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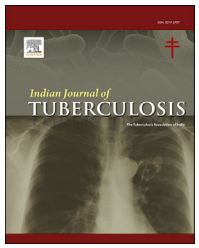

Editorial

Epidemiology of tuberculosis and respiratory diseases in the elderly: A global view

Reflecting on United States tuberculosis surveillance data, Powell and Farer noted 40 years ago that the rising age of tuberculosis was a sign of both success and failure.[1] Comparing recent secular trends in the epidemiology of tuberculosis in the world's two most populous countries shows that both China and India experienced a continuous increase in the proportion of bacteriologically confirmed tuberculosis cases in the age segment of the 65-year-old and older (Fig. 1).The trend in the relative increase of cases among the elderly in the two countries was remarkably parallel, albeit at a higher level in China. Only to a minor part can this change in the age of tuberculosis patients be attributed to the aging of the population: the slope of the latter is substantially smaller than that of the former. The pace of the demographic transition in the two countries is also remarkably similar, with China ahead of India in her population's aging. Careful interpretation of the surveillance data and other epidemiologic information does not suggest in any way an increase in tuberculosis in either country,[2–4] to the contrary. Powell's interpretation of "failure" would thus also apply here: some age groups benefit more than others, and the elderly are the likely (relative) losers in the respective control efforts, i.e., they experience a lesser decline in morbidity than other age groups. The "success" on the other hand is that a diminishing of transmission of *Mycobacterium tuberculosis* results by necessity in an increase in the age of the prevalently infected. It puts the oldest at a relatively increased risk of reactivation of remotely acquired infection compared to younger birth cohorts.[5] To what extent the aging of the tuberculosis patient population is also a "natural" phenomenon of the epidemic's behavior cannot be quite known. But prominent are the facts that the National Tuberculosis Elimination Programme (NTEP) of India has been placing over 2 million tuberculosis patients on treatment in 2021 alone and that the countrywide treatment success is greater than 80% in both the public and private sectors.[4] This makes it clear that the impact on curtailing transmission in the country must be so enormous as to make it certain that these accomplishments must have a substantial epidemiological impact. This is in contradistinction to the situation prevailing before[6] this large-scale effective, efficacious, and efficient program in the country was established.[7]

As the slope (the change) of the course depicted here is less biased than the intercept (the magnitude), the tuberculosis incidence among the elderly might even be more underestimated than notification data indicate. This is suggested elsewhere when comparing notifications with actual surveys, as elderly tuberculosis patients might become selectively less under the program's care than other members of the society.[8]

A thorough discussion of respiratory diseases other than tuberculosis is beyond the scope of this editorial comment. Thus, just three conditions shall be briefly highlighted here. One is metabolic, the other two specifically respiratory. All are of particular epidemiologic and clinical relevance in the elderly and they all affect the differential diagnosis of pulmonary tuberculosis.

1. Co-morbidity: diabetes mellitus

The prevalence of type 2 diabetes mellitus increases the risk of progression from latent infection with *M. tuberculosis* to clinically manifest tuberculosis approximately two-to threefold.[5,9] It has rapidly evolved into a major public health problem, notably so in south Asia.[10] It has also been noted to be particularly prevalent among the elderly in India.[11] Diabetes is causally associated with tuberculosis and may be associated with community-acquired pneumonia,[12] and it certainly is associated with COVID-19 pneumonia.[13]

2. Differential diagnosis: bacterial pneumonia

While pulmonary tuberculosis among the elderly may[14] or may not[15,16] remain clinically indistinguishable from that among younger adults, the radiographic manifestations generally appear to differ from those in the latter.[15,17] This renders the differential diagnosis from pneumonia even more

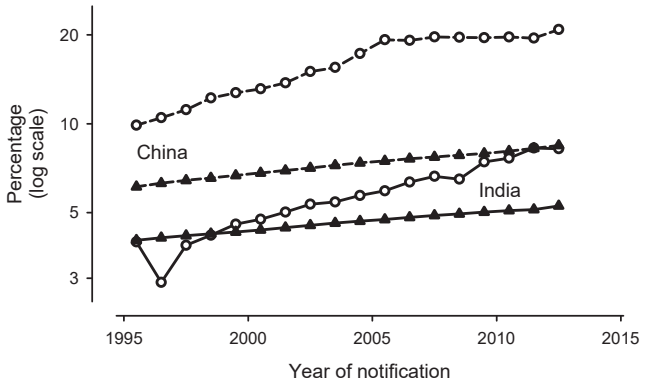

Fig. 1 – Secular trends in the proportion of notified patients with incident sputum smear-positive pulmonary tuberculosis aged 65 years and older (circles) and the proportion of the population in this age group (triangles), in respectively China (dotted lines) and India (solid lines). Data for tuberculosis extracted from World Health Organization annual global tuberculosis reports 1997–2013; data on population from Population Estimates and Projections, published by Knoema July 1, 2022 (https://public.knoema.com/erdvvie/population-estimates-and-projections).

challenging and is perhaps even more compounded in the elderly diabetic tuberculosis patient.[18] Among lower respiratory infections, pneumococcal pneumonia alone was estimated to have been globally responsible for almost as many deaths as pulmonary tuberculosis in the Global Burden of Disease Study.[19] Among adults, the incidence of community-acquired pneumonia increases with age and peaks in the elderly.[20] Because of the difficulties in differentiating pulmonary tuberculosis radiographically from pneumonia, it is essential that sputum examination by both microscopy and culture is mandatory for all patients presenting with signs or symptoms compatible with pulmonary tuberculosis.[14] Rapid nucleic acid amplification tests facilitate prompt diagnosis and provide simultaneously information about the susceptibility to the critical first-line drug rifampicin and additional drugs in case a line probe assay can be and is being used.

3. Two epidemics collide: tuberculosis and the SARS-CoV-2 epidemic

About five years into implementing and working on the End TB strategy of the World Health Organization,[21] the world got caught in the pandemic with SARS-CoV-2. COVID-19 has cumulatively cost an estimated 6.4 million lives as of mid-August 2022 (https://covid19.who.int). Furthermore, the COVID-19 pandemic has substantially interfered with progress in tuberculosis control and adversely impacted on gains that had heretofore been made.[22–25] The Honorable Minister for Health and Social Welfare, Government of India, Dr Shri Mansukh Mandaviya, congratulated the NTEP "for managing to navigate the pandemic with remarkable resilience".[4] This appreciation also holds the prospect and promise that the dedication of staff at all levels of the program will get the NTPE back on the charted path towards its goals in tackling the national tuberculosis epidemic.

Among a cohort of COVID-19-affected patients who had tuberculosis either before or simultaneously, 17% had the two diseases diagnosed in the same week.[26] Clinically, patients commonly had other co-morbidities (notably diabetes mellitus) and the course of either disease was complex and the outcome often fatal. Concomitant pulmonary tuberculosis generally seems to aggravate the outcome of COVID-19 (disease severity and death).[27]

4. Perspective

The age of tuberculosis patients will continue to rise with the improvement of the epidemiologic situation, resulting from an ever-improving quality of the NTEP in curtailing transmission. This prediction is epidemiologically coherent and is a *sequitur* for any tuberculosis epidemic in decline. It is not as paradoxically as it may seem also clearly a success story. Associated problems of care seeking, diagnosis, co-morbidity and with treatment and its tolerance among the elderly will remain critical and potentially increasing challenges for the NTEP. Certain interventions that have an important place among younger population segments (notably preventive therapy for presumed latent infection that can potentially progress to overt tuberculosis) can only play a niche role among the elderly if any. Thus, we cannot rely on them and there is no easy technical fix in sight for that component.

The current supplement of the *Indian Journal of Tuberculosis* endeavors to heighten awareness among clinicians and public health professionals alike about the many facets that may complicate diagnosis and treatment of tuberculosis among the elderly. It is often compounded by co-morbidity, be it respiratory, metabolic, or other. We must proudly emphasize and repeat that the rising age of tuberculosis patients is an epidemiologic distillation and quantifiable manifestation of the success of our efforts: it firmly plants a powerful message: India and many other countries have already curtailed transmission of tubercle bacilli during the past decades in the community and there cannot be any doubt that public and private sectors will jointly continue to successfully do so now and in the future.

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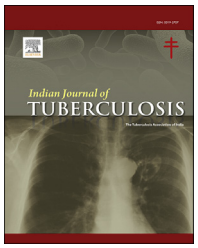

Editorial

Tuberculosis in elderly persons

The number of elderly (over the age of 60 years) is increasing in India due to increased life expectancy. Simultaneously the number of elderly persons suffering from tuberculosis has remained high in the country. Though concentrated efforts are being made to reduce the tuberculosis infection, the number has remained high among elderly. There is also a large burden of tuberculosis in elderly who remain undiagnosed. The non-specific symptoms cause delay in arriving at correct diagnosis. Increased life expectancy, changes in the demographic profile and atypical presentation of the clinical features of tuberculosis have posed many challenges in the management of tuberculosis in elderly.

Every year 10 million people fall ill with Tuberculosis, and despite being a preventable and controllable disease 1.5 million people die from TB each year in the world.[1] The prevalence of tuberculosis is 16% among elderly patients in India. Such a high number has necessitated for concentrated efforts to control the condition effectively. Most persons are exhibiting unfavorable outcomes. Looking at this,[2] Government of India has given a clarion call to achieve the target of End Tuberculosis in India by 2025. Looking at the increased burden, National Tuberculosis Elimination Program has made an ambitious plan to eliminate the condition by 2025.[3]

The susceptibility of elderly to tuberculosis has increased due to the lowered immunity,[4] on account of presence of co-morbid conditions, such as diabetes mellitus type 2,[5] hypertension, cardiovascular diseases, chronic kidney diseases, chronic obstructive pulmonary disease, and malignancy. The immunity shows a decline with Immunosenescence. Use of immunosuppressive agents makes the immunity less active. The susceptibility to the disease is also increased in the background of malnutrition, chronic alcoholism,[6] pollution, living under unhygienic conditions[7] and smoking.[6] Further the response to treatment is less. The under privileged and people from unorganized sector have financial issues which becomes a hindrance in continuing treatment. The low adherence and loss to follow-up is quite high among elderly[8] All these conditions enable the infection to lurk in them and they become a source of infection to others.

There is need for proper screening, treatment and follow-up in the elderly age group. Constant watch has to be kept on those having co-morbid conditions. An early diagnosis and initiation of treatment enables to have a better outcome.

Many cases appear to have link to the reactivation of lesions that had remained dormant over many years. Many elderly patients present with nonspecific symptoms and the condition is missed for a long period of time.[9] Many elderlies are not able to take care of themselves, and there is poor adherence to the treatment and they fail to complete the prescribed course and there is an increased rate of treatment failure. Further Multi-drug resistant strains and Rifampicin-resistant strains put great hurdles to achieve success in the therapy.[10] Community acquired pneumonia[11] in winters and in Invasive pneumococcal disease in unimmunized people pose a challenge Opportunistic infection which may be bacterial, fungal,[12] viral, parasitic[13] etc. are not only difficult to diagnose but also to treat.

Further there are many potential interactions between antituberculosis drugs and other additional medications used by the elderly for the management of co-existing diseases. Many elderly patients fail to complete the treatment prescribed. It further increases the risk of treatment failure with advancing age.

Co-morbidities, which are more common in older patients, may mask the symptoms of TB. Elderly patients exhibit poor tolerance of anti-tuberculosis drugs. It is encountered in 63% of elderly patients compared to 54% seen in younger patients.[14] Many older patients fail to compete the prescribed treatment resulting in a higher risk of treatment failure.

Since many of them are taking medication for the co-exiting diseases, they often fail to adhere to the prescribed treatment against tuberculosis and many a times they exhibit poor tolerance to the drugs administered. They are to be cared properly and impress on the need of regularity in the treatment, which may necessitate to given special attention by the care-giver.

RESPIRATORY vaccines[15] increase the respiratory hygiene as well as immunity and are beneficial in these patients.

Respiratory Physiotherapy, have a supportive role in management.

Conflicts of interest

The author has none to declare.

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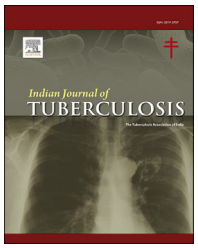

Viewpoint

Viewpoint on tuberculosis in elderly in India

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ABSTRACT

With increase in the number of the elderly population in India, the number of patients suffering from tuberculosis has shown an increased prevalence in the elderly. In many of them, the condition is linked to the reactivation of the lesions that were dormant. Immunosenescence appears to play an important role in activating the lesions. The clinical features are often non-specific and pose difficulties in the diagnosis. Radiological changes in the chest, though are suggestive, the microbiological proof is difficult. Though effective drugs are available, often they tolerate them poorly. There is poor adherence to the therapy leading to therapeutic failure. Co morbidities and physical dependency contribute to failure of therapy.

1. Introduction

Over the last century life expectancy has increased dramatically. The number of elderly persons is rising all over the world including India. The population of elderly persons (aged 60 years and above) in our country has increased exponentially from 77 million at the beginning of last century to around 100 million now, forming 9% of total population of the country. Thus, a demographic change has made the country a 'graying nation'.

Tuberculosis being common in the country, the number of elderly persons associated with tuberculosis has also increased. They have to receive proper treatment for their ailment. If they do not receive proper treatment for a proper duration, the infection persists in them and they become a source of infection to others. Many of these individuals exhibit poor response to the treatment.

2. Prevalence

Nehal et al. in study carried out in South India found a high prevalence of tuberculosis among elderly (18.7%) where pulmonary tuberculosis was more commonly noted (82.8%). The condition was more frequent among smokers. They had diabetes as co-morbid condition.[1]

Ananthakrishnan and coworkers found tuberculosis in 14% of elderly individuals in Tamil Nadu. Of them 47% were newly detected sputum positive cases. Those aged 70 years and above exhibited a higher risk of unfavorable outcome. This was noted especially in those undergoing retreatment, and those receiving community-based DOT therapy. They also showed presence of co-morbid conditions such as diabetes, hypertension and cardiovascular diseases. There was higher mortality among them, and they needed special attention.[2]

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3. Diagnostic difficulties

Elderly persons with tuberculosis form a vulnerable group showing high mortality. The diagnosis poses difficulties as they exhibit many atypical features, often symptoms are similar to other age-related diseases. These patients show adverse drug reactions frequently.[3]

More number of elderly patients with tuberculosis exhibit treatment failures due to poor adherence to treatment, poor tolerance to treatment and presence of co-morbid conditions.[4]

3.1. *Treatment difficulties*

The treatment of elderly patients with tuberculosis is similar to that given to younger patients. However, the adverse reactions such as hepatotoxicity are more common in elderly.[5] Streptomycin is not advised in elderly patients. Drug interactions are more frequent in them. Since rifampicin increases metabolic degradation of drugs such as corticosteroids, hypoglycaemic agents and oral anticoagulants, there is a need to adjust their dosage.

Tuberculosis continues to be a major cause of morbidity and mortality in India. The ubiquitous organism causing tuberculosis lurks in deeper tissues of the host, and remains dormant, and inaccessible, and flares up after a gap of many years. It changes its garb and becomes refractory to various drugs used against it. It attacks those with altered immune status. The tubercle bacilli in their attempt to survive develop strains of organisms that become drug resistant. Since the unknown sputum positive cases are the ones largely responsible for propagating infection, satisfactory control of tuberculosis still eludes our efforts.

The disease takes its origin from the persons with pulmonary tuberculosis discharging tubercle bacilli. The infection is transmitted successfully to contacts aerogenously and is maintained in the community. The disease can be easily diagnosed by clinical and radiological methods and confirmed by sputum smear examination. It is only by identifying those infectious individuals and rendering them non-infectious through chemotherapy that the chain of transmission of tubercle bacilli from person-to-person can be broken.

Anti-tuberculosis drugs used in right combination, proper dosage and duration can effectively arrest and cure the disease. However, the chemotherapeutic triumph gets defeated in practice by inadequate regimens, irregular intake of drugs, frequent interruptions, and early discontinuation of drug intake, drug toxicity and drug resistance.

Despite extensive tuberculosis-control efforts of the World Health Organization (WHO) and local health departments, the tuberculosis (TB) epidemic continues to ravage the world, affecting susceptible individuals including the elderly (>65 years old), and representing a global health problem. Majority of these individuals carry tubercle bacilli in dormant lesions that can get activated as the immunity wanes.[6]

4. Distinct entity

Tuberculosis forms the leading infectious disease causing morbidity and mortality in the country. Elderly persons succumb to this malady frequently. Tuberculosis often is associated with co-morbidities such as hypertension, diabetes, heart failure, renal diseases, malignancy and osteoarthritis. Often they are smokers and alcoholics. Even after the recognition of the condition, often the patients fail to adhere to the intake of medication, and often exhibit poor tolerance to the medication. It leads to treatment failure. Many of them are lost to follow-up.[3,5]

There is a link between the cases of tuberculosis in elderly and the reactivation of lesions that had existed as dormant lesions for many years,[7] Activation of these lesions appears to be due to senescence of the immune system occurring in advancing age. The patients often fail to reactivate previously acquired immunity.[8]

Tuberculosis does not manifest with the classic features and the symptoms are non-specific and less pronounced. Many a time the diagnosis poses many difficulties. They find difficulty to bring out sputum and it poses difficulty to make a diagnosis based on microbiology.

Every year 10 million people are attacked by tuberculosis despite the condition being preventable and curable, and 1.5 million persons succumb to tuberculosis in the World.[9]

Presence of many coexisting factors, make tuberculosis a distinct entity in elderly persons. The factors may be summarized as follows:

Immunosenescence.
Inability to reactivate previously acquired immunity.
Presence of comorbidities.
Interactions between the anti-tuberculosis agents and medications.
Drug resistance.
Poor adherence to the medication.
Treatment failure.

Elderly persons exhibit a progressive fall in lung function with advancing age. They exhibit decreased lung elastic recoil and compliance of the chest wall. There is abnormality of pulmonary functions in the form of decreased forced expiratory flow rates and decreased lung elastic recoil. They are unable to cough properly and bring out the secretions in the airway. Such a situation favours occurrence of infections including tuberculosis infection.[10] These individuals exhibit decreased strength of respiratory muscles. They exhibit under nutrition and sarcopaenia.

Elderly persons with immunosenescence, co-morbid conditions, and influence of advancing age, malnutrition, and close contact exhibit an increased susceptibility to infections including tuberculosis. Often these conditions are conducive for reactivation of tuberculosis.[11] Elderly persons in the background of tissue ageing, exhibit an increased level of inflammatory cytokines and an increased oxidative stress, and hyperglycaemia facilitate survival of *M. tuberculosis* within the cells.

4.1. *Clinical features*

The clinical features of tuberculosis in the elderly are often atypical. The classical features of tuberculosis such as fever, and cough may not be apparent. Many complain of decreased appetite, weakness and weight loss. In some the condition may lurk for a long period of time to result in fibrosis of a lobe resulting in flattening of the chest, tracheal shift, impaired note over the chest and bronchial/broncho-vesicular/tubular breath sounds with crackles. Many-a-times, the comorbidities mask the symptoms and underlying tuberculosis lurks inside, the condition may be confused with bronchogenic carcinoma as both conditions develop in people having history of smoking. The diagnosis is often delayed. Radiologically there is often involvement of multiple zones exhibiting infiltrates.[12]

There may be atypical radiological abnormalities with presence of infiltrates in the lower lobes, nodular opacities, or mass lesions. Elderly persons often find difficulty to bring out the sputum. Sometimes it has to be induced by use of nebulizers. However the microscopy has limitations in demonstrating presence of acid-fast bacilli in the sputum. In nearly half the number of cases it turns out to be negative. The sputum samples are to be cultured either in Lowenstein-Jensen solid medium or in liquid medium. If the culture is positive it has to be tested for their susceptibility to commonly used anti-tuberculosis agents. The culture procedure delays to confirm the diagnosis as *M tuberculosis* show a slow growth.

4.2. *Treatment*

Instead of undertaking many expensive tests to confirm the diagnosis, it has to be made on clinical suspicion and the treatment has to be initiated without waiting for the microbiological confirmation. At the same time the co-existing diseases are to be managed.

There are no specific guidelines for the management of tuberculosis in the elderly. The condition has to be managed as per general guidelines. However, a watch has to be kept on the side effects as the elderly exhibit poor tolerance to anti-tuberculosis drugs. Streptomycin is not advocated. Many of the routinely used anti-tuberculosis drugs (isoniazid, pyrazinamide, and rifampicin) exhibit hepatotoxicity and presence of jaundice, and abnormal liver function tests are to be looked.[13] As they have a decreased renal and hepatic clearance, the chances of drug-induced hepatitis are great.

A short-course chemotherapy with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) as the initial intensive therapy for two months, followed by two drugs (isoniazid and rifampicin) for 4 months as continuation therapy is ideal.

However many patients show high rate of failure due to many reasons mentioned below [14]:

Inadequate regimens.
Inadequate intake of drugs.
Premature stoppage of drug taking.
Drug toxicity.
Initial drug resistance.

Multi-drug resistant (MDR) tuberculosis is being increasingly recognized and *M tuberculosis* exhibit resistance to two most effective antituberculosis drugs, isoniazid and rifampicin. The cause appears to be due to[14].

Poor adherence to treatment.
Prescription of inappropriate combination of drugs.
Prescription of inadequate dosage of drugs.
Inappropriate rhythm of administration.
Use of unrelated combinations.
Addition of another drug toa failing regimen.
Erratic drug supply.

The treatment of MDR tuberculosis poses many challenges to the treating physician. The treatment is less effective, more toxic and expensive. A detailed history of previous treatment of tuberculosis has to be obtained. It should include the nature of drugs, the dosage, duration and regularity of their intake.

Polypharmacy should be avoided in the elderly as the drug–drug interactions can bring about a change in the concentrations of the drugs administered There is an increased case fatality, default and failure rates despite directly observed treatment. Gaur and coworkers have stressed the need for intensive motivation and stringent monitoring among tuberculosis patients over 65 years of age.[15]

Elderly patients with tuberculosis exhibit poorer tolerance to the antituberculosis drugs, difficulty to adherence to the treatment, decreased completeness of treatment and higher risk of treatment failure.[16]

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Viewpoint

Drug resistant tuberculosis among elderly: Challenges

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ABSTRACT

The article deals with challenges faced by the geriatric populations while on MDR treatment. Risk factors like tobacco use, low socio-economic status, previous disease, longer delays in seeking treatment and reduced mobility are some of the challenges while initiating MDR treatment. Other issues like drug-related adverse events and increased co-morbidity pose a major challenge while treating patients. Susceptibility among the geriatric age group includes various anatomical and physiological changes including nutritional deficiencies and co morbidities.

According to estimates the geriatric population may increase from 841 million people in 2013 to 2 billion plus people in 2050.[1] Tuberculosis (TB) is emerging as a significant health problem among the geriatric population.[2] TB notification rates world over occur amongst 45–55 year old. Tuberculosis among the elderly population is high as younger people go for health seeking early and elderly usually ignore their symptoms and seek care very late. They are susceptible to infectious diseases of respiratory tract, leading to high morbidity and mortality when compared with younger individuals.[3]

1. Risk factors

Risk factors of acquiring infection among elderly are delayed treatment seeking, co-morbidities, tobacco use, low socio-economic status and, adverse reactions during treatment. Connection is well established between MDR-Tuberculosis and social determinants. Other factors of importance are inadequate therapeutic regimen and doses, Poor quality of drugs and poor adherence to treatment. Another set of factors include prolonged hospitalization, alcohol, HIV infection, co-morbidities, malnutrition, day to day dependence, social

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isolation, use of corticosteroids, communal living along with closeness among residents are some factors that may increase the chances of acquiring/spreading infection. Factors like social marginalization, reduced mobility and financial dependency affect the health seeking behavior of patients. As per studies, older caretakers with TB pose a risk to young children whereby grandparents perform child-care duties.[4,5] Elderly ignore their symptoms thinking that they may be related to changing weather, air pollution or smoking etc.

2. Disease presentation

Symptoms among geriatric are often non-specific, leading to delayed diagnosis and advanced stage of disease at presentation.[2] Most cases are linked to the reactivation of dormant lesions.[3,6] A study from China concluded that the proportion of drug resistant cases and the rate of cavitary and drug resistance disease were more common in males with history of smoking or drinking and having COPD or diabetes. A number of studies support this finding.[4,7–9] Other studies concluded that old age itself is a risk factor for developing MDR-Tuberculosis.

3. Radiological findings and diagnosis

Differences were found in radiological findings between younger and elderly patients suffering from Pulmonary TB.[3] Cavitation, was common among younger population. Infiltrates were common among the elderly patients when compared with younger age group. In a cross-sectional study among elderly, bilateral multiple zone involvements were observed in both the age groups. As per a study elderly patients may present with features, like middle or lower lobe infiltrates, mass-like lesions or nodules which may appear like cancers, bronchopneumonia without cavitation or non resolving infiltrates.[1] Also elderly people usually suffer from chronic bronchitis, interstitial lung disease etc., making radiological diagnosis difficult for clinicians.

4. Challenges in management

High prevalence of drug resistant Tuberculosis and its management is a challenge for developing countries including India. Challenges in the management of DRTB among the elderly are suboptimal treatment adherence, adverse drug events and high treatment costs involved in MDR/XDR-Tuberculosis management. Another important issue is the reduced mobility among the elderly and chronic obstructive pulmonary disease (COPD) which has high mortality and high prevalence rates among the elderly in along with Tuberculosis. Research is going on to understand the link between HIV and Tuberculosis among the elderly. Elderly patients may develop atypical forms of disease including extra pulmonary TB. Care for the geriatric becomes much more complicated due to drug-related adverse events which further complicate the case. Nutritional deficiencies and metabolism also increase vulnerability. Strong connection has been established between diabetes and Tuberculosis among the elderly.

5. Conclusion

Various studies have been undertaken on TB and DRTB but more research needs to be undertaken on geriatric Tuberculosis. No microbiological data is available regarding disease burden in geriatric Tuberculosis patient. In France (2019), the percentage of notified cases of TB disease was 17.5% among the geriatric, 9.8% in more than 75 years and 6.3% in over 80 years. As per Morris et al pulmonary Tuberculosis in elderly patients should be considered as a different entity of diseases.[10] Tuberculosis treatment among elderly includes isolation, contact screening, and a prolonged use of combinations of toxic drugs (ATT) which can induce drug–drug interactions. During treatment conditions like under nutrition, co-morbidities have to be taken into account. As per a study an all inclusive management, associating geriatricians and infectious disease specialists, is required in these vulnerable patients.[3] Early screening and initiation of treatment along with nutritional management are an essential part of management. Partnerships between organizations are essential for better management of cases. As per an article management of an elderly tuberculosis patient should be based on a standardized erotological assessment. Tools which assess cognition, functional addictions, social support, multiple medications, and other risk factors are available and should be utilized.[3] Elderly need to be prioritized in all aspects of MDR Tuberculosis (Diagnosis and treatment). Health systems equipped with integrated services will have to address the challenge of ageing population. Giving due importance to tuberculosis prevention, active case finding and adhering to treatment among the elderly will exert positive influence through families society as a whole.

Conflicts of interest

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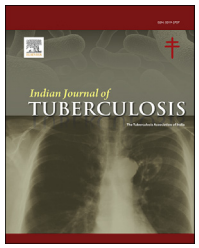

Review article

Challenges in diagnosis and treatment of tuberculosis in elderly

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ABSTRACT

Tuberculosis (TB) is a major infectious disease worldwide. Early diagnosis and prompt treatment reduces the transmission, morbidity and mortality in tuberculosis. Elderly (age >65 years) have many risk factors to develop tuberculosis. Recent survey in India showed incidence of TB higher in elderly. They may not have classical symptoms, clinical and radiological signs of TB which can lead to delayed diagnosis or misdiagnosis. In addition, elderly have many comorbid and coexisting diseases which make diagnosis and treatment of TB challenging. Comorbidities, poor general health status and other medications may lead to increased drug adverse reactions and poor adherence to treatment in elderly. Hence special emphasis should be given to elderly for early diagnosis and treatment. Elderly with multiple comorbidities require individualized approach for better outcome.

According to World Health Organization (WHO) estimates, India has the world's largest burden of tuberculosis. In 2020, India accounted for 26% of the incident TB cases across the globe.[1] Nearly 40% of Indians are estimated to be have latent TB.

As per WHO TB statistics for India for the year 2021, incidence of TB in India is 2,590,000 million cases. As per the Global TB Report 2021, the estimated incidence of all forms of TB in India for the year 2020 was 188 per 100,000 populations.[1] The total number of incident TB patients (new & relapse) notified during 2021 was 19,33,381 which was 19% higher than that of 2020 (16,28,161). In 2020 & 2021 there was a reduction of 14% and 9% in the number MDR patients put on treatment as compared to the estimated numbers.[1]

National TB prevalence survey in India 2019-21 showed higher prevalence of TB in older age group, males, malnourished individuals, smokers, alcoholics, and diabetics.[2] Majority (64%) amongst the symptomatics did not seek any health care services. The reasons for this were ignoring the

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symptoms (68%), not recognising the symptoms as TB (18%), self-treatment (12%) and couldn't afford to seek care (2%).

Worldwide the number of elderly people is steadily on the rise. Elderly constitute 9.3% of global population in the year 2020. This is expected to increase to 16% by the year 2050. There are 138 million elderly people in India in 2021, 67 million men and 71 million women.[3] An increase of nearly 34 million elderly persons was seen in 2021 compared to 2011 in India.

With advancing age, the risk factors to develop TB increases. Prevalence of diabetes, under nourishment, immunosuppression, other chronic illnesses like Liver disease, renal disease, autoimmune diseases, and malignancies are more in elderly compared to younger age groups.[4] All these increase the risk to develop tuberculosis. Health seeking behaviour in elderly may be poor. Due to poor social and financial support, limited mobility, poor access to health care services, many elderly people may not seek health care advise early and may not have optimal management of their illness. Cognitive impairment, poor memory, lack of proper caregivers may also lead to poor management of chronic illnesses in elderly.[4] Sub optimal control of diabetes and other chronic illnesses will further increase the risk of developing TB.[5] Diminished immune responses, especially cell mediated immunity with age makes elderly more susceptible to develop active TB.[6] Latent TB can progress to active disease in elderly due to the above risk factors.

Pulmonary tuberculosis is the most common form of active TB. People with pulmonary TB spread the disease to others by droplet transmission. Majority of patients with pulmonary TB patients exhibit symptoms like fever, cough, chest pain, hemoptysis, anorexia & weight loss. Under NTEP anyone with one or more of the above symptoms should be screened for TB. But elderly may not have classical symptoms suggestive of pulmonary TB. Elderly are more likely to have atypical symptoms like general deterioration in overall health, weight loss, chronic fatigue, cognitive impairment and low grade fever in varying combination.[7] Elderly my not express their symptoms due to cognitive impairment, poor memory, lack of awareness, ignorance of symptoms, poor social and financial support.[5] Multiple comorbidities in elderly may contribute to the complex and non-specific symptoms.

TB in elderly can coexist or complicate other lung diseases. Prevalence of other lung diseases like pneumonia, bronchogenic carcinoma, bronchiectasis, COPD, Bronchial asthma, occupational lung diseases and interstitial lung diseases are also more in elderly. All these chronic lung diseases increase the risk to develop pulmonary TB.[5] Steroid therapy in patients with obstructive airway disease and connective tissue disease associated ILD increase the risk for developing TB. Immunosuppression and chemotherapy in cancer patients increase the risk to develop TB. Overlap of symptoms pose a challenge for early clinical suspicion of TB in these patients with chronic lung disease. TB in elderly can present with acute or subacute symptoms mimicking pneumonia.[5]

Increased prevalence of TB in elderly will pose a greater risk of transmission other household contacts. Large number of elderly population in India can pose a challenge to National tuberculosis elimination programme. The risk of transmission to other household contacts may be higher in India as joint families with overcrowding and poor ventilation is common.

Pulmonary TB is suspected by symptoms and chest x ray is often helpful as an initial screening tool. Majority of patients with pulmonary TB show chest radiological abnormalities. Upper lobe infiltrates, cavitory lesion in upper lobe with surrounding infiltrates and bilateral infiltrations predominantly in upper lobes are the typical chest x-ray features in TB. Normal chest x ray, consolidation in upper lobe, cavity in lower lobe, cavity with air fluid level, lower zone infiltrates are more common in elderly.[8] These lesions can be mistaken for lung abscess (cavity with air fluid level), bronchiectasis (lower lobe infiltrates) pneumonia (upper lobe consolidation). Chest x ray may be normal in patients with endobronchial TB and in early TB. Presence of comorbid chronic lung diseases also will lead to atypical radiological features. Awareness about atypical radiological features will help in early diagnosis of TB in elderly. Comorbidities play an important role in atypical radiological lesions in elderly. Elderly with any radiological abnormality should be evaluated for TB.

Elderly are more likely to have relapse of TB.[9] Chest radiological differentiation of active from inactive TB may not be possible in such patients who had previous pulmonary TB.[10]

In a high burden country like India TB and lung cancer can coexist. Pulmonary tuberculosis is a confounder for bronchogenic carcinoma. In India delayed diagnosis of lung cancer is common, one of the major reason being misdiagnosis as TB in the early stages of lung cancer.[11] Symptoms and radiology overlap in TB and malignancy. One can mimic the other; Both can co-exist, more so in elderly and chronic smokers with high smoking index. History of pulmonary TB is an independent risk factor to develop lung cancer.[12] Pulmonary TB coexisting with lung cancer can lead to miss-diagnosis, delay in diagnosis & diagnostic dilemma in TB.[11] Malnutrition, immunosuppression due to malignancy and its treatment increases the risk of TB in patients with bronchogenic carcinoma.[13] One can worsen the other. Smoking and advancing are the common risk factors to both the diseases. Symptoms like cough, chest pain, hemoptysis, anorexia and weight loss are common to both the diseases. In countries with high incidence of TB, lung cancer often gets misdiagnosed as TB resulting in delayed diagnosis of cancer. In countries with low incidence of pulmonary TB & high incidence of lung cancer, TB often gets misdiagnosed with the result of delayed treatment and unnecessary diagnostic procedures.[14] Hence careful systematic evaluation is the key to early diagnosis.

Miliary TB, disseminated TB and extra pulmonary TB (EPTB) are also more common in elderly.[15] EPTB has no specific diagnostic symptoms. Symptoms of EPTB depend on the organ involvement. Elderly with multiple comorbid diseases with immunosuppression can have extensive TB, Miliary TB and disseminated TB.[16] TB can progress very rapidly in them. TB in elderly can mimic other infectious or malignant diseases.

Bone and joint TB is more common in elderly.[16] Since osteoarthritis and osteoporosis is also more common in elderly, differentiation may be difficult. Extra pulmonary TB in elderly may be more challenging for diagnosis as symptoms, signs and imaging finding are often nonspecific & mimic other diseases of the effected organ. Definitive diagnosis of extra pulmonary often needs biopsy from the site of lesion. Due to

multiple comorbidities and poor general health invasive procedure carry higher risk and complications in elderly.[16]

Sputum examination is the simplest investigation for definitive diagnosis of pulmonary TB. When sputum smear is positive or CBNAAT detects MTB, diagnosis is confirmed. Elderly may not be able to produce a proper sputum sample for examination even by sputum induction. Poor general health, inability to expectorate due to poor cognitive function and neuromuscular debility in elderly lead to inability to produce a proper sputum sample.[17] This may lead to less smear positivity rate in elderly. When sputum analysis is non informative, further evaluations like CT scan, bronchoscopy, and biopsy from the site of lesion may be required for definitive diagnosis of pulmonary TB in elderly.

Poor access to health care, neuromuscular debility, cognitive impairment, poor social support and financial constraints may lead to delayed health seeking behavior in elderly.[15] This can lead to delayed diagnosis of TB. Delay in diagnosis will lead to increased transmission, more extensive disease, disseminated disease, increase in morbidity and mortality. Sequelae and complications are more whenever there is a delay in diagnosis and initiation of treatment in TB.

Atypical symptoms and signs, atypical radiological features, inability to produce proper sputum sample and presence of comorbidities often require proper detailed evaluation in elderly for definitive diagnosis. Presumptive diagnosis of TB is more likely to be wrong in elderly due to atypical symptoms and signs, multiple coexisting diseases and comorbidities.[18] Some elderly may not be fit for invasive diagnostic investigations which again will pose a diagnostic challenge. Elderly may be more at risk to develop complications during invasive diagnostic procedures due to comorbidities. Hence least invasive investigations should be done first in elderly. Careful risk benefit ratio should be weighed before invasive investigations.

Elderly have many risk factors to develop drug resistant TB. Comorbidities like diabetes, smoking, immunosuppressive conditions, chronic renal disease, chronic liver disease, other debilitating illness increase the risk of primary and acquired drug resistant TB.[19] Elderly may be less compliant with medication due to impaired memory, poor economic and social support, increased pill burden due to comorbidities, impaired GI absorption and increased adverse drug reactions.[20] Multiple commodities requiring medications, increased risk of drug interactions and deteriorating organ function with age is the main cause for increased drug adverse reaction.[21]

Elderly patients are particularly at risk of drug interactions during treatment of their tuberculosis. Drug interactions can occur with anti TB drugs, mainly with Rifampicin, INH and fluoroquinolones.[22] Rifampicin induces human P450 cytochrome oxidases. This can lead to increased metabolism of drugs metabolized by this enzyme leading to lowering their efficacy. Efficacy of Anti-arrhythmic drugs, macrolide antibiotics, Cephalosporins, oral anticoagulants, phenytoin, Lamotrigine, tricyclic antidepressants, oral antifungals, oral contraceptives. Anti-retroviral drugs may be reduced by rifampicin.[23]

Isoniazid inhibits the cytochrome P450 system. It also inhibits monoamine oxidase (MAO-I). Adverse effects of Disulfiram, Acetaminophen, Carbamazepine, valproate, phenytoin, theophylline may be increased by INH.[23]

Delamanid is a CYP3A4 substrate. Serum levels of Delanamid is reduced when co-administered with strong CYP3A4 enzyme inducers like Rifampicin. Lopinavir/ritonavir, clofazimine increase the adverse effects of Delamanid.[23] The risk of QTc prolongation is increased when Delamanid is administered with fluoroquinolones and in patients with hypoalbuminemia.

Comorbidities and poor compliance in elderly may lead to sub optimal response to anti TB medications. They may require more duration of treatment. TB in elderly may not respond if comorbidities are not treated properly. Poor control of diabetes is a major risk factor for treatment failure in TB. Comorbidities may necessitate drug dosage modification or change in regimen which may not be very effective or require prolonged treatment. This may lead to poor compliance and treatment failure.

Morbidity and mortality in elderly with TB is more.[21] This may be due to more incidence of drug resistant type of disease, poor compliance, delayed diagnosis, complications of TB, drug adverse reactions, multiple comorbidities and sometimes age related decline in health.

Compliance with anti TB drug is likely to be more in elderly. Financial constraints, poor social and psychological support, multiple comorbidities, increased drug toxicity due to high pill burden, poor neurocognitive functions are the factors which increase the chances of poor drug compliance in elderly.[24] Proper psychological, financial and social support, proper follow up and monitoring for drug adverse reactions and individualized drug dosage will improve the compliance.

Elderly have many inherent risk factors to develop drug resistant TB. These include diabetes and other immunosuppressant conditions, multiple comorbidities, less compliance to treatment and recurrence of TB.[25]

Treatment of drug resistant TB in elderly can be challenging. Institutional care is often challenging in elderly with poor cognitive function and neuromuscular debility. Multiple comorbidities may increase the drug adverse reactions and may necessitate dosage modification or avoidance of certain drugs.[22] Newer, short term MDR TB regimens may be contraindicated in patients with cardiac arrhythmias. Cardiac comorbidities are more common in elderly.

Comorbidities can lead to significant worsening in TB. Hence all elderly should be evaluated for possible comorbidities and should be managed properly.

1. How to overcome the challenges?

1.1. *Early diagnosis*

Always consider TB as a differential diagnosis in elderly with any respiratory symptom/chest radiological abnormality/unexplained deterioration in health/worsening of underlying chronic diseases without any obvious cause. Elderly with uncontrolled diabetes & unexplained weight loss should be evaluated for tuberculosis. TB can coexist with many other chronic diseases. Be aware of this & evaluate whenever necessary. Whenever diagnosis is uncertain, proper imaging

(Ultrasound/CT scan) bronchoscopy, biopsy from the site of lesion may be needed. Elderly should be evaluated for risk factors and comorbidities once TB is diagnosed.

1.2. *Treatment*

Drug dosage should be individualized considering the risk factors and comorbidities. Care taker should administer the drugs if patient is not capable of self-care. Evaluate and optimize treatment of all comorbidities. Proper follow up and periodic evaluation for response to treatment and drug adverse reactions is essential. Home visit by health care workers may improve the compliance.

There are no definitive guidelines for management of TB in elderly. Since elderly constitute a high risk group, guidelines are needed for management of TB in elderly. Guideline emphasizing screening, indications for evaluation, algorithm for evaluation, evaluation for comorbidities, individualized approach, monitoring for adverse drug reactions, social and financial support, management of comorbidities and drug interactions is essential for management of TB in elderly.

