Review

Role of Pulmonary Mycoses in Tuberculosis Disease—An Indian Perspective

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Review

Role of Pulmonary Mycoses in Tuberculosis Disease—An Indian Perspective

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Abstract: Tuberculosis poses serious challenges to healthcare personnel as it continues to be highly prevalent in a developing country like India. Several prominent strategies have been adopted to control this contagious infection, but the incidence rate remains high. Many studies have linked fungal infections and tuberculosis, apparently elevating concerns in the TB elimination program. Hence, it is essential to understand the mechanism underlying TB co-infection and pulmonary mycoses to combat the problems caused by these diseases successfully. In addition, differential diagnosis of TB and fungal infections is equally essential to initiate appropriate treatment. In this review, we have documented the findings of TB and fungal diseases individually and as coinfection, focusing on Indian perspectives. Misdiagnosis of fungal diseases as Tuberculosis in many studies elucidates the need for simultaneous diagnosis of both infections for appropriate diagnosis.

Keywords: Tuberculosis; fungal; diagnosis; therapy; pathogenesis; prophylaxis; mycoses; infectious

1. Introduction

Though preventable and curable, tuberculosis caused by *Mycobacterium tuberculosis* remains the second leading cause of mortality due to a single infectious agent next to the COVID-19 infection in 2022, WHO Global Tuberculosis Report stated [1] Pulmonary tuberculosis continues to be a serious concern in India and is consecutively enlisted in the top 20 TB high burden countries despite strong measures taken by our health department [2]. Pathogenic fungi cause pulmonary mycoses via inhalation of spores, which disrupt the normal functioning of bronchial and lung tissues, resulting in pulmonary fungal disease. Further, a rapid surge in fungal infection recently is attributed to other pre-existing clinical conditions such as tuberculosis, HIV/AIDS, and substantial use of immunosuppressive drugs which enables these opportunistic fungi to attack the host, who are immunocompromised by the disease listed above [3,4] Commonly, pulmonary fungal infections are caused by *Aspergillus, Cryptococcus, Pneumocystis [5]*, Candida [6], Mucor [7], and endemic fungi which include *Blastomyces, Coccidioides and Histoplasma [8]*.

It's been reported that people recovering from tuberculosis are prone to pulmonary fungal coinfections and were mostly misdiagnosed as cases of relapsed PTB [9]. However, some clinicians do not pay enough attention to this problem. Another alarming fact is that there is an increase in misdiagnosis of patients with invasive fungal infections, such as tuberculosis, and vice versa, due to similar clinical presentations leading to wrong or delayed treatment of the patients.[10], Therefore, studies on co-infection with PTB and pulmonary fungal infection are needed so that these patients may get treated for antituberculosis or antifungal agents promptly. To attain this, a differential diagnostic algorithm for TB and other fungal infections is required. While tuberculosis diagnostic methods are well designed and implemented in routine programmatic setups, many labs still rely on classical diagnostic tests for fungal infections, such as direct visualization, radiological evidence, and culture, which have very low sensitivity and specificity. In this review, we attempted to compile the

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Indian studies focusing on fungal infections with special reference to TB coinfection, misdiagnosis, and treatment.

2. Pulmonary Fungal Infections

A. Pulmonary Aspergillosis

Pulmonary Aspergillosis can be broadly classified into three types based on clinical presentation [11].

1. Allergic Bronchopulmonary Aspergillosis,
2. Chronic Pulmonary Aspergillosis,
3. Invasive Pulmonary Aspergillosis.

2.1. Allergic Bronchopulmonary Aspergillosis (ABPA)

The common aetiological agent of ABPA is reported to be *A. fumigatus* [12] and is followed by other species such as *A. flavus*, *A. niger*, and *A. oryzae* [13]. The characteristic features of ABPA in conventional CT are bronchiectasis and mucoid opacities in the shape of toothpaste or a finger in a glove [14].

2.2. Invasive Pulmonary Aspergillosis (IPA)

Inhalation of Aspergillus conidia results in IPA, and the subspecies of *A. fumigati* (*A. fumigatus, A. lentulus,* and *A. udagawae*) are involved in this common form of aspergillosis [15]. Other significant species involved in the disease are *A. flavus*, *A. nidulans*, *A. terreus,* and *A. niger.* Extensive use of corticosteroids in non-neutropenic patients eventually results in invasive aspergillosis. A few symptoms of IPA patients include prolonged fever, nonproductive cough, chest pain, and hemoptysis [16], which are similar to TB, leading to confused CT results [17].

