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Mycosis as Co-Infection among Tuberculosis Infected Patients in some Countries: A Systematic Review

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Abstract
Mycobacterium tuberculosis is the causative agent of tuberculosis (TB) which renders patients in serious immunological dilemma, due to diseases compounded by the drugs they take. Mycosis (such as candidiasis) as opportunistic infection, utilizes this situation to establish and manifest in the same patient. The review was to assess some mycotic infections among TB patients in some high TB burden countries. Data on mycotic agents mostly Candida and Aspergillus species were obtained from published researches using different search engines like Google scholar and ask.com among others. High prevalence of mycotic agents were found amongst the TB patients, for instance, out of 75 TB positive patients, 30(40%) were found to be co-infected with Candida species according to one of the study. It was also discovered that, same TB patient could be co-infected with different fungal species like Candida and Aspergillus at the same time. The review further highlighted highest isolation rate of Candida albicans against the other non albican species and also indicated that males were more at risk of the co-infection in this category of patients. It was also discovered that some TB patients could be co-infected with Candida or Aspergillus while others with both species. It could therefore be concluded based on the review that, a Mycobacterium tuberculosis infected (TB patient) is prone to many other opportunistic pathogens, including various mycotic agents.

Keywords: Mycosis, Mycotic agents, Opportunistic infection, TB patients

INTRODUCTION
Opportunistic mycosis is a common problem associated with many infections including tuberculosis across the globe, *Candida* species are among the front line opportunistic mycotic agent in that regard. The rate of opportunistic fungal infections has been on the rise in recent years, especially among patients affected by other diseases, long term use of antibiotic therapy and those with immunocompromised immunity.

Out of the known *Candida* species, *Candida albicans* emerged as the most potentially pathogenic fungus instead of normal mucosal commensal in patients with broncho-pulmonary diseases, increased use of broad spectrum antibiotics and immunosuppressive drugs made it more relevant in that regards, even though respiratory candidiasis secondary to pulmonary tuberculosis has been documented in the past (Latha *et al*., 2011) more so, the infection could be due to resurgence of tuberculosis in the background of the HIV epidemic (Ochieng *et al*., 2005).

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People are in more fears, as a result of changes in respiratory fungal community and its relevance in patients with pulmonary tuberculosis these days, due to changes in their infection pattern (Latha *et al*., 2011) Although *Candida albicans* continues to dominate species in pulmonary candidiasis (Fidel *et al*., 1999; Badiee and Alborzi 2011; Latha *et al*., 2011), many other non- *albicans Candida,* are increasingly infecting humans, where some are linked to specific groups of factors others are associated to particular patients types (Trofa *et al*., 2008). Presently, tuberculosis appears to be a public health issue, as about two million people die of the disease annually with additional nine million being newly affected (De Backer *et al*., 2006). According to reports in India, for instance, the rate of all types of tuberculosis, in the average, stands at around 5.05 in one thousand, similarly, the rate of smear-positive incidence, is averagely 2.27 in a thousand, however, annual incidence rate of smear positive was found to be 84 in 100,000; But same illness also occurs in other body parts, not only lungs i.e extra pulmonary tuberculosis (Chakraborty, 2004). Plate I shows some presentations of extra pulmonary tuberculosis.