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Dr. Vishnu sharma. M– Manuscript preparation, literature review.

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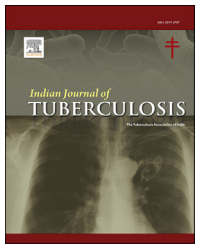

Review article

Geriatric tuberculosis in India-challenges and solutions

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ABSTRACT

India has the highest burden of tuberculosis (TB) in the world. Despite a national program for control and elimination of TB, there is a lot to achieve to effectively diagnose and treat TB. One important aspect that often remains ignored is geriatric TB. This article focuses on the challenges in clinical presentation, diagnosis and treatment of geriatric TB along with some suggested solutions.

1. Introduction

Tuberculosis (TB) is a notoriously chronic infectious disease caused by *Mycobacterium tuberculosis* (MTB) and has the highest global burden in India with a 21% prevalence rate. As per the Global TB Report 2021, the estimated incidence of all forms of TB in India for the year 2020 was 188 per 100,000 population. The total number of TB patients (new & relapse) reported during 2021 was 19,33,381 which was 19% higher than that of 2020. As per the Global TB Report 2021, the estimated mortality rate among all forms of TB was 37 per 100,000 population in 2020. There has been a slight increase in the mortality rate due to all forms of TB between 2019 and 2020 by 11% in the country. In absolute numbers, the total number of estimated deaths from all forms of TB excluding HIV, for 2020 was 4.93 lakhs (4.53–5.36 lakhs), which was 13% higher than the 2019 estimate. The total number of reported deaths among Drug Sensitive-TB patients notified in 2020 was 76,002 (4.3% of the total notifications of 2020) which is 15.4% of the estimate for the country.[1]

It has been well established that both innate and adaptive immune responses are required for host control of tuberculosis infection.[2] In a patient infected with TB, host cellular immune response determines whether an infection is curtailed at the latent phase or it progresses to active tuberculosis infection. Efficient cell-mediated immunity is essential to permanently arrest the infection at the latent or persistent stage, but if the initial infection in the lung is not controlled or if the immune system becomes weakened, *M. tuberculosis* can cause active tuberculosis. Besides, in geriatric patients, there is decreased elastic recoil of the lungs, decreased respiratory

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muscle strength and decreased cough reflex; all of which contribute to decreased clearance of respiratory secretions. Therefore, it is expected that with age, there is increased host susceptibility leading to the public health importance of geriatric TB.[3]

TB can involve almost all anatomical locations of the human body. Pulmonary TB (PTB) and Extrapulmonary TB (EPTB) both are seen across all parts of India and among all age-groups. While special populations like paediatrics, pregnant and comorbid patients are given special attention, geriatric TB remains an ignored entity. There are multiple challenges in terms of both diagnosis and treatment of TB in geriatric patients. In this review article, the challenges regarding the clinical presentation, microbiological diagnosis and treatment of Tuberculosis in geriatric population are discussed.

2. Challenges in clinical presentation of geriatric TB

India has the highest burden of TB in the world. Coupled with that, there is an increase in the average life expectancy. So it is of great concern that in coming times, the proportion of geriatric TB will increase.[4] Unlike paediatric TB, there are no separate guidelines for diagnosis and treatment of tuberculosis in geriatric population in India.[5] The importance of separate focus on geriatric TB stems from the fact that they may present with the atypical clinical profile and non-specific symptoms. The diagnostic dilemma is further complicated with the comorbidities and increased risk of underlying malignancy.[6]

Nearly three quarters of adult TB patients have pulmonary involvement. However, the risk of extra pulmonary manifestations including miliary, neurological and genitourinary symptoms increase with age.[7] The clinical features of TB in elderly may be nonspecific, limited to weight loss, cough and dyspnoea without any documented fever. However, apart from tuberculosis, underlying chronic organ dysfunctions as well as malignancies also have to be kept as the differential diagnosis. Pleural involvement is also more common in elderly.[8] A study done in geriatric TB patients found nearly half of the patients had pleural effusion or thickening.[9] A close differential, besides being a risk factor for TB, in elderly is bronchogenic carcinoma. It has also been seen that nearly 5% of elderly population present with simultaneous lung tumours with pulmonary TB, which may lead to diagnostic delay of either or both the diseases.[10]

3. Challenges in diagnosis of geriatric TB

Among the elderly patients, microbiological diagnosis of Tuberculosis, especially EPTB is often challenging. It is largely due to the very small number of tubercle bacilli (pauci-bacillary) in the samples collected in EPTB.[11] In geriatric populations, the issue is coupled by difficulty in collecting optimal fluid or tissue samples and limited amount of sample available.[12]

The demonstration of acid-fast bacilli by Ziehl Nielsen (ZN) staining is an inexpensive and widely available technique but it lacks sensitivity in extrapulmonary samples due to low bacilli load. Obtaining microbiological samples may be difficult even in pulmonary cases as elderly patients are often unable to spontaneously expectorate sputum. Consequently, other methods to acquire respiratory samples may be required; for example, induced sputum production by nebulizing with hypertonic saline or bronchoscopy. However, the risk of procedures like bronchoscopy should always be weighed carefully, especially in patients with underlying comorbidities and respiratory failure. Recently, next generation sequencing has also been used in diagnosis of tuberculosis in patients where diagnosis could not be obtained from the conventional sputum-based genotypic or phenotypic tests. Culture remains the gold standard for microbiological diagnosis of TB. Liquid culture systems like MGIT (mycobacteria growth indicator tube) are preferred over conventional culture (Lowenstein Janssen media) techniques due to higher sensitivity and shorter turn-around time (6 weeks vs 8 weeks in LJ media). A positive culture also provides an ideal platform to perform susceptibility testing by first-line and second-line line probe assay (LPA). Cartridge based nucleic acid amplification test (CBNAAT) has been demonstrated to be a highly useful molecular test in EPTB as it has a very short turnaround time (2 hours). It can be performed from almost all specimens collected and also provides valuable information on rifampicin resistance.[13]

Therefore, all efforts are required to obtain microbiological evidence of TB to confirm the diagnosis and to decide on the appropriate antitubercular drugs regimen. If there is no microbiological evidence of tuberculosis, indirect diagnostic tests including tuberculin skin test (TST) or interferon gamma release assay (IGRA) can also be utilized. Both TST and IGRA are only markers of infection with MTB. These tests are unable to differentiate between infection and disease. While positivity of TST declines with age, that of IGRA is generally maintained and may have a better sensitivity at making a clinico-radiological diagnosis.

Most cases of geriatric tuberculosis are because of reactivation which may be because of decline in immune response due to comorbidities and malignancies. The increased risk of severe infections also increases with age because of immunosenescence.

Among radiological investigations it has been found that lung cavitation is less common in elderly. On the other hand, bilateral multiple zones involved in the lung along with the involvement of pleura and other extra pulmonary sites are more common in elderly population. The elderly can also present with atypical radiological features like involvement of the middle lobe or lower lobe rather than upper lobe along with nodules or masses which have to be differentiated from malignancy.

4. Challenges in treatment of geriatric TB

It is very important to remember that elderly population generally have comorbidities for which they are on multiple drugs. Because of this, even in drug sensitive TB, the therapy must be evaluated for drug interactions.[14] It has also been found that there is a poor tolerance for the TB drugs with a

higher rate of side effects in the elderly.[15] The influence of aging on hepatotoxicity can be complicated by the underlying chronic liver disease, hepatotoxic drugs and alcohol intake. Due to decreased renal clearance in elderly, many TB drugs have to be given in reduced doses or in alternate day formulations. Ethambutol can cause decreased visual acuity which may be confused with presbyopia in elderly. Hence, a baseline ophthalmological examination can be done in patients who are being prescribed ATT.

Compliance to treatment for tuberculosis is also decreased in the elderly because of increased forgetfulness, lack of social support, hesitancy to take medications and increased frequency of adverse events. Because of this, directly observed therapy is particularly important in geriatric TB. The outcome of TB in elderly is also poor with mortality increased by nearly 6 folds.[16]

5. Suggested solutions and the way ahead

There is a need for administrative measures including focussed guidelines at national and regional level for diagnosis and management of geriatric tuberculosis so that appropriate training of healthcare staff for the same can be done. The treating physicians need to be sensitized regarding the above-mentioned challenges for geriatric TB through medical education programs. The recent undergraduate medical curriculum in India stresses on both obstructive airway disease and tuberculosis as the core competencies under respiratory medicine.

The knowledge of challenges faced in diagnosing and treating geriatric TB can be included in the undergraduate medical curriculum so that there is early realization of understanding the issues pertaining to this neglected group of patients. Self-help groups and assistance by local health workers including Anganwadi workers can also ensure treatment and follow-up compliance. Financial assistance can help cater to the needs for nutritional costs to elderly who do not have any source of income.

A detailed clinical history along with examination, vigilant follow up, and appropriate treatment protocols with compliance can reduce morbidity and mortality of geriatric TB. Availability of newer diagnostic tests in the national program like Gene Xpert ultra and gene sequencing can help in making a diagnosis in elderly where microbiological samples are scanty. A baseline routine organ function tests and ophthalmological examination can help individualize ATT therapy.

In the past 2 years because of the covid pandemic, multiple lockdowns and diversion of healthcare resources, TB notification has fallen.[17] The geriatric population also faces difficulty in arriving at a healthcare facility for timely investigation and diagnosis. So, all efforts should be made to minimize the number of visits in making diagnosis and initiating treatment. Telemedicine[18] can also help in monitoring the geriatric TB patients for symptoms, adverse drug reactions of TB drugs and clinical response to therapy.

It is the need of the hour to provide the necessary focus on geriatric TB to decrease the morbidity and mortality among the elderly. After 75 years of independence, as India has more than doubled its life expectancy to 70 years, it behoves us to give due focus to its geriatric population in diagnosing and treating this curable disease.

Conflicts of interest

The authors have none to declare.

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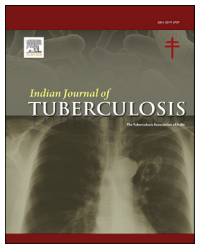

Review article

Respiratory vaccination

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ABSTRACT

Vaccinations are among the most cost-effective preventive health strategies to reduce healthcare costs and prevent morbidities. Every year, many adults and elderly encounter hospitalization because of infectious respiratory diseases. Among these, viral and bacterial pneumonia, tuberculosis, diphtheria and pertussis infections are some of the diseases that can be prevented and managed with fewer complications, with adequate preventive immunization. This review tries to outline the vaccines available for the prevention of these respiratory ailments along with their schedule and dosages.

1. Introduction

Viral pneumonia including those caused by coronavirus disease (COVID-19) and influenza, bacterial pneumonia, tuberculosis, diphtheria, and pertussis infections are a group of vaccine-preventable diseases that adversely affect the respiratory system with considerable morbidity & mortality, particularly in older adults. Over the years, vaccination in adults has assumed importance as global vaccination programs have demonstrated a significant reduction in healthcare-associated economic burden.[1] The long-term health benefits of vaccination have gained increased recognition in the last few years due to COVID 19 pandemic. This review attempts to outline the vaccines available for the prevention of respiratory ailments along with their schedule and dosages.

2. Covid-19 vaccinations

2.1. *Introduction*

Coronavirus disease (COVID-19) is an infectious disease with predominant respiratory involvement and is caused by the 'SARS-CoV-2' RNA virus of the family *Coronaviridae*. Prevention of COVID-19 disease has been challenging because of the constantly changing nature of the virion. Until October 2021, a total of 322 potential vaccine candidates were identified by World Health Organization (WHO) that confer immunity by

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producing either neutralising antibody and/or cell-mediated immunity.[2]

2.2. Vaccine

The SARS-CoV-2 virus has a large genome encoding gene for proteins that are responsible for viral replication and propagation. The spike protein is the most immunogenic that produces neutralizing antibodies, which confer protection by blocking infection. Depending on the technologies used, vaccines have been developed that include mRNA vaccines, replication-defective viral vector vaccines, inactivated viral vaccines, protein subunit vaccines, and virus-like particle vaccines.[3] The efficacy against symptomatic COVID 19 varies from 50 to 78% for inactivated vaccines, 66–91% for viral vector vaccines, and 94–96% for m RNA and subunit vaccines against different variants. In India, Covishield® (AstraZeneca vaccine manufactured by Serum Institute of India), Covaxin® (Bharat Biotech Limited) and Russian-made Sputnik - V are available as approved vaccines [Table 1]. Long term evaluation of the immune responses of these vaccines is required due to the constant changing nature of the virus.

3. Influenza vaccination

3.1. Introduction

Influenza or 'flu' is an acute, contagious viral respiratory illness with serious outcomes in many patients. The disease commonly occurs in the upper respiratory tract, nose, and throat, but at times can descend to the lungs, resulting in severe pneumonia requiring mechanical ventilator support. Viruses causing Influenza are enveloped viruses from *Orthomyxoviridae* family with negative-sense single-stranded RNA. Of the 4 types (Types A, B, C, D), human influenza is known to be caused primarily by type A and B viruses. These strains have a propensity for causing epidemics and pandemics because of their typical genome structure, which causes mutations responsible for antigenic shifts and drifts.[4]

3.2. Vaccines

Annual influenza vaccination has demonstrated efficacy in reducing morbidity in high-risk groups such as children, pregnant women, the elderly, immunocompromised, patients with co-morbid conditions such as diabetes, and health care workers. Under the aegis of WHO, technical consultations are held by the *Global Influenza Surveillance and Response System* (GISRS)[5] on the prevalent viruses in February and September every year around different parts of the world to recommend the type of vaccine for each area. The antigenic composition is thus proposed as 'Northern Hemisphere' and 'Southern Hemisphere' vaccine, based on the antigenic characteristics of circulating influenza viruses, to provide maximum effectiveness. There are two types of vaccines recommended by the WHO: killed and live-attenuated.[5,6] (Table 2).

The live attenuated influenza vaccine (LAIV) is an intranasally administered, trivalent vaccine containing two influenza A strains: one H1N1 type, one H3N2 strain, and one influenza type B strain (each 15 mg) based on the circulating strains. It is recommended in influenza outbreaks only to immunocompetent, non-pregnant populations between 2 and 49 years of age.

Killed Inactivated Influenza vaccine (IIV) may be trivalent or quadrivalent and consists of a virus propagated in embryonated eggs or appropriate cell cultures. These vaccines, available as a 0.5 ml solution in a prefilled syringe, have at least two strains of the prevalent influenza A Virus and one or two strains of the Influenza B virus. Annual influenza vaccination is recommended for everyone above the age of 6 months, with rare exceptions. It may be given half yearly to children, the elderly, or those with severe co-morbidities.

After the vaccination, the antibodies appear around two weeks and reach maximum titer by about a month. In India, vaccination is recommended before October, if possible, and should continue as long as influenza viruses are in circulation. The epidemiological survey suggests that every year, peaks of influenza are seen around the rainy season and before the onset of winter.[7] However, as the virus is circulating throughout the year in different parts of India, the vaccine could be given at any time with the latest available strain, irrespective of the season.7 Common adverse effects include tenderness, redness, or swelling at the site of the injection that may appear up to 1–2 days after vaccination.

4. Pneumococcal vaccination

4.1. Introduction

Pneumococcal disease (PD) consists of infections caused by a lancet-shaped, gram-positive, facultative anaerobic bacterium called *Streptococcus pneumoniae*. This pathogenic bacteria with more than 100 known serotypes, remains a major cause of hospitalization due to respiratory illness. It is also the single most bacterial agent causing pneumonia, sinusitis, otitis media, exacerbation of bronchitis, and invasive infections like bacteremia and meningitis.[8] Over the years, streptococcal pneumonia is increasingly more common among the elderly, especially with co-morbidities like COPD, diabetes, chronic renal failure, congestive heart failure, chronic liver diseases, etc.

4.2. Vaccines

There are two types of vaccines available for protection against PD.[9] The first is Pneumococcal polysaccharide vaccine (PPSV) 23 containing long chains of polysaccharide molecules that make up the surface capsule of 23 types of pneumococci, including serotypes 1, 2, 3, 4, 5, 6b, 7f, 8, 9v, 10a, 11a, 12f, 14, 15b, 17f, 18c, 19f, 19a, 20, 22f, 23f and 33f. Another vaccine is Pneumococcal Conjugate Vaccine (PCV) 13, which contains capsular polysaccharides from 13 serotypes (1, 3, 4, 5, 6a, 6b, 7f, 9v, 14, 18c, 19a, 19f, and 23f). One dose (0.5 ml) of the vaccine contains 25 micrograms of each capsular polysaccharide antigen dissolved in isotonic saline with 0.25% phenol as a preservative. In conjugated vaccines, the bacterial

Table 1 – COVID 19 vaccine technology platforms with characteristics of vaccines.

Platform	mRNA	Replication defective viral vector	Inactivated pathogen	Protein subunit	Virus like particle
Type of vaccine candidate	mRNA encapsulated with lipid nanoparticle of a disease-causing virus	A safe virus transfers the instructions for making antigens from the disease-causing virus into cells	Disease-causing virus inactivated by high temperature, chemicals or radiation	One or more antigens of virus which causes disease	Bacteria engineered with recombinant spike proteins from SARSCoV2
Target antigen	S protein	S protein	Whole virus	S Protein	S Protein
Immune response	Neutralizing antibodies, Virus specific Th1 and CD8 +T cell responses	Neutralizing antibodies, Virus specific Th1 and CD8 +T cell responses Skewed CD4+T cell responses	Humoral immune response mainly: Neutralizing antibodies	Neutralizing antibodies in high titres	Neutralizing antibodies
Immunization regimen	**mRNA-1273:** 0.5 ml, 2 doses, 28 days apart **BNT162b2**: 0.3 ml, 2 doses 21 days apart	**AZD1222 (ChAdOx1):** 0.5 ml, 2 doses, 12 weeks apart **Ad26.COV2.S**: 0.5 ml, one dose **Sputnik V**: 2 doses, 21 days apart	**BBIBP-CorV**: 4 ug in 0.5 ml, 2 doses 21 days apart **CoronaVac**: 3 μg in 0.5 mL **Covaxin**: 6 μg, 2 doses 2 weeks apart	**NVX-CoV-2373**: 5 μg of the recombinant vaccine + 50 μg of matrix-M1 adjuvant, 2 doses, 21 days apart	**CoVLP**: 3.75 ug, 2 doses, 3 weeks apart
Advantages	No live components, so no risk of the vaccine triggering disease	Lyophilized vaccine can be stored at 2–8 °C Safe as the virus cannot replicate Large scale production and greater immunogenicity	Safe as has no live components Easy to store Simple to manufacture	Stable, no risk of live virus, well established technology	Good safety profiles efficacy of attenuated vaccines and the safety of subunit vaccines Can be stored at 2–8 °C
Disadvantages	Requires ultra-cold storage (−80 °C/−20 °C) for long term storage Shelf life at 2 to 8 °C: 30 days Shelf life at room temperature:12 hours	Requires to be stored at −18 °C Pre-existing immunity to the vector could reduce the immune response	Risk of vaccine-enhanced disease Requirement for booster doses	Adjuvants required with evaluation of best components; hence complicated process of manufacture	Complexity in their development Booster immunization required
Safety concerns	Anaphylaxis, myocarditis	Anaphylaxis, TTS, CVST, GBS, myocarditis Sputnik v: Nil	PR, ReA with CoronaVac NR with others	not reported	not reported

Table 2 – Recommended formulations of Influenza vaccines (WHO) (*Adapted from* Recommended composition of influenza virus vaccines for use in the 2022 southern hemisphere influenza season. Global influenza programme; World Health Organization).[6]

Type of Vaccine	Egg based vaccine	Cell- or recombinant-based vaccines	Egg based vaccine	Cell- or recombinant-based vaccines
Southern hemisphere influenza vaccines (2022)				
Composition	Tetravalent • A/Victoria/2570/2019 (H1N1) pdm09-like virus •A/Darwin/9/2021 (H3N2)-like virus •Austria/1359417/2021 (B/Victoria lineage)-like virus •B/Phuket/3073/2013 (B/Yamagata lineage)-like virus	•A/Wisconsin/588/2019 (H1N1) pdm09-like virus •A/Darwin/6/2021 (H3N2)-like virus •B/Austria/1359417/2021(B/Victoria lineage)-like virus •B/Phuket/3073/2013(B/Yamagata lineage)-like virus	Trivalent •A/Victoria/2570/2019 (H1N1)pdm09-like virus •A/Darwin/9/2021 (H3N2)-like virus •B/Austria/1359417/2021 (B/Victoria lineage)	•A/Wisconsin/588/2019 (H1N1)pdm09-like virus •A/Darwin/6/2021 (H3N2)-like virus •B/Austria/1359417/2021 (B/Victoria lineage)-like virus
Northern hemisphere influenza vaccines (2022–23)				
Composition	Tetravalent •A/Victoria/2570/2019 (H1N1) pdm09-like virus; •A/Darwin/9/2021 (H3N2)-like virus; •B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and •B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.	•A/Wisconsin/588/2019 (H1N1)pdm 09-like virus •A/Darwin/6/2021 (H3N2)-like virus •B/Austria/1359417/2021 (B/Victoria lineage)-like virus •B/Phuket/3073/2013(B/Yamagata lineage)-like virus	Trivalent A/Victoria/2570/2019 (H1N1) pdm09-like virus; A/Darwin/9/2021 (H3N2)-like virus B/Austria/1359417/2021 (B/Victoria lineage)-like virus.	•A/Wisconsin/588/2019 (H1N1)pdm09-like virus •A/Darwin/6/2021 (H3N2)-like virus •B/Austria/1359417/2021 (B/Victoria lineage)-like virus.
Immune response	Neutralizing antibodies B cell responses	Cellular responses Neutralizing antibodies B cell responses	Neutralizing antibodies B cell responses	Cellular responses Neutralizing antibodies B cell responses

Table 3 – Recommendations for use of 15-valent PCV in series with PPSV 23 or PCV20 in pneumococcal conjugate vaccine-naïve adults aged ≥19 years (United States, 2022)[10].

Medical indication group	Specific underlying medical condition	Age group, yrs	
		19–64	≥65
None	None	None	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥ 1 years later*
Underlying medical conditions or other risk factors	Alcoholism Chronic heart disease† Chronic liver disease Chronic lung disease¶ Cigarette smoking Diabetes mellitus Cochlear implant CSF leak Congenital or acquired asplenia Sickle cell disease or other hemoglobinopathies Chronic renal failure** Congenital or acquired immunodeficiencies**,†† Generalized malignancy** HIV infection** Hodgkin disease** Iatrogenic immunosuppression**,§§ Leukemia** Lymphoma** Multiple myeloma** Nephrotic syndrome** Solid organ transplant**	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥ 1 years later§	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥ 1 years later*

polysaccharides are covalently conjugated to an immunogenic carrier protein, CRM197 (genetically detoxified diphtheria toxin).[9]

Recently, the Advisory Committee on Immunization Practices (ACIP) recommended 15-valent PCV (PCV15) that contains pneumococcal polysaccharide serotypes 22F and 33F in addition to the PCV13 serotypes.[10] (Table 3) It also recommended 20-valent PCV (PCV20) for PCV–naïve adults who are either aged ≥65 years or aged 19–64 years with underlying conditions. It was recommended that when PCV15 is used, it should be followed by a dose of PPSV23, typically ≥1 year later. Recently, a new 10-valent WHO pre-qualified PCV 10 has been launched by Serum Institute of India, Pune that is specially tailored to the various serotypes prevalent in India and other selected regions of the world.[11] It has demonstrated comparable safety and immunogenicity in randomized trials against licensed pneumococcal vaccines across diverse populations of India and Africa.

PPSV23is a sterile, clear, colourless liquid vaccine that is given subcutaneously as a single dose. Revaccination may be recommended for persons exhibiting an increased risk for pneumococcal infection and for those who are likely to have a rapid decline in pneumococcal antibody levels after 5 years. ***PCV13*** is administered in a dose of 0.5 ml intramuscularly in the deltoid muscle of the upper arm. Common mild adverse reactions include injection site pain, muscle pain, fatigue, headache, and joint pain. A new recommendations policy has been released by CDC for the adult pneumococcal vaccine (Table 3) to improve vaccine coverage among adults and the elderly.[9,10].

5. Bcg vaccination

5.1. *Introduction*

Tuberculosis has been a major global public health problem for a considerable time, with more than 10 million new cases of tuberculosis and 1.5 million deaths reported in the year 2018.[12] The worldwide annual risk of childhood TB infection in high-burden countries like ours is estimated to be 0.5–2%.[13] In India, the country with the largest share of the global burden, more than 2.4 million cases of TB were seen in 2019. Of these, more than a third were sputum positive, posing a serious threat of community spread. The threat is amplified by the silent epidemic of diabetes and HIV infection in the adult population leading to the reactivation of disease in many previously exposed individuals.

5.2. *Vaccines*

The vaccine against TB prevention is a live attenuated, culture preparation of the 'Bacillus of Calmette and Guerin' (BCG) strain of *Mycobacterium bovis*. The freeze-dried BCG preparation is delivered in vials, containing 50 mg wet weight of BCG substrain TICE live antigen. For an adult dose, 1 ml, and for pediatric vaccines, 2 ml of sterile water for injection is added at 4–25 °C, for reconstitution of the vaccine.

Epidemiological data suggest that the protective efficacy of BCG is unpredictable and may vary from 80% to 0%.[14] Since 1985, the universal program of immunization has provided a good reach of BCG vaccination in India, though some areas of the country lack coverage. BCG vaccination cannot prevent natural pulmonary TB infection and its complications, it does manage to reduce the hematogenous spread, thereby improving efficacy in the prevention of disseminated TB and TB meningitis. WHO has not recommended a booster dose because of a lack of efficacy data.[14]

Contraindication to the BCG vaccine includes a positive Mantoux test as it may result in severe local inflammation and scarring. The vaccine is also avoided in immunocompromised individuals (e.g., chronic steroid users, HIV-infected, or post-organ transplant recipients). There is a lack of safety data on BCG vaccination in pregnancy. Common adverse effects include redness, swelling, and mild tenderness at the local injection site.

6. Diphtheria and pertussis vaccination

6.1. *Introduction*

Diphtheria is a localized infection of the mucus membranes of the throat, caused by a bacteria called *Corynebacterium diphtheriae*. The infection demonstrates its lethal effect through the elaboration of a toxin and can be fatal, if untreated. Pertussis, also known as whooping cough, is a highly infective disease of the respiratory tract caused by a gram-negative, encapsulated bacterium, *Bordetella pertussis*. This common childhood infection can also affect adults, with a higher risk of severe pneumonia in the elderly with diabetes, asthma, and COPD.[15]

Both the infections are transmitted by airborne respiratory droplets during coughs or sneezes, or by infected salivary secretions as during kissing or sharing drinks. The infectivity is particularly high in the early stages of illness, though a patient can continue to spread the disease for up to 21 days after the appearance of symptoms. Due to active vaccination and passive immunity exceeding 90%, the incidence of diphtheria and pertussis in children has decreased dramatically. However, in some areas, re-emergence is seen in adults due to waning immunity; hence there is a need for booster doses of diphtheria and pertussis vaccine.[15,16]

6.2. *Vaccines*

The diphtheria vaccine contains a toxoid (a modified vaccine of the diphtheria toxin) and is given intramuscularly in the form of the DTaP/IPV combination vaccine. Each 0.5 ml dose consists of Diphtheria toxoid (30 IU), Tetanus toxoid (40 IU), pertussis toxoid, and filamentous haemagglutinin (25 μg each), and inactivated poliomyelitis virus (type 1: 40, type 2:8, type 3:32 D antigen Units).

A routine booster with Tdap (standard quantities of tetanus and reduced quantities of diphtheria and acellular pertussis) is advised above the age of 7 years in the dose of 0.5 ml intramuscularly.[17] Pregnant females should get a Tdap booster during the third trimester, to help protect the newborn from pertussis. Unvaccinated adults should get a dose of Tdap and those vaccinated should receive a booster

dose of either Tdap or Td (a different vaccine that protects against tetanus and diphtheria but not pertussis) every 10 years or after 5 years in the case of a severe or dirty wound or burns.[17]

Common adverse effects include pain at the local injection site, redness, and localized swelling. Contraindications include a serious allergic reaction to any of the components of the vaccine or a history of encephalopathy without an obvious underlying cause, occurring within 7 days of administration of a pertussis vaccine.

7. Conclusions

COVID 19 pandemic has brought a much-needed spotlight on adult immunization as a potent way of preventing severe respiratory diseases. However, many issues regarding the efficacy, safety, and cost-benefit analysis of an adult vaccination program in India remain unaddressed.[15] Though the preventive measures for respiratory diseases through vaccination are being practiced sparsely, the operational challenges keep the coverage inequitable among a vast majority of our population. An urgent need thus exists for the inclusion of adult vaccination in the national universal immunization program, to reduce morbidity and excessive healthcare cost burden of respiratory diseases.

Conflicts of interest

The authors have none to declare.

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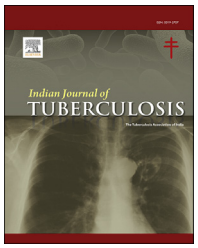

Review article

Clinical spectrum of TB in elderly in a TB & respiratory institution

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ABSTRACT

Tuberculosis has maximum burden among young population in developing countries like India. However, children and elderly form a special group where TB may have atypical presentation. This presents with epidemiological, diagnostic and treatment challenges in these groups which may need special attention in the national programmes for TB. Due to atypical presentation, elderly population is vulnerable to frequent misdiagnosis and disease may already be in advanced stage when correct diagnosis is made. Not only this, adjustment of drug dosages and high chances of adverse drug reaction make the management of TB more complicated in elderly. Mortality due to TB is also higher in this group as compared to young patients of TB. This view point briefly highlights the epidemiological, clinical and disease outcome aspects of TB disease in elderly patients.

1. Introduction

Globally, tuberculosis (TB) related deaths were expected to have killed 1.3 million human immunodeficiency virus (HIV)-negative individuals and 214,000 HIV-positive individuals in 2020. Globally, an estimated 9.9 million persons contracted TB in 2020, a modest decrease from 2019 but a slower reduction than in 2019.[1] With around 1.9 million total TB cases in 2021, India contributed to about one-fourth of the worldwide TB burden.[2]

Although TB affects people of all ages, middle-aged adults and the elderly (as defined by age group more than 60 years) are the age categories most frequently affected.[3] Contemporary medicine has increased the growth in life expectancy and the elderly's increasing susceptibility to TB. For India, TB is a concern. According to recent research, south India had a 15.6% prevalence of TB among the elderly.[4] The detection rate for TB in the elderly is around 25% lower, and the majority of cases are misdiagnosed. To make matters worse, TB mortality in the elderly is six times higher.[4,7] Therefore, more study is

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required to identify the variables linked to poor outcomes in the elderly TB population, which our national TB programme should also address.

2. Physiopathology and issues with the elderly

The majority of elderly tuberculosis cases are associated with lesions that reactivate after lying latent for a number of years. Immune changes are responsible for these lesions becoming active. Immune system changes are brought on by senescence, most notably a decrease in immunity that was previously acquired, as well as other factors.[5] Co-morbid conditions in the elderly, such as diabetes mellitus (DM), HIV infection, immunosuppressive medications, malnutrition, and underlying cancer, may make them more susceptible to TB.[6,7] Elderly patients have difficulty adhering to treatment because of drug reactions that can be harmful, which calls for enhanced monitoring.

Age-related lung reserve and elastic forces reduction occurs in the lungs. In addition, there is a loss of respiratory muscle strength, a reduction in ciliary motility, an increase in kyphosis, a decrease in chest wall compliance, and a consequent drop in lung protective function.[8,9]

Individual vulnerability, immune-senescence, corticosteroids and immunosuppressants, as well as subpar living conditions, are particular conditions in elderly that favour TB infection. Age-related anatomical and physiological changes, malnutrition, and concomitant conditions all contribute to an increased risk of infection and, more specifically, an increased chance of serious illness.[10] Because fewer immunologically naive T cells are produced from the thymus and fewer T cells are able to form immunological memories, intracellular pathogen infections like TB are more likely. Immunosenescence is consistent in part with lymphopenia. Inflammaging, or the rise in inflammatory cytokine levels, together with typical tissue ageing all enhance the likelihood of infection. Increased oxidative stress and chronic inflammation, decreased neutrophil and macrophage phagocytic capacity, and impaired natural killer cell activity all play crucial roles in *M. tuberculosis*' ability to live intracellularly.[10]

3. Clinical spectrum

The most typical radiological marker of TB in hospitalised patients is multi-lobar involvement, whereas it is consolidation and/or coupled with cavitation in outpatients. Although TB can appear in a variety of ways, the most prevalent presentation in aged people is pulmonary involvement.[11] The age-related co-morbidities have frequently obscured the condition, lengthened the time it took to diagnose it, and worsened its severity.[12] Also, the typical symptoms like cough, night sweats, pyrexia and loss of weight are less frequently seen in elderly.[13]

At the author's institute, a retrospective study of 7439 TB patients enrolled in the national programme over a five-year period (1996–2001) was conducted.[14] The ratio of male to female TB patients in the older age group was 3 to 1, compared to 1.4 to 1 in the younger age group. The incidence of pulmonary TB was also significantly greater than extra-pulmonary TB in the older age group (16:1) than in the younger age group (4:1). Additionally, older TB patients had considerably lower cure rates (69.2% vs. 80.7%) and sputum conversion (75.3% vs. 85.7%) as compared to younger TB patients.

4. Microbiological diagnosis

The diagnosis is typically made on the basis of clinico-radiological findings in older individuals since they frequently cannot generate enough sputum. This creates yet another opportunity for misdiagnosis or subpar care. In most institutions, the AFB smear is the primary method used to diagnose TB, and poor or insufficient sample quality might result in falsely negative results.[8] Although the diagnosis has been more reliable since the introduction of genotypic tests, there have been instances of false negative findings if the sample itself is subpar or sputum is given in place of saliva.[15] Given the brittleness of the skin tissue in the older population, the Mantoux skin test for TB has also not proven to be very reliable. In 1990, Kosela et al conducted a prospective population-based study and found that young people were more likely than older people to convert to Mantoux.[5] The elderly exhibited more unusual symptoms.

5. Diagnostic imaging

We have computed tomography (CT) scan and a chest X-ray at our disposal for radiological diagnostics. Almost all primary health institutions in our nation now have chest X-rays, however the results are frequently not as reliable for TB diagnosis as we might hope. Endobronchial spread, the military pattern, mediastinal adenopathy, multilobar infiltrates, unilobar infiltrates, cavitation with consolidation, lung abscess, pleural effusion, and occasionally even grossly normal X-ray images are signs of tuberculosis.[16] Morris conducted a prospective research on elderly tuberculosis-infected patients.[8] He discovered that all of the 93 elderly patients with pulmonary tuberculosis had radiological signs of inflammatory alterations; 7% of these features were exclusively apical, 48% were in the mid and basal zones, and 46% had a mixed picture.

The CT scan of the chest is now necessary, and the most frequent results are the appearance of a tree in bud, consolidation with or without cavitation, and the presence of necrotic lymphadenopathy. When in doubt, percutaneous biopsy can be used to sample organ lesions for tuberculosis culture.[12] However, in a developing nation like ours, where access to CT scan features is limited, there is a delay in diagnosis when an unusual presentation occurs.

The older patient may have unusual radiological findings, such as infiltrates in the middle or lower lobes, lesions or nodules that resemble tumours more than normal masses, widespread bronchopneumonia without cavitation, or infiltrates that don't go away. When diagnosing lesions in elderly patients, it's common to mistake them for lung cancer or community-acquired bacterial pneumonia.[17] The results of

a retrospective investigation on patients in Delhi between 2005 and 2010 revealed that pulmonary TB frequently involved both upper and lower lobes, and that geriatric TB was less likely to have upper lobe predominance and cavitary lung lesions.[18]

6. Co-morbidities

Due to age and lifestyle-related issues, the elderly frequently have many comorbidities, which broaden the disease's scope, lengthen the illness's duration, or make treatment more difficult. Smoking-related lung disease and substance abuse, such as alcohol and cigarette addiction, are the most frequently encountered lifestyle-related illnesses.

Smokers with COPD already have weakened lungs, and an additional TB infection lowers the patient's quality of life while complicating the lung function status. Untreated chronic drinking compromises the liver's cells, and many of these individuals get transaminitis or acute liver injury when anti-tubercular medications are administered. These individuals' reduced albumin levels also contribute to the disease's protracted course and poor recovery status.[5] In 1989, Morris examined 93 TB patients and found that the following biochemical abnormalities predated treatment: hyponatremia (60%), hypokalemia (42%), and hypoalbuminemia (83%) and elevations of bilirubin (20%), alkaline phosphatase (62%), aspartate transaminase (77%) and lactic dehydrogenase (74%) after treatment.[8]

Diabetes mellitus (DM), hypertension, ischemic heart disease, and medical renal disease are age-related comorbidities that are frequently seen. All of these conditions make it difficult for an individual to follow an anti-TB drug regimen, lengthen the time spent receiving therapy, and frequently increase the risk of rare complications, poor recovery, and death.[19] According to a meta-analytical assessment from 1998, diabetes, COPD, and cardiovascular disease were all more prevalent in older patients ($P < 0.05$), although alcoholism was more prevalent in younger individuals ($P < 0.05$).[19] Elderly people are particularly vulnerable to complications throughout the course of the illness, with slow recovery time, disease progression despite treatment, the development of electrolyte imbalance, renal and hepatic compromise, and pulmonary complications like pneumothorax, empyema, or hemoptysis being the most frequently reported.

Aspiration pneumonia, electrolyte imbalances, hypoglycemia, renal and liver damage, hospital acquired infections, etc. are prevalent issues among elderly inpatients.[20] Lower albumin levels and lower total leukocyte counts were more frequently lower among older patients, according to a meta-analytical evaluation from 1998 ($p < 0.01$). In older individuals, the tuberculin skin test was less frequently positive ($p < 0.01$).[16]

According to a 2011 study done in Tamil Nadu, 47% of all TB patients were new sputum positive and 14% of all TB patients were older.[21] They were 38% more likely than all other TB patients to experience negative treatment outcomes. There was a relative risk of 1.5 for worse treatment outcomes among older TB patients who were over the age of 70.

7. MDR TB and elderly

The dreaded development of multi-drug resistance tuberculosis (MDR-TB) in the aged population is one of the most feared causes of treatment failure and sluggish disease progression.

From 2004 to 2019, a retrospective investigation was carried out in Shandong, China.[22] 4368 senior (>60 years) primary TB cases were among the 12,661 total primary TB cases. Rifampicin-resistant (RR-TB) and MDR-TB infections made up, respectively, 17.19% and 2.29% of these. MDR-TB, PDR-TB, and RR-TB prevalence rates rose by 160.00%, 18.18%, and 231.82%, respectively, between 2004 and 2019.

Due to the presence of nephrotoxic and cardiotoxic medicines, MDR TB requires a lengthier treatment course than ordinary TB does. Often it results in change of regimen, prolongation of regimen and might lead to poor drug compliance and often treatment failure.

8. Diabetes and TB in the elderly

DM is one of the most typical co-morbidities connected to aged people. Insulin resistance can result in a number of issues. A little more than 40% (39.5%) of diabetics are 65 years or older. According to tests for fasting plasma glucose, oral glucose tolerance testing, or glycosylated haemoglobin (HbA1c), about 21% of persons aged 65 years have a known diagnosis of diabetes, and almost the same percentage (16%) do not.[23]

One study indicated that 29% of tuberculosis patients had diabetes (known diabetics made up 20.7% of the population, while new cases of diabetes made up 8.3%).[24] Alcohol consumption, family history of diabetes, older age, and sputum positive were all strongly related with diabetes. Diabetes has a variety of implications on the illness pattern, from the presentation to the course of treatment and the final result. The senior diabetic population presents in an unusual way; the majority of them have lower lung field tuberculosis. Miliary presentation and central nervous system tuberculosis are also on the rise in elderly. The likelihood of a prolonged illness with poor outcomes, an increase in mortality, the emergence of renal problems, as well as the emergence of drug-resistant TB, has frequently increased.

9. The elderly and TB and cancer

According to a study, the incidence of secondary lung cancer among primary cancer patients in the cohort with TB was 1.67 times higher than in the cohort without TB.[25] When compared to the TB population, conditions like these (cardiovascular accident, chronic renal illness, and chronic obstructive pulmonary disease) markedly raised the chance of subsequent lung cancer. The aged population frequently possesses these risk factors.

The elderly population frequently smokes continuously, which increases their risk of lung cancer over time. The most frequent presenting symptoms are loss of appetite, weight

loss, and cough. Fever is sometimes a deceiving symptom; patients frequently are unaware of their own fever episodes or unwittingly report fake feverish episodes. Elderly populations with a high risk of lung cancer need to undergo the proper screenings. Additionally, persons with a history of TB run the risk of developing lung cancer (adenocarcinoma) in the damaged parenchyma.[26]

10. Complications and mortality related to tuberculosis after treatment

The elderly population is also most susceptible to side effects after treatment. The persistent thin-walled hollow cavity, fibrosis with bronchiectasis, broncholithiasis, hemoptysis, and obstructive and restricted airway disease are the pulmonary parenchymal sequelae. Pneumothorax, residual pleural thickening, fibrothorax, and persistent hydropneumothorax are the pleural sequelae.