2.3. Chronic Pulmonary Aspergillosis (CPA):

The fungal pathogen causing CPA in most patients is *A. fumigatus* [18]. Incidentally, it is observed that one in five TB-negative patients after treatment with ATT might suffer from CPA [19]. A study in 2022 reported that the incidence of CPA emerging in PTB patients was estimated to be 363,601 cases and 42,766 deaths - 10.5% of total PTB deaths [20]. In addition, various studies and case reports elucidate the significance of CPA in PTB patients (Table 1). These findings indicate the importance of diagnosing CPA as part of the TB diagnostic algorithm in the program. Other predisposing factors for developing CPA into a serious illness are nontuberculous mycobacterial infections (NTM) and ABPA [21]. CPA is further subdivided into five types based on their colonization and disease development as follows

1. Aspergillus nodules,
2. Simple Aspergilloma,
3. Chronic Cavitary Pulmonary Aspergillosis
4. Subacute Invasive Pulmonary Aspergillosis,
5. Chronic Fibrosing Pulmonary Aspergillosis

Table 1. Recent studies on Aspergillosis with or without TB across India.

Type of Aspergillosis	Reported State & Year	Type of Study	Study population	Number of isolates	Salient Findings	Reference

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Chronic Pulmonary Aspergillosis	New Delhi 2024	Prospective	255- Recruited 158- Completed follow up	11.1% were positive at baseline, and 27.5% were positive at the end of ATT	CPA may arise after anti-tubercular treatment or be present at the time of diagnosis in patients with newly diagnosed tuberculosis.	Jha *et al.* [22].
Chronic Pulmonary Aspergillosis	Chandigarh 2024	Prospective	111- Of which 53 were control	52.25%- Proven CPA	Compared to controls, those with CPA related to PTLA exhibit reduced Th-1 response and decreased neutrophil oxidative burst.	Chirumamilla *et al* [23]
Chronic Pulmonary Aspergillosis	Maharashtra 2023	Cross-sectional/Observational	42	9.5%	Serological diagnosis is necessary for detecting CPA in patients with or without TB due to similar clinical features.	Rajpurohit *et al* [24]

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Chronic Pulmonary Aspergillosis	New Delhi 2022	Prospective-Observational	130	24.2%	While a differential diagnosis is needed for CPA and TB, the mediastinal necrotic lymph node is the proper CT finding for differentiating between recurrent TB and post-TB sequelae.	Bharath et al. [25]
Chronic Pulmonary Aspergillosis	India 2022	Estimation Analysis	-	-	Comprehensive estimation of total CPA burden in pulmonary TB patients	Denning et al. [20]
Chronic Pulmonary Aspergillosis	Chandigarh 2023	Retrospective	434 subjects and 20 disease controls -	-	The significance of Erythrocyte Sedimentation rate (ESR) and C-reactive protein (CRP) in CPA diagnosis	Sehgal et al [26]

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					among Post Tuberculosis Lung Disease PTLD has been established by this study.	
Aspergilloma	Uttarakhand 2023	Case Report	-	1	This Case was reported after a decade of undergoing ATT where, unusually, Aspergilloma was found as a mass in the intrabronchial region instead of a lung cavity.	Lahiri et al [27] [59]
Invasive Pulmonary Aspergillosis	Chandigarh 2022	Case Report	-	1	Sequelae of COVID-19 complicated by TB and IPA	Gandotra et al. [28]

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Chronic Cavitary Pulmonary Aspergillosis	Karnataka 2022	Case Report	-	1	About 20 years ago, a patient had tuberculosis and aspergilloma. COVID-19 had reactivated latent aspergilloma, and the condition developed into CCPA, a more severe form of aspergillosis.	Chaurasia et al [29]

2.4. Aspergillus Nodules

Of the subtypes of CPA, *Aspergillus* nodules are relatively rare and are characterized by the CT finding of one or more nodules with or without cavities [30]. Minor or no symptoms represent this type of CPA and can only be diagnosed with histological evidence of necrosis severed by the presence of *Aspergillus* [31].

2.5. Aspergilloma

Simple Aspergilloma is indicated by a single fungal ball with radiological or microbiological evidence of *Aspergillus* species in immunocompetent individuals. Similar to *Aspergillus* nodules, this condition also accounts for minor or no symptoms [32].

