

Tuberculosis among patients Infected with Human Immunodeficiency Virus

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Abstract: Human immunodeficiency virus infection (HIV/AIDS) have given more importance to tuberculosis, which was discovered a century ago. HIV infection is the most important factor for the development of tuberculosis. Initially *Pneumocystis carinii* pneumonia among homosexual men was discovered. The risk for patients with AIDS developing TB is 170 times higher and risk for death reported to be twice that HIV infected patients without TB. HIV infection suppresses the immune system, making patients susceptible to opportunistic infections (OIs), with high mortality worldwide. Latency and reactivation of tuberculosis is similar to reactivation of *Burkholderia pseudomallei*, cryptococcosis, and histoplasmosis. Cellular immunity impairment is a predisposing factor to development of clinical disease. Patients with CD4-Tcell counts (>200-300 mm³) generally will have classic TB, with apical cavitory lung disease, respiratory symptoms, fevers weight loss. TB may accelerate the progression of HIV infection by activating expression of HIV from macrophages and immune reconstitution syndrome (IRIS). Patients with advanced pretreatment immunodeficiency had persistently increased risk of TB during HAART, this may reflect limited capacity for immune restoration among such patients. Four drugs are recommended e.g., INH, 330 mg orally, rifampin, 600 mg orally daily, pyrazinamide 20 to 35 mg/kg orally daily, and ethambutol 15 to 25 mg/kg daily. Frequent treatment for MAC include macrolides, with rifampin or ciprofloxacin added. CDC recommendations for diagnosis, treatment and prevention of HIV-TB coinfection are beneficial.

Keywords: Tuberculosis, HIV infection, Pathogenesis, and Treatment

I. Introduction

In 1882 Robert Koch discovered *Mycobacterium tuberculosis*. There is evidence of spinal tuberculosis in Neolithic, pre-Columbian and early Egyptian remains. In the early 17th and 18th centuries, tuberculosis caused one fourth of all deaths in Europe. The modern era of tuberculosis began in 1946 with the demonstration of the efficacy of streptomycin (STM), and the availability of isoniazid (INH) in 1952, made tuberculosis curable in most patients and addition of rifampin (RMP) in 1970 allowed for even more effective combination therapy [1]. Tuberculosis (TB) continues to be a devastating disease worldwide, It is estimated to cause 3 million deaths annually [2]. In 1981, initially five cases of *Pneumocystis carinii* pneumonia among homosexual men were diagnosed and reported by the clinical investigators [3]. Acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 [3]. Human Immunodeficiency virus infection (HIV) is far by the most important predisposing factor for the development of TB. Experts believed that TB accounted for 30% of 5.0 million AIDS-related deaths in the year 2000 [4]. The risk for a patient with AIDS developing TB is 170 times higher than for a non-immunocompromised person. The risk for death in HIV-infected patient with TB was reported to be twice that in HIV-infected patients without TB, independent of CD4 cell count [5]. The hallmark of infection is immune suppression. Making patients susceptible to opportunistic infections (OIs) [6]. In 2013 of the estimated 9 million people who developed TB an estimated 1.1 million (13%) were HIV positive, and there were 360,000 deaths from HIV associated TB equivalent to 25% of all TB deaths, and around 25% of the estimated 1.5 million deaths from HIV/AIDS [7]. Clinical presentation depends largely on the overall immune status of the patient. Patients with CD4 cell counts (>200-300/mm³) generally will have classic TB. [8]. Diagnosis include cavitory lung disease, respiratory symptoms, fevers and weight loss, demonstrations of *M. tuberculosis* in sputum smear for acid-fast bacilli (AFB), cultures using radiometric system (BACTEC) [8,9]. The introduction of highly active antiretroviral therapy (HAART) has exerted a profound effect on the epidemiology, natural history, clinical manifestations, and responses to treatment of OIs [10]. Centers for Disease Control and Prevention (CDC) recommends early diagnosis, effective treatment of TB-HIV infected patients are critical for curing TB, minimizing the negative effects of TB on the course of HIV and preventing the transmission of *Mycobacterium*

tuberculosis to other persons in the community[9].The paper reviews the current literature, *Mycobacterium tuberculosis* infection, and treatment in the HIV/AIDS patients.