Some patients with pulmonary TB sequelae go on to develop chronic ventilatory dysfunction in the future and end up needing long-term oxygen therapy or noninvasive ventilation, which lowers their quality of life.[11] According to a Korean study, older people have a greater rate of TB-related mortality (1.3% vs. 11.1%).[27] Similar to this, an Indian study found that mortality rates were 12.5% in the 65 and older age group compared to 5.5% in the middle age group.[24]

In a South Indian study with 1259 participants, 42 (4.3%) of the participants were reported dead at the end of the follow-up period.[7] It was discovered that there was a statistically significant difference between the percentage of senior TB patients who were marked dead (9.3%) and those who weren't (3.4%) (p value < 0.001).

2014 saw the completion of a research on elderly TB inpatients by Lin et al.[28] The overall mortality rate among 2016 cases during the study period was 12.3%, and the mean age at death was 74 years. The cause of 17.3% of all TB deaths was TB. The patient died of septic shock in the majority of TB-related deaths, which happened early (median survival: 20 days).

11. Conclusion

TB in the elderly population poses a number of epidemiological, diagnostic, and therapeutic problems. In the senior age range, TB can present in a variety of atypical ways that can cause misdiagnosis or delay in diagnosis, which can lead to individuals being identified at an advanced stage of the illness. Anti-TB medications can cause adverse pharmacological responses more frequently in geriatric people. Additionally, mortality rates are higher for this age range. The senior age group may require special consideration in the national TB elimination programme because of these difficulties, including early diagnosis, specialised care, and the early start of suitable treatment.

Conflicts of interest

The authors have none to declare.

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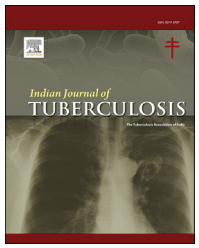

Review article

Challenges in treating tuberculosis in the elderly population in tertiary institute

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ABSTRACT

Tuberculosis (TB) epidemic is most prevalent in the India with increase in mortality and morbidity. Ongoing elderly population as a result of increase in health care facilities are at high risk of TB. Elderly people are four-fold more prone to TB. Most cases of TB in the elderly result from reactivation of latent TB due to immunosenescence. Major challenge in dealing with therapeutic aspects of elderly patients is recognising frailty to prevent loss of independence.

Challenges facing with elderly TB are difficult to reach out to hospital because of poor health seeking behaviour especially elderly female either due to ignorance or neglected by the family members, atypical presentation mimicking other disorders leading to diagnostic delay, if at all diagnosed impoverished tolerance and adherence to treatment due to various factors like associated comorbidities leading to pill load, impaired renal and hepatic functions with aging and stigma. Emerging resistance with usage of non-standard treatment regimens lead to unpropitious outcomes and increases mortality. The mortality rate is six times higher in elderly compared to younger individuals. Hence elderly people need tertiary level health care facilities for enhancing the diagnosis and appropriate management of tuberculosis and its complications. New set of guidelines to be made for elderly to increase adherence and tolerance thereby decreasing drug interactions and adverse drug reactions.

With the increased prevalence of TB in the elderly, it is the need of the hour for India, to focus on this vulnerable population as they are a potential source of infection in the community. Awareness to be created among the elderly community regarding this deadly disease and its outcomes to increase their health consciousness and medical attention. Priming the special focus on females coterie as they are the most neglected population in our society.

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1. Introduction

Tuberculosis (TB), the life-threatening single infectious disease is bothersome for India, causing maximum morbidity and mortality globally.[1] When tuberculosis cases are marked India stands prominent in the world by contributing to almost one-fourth of the global TB burden.[2] Population above the age of 60 years are defined as elderly according to the government of India.[3] With the increase in health care facilities globally average life expectancy is getting longer and as a result elderly population is increasing. According to a report from the Technical Group on Population Projections for India and States 2011–2036, in India in 2021 there are nearly 138 million elderly persons (71 million were females, 67 million were males).[4] The estimated incidence of all forms of TB in India for the year 2020 was 188 per lakh population (129–257 per lakh population) as per the Global TB Report 2021. The incidence of TB notified during 2021 was 19% higher than that in 2020. Out of the total TB cases notified in 2021, 60.7% were men and 39.1% were women.[5]

Elderly people are four-fold more prone to TB.[6] Many older individuals reside in constellating settings, challenging infection control by increasing the potential risk of TB transmission. TB in the elderly presents with non-classical symptoms hence there is a diagnostic delay. Most of the cases lead to unpropitious outcomes and increases mortality due to impoverished tolerance and adherence. A higher number of cases have been diagnosed after death among the elderly suggests that TB frequently remains camouflaged.[7] The mortality rate is six times higher in elderly individuals when compared with younger individuals.[8] Hence elderly people need tertiary level health care facilities for enhancing the diagnosis and appropriate management of tuberculosis and its complications.

2. Risk factors

The elderly are often suffering from psychological issues and cognitive impairment like dementia, Alzheimer's disease, memory loss, depression and anxiety. Elderly populations being socially segregated by their families due to various reasons are associated with a high prevalence of depression and other mood disorders.

Older people are polypathological with comorbidities, compromised metabolism and multiple age-related physiological changes within the body making them fragile and more susceptible to environmental opportunistic microorganisms.

Age-related factors like decreased health-seeking behaviour, decreased mobility, dependency, paucity of hygiene habits and sanitation due to impaired functional status are other risk factors which increase susceptibility to TB.[9–11]

The most relevant clinical markers of a state of frailty are malnourishment, falls, pathological fractures, incontinence and cognitive disorders like Alzheimer's disease or delirium.

The enhanced transmissibility of tuberculosis within congregate settings, such as old age homes, or homeless shelters, has raised concerns about tuberculosis infection transmission in the elderly population.[12]

It is common for the elderly to be stressed out because of various reasons like a compulsion to work, income insecurity, unemployment and loss of a spouse.[13]

There is a predominance of elderly TB in the male population as a counterpart, less incidence of TB in elder females might be a result of either self-negligence or negligence of family, increased dependence, ignorance and poor health-seeking behaviour.

Other factors like poor education, malnutrition, alcohol consumption, ignorance and negligence are significantly associated with an increased prevalence of elderly TB.[14,15]

As age progresses there is augmenting incidence of non-communicable diseases. About a three-fold rise in active TB risk is associated with Type - 2 diabetes mellitus (DM).[16] Incidence and severity of TB increase with age in patients with COPD (Chronic Obstructive Pulmonary Disease).[17]

In patients who have concurrent disorders like interstitial lung disease (ILD), bronchial asthma (BA), COPD, haemolytic anaemia, leukaemia, lymphoma, rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, polymyalgia rheumatica, contact dermatitis, pemphigus Vulgaris, adrenal insufficiency, inflammatory bowel disease, autoimmune hepatitis, keratoconjunctivitis, organ transplantation, nephrotic syndrome, multiple sclerosis are on long term corticosteroid therapy leading to immunosuppression leading to increased vulnerability to TB infection.[18]

As we age certain changes occur in the immune system which makes our immune system feeble conflicting to a substantial rise in the risk of infection causing an inclination to reactivation of TB,[19] the reasons being that increased susceptibility in elderly people include immunosenescence, various anatomical and physiological changes linked to ageing, as well as comorbidities and malnutrition.

Due to immunosenescence, there is decreased output of immunologically naive T cells from the thymus resulting in reduced lymphocyte count, along with the impaired ability of reactive T cells in achieving immunological memory, both enhancing intracellular pathogenic infections such as TB.[20]

Over 90% of TB cases result from reactivation of latent TB infection rather than recent transmission among elderly individuals.[21]

Air pollution, industrialization and an increased number of motor vehicles cause an increase in polluted surroundings, lack of fresh air and habits like smoking cause an increase in airway disorders and cancers. Lifestyle modifications like altered eating habits and increased nightlife lead to an increase in BMI (Body Mass Index) causing Obesity, DM, hypertension (HTN), sleep disorders and other non-communicable diseases. India still being developing country has a lot of slum areas, overcrowded places and superstitions, all of these factors favour the transmission of communicable diseases. Therefore, diseases like TB pose threat to our country and are difficult to eliminate.

3. Challenges faced during evaluating a case of Tb in the elderly

Elderly people with TB are more likely to present atypically with non-specific clinical symptoms like breathlessness,

anorexia, and mood changes which may be misdiagnosed as aging lung changes.[22–24]

Extrapulmonary TB (EPTB) presents as TB meningitis, renal, bone and joint infection (mostly affects the dorsolumbar spine and large joints) and is common in the elderly.[25,26] EPTB involving joints were considered degenerative arthritis leading to a delay in diagnosis.[27]

Miliary TB, a form of disseminated TB is also relatively common in the elderly. According to WHO (World Health Organisation), major challenges are associated with multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), TB associated with HIV, and weak health care systems.[28]

Now there is evidence that cortical and subcortical structures play a decisive role in cough reflex. By their nature, reflexive cough activates both sensory and motor areas in the cortex. The sensory component, including the sensory cortex in reflexive circuits, seems to be more vulnerable to ageing than the motor component.[29] Due to impaired cough reflex, there is a dwindled ability to produce high-quality sputum specimens lowering the sputum positivity rate.

False negativity of TST results from immunosuppression and energy.[30]

Usually, it takes a long time from presentation to initiation of treatment in elder individuals as older adults are less likely to exhibit classic TB radiologic findings like upper lobe predominance, cavitation and lymphadenopathy.[23]

Older patients are 50% more likely to have other atypical features such as pleural effusions, pleural thickening, nodular lesions, military patterns and consolidations and are twice as likely to have involvement of lower lung fields when compared to younger patients.[15]

Unavailability of resources at primary level health care centres, makes the diagnosis of tuberculosis in the elderly further late and favours its poor outcome.

Bronchogenic carcinoma is considered the commonest differential diagnosis in the elderly. Few of the authors showed that approximately 5% of elderly patients, presented with both tumours of the lung and pulmonary tuberculosis. Other differential diagnoses include pneumonia due to other pathogenic organisms, lymphomas and fibrotic lung disease.[10] Autoimmune diseases and outlandish radiological findings may create further confusion inferring in difficult and overlooked diagnosis of TB. From our experience it was difficult to differentiate interstitial lung diseases from pulmonary tuberculosis cases when associated with fibrotic changes.

Non-resolving pneumonia often being one of the differential diagnoses of pulmonary tuberculosis, its diagnosis needs further invasive investigations like bronchoscopy, Ultrasound (USG) guided Fine needle aspiration cytology, ultrasound-guided biopsy, Computed Tomography (CT) guided Fine Needle Aspiration Cytology (FNAC) and/or biopsy.

The elderly are also more likely to have incomplete documentation of diagnosis and screening for risk factors related to immunosuppression.[31] Minimally invasive diagnostic intervention needs to be considered in elderly patients who are unable to expectorate sputum. Usage of Flexible fibreoptic bronchoscopy (FOB) in obtaining bronchial washings and bronchial biopsy specimens in elderly patients has a feasible role and is contemplated as a valuable diagnostic option.[32] On histopathology of various tissue samples obtained from lymph node, pleura, liver, synovium, bone marrow revealed the characteristic granulomatous inflammation with caseous necrosis were useful in establishing the diagnosis of tuberculosis.

Elderly people being fragile and anxious mostly deny even less invasive diagnostic procedures.

In the physician's view, many may dissuade the elderly from screening for latent TB infection (LTBI) whom they deem too decrepit in tolerating treatment. In patients' view, they are afraid and anxious about diagnostic interventions and often disagree even on repeated counselling.

India being a developing country most of the elderly people who reside in rural areas with sub-optimal medical facilities reach quacks (non-registered medical practitioners) initially, missing the golden period of diagnosis favouring the progress of disease and its outcome.

Henceforth diagnosis in the elderly is considered difficult and often delayed.[33]

In the olden days due to limited resources, lack of availability of Cartridge-based nucleic acid amplification test (CBNAAT) and other invasive procedures TB was underdiagnosed. Now advanced technology led to early diagnosis of TB showing appropriate prevalence.

During the pandemic era, unavailability or decreased focus on other diseases lead to increased transmission and progression of disease in already diagnosed TB cases causing an increase in the prevalence of TB.

4. Challenges while treating Tb in the elderly

Older individuals are more likely to have comorbid chronic diseases including diabetes, renal impairment, and immunosuppression related to both HIV and others.[34]

Elderly patients require psychological motivation before initiation of an anti-tubercular treatment (ATT) regimen when associated with comorbidities which lead to pill load.

Elderly people face age-related sensorineural hearing loss making counselling even more difficult and ineffective.

Superimposed viral infection in the COVID-19 pandemic increased anxiety, and fright of death in patients, causing reduced mobility, and decreased drug distribution leading to a significant increase in the amount of treatment failure cases.

Safety, tolerability, and efficacy of treatment are salient concerns during the treatment phase of elderly patients. Significantly lower plasma concentrations of anti-tubercular drugs were seen in patients with comorbidities like diabetes or HIV co-infection decreasing their therapeutic efficacy.[35,36] Patients when on Immunosuppressive therapy show delayed response to medication and progression of disease even when started on ATT.

With increasing age, there is a declination in renal and hepatic function which may pose difficulties in the metabolism of anti-tubercular treatment. Increasing adverse effects require adjustment of dose, hence routinely used fixed drug combination given under National Tuberculosis Elimination Programme (NTEP) can't be prescribed. The paucity of

availability of individual ATT drugs causes noncompliance, interruption of treatment and favour emergence of resistance.

When the elderly present with renal failure and hypoalbuminemia, they may have a major risk of drug interactions making them intolerant to treatments and poor compliance.

Adverse drug reactions are twice as prevalent among older patients.[37] Hepatoxicity is the primary concern in older adults. Drug-associated hepatic events are more commonly seen with pyrazinamide (PZA). Consequently, clinicians may avoid PZA in older adults by initiating a non-standard drug regimen, potentially placing patients at higher risk for treatment failure.[38] In elderly patients with tuberculosis due to irregular interrupted ATT use there is refractory disease needing a prolonged treatment regimen. Extension of treatment, usage of nonstandard treatment regimens and comorbidities are commonly attributed to the worsening and severity of the disease.

Most of the elderly have comorbid conditions requiring the usage of drugs like oral hypoglycaemic agents, anticoagulants, anti-epileptics, along with ATT which may lead to drug interactions and alter their metabolism thereby rendering in curtailing the efficacy of drugs.

As per NTEP guidelines, a fixed drug combination (FDC) is given to all patients according to weight. This may cause either under dosage or over dosage of certain drugs. Under dosage may lead to treatment failure and increase drug resistance. While overdosage causes adverse effects leading to poor compliance.

In addition to increased adverse drug reactions, visual impairment, hard of hearing, poor memory and reduced mobility may cause indigent adherence to the drug regimen.[15]

Given the risks of adverse medication events and concerns of frailty and low body weight in older patients, official guidelines recommend monthly weight monitoring in the assessment of treatment response and dose adjustment.[39]

Many patients also experience loss of income, stigmatization, and lack of social support which render them noncompliant during the treatment phase.[40]

Social isolation from family members in view of limiting the spread of TB bacilli to their grandchildren causes dejection in patients and abates self-esteem sovereign to wane treatment adherence.

Elderly TB patients show delayed clearance and conversion of sputum.[10] The high bacillary load could be the possible reason for this lower conversion rate of the sputum. Another reason could be the higher rate of adverse reactions, drug interactions, and comorbidities leading to dosage reduction and poor absorption of anti-tubercular drugs among the elderly.[41]

As per NTEP guidelines, both children and adults have the same regimen with differences in dosing. To our knowledge elderly have poor compliance than children due to all the above-said factors like pill load, adverse reactions and laxity towards health.

Assess patients' access to clinical services for safe treatment administration and monitoring, to assess social support which may include emotional companionship or material support. But at the same time, failure in identifying this mounting burden of elderly TB cases could be a challenge to National Tuberculosis Elimination Programme (NTEP) in achieving the end TB 2025 targets of our country.[42]

During the pandemic era improper supply of TB medication led to irregular treatment which in turn led to increase in the prevalence of drug-resistant TB. Based on all the above-said circumstances it is difficult to achieve elimination of TB by 2025.

5. Our own experiences

From our experience, most of the elderly brought to the tertiary centre are presenting with less classical symptoms suggestive of tuberculosis like shortness of breath, anorexia, and mood changes. Sometimes usual presentations like chronic cough with expectoration and fever may be confounded by comorbidities, making the diagnosis of tuberculosis more difficult and delayed.

Patients presenting with non-tuberculous conditions like exacerbation of COPD and Interstitial lung diseases, and malignancy were incidentally diagnosed with tuberculosis on detailed evaluation of underlying conditions. Therefore, TB should be thoroughly checked and ruled out among the elderly even though presented with conditions other than TB.

Ours being Nodal TB centre patients with suspected TB, EPTB and atypical presentation are being referred from various departments and regions. EPTB is common among older people and they are being referred to the pulmonology dept. at the end from various departments like Neurology, Orthopaedics, Psychiatry, Dermatology and others. So, a diagnosis to be made after a thorough investigation.

As the sputum positivity rate in elderly TB cases is low, most of these patients were thought as other differential-diagnosis like non-resolving pneumonia, or malignancies and were referred to tertiary centres like ours for further evaluation. With the help of various equipment available at our hospital, imaging like HRCT CHEST and invasive procedures like USG guided FNAC and biopsy, Bronchial washings for CBNAAT, CT guided biopsy of lung lesions it is feasible and easy to evaluate and diagnose the cases of TB with different presentations.

We are sharing a few of the rare and atypically presented cases which are ultimately diagnosed as tuberculosis through invasive procedures.

1) Elderly female presented with left pleural effusion with left breast lump masquerading as malignancy. On the

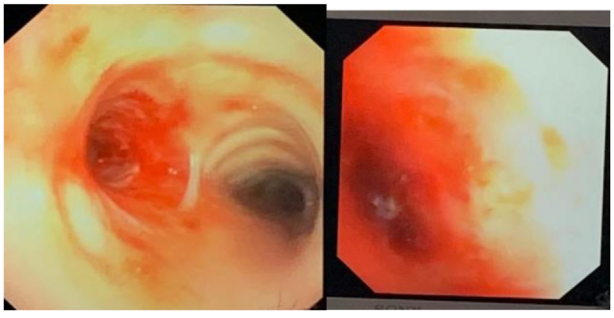

Fig. 1 and 2 – Bronchoscopic view of the above patient showing stenosis of left main bronchus.

evaluation of breast lump FNAC reported chronic granulomatous inflammation, MTB with Rifampicin resistance was detected in both pleural fluid CBNAAT and CBNAAT from breast aspirate.

2) Elderly female presented with multiple comorbidities i.e., DM, HTN, CAD with B/L pleural effusion and B/L pneumonia. Early sputum AFB was negative for MTB and exclusion of pulmonary oedema and CAP was done. Induced sputum CBNAAT was reported as drug-sensitive TB.
3) Elderly male presented to the emergency room (ER) with Diabetic ketoacidosis (DKA) with symptoms of anorexia and night sweats. CT chest was done after stabilization as a routine in pandemic era showed miliary nodules in both lung fields. As sputum was negative for MTB, bronchoscopy was done and MTB was detected from bronchial washings.
4) Elderly male presented with right lower lobe necrotizing pneumonia which rapidly turned into large lung abscess. Sputum CBNAAT and culture were negative. After stabilization bronchoscopy done and MTB detected from bronchial washings.
5) Elderly female presented with right upper lobe collapse posted for bronchoscopy which showed intrabronchial growth. Biopsy from that growth sent for HPE reported as chronic granulomatous lesion with caseous necrosis.
6) Elderly male presented with nonspecific respiratory symptoms from 2 months with elevated ESR and TC. Sputum was negative for MTB but later diagnosed as endobronchial TB through bronchoscopy. Figs. 1 and 2 depicts bronchoscopic view of the case.
7) Elderly female presented with left lower lobe consolidation with hilar and para-aortic lymphadenopathy. Sputum examination was negative for MTB and culture. Bronchoscopy revealed black bronchial mucosa. Biopsies from black bronchial mucosa were negative for malignancy and granuloma. MTB was detected from bronchial washings. Fig. 3 depicts blackish mucosa.
8) Elderly male presented to Orthopaedics outpatients department(opd) with chronic backache and B/L lower limb weakness. MRI spine showed extensive destruction of L1 vertebrae thought to be metastasis. On further evaluation for primary CT chest showed an extrinsic thick-walled cavitary lesion in the left lower lobe. CT-guided biopsy confirmed as diagnosis of TB. Fig. 4 depicts radiographic findings of the case.
9) Elderly female presented with B/L recurrent pleural effusion. After excluding systemic causes, malignancy and tuberculosis. Thoracoscopy was done and confirmed the diagnosis of TB through pleural biopsy. Fig. 5 depicts thoracoscopic view of the case.
10) One of the case series conducted on elderly patients in our hospital included 30 cases of endobronchial growth evaluated under bronchoscopy, 5 of them were diagnosed as Tuberculosis indicating that not all the endobronchial growths are malignancies.
11) In Another study on the role of bronchoscopy in the determination of non-resolving pneumonia among the elderly in 42 patients, 7 among them were diagnosed with Tuberculosis.

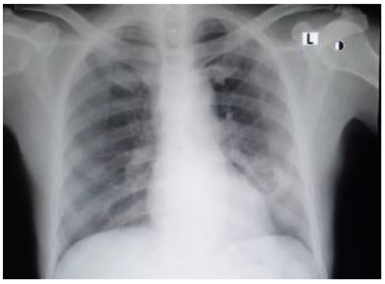

Fig. 4 – Chest radiograph PA view showing eccentric cavity in left lower zone.

TB being endemic in India involves any organ with variable presentations like endobronchial lesions, non-resolving pneumonia and breast abscess.

So, considering all the above-said situations detailed evaluation is to be done on the elderly even though presenting with non-tuberculous conditions. Being a tertiary centre prompt diagnosis can be made through various procedures without being misdiagnosed or the initiation of trial ATT which can be bothersome to the patient.

Few of the elderly refuse invasive procedures even after repeated counselling either due to frightening or superstitions leading to the advancement of the disease.

Advanced disease and its complications with the unstable presentation, making them non-tolerable to treatment.

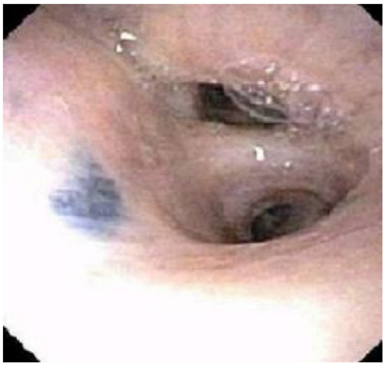

Fig. 3 – Bronchoscopic view of right bronchus intermedius showing blackish mucosal patch.

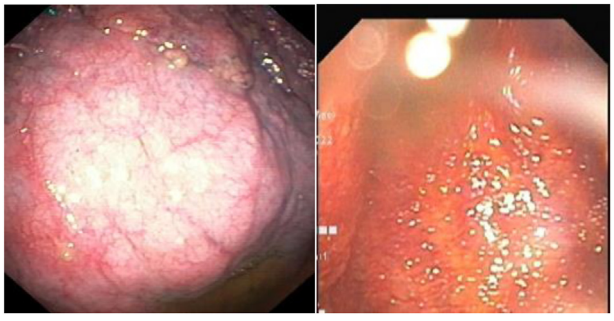

Fig. 5 – Thoracoscopic view of parietal pleura showing small nodules.

6. General outcome and our recommendations

Treatment outcomes of Tuberculosis in older adults are often poor due to delayed diagnosis, increased rates of drug-related adverse events, comorbidities, immunosenescence and overarching poverty.[37,43] COVID-19 pandemic had decreased diagnosis of cases, because of non-availability and scanty distribution of drugs there was increased missing of doses causing irregular treatment for diagnosed cases, leading to increased mortality and morbidity of TB cases.

Superimposed viral infection in elderly TB patients emanated to poor outcomes.

Unfavourable outcomes like ***treatment failure*** were more among elderly male patients, pre-treated TB patients, higher ***mortality*** seen in patients associated with uncontrolled comorbidities, ***emerging resistance*** is also more in the elder because of non-adherence to treatment, and use of non-standard regimens.

Considering all the above said challenges faced during evaluating and treating the elderly with our experience we would like to get to your notice that set of guidelines to be prepared for the elderly keeping all these aspects in mind and adjust the dosage of drugs. We allude that it will be better to give individual drugs with appropriate doses and dosages depending on their condition rather than fixed drug combinations. That can decrease drug interactions and increase the efficacy of drugs.

ASHA workers, ANMs and peripheral PHC medical officers have a significant role to play in increasing adherence in elderly TB patients. The motivation of patients and their family members are required to increase compliance. Old age home runners and field workers need to be counselled to decrease stigma.

Special awareness programmes, posters and skits are to be conducted in demonstrating the outcome with and without anti-tubercular treatment. As most of the elderly are limited to the place they stay television advertisements may show beneficial effects in awaking awareness.

Undernutrition and TB form a vicious cycle, where undernutrition predisposes to acquire TB, while TB could intensify undernutrition. Nutritional support for TB patients improves weight gain, muscle strength, adherence to therapy, quality of life, and reduces mortality. It also lessens the time of sputum conversion and greater sustained microbiological cure, thereby decreasing relapse of TB disease.

Cost-push inflation leads to an increase in undernutrition. Even though programmes like Nikshay Poshan Yojna are being implemented undernutrition has become questionable. So extra measures to be taken in improving nutrition to lessen the burden of TB.

The future of respiratory diseases in the elderly is inclining. Ageing lung has compromised lung function upon those various factors like pollution, smoking and industrialization increase the prevalence of airway disorders. Arteriosclerosis and a decrease in membrane diffusion capacity of the lung with ageing with co-existing comorbidities favour the development of Pulmonary hypertension impairing the prognosis in recurrent PTB cases in the elderly. Structural changes in lungs with ageing and modified lifestyle, current trends cause varying parenchymal disorders.

7. Conclusion

With the increased prevalence of TB in the elderly, it is the need of the hour for India, to focus on this vulnerable population as they are a potential source of infection in the community.

Awareness to be created among the elderly community regarding this deadly disease and its outcomes to increase their health consciousness and medical attention. Priming the special focus on females-coterie as they are the most neglected population in our society.

Routine assessment and recording of comorbidities, dedicated monitoring and reporting of outcomes and fraternizing with the National programme of non-communicable diseases (NPCDCS) for comprehensive management of co-morbidities are esteemed.

By increasing tertiary care centres and the availability of various diagnostic modalities in them we can enhance early diagnosis of elderly TB and henceforth a fruitful outcome for them.

Tolerance and adherence to TB treatment involve education and training of both caregivers and patients and if necessary, multidisciplinary management involving geriatricians and infectious disease specialists, based on close collaboration is justified throughout care to optimize a favourable outcome in these amass of liable patients.

Conflicts of interest

The author has none to declare.

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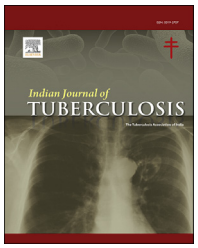

Review article

Business opportunities for aged specially for under privileged

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ABSTRACT

The aged population is increasing so are the business opportunities. Though there are lot of opportunities for the under privileged, it is the skill-based job that is taking a back seat. Apart from health issues that restricts their participation, there is gross difference among urban and rural aged. The opportunities for the urban aged are more while the rural aged continues to do same work till their health permits. Elderly women are utilizing their cooking skills and creating the business opportunities. Various NGO's and Government schemes are now available for providing business opportunities which has to be materialized and the aged should get trained and also learn new skills to grab the opportunity, while taking care of their health too.

1. Introduction

The aged (>60 years) are exponentially increasing in number in India. The retirement age is 60 years as on now which cannot be debated in this context. In India, every day, around 15,000 people turn to 60 years. We look towards the aged in two categories namely, biological and functional ageing. Biological ageing is just a number while functional ageing is being active irrespective of age and multi-morbidity. Senior citizens are a wealth of resources. Their experience and professional expertise are waiting to be channelized into meaningful deliverables which can play a key role in increasing national productivity.[1]

2. Demography

As per the national records, the elderly population in India stood at 134 million in 2020. Of the total population in the country, the share of senior citizens is expected to increase from 12.5% by 2026 to more than19.5% by 2050. According to the social survey estimates, more than 80% of this population stated that they are leading a vulnerable and disconnected existence without adequate access to quality healthcare, safety systems, financial security and social support. This showcases an urgent need to have an integrated operating system, enabling elders to have a dignified and safe ageing experience.[2]

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3. Insight

The aged do not wish to depend on their children as the dignity matters, and hence are looking for job opportunities and now they are available across India.

The older people not only can get opportunities but they can also employ people for jobs. This has an added advantage.

There are two situations prevailing in India as far as senior citizens are concerned. One, the older people in urban areas after their retirement, look for another job while the older people in rural areas continue to work till their functional capacity supports.

The older people till their age of young old (60–74 years) are mostly active and continue to work, while in age group of old (75–84 years) and very old (>85 years) cannot work and become dependent on their family members.

3.1. *Advantages of having aged in business*

The aged will have following features.

1. Maturity.
2. Experience of know-how.
3. Punctual.
4. Stable.
5. Cost less to the company.
6. Disciplined and are.
7. Willing for flexible work-life balance.

The challenges are.

1. Multiple comorbidity.
2. Chronic diseases which reduce their functional capacity especially Chronic Obstructive Lung Disease, Pulmonary Tuberculosis, Congestive cardiac failure.
3. Differently abled conditions like blindness, hearing loss, stroke with its squeal, bedridden, parkinsonism and dementia.
4. Habits like Alcohol dependence and Tobacco consumption which has negative impact on functional capacity.
5. The aged not having skills so to fit in new job opportunities.
6. The aged with look for new opportunities only if required or else he will continue to live with his savings or have children to support as source of income. This means not all the aged require opportunities.

4. What is done now?

The Government of India and Various Non-Governmental Organisations are now providing business opportunities for the senior citizens. They conduct large scale "Job Fairs" involving job providers and senior citizens. Most of the programs end with providing business opportunities during the meetings. One such example is 60+ job fair organized in Bangalore every year.

4.1. *Jobs 60+*

The Nightingales Medical Trust, Bangalore not only gives training in computer learning and skill-based training also provide and explore opportunities of employing the senior citizens.[3]

The results are astonishing. Of the 350 employers registered with them as of now, around 250 came on board in the last three years. Of the 2655 senior citizens who got placements at these companies — both part-time and full-time — around 1600 took place in the same three-year time period.[4]

5. What else can be done?

There are lot of challenges the aged population has while looking for business opportunities.

The aged should undergo training in computer system learning, mobile phone repairs, education related class for under privileged, consultancy services, tuition for kids, health care services for the bed ridden, volunteer for community health services, hospitality services, start yoga or aerobic exercises as per their expertise, tourism related services, turn their hobbies in to business and guiding the youngsters in new ventures. For all these ventures, the government of India is providing financial assistance in for of Start-Ups.[5]

The National Institute of Skilled Department (https://nisd.edu.in/Home#) is providing training opportunities in various fields, but only for youngsters. This should be extended to the aged as well.

5.1. *Aged females*

Across the world there is Feminization of aged. The Indian aged women are doing yeomen services in creating jobs in field of food and eatery production. Home based preparation of various food stuffs like Papad, khakra, pickles, paper bags for medical stores and stationery shops are being carried out which creates source of income for them and also can employ few people. By doing this they are maintaining their dignity, are self-reliant and not subjected to abuse. The older women are source of babysitting, day care provider and security for the whole family until she is active. Once the aged women fall sick, it is she receives less care. It is pity that the aged women are always at the receiving end.[6] The NGO's need to promote such home-based business on large scale.

The business model for the aged women should think of work from home facilities. Secondly flexible working hours. This will improve the number of aged seeking job opportunities.

5.2. *Business opportunities*

The Ministry of Social Justice & Empowerment has launched following schemes to create business opportunities for the aged.[7]

1. Senior Able Citizens for Re-Employment in Dignity (SACRED):

As we are aware that the senior citizens have experience, time and energy which can be used by the business enterprises looking for stable employees with experience. The Human resources cells of many private enterprises seek

experienced but stable persons in certain positions which only can be provided by the aged.

2. Action Groups Aimed at Social Reconstruction (AGRASR Groups): The Elderly Self-Help groups are formed in which the Senior Citizens are encouraged to form Self-Help Groups (SHGs), which will provide them with a platform to share the time constructively with each other.

5.3. *Promotion of the health in aged*

It is very important that all the aged persons maintain good health and remain active. They should follow healthy life style measures, stop smoking and alcohol consumption if doing, get regular health check-up, get vaccinated against pneumonia and take their medicines regularly.

6. Conclusion

Just being aged, having diseases, differently abled, they should not be devoid of the business opportunities. The main goal in providing business opportunity shall be to ensure dignified life for the aged. By self-reliant they are less likely to be abused by their children. The social medial can boost the opportunities of the business carried out by the aged.

The aged, if in active state or with disability should have opportunity for earning as in present days the work from home concept is accepted norm.

The health-related disabilities should be considered and new innovations for such aged people is need of the hour. The aged should approach the Ministry of social justice and empowerment for various assistance schemes.

Conflicts of interest

The author has none to declare.

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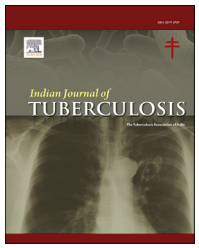

Review article

Non-tuberculous mycobacterial infections in geriatric patients—A neglected and emerging problem

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ABSTRACT

The diseases caused by Non-tuberculous mycobacteria (NTM) has increased steadily in the last two decades. Increase in incidence of NTM infections are being reported in elderly people as they are more susceptible and often experiencing high morbidity. There is prediction that NTM infections will further rise because of expected increase in elderly population by 2050. Given the importance of NTM infection in the elderly, the interest in studying NTM characteristics in the aged population is increasing. In this review, we summarize the characteristics of NTM infection among elderly patients. We focus on epidemiology, clinical presentation, and treatment options of NTM in this age group. We highlight the differences in the diagnosis and treatment between rapid and slow growing mycobacterial infections. The current recommendations for treatment of NTM have been discussed. Finally, we have reviewed the prognosis of NTM disease in elderly patients.

1. Introduction

Non-tuberculous mycobacteria (NTM) are ubiquitous and widely found in water and soil, as well as residential environment. Survival in these ecological niches is supported by their ability to form biofilms.[1] Until recently, NTM were considered transient colonizers in humans, today their association with disease is now well recognized and accepted as a growing problem.[2] The rise in NTM infections is possibly due to multiple factors, including a growing age group of at-risk populations coupled with constantly improving diagnostic capacities. More than 200 species of NTM are currently recognized, with the list ever growing.[3] NTM taxonomy is crowded and complicated, and different species may be more prevalent in specific geographic settings or milieus.[4] NTM may

Abbreviations: L J media, Lowenstein Jensen Media; MGIT 960, Mycobacteria Growth Indicator Tube.

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cause pulmonary nodular and fibrocavitary disease as well as extra-pulmonary disease such as cutaneous, bone, disseminated NTM infections and frequently affect patients with predisposing conditions, e.g., post tuberculosis sequel, bronchiectasis/chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) as well as people living with HIV.[5] Repeated exposure to environment inhabited by NTM is an accepted mode of transmission.[6] Infection is frequently acquired through inhalation from aerosol, showers or inoculation by trauma, surgery and acupuncture. Outbreaks due to NTM are also well reported in the literature.[7,8] Elderly people are more susceptible to NTM and would most likely need health and long term caring services. The average age for NTM infection is reported between 50 and 70 years old.[9,10] It was shown that age is an important prognostic factor for NTM disease. Elderly HIV population is another concern. Out of 34 million people living with HIV infection in the world, HIV associated NTM has become an another important health concern in the coming years. Nontuberculous mycobacterial (NTM) lung diseases are recognized chronic condition all over the world and is associated with substantial morbidity and mortality.[9,11]

In this review, we summarized the characteristics of NTM infection among elderly patients. We focused on epidemiology, clinical presentation and treatment options of NTM in this age group. Finally, we reviewed the prognosis of NTM disease in elderly patients.