2.6. Chronic Cavitary Pulmonary Aspergillosis (CCPA)

Complex Aspergilloma, an old surgical term now called CCPA [33], showcases parenchymal disease surrounded by a thick-walled cavity [34]. Contrary to *Aspergillus* nodules and Aspergilloma, the incidence of CCPA is high, and several reports have been documented for its role in previously treated TB patients. CT image portrays single or multiple cavities with characteristic residues in the lung [35].

2.7. Subacute Invasive Pulmonary Aspergillosis (SAIA)

Occasionally called semi-IPA and chronic necrotizing pulmonary aspergillosis [36], SAIA is similar to CCPA in radiology, with only the distinction of rapid progress in the former condition.

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Clinical conditions that make the host vulnerable to SAIA are diabetes, malnutrition, corticosteroid use, connective tissue disorders, HIV infection, and COPD [37].

2.8. Chronic Fibrosing Pulmonary Aspergillosis (CFPA)

The final stage of CPA is expressed as CFPA, which is more commonly reported along with CCPA than other types of CPA [38]. Since this condition overlaps with different forms of CPA, a distinctive diagnosis is impossible. [21].

2.9. Pulmonary Cryptococcosis

Though 30 species of Cryptococcus are identified, *C. neoformans* and *C. gattii* are known to cause human infections [39]. Invasive fungal diseases in immunocompromised individuals are known to be caused by *C. deneoformans* [40], while *C. gattii* depose infection in immunocompetent individuals [41]. CT findings of pulmonary cryptococcosis (PC) include pulmonary nodules, patchy shadows, ground glass attenuation, interstitial changes, and cavitation. In addition, the left lower lung seems to be involved most frequently in immunocompromised patients and is prone to be misdiagnosed as tuberculosis or tumor [42]. Although not common, studies from various parts of India have been reporting the coinfection of tuberculosis with cryptococcosis, emphasizing routine monitoring (Table 2).

Table 2. Recent studies on Cryptococcosis with or without TB across India.

Reported State/ Year	Type of Study	Study Population	Number of isolates	Site of infection	Salient Findings	Reference
New Delhi 2019	Case Report	-	1	Lung	Initially treated for TB due to misdiagnosis but later diagnosed as Cryptococcosis.	Meena et al. [43]
New Delhi 2019	Case Report	-	1	Thoracic spine	Empirically treated for TB before being diagnosed with Cryptococcus Osteomyelitis and was treated with voriconazole for 8 weeks.	Adsul et al. [44]
New Delhi 2018	Case Report	-	1	Lung and CNS	Disseminated Cryptococcosis mimicking TB-	Ismail et al [45]

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					Reported in an immunocompetent child	
New Delhi 2016	Case Report	-	1	Lung	The co-existence of Pulmonary Cryptococcosis and tuberculosis was reported. Treated with fluconazole and anti-tubercular therapy	Jain et al [46], [47]
New Delhi 2016	Case Report	-	1	Lung	They had a history of TB, a right lower lobe mass similar to a lung tumor, but was eventually diagnosed as Cryptococcoma through CT and histopathological examination.	Pawar et al [47]
Chandigarh 2017	Retrospective	42	2	Lung	This introspects the significance of Fine Needle Aspiration Cytology(FNAC) as a rapid method of diagnosis in immunocompromised patients.	Sharma et al. [48]
New Delhi	Case	-	1	Lung /	A 65-year-old adult	Ranjan et al

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2015	Report			Adrenal gland	male with no history of TB was reportedly diagnosed with Cryptococcosis mimicking TB. Still, CT findings indicated that the abnormality was due to the fungal pathogen Cryptococcus spp.	[49]

2.10. Pneumocystis Pneumonia

Pneumocystis pneumonia (PCP) is caused by an opportunistic pathogen named *Pneumocystis jirovecii [50]*. It is an ascomycete fungus that was previously categorized as a protozoan due to its similarity in morphology and drug susceptibility [51] but later as fungi based on RNA analysis [52]**.** The clinical manifestations of PCP are illustrated by the subacute onset of dyspnoea, nonproductive cough, and low-grade fever [53]. Few studies and case reports have been recorded on Pneumocystis Pneumonia and TB across India (Table 3). This could be due to its coexistence in the HIV population, where one of the diseases gets diagnosed, and by the time the other one is suspected, the patient dies. [54].