II.Epidemiology

Tuberculosis (TB) has been an affliction of humankind since before recorded history. Inspired writers such as John Bunyan to aptly describe this deadly and mysterious disease in 1660 as “the captain of all these men of death that came against him to take him to the grave”[11] In the United States, *M.tuberculosis*(MTB) infects an estimated 1.5 million persons. Tuberculosis reemerged between 1985 and 1992 and approximately 67,000 more cases occurred than would have been estimated had the earlier rate of decline continued[4].Each year since 1992 the number of tuberculosis cases have declined to 16,377 in the year 2000 for a rate of 5.8 cases per 100,000 population, and approximately 25 % to 30 % were HIV co-infected[12,13]The groups with greatest increases in rates of TB,especially black and Hispanic men 25 to 40 years of age, are also the groups with highest rates of HIV infections demonstrating how closely intertwined these two epidemics have become[9].Anonymous HIV testing of serum from TB clinics demonstrated that as many as 40% of all TB patients are HIV infected[14].This among AIDS-related OIs because it is contagious to otherwise healthy persons. This combined with several nosocomial outbreaks affecting both patients and staff [15], has led to extensive reconsideration of hospital infection control efforts [16].Finally, resistant TB has been increasing, especially in urban areas, and is particularly difficult to treat in the HIV-infected patient [17].At the same time the number of foreign-born persons with tuberculosis, and their proportion of the total cases, have continued to increase. Disease risk is highest within the first years after immigration[9].The control of tuberculosis in foreign-born individuals will be of major importance in meeting the goals for eliminating tuberculosis in U.S.[9].Tuberculosis remains tremendous problem outside United States. It is estimated that one-third of the world’s population, almost 2 billion persons, is infected with *M.tuberculosis*.For this reservoir come 8 million new tuberculosis patients and approximately 3 million deaths each year[12].Thus,95% of tuberculosis disease occurs in the developing countries, where there are few medical or public health resources and where concomitant HIV infection is common[12].

III.MTB a unique pathogen

The genus *Mycobacterium* is divided into about 30 species of which are very well characterized and defined[18].*Mycobacteria* have been isolated from various sources including soil, animal and human feces, marshland, water, including lakes,, and domestic water supplies)vegetation and human skin. Studies in Uganda indicate that distribution of saprophytic mycobacteria is dependent on the environmental conditions including ph. Although rarely causing overt infection, these environmental organisms are able to elicit an immune response in man which has been studied by means of a set of skin testing[19].The lipid content of mycobacteria may be as high as 40 per cent of the total dry weight and is mostly found in the cell wall. These lipids may play a role in the virulence of the infecting strain and second they may influence the immunological response to infection. The principal lipids encountered in mycobacteria are mycolic acids, glycolipids, phospholipids and the mycosides[20].

The *Mycobacterium tuberculosis* (MTB), contains seven species in the genus *M.tuberculosis*,family that causes human tuberculosis and zoonotic disease and *M.tuberculosis*avaincomplex (MAC) share 99.9% sequence identity and likely evolved from a single clonal ancestor[21].*M.tuberculosis* causes the vast majority of human tuberculosis.*M.bovis* causes diseases in cattle and spreads to humans through animal contacts and consumption of unpasteurized milk. A recent cluster investigation of six tuberculosis cases in the United Kingdom demonstrated that *M.bovis* can be transmitted from human to human[22].*Mycobacterium africanum* and *M.canette* are both rare cases of tuberculosis in Africa.*M.capare*,another cattle pathogen,*M.microti*, a pathogen from rodents, and *M.pinnipedi*, a pathogen from seals, have been reported to cause zoonotic tuberculosis in humans[1].Humans are the only reservoir for the species *M.tunberculosis*,although many animals are susceptible to infection[23].Some has postulated that ancient ancestors of *M.tuberculosis* infected hominids in East Africa 3 million years ago, and has since coevolved with its humans host[24].*M.tuberculosis* is an aerobic, non -spore forming,non- motile bacillus with cell wall content of high molecular weight lipids. Growth is slow, the generation time being 15-20 hours, compared to much less than 1 hour for most common bacterial pathogens and visible growth takes 3 to 8 weeks on solid media.The organism parallel, producing the colony characteristic or serpentine cording.Complete genome sequence that have been reported include the H37Rv laboratory strain of *M.tuberculosis* and XDR strains of *M.tuberculosis* and the BCG strain of *M.bovis*[25].