2. Recognition of NTM as a global concern

The global burden of NTM disease is largely unknown. Currently, the majority of NTM diseases are not notifiable, although the incidence of pulmonary infection by NTM has been reported to be increasing. A formal epidemiological evaluation of this disease has been deficient until recently. According to a laboratory assessment from 1993 to 1996 performed by the Centers for Disease Control and Prevention, the rate of positive NTM cultures was 7.5—8.2 cases per 100,000 persons. However, a recent survey showed a positive culture rate of 17.7 per 100,000 in non-HIV patients in the U.S. Pulmonary disease with *Mycobacterium avium* complex (MAC) has been reported to be 0.2 cases per 100,000 in Europe and investigators from the United Kingdom estimated the incidence of NTM respiratory disease 2.0 per 100,000.[9,12–18] Over the last 18 years, a study revealed that NTM isolates have increased in the Scottish Borders region and, interestingly, these cases have occurred predominantly among elderly. In line with these results, a study performed in the US demonstrated that the prevalence of pulmonary NTM disease was highest in people aged over 50 years (15.5 cases per 100,000 persons). A report from Australia showed an increased number of NTM infection from 1999 to 2005 especially in elderly women. Lai et al showed the incidence of NTM increased in Taiwan from 2000 to 2008.[19] Al-Houqani et al demonstrated in a population-based study in Ontario, Canada that MAC lung disease increased substantially with age; from 1 in 100,000 in people <50 years old to 48 in 100,000 people over 79 years.[20] MAC is a ubiquitous bacterium causing disease in human as well as animals in Europe, US and many regions of the world. It is a well-known pathogen for causing pulmonary disease in elderly women known as Lady Windermere syndrome that presents with isolated middle lobe or lingular bronchiectasis.[21] *Mycobacterium kansasii* followed by *Mycobacterium fortuitum*, *Mycobacterium scrofulaceum*, *Mycobacterium chelonae* and *Mycobacterium xenopi* are reported as most common isolated pathogens after MAC.[21,22]

2.1. *Recognition of NTM in India*

In countries with high burden of TB, including India, NTM pulmonary disease often goes unrecognized and is misdiagnosed as pulmonary TB because clinical presentation of NTM and *Mycobacterium tuberculosis* (MTB) diseases are indistinguishable from each other. In India specific risk factors are underlying chronic lung disease, previous tuberculosis, surgical-site infections, post injection abscesses, osteomyelitis, catheter-related bloodstream infections, HIV infection, cystic fibrosis, and work in the mining industry. Non Tuberculous Mycobacteria rates of infection and disease has significantly increased in recent years and infection rates widely depend on population and geographic location.[23–25] The prevalence of NTM in India varied from 0.7% to 34%. According to a study in Northern India prevalence was estimated to be about 29%. In Chandigarh, the incidence of NTM was estimated to be around 7.4% and in Delhi, it was found to be 8.3%. Prevalence of NTM in pulmonary specimens was around 17.4% in Kolkata. In south India, the prevalence of NTM was around 3.9%, according to a study in Vellore. Thangavelu et al study found the prevalence to be 1.1% with 0.7% among pulmonary specimens and 0.4% among extra pulmonary specimens. Sharma et al discussed the details of 13 Indian studies published between 1985 and 2019. Most of these studies have reported NTM isolation rates from laboratories without describing clinical features and treatment details. Two studies were done exclusively on extra pulmonary specimenand 11 studies on both pulmonary and extra pulmonary specimen. NTM isolation prevalence varied between 0.38% and 23.7%. Six of these 13 studies reported NTM prevalence $\leq$1 per cent among TB suspects.[26]

3. Risk factors for NTM in elderly

NTM pulmonary infection typically occurs in two different groups of patients. The first group of patients usually are white middle-aged or elderly men who have classic mycobacterial risk factors such as smoking, alcohol abuse, structural lung diseases, and other comorbid conditions. The second group are mainly elderly nonsmoking women without any of these risk factors.[27] Patients with structural lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, previous tuberculosis, pneumoconiosis and alveolar proteinosis are more at risk of NTM disease. Considerably, structural lung disease has higher

prevalence in elderly.[28–31] Genetic abnormalities in the cell immunity pathway like interleukin-12/interferon-γ synthesis, cystic fibrosis transmembrane conductance regulator (CFTR) mutations, human leukocyte antigen (HLA) alleles, polymorphisms of solute carrier 11A1, and the vitamin Dreceptor cause increased vulnerability to systemic NTM disease.[32,33] Impaired IFN-gamma pathway such as IFN-γ deficiency may also play a role for increasing susceptibility to NTM.[34,35] In HIV patients, disseminated NTM infection typically happens just after the CD4 T-lymphocyte cell counts drop lower than 50/μl, suggesting that T-cell activities or cytokines are necessary for mycobacterial resistance.[36] Lady Windermere syndrome is a typical example of NTM presentation in patients without any classical risk factors. It presents with right middle lobe and/or lingua involvement. It is proposed that this syndrome may be associated with a fastidious habit of voluntary cough suppression that causes secretions accumulation, which is ideal for growth of the organisms.[21] Patient is commonly older age white female with no history of smoking and also without any previous lung diseases.[37] Certain physical phenotypes seem to be more common among them, including a tall slender body habitus, scoliosis, pectus excavatum and mitral valve prolapsed.[38,39]

4. Clinical presentation of NTM in the elderly in comparison to the adults

Among the elderly, NTM can lead to both asymptomatic infection and symptomatic involvement. The most common clinical manifestation of NTM disease in this group of patients is lung disease, with MAC being the most frequent infection in both US and Europe.[40] Conversely to the older patients, children the clinical presentation of an NTM infection typically consists of a chronic unilateral cervical lymphadenopathy with spontaneous drainage and fistula.[41] Nearly all old aged patients have chronic or recurring cough along with sputum production, dyspnea, chest pain, hemoptysis, fatigue, fever and weight loss. Diagnosis is often hampered by symptoms caused by coexisting lung diseases. Many times NTM diagnosis may be missed in a patient with non-CF bronchiectasis who chronically experiences all mentioned symptoms.[42,43] Physical examination is nonspecific as well and may reveal underlying pulmonary pathology, such as COPD and bronchiectasis. On auscultation, findings might consist of rhonchi, crackles and wheezes. In HIV patients, NTM accompany by symptoms such as fever, night sweats and weight loss. However, fever may be undetectable in some of elderly patients with pulmonary infection.[44] Older patients with Lady Windermere syndrome commonly present with the characteristic nodular-bronchiectatic changes and tree-in-bud appearance in high resolution computed tomography.[45] The nodular-bronchiectatic pattern has commonly been accompanied with MAC, although other species, including *Mycobacterium abscessus* in the US and *M. xenopi* and *Mycobacterium malmoense* in Europe, are also commonly related to this form of disease.[46] NTM's are also commonly observed in the elderly women with scoliosis, pectus excavatum, and mitralvalve prolapse without severe cardiopulmonary disease or significant smoking history. A slim body build besides other musculoskeletal or soft tissue aberrations and a high incidence of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations have now been reported with NTM disease.[47,48]

5. Diagnostic evaluation & diagnostic methodology

Diagnosis of NTM can be made on the basis of clinical, radiological and microbiologic criteria for pulmonary and extra pulmonary diseases. Clinical criteria includes either or both pulmonary/systemic Symptoms. Radiological Criteria: Radiologic Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules and appropriate exclusion of other diagnoses. In microbiological criteria, positive culture results from at least two separate expectorated sputum samples and having same organism is must. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures. Diagnosis of NTM may be done with even single positive culture results from bronchial wash, bronchial lavage, transbronchial, other lung biopsy with mycobacterial histologic featues granulomatous inflammation.[12]

6. Methods of NTM detection

a) **Acid-fast microscopy:** It is a simple, cheap and rapid conventional method for identifying acid fast bacilli in patients with mycobacterial infections. The specificity of AFB staining for detecting acid-fast bacilli is high, however, the overall sensitivity of the microscopy test is low to moderate only 22–65%. Currently, there are different methods of acid-fast stains that Ziehl-Neelsen stains are the most commonly used followed by florescent staining and Kinyoun staining.[49]
b) Mycobacterial culture: Culture is still the mainstay of NTM diagnosis. Thus, laboratories serving populations for whom NTM is a health concern, should optimize their mycobacterial culture methods to maximize the sensitivity of culture. In the solid culture media Lowenstein Jensen (LJ) media is the most popular media for isolation of NTM. Among the liquid culture media the BACTEC MGIT-960 system is the most commonly used method for NTM isolation. Other liquid culture systems available are BACTEC - 460 (BD Bioscience) BacT alert (BioMerieux), Versa TREK (Trek Diagnostics).[50]
c) Molecular detection: A commercial assay is now also available. The GenoType Mycobacteria Direct (GTMD; Hain Lifescience, Nehren, Germany) is a line probe assay. The Accu Probe (Gen-Probe Inc., San Diego, CA) nucleic acid hybridization kits allows for rapid identification of the MTB complex, the M. avium complex, *M. kansasii* and *M. gordonae*. This assay offers rapid identification within hours as soon as sufficient colonies are achieved following growth in culture.[51] HPLC for mycolic acids of the cell wall has been approved to be a rapid (less than 2 hours) and inexpensive method to recognize a wide range of mycobacteria species either from sputum or culture.[52]
d) Polymerase chain reaction (PCR) and Restriction fragment length polymorphism (RFLP): This rapid tool usually is

performed on AFB isolates that grow either in liquid or on solid media.[53,54]

e) Gene sequencing allows a highest level of discrimination and identify all possible species, but is only feasible for laboratories with access to sequencing facilities. The target gene sequencing i.e hsp 65, rpoB genes and the 16S–23S internal transcribed spacer (ITS) offer high discriminatory power and can identify up to subspecies level.[50,52,55–57]

f) A new tool for species identification of NTM is matrix-assisted laser desorption ionization–time of-flight (MALDI-TOF) mass spectrometry. The discriminatory power of the MALDI-TOF method largely depends on the quality of its database, and this remains a drawback in comparison with the gene-sequencing methods.[58]

6.1. *Treatment NTM in elderly patients*

Antibiotic therapy for NTM disease involves multiple medications. Consequently, the risk of drug toxicities is relatively high, especially in elderly subjects. A decision to treat NTM is mainly based on clinical and radiological characteristics. The treatment of pulmonary NTM disease, as outlined in the latest ATS/IDSA guideline, based on NTM species isolated during investigation. Antibiotic therapy is planned by the species identified, the pattern and the extent of lung involvement and possibly drug susceptibility testing. It was shown that not offering a treatment to the patient who met NTM diagnosis, or poor therapeutic response for any reason including inappropriate antibiotic therapy may conclude extensive pleural thickening, atelectasis, advance bronchiectasis and cavitation.[59-61]

7. Prognosis of NTM in elderly

NTM-related mortality is increasing and there is a strong association between age and NTM mortality. The mortality rate from NTM infections like lung, skin and so on is low, but mortality rate due to disseminated NTM infection is reported to be about 30%–40%.[62] Indeed, the mortality was found to be higher in patients older than 65 years. Besides male gender and high levels of comorbidities, advanced age was assumed to be a strong predictor of five-year mortality. Additionally, according to the British Thoracic Society studies, *M. xenopi* was reported with the highest mortality rate.[63] The impact of pulmonary NTM on pulmonary fibrosis, pulmonary hypertension and airway diseases is unclear and should be investigated.

8. Future directions

The incidence of NTM infections is growing, probably due to a combination of factors including advancing age. They are being recognized with improvements in laboratory methodology, liquid culture techniques and advance molecular methods. Because of the ubiquitous nature of NTM as environmental pathogens, it is vital to differentiate between clinical disease and colonization. There is a considerable variation in treatment management that should be deliberated before starting the treatment. While the US and European populations are aging and NTM diseases are rising in elderly population with a high mortality rate, we would hope to see an increasing focus on research in NTM infection, and multi-center trials. Creation of regional referral institutions can improve management of this challenging group of diseases.

Conflicts of interest

The authors have none to declare.

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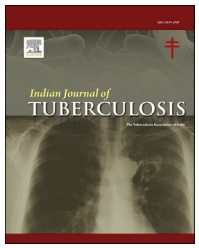

Review article

Immune issues in elderly with TB

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ABSTRACT

The article reviews the immune changes in the elderly with particular reference to susceptibility of elderly to Tubercular infection whether new or LTBI and in the light of recent advances in the field of immune mechanisms of tubercular infection. An primary understanding of the host response to infections and *M. tuberculosis (M.tb)* infection in particular helps to better understand the various issues of immune response to tubercular infection in the elderly.

Immune mechanisms of ageing in particular deal with the twin unique mechanisms and terms particular to aging- *Immunosenescence* and *Inflammaging*. In the elderly patient both the Innate and the Adaptive immune responses are affected at various levels. The M.tb bacteria encounters the innate immune system initially and thereafter the response is from the cells of the adaptive immune system.

The *M.tb* bacillus which enters through the respiratory system to the bronchioles and alveolus encounters the immune system at three levels which are the Resident structural i.e. alveolar epithelium, Resident innate i.e. the alveolar and pulmonary macrophages and the Infiltrating innate i.e. the neutrophils and monocytes. Increased inflammatory changes present in the lung mucosa has been associated with changes in multiple innate molecular defence mechanisms that could influence the ability of *M.tb* to establish an infection, the various cellular mechanisms involved and the evasive strategies evolved by the *M.tb* to survive and disseminate are briefly described.

The susceptibility of the elderly to develop and succumb to TB may be a direct impact of increased inflammation at every stage of infection. *M.tb* is a potent stimulator of multiple inflammatory responses and added to a basal inflammatory state with evasiveness of *M.tb* bacilli, enable it to overcome and disseminate, increasing the morbidity and mortality in the infected elderly. Hopefully a better understanding of the immune mechanisms involved will enable better preventive, diagnostic and treatment modalities.

Abbreviations: Mycobacterium tuberculosis, M.tb; Latent Tubercular Infection, LTBI; Active Tubercular Disease, ATB; Alveolar Epithelial Cells, AT; Alveolar Lining Fluid, ALF; Toll Like Receptors, TLR; Complement receptor 3, CR3.

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1. Introduction

Tuberculosis continues to be one of the world's most lethal infectious disease and is more prevalent in the elderly among the high-risk groups.

Prevention and control strategies in the elderly continues remains a clinical and epidemiological challenge. Clinical features of TB in older adults may also be atypical, non-specific and often confused with other age-related diseases or worsened by comorbid conditions. These underlying co-morbid illnesses whether in acute or chronic presentation when added to malnutrition and biological changes of ageing, affect normal protective barriers, impair microbial clearance mechanisms and add to the age-related decline in cellular immune responses to infecting agents. Though the majority of individuals exposed to *Mycobacterium tuberculosis(M.tb.)* are able to control infection in the form of Latent TB Infection (LTBI), an estimated 5–10% of people exposed to *M.tb* may develop Active Tubercular disease (ATB). The elderly is also susceptible for reactivation of latent TB (LTBI). The awakening or reactivation of dormant lesions may be attributed to changes in the immune system related to senescence and comorbid disease. The mortality rate is also higher in the elderly population with tuberculosis.

This article reviews the immune changes in the elderly with particular reference to susceptibility of elderly to Tubercular infection whether new or LTBI. An primary understanding of the host response to infections and *M. tuberculosis (M.tb)* infection in particular is essential to understand the immune issues of ageing and tuberculosis.

2. Immune mechanisms in ageing

The elderly are generally considered to be more susceptible to infectious disease. Two unique terms and mechanisms we need to be familiar with going forward are **Immunosenescence** and **Inflammaging**. **Immunosenescence** is a decline in immunity with ageing and is characterised by defects in the hematopoetic bone marrow, impaired peripheral lymphocyte migration, maturation and function and also the effects of the age-related involution of thymus gland.

Inflammaging (a term coined by Franceschi et al., 2000) adds a newer dimension to aging studies and denotes that the aging process has a chronic progressive proinflammatory phenotype. Inflammaging plays an increasingly important role in the rate of aging and age-related diseases. Although its multifactorial, the main causes of inflammaging are the accumulation of pro-coagulation factors, cell debris such as circulating mitochondrial DNA (cmtDNA), gut dysbiosis, and immune senescence of ageing cells. **Inflammaging** is also associated with an increase in the levels of circulating pro-inflammatory cytokines such as TNF and IL-1β and is detailed later.

In the elderly patient both the **Innate** and the **Adaptive immune responses** are affected at various levels. The M.tb bacteria encounters the innate immune system initially and thereafter the response is from the cells of the adaptive immune system. A deeper understanding of the subject hopefully in a simpler manner is presented below.

3. The tubercular infection

In brief, *M. tb* is an intracellular pathogen transmitted by the inhalation of aerosolized, bacteria-containing droplets. Innate immune cells in the lungs, which act as first responders are primarily alveolar macrophages, dendritic cells, monocytes, and neutrophils that readily phagocytose *M. tb* and are the earliest defenders against the pathogen. Recognition and transformation of bacteria-containing phagosomes into acidified, antimicrobial compartments is an important early part of defense against *M.tb*. This eradication of pathogens via fusion with lysosomes and consequent acidification of the pathogen-containing the phagolysosome however is not always perfect and bacteria can survive in this environment. The *M.tb* is able to survive and replicate in the phagosome by inhibiting phagosomal maturation and phagolysosomal generation by a variety of mechanisms. The *M. tb* also counters the nitrosative, oxidative, hypoxic, and nutrient-poor phagosomal environment by its expression of stress-adaptive genes.

The *M. tb* infection results in a hallmark lesion called the **granuloma**, which are aggregates of infected and uninfected myeloid cells circumscribed by a lymphocytic cuff. While the granuloma is thought to prevent bacterial dissemination to extrapulmonary sites it can also become a site or niche for long-term bacterial persistence.

The physical changes in the lungs as a result of ageing and comorbid illness or earlier pulmonary conditions would also have affected the normal physiological barriers in the lung. Though the lung is the primary portal of entry for *M.tb*, the impact of the aging lung has only of late been considered as a factor that may define susceptibility to TB in the elderly. The elderly experience a **decreased lung elasticity,** diminishing **strength of respiratory muscles** and added to age/disease related **lowered vital capacity**, impairs the expulsion of infectious agents through cough reflex, sneezing or breathing. Also increased incidence of aspiration into the lung occurs with ageing, and age-associated inflammatory disease such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis, make the elderly more vulnerable to have a pulmonary environment that favors the establishment of any infection, including *M.tb* infection.

The *M. tb* bacilli has also evolved various strategies to evade and to subvert the human immune responses so as to persist within a host and it is become more evident that the immune response to *M. tb* infection involves contributions from different types of innate and adaptive immune cells which are elaborated below.

4. Effect of ageing on the immune response in tuberculosis

The *M.tb* enters the respiratory system to the bronchioles and the alveolus. The bacterium then resides within the lung

mucosa that lines the alveolus, and it is there that the Bacterium is exposed to **soluble innate components** (*like* surfactant proteins, complement, hydrolases, antimicrobial peptides, antibodies, etc.)

Thereafter it encounters the defences of the innate immune system at levels of.

- **Resident structural (alveolar epithelium and alveolar lining fluid)**,
- **Resident innate (alveolar and pulmonary macrophages)** and the
- **Infiltrating innate (neutrophil, monocyte) cells**

that determines the progress of *M.tb* infection.

An inflammatory lung environment in the ageing individual has the potential to alter each of these interactions between host cells and *M.tb*.

The various immune responses at different levels are further elaborated as below.

1. **The role of Alveolar epithelial cells (AT) and alveolar lining fluid (ALF)**.

The Lung mucosa or ALF is generated, secreted, and recycled by the alveolar epithelial cells which is essential for proper lung maintenance. In the aged individual, senescent ATs lead to **a reduction in lung recycling** and which in turn can cause a low level of persistent lung inflammation. Added with the systemic inflammaging that is already present in the circulation, ALF in old age will have an increasing inflammatory profile. ALF also increased levels of TNF, IL-6 and IL-1β, showing that inflammatory cytokines were present in pulmonary fluids of the elderly.

Increased inflammatory changes present in the lung mucosa has been associated with **changes in multiple innate molecular defense mechanisms** could also influence the ability of *M.tb* to establish an infection. **Surfactant proteins A and D (SP-A, SP-D)** as well as **components of the complement system, notably C3b**, were noted to be **increased in** ALF of the elderly.

The SP-A regulates apoptotic cell clearance and increases phagocytosis of *M.tb* by macrophages, by an opsonin like mechanism whereby there is direct interaction between SP-A and macrophage receptors resulting in regulation of inflammation and oxidative response. This also results in regulating the expression of Toll-like receptors (TLRs) and mannose receptors (MR) in the macrophages.

Surface protein D (SP-D) however decreases *M.tb* association with macrophages and drives phagosome-lysosome fusion of those *M.tb* that are phagocytosed. SP-A and SP-D can contribute to an increased *M.tb* virulence by improving the *M.tb* association to lung epithelial cells.

By activation of the classical and alternative complement system, C3 can also opsonize *M.tb*, and initiate phagocytosis by interaction with CR3 on macrophages. Lung hydrolases can modify the cellular envelope of *M.tb*, altering the interactions between *M.tb* and host cells.These cell wall alterations have been shown to affect *M.tb* phagocytosis by macrophages and neutrophils, and allow these cells to improve control of *M.tb* intracellular growth, thereby decreasing inflammation and subsequently the tissue damage.

The levels of surfactant proteins, complement components and hydrolases may be altered through dysregulation of their homeostatic production with increasing age or they may be altered to compensate for host-mediated changes in their function. **Surfactant lipid oxidation** is observed in surfactant of elderly individuals, where a reduction of dipalmitoylphosphatidylcholine (DPPC) and elevated POPC (oxidative form of DPPC) were noted. Surfactant lipids like DPPC are vital for SP-A function. SP-A binds to DPPC and not to POPC suggesting that soluble SP-A is susceptible to oxidation in ALF in the elderly.

An understanding of the changes in innate immune molecule levels in the lung of an ageing individual have only recently been studied and it is presently not known on how these changes translate to modification of function of individual cells.

It is assumed that changed levels or function of complement, surfactant proteins, and hydrolases in the lung environment with ageing will modify the manner by which *M.tb* associates with different receptors on resident epithelial cells, macrophages or infiltrating neutrophils and trigger different uptake mechanisms, thereby resulting in altered trafficking patterns upon entry into the macrophage. This affects the long-term survivability of *M.tb* within the macrophage. Also the intrinsic differences in functioning of aged macrophages could amplify the increased vulnerability of the aged to *M.tb*.

2. **Alveolar and pulmonary macrophages**

The increased inflammation and altered molecular innate environment in the lung cause significant functional effects on the resident cells that are the first to encounter *M.tb*. The alveolar macrophage is the primary niche or incubator for *M.tb* survival during infection, and it is one of the first host cells to encounter *M.tb*. Initial recognition of *M.tb* is accomplished by phagocytic receptors (*i.e.* complement receptors, mannose receptor, and SP-A/D) and also signaling receptors (*e.g.* Toll-like receptors), that lead to a specific uptake pathway which is able to modify the ability of *M.tb* to survive and persist in host cells. On recognition of *M.tb*, the bacterium will be phagocytosed and internalized, directing the bacterium into a phagosome/early-endosomal compartment. The macrophage will proceed to attempt and fuse the phagosome with the lysosome, in a process called **phagosome-lysosome (P-L) fusion** with the goal of eliminating *M.tb*.

The *M.tb* has developed ways to avoid P-L fusion, allowing it to exist in an early-endosome-like compartment for a long period. Also degradation of the phagosome may occur, facilitating *M.tb* to escape into the cytosol for further replication. So the ***M.tb* may survive either by blocking P-L fusion** or **escaping from phagosomes into the cytosol.** The stimulation of autophagy is also been shown to suppress *M.tb* intracellular survival. As previously mentioned the Autophagosomes could also be an incubator or site for *M.tb* intracellular survival. Together with *M.tb* uptake, autophagy, and P-L fusion, resident macrophages respond to infection by secreting numerous inflammatory cytokines and chemokines that serve to attract infiltrating innate cells and to activate cells of

the adaptive immune system. It is assumed that the **receptor mediated uptake and recognition, and effector functions of macrophages will be altered in old age.**

3. **Innate cellular mechanisms are thought to be dysfunctional** and/or **reduced** with progressive age or comorbidity.

The Myeloid cell series may also have a **reduced production of inflammatory cytokines** in response to immune insult.

Decreases in cytokine secretion is explained by altered TLR function with age. The decreased TLR expression on macrophages correlates to reduced inflammatory cytokine production after immune stimulation. The impaired pro-inflammatory cytokine secretion by aged macrophages did not correlate with altered TLR expression and instead correlated with altered TLR-signaling components in the cell. Some pathways seem to be affected with age in the macrophage, with TLR2 and TLR4-related stimuli resulting in decreased cytokine secretion, but cytokine secretion by macrophages after IL-2 stimulation did not alter with age. Hence the phagocytic, inflammatory, and migratory capacities of the macrophage are shown to have important alterations with ageing.

The changes in **IL-12 or TNF production** in the lung during *M.tb* infection in elderly are highly important to *M.tb* pathogenesis. TNF is required for the macrophage activation and recruitment to the infection site and granuloma formation. IL-12 is produced by macrophages in the lung as a response to *M.tb* infection, and is essential to Th1 mediated immunity and long-term control. Various other inflammatory cytokines (such as IL-6 and IL-1β) are increased in macrophages from the naïve aged lung and are required for *M.tb* control.

The long-term effects of inflammation may possibly impact granuloma formation and maintenance of chronic infection. These factors indicate that resident cells not only respond and become activated by the local inflammatory environment but also directly contribute to the persistent local inflammatory environment at basal levels.

TLR expression and signaling responses may be altered in old age. TLR2 is the dominant TLR that recognizes lipoproteins/lipopeptides on *M.tb* and stimulates cytokine release. This inflammatory state causes an increased activation state in pulmonary macrophages and those macrophages in the lung add to the inflammatory environment at basal state and in response to *M.tb* infection. So this inflammatory response that is associated with increased P-L fusion in macrophages *in vitro* and production of IL-12 and IFN-γ *in vivo* is associated with a reduced *M.tb* bacterial burden early in the lungs.

4. **The role of T cells particularly the resident $CD8^+$ T cells**

The age-related decline in output of T cells from thymus is compensated by an increase in the lifespan of naïve CD4 + T cells mediated by decreased level of the pro apoptotic molecules. But these naïve T cells may be functionally defective.

A robust antigen specific CD4 + T cell response and production of T-helper1 (TH1) associated cytokines such as interferon gamma (IFN-γ) interleukin 12(IL-12) & TNF are necessary for immunity against TB. A low antigen specific CD4 + T cell proliferative capacity and decrease in killer (NK) cell activity have also been demonstrated in elderly. These factors likely lead to reactivation of LTBI or development of disease of exogenous infection in elderly.

The conventional T cells respond to *M.tb* by antigen-specific (MHC-TCR) recognition of *M.tb* peptides and subsequent activation and secretion of IFN-γ. The IFN-γ, secreted by antigen specific CD4 and CD8 T cells, is an essential cytokine for **long-term control of *M.tb***, with memory CD4 T cells secreting more IFN-γ secretion than memory CD8 T cells.IFN-γ is essential for macrophage activation, enhancing phagocytosis and killing, and is important for stabilization of *M.tb* infection. With increasing age, **antigen specific CD4 and CD8 T cell responses decline in number/frequency** or may be **delayed in their generation** leaving a gap between early innate control and the recruitment of antigen specific T cells migrating to the tissue site to control infection.

Also the memory CD8 T cell population shows certain changes with age. There is a decrease in the proportions of naïve CD8 T cells relative to memory CD8 T cells in aged hosts. CD8 T cells in old age have reduced diversity of both the naïve and memory CD8 T cell receptor repertoire which have been attributed to impaired immune responses of aged hosts to vaccines and viral infections. For e.g. Chronic infection as with cytomegalovirus (CMV) in humans, may also contribute to poor immune function of T cells in the elderly.

5. Conclusions

The present article attempts to summarise the immune responses, both innate and adaptive, to tubercular infection and with particular reference to the elderly. The susceptibility of the elderly to develop and succumb to TB may be a direct effect of increased inflammation at every stage of infection. *M.tb* is a potent stimulator of multiple inflammatory responses added to a basal increase of inflammation associated with aging or comorbidities, which may lead to an overwhelming inflammation that further results in tissue damage and muscle wasting, pulmonary cellular infiltration, dissemination and systemic symptoms that feed into the environment that *M.tb* survive and thrives in. Better understanding of immune mechanisms and evolving research both in the vaccine field and in newer immunodiagnostic modalities like IGRA testing etc which will help in better prevention, diagnosis and management of Tuberculosis, especially of the elderly in future.

Conflicts of interest

The author has none to declare.

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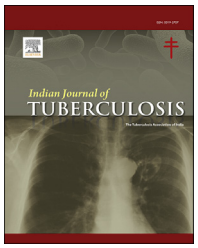

Review article

Utilization of health care services by elderly for respiratory diseases including TB - Challenges

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ABSTRACT

Progressive functional decline of all body organ systems in association with decreased immunity makes elderly vulnerable to all types of diseases including respiratory diseases. Advances in medical fields have resulted in increasing proportion of elderly globally. Healthcare demands of elderly population are complex. Provision of healthcare services for this continuously increasing population subgroup & ensuring their adequate utilization is full of challenges. These are demographic, socioeconomic, financial, physical accessibility, quality of healthcare services, attitudinal & transportation related. Large size of this subgroup with special healthcare needs in context of limited available resources of middle income country like India is the biggest challenge. Poor educational status & socioeconomic condition of Indian elderly, dependence on family, absence of formal social security & healthcare security complicates situation further. Condition of elderly females is particularly worse. In view of poor physical ability with often associated physical disability makes accessibility of healthcare services also significant factor. Overcoming negative attitudinal factors prevalent in Indian elderly & make them utilize available healthcare services is another huge challenge. Quality of healthcare services in form of availability of required expertise & equipments, attitude of healthcare providers towards elderly patients & convenience in utilization of these services also play an important role. Special provisions in TB control program for elderly in view of their complex needs, high prevalence, morbidity & mortality are also required.

1. Ageing

Ageing is a complex biologic process that is characterized by irreversible functional and anatomic changes in the body, resulting in increased susceptibility to disease processes. Ageing causes gradual decline in almost all body functions. Cardiac, respiratory, renal & sensory functions, nerve conduction, muscle strength, agility, cancer, diabetes, and mental illness, sustained physical activity and muscular coordination

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all get adversely affected. Thermoregulatory mechanism also gets affected making elderly vulnerable to extreme changes in weather.

The physiological decline in the normal functioning of the body results in poor mobility, vision, hearing, digestion & memory. Elderly are affected with number of physical and mental health as well as social problems. In addition to chronic illnesses specific to old age, other diseases present earlier may also get aggravated due to cumulative effect of illness over the years & weakening of body defences.

2. Effect of ageing on respiratory system

Shortness of breaths can be a normal consequence of ageing but can also be an important symptom of cardiovascular or lung disease. Bronchial ciliary function decreases with ageing. This along with loss of respiratory muscle power leads to mucous accumulation in dependent parts. It may reduce ventilation in lower parts of the lungs in the elderly. Pulmonary distensibility and total alveolar exchange surface reduce. With ageing the lungs loose elasticity, but functional residual capacity increases, which at age of 60 years is approximately 60 per cent of the total lung capacity. Gas exchange gets affected. Arterial oxygen pressures (PaO_2) are reduced with age. Fibrosis of small pulmonary artery intima increases vascular resistance. Compromised host defence mechanisms increase vulnerability to infections. Pneumonia and influenza are significant contributors to mortality in old age. Reactivation of granulomatous diseases, e.g., tuberculosis, also occur more frequently.

Respiratory diseases are an important cause of morbidity & mortality in elderly. Prevalence of respiratory diseases in elderly varies widely in literature, partly due to different methodology adopted for diagnosis. It has been reported to 10.2%–21.9%.[1,2,3,4] Prevalence of COPD has been estimated to be as high as 20%–30% in patients >70 years of age.[5,6]

3. Challenges

3.1. *Demographic challenges*

Improvement in health services have increased life expectancy. Number of elderly is increasing all over the world & it is expected that by 2030 every 6th person will belong to old age (>60 years) group. At this time the share of the population aged 60 years and over will increase from 1 billion in 2020 to 1.4 billion & by 2050 it will double to be 2.1 billion. The share of elderly in world population will grow from 12% in 2015 to 22% in 2050. Even 80+ population will grow three times to 426 million between 2020 and 2050.

This demographic shift (population ageing) was initially seen in developed countries. In Japan elderly comprise one third of county's population. Now this trend has set in low- and middle-income countries also. By the middle of this century major share (80%) of global elderly population will be in these countries. All such countries including India face major challenges to ensure that their health and social systems are ready to deal with this demographic shift.[7] In most of the western world, advanced stages of development preceded population ageing, allowing them to meet the challenges arising from this demographic change. But it is not true for many developing countries like India.

This demographic change is result of combined impact of increasing life expectancy and declining fertility. Life expectancy at birth in India increased from 37 years in 1950 to 65 years in 2011.[8] During the same period fertility rates in India have declined from 5.9 to 2.6 children per women.[9]

Biologically no age demarcation can be taken to define elderly. But for policy making and implementation purposes it needs to be specified. For most of Government of India policies 60 years of age is taken to define elderly. National Policy on Older Persons defines senior citizen or elderly as a person who is of age 60 years or above.[10]

In comparison with the global standards healthcare infrastructure in India is grossly inadequate. Accessibility of healthcare service as well as quality of patient care needs to be improved drastically. In 2009, the number of beds available per 1000 people in India was only 1.27, which is less than half the global average of 2.6.[11] India has an average 0.6 doctors per 1000 population against the global average of 1.23. This deficiency is further compounded by uneven distribution. "Doctors to population" ratio is lower by 6 times in rural as compared to urban areas.[12] Public healthcare spending is amongst the lowest in the world. It is less than half the global average on a "percent of GDP" basis. Majority of health care spending is out of-pocket by end user at the point of service.[13]

Health care infrastructure is as such inadequate in India. But even that is not utilized properly by elderly. Elderly are a unique population subgroup with their own problems in utilizing available health care services. Number of Indian as well as international investigators have tried to understand the factors affecting utilization of health care services by elderly. Factors influencing utilization of health care services can be socio-demographic, financial, quality of health services related factors, personal attitude & belief of elderly, accessibility & transportation related factors.

3.2. *Socio-economic challenges*

Education is a big empowerment tool. Illiteracy makes one more vulnerable. As per National sample survey organization (NSSO) 2007-08, 23% males & 56% females were illiterate in urban areas.[14] Literacy level among elderly in rural areas was much worse, illiteracy rate amongst elderly males & females being 56% & 87% respectively. As education has significant effect on ones social & financial status, illiteracy & low education levels are important contributors to pathetic condition of Indian elderly. Education improves awareness, attitude & makes one more conscious of his/her rights. As will be discussed later negative attitude towards old age is significant contributor to poor utilization of health services by elderly.

Central statistics office (CSO) data 2016 noted high widow/widower-hood amongst elderly. 22% elderly according to it were widowed.[15] This possibility keeps increasing with age. Loss of spouse has detrimental effect on physical as well as mental health of elderly. Female elderly outlive their male spouse more commonly. As per 2001 census about half of all elderly women were widowed while only 15 per cent of elderly

men were widowers.[16] Due to socio-cultural gender differences & as such poor status of Indian females effects of loss of spouse are much more devastating for elderly females. Loss of spouse affects social well being as well as financial security of females. A study reported devastating effect of widowhood on financial status of elderly females in India.[17]

In absence of formal social security cover, ownership of movable/immovable property assets serves as social security measure for majority of elderly in India. Here also condition of females is worse. Less than half the elderly females have ownership as compared to their male counterparts. This difference in lower socioeconomic strata is even more.[18] To provide universal social security system for all Indians, especially the poor, the under-privileged and the workers in the unorganised sector, Government of India launched the Atal Pension Yojana (APY) in May 2015.[19] But the pension to be provided through it is unlikely to enable elderly to fulfil their healthcare needs.

In our country traditionally family has been the only support during old age. As per National sample survey organization (NSSO) 2004, more than 80% elderly in our country were living in joint family. Many other studies have reported joint family system as most common.[20,21] This data points to joint family arrangement still being the most important informal support structure in old age. But slowly joint family system is crumbling. In a developing country like us where resources are limited, the challenge of fulfilling the demands of this rapidly increasing elderly population by Government alone is unlikely to be overcome. Thus joint family system needs to be strengthened. Through an Act in 2007' Government has made it binding for children to take care of their parents. But for it to be really successful, sensitization of society through education & awareness regarding needs of senior citizens is very important.

Financial dependence compromises decision making power & ability to live life with dignity. According to 'Report on the Status of Elderly in Select States of India, 2011' 50.4% elderly were fully & 26.1% were partially dependent on family members financially.[22] Another study reported two third elderly were dependent on family for finances.[23] This dependence is much more in female elderly. As per a report more than one fifth elderly in our country face some kind of abuse from their children[24] While on one hand this situation increases likelihood of elderly needing health services more (for physical as well as mental well being) on the other hand it decreases possibility of elderly actually using them.

Large number of elderly in our country are forced to work in old age. Because of poor physical ability and energy as compared to young, elderly are mostly employed as part time labour, more so in rural areas.[25] As per 2001 census 44% elderly male & 9% females in urban area were working. While these figures are 39% & 7% respectively in 2007–08 National sample survey organization (NSSO) survey.[26] This rate has been found to be higher in developing countries than developed one & rural than urban areas in our country. Alam M et al found that 71.3% (1615/2265) elderly were working due to economic or other compulsion while only 28.6% (648/2265) were working by choice.[22] These findings are another reminder of grim condition of elderly in India.

Very poor rate of health insurance cover amongst elderly in available literature. According to a 2008 study fewer than 10 percent of Indians have health insurance, and more than 70% of health care spending is paid out-of-pocket.[27] The situation becomes aggravated further by the fact that majority of health security policies exclude elderly due to age limits or due to presence of pre-existing conditions. Other investigators have also noted very low level (only 1%) of health insurance in Indian elderly.[28] Only those in the formal and civil service sectors like defense, civil services, and the railways have this previlege even after retirement.[29–32] Most insurance plans only cover inpatient hospital expenses, so even elderly with insurance cover have to incur high expenditure on outpatient consultation and drug expenses.[33] This data suggests that a very large majority of elderly have to do out of pocket expenditure on health. This is the phase of life when they need healthcare services most. In times of increasing health care costs absence of health insurance is a big handicap in seeking health services. Poor economic status, high financial dependence along with absence of health security cover presents a very dismal picture. This data makes it imperative for policymakers to provide some comprehensive health care cover for elderly.

3.3. *Financial challenges*

Finance related factors are the most important factors in influencing health care utilization as reported by number of studies. A community based study on rural population of south India to identify factors affecting health care seeking behaviour highlighted importance of finances. **Most common reason for preferring public health facility was availability of services, free of cost.**[34]

In a North Indian study on 200 rural elderly to study healthcare service utilization, c**ommonest reason for not seeking healthcare services was affordability (37%).** Other reasons cited by participants were that 'ailment was not serious', lack of trust in doctors' and ignorance.[35]

Another study on 400 elderly reported **poverty was major factor affecting health seeking behaviour**. Two third participants in this study felt spending on treatment was waste of money while about one third cited lack of money as the reason for not utilizing health care services. More than 41% blamed poor attitude of healthcare worker.[36]

Besides affordability availability & accessibility of health care facility has also been found to have significant effect on health care utilization. In a study on 987 rural elderly at Ballabgarh **affordability was the most common reason (32.4%) affecting** health seeking behaviour.[3] **Carelessness (31.6%) and disillusionment (23.5%) due to previous problems not being satisfactory addressed were the other reasons cited** for not seeking any treatment.

A rural Odisha study on elderly highlighted **importance of cost of treatment, availability, accessibility of health services & ability of doctor to satisfy the patients in influencing health care utilization.**[37] More than two third elderly visited nearby private clinic for outpatient treatment. The main reason given for visiting private clinic was long distance of hospital (16 km) away. Non availability of doctor most of the time was cited by 45% respondents. Dissatisfaction with doctor & long waiting

was the reason for avoiding government hospital by some. Interestingly more than 70% preferred government hospital for hospitalization. Main reason for this kind of behaviour was financial. Financial problem was also cited as most common reason **for not taking any treatment.** Majority of study population were poor & thus unable to bear cost of treatment.

3.4. *Physical accessibility*

Accessibility of health care services is an important determinant of health care utilization. Health care facilities are disproportionately concentrated in urban areas. Effect of distance of health care facility on health care utilization has been studied by many researchers. Long distance as the reason for not utilizing health care services was cited by 27% & 48% elderly respondents respectively in a rural Assam & rural Bengal study.[38,39] In another study 19% elderly gave this reason for non utilization.[40] Distance is likely to pose more difficulties for elderly in utilization of health care services in view of their own poor physical health & need of an accompanying person especially if distance to health care facility is more. Another study in Faridabad found few elderly reporting distance as a barrier to health care utilization.[3]

A cross-sectional study on 354 elderly by Goel et al in Meerut found that 96% had never used any Geriatric welfare service. About half of the elderly (46%) were not even aware of this facility. **Lack of awareness & distance was predominant reason for non utilization of health services in this study.**[41]

Even availability is not enough as exemplified by a Karnataka study according to which only one third were aware of geriatric welfare services and less than 15% used them.[42]

Despite respiratory diseases being significant cause of morbidity in elderly, very few Indian studies have focused on health care utilization by elderly for respiratory disease. G. Sudha et al conducted a study on factors influencing the **care-seeking behaviour of chest symptomatic.**[43] Participants involved both rural and urban elderly. 15,127 persons residing in study area for >15 years were included. 340 (3.9%) urban and 349 (5.5%) rural elderly reported respiratory symptoms. In both population chest symptoms were significantly associated with increasing age. Private health care facilities were preferred both by urban & rural participants, 57% & 48% respectively. Proximity to residence and good quality were the main reasons cited for it. Almost half the respondents did not perceive their symptoms to be severe enough needing consultation. Unaffordability (46%) and lack of time due to work pressures (25%) were the other reasons given for not seeking treatment. **Socio-economic factors like literacy and income of family significantly influenced care-seeking behaviour**.

Another important factor regarding health seeking behaviour of rural elderly is using over the counter medication from medical stores & quacks. This type of health seeking behaviour was also noted by Ray et al in rural Bengal where 35.9% were using services of unqualified practitioners (quack).[44] Non availability of qualified medical practitioners in rural India as well as ignorance & financial reasons are responsible for it. To avoid fees of medical practitioner also many patients tend to take medicines directly from medical stores.

3.5. *Quality of health services*

Quality of available health care services is an important determinant of health care utilization. Quality of health care services has got many components ie infrastructure & organization of facility, availability of expertise & equipments as per requirements, behaviour of health care providers, their ability to address concerns of patients, giving them enough time & satisfy them, convenience in getting the service in the form of crowding, waiting time. In case of government services availability of free medicines & levying of user charges are also significant factors. These problems regarding government health facilities in India is a well known fact. These factors make accessing healthcare services especially difficult for elderly considering their poor physical condition.

A lack of staff, drugs, and equipment plague the public system, while the private sector is largely unregulated with serious complaints regarding poor quality of care and unethical behavior.[45] Several indigenous systems of medicine also operate amidst the formal public and private systems, and offer treatments which may be more accessible, affordable or acceptable to the rural elderly.[46,47] According to one study 36 million people in India fall below the poverty line each year due to expenditure on health care.[48] Despite all this a large portion of the population choose to bypass free public services to pay out-of pocket in private institutions.[49,50] This fact reflects poor quality and accessibility of government health care services.

A number of studies have documented poor utilization of health care services in rural area as compared to urban areas. Poor quality of Government health care services in rural India & their negative effect on health care utilization was highlighted by Karamkar and Chattopadhyay in a cross sectional study on elderly in a rural area of Singur block of West Bengal.[51] Significant number of elderly ie 28.22% sought no treatment. Only 13.88% sought treatment from government health facility. Fixed outdoor timing and indifferent attitude of staff at government facility was cited as the reason for poor utilization of this facility.

An AIIMS study found carelessness (31.6%) and disillusionment (23.5%) due to previous unsatisfactory experience as second & third most important reasons for avoiding treatment by elderly for their self reported problems.[3] Various other studies have reported out-of-pocket costs, long queues, disrespectful treatment by facility staff, medication stock-outs and perceived ineffective care as barriers to health care utilization.[52,53,54]

Another aspect regarding respiratory care is acute shortage of pulmonologists in India. As per a 2020 report there are only around 2500 registered qualified chest specialists (pulmonologists) in India. There are only 700 postgraduate seats for pulmonary medicine in India. Respiratory health problems of elderly are complex, many a times sequelae of past illnesses. Improper diagnosis & management adds to woes of this already vulnerable population.[55]

3.6. *Attitudinal challenges*

Attitudinal factors as barriers to health care utilization by elderly are unique to our society. Illiteracy, ignorance, poverty,

socio-cultural conditioning lead to fatalistic attitude in old age. Old age has been described as a curse in ancient Indian literature. Many elderly consider poor health as a part of normal ageing. They are resigned to bear with ill effects of diseases. There are also many misconceptions about need & effects of treatment. Besides many of them also resort to non-scientific methods.