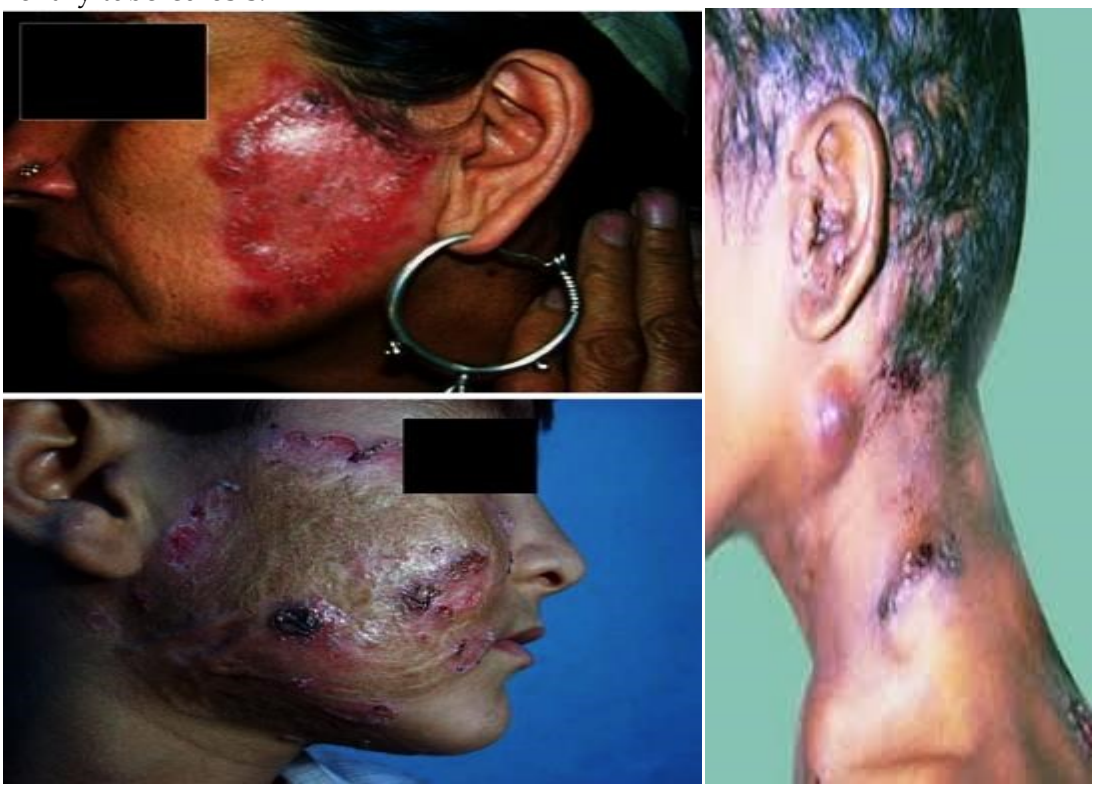

Plate I: Extra pulmonary tuberculosis presentation, (Dylan, 2018)

According to available past records, rate of tuberculosis keep elevating due to higher HIV infection, inter-countries movement of people, especially from high prevalent nations, increased rate of homeless and drug abuse, are all contributors of the disease (De Backer *et al*., 2006).

There is also increased level of these opportunistic mycosis in patients with TB, as a results of anti TB drugs with non-specific action and depressed immunity which enable fungi to proliferate, resulting in negative consequences on the patients affected (Naz and Tariq, 2004). In the disease, case mortality can be as high as 90% in immune-compromised patients but immune-competent patients generally respond well to antifungal therapy which results in lower mortality rate in this group of patients (Bulpa *et al*., 2007; Meersman *et al*., 2007). Mostly, fungal infections in the lungs, often pose a difficult diagnostic challenge due to unclear clinical syndrome in some cases, in India and other developing countries for example, the problem is

further aggravated by preponderance of pulmonary tuberculosis and limited diagnostic mycology laboratories (Randhawa, 2000).

Clinical and radiological characteristics of fungal infections resemble that of TB, leading to misdiagnosis of fungal infections as tuberculosis, this makes the patients suffer from avoidable complications of unwarranted therapy. The disease is associated with increasing consequences worldwide, especially, due to *Aspergillus* species which has the ability to form tangled mass of fungal hyphae (aspergiloma), in cavities generated by tuberculosis in patients' lungs (Bansod, 2008). Plate II shows how cavities are produced in the lungs by chronic TB infection and how the cavity is later occupied by *Aspergillus* to form aspergilloma (fungus ball).

