tuberculosis infection. A peripheral blood sample from the patient is collected and incubated overnight with mycobacterial antigens. The amount of IFN-? produced is then assessed. The use of mycobacterial antigens such as early secreted antigen 6 (ESAT 6) and culture filtrate protein 10 (CFP-10) that are present in M. tuberculosis but not in BCG or most other nontuberculous mycobacteria, enhances the specificity of these new tests. In-vitro assays also offer the advantages of being performed in a single visit, have little interobserver variability and no boosted responses on repeated testing.[15] This antigen-specific testing has been used in human populations and has been effective in differentiating between tuberculosis infection and prior BCG vaccination or exposure to nontuberculous mycobacteria with a sensitivity of 89% and a specificity of 98%.[16]

Active Tuberculosis:

The gold standard for the diagnosis of TB is the demonstration of Mycobacterium tuberculosis on smear or culture. The major limitations of smear microscopy are its low sensitivity. At best, only 50 to 70% of patients with TB are sputum smear positive. Traditional culture techniques on solid media are more sensitive than smear microscopy but require several weeks to 2 months to demonstrate the presence of M. tuberculosis. Enriched liquid culture methods such as the BACTEC™ 460 TB methods that detects radiolabeled $^{14}CO_2$ released from the media by replicating bacilli and the simple Mycobacterial Growth Indicator Tube (MGIT) system are now more widely used and can often provide more rapid results.[17]

Perhaps the most promising novel diagnostic techniques involve the use of nucleic acid amplification methods to identify M. tuberculosis.[18] In one study done in Kenya, the sensitivity of PCR-based diagnosis was found to be 93% while the specificity was 84%.[19] .Nucleic acid amplification tests have a sensitivity of 84 to 92% in sputum smear positive patients and 41 to 75% in smear negative patients with an overall specificity of 96 to 99%.[20]

Testing urine and the serum to detect antigens of M. tuberculosis or patient antibodies to mycobacterial antigens or combinations of antigens has also been proposed as a potential diagnostic tool for TB, but to tubercle bacilli and may enter human testing soon.[32]

Multidrug -Resistant Tuberculosis:

Multidrug-resistant TB occurs when resistance develops to two or more anti-TB drugs, specifically isoniazid and rifampin.

Multidrug-resistant TB can be classified as primary (initial) or secondary (acquired). Primary resistance occurs with the detection of drug resistance in a patient with TB who has never been treated with anti-TB medications. This may occur as a result of random, spontaneous genetic mutations, as is the case with any large population of bacteria, regardless of their exposure to antibiotic agents, or through initial infection by drug-resistant TB. Secondary Multidrug-resistant TB occurs when drug-resistant organisms develop as a result of the inappropriate use of anti-TB medications or patient noncompliance with the prescribed therapy. This definition presumes that the patient was initially infected by drug-susceptible organisms.[33]

The only way to diagnose MDR-TB is by drug susceptibility testing.[34] Conventional methods require growth of mycobacteria in solid culture, which can take up to 2 months, but recent studies using molecular methods such as line probe assays, molecular beacons and PCR and phenotypic assays using luciferase reporter phase and amplified bacteriophage techniques have been promising.[35] Line probe and bacteriophage assays for rifampicin susceptibility testing are commercially available.

Treatment of MDR-TB has been increasingly successful over the last decade, with reported cure rates over 80% in many settings. This is especially true when fluoroquinolones and adjuvant surgical therapy are used.[36] Even in resource-poor settings, MDR-TB treatment has been successfully implemented and global programs to treat the disease are now expanding.[37]

Treatments in Development:

Several anti-TB drugs in development are variations of existing drugs. Nitroimidazole (PA-824)38and an ethambutol analog (SQ-109)[39] are currently being evaluated in preclinical trials. Some quinolone antibiotics, including moxifloxacin40and gatifloxacin, [41] are also being tested in clinical trials for efficacy in patients with TB. A quinolone derivative, diarylquinoline R207910, is being evaluated in early clinical trials for efficacy against TB. This agent appears to inhibit both drug-sensitive and drug-resistant M. tuberculosis, possibly because of a unique mechanism of action that targets the proton pump of ATP synthase.[42]

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