Effect of negative attitude on health care utilization has been well documented in literature. In a study 39.6% elderly did not seek treatment for their illness due to their belief that it is part of old age, while 36.8% considered their morbidity as minor illness requiring no treatment.[38] Fear of discovering a serious illness & unneeded tests led 18.1% and 16.3% elderly respectively to avoid treatment in a rural Bengal study.[44] Sharma et al reported the most common reason for not seeking health care was the perception of disease as an age related phenomenon (49.6%).[40] A study in Nepal found 'ignorance due to old age' & 'trust on God for healing' being reasons for not seeking treatment by 64% & 8% elderly respectively. Goswami et al. also noted fatalistic attitude as a reason for not seeking any treatment by elderly.[3]

This data emphasizes the need of creating awareness & bringing about attitudinal change in society as a whole regarding problems of old age. Society also needs to be educated to treat old age as just another phase of life which can be enjoyed provided all problems are properly addressed to.

Mental health is even more neglected aspect of health. As per a Goa study, despite being commonly found in geriatric population, certain mental health deficits were not considered needing medical help. Conditions like dementia are viewed as normal ageing phenomenon. Access to mental health services in the medical sector are limited, and, thus, in most cases regular proper care was not provided. Consequently, "dependency anxiety" was a commonly seen in elderly, i.e., elderly tried to decrease their dependence on the family and had anxiety about informing them about their health problems.[56]

3.7. *Transportation*

Distance is only one part of transportation problem & availability of good transport facilities will negate the effect of small difference in distance. Transportation problems in elderly are unique & has many aspects ie: inconvenience, long time taken, vehicle availability, availability of companion & need for more than one companion to accompany. Transportation problems are more likely to affect health care utilization by elderly in view of their weak body, illness, physical disabilities & increasing need of a companion. Transportation problems also put indirect costs on utilization. So even availability of free medical services get affected by transportation due to financial reasons.

Availability of transport & commuting time have been found to affect also the choice of health care facility. In a Tamil Nadu study 9% elderly switched to private facilities from government one due to lack of transport.[43] Similarly in a Dharan, Nepal study commuting time of more than 30 min significantly affected choice of small private clinics over BPKIHS, Dharan a large medical college facility ($p = .001$).[36]

4. Tuberculosis & elderly

Effect of increasing elderly population will also mean larger number of elderly tuberculosis patients. As such elderly are more vulnerable to tuberculosis due to poor immunity, malnutrition, neglect & poor socioeconomic status. Considering social belief system, elderly with tuberculosis are more likely to face neglect & isolation. Sputum conversion rate at end of intensive phase has been found to be poorer in elderly with tuberculosis in comparison to non-elderly patients.[57–59] One reason for it could be the higher rate of adverse reactions, drug interactions, and comorbidities in elderly forcing dosage reduction. Elderly are also likely to have poorer absorption of anti-tubercular drugs.[60] Studies have reported rate of unsuccessful treatment outcomes such as bacteriological or clinical failure, death also higher among elderly.[61] At present there are no specific policies for elderly patients with tuberculosis. Considering special needs & profile of this population subgroup, they should be given special attention to make TB control program successful.[62]

5. Conclusion

Provision of specially designed, good quality healthcare services for rapidly increasing population of elderly in India is full of challenges considering limited resources of our country. Improvement in overall socioeconomic condition of elderly & correction of negative attitudinal factors in elderly is another aspect of challenges related to adequate utilization of healthcare services by elderly.

Conflicts of interest

The authors have none to declare

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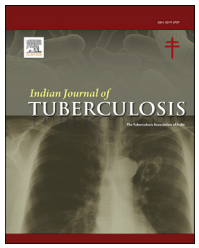

Review article

Interventional pulmonology in elderly in tuberculosis and respiratory diseases-challenges

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ABSTRACT

With the increasing number of the elderly population, the number of people with respiratory diseases along with other comorbidities is also increasing. With the good number of available evidence, the use of interventional pulmonary procedures is also increasing.
However, the studies on the safety and therapeutic benefit of these procedures in the elderly population are limited. Because of the paucity of data, we decided to do a systematic review of the scientific literature that is currently available, to boost confidence to do these procedures by clinicians.
This review deals with the procedures that are commonly performed in elderly respiratory patients, their indications, safety and the diagnostic and therapeutic yield, and compares them with the results in the younger population. It also focuses on the safety of anaesthetic techniques used for these procedures in the elderly.
The bottom line of this review is that there is no significant difference between the older and younger age groups with regard to the above parameters and that age alone is not a criterion to decide whether the patients may undergo interventional pulmonary procedures.

1. Introduction

In the past few decades, the knowledge in respiratory medicine has grown leaps and bounds. The role of interventions in the diagnosis and management of respiratory conditions has significantly improved with the advent of newer modalities. There is a significant shift from thoracic surgical techniques to minimally invasive Interventional Pulmonology (IP) techniques done by pulmonologists. It is more so in the realm of tuberculosis, interstitial pneumonia, thoracic malignancies, interstitial lung diseases and other respiratory diseases, which are more common in the elderly.

Multimodal treatment options including Endobronchial ultrasound (EBUS) – both linear and radial, Cryo biopsy, Navigation bronchoscopy, photodynamic therapies and medical thoracoscopies have all helped to diagnose and in many cases, manage these diseases with much less discomfort to the patients. More and more elderly patients now

Abbreviations: IP, Interventional Pulmonology; cTBNA, Conventional Transbronchial needle aspiration; EBUS, Endobronchial ultrasound; EBUS TBNA, Endobronchial ultrasound guided trans bronchial needle aspiration; BAL, Bronchoalveolar lavage; FB, Flexible bronchoscopy; BW, Bronchial Washings; TBB, Transbronchial biopsy; EBB, Endobronchial Biopsy; FOB, Fibre optic bronchoscopy; EUS-B, Endoscopic ultrasound using bronchoscope; BTVA, Bronchoscopic thermal vapour ablation.

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undergo these procedures with ease as the chance of complications is much lesser compared to procedures like CT-guided biopsies, mediastinoscopies and open lung biopsies.

Since the prevalence of lung diseases and their complexities increase as age progresses, the need for interventional procedures also increases.[1] During the past, two to three decades the safety of the above interventional procedures has significantly improved and a lot of studies have clearly shown an acceptable safety margin. The studies which evaluated the indications and safety of IP procedures especially bronchoscopy in elderly patients have used a varying cut-off for age, but the World Health Organisation and the consensus is those whose chronological age of above 65 years.[2,3] The British thoracic society recommends performing bronchoscopy based on clinical needs rather than chronological age.[4] The present review aims to look at the indications and safety of IP procedures in the elderly for various respiratory diseases.

2. Methods

We searched Pubmed and Scopus with keywords like elderly, bronchoscopy, medical thoracoscopy and older patients. We took those articles in English and the ones conducted on human beings only.

3. Results

3.1. *Bronchoscopic techniques*

3.1.1. *General indications*

The main medical conditions for which bronchoscopy was used were for the diagnosis and staging of lung cancer, pneumonia/consolidations, removal of foreign bodies, collapse/atelectasis and hemoptysis, of which most common were lung masses and pneumonia.

The diagnosis of tuberculosis in the elderly population is particularly difficult as these patients present with insignificant symptoms which could be easily overlooked. Atypical clinical presentations coupled with a variety of radiographic features, poor cough reflux and limited clearance of secretions due to poor effort and sputum smear negativity in the elderly contribute to the difficult diagnosis. Thus in this group of patients' Flexible bronchoscopy (FB) coupled with bronchoalveolar lavage (BAL) and other bronchoscopic techniques play a very important role.[5] The need for Transbronchial needle aspiration (TBNA) both conventional (C-TBNA) and endobronchial ultrasound (EBUS-TBNA) in cases of mediastinal adenopathy cannot be underscored. Bronchoscopic therapy is also used for the treatment of endobronchial tuberculosis and its complications. This includes procedures like airway dilatation, stenting and also the use of both hot and cold techniques to the airway.

3.1.2. *Procedures done*

The procedures performed through bronchoscopy are bronchial washings (BW), BAL, endobronchial biopsies (EBB), transbronchial biopsies (TBB), TBNA/true cut biopsy and foreign body. The most commonly employed ones were washings and lavage (see Table 1).

3.1.3. *Anaesthesia/sedation employed*

Sedation given as premedication and during the procedure provides comfort and tolerance during the bronchoscopic procedure. It also increases the willingness of the patient to undergo a repeat procedure. The British thoracic society guidelines recommend providing adequate sedation to the patients during the procedure unless contraindicated.[4] The type of analgesia, anaesthesia and sedation will vary between geographical areas, the experience of the bronchoscopists, the route of intubation (nasal/oral), the use of local anaesthetic (cricoid anaesthesia/lignocaine "on the go"), the dose of anaesthetic used, the procedure being done and complications during the procedure.[4]

Ageing can increase the susceptibility to anaesthetic drugs, which can at times lead to respiratory failure and other increased complications, if not used judiciously.

Most bronchoscopists use topical lignocaine for the procedure. It is given as injecting lignocaine through the cricothyroid membrane, directly into the trachea, before the procedure along with lignocaine local installation – 2ml of 2% lignocaine given as "spray as you go" technique. Ameer et al compared the systemic absorption of topical lignocaine in the elderly and young adults and found that despite giving a high cumulative amount of lignocaine topically, the plasma concentration never reached high to cause toxicity. But in those patients who have cardiovascular (on antihypertensive, antiarrhythmic drugs) and liver disease, while given higher doses, they have to be closely monitored to look for toxicity.[18]

Midazolam (short-acting benzodiazepine – better preferred) or diazepam with or without fentanyl was the common sedation employed.[6,7,10,11,16,17] Most studies did not show serious side effects. Many patients had mild desaturation, which was also related to the type of procedure they were doing, which became better by providing external oxygen. Few patients had hypotension and minor bleeding. None of them were major side effects and did not warrant stopping the procedure.

The study by Watts et al, compared premedication with oral temazepam plus nebulised lignocaine (new treatment) to an established regimen of intravenous alfentanil (control) for patients of age more than 75 years. The primary outcome measure was the lowest oxygen saturation recorded after the administration of IV drugs and also 30 min post-bronchoscopy. They did not find any difference in outcome and both the regimens were safe.[19]

Evision et al have shown in their study on accuracy and the safety of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) in lung cancer patients that older patients had higher procedural tolerability despite a lower dose of sedatives being administered.[20]

3.1.4. *Diagnostic yield of conventional bronchoscopy and BAL and biopsy in elderly*

The majority of studies compared the diagnostic yield in elderly patients versus the younger age group. The concurrence from all the studies is that the yield does not correlate with age. Sarinc Ulasli et al have shown that the diagnostic yield of bronchoscopic procedures like BAL, bronchial

Table 1 – Procedures, indications, the anaesthesia given and complications seen in various studies in bronchoscopy in elderly – flexible or rigid.

Author	Patient number (n)	Procedures	Indications	Anaesthesia/ sedation	Complications
Macfarlane/1981[6]	204	Diagnostic Flexible Bronchoscopy (FB) (EBB, TBB)	Pneumonia/ atelectasis/masses	Fentanyl, droperidol iv	respiratory distress
Knox/1988[7]	60	Diagnostic FB (EBB)	Pneumonia/masses	Diazepam, fentanyl iv	respiratory failure
Haga/2014[8]	65	Diagnostic FB	Foreign body removal/others not specified	Not available	fever, bleedings, hypoxaemia, bronchospasm, pneumothorax
Haga/2016[9]	66	Diagnostic FB	Malignancy/ pneumonia/ILD	Not available	bleedings, hypoxia events, fever, bronchospasm and pneumothorax
Sarinc Ulasli/2014[10]	367	Diagnostic FB (BW, BAL, EBB, cTBNA, TBB)	Masses/infectious disease/hemoptysis	Midazolam iv	bleedings, respiratory depression, bronchospasm, death
D'Ippolito/2007[11]	191	Diagnostic FB (EBB, BAL, TBB)	Masses, atelectasis, clearing of secretions	Diazepam in selected cases	None
Boyd/2009[12]	8	8 FB, 1 RB	Foreign body removal	Not available	Bleeding, hypoxia events
Rokach/2008[13]	150	Diagnostic FB (EBB, TBB)	Masses/pneumonia	Not available	None
Vitale/2016[14]	43	cTBNA	malignancy	Conscious sedation	None
Kanemoto/2006[15]	76	Diagnostic FB (BW, BAL, EBB,TBB)	Masses/nodules	Not available	None
Noda (2020)[16]	102	Diagnostic FB (transbronchial brushings TBB)	Malignancy/Non tubercular mycobacteria/ organising pneumonia	Midazolam i.v/ lignocaine inhalation	None
Davoudi/2008[17]	18	Therapeutic Rigid Bronchoscopy (laser, stenting) dilation)	Malignant and benign airway obstruction	Midazolam, propofol, fentanyl and remifentanil iv	hypotension; moderate bleedings, hypoxia, bronchospasm

mucosal biopsy, bronchial washing and conventional TBNA in the elderly is not different from the younger age group.[10] A similar study by Rokach Ariel et al has shown a diagnostic yield of 63% in octogenarians and 52% in the control group ($P = 0.04$) and the diagnostic and therapeutic benefit was 88% in the octogenarians and 87% in the control group.[13]

Pociene et al studied age as a risk factor for complications during or after bronchoscopic lung biopsy. They studied 768 patients of which only (57; 7.25%) patients had complications. (27; 3.4%) patients developed pneumothoraxes and (30; 3.8%) patients had bleedings. Most of the pneumothoraxes (19; 70%) required chest drainage and most bleedings (26; 86%) were classified as mild.[21]

3.2. *Rigid bronchoscopy*

Davoudi et al studied the use of rigid bronchoscopy as a therapeutic procedure in 18 octogenarian patients under general anaesthesia with spontaneous assisted ventilation. The therapeutic procedures done were bronchoscopic balloon dilatation, tumour debulking, laser resection and stent placement. The complications were hypoxemia - intraoperative (1 patient) and postoperative (9 patients), hypotension requiring vasopressors (7 patients). All patients recovered well with standard care.[17]

Foreign bodies are very common in extremes of age. Studies by Rokach, Boyd, Haga and Allan have described the removal of foreign bodies in the elderly with a flexible scope with very good results and with minimum complications.[8,9,12,13,22] Boyd et al showed that foreign bodies occur three and a half times as likely to occur in those ≥75 years of age compared to those <75 years.[12]

3.2.1. *Safety and tolerability*

Most of the studies did not show any significant difference in the safety and tolerability in older age group patients compared to younger age group, except for the study by Rokach et al and Haga T et al. Rokach et al study revealed a higher rate of mortality and adverse events in elderly including arrhythmias and hypoxemia.[13] Haga et al showed in their multivariate analysis that transbronchial biopsy procedure and age is a risk factor for complications.[9] None of these studies found these complications were statistically significant even though their absolute number was higher.

Scala et al studied the use of early fiberoptic bronchoscopy (FOB) during non-invasive ventilation in patients with decompensated chronic obstructive pulmonary disease due to community-acquired pneumonia (CAP). In this prospective matched case–control study, they enrolled 15 study patients and 15 control patients, with a mean age of 80 years and FOB was done in this study group of decompensated COPD due to CAP, who were candidates for mechanical ventilation due to

Table 2 – Anaesthesia, overall yield, safety/complications of EBUS procedure in elderly.

Author	No of older patients	Comparison with younger age group	Anaesthesia	Overall yield	Safety/ complications
Dhooria et al (2020)[24]	258	yes	midazolam, pentazocine, fentanyl as required	Similar specimen adequacy/lower positivity rate.	Sustained hypoxemia/ bleeding, and intolerance to the procedure. Not statistically different
Demİrcİ et al (2018)[25]	203	yes	topical lidocaine spray/midazolam	Good diagnostic accuracy compared to younger age group	mild respiratory depression, bleeding, agitation, transient tachycardia, fever - all minor complications. Not statistically different
Evision et al (2014)[20]	198 patients >70 years of age.	Yes	alfentanyl and midazolam	Diagnostic accuracy – 96% in older patients and 90.2% in younger patients	bleeding and prolonged post-procedure hypoxia (0.4%) and minor complications (6.7%). not statistically different
Yıldızeli et al (2018)[26]	39 (patients more than age of 70)	Yes	1% lidocaine spray and 1 ml of 1% lidocaine with salbutamol nebulization for local anaesthesia/ midazolam	Good diagnostic yield compared to younger age group	Hypoxia/fever/ tachycardia
Okachi et al (2013)[27]	34 patients with age >70 years	Yes	2% lidocaine topically/midazolam	Good yield compared to the younger group	Paroxysmal atrial fibrillation in one patient/younger age group had more complications
Niwa et al (2022)[28]	111 patients (age >80 years)	no	midazolam and fentanyl	Diagnostic rate – 75%	Oversedation/chest pain/hypoxemia/ arrhythmia. All were minor complications.

the inability of these patients to clear the secretions. They concluded that non-invasive ventilation with early therapeutic FOB performed by an experienced team is a feasible, safe and effective alternative strategy to therapeutic intubation and mechanical ventilation to remove copious secretions.[23]

3.3. *Endobronchial ultrasound – transbronchial needle aspiration (EBUS – TBNA)*

Quite a few studies are available looking at the safety and challenges of EBUS procedure in the elderly. Most of them have given a comparison between the older age versus the younger age group. The majority of the studies have taken a cut-off of age above 70 for the elderly.

Most of the studies used conscious moderate sedation which utilises a combination of an intravenous benzodiazepine and opioid to achieve reduced consciousness so that the patient can support their airway and respond to commands (see Table 2).

Most of the studies did not show any significant increase in complication rate compared to the younger age group. All the complications were reported to be minor. EBUS TBNA was a safe procedure which can be done under mild to moderate conscious sedation in the elderly. It also gave a good diagnostic yield in the elderly.

Endoscopic Ultrasound done using a bronchoscope (EUS-B) is a novel technique of using the EBUS scope through the oesophagus and doing the TBNA procedure for sampling mediastinal nodes. It is usually performed when the node is inaccessible through the airway or when the patient is sick enough to tolerate airway procedures. The study by Oki et al on the safety and yield of EUS-B had patients with a mean age of 65 (28–83). They did not look specifically into the elderly population. They had a high diagnostic yield (90%) along with good tolerance with EUS-B. The advantage of using EUS-B was good tolerance with fewer doses of anaesthetics and sedatives required, shorter procedure time, and fewer instances of oxygen desaturations during the procedure.[29]

Vitale et al. did a study on the diagnostic yield and safety of conventional TBNA (C-TBNA) in the elderly. They compared patients above 70 years of age against those less than 70 years of age and found that there was no significant difference in either the diagnostic yield or the complication rate. Reported complications were minor bleeding and poor tolerance.[14]

Currently, we have many more procedures that are being done in the elderly. For emphysema patients, bronchoscopic thermal vapour ablation (BTVA), endobronchial valves and the use of polymeric sealants are safe in older age group patients. Similarly, microwave ablation of tumours through bronchoscope is safe in this group with minimal complications. Most of the patients for these studies are elderly as it is more prevalent in this age group.

3.4. *Pleural procedures*

Pleural procedures are commonly done in the elderly. Pleural aspiration (thoracentesis), closed and pleuroscopic (medical thoracoscopic) pleural biopsy, Intercostal tube insertion, medical thoracoscopy and pleurodesis are the common procedures done in this group of patients.

Thoracentesis when done under ultrasound guidance, is a very safe procedure.[30] The complications that can happen are iatrogenic pneumothorax, bleeding (hemothorax), and injury to the diaphragmatic, liver or spleen. The usual cause of hemothorax is an injury to intercostal vessels. In the elderly, the intercostal vessels are more tortuous, so there is a high chance of inadvertent injury if it is not under ultrasound guidance.[31,32]

Elderly patients have more chance of cardiac comorbidities and since many of them would be on antiplatelet therapies, the chance of bleeding is higher. The addition of ultrasound guidance will give much-needed safety to the procedure for these patients.30,31,32

4. Conclusion

The elderly population requires more interventional pulmonology procedures as they have a higher prevalence of infections, malignancy and other pleural diseases. Most of the studies have very clearly shown that with adequate precautions, IP procedures are very safe and can be done with the ease with which we do for the younger age group.

There was no significant difference in the diagnostic yield, therapeutic efficiency and complication rates when compared with younger patients. The sedation we give for the younger patients was equally effective and safe for the older age group too. There were a very limited number of sedation-related side effects and most of these complications were minor and expected. Further studies are required for IP procedures like BTVA, use of endobronchial valves and pleural procedures like medical thoracoscopy to confirm their safety, yield and therapeutic efficacy of the anaesthesia given.

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Conflict of interest

The author has none to declare.

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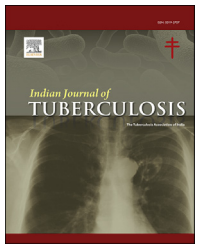

Review article

Opportunistic infections in elderly TB patients

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ABSTRACT

Since ancient times, tuberculosis has been a lethal infectious illness. The elderly are particularly susceptible to various illnesses, including tuberculosis. Tuberculosis (TB) and people ageing weaken the immune system, thus increasing the risk of getting other co-infections. Most elderly TB cases are associated with the reactivation of dormant lesions, and these lesions have reactivated due to immunosenescence. Elderly patients have a greater mortality rate from tuberculosis and other co-infections. Active infection signs and symptoms are generally less severe in the elderly. The interaction of structural lung damage, prolonged inflammation, bacterial and fungal colonisation of the respiratory system, and mucociliary insufficiency causes recurrent infections.

It is imperative to use all available tools to make a microbiological diagnosis in diagnostic challenges in atypical cases. The therapeutic management of older people presents a significant difficulty in identifying frailty to prevent loss of independence.

1. Introduction

TB is a significant issue in the elderly population due to various factors. Immunosenescence due to ageing, additional aged comorbidities, other associated co-infections and potential interactions between antituberculosis drugs and other medications. This is not surprising given that tuberculosis is a destructive disease that causes cicatrization, parenchymal or effected tissue remodeling, bronchiectasis, and fibrosis of the lung, resulting in decreased lung volumes and an influence on pulmonary function. Lung senescence is enhanced, particularly in the presence of smoking and pollutants.[1] Underlying TB weakens the immune system further in the elderly and makes them susceptible to multiple opportunistic infections (see Table 1).

Colonization and invasion with non-tuberculous mycobacteria (NTM) and *Aspergillus fumigatus* are frequent in those who have some degree of lung deterioration.[2]

Tuberculosis and other pulmonary opportunistic infections such as COVID-19 primarily affect the lungs. They have similar coughing, fever, and difficulty breathing symptoms, but tuberculosis has a more extended incubation period and a slower disease onset. In various studies, the estimated TB prevalence among COVID-19 patients is 0.37–4.47 per cent.[3]

This review aims to summarise, synthesise, and evaluate the literature on other opportunistic infections, pathophysiology, diagnosis, treatment, and outcome in elderly tuberculosis patients.

2. Pathophysiology

2.1. *Age-related physiological and structural changes*

Many respiratory changes are associated with advancing age, such as a decrease in lung elastic recoil, a reduction in

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Table 1 – Spectrum of infections in elderly tuberculosis patients.

Opportunistic infections in elderly TB patients			
Bacterial	Fungal	Viral	Miscellaneous
Streptococcus pneumoniae	*Aspergillus fumigatus*	SARS CoV-2	*Non-tuberculous mycobacteria*
Klebsiella pneumoniae	*Pneumocystis jirovecii*	*Influenza*	*Plasmodium spp*
Pseudomonas aeruginosa		VZV	*Strongyloides stercoralis*
Staphylococcus aureus		*Adenovirus*	*Leishmania donovani*
Haemophilus influenzae		*Parainfluenza*	
Burkholderia cepacian complex		*Rhinovirus*	
Stenotrophomonas maltophilia		*RSV*	
		hMPV	
		hBCV	

respiratory muscle compliance, and a decrease in lung capacity. Poor nutrition is also common in elderly people and can cause respiratory muscle dysfunction and sarcopenia.[4] Excessive inflammation and enhanced production of lung matrix-degrading proteases are prevalent during TB, suggesting that host immune responses play a prominent role in lung destruction. The severity of lung damage may be determined by variation in host genes that affect these immune responses, although this theory is largely untested.[5] Also, with alteration in the anatomy after pulmonary tuberculosis or extrapulmonary tuberculosis there is a risk of increase bacterial infections in subsequent years.

2.2. *Immunosenescence*

Immunosenescence is commonly associated with lymphopenia, decreased output of immunologically naive T cells from the thymus, and decreased immunological memory of T cells.

2.3. *Inflammaging*

The rise in inflammatory cytokine concentrations (termed "inflammaging") and tissue ageing are susceptible to an increased risk of infection such as tuberculosis and herpes family (HSV I/II, VZV, CMV).

Beginning to grow older is linked to an increase in an individual's basal inflammatory state and predisposition to many diseases, including infectious diseases. Evidence is overwhelming to support the idea that inflammation and disease susceptibility are linked in the elderly.[6]

Also, with the development of immunosenescence and inflammaging in patients of ongoing tuberculosis, there is tendency to have severe infection with marked lung injury by respiratory viruses such as SARS CoV-2 and influenza.

2.4. *Tuberculosis induced lung injury*

These are the anatomic and physiological changes in the chest or other part of the body. In pulmonary tuberculosis sequelae, whether primary or secondary, even after therapy and bacteriological cure there can be dysfunction in the form of parenchymal, airway disease, pleural/chest wall, vascular, and mediastinal.

These modifications can produce pulmonary impairment, ranging from subtle symptoms to severe shortness of breath, increasing mortality risk from respiratory causes.

2.5. *Lung injury and dysfunction mediators in tuberculosis*

Immune mediators of TB, smoking and host immune response are responsible for tissue remodelling and organ impairment. It represents transcription factors, cytokines, and chemokines that promote the production of tissue-degrading enzymes or directly induce cavitation and/or fibrosis. The picture (Fig. 1) depicts matrix metalloproteinases (MMPs) that cause granuloma and cavitation.

Moreover, cigarette smoking is a risk factor for pulmonary infections as well as a cofactor in fast lung function decline, decreased exercise tolerance, and poor QoL.[7]

3. Infections in elderly tuberculosis patients

3.1. *Bacterial infections*

The microbiology of recurring infections is confined to post-TB non-cystic fibrosis bronchiectasis individuals. Data from studies on all non-cystic bronchiectasis patients, particularly in high TB endemic areas, can be generalised. *Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis,* and *Staphylococcus aureus* are commonly associated with infectious exacerbations. *Burkholderia cepacia complex, Stenotrophomonas maltophilia*, and other Pseudomonadaceae family members are increasingly being identified as pathogenic organisms. This shift has been ascribed to advancements in microbial detection, improved sputum monitoring, and long-term suppressive antibiotic therapy.

3.2. *Fungal infections*

Chronic pulmonary aspergillosis (CPA) entails a variety of disease patterns that frequently overlap. Chronic cavitary aspergillosis (CCA), chronic fibrosing aspergillosis (CFA), aspergilloma, and Aspergillus nodules are the most common subtypes of CPA. The causative species is *A. fumigatus*, but infections with *Aspergillus niger* and *Aspergillus flavus* have additionally been reported.[8] CPA's clinical features are typically non-specific and indolent in onset in most cases, going unnoticed. Weight loss, a chronic productive cough, fatigue, dyspnoea, and hemoptysis are all common symptoms. In the absence of a concurrent CCA or CFA, a simple aspergilloma often causes few or no symptoms.[9] *Pneumocystis carinii*

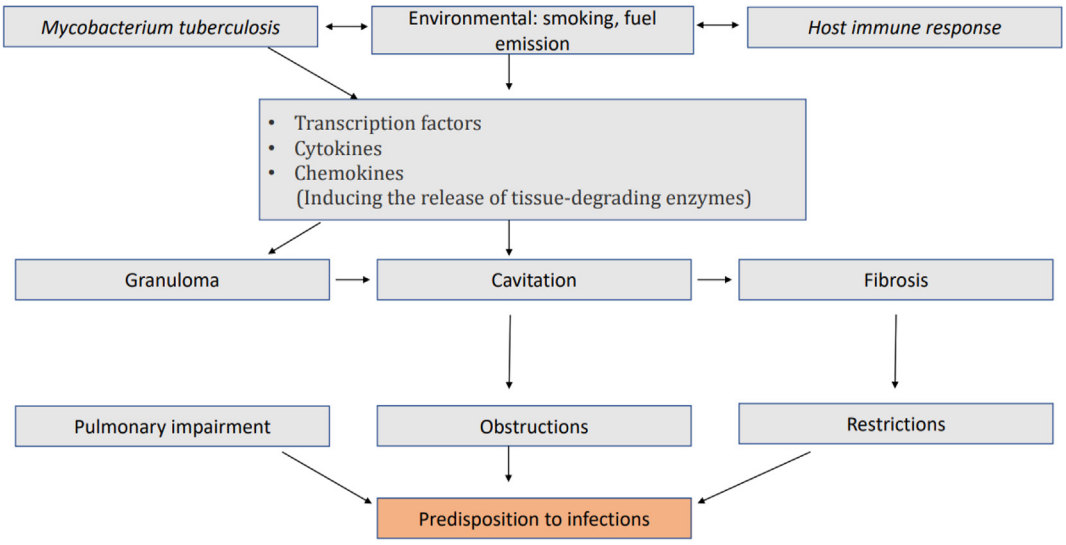

Fig. 1 – Pathological processes of TB tissue remodelling and lung dysfunction.

pneumonia (PCP) and TB are prevalent lung infections in people living with HIV; their relative occurrence varies by region.[10] Nonimmunocompromised older people are commonly colonised by Pneumocystis, indicating that they participate in the *Pneumocystis jirovecii* transmission cycle as a reservoir of this infection for immunocompromised susceptible individuals.[11]

3.3. *Viral infections*

Underlying TB disease may enable viral co-infection, which may result in a different TB disease presentation or more severe TB disease. In the case of tuberculosis, elderly age is a risk factor for active TB with poor treatment results.[12] Though most of the respiratory viruses remains the same in all age group there are few which have significant impact especially in children, elederly or immunocompromised states, especially with Adenovirus (AdV), Influenza A/B virus, Parainfluenzavirus 1–4 (PIV), Varicella Zoster virus (VZV), human Rhinovirus A/B/C, Respiratory syncytial virus A and B (RSV), human Bocavirus 1–4 (hBCV), human Metapneumovirus and SARS CoV-2.[13] In the elderly, the clinical manifestation of these infections might be subtle, with atypical presentations such as delirium, and may be complicated. Respiratory failure caused by SARS and COVID-19 is widely reported in the elderly.[14]

3.4. *Non tuberculous mycobacteria*

Complications of pulmonary TB are classified. *Mycobacterium avium*-intracellulare complex is the most frequently isolated NTM from lung samples (MAC). Another prominent cause of progressive pulmonary illness is *Mycobacterium kansasii*. Patients who have pre-existing structural lung illness, such as bronchiectasis or previous tuberculosis, are at risk of acquiring NTM lung disease.[2]

3.5. *Parasitic infections*

Human co-infection with TB and parasitic illnesses is a major public health issue in co-endemic areas of developing nations such as in India. *Plasmodium spp, Leishmania donovani and Strongyloides stercoralis* have all been identified as risk factors for one another. Co-infection can severely suppress the host's immune system. Furthermore, parasite infection can modify the protective immunological response to BCG immunisation against *Mycobacterium tuberculosis*.[15]

4. Prevention and vaccination

Co-infection with influenza and tuberculosis can compromise host immunological responses, increasing susceptibility to subsequent bacterial infections.[16] Individuals with suspected influenza infection may benefit from immediate empirical antiviral medication to reduce the likelihood of catastrophic consequences. Most worldwide recommendations advocate seasonal influenza vaccination for people with chronic lung diseases.[17]

Tobacco smoking poses a risk factor for respiratory infections and is a facilitator of accelerated lung function deterioration, decreased exercise tolerance, and poor QoL. Comprehensive smoking cessation in parallel with respiratory rehabilitation centers is likely an essential strategy for reducing infective exacerbations in patients with established lung disease.[18]

5. Diagnostic challenges

Diagnostic testing for any age group are dependent on available resources and accessibility, which may be restricted to none for the homeless and jailed, while there should be parity in testing and treatment provision. When the elderly have an impaired cough reflex, they may have additional technical challenges in producing adequate respiratory samples for testing, such as for tuberculosis. A low-quality respiratory sample will invariably delay diagnostic and contact tracing attempts.

A strategic laboratory approach is required for the rapid detection of viruses, atypical bacteria causing severe acute respiratory infections, such as Influenza and SARS-CoV-2, as well as discrimination from other prevalent bacterial illnesses. This strategy necessitates the integration of traditional virology and atypical bacteria assays, molecular platforms that combine nucleic acid extraction and PCR or real-time PCR, and rapid molecular tests utilised at point-of-care labs. Positive results from single or multiplex RDTs may result in appropriate cohorting and care of infected patients.[19] The identification of *M.tuberculosis* is required for the diagnosis of active tuberculosis. TB bacilli, most commonly found in respiratory specimens. Despite the fact that culture remains the "gold standard" in terms of sensitivity and specificity, effective molecular tests for DNA from TB bacilli is being utilised on platforms and in point-of-care testing.[20]

6. Conclusion

In the elderly, tuberculosis is common and requires particular care. If immunosenescence encourages reactivation of the multiple associated co-infections, whether or not exacerbated by therapies (corticosteroids, immunosuppressants, anti-cancer chemotherapy), HIV infection must be systematically searched for. The use of systemic steroids is primarily responsible for the reactivation of tuberculosis along with other opportunistic infections ranging from bacteria, fungal, viral, or parasitic. The diagnosis of TB in the elderly is complex, requiring contact screening, often in long-term care facilities, with the efforts to improve the yield of the sputum in the context of an often precarious general condition (undernutrition, co-morbidities, cognitive disorders) due to active systemic infection and old age. To maximise treatment for these vulnerable individuals, multidisciplinary therapy including geriatricians and infectious disease experts is recommended.

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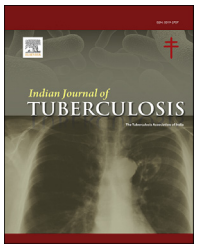

Review article

Challenges of diabetes in elderly TB patients

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ABSTRACT

Diabetes mellitus (DM) and tuberculosis (TB) are worldwide health burdens post-COVID-19. TB is the second-leading cause of death by a single infectious microbe. There is much evidence around the world about the responsibility of TB-DM co-morbidity. Both TB and DM prevalence is high in low- and middle-income countries. Especially the elderly with diabetes are more prone to TB infection due to compromised immune systems. Diabetic patients are three times as likely to develop tuberculosis as non-diabetic patients. DM interferes with the status of TB and leads to undesirable outcomes in the treatment of TB. This may later lead to the development of multidrug-resistant tuberculosis (MDR-TB). The coexistence of TB and DM leads to a high mortality rate and therefore becomes an enormous challenge for the medical field. This viewpoint includes the most current information about TB and DM, disease complications, treatment strategies, challenges to be faced in disease management and the importance of TB-DM bidirectional screening in older adults, which helps in early detection and better treatment programme.

Despite rapid medical development, diabetes mellitus (DM) and tuberculosis (TB) remain a global burden affecting millions yearly. Tuberculosis is one of the leading infectious diseases caused by *Mycobacterium tuberculosis* which is very common in diabetic patients. When a susceptible person inhales the droplets containing tuberculosis bacilli, the host's immune response limits the spread of TB infection, which results in a localised disease without any symptoms (asymptomatic). In diabetic patients, tuberculosis usually remains asymptomatic, most likely leading to drug-resistant tuberculosis.[1] Recent reports have identified tuberculosis as the 13th leading cause of death and the 2nd leading infectious disease after COVID-19. Two-thirds of the world's TB cases are reported in eight large countries, followed by India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa. An estimated 10 million people were infected with tuberculosis globally in 2020.[2] DM is a chronic metabolic disorder characterised by high blood glucose, one of the fastest-growing health conditions in the 21st century. In 2021 an estimated 537 million adults (20–79 years) had diabetes; one in two (240 million) adults with diabetes are not diagnosed.[3] The World Health Organization (WHO) has recognised DM as a worldwide epidemic that primarily affects low- and middle-income counties, where 80 per cent of all

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related deaths occur.[4] A collaborative framework led by WHO and the International Union Against Tuberculosis and Lung Disease (Union) aims to deal with the prevention and control of TB and DM.[5]

DM is considered a well-known risk factor for TB. Not only DM, but there are also some other risk factors associated with TB, which include ageing, smoking, alcohol consumption, chronic kidney disease (CKD), being underweight, malnutrition, chronic lung disease, and immunosuppressants.[1] However, the high prevalence of TB and multidrug-resistant TB (MDR-TB) are associated with DM, which has become a severe medical problem.[6] DM is more common among the elderly, and diabetic patients are three times more likely to develop TB. The prevalence of MDR-TB co-morbidity is the highest in the elderly.[7] "The majority of DM among TB patients ranged from 1.9% to 45% with a prevalence of 16% (Median with interquartile range - IQR 9.0%–25.3%). Whereas the worldwide prevalence of tuberculosis among patients with diabetes is low the median , the prevalence of TB cases in patients with DM was 4.1% (IQR 1.8%–6.2%) which usually ranged from 0.38% to 14%".[8] In another study, the prevalence of DM in TB patients was 42.6%, 92 of whom were diabetic among the 216 TB patients tested.[9]

There is a positive association between DM and MDR-TB, where DM accelerates the rate of MDR-TB.[10] TB in diabetic patients in India reveals that men are more likely to have TB than women; therefore, men are more likely to develop co-morbidities.[11] The incidence of MDR-TB in patients with DM was higher in those who did not, with an increase of 1.6–3.8 times in MDR-TB. The prevalence of MDR-TB among older adults has increased from 14.3% to 18.2%.[12] 10.4 million people were reportedly infected with tuberculosis in 2015. Five hundred eighty thousand suffered from MDR-TB, while only 125,000 were detected and reported. One hundred and eleven thousand people received treatment for MDR-TB in 2014; while there was no effective treatment, 190,000 MDR-TB patients died.[6]

Cell-mediated immunity plays a significant role in the host defence against *M. tuberculosis*, where Th1 cells producing INF-gamma and CD4-T cells are activated during TB infection. Cellular-mediated impaired immunity increases the risk of tuberculosis being reactivated. Ageing and DM are the two critical factors in reducing IFN-γ, increasing TB susceptibility. Diabetes in elderly persons may further alter Protein-Energy Malnutrition (PEM), which results in the impairment of T cells, increasing the risk of developing active TB.[13] TB-DM coexistence complicates treatment strategy. Treatment of (MDR-TB) is even more difficult. MDR-TB occurs when *M. tuberculosis* is resistant to two essential TB medications, rifampin and Isoniazid.[14] In some cases, MDR-TB may develop into XRD TB when the bacterial strain is resistant to rifampin, Isoniazid, fluoroquinolone, and at least one additional Group A drug, bedaquiline or linezolid.[15]

DM and TB interact, and one worsens the condition of the other in patients with DM-TB; it delays treatment, which can also affect the cure rate.[7] DM also increases the risk of treatment failure. Treatment of TB in the elderly is risky; 65-year-olds have a higher mortality rate (almost tripled) than those under 65.[16] The cure rate for susceptible drug TB is 96%, and the cure rate for MDR-TB is 54%, so it is considered a deadly disease.[17] The incidence of DM was higher among patients with MDR-TB (47.2%) than patients those without MDR-TB (28.1%).[14] According to WHO 2022 guidelines, the new TB regimens include: 1) BPaLM 6-month regimen (bedaquiline, pretomanid and linezolid and moxifloxacin. 2) BPaL 6-month regimen without moxifloxacin in pre-XDR-TB patients. 3) 6–9 months/9–12 months modified short regimen comprises three Group A drugs".[15] A high risk of developing tuberculosis and reactivating old tuberculosis is commonly observed in patients with diabetes. Uncontrolled, undiagnosed or belatedly diagnosed diabetes worsens the status of TB and negatively affects treatment outcomes. Screening for active TB disease in patients with DM and screening for DM in patients with TB contribute to early detection for better treatment.[18]

TB screening in patients with DM is recommended in areas with a prevalence rate of 100 per 100,000 population. The gold standard for diagnosing TB-DM patients is FBG (Fasting Blood Glucose) and HbA1c. Patients with FBG $\geq$7 mmol/l ($\geq$126 mg/dl) or HbA1c $\geq$ 6.5% ($\geq$48 mmol/l) are considered diabetic.[19] Drug resistance is the major problem in TB-DM treatment, which is more commonly seen in TB-DM patients than non-DM-TB patients. In patients with TB-DM, there is a high risk of isoniazid resistance[20] and rifampin resistance[21] than in non-DM-TB patients. The rates of drug-resistant TB (DR-TB), polydrug-resistant TB (PDR-TB), isoniazid (INH)+streptomycin resistant (SM) TB, were found to be 21.83% and 16.96%, 6.10% and 3.80%, 4.93% and 3.13%, in TB-DM and non-TB-DM cases respectively.[22] At the same time, Isoniazid interrupts the control of blood glucose levels by interacting with metformin[23].

New treatment guidelines provided by the Revised National Tuberculosis Control Programme (RNTPC), national programmes in India and WHO, proper screening and novel diagnostics should be seriously considered to reduce adverse treatment events in TB and DM, especially in elderly populations, reduce the global health burden. In the case of DM management in India, traditional/alternative medicine prescription is followed. Too many options with questionable quality products are also responsible for confused DM management. This leads to the complex management of TB and related co-morbidities in elderly diabetes.