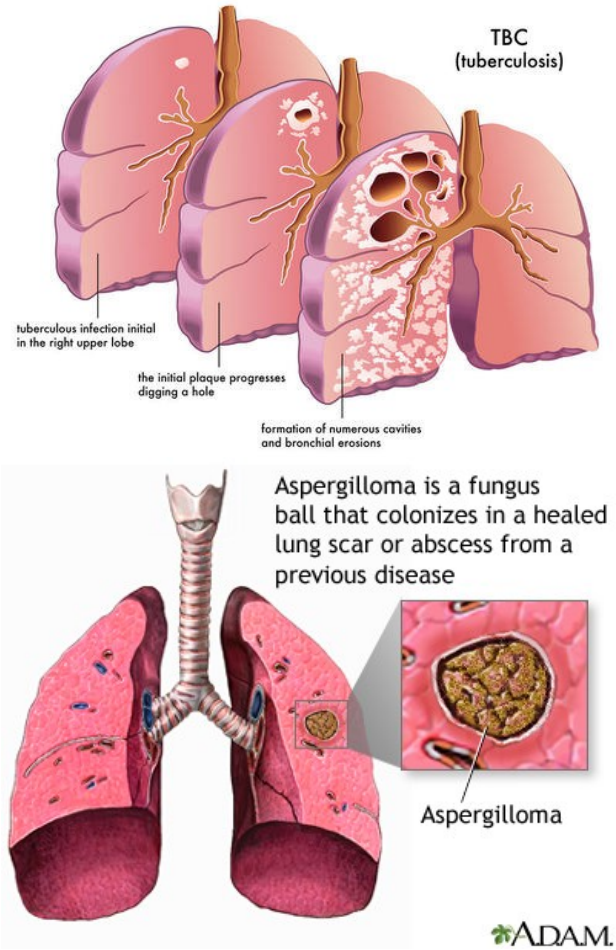

Plate II: Cavities produced by tuberculosis in affected lungs (Procto, 2013) Aspergillus utelizes the cavity to form fungus ball (Mount Sinai school of Medicine, 2019)

Tuberculosis is well known to be one of the oldest diseases and records have shown that about 1.7 million of those infected die annually worldwide, the disease also has an annual infection rate of about 2 million people worldwide, consequently, in India for instance, around 330,000 people die of the disease per year (Inside Indian, 2009; Mamkiericz, 2010).

Literature have shown that, India accounts for up to one-fifth of global incidence of TB and associated secondary infections such as mycoses and known to top the list of 22 high TB burden nations of the world (CDC, 2005).

Based on various studies, the incidence of life-threatening fungal infection has been on the rise and the increasing incidence has been correlated with increasing number of immunocompromised patients (Bodey *et al*., 1992; Denning, 1998).

As been documented, *Candida albicans* has emerges as pathogenic fungus in patients with bronchopulmonary disease, which may be due to increased use of broad spectrum antibiotics and immunosuppressive drugs (Ochieng *et al*., 2005; Latha *et al*., 2011).

Although fungi are opportunistic and depending on the types, are normal flora or ubiquitous (found in the environment), their infections are mostly acquired by inhalation of contaminated soil or due to weaken immunity of the involved subjects and through others sources (Fraser *et al*., 1992), for example, *Cryptococcus neoformans* can infect people with sound immune systems at a rate of 0.2 cases per million populations per year. However, HIV/ AIDS patients are more at risk, with approximately 80-90% of them eventually coming down with cryptococcosis (Crawford, 1993).

Cryptococcosis is caused by members of the *Cryptococcus neoformans* species complex, comprising the three variants *C. neoformans v. neoformans, C. neoformans v. gattii (Cryptococcus gattii)*, and *C. neoformans v. grubii* (Saubolle, 2000).

People get infected by Cryptococcus species as a result of inhalation of the its spores in the air, and the rate of the disease is found to by high in the past 2 decades, due to HIV and use of immuno-suppressive agents (Dromer *et al*., 1996). Plate III shows fungal infectious propagules being inhaled into the lungs.