IV. Pathogenesis

Transmission.Humans are the only important reservoir of *M.tuberculosis*,although some animals are susceptible to this organism. Spread of *M.tuberculosis* is almost exclusively by small particle aerosols termed droplet nuclei, and rarely by contaminated dust or fomites. Airborne particles bearing organisms are generated by coughing ,sneezing, and even speaking or singing[12].Inhaled droplet nuclei, each containing two to three

bacilli, are sufficiently small size (1-5µm) to be deposited into the alveolar space [12]. Although a single organism is sufficient to infect animals, most human infections follow exposures to many more droplet nuclei and bacilli. The transmission depends on the number of bacilli expelled, their concentration in the air over time, the duration of an exposure to contaminated air, and host immunity [12].

Primary infection results from exposure to airborne organisms produced by someone with active pulmonary tuberculosis. Organisms reach the alveoli (most often in the middle or lower lung zones), multiply intracellularly in alveolar macrophages, and silently spread through lymphatics to hilar or other regional lymph nodes, and then through the bloodstream to many sites [26]. *M.tuberculosis* bacilli continue to grow at some of these sites for 2 to 12 weeks until, in an immunocompetent host, cell-mediated immunity develops [12]. At this stage granulomas are formed and growth of organisms is inhibited, they are not killed. Consequently organisms that have been dormant can become reactivated [27]. In approximately 5% of normal hosts the original infection cannot be contained and clinical disease develops rapidly or within the first two years. In the remaining 95% the original infection is controlled and remain subclinical [12].

Reactivation of primary infection. Clinical disease develops in 5% of immunocompetent persons at a time remote from the initial infection as a result of endogenous reactivation of a previously established quiescent focus [12]. The preferential sites for reactivation are those of persistently high oxygen tension. These include the superior lung segments (except anterior) kidneys, bones, and CNS [12].

Exogenous post primary reinfection occurs because protection following a primary infection is incomplete and may wane over time, even in immunocompetent patients [28]. The frequency of exogenous reinfection varies with the risk of infection [29]. With low risk, post primary tuberculosis almost always is reactivation disease [29]. However, reinfections contribute to tuberculosis in HIV-infected persons and may account for significant proportion of adult disease in areas of the world with high rates of tuberculosis [30].

Latency of Tubercle bacilli. There is a great similarity of latency or dormancy in tubercle bacilli and *Burkholderiapseudomallei* (causative agent of melioidosis). In melioidosis most disease is from recent infection, but latency with reactivation is described up to 62 years after exposure. Intracellular survival of *B.pseudomallei* in human and animal hosts is likely to explain the ability for latency [31,32]. Similar latency and reactivation of infection also been reported in cryptococcosis and histoplasmosis [33]. In tubercle bacilli there is a firm experimental foundation showing that tubercle bacilli may persist for long periods in vivo in a viable state but non-multiplying state. This state has been demonstrated in infected mice, either as a consequence of drug treatment or because of the forces of cellular immunity to infection [34,35]. Hart and Rees in some ingenious experiments, have shown that tubercle bacilli, which in vivo are non-multiplying are still fully viable [36].