Conflicts of interest

The authors have none to declare.

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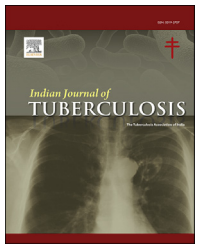

Review article

MDR tuberculosis in elderly

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ABSTRACT

Tuberculosis is very common in young population, but it has emerged in a significant number in geriatric/elderly population (>60 Yrs. of age) as the population is ageing. Most cases of TB in the elderly are linked to the reactivation of lesions that have remained dormant. The awakening of these lesions is attributable to changes in the immune system related to senescence. Mortality rate from tuberculosis remains higher in elderly patients. Diagnosis is difficult as symptoms of active TB are nonspecific and less pronounced in the elderly.

MDR TB is known to occur in poorly compliant patients (non-adherence) and this can be a major issue in elderly due to loss of independence and frailty resulting in treatment failure. Multidisciplinary management, involving geriatricians and infectious disease specialists is essential throughout care to optimize a favourable outcome in these vulnerable patients.

1. Introduction

Significant emergence of Tuberculosis in the elderly has been seen in elderly/geriatric population as we are heading towards an ageing population. Reactivation of Tuberculosis cases has been a major cause of the surge in cases in this population which is mostly related to changes in the immune system due to senescence. Also, the diagnosis of this disease in the elderly is more difficult due to nonspecific symptoms and less prominence. The mortality in this population is higher as compared to the younger ones.

Nonadherence (noncompliance) to the treatment is a major underlying factor for MDR TB cases in the elderly.

2. Definition

Multidrug-resistant TB (MDR TB) is caused by *M tuberculosis* strains that are resistant to at least Rifampicin or both Rifampicin and Isoniazid.

3. Epidemiology

Although the presence of TB is seen all over the world, most of the people developing it reside in low- and middle-income countries.[1]

World Health Organization (WHO) regions of South- East Asia (44%), Africa (25%) and Western Pacific (18%), Eastern Mediterranean (8.2%), the Americas (2.9%) and Europe (2.5%) contained most of the TB cases in 2019.

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Two-thirds of the global total number of cases reside in just Eight countries in Asia and Sub- Saharan Africa: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6%), Pakistan (4.4%), Bangladesh (3.6%), and South Africa (3.6%).[2]

Looking at Worldwide figures, around half a million people have developed Rifampicin Resistant (RR) TB – 78% had MDR TB (see Fig. 1).

Global figures show that in 2019, 3.3% of new TB cases and 17.7% of previously treated cases had MDR/RR TB.

4. Drug resistant Tb in elderly

Although there are no global aggregate data for the exact prevalence of MDR TB strains in the elderly, there are data available that says that drug resistance was significantly lower for all TB drugs resistance (6.5% vs 13.9%) and for MDR TB (0.6% vs 3.1%) in Germany in 2011.[3]

5. HIV and Tb in elderly

The incidence and prevalence of HIV-associated TB in the elderly are growing with the ageing population. Therefore, screening for HIV at the time of diagnosis of TB is needed irrespective of age.

Commonly encountered issues regarding co-treatment of TB in HIV are optimal timing of initiation, drug interactions, drug tolerability as well as prevention and timely treatment of Immune Reconstitution Inflammatory Syndrome encountered with TB treatment in the HIV population.

6. Pathophysiology in elderly

1. Progressive decline in lung functions with age.
2. Atypical presentation of symptoms of TB in the elderly population like chronic fatigue, weight loss, loss of appetite and anaemia, etc.
3. Physiological age-related changes like reduced lung elastic recoil and reduced chest wall compliance lead to impaired inspiratory muscle strength making the elderly population more vulnerable to various infections including TB.
4. Compromised diaphragmatic performance due to increased AP thoracic diameter and dorsal kyphosis.
5. Impaired clearance of airway secretions due to reduced expiratory flow rates lead to increased incidence of airway infections and also higher chances of aspiration.
6. Senescence of the immune system, and polypharmacy which may include certain immunosuppressive drugs like corticosteroids etc., further increases the chances of developing TB in this population.
7. A Senescent immune system combined with Lymphopenia, and various comorbidities like Diabetes further raise the chances of developing TB in the elderly.
8. Other possible mechanisms making this population susceptible to infections are increased oxidative stress and reduced phagocytic capacity of neutrophils, macrophages and natural killer cells.

6.1. *Diagnosis of MDR-Tb*

6.1.1. *Clinical findings*

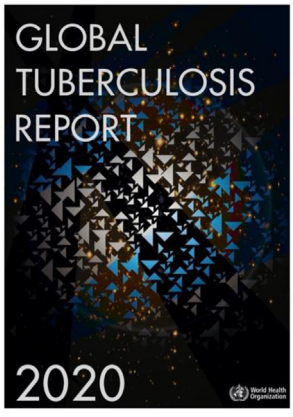
Common presentations of TB in the elderly are a chronic progressive history of weight loss, discomfort, cough, dyspnea, fever and night sweats and chest pain unlike any specific presentation in the young.

The commonest form of TB in the elderly is Miliary TB with chronic indolent low-grade fever in the absence of any focal signs or symptoms.

Further complications in diagnosis arise due to poor memory, hearing impairment, poor visual acuity, and impaired speech.

A study from Brazil compared 117 patients >60 years of age and those aged 15–49 years and found that symptoms like dyspnea and weight loss were predominant in the older age group.[1]

Global and National magnitude of TB & DR-TB



Estimates of TB Burden (2019)	Global	India		
	Numbers (Lakh)	Numbers (Lakh)	Rate (Per Lakh)	% Global burden
TB incidence	100	26.4	193	26%
TB mortality (including TB-HIV)	14	4.45	33	32%
Multi Drug Resistant TB	4.65	1.24	9.1	27%

Fig. 1 – Global and National Burden of MDR TB.

A Korean study of 326 patients showed that symptoms of hemoptysis and fever were more frequent in the population <65 years of age while in the elderly weakness, anorexia and mental changes were seen more frequently.[4]

Advanced age leads to upper lobe fibrosis and volume loss with associated ipsilateral mediastinal shift and diminished breath sounds.

Pleural thickening and/or effusions are seen in up to 50% of TB cases in the elderly.

Approximately 5% of elderly patients with TB can present with lung cancer. Other close differentials include pneumonia caused by other organisms and lymphomas rarely.

Associated comorbidities and other extrapulmonary diseases like Anemias, dyselectrolytemias and Low serum Albumin levels can also cause mimic symptoms of TB.

7. Radiological Findings

Radiological findings differ among the elderly in TB wherein Cavitation is seen more commonly in the younger population while lung infiltrates are more frequent in the elderly (65.76% vs 35.25%).[5]

Also, atypical radiological findings such as involvement of Middle or Lower lobes, nodules or mass-like lesions, extensive bronchopneumonia without cavitation or non-resolving pneumonia are frequently seen in the elderly that may lead to misdiagnoses.

8. Microbiological findings

The study done by *A.K. Verma et al* showed a high number of MDR/XDR TB cases among geriatric patients at tertiary TB care hospitals.[6]

Qi An et al from China also reported an increasing incidence of MDR TB (17.9%) in the elderly population.[7]

AFB staining is still the most widely used rapid diagnostic method for TB although its sensitivity in sputum specimens is just 50% or even less and it's almost always negative in pleural fluid specimens.

Its diagnostic value in the elderly is even less as they hardly produce sputum so other methods to collect sputum in these patients can be tried like Bronchoscopy guided BAL or induced sputum with Hypertonic saline. But of course, the risk-benefit ratio of procedures like Bronchoscopy must be carefully weighed for diagnostic purposes.

9. Identification of MDR TB based on DRT (Drug resistance testing) and DST (Drug susceptibility testing)

DRT: This test detects specific genetic mutations associated with resistance to a particular drug. Both respiratory and non-respiratory specimens can be subjected to DRT.

DST: These are phenotypic tests wherein bacteria are grown and subsequently tested for drug susceptibility using various drug-containing media (see Fig. 2 and 3).

Various methods are summarised in the figure below:

10. Latent TB detection

Frequently used Indirect Diagnostic tests to detect latent Tuberculosis infection (LTBI) such as Tuberculin Skin test (TST) or Interferon Gamma Release Assays (IGRAs) may not be useful in the elderly population due to their fragile skin and because the positivity rate continues to decline after 65 years of age. [55% in patients aged 70–79 years and 33% in patients >80 years for TST and 79 and 75% respectively with Interferon Gamma Release Assay (IGRAs)]. This discrepancy was thought most likely due to comorbidities.[8]

IGRAs could potentially be used in the elderly population with a strong suspicion of TB but inconclusive other investigations although TST/IGRA can't differentiate between old and new TB infections.

11. Treatment of MDR TB[9]

Drugs for MDR TB are divided into three groups to choose from as below:(see Table 1)

In the absence of Bedaquiline, 5–6 drugs combination from the three groups should be used for 18–24 months. Compliance is a major issue for the elderly.

- Regimen for Isoniazid resistant TB: **6 (H)REZ-Lfx** (6-month treatment regimen composed of Rifampicin, Ethambutol, Pyrazinamide, Levofloxacin. Isoniazid can be added if 4-drug FDC (HREZ) will be used)
- Shorter regimen for MDR/Rifampicin resistant TB: **4–6 Bdq(6m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto/5Lfx/Mfx-Cfz-Z-E** (shorter all-oral bedaquiline -containing regimen)
- Shorter regimen for MDR/Rr-TB with Quinolone resistance: **6–9 Bdq-Pa-Lzd** (6–9 month treatment regimen composed of Bedaquiline, Pretomanid and Linezolid – BpaL regimen)
- Longer regimen for MDR/RR-TB: **18 Bdq(6m)- Lfx/Mfx-Lzd-Cfz** (18 – month treatment regimen composed of Bedaquiline for the first 6 months and Levofloxacin or Moxifloxacin, Linezolid, Clofazimine for 18 months)

Since 2016, The Ministry of Health and Family Welfare has incorporated Bedaquiline in the Revised National Tuberculosis Control Programme (RNTCP) and introduced it in six tertiary care centres in Delhi, Mumbai, Chennai, Ahmedabad and Guwahati.

12. Pharmacokinetic issues and drug–drug interactions

Multiple organ dysfunctions are seen more frequently in elderly leading to frequent dosage adjustments of various TB drugs and common side effects (Fig. 3).

Conventional doses of rifampicin and Isoniazid can be used in renal dysfunction as they are metabolized in liver, except in GFR<30 ml/min where it is recommended to reduce the daily dosage or space out the doses.

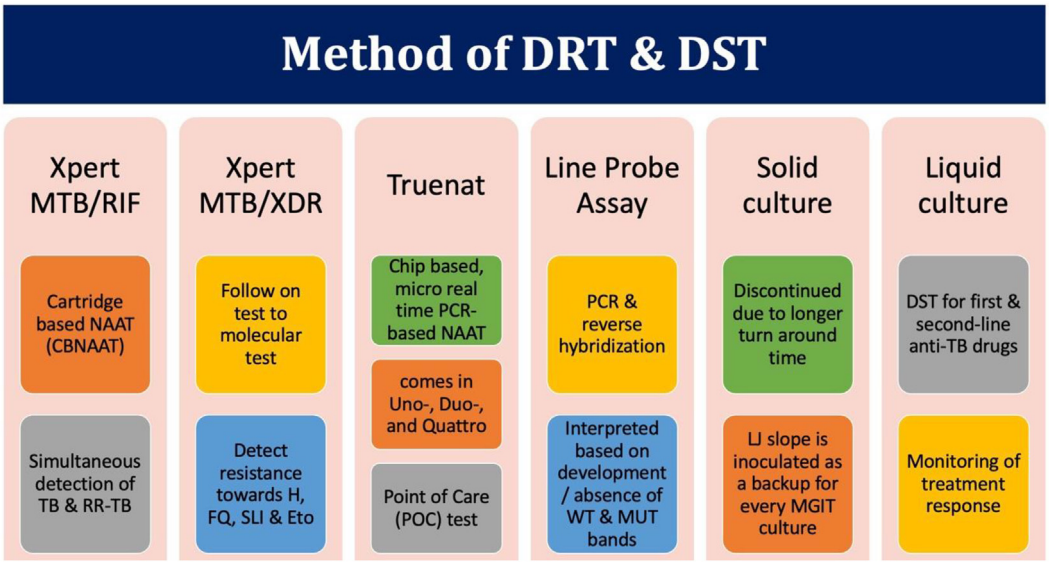


Fig. 2 – Methods of Drug Resistance and Sensitivity Testing. (Source: PMDT guidelines 2021).

Pyrazinamide, although metabolized by the liver but due to its accumulation in patients with renal impairment needs an interval of at least 48 hours or three intakes per week just like Ethambutol.

Polypharmacy in the elderly can lead to frequent and significant drug–drug interactions.

Rifampicin being a potent Cytochrome P450 enzyme inducer leads to reduced serum concentrations of numerous drugs resulting in their subtherapeutic concentrations whereas Isoniazid, a potent enzyme inhibitor has the opposite effect on serum drug concentrations.

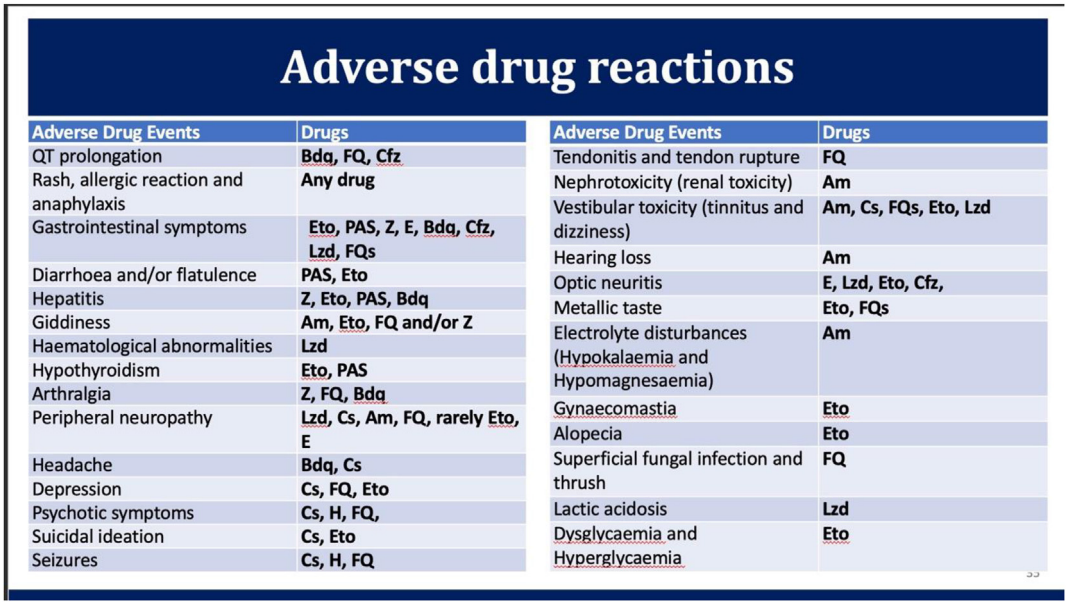
The above effect on enzyme induction and inhibition by Rifampicin and Isoniazid respectively should be considered with TB drugs.[10]

Measuring plasma TB drugs concentration has shown to be of therapeutic benefit in cases of suspected noncompliance and drug interactions.

13. Treatment outcome

Incomplete treatment, as well as a higher risk of treatment failure, is more common in the elderly population especially when it comes to MDR TB due to its longer duration.

Other complicating factors responsible for the reduced effectiveness of TB drugs in this population are disease severity, congregate residences, homelessness, etc.



Adverse Drug Events	Drugs
QT prolongation	Bdq, FQ, Cfz
Rash, allergic reaction and anaphylaxis	Any drug
Gastrointestinal symptoms	Eto, PAS, Z, E, Bdq, Cfz, Lzd, FQs
Diarrhoea and/or flatulence	PAS, Eto
Hepatitis	Z, Eto, PAS, Bdq
Giddiness	Am, Eto, FQ and/or Z
Haematological abnormalities	Lzd
Hypothyroidism	Eto, PAS
Arthralgia	Z, FQ, Bdq
Peripheral neuropathy	Lzd, Cs, Am, FQ, rarely Eto, E
Headache	Bdq, Cs
Depression	Cs, FQ, Eto
Psychotic symptoms	Cs, H, FQ,
Suicidal ideation	Cs, Eto
Seizures	Cs, H, FQ

Adverse Drug Events	Drugs
Tendonitis and tendon rupture	FQ
Nephrotoxicity (renal toxicity)	Am
Vestibular toxicity (tinnitus and dizziness)	Am, Cs, FQs, Eto, Lzd
Hearing loss	Am
Optic neuritis	E, Lzd, Eto, Cfz,
Metallic taste	Eto, FQs
Electrolyte disturbances (Hypokalaemia and Hypomagnesaemia)	Am
Gynaecomastia	Eto
Alopecia	Eto
Superficial fungal infection and thrush	FQ
Lactic acidosis	Lzd
Dysglycaemia and Hyperglycaemia	Eto

Fig. 3 – Adverse Drug reactions to Drugs used in MDR TB. (Source: PMDT Guidelines 2021).

Table 1 – Groups of Drugs used for MDR TB.

Groups and Steps	Medicine	Abbreviation
Group A:	Levofloxacin or	Lfx
Include all three medicines	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B:	Clofazimine or	Cfz
Add one or both medicines	Terizidone	Trd
Group C:	Ethambutol	E
Add to complete the regimen and when medicines	Delamanid	Dlm
from group A and B cannot be used	Pyrazinamide	Z
	Imipenem-cilastin or	Ipm-Cln
	Meropenem	Mpm
	Amikacin	Am
	(or Streptomycin)	(S)
	Ethionamide	Eto
	Prothionamide	Pto
	P-aminosalicylic acid	PAS

Source: WHO Operational Handbook Of TB Treatment – 2020.

Due to the above-mentioned reasons, mortality in Tb remains high in older patients, specifically in the age group >70 years.[11]

14. Public health aspects (prevention)

Possible measures that could reduce the incidence of active cases of TB in the elderly population include poverty reduction, adequate health measures, LTBI preventive treatment, adequate ventilation in closed areas, and optimization of nutrition, thereby improving their general health.

The CDC in the USA has established certain recommendations for surveillance, control and reporting of TB in long–term care facilities which include initial TST and then done annually for all new residents and employees. Chest radiography is then performed for all TST-positive cases to identify active TB cases and their timely treatment.[12]

15. Conclusion

MDR Tb in the elderly is not a rare entity and warrants special attention and treatment due to its atypical presentation, difficult diagnosis, treatment complications due to extensive dosage adjustments, drug interactions and compliance issues.

Reactivation of infection due to senescent immunity and ongoing treatment with immunosuppressives (corticosteroids, chemotherapy, etc.) further complicates the disease course.

HIV–Tb coinfection is one aspect that should not be ignored and actively sought for in the elderly population.

Also, it is important to consider other issues like malnutrition, associated comorbidities and cognitive disorders that can make treatment of TB in this vulnerable population even more complicated.

Thereby comes the imperative role of multidisciplinary management involving Geriatricians, Infectious Disease specialists to optimize the treatment to ensure a favorable outcome in this special population of our society.

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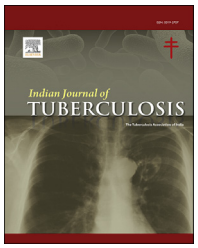

Review article

Sleep disorders in elderly population suffering from TB and respiratory diseases

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ABSTRACT

Sleep disorders (SD) are more frequent in the elderly population than younger counterparts. The underlying SD has a more severe impact on cardiorespiratory fitness. In elderly population with respiratory disorders, incidence and baneful influence of sleep disorders are extremely high. Insomnia in elderly is very common probably due to age related changes, underlying co morbidities and multiple medications. With aging there is decrease in duration of slow wave sleep and increase in NREM stage 1 and 2 sleep, which increases number of spontaneous arousals. Compared to younger people, elderly individuals tend to sleep earlier and wake up earlier due to changes in their normal circadian rhythm. Poor sleep quality and restless leg syndrome are higher in Tuberculosis patients. Disturbances in immune regulation due to chronic insomnia may exacerbate chronic infections like TB. Because many respiratory diseases and medications are known to cause sleep disturbances, it is important to assess treatable medical conditions and insomnia inducing medications before initiating hypnotics. Diagnosing sleep disordered breathing (SDB) in ILD patients is particularly important as nocturnal oxygen desaturation is associated with poor prognosis and could possibly be a cause of pulmonary hypertension. In patients with pulmonary hypertension (PH) and underlying obstructive sleep apnoea, CPAP therapy may help to reduce the PH. Addressing sleep disorders will be highly beneficial in elderly COPD patients with sleep disorders. This article reviews different SD, its effects and the treatment benefits in improving the quality of life and reducing the risk of progression of respiratory dysfunction in elderly population with TB and respiratory diseases.

Abbreviations: COPD, Chronic obstructive pulmonary disease; ILD, Interstitial lung disease.

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1. Introduction

Sleep is an important component of wellness & health across the lifespan. Sleep related breathing disorders (SBD) are usually a gray area in the field of clinical medicine. SBD are seen more in elderly than in younger patients. Older people spend more time in the lighter stages of sleep than in deep sleep. SBD potentially aggravate existing illness or worsens underlying comorbidities and leads to poor quality of life. In elderly with chronic respiratory disease including tuberculosis, obstructive airway diseases & ILD the symptoms of SBD are often neglected. Sleep schedule in older people is shifted forward because the circadian mechanism becomes less efficient. SBDs are a common cause of depression in the elderly which leads to lack of motivation. Depression and anxiety disorders, common among people over 65 years of age, frequently contribute to insomnia.[1] Risk factors for depression in older people include loss of spouse, retirement, social isolation, comorbid disease and onset of dementia.

Because of the depression or low mood they have poor quality of life, thereby predisposing them to a high risk to skip the drugs and defaulting treatment especially antitubercular treatment in a developing country like India. Elderly patients in India have increased incidence of tuberculosis and other chronic respiratory diseases. The articles showing association between respiratory comorbidities and sleep are few. Therefore, it is relevant to evaluate sleep in elderly patients particularly those with chronic respiratory diseases. Sleep architectural changes over the lifespan are not pathologic, but this makes them more vulnerable to sleep disturbances.[2] Obstructive sleep apnea (OSA) and periodic limb movements in sleep (PLMS)are the two primary sleep disorders that increase with age. Chronic pain disorders (eg, osteoarthritis, metastatic diseases) have rest pain and are one of the most common reasons cited by the older population for poor sleep. Left ventricular failure associated with orthopnea and paroxysmal nocturnal dyspnea can lead to frequent awakenings. Patients with chronic obstructive pulmonary disease (COPD) have nocturnal worsening of hypoxemia, which occurs predominantly during REM sleep .10–15% of COPD patients have concomitant OSA that worsens nocturnal gas exchange.[3] Concurrence of OSA and COPD is termed "overlap syndrome" and occurs in approximately 1% of adults in the general population.[4] Other factors that contribute to poor sleep include benign prostatic hypertrophy (BPH), lower urinary tract symptoms (LUTS), and detrusor instability. Inadequate sleep is also associated with significant morbidity and mortality in older adults. Patients with sleeping difficulties report decreased quality of life and endorse more symptoms of depression and anxiety when compared to those without sleep difficulties. Articles regarding SBD in chronic respiratory diseases are less, while the articles regarding sleep related breathing disorders in Tuberculosis are very few. So, this review article was planned to consolidate the available literature in subject and to stress the importance of evaluating SDB in old age in various chronic respiratory diseases and comorbidities and thereby decreasing progression of disease and improving the quality of the life.

2. Normal age-related sleep change in elderly

Changes in the sleep patterns are a part of the normal ageing process. In a normal person sleep progresses through NREM stages N1 through N3 followed by a period of REM occurring in a cycle of every 90–110 minutes into sleep. As the night progresses, there is a reduction in N3 and increase in REM sleep. Older people have difficulty falling asleep and in staying asleep, due to frequent arousals. Sleep gets shorter and lighter with increasing age. A meta-analysis of 65 studies representing 3577 healthy subjects has shown that the total amount of sleep decreases by about ~10 minutes per decade.[5] Sleep latency increases with age, and the REM latency, sleep efficiency and amount of stage R decrease (Table 1).

The net result of these changes is that older people spend more time in the lighter stages of sleep (N1 and N2) than in deep sleep (N3).[6,7] This is known as sleep fragmentation with ageing where elderly persons wake up several times during the night. Up to the age of 60 years, the percentage of N3 sleep decreases linearly at 2% per decade.[8] The percentage of REM sleep also diminishes, although the decline is more subtle. As with N3, the percentage of REM sleep appears to plateau after the age 60 years (Table 2 and Fig. 1).

3. Age related changes in circadian rhythm

Many physiologic processes in our body such as blood pressure, hormone release including our control on sleep–wake cycle areregulatedby circadian rhythms which are 24-hour intrinsic physiological cycles.[9,10] Older adults in general sleep and wake at earlier times than do young adults, and in general they are more likely to report Advanced Sleep Wake Phase Disorder (ASWPD) than young adults.[11] These patients report inability to stay awake in the evening and have earlier onset of sleepiness in the evening and have earlier morning awakening. Treatment of ASWPD may require only reassurance if the patient can adapt his or her life to their circadian rhythm. Chronotherapy (sleep schedule) may be used with a progressive phase advance around the clock (going to the bed earlier and earlier) until the desired bedtime is reached but is not practical for most patients. Daytime wakefulness is affected by phase advance, with older adults being more alert in the morning and more somnolent in the evening. Napping during the day is common in older adults, results with regard to the benefit or harm of this practice are inconclusive.[12]

Table 1 – Age related changes to sleep architecture.

	Decreased	Increased
Sleep parameter	• Total sleep time • Sleep efficiency • Slow wave sleep • Rapid eye movement sleep	• Time awake after sleep onset • Number of arousals from sleep • Sleep latency

Table 2 – Characteristic age related changes to sleep architecture.

Total sleep time decreases
Sleep onset or latency becomes delayed
Increased daytime napping
Increase in awakenings and arousals
Decreased sleep efficiency
Increased stage 1 and 2 sleep
Decreased stage 3 and 4 sleep or slow wave sleep
Circadian phase advanced (i.e. early to bed and early to rise)
Decreased rapid-eye movement sleep
Fewer sleep cycles through per night

4. Risk factors for sleep disturbances in older adults

Sleep disturbances in elderly population complicate physical and mental illness,[13] increase the risk of mortality and lead to poor quality of life in this subset of population.[14] Identifying the specific risk factors which increase the risk of developing sleep disturbances will make as much wiser to target specific interventions and in turn improve the overall health and quality of life of our aging population.

After an extensive review of current evidence and literature it was found that female gender was identified as an independent risk factor for future sleep disturbances particularly in older adults.[15] Poor physical health and depressed mood was associated with deterioration in sleep quality in 10/13 studies reporting the symptoms of low mood or depression.[16]

When examining specific chronic diseases, heart disease emerged as an independent predictor, associated with a 67–68% increased risk of incident insomnia symptoms.[17] Other relevant risk factors include lower economic status, marital quality and perceived stress, recent life events, preclinical dementia, long-term benzodiazepine and sedative use, low testosterone levels, and high levels of inflammatory markers[18]

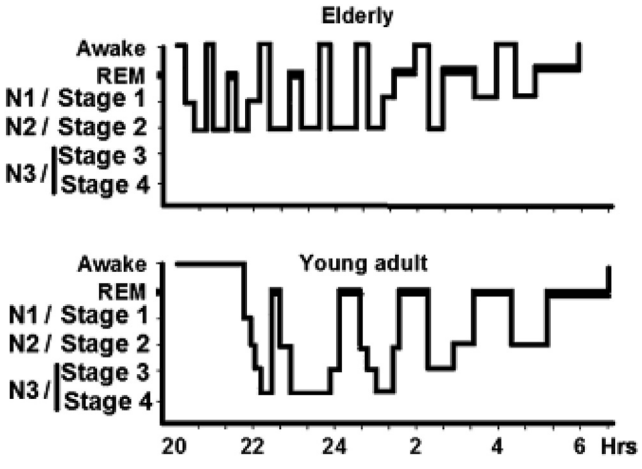

Fig. 1 – Sleep architecture in young adult and elderly. In older people, sleep is marked by repeated arousal, reduction in deeper sleep stages, early sleep onset and early arousal.

5. ILD and sleep

Interstitial lung disease (ILD) is a group of lungdiseases that includes inflammation and fibrosis of theinterstitium of the lung.[19] A large subgroup of ILD belongs to autoimmune diseases for example, scleroderma that involve lungs and are also associated with iron deficiency anaemia, which cancontribute to restless legs syndrome. Scleroderma may result inesophageal dyskinesia and reflux, which are known to disruptsleep, hence while dealing a patient with ILD one should always screen autoimmune diseases. The respiratory physiology of ILD is rapid, shallow breathing pattern to both at rest and with exercise and is common among ILD patients.[20] However, Mc Nicholas WT et al commented that respiratory rate decreases during sleep in ILD patients[21] while some authors suggested that respiratory rate remains unchanged during sleep.[22]

Regarding the stages of sleep, stage 1 and 2 both increase during sleep in ILD and in IPF.[22] REM sleep, slow wave sleep and sleep efficiency is reduced as the data suggests from various studies on ILD, IPF, systemic sclerosis ILD.[22,23,24,25] On the other hand arousal index is increased among both IPF and ILD patients while asleep.[22]

Nocturnal desaturation (NOD) is common among ILD patients which is defined as pulse oximeter saturation (SPO2) < 90% at least 30% of sleep time, more than 4% fall from baseline saturation.[26] Troy et al suggests that NOD in IPF patients is associated with poor prognosis of the disease among the ILD patients' similar findings were also reported in other studies[27,28].

ILD's specially IPF presents with obstructive sleep apnea, high apnea-hypopnea index (AHI), and oxygen desaturation index.[19] The same can be seen in the Korean patients with ILD were prevalence of OSA in ILD patients was 53.5% and IPF patients showed a higher prevalence of OSA than other ILD patients, similar findings were seen in Pihtili A et al were prevalence of IPF was 82%.[29,25]

The exact mechanisms involved in association of OSA and ILD and have not yet been clear, one of the proposed hypothesis is, the lower lung volumes observed in ILD might promote OSA by reducing traction in the trachea and increasing pharyngeal collapsibility,[29] whereas some authors suggests high level of circulating KL-6 levels in OSA patients is responsible for increased alveolar wall permeability and alveolar injury.[30] The other possible mechanism contributing to SDB and ILD are illustrated in Fig. 2.[27]

6. SDB in elderly COPD

In elderly COPD patients sleep quality is impaired with reductions in total sleep time, stage N3 sleep, and REM sleep, whereas the wakefulness after sleep onset (WASO) and stage N1 sleep are increased. Patients often complain of insomnia but may also complain of daytime sleepiness if an overlap of OSA is also present.

It is likely that in COPD patient factors such as cough, nocturnal dyspnea, and medication side effects have greater effect than transient hypoxemia on sleep quality. In many

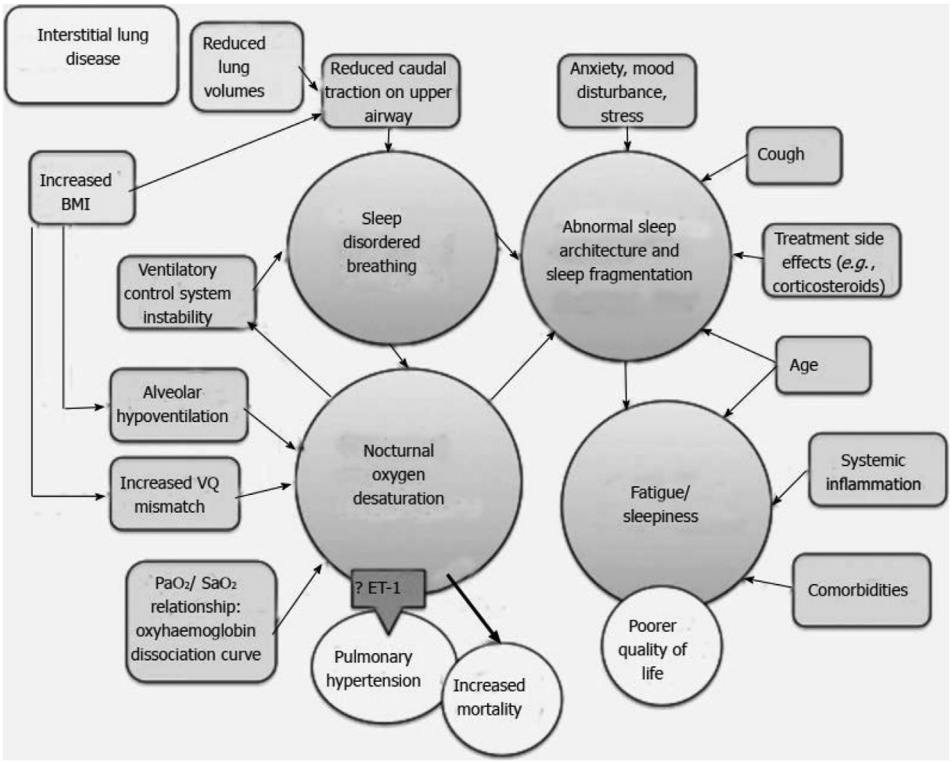

Fig. 2 – Mechanisms contributing to SDB in ILD patients.

COPD patients, the nocturnal oxygen desaturation (NOD) is confined to the last few REM periods of the night and is less than 15 minutes.

A sawtooth pattern on nocturnal oximetry in a patient with COPD suggests the possibility of coexisting sleep apnea (overlap syndrome). During sleeping in elderly COPD patients, the baseline arterial oxygen saturation (SaO_2) falls 2%–4% from the awake baseline with minor fluctuations during non–rapid eye movement (NREM) sleep until much larger drops are noted during REM sleep (stage R). In contrast, a typical oximetry of a patient with the overlap syndrome shows a low baseline sleeping SaO_2 and a sawtooth pattern consistent with repeated discrete events. Oxygen desaturation is also worse during REM sleep (Fig. 3).

In healthy individuals sleep has various effects on breathing, such as changes in central respiratory control, lung mechanics and muscle contractility, these changes in an elderly COPD patient can lead to significant hypoxaemia and hypercapnia.[31] The possible reason could be hypoventilation, which in turn is more pronounced during REM-sleep, due to numerous factors which are illustrated in Fig. 4.[31]

During sleep the upper airway resistance in supraglottic airway increases, as a result the calibre of these airways decreases. At the same time arterial carbon dioxide tension (CO2) increase, this increased arterial CO2 tension act as a dilator to the supraglottic airway. In COPD patient this dilatory response of the supraglottic airways to increases in arterial carbon dioxide tension (PaCO2) is significantly low, which further contribute to nocturnal hypercapnia and hypoxaemia. Quality of sleep is impaired in an aged COPD patient which contributes to chronic fatigue, sleepiness, and poor overall impairment in quality of life and insomnia. The prevalence of insomnia among COPD patients is as high as 27%.[32] This insomnia is the reason for greater use of hypnotic medications in subjects with COPD compared with the general population.[33] Furthermore, the relationship between cigarette smoking and sleep disturbances is well known, as nicotine stimulates the nicotine-acetylcholine receptors in the brain and disturbs sleep, therefore a physician should always encourage a smoker COPD to quit smoking which is not only a non-pharmacological treatment but also for a better sleep hygiene.

COPD and OSA can co-exist in a patient and is already been known for more than a decade. Few factors in a COPD patient which promotes OSA are, rostral fluid shift in the supine position, upper airway inflammation due to cigarette smoking.[34,35] However there are some factors which indeed protect the patients from OSA such as low body mass index (BMI), lung hyperinflation, older age, diminished REM sleep.[36]

Relation of COPD medications and OSA, upper air collapsibility is inversely related to use of inhaled corticosteroids, hence use of same may act as predisposing factor in a COPD patient to develop OSA. On the other hand, Theophyllines have been reported to reduce AHI in COPD patients.[37] Walter T. McNicholas et al have mentioned few helpful physical signs which corelates with SDB and COPD which includesobesity, nasal congestion, signs of right ventricular failure including peripheral oedema, and abnormal blood gases.[36]

Diagnosis of SDB in COPD starts from a basic diagnostic tool, overnight pulse oximetry which is a simple test to detect

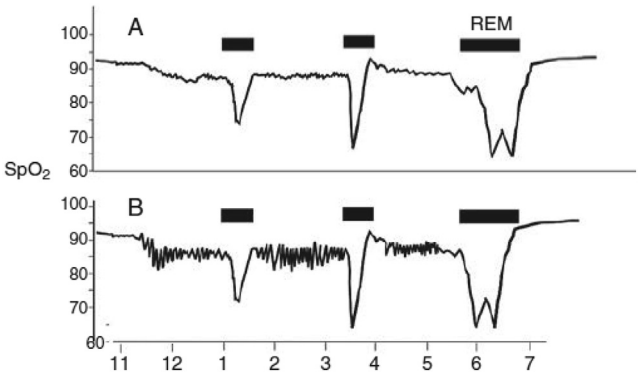

Fig. 3 – Sawtooth pattern on nocturnal oximetry in a patient with COPD.

overnight sustained or transient desaturations/hypoxemias. However, this test does not differentiate between central and obstructive apneas. The next test in the pipeline is the home sleep apnea test (HSAT) which can easily be done at patients' home, in addition to pulse oximetry it also detects respiratory effort, oro-nasal flow, actigraphy pattern and/or sleep position. Although it's easy for the patient but there have been some reports of recording failures with HSAT.[36] American Academy of Sleep Medicine (AASM) recommends in-laboratory PSG as the gold standard method to diagnose the full range of COPD-specific SDB.[38]

7. SDB in elderly TB

Insomnia or sleep disturbances have often been reported as a common problem among those on treatment for TB. The disease symptoms of TB such as cough, fever, dyspnea, pain, nausea and various adverse drug reactions (ADRs) leads to sleep deprivation and poor sleep quality. Infections like TB are exacerbated when there is chronic insomnia i.e., sleep deprivation for than 3 months due to disturbances in immune regulation.[39] Tuberculosis (TB) can affect sleep and can predispose patients to chronic diseases like diabetes mellitus. On the other hand, sleep deprivation and diabetes mellitus can worsen tuberculosis. Diabetes mellitus (DM) is a widely known risk factor for tuberculosis (TB), and individuals with diabetes have approximately 3 times higher risk of developing active TB than individuals without diabetes as reported by previous metanalysis.[40] Due to impaired glucose handling, TB predisposes individuals to diabetes mellitus, and diabetes mellitus on the other hand further hampers human immune defence mechanisms, thereby altering the symptoms and treatment outcomes of TB.

Various factors such as DM, HIV infection, smoking, and alcohol consumption, which may weaken the immune system, place individuals at a greater risk of developing active TB.[41] Sleep quality is an important predictor of immunity. Poor sleep quality and short sleep duration have been reported to affect an individual's immunity,[42] with increasing susceptibility to respiratory pathogens. In the study conducted by Tingyan et al in 2019 it was found that poor sleep quality in patients with a DM course greater than 5 years was independently associated with a more than 3 times higher risk of PTB, and people with DM shared a number of risk factors for PTB, including smoking, alcohol consumption, history of TB contact, and impaired immunity.[43]

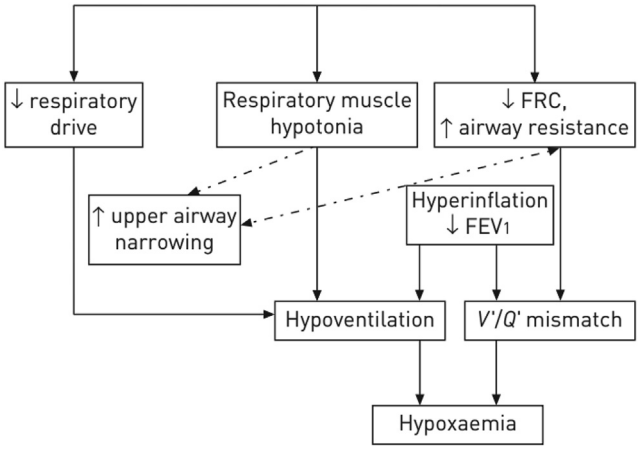

Fig. 4 – Illustration showing profound hypoventilation & hypoxemia in REM sleep.

8. Sleep & pulmonary hypertension

At present pulmonary arterial hypertension (PAH) is defined as a, mean pulmonary artery pressure (mPAP) greater than 20 mm Hg, pulmonary arterial wedge pressure (PAWP) less than or equal to 15 mm Hg, and pulmonary vascular resistance greater than or equal to 3 Wood Units.[44] SDB can lead to group 3 PH (Pulmonary Hypertension), in which OSA is the most common. The prevalence of PH in patients with OSA ranges between 17% and 70%.[45,46] The possible explanation of PH in SDB are, (a)Hypoxic and Hypercapnic pulmonary vasoconstriction, (b) Sympathetic overstimulation(c) Increased inspiratory effort.