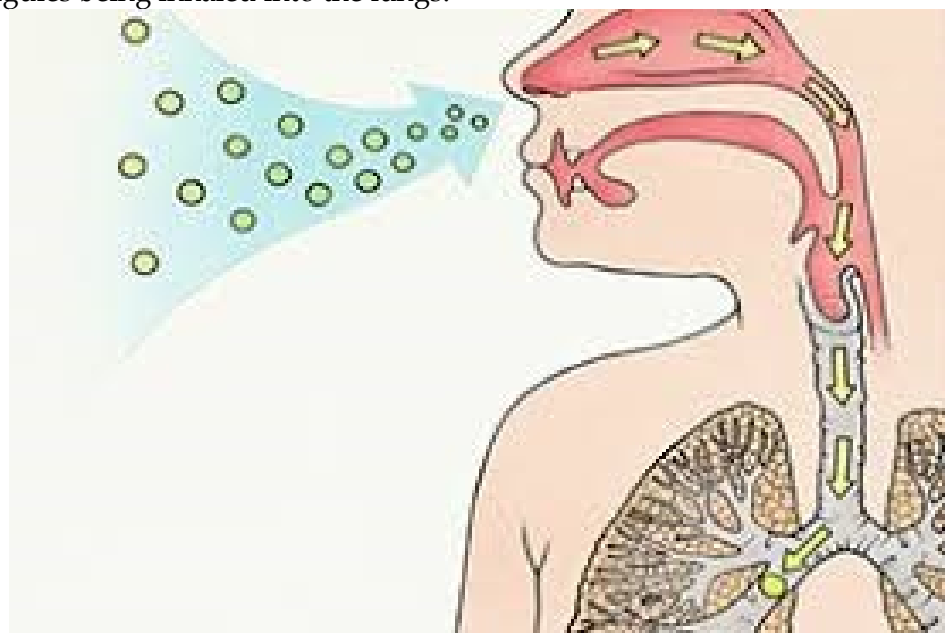

Plate III**:** The infectious propagules (spores) of fungi inhaled to the lungs (Speciality medical dialogue, 2016)

Infection with *Aspergillus* (Aspergillosis) refers to a wide range of diseases caused by the genus *Aspergillus*, these include invasive aspergillosis, allergic bronchopulmonary aspergillosis and pulmonary aspergilloma (Sarosi, 1997).

It is widely believed that every person inhale spores of one of the commonness opportunistic fungal pathogens, *Aspergillus fumigatus,* which is a serious pathogen among people with suppressed immunity, but the spores are easily contained in immunoconpitent individuals (Sarosi, 1997). However, these mycotic agents can turn pathogenic, overcoming the host

defense in organ transplant patients, HIV infected individuals, those with leukemia and other conditions that make the patients immunity down (Takagi *et al*., 2011).

It is on record that, *Aspergillus flavus* is a common environmental mold and can cause storage problems in stored grains, it can also be a human pathogen, associated with aspergillosis, otomycotic, corneal and nasoorbital infections, because many strains produce significant quantities of aflatoxin, which is a carcinogenic in nature and acutely toxic compound and can also produce allergenic spores (George, 1998).

Aspergillosis is caused predominantly by *A. fumigatus,* the fungal agent commonly inhabits hays and grains, in case of their diagnosis in histology laboratory, the fungus is identified in different forms, like fungal ball and fragmented hyphae (Takagi *et al*., 2011).

Candida infections is also referred to as candidiasis or thrush, they are opportunistic mycosis caused by the different species of the genus Candida, in which *Candida albicans* is believe to be the most common causative agents. The disease ranges from superficial infections, such as oral thrush and vaginitis, to the more serious systemic and potentially life- threatening diseases (Petro, 2008) *Candida* infections that reaches systemic level, are also referred to as candidemia, and are mostly associated with severely immunocompromised persons, such as cancer, transplant and AIDS patients. On the other hand, superficial infections of skin and mucosal membranes by *Candida* causes local inflammation and discomfort, and are common in many human populations (Geiser, 2009)

India

Kali *et al*. (2003), in the Mahatama Gandi Medical College and Research Insititude Pondicherry, India, studied 382 TB suspect out of which 75(19.6%) were found to be positive for the disease using ZN-staining technique. From these 75 TB positive patients 30(40%) were found to be co-infected with *Candida* species after screening. Out of the species of *Candida* recovered, *Candida albican* was the predominant isolate (50%) against *Candida galabrata* and *Candida tropicalis* which had (20%) each. According to the findings females had the highest prevalence (62.5%) while males had (29.4%). It was also noticed that, *Candida* species were found in (45.0%) of outpatients with multiple/co-infections and of the 30 patients with candida co-infection, nineteen 19(63%) still exhibited pulmonary symptoms even after treatment for ≥ 2 months. The results also showed that, even though, *Candida albicans* was the most common sputum isolate, in this group of patients, non-*albicans Candida* species were also represented with high prevalence 12 out of 19 cases (Kali *et al*., 2013).