Virulence factors and pathogenesis. The capacity of *M.tuberculosis* to produce progressive disease may involve certain toxic factors, such as cord factor, perhaps other lipid constituents, oxygen requirement, catalase activity and ability to solubilize iron. However, none of these, singly or together, can account completely for virulence, nor can any one or all of these account for the high virulence of certain strains, the low virulence of others, or the lack of virulence of mutants of virulent strains [37-40].

Cellular immunity and its role in pathogenesis. Cellular immunity impairment is a predisposing factor to development of clinical disease. The major host defense against *M.tuberculosis* is the macrophage-lymphocyte system, which is influenced by host genetic factors [26]. *M.tuberculosis* infection elicit a Th1-type immune response involving interferon- γ and tumor necrosis factor α (TNF- α) that activates macrophages to become more bactericidal through the generation of reactive nitrogen intermediates, and leads to granuloma formation [26,27]. The importance of TNF α has been emphasized by the recognition that use of infliximab, and anti-TNF α monoclonal antibody, is associated with the development of active tuberculosis, including extra pulmonary and disseminated disease [41]. Analogous immunologic events also are responsible for many of the clinical finding in tuberculosis [26].

Mycobacterial strain plays a role in the development of disease, but these are poorly understood. Strains vary in their ability to be transmitted and cause infection, elicit cytokines, and grow in animals and macrophages [42]. However, genetic analysis of at least one hyper transmissible *M.tuberculosis* strain has not yielded clues to strain virulence [42].

V. Clinical manifestation

Clinical manifestation depends largely on the overall immune status of the patient [8]. Patients with high CD4 counts (>200-300 mm³), generally will have classic TB, with apical cavitory lung disease, respiratory symptoms, fevers, weight loss [8]. As immunity wanes, presentations become less specific, and diagnosis become more difficult as atypical chest radiographic features and extra pulmonary TB are encountered. The most common extra pulmonary manifestations are asymmetric lymphadenopathy, pericarditis, pleurisy bone disease, and skin lesions. Fever weight loss, and fatigue may be the only symptoms with disseminated TB, mimicking lymphoma, CMV disease, AIDS wasting syndrome, MAC, and other diseases [5]. Hilar or mediastinal

adenopathy may be the primary chest radiographic abnormality. In addition, pulmonary TB may show lobar and interstitial infiltrates resembling primary TB and 10 % to 20% may have normal radiographs. Thus HIV-induced immunosuppression may result in unusual presentations and delay the diagnosis [8].

HIV/TB co-infection interact in several ways: (i) HIV-infected persons latently infected with TB develop reactivation TB at a rate of 8% to 10% per year, rather than 5% to 10% per life time[14];(ii) HIV-infected persons exposed to an infectious index case develop acute TB at a rate as high as 40% over 6 to 12 months rather than 2% to 5% over 2 years in normal host[8];(iii) TB may accelerate the progression of HIV infection by activating expression of HIV from macrophages[5];and(iv) immune reconstitution syndromes may occur.

TB is the most common opportunistic infection associated with HIV/AIDS in many parts of the world. TB causes death in 13% of AIDS patients worldwide[43]. TB is uncommon among U.S.-born patients who have not had exposure to known cases or who have not spent time in high-risk environments such as correctional facilities, shelters or drug treatment centers. TB is a special risk in patients with HIV infection because the conversion rate from latent disease to active disease is 35 to 162 per 1000 person-years of observation for patients with HIV, as opposed to 12.9 per 1000 person-years for the general population. In contrast to most other HIV-related opportunistic infections, CD4⁺ T-lymphocyte count is not a useful predictor of increased risk for disease[44]. The manifestations of TB among patients with HIV/AIDS depend on host immune status. For patients who have CD4⁺ T-lymphocyte counts higher than 350 cells/ μ L, manifestations of pulmonary disease are not substantially different from the general population. Extra pulmonary disease is more common. For patients with lower CD4⁺ T-lymphocyte counts lower lobe pulmonary disease, military disease, cavitation, effusions, adenopathy, and extra pulmonary disease are more common[45].