Effects of treatment of sleep-related breathing disorders on pulmonary hypertension have been studied in past where it has been suggested, that with CPAP therapy for management of OSA over time may help to reduce the PH[47].

9. Periodic leg movements and restless legs syndrome in elderly patients

Restless leg syndrome (RLS) is one of the most common causes of sleep disturbance in elderly patients and affects up to 10% of the general adult population and in up to 2–3% patients it can be severe.[48] RLS is mainly characterised by strong urge to move the limbs frequently along with paraesthesia like symptoms. Because the symptoms of RLS are more common during evening or night, they present with difficulties initiating and/or maintaining sleep. RLS is typically associated with periodic leg movements of sleep (PLMS) when assessed by means of polysomnography. RLS patients with idiopathic RLS have shorter total sleep time (TST), sleep fragmentation along with long sleep latencies and a higher arousal index compared with controls. PLMS can disrupt sleep and contribute to hypersomnia among OSA patients with

comorbid RLS. Presence of sleep disturbances in RLS can worsen the quality of life. The association of RLS and OSA could be additive and worsen the outcome of individual disease alone.[49]

10. Management of SDB in elderly patients with respiratory diseases

10.1. *Primary insomnia*

Sleeplessness that is not attributable to a medical, psychiatric, or environmental cause is defined as primary insomnia. Older people often have a phase advance in their circadian rhythm that leads to earlier sleep onset and earlier awakening. Evening light therapy appears to be a particularly effective treatment for early-morning insomnia from a phase-advanced circadian rhythm.[50] Timed exposure to bright light has improved sleep efficiency and increased total sleep time, rapid-eye-movement (REM) sleep and slow-wave sleep in older people. Benzodiazepines when used for treatment, therapy should be started with half the maximal dose recommended for younger adult patients and titrated slowly to encourage patients and limit their use to 2 or 3 nights per week. For sleep-onset insomnia, a short-acting agent such as triazolam or oxazepam may be effective. Long-acting benzodiazepines such as diazepam, flurazepam and chlordiazepoxide are not recommended for elderly patients. Non-benzodiazepine agents include zolpidem, zaleplon, zopiclone and eszopiclone are effective in the short-term treatment of insomnia.

10.2. *Sleep related movement disorders*

Treatment of RLS and PLMS is largely directed at symptom control. Caffeine-containing foods and beverages that can exacerbate symptoms should be reduced or eliminated. Medications known to aggravate symptoms of restless legs syndrome (e.g., calcium-channel blockers, metoclopramide, phenytoin, SSRIs) should be avoided. Iron supplements are indicated if test results for ferritin are less than 50 μg/L.[51] Clonazepam in a dose of 0.5–1.0 mg at bedtime is frequently employed, which may be sufficient to reduce symptoms to more tolerable levels. Even when periodic leg movements continue, this treatment may enable the patient to sleep without waking, despite the motor activity. Three Dopaminergic agonists -ropinirole, pramipexole & rotigitine patch are FDA approved for RLS treatment.

11. COPD and sleep management

Management of sleep disorders in COPD leads to a significant reduction of COPD-related morbidity and may also play a role in preventing COPD exacerbations. The goal of therapy is to improve hypoxaemia and hypercapnia during sleep, quality of sleep and health-related quality of life. In COPD OSA overlap the gold standard treatment modality as various guidelines recommends is CPAP. It has been seen that, with initiation of CPAP therapy in such cases the rate exacerbation, daytime sleepiness decreases and it also has a positive effect on mortality outcomes.[36] Another entity to manage is sleep related hypoventilation in COPD, where the goal is to manage the daytime hypercapnia and improve health-related quality of life. BiPAP (Bi level positive airway pressure) has some proven role in the current literature. Insomnia among COPD patients, many studies suggest it can be successfully managed with behavioural and cognitive therapy however, whether to use benzodiazepines and other sleep induction medication is not clear in the literature hence one should be very cautious when using such agents.[36]

12. Conclusion

With increasing age, changes in sleep pattern are common, making the geriatric age group more vulnerable to SBD. Elderly people seem to have more prevalence of TB & chronic respiratory diseases as compared to the younger population. Sleep disorders have significant negative impacts on the respiratory function. Moreover, a combination of older age along with chronic respiratory diseases drastically increases the risk of sleep related breathing disorders, faster progression of underlying disorders and poor quality of life. It is possible to overcome this by proper awareness, seeking early medical help, early diagnosis and treatment of the same. Sleep disorders in elderly TB is a neglected area in various TB programs. It is important in TB burden countries. Elderly 'difficult to control COPD phenotype' needs polysomnographic work up in appropriate clinical scenario. Progressive diseases like ILD need evaluation and treatment of associated SBD. Finally, one of the worst outcomes of SBD is pulmonary hypertension, which may be a cause or worsening factor in various respiratory diseases. We recommend all pulmonologists to search for sleep disorders in all elderly population with TB and chronic respiratory diseases, investigate for it and treat if needed.

Conflicts of interest

The authors have none to declare.

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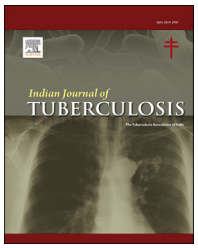

Review article

Challenges in physiotherapy of managing respiratory diseases in elderly population

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ABSTRACT

Introduction: Lung function is a convincing prognosticator of longevity. With advancing age, there are many irreversible functional and anatomic changes in the body, making elderly susceptible to disease processes. As people age, the respiratory system experiences a number of anatomical, physiological, and immunological changes, predisposing risk of many chronic lung diseases (CLDs). Respiratory tract infections, TB, chronic obstructive pulmonary disease (COPD), and interstitial pulmonary disease are examples of common respiratory diseases (CRDs). The risk factors are mainly smoking, exposure to air pollution both indoors and outdoors, allergies, occupational exposure, poor diet, obesity, inactivity. Between 25 and 80 years the lung function and aerobic capacity each decline by ~40% limiting physical function and promoting multimorbidity. In elderly, skeletal muscle dysfunction causes age-related multifactorial health disorders such sarcopenia and frailty, a recognised symptom of chronic respiratory disease.

Methods: This perspective article highlights the importance of pulmonary physiotherapy in elderly with chronic lung disease and other chronic respiratory disorders. Common symptoms frequently experienced are dyspnoea, fatigue, decreased exercise tolerance, peripheral muscle dysfunction, and mental disturbances. An individual's symptoms, physical functioning, quality of life (QoL), hospitalisation, and morbidity goals are all addressed by a pulmonary rehabilitation programme (PRP). Pulmonary physiotherapy, an extensive patient-tailored intervention as exercise training, education, and life style modification is prescribed on the basis of a thorough personalised assessment.

Result: Through pulmonary physiotherapy, the goal is to restore the quality of life of elderly with chronic respiratory diseases and to encourage their long-term adherence to health-improving behaviour. The older patients learn to accept and overcome the reality of their illness rather than sticking to its limits.

Conclusion: Multidisciplinary approach with a customized and comprehensive program makes the difference between living a fulfilling life and living a life with pulmonary disabilities.

Abbreviations: PNF, Proprioceptive Neuromuscular facilitation.

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1. Introduction

Lung function is a convincing prognosticator of longevity.[1] With advancing age, there are many irreversible functional and anatomic changes in the body, making elderly susceptible to disease processes. As people age, the respiratory system experiences a number of anatomical, physiological, and immunological changes, predisposing risk of many chronic lung diseases (CLDs).[2] Between 25 and 80 years the lung function and aerobic capacity each decline by ~40% limiting physical function and promoting multimorbidity.[3] As we get older asthma, respiratory tract infections, TB, chronic obstructive pulmonary disease (COPD), and interstitial pulmonary disease are examples of common respiratory diseases (CRDs).[4] The risk factors for CRDs have been identified, and they mainly include smoking, exposure to air pollution both indoors and outdoors, allergies, occupational exposure, poor diet, obesity, inactivity.[5] (Fig. 1. Common risk factors for chronic respiratory diseases in elderly).

Skeletal muscle dysfunction, which causes age-related multifactorial health disorders such sarcopenia and frailty, is a recognised symptom of chronic respiratory disease.[6]

Elderly people with chronic obstructive pulmonary disease (COPD) and other chronic respiratory disorders frequently experience dyspnoea, fatigue, decreased exercise tolerance, peripheral muscle dysfunction, and mental disturbances.[6]

An individual's symptoms, physical functioning, quality of life (QoL), hospitalisation, and morbidity goals are all addressed by a pulmonary rehabilitation programme (PRP). Through pulmonary physiotherapy, older patients learn to accept and overcome the reality of their illness rather than sticking to its limits. Multidisciplinary approach with a customized and comprehensive program makes the difference between living a fulfilling life and living a life with pulmonary disabilities.[6]

2. Changes in respiratory system

2.1. *Structural changes*

Chest wall compliance decreases as we age due to structural changes to the thoracic cage. The thoracic vertebrae's height is decreased as a result of age-related osteoporosis. Thoracic cage stiffening from rib cage calcification and age-related kyphosis from osteoporosis lowers the thoracic cage's capacity to expand during inspiration and hinders the diaphragm's ability to produce an efficient contraction mechanically.[2] Intercostal and diaphragmatic muscles lose their ability to contract efficiently impacting lung function.[7]

2.2. *Physiological changes*

The main functioning respiratory parts of the lungs are the alveoli, which have a capillary network for gas exchange, and the airways that allow air to enter and exit the alveoli. Despite the fact that the number of alveoli, alveolar ducts, and capillary segments remains constant at adulthood, alveolar size and alveolar-capillary surface area significantly increase with ageing.[8] Advanced age is linked to changes in alveolar depth and acinar airway lumen brought on by compensatory remodelling. Increased individual diameters of alveoli reduces surface tension forces, results in decreased elastic recoil of the lungs, and increased end expiratory lung capacity.[9,10] Older people may then experience some airways narrowing or closing during normal tidal breathing, which lowers the amount of air that is exhaled from the lungs during expiration and raises functional residual capacity.[11]

At the level of proximal and distal airways, the decreased collagen patency leads to air trapping and loss of surface area for gas exchange. An additional factor affecting gas exchange effectiveness is a decline in carbon monoxide's diffusing capacity, which happens at a rate of roughly 5% every decade. A reduction of pulmonary diffusing capacity, due to ventilation-perfusion mismatch leads to increased work of breathing.

The efficiency of mucociliary clearance declines with ageing. Both environmental factors, such as smoking, and genetic predisposition affect how quickly these changes take place. The decreasing respiratory reserve caused by ageing patients' decreased elastic recoil and compliance leads to acute diseases such pulmonary edema, pneumonia, and bronchospasm (Fig. 2: Physiological changes in aging lung).

2.3. *Immunological changes*

The lung has developed numerous defence mechanisms to maintain homeostasis and react to outside stimuli. Diverse array of immune cell types plays important role in the initiation and resolution of innate and adaptive immune responses in the lung. An imbalance between inflammatory and anti-inflammatory systems leads to immunosenescence, or the ageing of the immune system. Generation of proinflammatory cytokines is augmented by lifetime chronic antigen stimulation, oxidative stress, and oxygen free radical production. Age-related alterations in innate and adaptive immune responses in the lung have been linked to poor prognosis and recovery in pulmonary inflammatory disorders.[7]

3. Impact of aging on lung disease

Physiological and molecular changes that occur in the ageing lung lead to development and progression of lung ailments like COPD, IPF, acute respiratory distress syndrome (ARDS), and pneumonia.[7] These changes include decreases in the volume of the thoracic cavity, reduced lung volumes, and alterations in the muscles that aid respiration.

It is crucial to understand how age changes the body and impacts the respiratory system. In elderly, the normal lung function is impacted with changes to spine, muscles, and ribs over time. In older adults, including men and women, the prevalence and incidence of hyperkyphosis range from about 20 percent to 40 percent. The fraction of exhaled volume in 1 second (FEV1) and vital capacity (VC) significantly decreased with increasing vertebral angle over 55°.[12] Also, the efficiency and reduction of lower rib movement during inspiration may be impacted by the angle of the muscle fibres in reference to the ribs. With increasing demands, there is an inability to ventilate with decline in respiratory muscle strength and flexibility.[13]

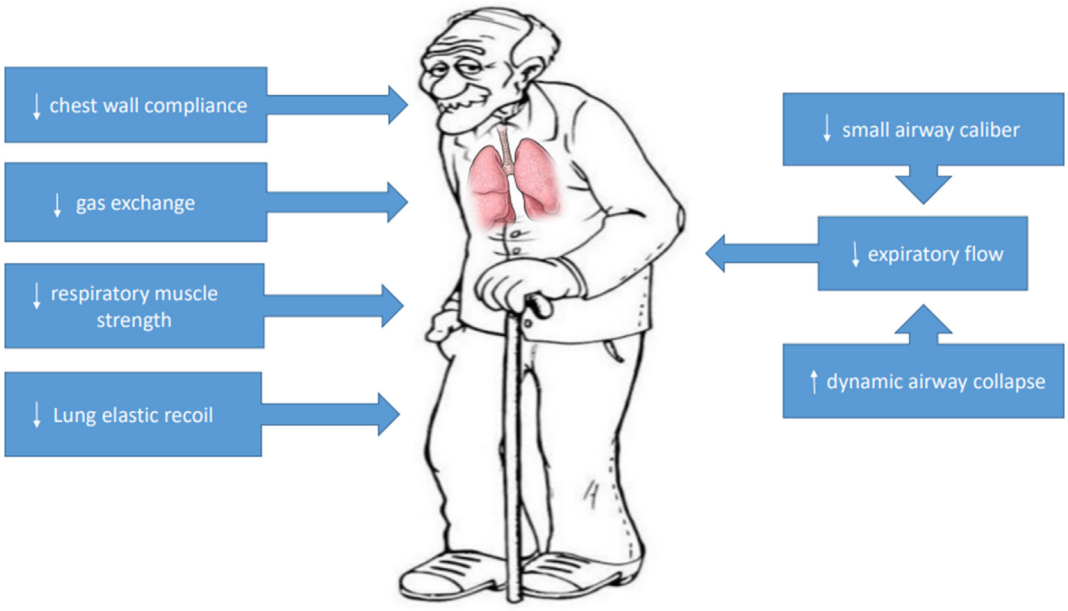

Fig. 1 – Common risk factors for chronic respiratory diseases in elderly.

During illness in older individuals there is increased risk of respiratory failure, due to the inability to meet with increased metabolic demands of oxygen as a result of decreased respiratory muscle strength, cellular energy reserve and reduced overall muscle function.[14]

Mucous clearing ability reduces with age. Any reduction in the respiratory muscles' strength will have a significant impact on a person's capacity to produce the force necessary for an effective cough. Aging is related to reduction in both inspiratory and expiratory muscle strength[15] (Fig. 3: Physiological changes for poor airway clearance with aging).

A decline in lung function promotes multimorbidity through limitation of physical function in elderly. In active elderly, the decline in pulmonary function results in ventilatory limitations during exercise, affecting the ability to have adequate health benefits of physical activity. Aging's impact

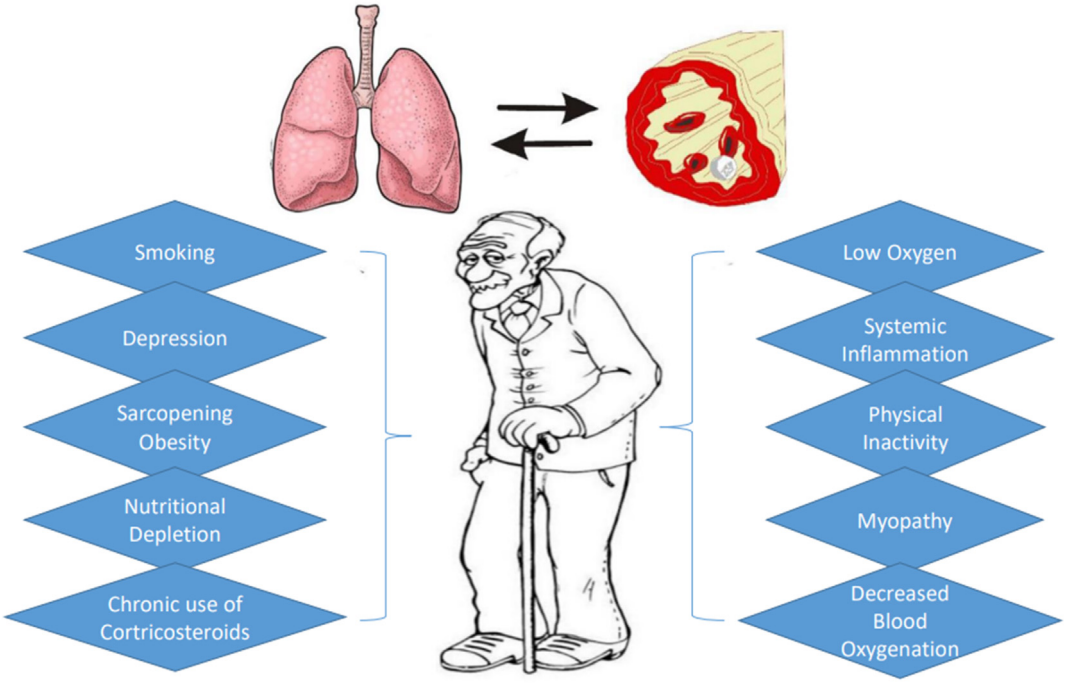

Fig. 2 – Physiological changes in aging lung.

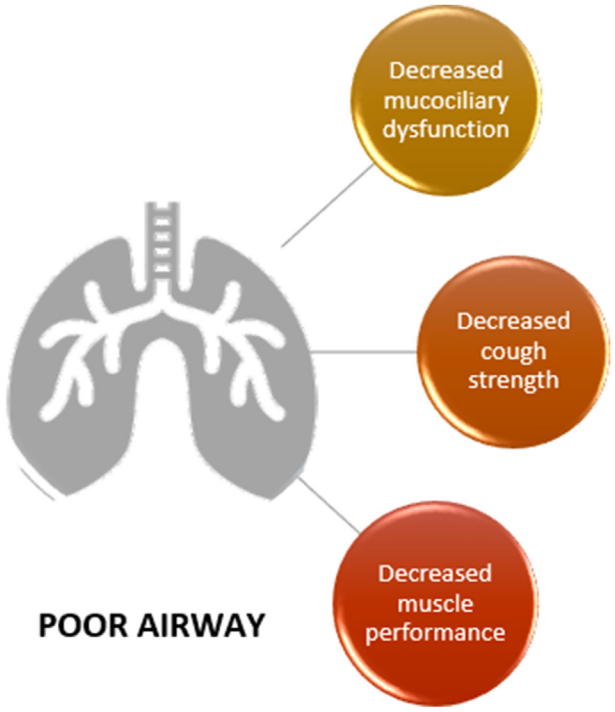

Fig. 3 – Physiological changes for poor airway clearance with aging.

on an individual's ability to exercise varies greatly and is influenced by their level of fitness and regular physical activity. In addition to diminished lung function, other age-related changes such as decreased heart rate responsiveness, cardiac output, and peripheral muscle mass may be responsible for the decline in VO2 max with age.[2]

In elderly with chronic respiratory diseases, sarcopenia and frailty are commonly observed with multi system decline. Sarcopenia and frailty in older individuals have been utilised for risk classification, to forecast unfavourable outcomes, and to trigger intervention targeted at slowing decline in those most at risk.[5]

4. Physiotherapy for management of respiratory diseases in elderly

Pulmonary physiotherapy is being recommended as an extensive patient-tailored intervention that includes exercise training, education, and behavioural change and is prescribed on the basis of a thorough, personalised assessment. Its goal is to improve the physical and psychological conditions of people with chronic respiratory diseases and to encourage their long-term adherence to health-improving behaviour.[16]

Pulmonary physiotherapy is not recommended for people with severe cognitive impairment or psychiatric disorders, organ failure (e.g., hepatic or renal failure, uncontrolled infectious or inflammatory disease), unstable comorbidity (such as unstable angina, uncompensated congestive heart failure, etc.), severe exercise-induced hypoxemia, inability to exercise, lack of motivation, no adherence, insufficient financial resources, or persistence of smoking.[17–19]

A collaborative, multidimensional framework and assessment method called the comprehensive geriatric assessment (CGA) is used to evaluate elderly with chronic respiratory diseases. These individuals frequently experience multimorbidity, making their care more challenging. The CGA's strength resides in the fact that it is a multidisciplinary, holistic assessment of elderly's health and wellbeing. It emphasises on the depth and breadth of quality of life, functional status, prognosis, and outcome. Interdisciplinary teams including physicians, physiotherapists, nurse, psychologists, nutritionists, behavioural specialist, occupational therapists and social workers, utilise a variety of standardised tools to assess patient functioning, impairments, and social supports.[17–19]

Fatigue, coughing, weakness, and dyspnoea at rest or/and during exertion are the most frequently reported symptoms. Since it is necessary to determine the extent of ventilatory impairment, confirm the diagnosis of the underlying condition, and check the effectiveness of pharmacologic therapy, pulmonary function tests (PFT) should be routinely included in an elderly thorough pre-respiratory physiotherapy examination.[6]

The most common standardized tools used for respiratory symptom assessment include 6 Minute walk test (6MWT) which is a measure to quantify the functional capacity of the targeted individuals, Modified Borg scale (MBS) addressing dyspnoea at various levels of activity, Fatigue severity scale (FSS) measuring individuals' level of fatigue and Physical activity readiness questionnaire (PAR-Q) monitoring the level of physical activity, Timed up and go test (TUG) for balance, cognition can be assessed with Mini Mental Status Examination (MMSE) and eventually target the quality of a growing elderly by various quality of life scales such as SF36, SF12 (Fig. 4: Comprehensive Physiotherapy Assessment).

5. Management

With chronic respiratory diseases, physiotherapy is recommended to patients to manage dyspnoea and regulate symptoms, maintain mobility and function, and improve or support airway clearance and cough. In elderly with co-existing multimorbidity, exercise prescription including strategies and intervention for airway clearance, positioning and breathing manoeuvres are planned, keeping in account their polypharmacy. Physiotherapy can help with pain and postural and/or muscular dysfunction, as well as with increasing incontinence, especially when coughing and doing forced expiratory manoeuvres. Physiotherapists have a key role in providing pulmonary rehabilitation and could be crucial in providing non-invasive ventilation.[20,21] Some complementary therapies may be appropriate in some situations (Fig. 5. Physiotherapy Management and outcomes).

The physiotherapist suggests a specialised, tailored exercise regimen based on the patient's particular goals and demands. Exercise training is the best technique to improve muscular function.[6] Various breathing manoeuvers such as Incentive spirometry, Diaphragmatic breathing exercises, chest PNF, relaxed breathing techniques, energy conservation

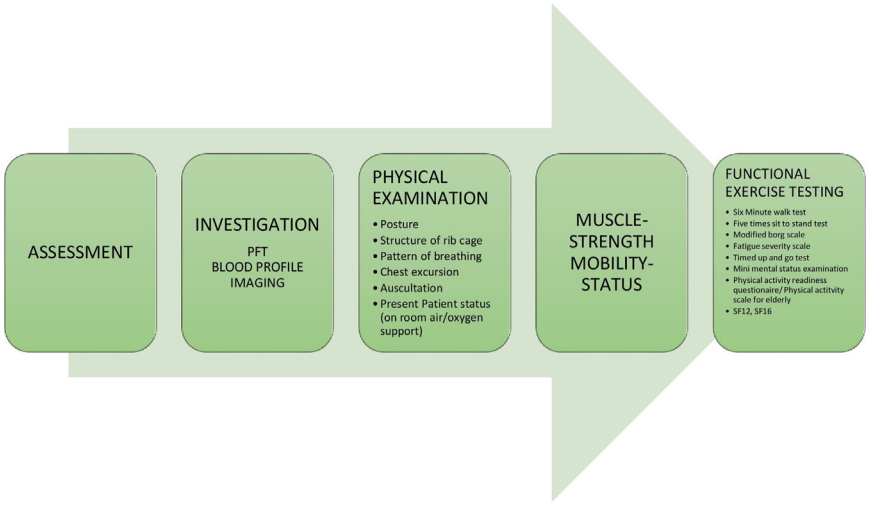

Fig. 4 – Comprehensive physiotherapy assessment.

techniques, inspiratory muscle training (IMT) can improve lung function as reducing dyspnoea, improving inspiratory muscle strength, functional exercise capacity and overall quality of life.[20] Due to secretory overproduction and inadequate clearance, mucus builds up, which encourages inflammation and frequent respiratory exacerbations. Several airway clearing techniques (forced expiratory techniques (FET), active cycle of breathing technique, autogenic drainage, manually assisted coughing manually or/and with use of PEP device, mechanical insufflation-exsufflation) can be applied to enhance mucociliary clearance.[22] Other interventions include walking as part of functional movement training, long-term regular walking, walking sideways, backwards, and forwards as part of aerobic and balance training. Overall, the majority of the aforementioned walking styles help healthy older subjects' lungs function.[22] With exercise training, there is an improvement in skeletal muscle performance, proprioception even though lung function may not change.[6]

Functional electrical stimulation improves muscle mass of the lower limbs and of the spine extensors markedly for locomotor ability and spine stability in old age. Integrate balance training, cognition training and prevention education for older adults.[20]

The physical activity and exercises should be tailored to the patient's unique needs in order to increase muscular strength, aerobic capacity, flexibility and balance with a goal to improve quality of life.[6] For those with poor work capacities, the starting effort ought to be light (i.e., three metabolic equivalents [METs], and workload increases ought to be modest (i.e., 0.5–1.0 MET).[22]

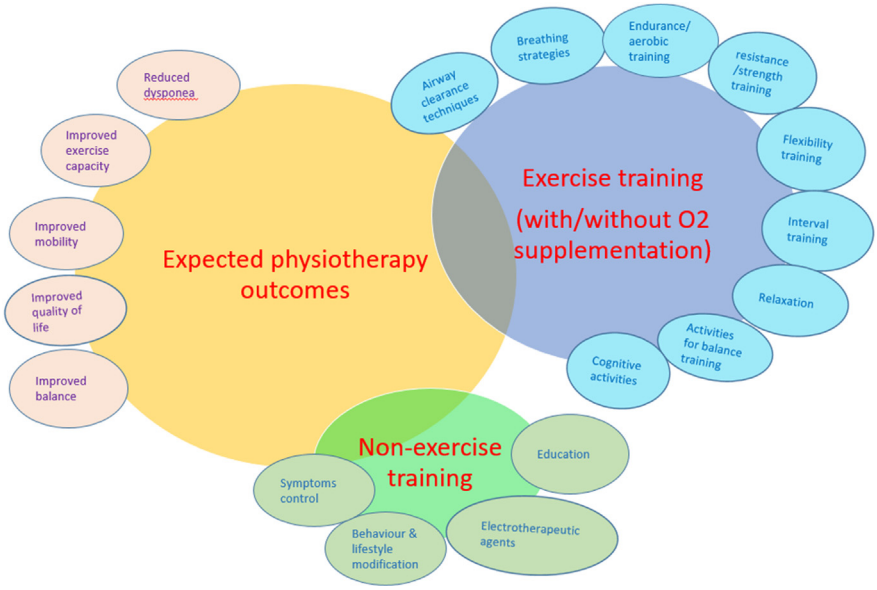

Fig. 5 – Physiotherapy Management and outcomes.

Table 1 – ACSM recommended parameters for elderly exercise prescription for 8–12 weeks[23].

Exercise Prescription	Frequency	Intensity	Time	Type
Endurance/Aerobic training	3–5 days/week	light-moderate intensity, as physically active as their abilities and conditions allow. RPE 4–6 on 0 –10 Borg scale	10–30 minutes per session; 150 –300 minutes per week	Walking, stationary cycle
Resistive/strength training	2 days/week	Light-intensity (40%–50% 1-RM)	8–10 exercises involving the major muscle groups; 1 set of 10–15 repetitions each	PRT for shoulder girdle, inspiratory & upper extremity muscles
Flexibility/Balance training	2 days/week	Stretch to the point of feeling tightness or slight discomfort.	Hold stretch for 30–60 seconds, 2–4 repetitions	slow movements that terminate in sustained stretches for each major muscle group using static stretches

PRT = progressive resistance training; 1-RM = one repetition maximum; RPE = rate of perceived exertion. RM- Repetition maximum is the most weight that can be lifted through a full range of motion, in good form, for one repetition.

5.1. *Special considerations*

Physiotherapist should monitor initial training sessions, and modifications should be made in response to symptoms; patients may be taught to use a heart rate or a dyspnoea scale to assess intensity.[24] Current evidence-based guidelines recommend pulmonary physiotherapy for improving disabling dyspnea, functional capacity, and health-related quality of life in elderly[25] are summarized in (Table 1. ACSM recommended parameters for elderly exercise prescription for 8–12 weeks).

6. Conclusion

Maintaining a high level of physical activity is a key component of healthy ageing and reducing multimorbidity. The pulmonary system dysfunction is likely a factor in exercise intolerance. The multi-organ system response to exercise in the elderly is compromised in a number of ways, which makes this challenging. It often impacts patients' abilities to respond to, adhere to, and tolerate treatment. To encourage older people to start and adhere to a fitness regimen presents with a number of problems as knowledge about exercise benefits or how to initiate an exercise/personal physical activity program. Other barriers may be lack of motivation, social support and isolation. Another fear among elderly is will exercise increase my pain, injury or discomfort. Though these concerns should be carefully considered because they might be extremely important and frequently realistic.

With the population's rising lifespan, it is imperative to increase the health span and get a more thorough understanding of how lung function changes over the course of a person's life. Physiotherapy approaches can add life to the years by improving their quality of life along with the functional capacity.

Conflicts of interest

The author declares that there is no conflict of interest.

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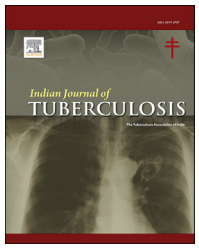

Original article

Detection of multidrug and extensively drug-resistance and mutation pattern in geriatric patients from North Indian referral institute

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ABSTRACT

Introduction: Geriatric population are predisposed to reactivation to tuberculosis (TB) and multi-drug resistance (MDR) due to deteriorated immune system. Limited data is available in this population hence present study is undertaken to study drug resistance and associated mutations among geriatric presumptive DR-TB patients by genotypic methods

Methods: From October 2011 to December 2018, demographic characteristics of enrolled patients was collected. Smear-positive processed sputum samples were subjected directly while cultures positive for Mycobacterium Tuberculosis (MTB) from smear-negative pulmonary and all extra-pulmonary samples were subjected to LPA. The LPA used were Genotype MTBDR *plus* (1st line LPA) for detection of susceptibility to rifampicin (RIF) and isoniazid (INH) and Genotype MTBDR *sl* (2nd line LPA), for susceptibility to fluoroquinolones (FQ) and aminoglycosides (AG).

Results: Total of 2041 samples were received from presumptive MDR-TB patients above 60 years of age during study period, of which 1406; 68.9% were within 60–70 year followed by 495; 24.3% within 71–80 year and 140; 6.9% more than 80 years. Total of 1055 MTB were detected, of which those diagnosed as RIF resistant were 117/1055; 11.2% including 89/1055; 8.5% MDR-TB and resistance to INH was in 84/1055; 8%. Total 67, 2nd line LPA gave valid results, of which 19/67 (28.4%) isolates were resistant to only FQ, and one isolate was resistant to AG.

Conclusion: Study finding highlights need for dedicated efforts for diagnosis, and treatment of geriatric tuberculosis. Suitable intervention at programmatic country level at country will help in strengthening tuberculosis control strategies in this population.

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1. Introduction

Elderly population comprising of people who are 60 years or more are increasing, due to better life expectancy.[1] It is expected that almost 23% of total population in developed countries would be more than 65 years of age by 2035.[2]

Physical frailty and physiological deterioration in ageing population considerably affects their immune system, causing reduced adaptive and innate immunity and dysregulated immune response. These factors lead to increased communicable and non-communicable diseases in elderly.[3] Also, this population is more prone to having diabetes, malnutrition, excess alcohol use, underlying malignancy and increased intake of drugs which further impair the cell-mediated immunity.[4] Therefore, endogenous reactivation and progression to TB or relapse of TB is high in elderly.[4,5] Immune impairment causes more severe consequences of Mycobacterial infection.[4]

TB in elderly has been emerging as significant health problem, with its unique set of problems.[3] Notified TB in elderly is increasing in Western Pacific region, Eastern Mediterranean and South East Asia.[2,6] In a study, it was seen that 13.8% of newly reported tuberculosis were patients aged 65 years and above, which doubled to 28.6% in subsequent decade.[7]

Challenges in diagnosing TB in elderly include less prominent symptoms, reduced ability to produce high quality sputum specimen and limitations of certain diagnostic techniques such as smear microscopy.[8–10] Furthermore, immune impairment could also lead to increased risk of drug resistant tuberculosis (DR-TB).[4] The ever increasing pool of elderly with active tuberculosis caused by reactivation of previous "latent" TB, if not detected timely is bound to lead to increased spread of TB & DR-TB.[9] Yet, there are barely any studies from the country in literature regarding prevalence of drug resistance in this population.

There has been improvement in detecting TB and drug resistant (DR-TB) in last decade, with advancements in molecular diagnostics. Line probe assay (Genotype MTBDR plus; Hain Life Sciences, Nehran, Germany), introduced in RNTCP in 2011 is molecular diagnostic test based on hybridization technology. Test can be performed on processed smear positive pulmonary specimens or cultures positive for Mycobacteria permitting rapid detection of mutations in gene coding for resistance to rifampicin (RIF), *rpoB* and isoniazid (INH), *katG* or *inhA*. Since 2018, second-line LPA has been introduced to detected resistance to fluoroquinolones (FQ) and aminoglycosides (AG), in cases resistant to RIF either/and INH. The LPA has markedly decreased turn-around time of diagnosing DR-TB for LPA among smear positive pulmonary samples to couple of days, besides providing an insight of genetic determinants of the disease.[11] The technology has been employed as main test for detection of MDR-TB and XDR-TB in all National/Intermediate Reference Laboratories (NRL/IRLs) of Tuberculosis in the country.

The present retrospective study was designed and therefore conducted to determine the drug susceptibility and associated mutations among geriatric presumptive DRTB patients using line probe assay.

Key Message

1. Study clearly shows substantial drug resistance among geriatric population.
2. Focused efforts for diagnosis and treatment of geriatric tuberculosis is required by means of policy change at national level
3. Strengthening of tuberculosis control strategies is required in this population.

2. Material and methods

2.1. Study design

National Reference Laboratory (NRL) in Department of Microbiology at National Institute of Tuberculosis & Respiratory Diseases, NITRD, receives samples of presumptive DR-TB from four districts of South Delhi catering to about 1 million population under program and patients attending outpatient Department (OPD) and inpatient (IPD) services for performing LPA. Total of 16,807 samples were received from four districts of Delhi, 22,663 samples from OPD and 7593 from indoor from October 2011 to December 2018.

2.2. Demographic details and inclusion criteria

The patients requisition forms and cultures, and drug susceptibility (DST) registers were referred for sourcing the demographic characteristics of the study population. The data included details of age≥60 years old patients, sex, location, type of TB, sample, and the presumptive MDR criterion of the enrolled patients.

The criterion for presumptive MDR–TB under the national program were treatment failure among new TB cases, smear positive cases that remained smear positive after the 4th month of treatment with retreatment regimen, and pulmonary TB cases who were in contact of known MDR –TB included any smear positive follow up or smear positive retreatment case at diagnosis in addition smear negative retreatment cases and all HIV/TB co-infected cases.

2.3. Sample collection and processing

Sputum samples (spot and morning) were collected from each patient in 50 mL wide –mouthed sterile falcon tubes. Various extra-pulmonary samples such as pleural fluid, fine needle aspiration (FNA), ascitic fluid were also received in sterile containers. All specimens were screened for the presence of acid-fast bacilli (AFB) by Ziehl-Neelsen staining or fluorescent microscopy. The samples were processed by the N-acetyl-L cysteine sodium hydroxide methods.[12] Samples were processed by N-acetyl-L cysteine-Sodium hydroxide (NALC-NaOH) method of digestion and decontamination to obtain concentrated pellet in 2 mL of phosphate buffer saline (PBS) at pH 6.8. Smear-positive processed sputum samples were directly processed for Geno Type MTBDR plus assay as per kit insert. All smear-negative processed pulmonary samples and

all extra-pulmonary samples were inoculated in MGIT 960 tubes for culture, and tubes with positive alerts were identified for presence of *Mycobacterium tuberculosis* by smear microscopy for serpentine cording and rapid immune-chromatographic test for detection of MPT 64 TB Ag (SD BIOLINE). Cultures identified as *M. tuberculosis* were subjected to LPA.[13]

2.4. 1st and 2nd line LPA

All smear positive and smear negative culture positive isolates were subjected to Genotype MTBDR V2.0 plus assay for detection of RIF and INH resistance as per the manufacturer's instructions during study period. Susceptibility to Fluoroquinolones (FQ) and aminoglycosides (AG) using Genotype MTBDRsl V2 assay, was detected for patients found to be resistant to INH or RIF from June 2017 to December 2018. Result of DNA strips was interpreted with helpof reporting card as resistant or sensitive for RIF or INH. Invalid or indeterminate based on the kit insert. In addition, presence of mutation bands and absence of sensitive bands were also recorded.[14]

Each LPA strips has three control zones (conjugate, amplification, and locus control for mycobacterium tuberculosis detection). Test was read as invalid/indeterminate in case of missing amplification band or non-interpretable result. Testing of LPA on any invalid results were repeated using processed sample deposits, stored at −20 °C.M. *tuberculosis* H37Rv (ATCC 27294) was run as positive control and sterile molecular grade water was run as negative control, in each run for quality control.

In Genotype MTBDR *plus*, for detection of RIF resistance, in *rpoB* gene there are eight *rpoB* wild-type (WT1-WT8) and four mutant probes (MUT1 D516V, MUT2A526Y, MUT2B H526D, and MUT3 S531L). For INH resistance detection, there are two genes *katG* and *inhA*. KatG has one WT and two mutant probes (MUT1S315T1 and MUT2S315T20; *inhA* has two *inhA* WT with four mutant probes (MUT1 C15T, MUT2 A16G, MUT3AT8C, MUT 3BT8A).[14]

In Genotype MTBDR*sl*, *gyrA* and *gyrB* genes detect FQ resistance. For *gyrA*, there are three wild type (WT1- WT3) and six mutant probes; (G88A, MUT1; A90V, MUT2; S91P, MUT3A; D94A, MUT3B; D94N&D94Y, MUT3C; D94G, MUT3D; D94H). The *gyrB* has 1 wild type (WT) and two mutant probes (MUT1; N538D, and MUT2 E540V). Aminoglycosides resistance is detected by *rrs* gene which has two wild types (WT1 and WT2) and two mutants (M1; A1401G and M2; G1484T). Low level resistance to kanamycin is detected by *eis* gene which has three wild types (WT1-WT3) and one mutant (M1; C−14T).[15]

In any of above assays, resistance is considered 'detected' when one or more mutant bands is present and resistance is considered as 'inferred' when WT band is missing without presence of specific mutation.[16] In case of all wild type present and no mutant present, is considered as resistance 'not detected'. Mixed pattern with all wild type present along with specific mutant was termed as hetero resistance.

3. Results

3.1. Study population

Total of 2041 samples were received from presumptive MDR-TB patients above 60 years of age. Proportion of elderly population among total presumptive DR-TB referred to culture and DST laboratory was 2041/47063 (4.3%). Of the samples received from elderly, 792 (38.8%) were from four districts of Delhi, 845 (41.4%) patients from OPD, and 404 (19.8%) admitted patients.

Among 2041 samples, 1561 were males and 480 were females (Ratio of 3.3:1). There was no significant change in this ratio from 2012 to 2018. Maximum number of patients were in age groups of 60–70 year (1406; 68.9%), followed by 71–80 year (495; 24.3%) and least number were in more than 80 years of age (140; 6.9%). Year-wise distribution of patient demographics is detailed in Table 1. Maximum presumptive DR-TB (2,041) patients were smear negative previously treated cases at diagnosis (975; 47.8%) followed by smear positive previously treated TB patients at diagnosis (705; 34.5%), cases found to be positive at follow up on first line drugs (203; 9.9%), treatment failure with first line drugs (102; 5.0%) and contacts of DR-TB (56; 2.8%). Details are provided in Table 1.

3.2. Smear microscopy findings

Out of 2041 samples, 1788 (87.6%) were pulmonary and 253 (12.4%) were extra-pulmonary. Of 1788 pulmonary samples of elderly, 1066 (52.2%) and 722 (35.4%) of patients were smear positive and smear negative respectively (Table 2). Among smear positives, proportion of 3+, 2+, 1+ and scanty were 28.3%, 16.3%, 32.5%, and 22.9%, respectively.