Another study involving 200 pulmonary tuberculosis suspect, Bhutia and Adhikari, **(**2015) in India, fifty four 54 equivalent of (27%) were found positive of various pathogens. Fourteen 14(7%) of the enrolled patients had only tubercle bacilli (AFB) as the pathogen they harbored while fungi including candida as primary etiologic agents were isolated in 16(8%) of the patients while as secondary etiologic agents, they were isolated in 4(2%) of the patients. AFB co-infection with fungus was in 2(1%), AFB with fungus and other bacteria 1(0.5%) and other bacteria with fungus without AFB 1(0.5%) based on the result. According to the study, it was also discovered that, *Aspergillus* species involved were, *Aspergillus niger* (2%) and *Aspergillus flavus* (1%). The *Candida* species isolated were *Candida albicans* (3.5%), *Candida tropicalis* (2%), *Candida krusei* (0.5%) and *Candida kefyr* (0.5%). Based on microscopic examination, presence of septed hyphae with dichotomous branching in 3(1.5%) patients and budding yeast cells with pseudohyphae, in 14(7%) patients were evident. Fungal culture yielded *Aspergillus* sp. in 6 (3%) patients and *Candida* species in 20(10%) patients. *Candida* species were recovered in 20(10%) patients by culture but in direct microscopy budding yeast cells with pseudohyphae

were detected only in 14(7%) patient, based on the results, the 6 culture positive (*Candida*) with absence of pseudohyphae in direct microscopy were considered to be commensals in the patients.

In what seems like multifungal species co-infecctions in TB patients, Babita and Prabhat, (2016), reported the presence of *Candida* species and *Aspergilus* species co-infecting Mycobacterium tuberculosis (TB) patients. In the study, 75 pulmonary tuberculosis patients were enrolled and their sputum samples collected appropriately. Of the samples collected, 19(20%) demonstrated the presence of fungal elements while 46 (61.3%) were negative of the fungi.

The result also showed that 18 (24%) of the cultures showed fungal growth, in which *Candida albicans* was isolated in 8 cases (44.4%), *Aspergillus niger* in 6 cases (33.3%), *Aspergillus fumigatus* in 3 cases (16.5%) while *Aspergillus flavus* occurred in only 1 case (5.5%).

Nigeria

In River State, Nigeria Ndukwu *et al*. (2016), worked on 300 Mycobactrium tuberculosis (AFB positive) patients, comprising of 166 male and 134 females. The findings of the study showed that 76(25.3%) were co-infected with *Candida* species. The species distribution of the isolates revealed, *Candida albicans* with highest prevalence rate 42(14%) the other species were *Candida tropicalis* 25(8.3%) and 9(3%) for C*andida stellatoidea*. According to the result, males had the highest co-infection rate 45 (27.1%) compared to females 31(23.1%) in the study area.

Ethiopia

In 2018, Nandihal and his co-workers reported on the research that engaged 100 TB positive patients based on sputum microscopy in designated microscopy centre (DMC). The result revealed co-infection rate of 32(32%) with regards to *candida* species. It was also indicated by the results that *Candida albican* and *Candida tropicalis* were the major causative agents as was found in (34.4%) co-infected followed by *Candida parapsilosis* (21.9%) (Nandihal *et al*., 2018).

Kenya

A study in Kenya by Mwaura *et al*. (2013), on 172 sputum samples, from both males 103(59.9%) and females 69(40.1%) participants respectively, 14(8.1%) were positive for fungal hyphae, 50(29.1%) were positive for yeast cells while 1(0.6%) of the specimens was positive for both yeast and gram positive rods. It was also observed that 1(0.6%) was positive for both yeast cells and fungal hyhae.

Species profile in the pulmonary infections in the enrolled TB subjects, indicated that, yeasts were isolated in 42(26.7%) of the samples, 33(19.2%) were *Candida albicans*, 3(1.7%) were *Candida dubliensis,* 1(0.6%) was *Candida guilliermondii* and 3(1.7%) were *Candida tropicalis*. *Cryptococcus lauretii* were also isolated from 2(1.2%) of the samples according to the results obtained.

CONCLUSION

Based on the review, we can deduce that, *Mycobacterium tuberculosis* patients are in many cases co-infected with other organisms including mycotic agents like *candidas, Aspergilus* and Cryptococcus species. *Candidas* and *Aspergilus* species also revealed high infection frequencies among the TB patients, suggesting the need for screening for fungal agents in all TB suspects especially in high TB burden regions of the world and is therefore of public health concern.

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