When HAART(ART) is initiated, a variety of clinical manifestations related to tuberculosis may occur. Soon after initiating ART, latent disease may become active, requiring specific chemotherapy. In addition, patients who initiate ART at a time when they have low CD4⁺ T-lymphocyte counts and high viral loads may manifest immune reconstitution inflammatory syndrome (IRIS). IRIS may manifest as clinical exacerbation at sites previously known to be involved by active disease or at sites that had been clinically silent until enhanced immunity caused clinical manifestations in response to viable or nonviable organisms [46].

Charbonnier and colleagues contend that TB is the most frequent opportunistic infection in patients infected by Human immunodeficiency virus (HIV). However when treating subjects with TB and HIV, interactions between antiretroviral and tuberculostatic treatment can be problematic, thus therapeutic adjustments which should be performed when treating patients co-infected with TB and HIV, the most important interactions between HIV and TB treatment, and the medical management of the IRIS [47].

Swaminathan and associates recommend the urgency of newer diagnostic tests that are sensitive and specific but easy to perform in remote and resource-poor settings. Treatment of HIV-TB co-infection is complex and associated with high drug burden overlapping drug toxicities, risk of IRIS and challenges related to adherence. From a programmatic point of view, screening of all HIV-infected persons for tuberculosis and vice-versa will help identify co-infected patients who require treatment for both infections [48]. Researchers in Nigeria reported 13.9% HIV/TB co-infection in 86 HIV patients [49]. Rabie and colleagues reported a case of tuberculosis paradoxical immune reconstitution inflammatory syndrome (IRIS) complicated by chylous ascites and chylothorax in a HIV-infected child. The case extends the clinical spectrum of IRIS[50]. Researchers in Cape Town, South Africa conclude that incidence of TB continues to decrease during the 5 years of HAART and so HAART may contribute to TB control in low-income countries than was previously reported from short-term follow-up. Patients with advanced pretreatment immunodeficiency had persistently increased risk of TB during HAART, this may reflect limited capacity for immune restoration among such patients [51]. Because of the severity TB-associated IRIS, some experts would not initiate HAART (ART) in previously untreated patients until the patient had received several weeks of or months of anti-tuberculous therapy. The risk for IRIS is greatest in the first two months after ART and in patients with initial CD4⁺ T-cell counts lower than 100 cells/ μ L. TB-associated IRIS can be difficult to distinguish from active TB, other opportunistic infections or drug toxicities [46].

Mycobacterium avium complex* (MAC)** disease has been much less common since the widespread use of ART. Despite declining incidence, the relative frequency of MAC infection compared with other OIs has not changed. MAC disease continues to be the most common systemic bacterial infection in AIDS and is responsible for significant morbidity. According to the CDC's Adult and Adolescent Spectrum of Disease (ASD) Project, the incidence of MAC declined 39.9% per year between 1996 and 1998, compared with 4.7% per year between 1992 and 1995[52]. The HIV Outpatient Study reported similar decrease in incidence rates in eight U.S. cities[53]. The prevalence of disseminated MAC for patients with CD4⁺ T-cell count less than 100 cells/ μ L is approximately 10%[54]; at autopsy, prior to ART and routine use of prophylaxis, the rate was approximately 50%[55]. Clinical manifestations of disseminated MAC is similar to MTB, with diarrhea, and high "spiking" temperatures and toxic appearance seen[56]. ***Mycobacterium kansasii is the second most nontuberculous mycobacterial infection in patients with AIDS[57].