3.3. Susceptibility pattern of first- and second-line antibiotics

Total of 1178 LPA were performed of which 1066 were performed on smear positive pulmonary samples and remaining 112 on cultures found to be positive for MTB as detailed in Table 2. Number of samples found to be indeterminate or invalid were 41/1178 (3.5%) while 82 (6.9%) samples were negative for MTB on LPA. Number of patients found to be MDR-TB and mono RIF resistant TB were 89 (8.5%) and 28 (2.7%) respectively. Total RIF resistant diagnosed were 117 (11.2%). Resistance to INH was found in 84 (8%) while in 854 (80.9%) strains, no resistance was detected to RIF and INH. There was no significant change in susceptibility to any of the antibiotics over the years (Table 2).

In 2017–18, total of 74 second-line LPA were put of which 67 (90.5%) gave valid results. Of valid second-line LPA, 19/67 (28.4%) isolates were resistant to only fluoroquinolones and one isolate was found to be resistant to injectables. No resistance was detected in either fluoroquinolones or injectables in remaining 47/67 (70.1%) isolates and no low-level kana isolate was seen.

Table 1 – Demographic details and type of patients for presumptive DR-TB.

Years	Number of samples from elderly/Total number of presumptive DR-TB samples received (%)	AGE IN YEARS			Males/ Females (ratio)	Demographic Location			Types of Presumptive DR TB				
		60-70 (%)	71-80 (%)	>80 (%)		Area (%)	OPD (%)	IPD (%)	Previously treated at diagnosis (%)	Smear negative re-treatment cases (%)	Follow up positive (%)	Failure (%)	Contact (%)
2012	124/2890 (4.3%)	89 (71.8%)	25 (20.2%)	10 (8.1%)	97/27 (3.6:1)	119/124 (95.9%)	5/124 (4.0%)	0	36/124 (29%)	46/124 (37.1%)	38/124 (30.6%)	4/124 (3.2%)	0
2013	137/2798 (4.9%)	95 (69.3%)	36 (26.3%)	6 (4.4%)	112/25 (4.5:1)	123/137 (89.7%)	14/137 (10.2%)	0	55/137 (40.1%)	41/137 (29.2%)	26/137 (18.9%)	4/137 (2.9%)	11/137 (8.0%)
2014	250/6191 (4.0%)	170 (68%)	59 (23.6%)	21 (8.4%)	193/57 (3.4:1)	85/250 (34.0%)	134/250 (53.6%)	31/250 (12.4%)	96/250 (38.4%)	103/250 (50.8%)	25/250 (10.0%)	21/250 (8.4%)	5/250 (2.0%)
2015	359/8295 (4.3%)	251 (69.9%)	83 (23.1%)	25 (6.7%)	271/88 (3.1:1)	62/359 (17.2%)	191/359 (53.2%)	106/359 (29.5%)	108/359 (30.1%)	187/359 (50.1%)	24/359 (6.7%)	28/359 (7.8%)	12/359 (3.3%)
2016	321/6315 (5.1%)	219 (68.2%)	80 (24.9%)	22 (7.0%)	254/67 (3.8:1)	97/321 (30.2%)	155/321 (48.2%)	69/321 (21.4%)	127/321 (39.6%)	130/321 (40.5%)	36/321 (11.2%)	21/321 (6.5%)	7/321 (2.2%)
2017	336/9442 (3.6%)	225 (66.9%)	88 (26.1%)	23 (6.8%)	252/84 (3.0:1)	117/336 (34.8%)	139/336 (41.3%)	80/336 (23.8%)	99/336 (29.5%)	179/336 (53.3%)	25/336 (7.4%)	15/336 (4.5%)	18/336 (5.4%)
2018	514/11168 (4.6%)	357 (69.4%)	124 (24.1%)	33 (6.4%)	282/132 (2.1:1)	189/514 (36.7%)	207/514 (40.2%)	118/514 (22.9%)	184/514 (35.8%)	289/514 (56.2%)	29/514 (5.6%)	9/514 (1.8%)	3/514 (0.6%)
Total	2041/47063 (4.3%)	68.90%	24.30%	6.90%	1461/480 (3.0:1)	792/2014 (38.8%)	845/2041 (41.4%)	404/2041 (19.8%)	705/2041 (34.5%)	975/2041 (47.8%)	203/2041 (9.9%)	102/2041 (5.0%)	56/2041 (2.8%)

OPD: Out patient Department; IPD: In patient Department.

Table 2 – Year-wise distribution of smear results and drug susceptibility for first line anti-tubercuar agents.

Years	>60 years Age	Sputum					EP (%)	LPA put	MTB Detected (%)	Sensitive (%)	MDR (%)	Mono R (%)	Mono I (%)
		3+	2+	1+	Scanty	Sm + (%)	Sm - (%)							
2012	124	17	14	43	4	78 (62.9%)	46 (37.1%)	0	86	84	64 (76.2%)	6 (7.1%)	4 (4.7%)	10 (11.9%)
2013	137	19	12	39	26	96 (70.1%)	41 (29.9%)	0	101	99	77 (77.8)	4 (4.0%)	5 (5.1%)	13 (13.1%)
2014	250	36	20	64	27	147 (58.8%)	103 (41.2%	0	163	147	121 (82.3%)	14 (9.5%)	5 (3.4%)	7 (4.8%)
2015	359	40	30	38	64	172 (47.9%)	124 (35.4%)	63 (17.5%)	178	162	129 (79.6%)	14 (8.6%)	6 (3.7%)	13 (8.0%)
2016	321	63	30	54	44	191 (59.5%)	85 (26.5%)	45 (14.0%)	208	182	143 (78.6%)	17 (9.3%)	7 (3.8%)	15 (8.2%)
2017	336	50	28	46	33	157 (46.7%)	115 (34.2%)	64 (19.1%)	182	153	128 (83.7%)	18 (11.8%)	1 (0.7%)	6 (3.9%)
2018	514	77	40	62	46	225 (43.8%)	208 (46.5%)	81 (15.8%)	260	228	192 (84.2%))	16 (7.0%)	0	20 (8.8%)
Total	2041	302	174	346	244	1066 (52.2%)	722 (35.4%)	253 (12.4%)	1178	1055 (89.6%)	854 (80.9%)	89 (8.4%)	28 (2.7%)	84 (8.0%)

Sm + (%): Smear positive, Sm - (%): Smear negative, EP: Extrapulmonary samples, LPA: Line Probe Assay.
MDR: Multi-drug resistance, R: Rifampicin, I: Isoniazid.

3.4. *Mutation pattern analysis of first- and second-line antibiotics*

For RIF resistant isolates due to *rpoB*, specific mutations/mutations detected were in 105/117 RIF resistant (89.7%) strains, of which commonest was S531L (86/117, 73.5%), followed by D516V (9/117, 7.7%), H526Y (7/117, 6.0%). The details of mutation patterns for RIF are provided in Table 3. In 12/112 (10.7%) RIF resistant strains, resistance was inferred. The inferred mutations included missing wild type bands WT8 (6/12; 50%), WT7 (3/12; 25%), W3–W4, W2 and W2–W3–W4 each were found to be (1/12; 8.3%), respectively. Three strains had more than 1 mutation. Mixed pattern to RIF with all wild type probes presents along with one or more mutant bands was found in 12/112 (10.7%) RIF resistant strains in which commonest mutation was M1 (4/12; 33.3%) (Table 3).

Resistance to INH was found in total of 173 strains, in which resistance was detected in 171/173 (98.8%) strains and inferred in 7/173 (4%) INH resistant strains as detailed in Table 4. Resistance due to *katG* gene was found in 139/173 (80.3%) strains. Among *katG*, resistance was detected in 136/173 (78.6%) strains and inferred in 3/173 (1.7%) strains. S315T1 was the commonest mutant found among 136/173 (78.6%) of INH-resistant strains and was the only *katG* mutant detected. In 40/173 (23.1%) *inhA* gene resistance was found, of which resistance was detected in 35/173 (20.2%) strains and inferred in 4 (2.3%) *inhA* strains. Mixed wild-type and mutant pattern to INH or hetero-resistance was found in 20/173 (11.6%) strains with *katG* mutation detected and 3/173 (1.7%) *inhA* strains.

Resistance to FQ was found in 19 isolates, all as *gyrA* gene mutation, with none in *gyrB* (Table 5). Resistance was detected in 16 (84.2%) isolates, of which commonest was D94G (6/16; 37.5%), followed by D94N/Y (5/16; 31.3%), A90V (4/16; 25%) and S91P (1/16; 6.3%). All three inferred mutation was missing wild type W3 (15.8%). Mixed pattern with all wild type probes presents along with one or more mutant bands was found in 2/19 (10.5%) FQ resistant strains.

Only one isolate was resistant to all aminoglycosides with inferred resistance due to missing WT1in *rrs* gene.

Table 3 – Distribution of mutations in rpoB gene in rifampicin resistant isolates.

rpoB		
WT	MUT	Total No
W2	–	1
W2,W3,W4	–	1
W3,W4	–	1
W3,W4	M1	5
W7	–	3
W7	M2A	4
W8	–	6
W8	M3	84
+	M1	4
+	M1,M2B	1
+	M2A	3
+	M2A,M3	2
+	M3	2
Total	117	

WT: Wild type, MUT: Mutant

Table 4 – Distribution of mutations in katG and inhA gene in isoniazid resistant isolates.

KAT G		INH A		TOTAL
WT	MUT	WT	MUT	
WT	M1	+	-	110
WT	M1	W1	M1	3
WT	M1	W1	-	1
WT	M1	W2	M3A	1
WT	M1	+	M1	1
WT	-	+	-	3
+	M1	+	-	20
+	-	W1	M1	23
+	-	W1	-	3
+	-	W2	M3B	4
+	-	W2	M3A	1
+	-	W2	-	1
+	-	+	M1	2
				173

WT: Wild type, MUT: Mutant

4. Discussion

In 2014, all Member States of WHO and UN (United Nations) endorsed WHO's End TB Strategy for 2030, which include 90% reduction of TB deaths and 80% decrease in TB incidence (new cases per 100,000 population per year) from 2015.[17] India, China, and the Russian Federation lead to 50% of world's cases of MDR/RR-TB leading to drug-resistant TB to be public health crisis.[17]

About 1.7 billion people across world have latent TB infection, which could lead to full blown active TB in lifetime.[17] End TB strategy necessitates focused attention and intervention in demographic subgroups who are at high risk of worse treatment outcomes.[1] Elderly are vulnerable group as deceased immunity makes them more susceptible to having TB, hence 90% of TB in elderly is due to endogenous re-activation of latent TB.[18] Any TB infection in elderly, if ignored or undetected will cause increased spread of TB as well as DR-TB.[9] In study from Mexico, individuals over 65 years, most patients had significantly higher rates of TB due to endogenous re-activation as well as had significantly higher rates of recently transmitted and reactivated tuberculosis as compared to younger. Older age was associated with treatment failure and death due to tuberculosis.[19]

Table 5 – Distribution of mutations in gyrA and gyrB gene in flouroquinolone resistant isolates.

gyrA		*gyrB*		Total
WT	MUT	WT	MUT	
W2	M1	+	–	3
W2	M2	+	–	1
W3	–	+	–	3
W3	M3B	+	–	4
W3	M3C	+	–	6
+	M3B	+	–	1
+	M1	+	–	1
Total				19

WT: Wild type, MUT: Mutant

In the present study, among elderly population, males were almost three times more than females at ratio of 3:1. This finding is consistent with previously reported studies.[10,20]

Mohrana et al found number of male TB patients to be much more than females TB patients among elderly as well as in younger age group of 18–59 years.[10] In previous study from our institute, proportion of males to female ratio among geriatric TB patients enrolled for TB therapy was 3:1 against 1.4:1 in younger population. In an international study by Hussein et al, males & females among elderly were found to be almost 1.9:1, however, in the younger population, comparable number of males & females had TB.[20]

In present study, maximum proportion of elderly patients were within 60–65 years (68.8%), followed by 65–70 years (24.2%) and few were 70 years and above (6.8%). Similarly, in the study from Orissa most patients were in age group 60–65 years (59%), (26%) were in the age group 65–70 years, and the remaining 14% were aged over 70 years.[10] As age increases, more elderly succumb to various underlying diseases due to falling immunity and aging process.

Almost equivalent proportion of elderly patients were found to be smear positive and smear negative, in the present study, which is 52.2% and 48.0% respectively. In our previous study from region across all age groups, smear-positive patients were almost three times of smear negative patients.[11] Most international/Indian studies have also shown that elderly patients have smear negative sputum significantly more than other age group patients.[19–21] However, in few studies, sputum smear showed similar positivity both in geriatric population and non-geriatric patients.[10,22] Non-specific symptoms of TB and high sputum negativity poses diagnostic challenge in elderly.[9] Older adults are more likely to develop atypical forms of tuberculosis such as tuberculous meningitis, renal or skeletal disease, forms of disease that are often harder to diagnose and treat than conventional pulmonary tuberculosis.[9] The LPA reduces turn-around time for smear positive samples, but the smear negative and extrapulmonary samples must first be cultured and if positive for MTB, can be considered for susceptibility and genotypic analysis by LPA. Also given requirement of sophisticated laboratory equipment, trained human resources, and culture facility for smear negative specimens, LPA is possible at IRL/NRL level laboratories only. In this context, newer diagnostic technologies with high sensitivity for smear negative samples for this age group. Thus Xpert/TRUNAT should be used as first diagnostics of choice for detection of TB routinely in elderly. This could help precise & early detection of TB, and arrest spread of TB.[21]

In present study, elderly constituted around 4.3% of the total presumptive MDR referred for DST and were new or previously treated or any follow-up smear positives/smear negative retreatment cases. The MDR-TB resistant rate in elderly was found to be 8.4%. World-wide surveillance of MDR-TB ranged from 9.4% to 36.5% from 1994 to 2000 while various Indian studies have reported MDR rates among presumptive MDR-TB varying from 17.4% to 53% among re-treatment cases.[23,24] This regional variation in prevalence of DR-TB is dependent on socio-economic factors and on the

type of criterion to consider patients as presumptive MDR-TB.[25] The MDR resistant rate of 8.4% and RIF resistant of 2.7% in present study, is almost half of MDR-TB rates reported from previous study from same area, which comprised of all age groups.[11] Finding of significantly lower percentages of MDR/XDR-TB in elderly than in younger age groups is consistent with other studies in the Indian Sub-continent.[21,26] Chinese study also reported significantly lower percentages of MDR/XDR-TB (7.11 and 0.65%) in geriatric than in younger age groups.[27] Higher rate of DR-TB in younger population is possibly due to their active lifestyle and motility on account of school, colleagues, work-places, which could make them more prone to contacting DR-TB than elderly.

Present study detected 8% of INH mono-resistant cases, similar to rate of 7.3 in younger age group (Singhal R). LPA has distinct advantage over other rapid molecular tests by detecting INH resistance cases, who need to be initiated on all oral H mono-poly DR TB regimen, regimen would be appropriately modified as per FQ resistance detected on SL LPA (PMDT 2019).

In present study, mutation S531L in *rpoB* gene was detected in 73.5% of RIF resistance cases, higher than previous study (59%).[11]

S531L mutation has been detected in rates varying from 50% to 70.5% in various studies.[28,29] Inferred mutation in *rpoB* of 10.7% was comparable to previous Indian and Vietnamese studies.[11,28]

Specific mutation S315T1 in *katG* was found in 78.6 of INH-resistant isolates, similar to previous study, 88.3%.[11] *katG* mutations contributes to most cases of INH resistance in high-burden countries leading to high-level INH resistance. Mutation in the *inhA* gene accounts for low-level resistance, found in 23.1%, similar as reported earlier.[11]

Elderly in some regions in India constitutes about 14% of all TB and if DR-TB, are prone to more severe complications and higher likelihood of unfavorable outcomes, than younger group. Increased drug-related adverse events and co-morbidity due to conditions such as diabetes and cancer adds on to unfavorable outcomes.[9,21] Treating TB in elderly is challenging as many elderly are less compliant/unreliable in taking medicines at the right time or in the right dose, which could be due to decreased memory, eyesight, underlying depression and lack of will-power to complete long course of treatment for multiple antibiotics, loss to follow up due to logistic issues for regular visits to treatment center or concomitant illness.[30] By ensuring good quality geriatric health services at the primary care level to address the specific needs of the elderly, follow-up rate in the elderly could be reduced. Also, engagement of community health workers to provide home care in elderly may contribute to better TB management.

As less number of susceptibility results for 2nd line LPA were available, more country-wide studies with higher number of patients to detect resistance to second-line drugs in geriatric population would be even more useful. Nevertheless, present study has sufficient data to depict a clear concern of MDR-TB/RR-TB/INH-mono TB in geriatric tuberculosis patients. This highlights need for designing separate line of early identification, diagnosis and treatment of geriatrics tuberculosis and strengthening tuberculosis control strategies in this population. Currently under-appreciated, tuberculosis among older adults will pose major challenges to global tuberculosis control in future. Hence, national tuberculosis programs should specifically focus on active case finding among older people. Appropriate administrative actions and gestures such as World Tuberculosis Day focused on elderly to raise awareness would go a long way to protect our old age patients.

Conflict of interest

We declare and disclose that there are

1) No third-party financial support for the work in the submitted manuscript

2) There is no financial relationships with any entities that could be viewed as relevant to the general area of the submitted manuscript.

3) There are no sources of revenue with relevance to the submitted work who made payments to us, or our institution, in the 36 months prior to submission.

4) There is no other sponsor of outside of the submitted work

5) No relevant patents or copyrights (planned, pending, or issued).

6) There is no other relationships or affiliations that may be perceived by readers to have influenced, or give the appearance of potentially influencing, what we wrote in the submitted work.

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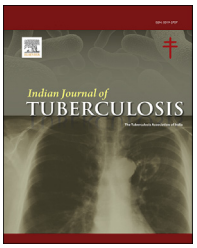

Original article

Urological problems in elderly patients of tuberculosis

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ABSTRACT

Development of tuberculosis is closely linked to poor socioeconomic condition, poor immune functioning and mental health including depression and anxiety. Elderly population becomes an important target group for the disease and deserves special attention.

Unique problem with genito urinary tuberculosis (GUTB) in elderly population is the diagnosis. One of the earliest symptoms of GUTB is increased urinary frequency which a large majority in elderly population may already have, owing to their enlarged prostates or an overactive bladder/detrusor over activity mediated centrally or peripherally, which are not uncommon in this group. When left undiagnosed and thereby untreated, GUTB usually leads to irreversible tissue damage and consequences range from abscesses, small capacity urinary bladder to renal failure.

1. Pathogenesis of GUTB

Tuberculosis in urinary tract of elderly can be considered as part of re surfacing or recalcitrant disease, usually, but not exclusively in the setting of reduction in immune status of the patient. These include elderly patients with diabetes mellitus, nutritionally deprived states, post major abdominal surgery involving GI tract, advanced malignancy with or without chemotherapy. The most common organ in the entire genito urinary tract affected by Tuberculosis is kidney, followed by epididymis, ureters, bladder, prostate and rarely phallus[1] (see Figs. 1–4)

The usual pathophysiology of affliction of genitourinary tract by mycobacterium tuberculosis (M.tb) is a hematogenous affliction of the renal papilla which may heal spontaneously but may harbor dormant bacilli for many years. These bacilli are shed periodically and eventually affect the lower ureters, bladder and distal urinary tract. The affliction of prostate and epididymis may alternatively also be by a de-novo hematogenous route. The typical lag period between the diagnosis of pulmonary Koch's and GUTB is almost ten years. Retrograde spread from bladder may occur after intravesical BCG therapy for non-muscle invasive transitional cell carcinoma of urinary bladder.

2. Clinical presentation

The frequent presentations are.

1) Fever which is usually low grade, but may be high grade with chills when there is an associated secondary infection

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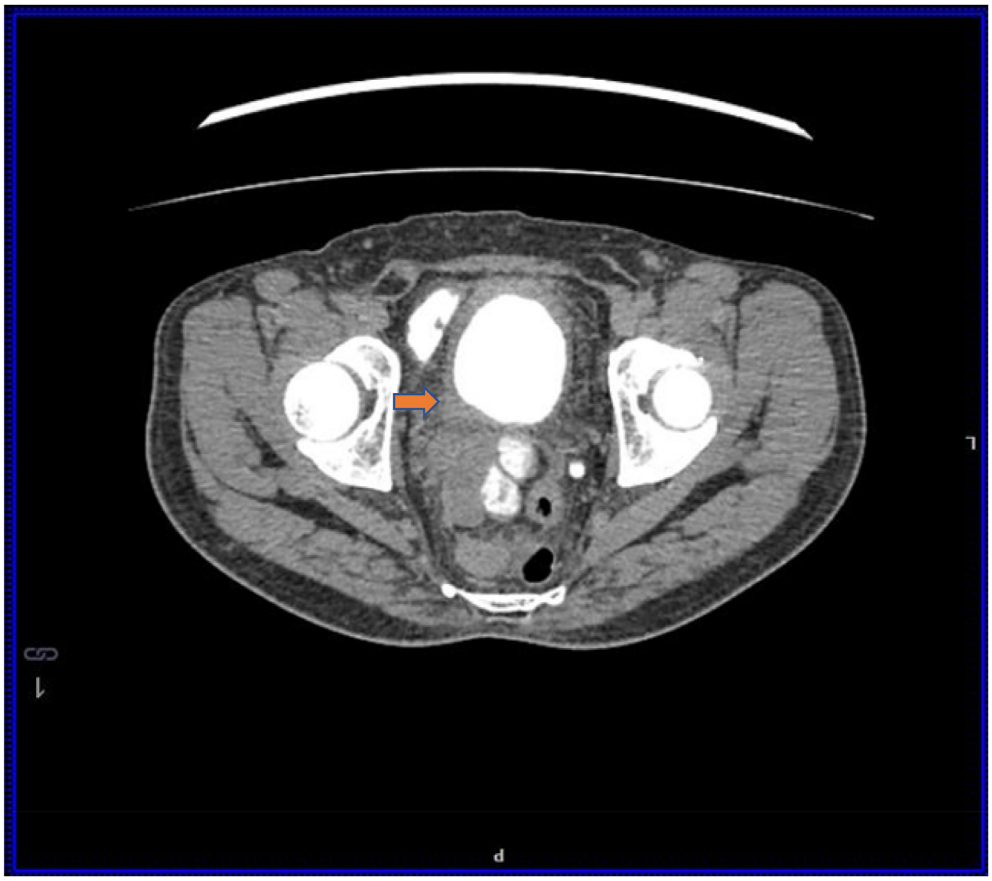

Fig. 1 – Thick-walled Urinary bladder.

in an obstructed calyx or entire renal unit. However, it is not uncommon to come across a patient with just constitutional symptoms like lassitude, loss of appetite and easy fatiguability without fever.

2) Flank pain is a characteristic sign of renal origin of any pathology. The typical colicky and abrupt onset nature of stone disease is characteristically missing. The pain is usually insidious in onset and gradually progressive in intensity. Pain may not be evident in prolonged and protracted illness as the patient may get used to it. With disease progression, the kidney may undergo a process called autonephrectomy which may occur in up to in 33% of patients with GUTB.[2] Autonephrectomy may be of caseo-cavernous type having cavitites filled with granulation tissue or of scarred fibrotic and calcified type resulting in a shrunken kidney.[3] End-stage renal failure develops in approximately 7% of cases[4]
3) Lower urinary tract symptoms are suggestive of inflammatory pathology. The most common symptoms would be frequency, urgency, nocturia, dysuria and suprapubic pain. As the disease progresses, urgency and urge incontinence set in due to small functional capacity of urinary bladder.
4) Hematuria in early disease may be cola colored urine and self-limiting This may signify an infection in a calyceal papilla and may be ignored or forgotten. Terminal hematuria is a symptom of tubercular cystitis. There are few drops of fresh blood at the end of micturition. In late stages GUTB may present with bladder contraction which is more common in the developing countries like India (12% vs. 4% cases in developed countries).[4,5] Initial hematuria signifies pathology in prostatic urethra and may signify tubercular prostatitis which may occur via either hematogenous spread or urinary contamination and is involved in 22%–49% of GU TB patients.[6] With hematogenous spread, patients are generally asymptomatic and prostatic lesions can be found in the periphery with sparing of the urethra. This later results in calcification and gland hardening. Infection via the urinary route often involves the urethra and manifests more like bacterial prostatitis
5) Scrotal lump is usually painless and is discovered due to some unrelated event. In elderly this may be picked up during examination.
6) Orificial TB, is a rare necrotic form of penile TB that marks advanced and severe TB elsewhere in the GU tract. It has been described in immunocompromised or severely debilitated patients.[7,8]
7) An exceedingly rare form of penile TB is papulonecrotic tuberculid (PNT). This is a cutaneous manifestation of TB on the glans penis and can occur in other skin areas as well. PNT of the penis has been described in Japan, South Africa, and India.[9]

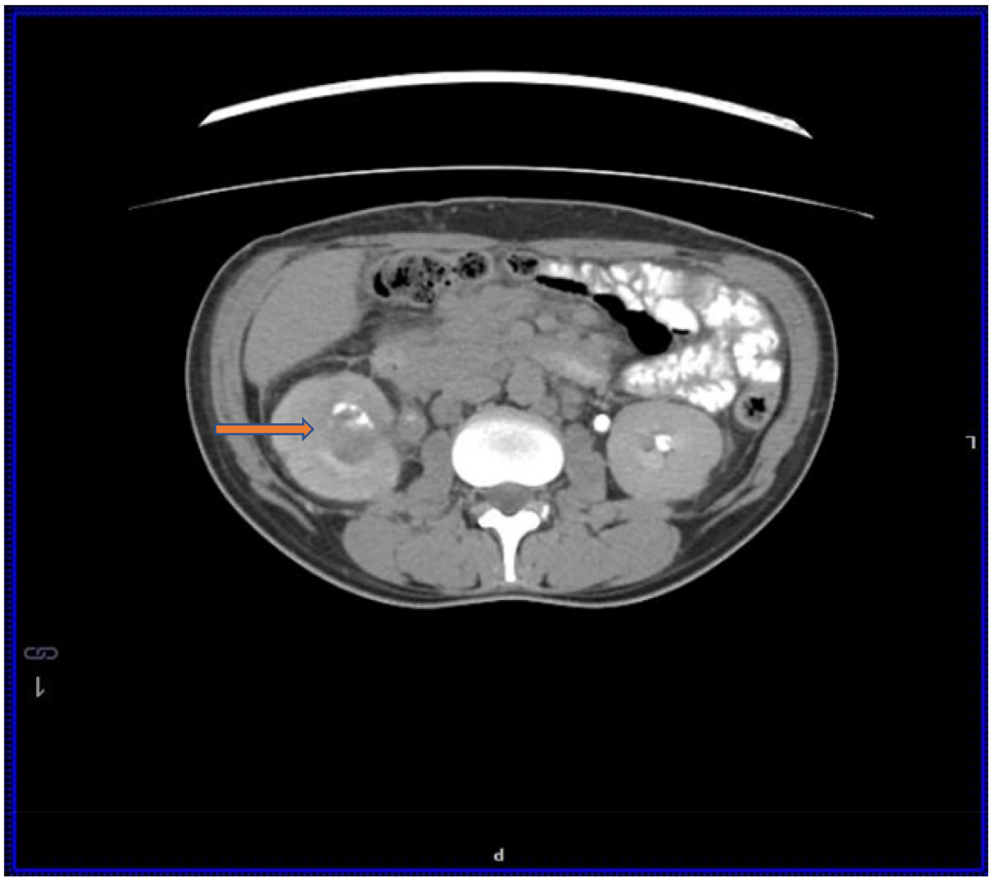

Fig. 2 – Thick contents in Rt hydronephrotic kidney causing filling defects.

3. Specific investigations

In a suspected case of Genito urinary tuberculosis (GUTB) following is the line of investigation.

1) Urine analysis by routine microscopic examination reveals an acidic pH with abundant microscopic pyuria, which does not grow any organism on usual microbiological techniques of aerobic culture (Sterile acidic pyuria). It is not uncommon to find persistent *E.coli* infections, the usual masquerading organism which is actually a superinfection in these units. The urine of these patients should be tested for presence of mycobacterial infection by following methods
   a) Overnight sample of urine for AFB smear and AFB culture on three consecutive days (sensitivity 80% and specificity 37%). False positive results of urine AFB smear may occur due to presence of mycobacterium smegmatis or nocardia, both of which may be present in the prepuce[10]
   b) Urine for Gene expert for M.tb (sensitivity 95% and specificity 87%)

Urine may also be simultaneously sent for fungal culture because clinically and radiologically these two conditions may be difficult to distinguish.

2) Screening ultrasound is a quick method for characterization of any abdominal mass, and renal masses are no exception. It may reveal the following
   a) Hydro nephrosis with or without hydroureter
   b) Calyectasis without hydronephrosis
   c) Thickening of the lining of renal pelvis and ureter
   d) Calcification of renal parenchyma
   e) Abscess in kidney
   f) Perinephric abscess.
   g) Small capacity thick-walled bladder with internal echoes
   h) Dilated seminal vesicles
   i) Heterogenous prostatic parenchyma
   j) Testicular abscess
   k) Epididymal nodules, abscess
3) Plain skiagrams may not contribute much and may lead to fallacious impression of urolithiasis. However, it may show calcification caused by TB, which is seen in more than 50% of patients.[11] It usually shows a small, shrunken, calcified "cement" or "putty" kidney, in which calcific rims outline the individual renal lobes; this pattern is characteristic of end-stage renal disease.
4) Intravenous pyelogram may be done to look for classical stigmata of urinary tract tuberculosis like
   a) Renal calcification
   b) Drooping Lily sign, which indicates a blocked or cut off superior calyx of kidney

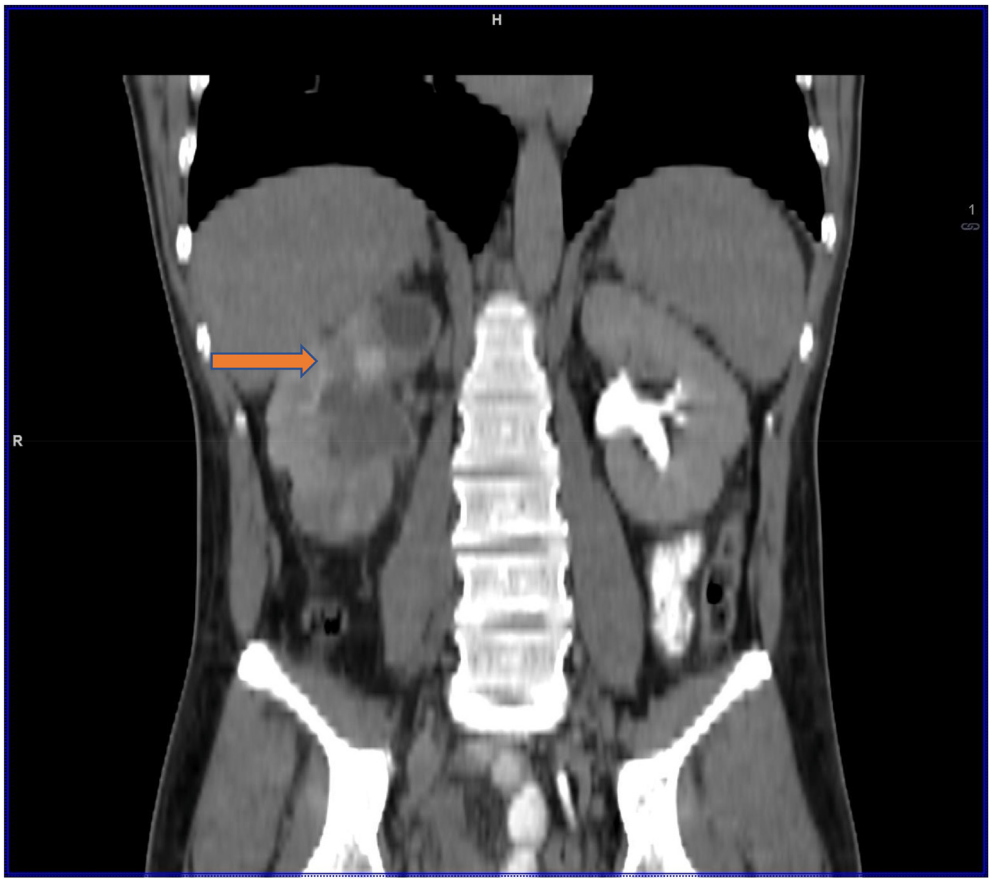

Fig. 3 – Scarred dilated right kidney with cavitation.

c) Beaded appearance of ureter, with more prominent involvement of lower one third.
d) Ureteral calcification
e) Small capacity thick-walled bladder, sometimes so small to be the size of human thumb, thus the name 'Thimble bladder'
f) The ureter may look like a "beaded corkscrew" as a result of nodular fibrosis along its entire length. The pipestem and corkscrew findings are highly suggestive of TB, particularly when seen concurrently with either kidney or bladder abnormalities.
g) The finding of a "hiked-up" renal pelvis, with sharp angulation of the pelviureteric junction, is known as "Kerr's kink".[11,12]

5) CT scan is a very good modality if available and affordable. If the renal function permits, Intravenous contrast may be given to study the details of disease process. In case there is clinical suspicion of intestinal involvement, oral contrast may be administered concomitantly. If there is clinical suspicion, it is a good idea to include sections from the thorax in the same sitting. CT scan confirms the exact pathology that is indicated by ultrasound or plain X ray. In fact, if possible, CT scan may be a single radiological investigation to clinch the diagnosis and make a therapeutic plan. Another main advantage of CT scan is to exclude a concomitant non urological abnormality. CT scan is also invaluable in differentiating a true perinephric abscess, which happens to be within the Gerota's fascia and a paravertebral abscess originating from caries spine. CT scan may pick up prostatic abscess and obstructed infected seminal vesicles and any abnormal collections and lesions in external genitalia. However, CT does have its disadvantages. In addition to having a higher radiation dose, it needs a normal renal function for administering the Intravenous contrast
6) MRI is reserved for use in patients with deranged renal function to characterize the intraabdominal lesions. Lesions in prostate and seminal vesicles may be better delineated by MRI rather than CT scan.
7) Radionuclide scan of the kidneys, preferably DTPA scan, are useful in assessing the GFR of individual renal unit apart from its drainage characteristics. Dilated systems need not necessarily be always obstructive, and this useful information can be obtained form DTPA scan. Renal units which have been affected by inflammation and obstruction and have a GFR of less than 10 ml per minute may not be suitable for reconstructive procedures. DTPA should be done in cases of affliction of kidneys and ureters before starting the ATT as a baseline and then periodically to exclude development of obstructive strictures of ureters as a sequalae of fibrosis resulting from healing of tubercular lesions.
8) Retrograde urethrogram (RGU) along with micturating cysto-urethrogram (MCU) should be considered if there is a

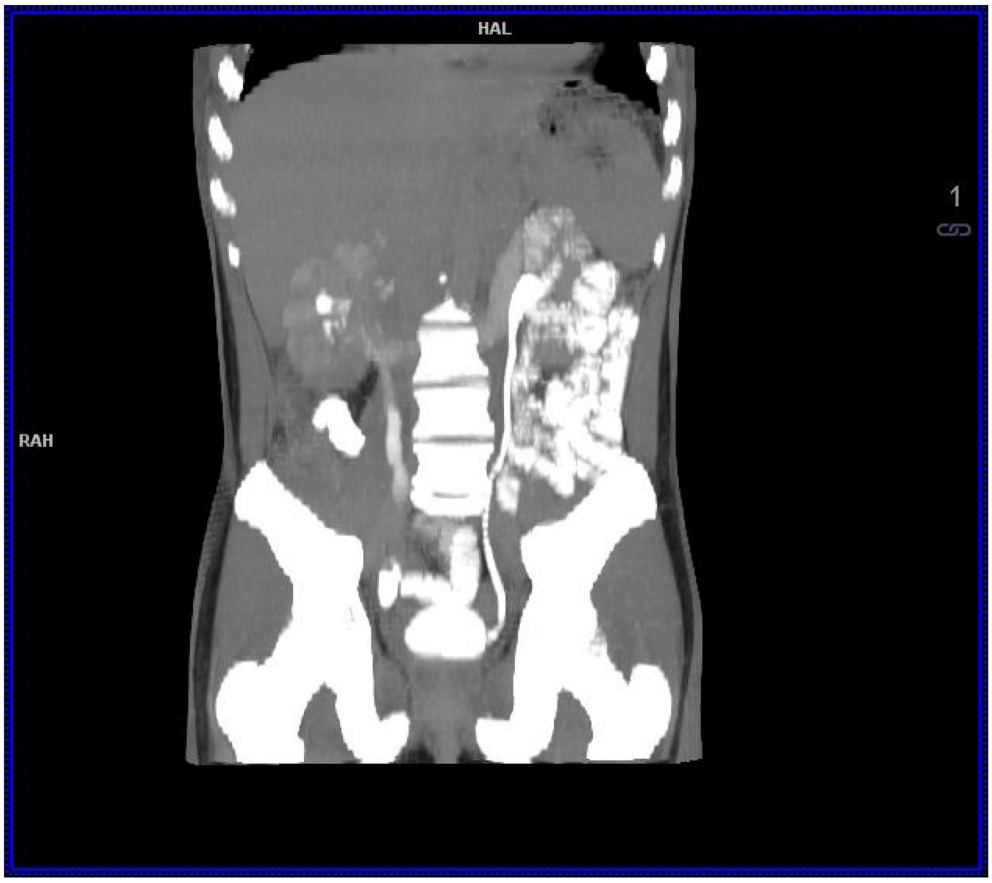

Fig. 4 – Thick dilated tortuous right ureter due to stricture in distal ureter.

suspicion of bladder outlet obstruction and vesico -ureteric reflux (VUR).

9) Any abscess or collections may be aspirated, and contents sent for microbiological investigation. Histological examination of the specimen obtained by biopsy from the lymph nodes or lesions from external genitalia may turn out to be rewarding.

Diagnosis of GUTB can be made through a combination of above investigations with suitable clinical background. The diagnostic test for GUTB is to identify AFB in urine or tissues. In case the diagnosis cannot be confirmed, and there is a suggestion of involvement of urinary bladder or ureter, cystoscopy should be planned.

3.1. *Cystoscopy in GUTB*

Cystoscopy should always be done under general anesthesia. The bladder is usually of small capacity lined by an inflamed, erythematous and friable mucosa. This bleeds readily and sloughs, rapidly deteriorating the vision through cystoscope. The ureters may be difficult to locate in view of inflammation obscuring the mucosal details Sometimes the ureters may be marked by thick purulent exudate trying to escape from the ureteric orifice. There may be 'golf hole or stadium type of ureteric orifices which may signify reflux. Cystoscopic picture may add to the circumstantial evidence of tuberculosis. In case the radiological studies have revealed a ureteric obstruction, an earnest attempt should be made to place a double J stent into the kidney to drain the obstructed unit and prevent cicatrization of ureter.

4. Management of GUTB

ATT is the sheet anchor of treatment and would depend upon the prevailing norms of the treatment regimes. Whenever possible, ATT should be modified according to the sensitivity of the isolated strain of M. tb. More than half of patients with GU TB require surgical management during their course of disease. Surgical interventions may be planned according to the presentation of disease. The optimal time of surgical intervention is after the intensive phase of therapy. This delay allows active inflammation to subside, the bacillary load to decrease, and lesions to stabilize.

1. Drainage of all collections preferably open drainage must be done and specimen for microbiological and histological examination be preserved.
2. If the disease has involved kidneys or ureters, DTPA scan must be done to assess the baseline function of individual renal units. If there is hydronephrosis and/or involvement of This stent should be left indwelling for an initial period

of 3 months of ATT. After this period, the stent may be removed, and the renal unit followed up by periodic DTPA scan to assess the need for surgical correction of any obstruction which may develop because of healing
3. In certain situations, because strictures and fibrous scars may be present, more than one PCN may be necessary. PCN must be followed by anatomical correction of the cause of obstruction later.[13]
4. Testicular abscess may necessitate orchidectomy in elderly men.
5. TURP may be done to remove infected obstructing prostatic tissue
6. Transurethral resection of ejaculatory duct may be done to relieve obstructed seminal vesicles.
7. Nephrectomy may be done for badly affected, poorly functioning kidneys. An attempt should be made to remove the entire ureter along with kidney.

4.1. *BCG cystitis*

Intravesical BCG is commonly used for treatment of non-muscle invasive transitional cell carcinoma of bladder. Infection due to BCG may result in severe symptoms which may be clinically indistinguishable from bacterial cystitis or immune mediated cystitis. Urine aerobic cultures may be used to identify the bacterial infections which may be treated appropriately. Presence of AFB in otherwise sterile urine, even after discontinuation of intravesical therapy may identify invasive infection of bladder by BCG. This may be treated with appropriately recommended medication.[14]

5. Special situations HIV

HIV treatment success potentially guarantees PLHIV reaching elderly age group and therefore a lifetime increase in probability of having a coexisting GUTB flare up by almost 30-fold.

With HIV and TB coinfection, each disease accelerates the other. All TB patients should be tested for HIV. Treatment in HIV-positive patients with GU TB should not be delayed. Treatment guidelines are similar to those for persons without HIV infection. Daily instead of intermittent treatment is recommended and preferred for HIV-positive patients.[15] Drug interactions with antiretrovirals can be complex and must be considered.

Conflicts of interest

The authors have none to declare.

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