Table 3. Recent studies on Pneumocystis pneumonia with or without TB across India.

Reported State/ Year	**Type of Study**	**Study Population**	**Number of isolates**	**Site of infection**	**Salient Findings**	**Reference**
Uttarakhand 2024	Case Report	-	1	Lung	HIV, Pneumothorax, and TB- A rare coexistence of three pathogens	Jithesh et al. [55]

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Maharashtra 2016	Retrospective	111- HIV Patients	3(5.76%)	Lung	Of the respiratory manifestations in HIV seropositive subjects, TB is the most common. Pneumocystis was also recorded in 3 patients.	Patil et al. [56]
Karnataka 2015	Prospective	74 PLHIV - People living with HIV (37 with diabetes mellitus (DM) and 37 without DM)	5% among DM and 18% among those without DM	Lung	EP-TB was diagnosed among 22% of the study population, while the study also recognized the significance of Pneumocystis infection	Indhira et al [57]
Karnataka 2015	Descriptive	164- HIV population	16%	Lung	Among opportunistic infections, 50% were reported as TB in this study.	Ramesh et al [58]

2.11. Pulmonary Blastomycosis

The inhalation of Blastomyces spore results in this fungal infection. The fungal agents involved in Blastomycosis include *Blastomyces dermatitidis, B. percursus*, and *B. emzantsi [59]*. Surprisingly, though the lung is the most common site of infection [60], the first human case of this infection was averred in the skin tissue [61]. This extrapulmonary spread could be attributed to a hematogenous initial lung infection [62]. The pulmonary form of the disease is expressed as pneumonia with an

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insidious course, while chest CT is non-specific, and infection limited to the lungs can mimic *M. tuberculosis [63] [64]*. One study of Blastomycosis misdiagnosed as TB was reported in the last decade from Kerala, India, in 2019. The patient was on empirical ATT for nearly a year due to an indefinite diagnosis. History of his travel to Chicago, which is endemic for Blastomycosis, stirred suspicion, and he was appropriately diagnosed [65].

2.12. Pulmonary Coccidioidomycosis

Soil inhabiting the arthroconidia of the fungi *Coccidioides immitis* and *Coccidioides posadasii* is responsible for pulmonary coccidioidomycosis [66]. The disease is reported rarely in places other than endemic areas [67] and is commonly associated with human and animal middens [68]. Though endemic to deserts in the United States and Central and South America, travel history to these countries has resulted in cases reported from other parts of the world [69]. It has been documented that about 19.5% of Coccidioidomycosis confirmed cases were infected with tuberculosis as well [70]. One case report has been documented so far from India where the diseased individual with a travel history presented with complaints of swelling over the neck and was clinically diagnosed as having tuberculosis. Further diagnosis by fungal stains, fungal culture, and serology confirmed Coccidioides, and a course of fluconazole was used for treatment [71].

2.13. Pulmonary Histoplasmosis

Histoplasma capsulatum, a dimorphic fungus, is accountable for establishing histoplasmosis infection [72]. Disease transmission is reported to be due to inhalation of spores in instances of soil disruption like cave excavation [73]. Chronic histoplasmosis is often characterized by nodule formation, and this clinical condition is termed chronic cavitary pulmonary histoplasmosis (CCPH) [74]. Major clinical features of TB, like radiological findings, pulmonary infiltrates, hilar lymphadenopathy, opacities of the lung, and pleural effusion, are also reported in histoplasmosis [75] [76]. Instances of Histoplasmosis misdiagnosed as TB across India have been recorded in Table 4.

Table 4. Recent studies on Histoplasmosis with or without TB across India.

Reported Year	Type of Study	Study Population	Number of isolates	Site of infection	Salient Findings	Reference
Rajasthan 2021	Case Report	-	1	Lung	Pulmonary histoplasmosis misdiagnosed as miliary tuberculosis	Agarwal et al [77]
Chandigarh 2020	Case Report	-	1	Skin, Lung	Disseminated TB and histoplasmosis co-infection was reported in a 50-	Anot et al [78]

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					year-old male.	
New Delhi 2019	Case Report	-	1	Lung	A 59-year-old female with a history of cutaneous TB was presented with manifestations such as fever and dry cough. Multi Drug Resistant-TB was suspected due to substantial evidence from CT images. Eventually a PET scan was performed which revealed soft tissue nodule, histopathological examination suggested the presence of *H. capsulatum*.	Dutta et al [79]