VI. Diagnosis

Gold standard of diagnosis requires culturing of *M.tuberculosis* from appropriate specimens. The sputum smear for acid-fast bacilli is approximately 50% sensitive in HIV infected persons, a rate similar to that among HIV-negative persons [58,]. Radiometric system (BACTEC) may speed the diagnosis. Because the initial acid-fast smear cannot distinguish *M.tuberculosis* from MAC, culture with identification and susceptibility tests must be routinely performed. Direct test of nucleic acid amplification for rapid diagnosis are available. Newer procedures using enzyme immunoassay (EIA) may make serologic testing for *M.tuberculosis* possible [58]. Direct Test) Gene Probe, San Diego CA, which targets ribosomal RNA, and the AMPLICOR, *M.tuberculosis* Test (Roche Diagnostic System, Basel, Switzerland), which targets DNA, specification of *Mycobacteria*, for clinical diagnosis and epidemiologic investigation, genotyping of *M.tuberculosis* and drug susceptibility testing [1].

VII. Treatment

CDC and the American Thoracic Society guidelines recommend that the minimal duration of therapy is 6 months for drug-susceptible TB in patients co-infected with HIV. If clinical or bacteriologic response is slow, they recommend treatment for a total of 9 months, or 4 months after culture becomes negative [9]. Four drugs are recommended e.g., INH, 300 mg orally, rifampin 600 mg orally daily, pyrazinamide 20 to 35 mg/kg orally daily, and ethambutol 15 to 25 mg/kg orally daily. Patients on HAART may experience drug interactions between rifampin and protease inhibitors and other commonly used agents. Rifampin induces the activity of cytochrome P450 CYP3A, which lowers the concentration of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, resulting in incomplete viral suppression [59]. Most experts, however advise against withholding ART until completion of TB therapy. **Three facts for treatment of TB in HIV infected patients must be noted that include:**

(i) ART should be administered when indicated

(ii) a short course regimen (6-9 months, dependent on the regimen) should be administered as directly observed therapy to enhance compliance, and

(iii) Rifabutin, at a lower dose (150 mg) is preferred over rifampin because of significant drug interactions of rifampin with protease inhibitors and non-nucleoside reverse transcriptase inhibitor.

Patients with CD4⁺-T-cells counts of less than 100/μL should receive daily therapy for first 2 months, and no less often than three times weekly during the remainder of treatment. This will minimize the risk of rifampin or rifabutin resistance developing on less frequent intermittent regimens [60]. Sputum culture and smear should be checked monthly to document clearing of infection. Persistent fever for more 2 to 4 weeks in a patient receiving standard for drug regimen suggests multi drug resistant TB (MDR TB). If susceptibility results are pending, treatment options should be guided by prior drug exposure, history of exposure to a case of MDR TB and the susceptibility patterns in the community. Drug fever and second infection should also be considered [14, 61].

Prophylaxis. Chemoprophylaxis with INH (300 mg daily) for 9 months should be administered to any HIV-infected patient with a tuberculin skin test induration that is at least 5 mm in diameter, once active TB has been ruled out. Chemoprophylaxis also should be initiated regardless of the tuberculin test in patients with history of positive results who were not adequately treated, a close contact with TB. Recent studies have shown that the results of anergy testing are not reproducible and that INH prophylaxis does not reduce the incidence of TB in HIV-infected patients with anergy. Therefore anergy testing is not recommended in this population [54].

Treatment of MAC patients. Active drugs include the macrolides (azithromycin and clarithromycin, and amikacin) [62]. Therapy initially should include a macrolide and ethambutol. A third agent, such as rifampin or ciprofloxacin, can either be included in the initial regimen or added if there is slow response. The addition of amikacin as fourth agent may be needed in some patients who fail to respond or who relapse [63]. Testing of isolates for clarithromycin or azithromycin resistance is recommended for all clinically significant isolates [64].

VIII. Conclusion

Tuberculosis is an ancient disease of mankind with risk for death in HIV-infected patients with TB is twice that in HIV-infected without TB. The tuberculosis control is the early diagnosis, treatment of TB among HIV-infected patients and prevention of tuberculosis transmission in the community. DC guidelines for the diagnosis, treatment and prevention of tuberculosis is useful.

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