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Telangana 2018	Case Report	-	1	Adrenal gland, lung	Hepatitis C confirmed, case with fever, treated for four months with ATT for suspected TB but was finally diagnosed as Histoplasmosis which mimics TB in clinical manifestations.	Ramesh et al [80]

2.14. Pulmonary Candidiasis

Opportunistic candidal infection is caused frequently by *Candida albicans*, although the incidence of disease by other members of the same genus is also increasing rapidly [81]. Candida, a commensal of the gut microbiome, shapes itself into a pathogen based on antibiotics, severe lapse leading to compromise of the gut integrity, host immune dysfunction, use of central venous catheter, surgery etc. [82]. Diagnosing pulmonary candidiasis is tedious as no specific clinical and radiographic presentations exist. Hence, pulmonary parenchymal invasion through histopathologic examination can be a more reliable method for diagnosis in patients with deep-rooted invasion, though such instances occur rarely. [83]. A systematic review and meta-analysis of different cross-sectional studies by Fishani et al. has established a significantly higher incidence of co-infection of Candidiasis among pulmonary tuberculosis patients in Asia and Africa [84]. Significant correlations between HIV, TB, and Candidiasis that were documented from India are included in Table 5

Table 5. Recent studies on Candidiasis with or without TB across India.

Reported State/ Year	**Type of Study**	**Study Population**	**Number of isolates**	**Site of infection**	**Salient Findings**	**Reference**
Uttarakhand 2016	Case Report	-	1	Lung	Coexistence of drug-resistant tuberculosis with invasive	Khanduri et al [85]

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					candidiasis	
Rajasthan 2016	Prevalence Study	60 confirmed Pulmonary TB patients	33	Lung	Prevalence of candidal presence in sputum samples among pulmonary tuberculosis patients was reported using SDA and ChromAgar cultures.	Astekar et al [81]
Maharashtra 2016	Prospective observational Study	45- Renal transplant recipients (RTR)	7	-	Among renal transplant recipients, TB with candidiasis and CMV with TB was found in 7 patients	Kumar et al [86]
Karnataka 2015	Descriptive Study	164- HIV positive patients	80	Lung	This study reported that TB and candidiasis were most frequently occurring opportunistic infections among HIV patients which	Ramesh et al [58]

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					were concreted by several other studies from India.	

2.15. Pulmonary Mucormycosis

The order Mucorales includes different genera such as Rhizopus, Mucor, Lichtheimia, Rhizomucor, Cunninghamella, and Apophysomyces spp involved in establishing the invasive fungal infection called mucormycosis [87]. Diabetes mellitus, solid organ transplant, chronic renal failure, hematological malignancy, acute myeloid leukemia, and tuberculosis are the predisposing risk factors for mucormycosis [88]. Clinical features include ground-glass lesions, reverse halo signs, necrosis, lobar and segmental consolidation, and single or multiple lesions [89]. Studies and case reports on mucormycosis documented across India have been described in Table 6.

Table 6. Recent case reports on Mucormycosis with or without TB across India.

State	Year	Site of infection	Salient Findings	Reference
Chandigarh 2015	2015	Lung	Coinfection of Tuberculosis and mucormycosis in a diabetic patient was reported.	Aggarwal et al [90]
Puducherry 2016	2016	Lung	Pulmonary TB with mucormycosis co-infection was demonstrated in a diabetic patient admitted to the intensive care Unit.	Dube et al [91]
New Delhi 2020	2020	Lung	Disseminated pulmonary mucormycosis and tuberculosis co-infection in a diabetic patient was reported.	Ramesh et al [92]

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Uttar Pradesh 2015	2015	Lung	Pulmonary artery aneurysm, a rare condition, and its association with pulmonary mucormycosis was reported.	Ramachandran et al [93]

3. Diagnosis

The Fungal Priority Pathogen List released by WHO in 2022 underscores the need for quick measures to prevent, diagnose, and appropriately treat fungal pathogens [94]. Some of the proven diagnostic tools available for detecting pulmonary mycoses can be broadly categorized into histopathological and culture methods, while radiological, immunological, and molecular techniques are considered for probable diagnosis [95]. Figure 1 shows diagnostic techniques for suspected pulmonary fungal infections in presumed TB patients who have been microbiologically determined to be non-TB patients, with confirmed possibility of bacterial and viral pneumonias ruled out.

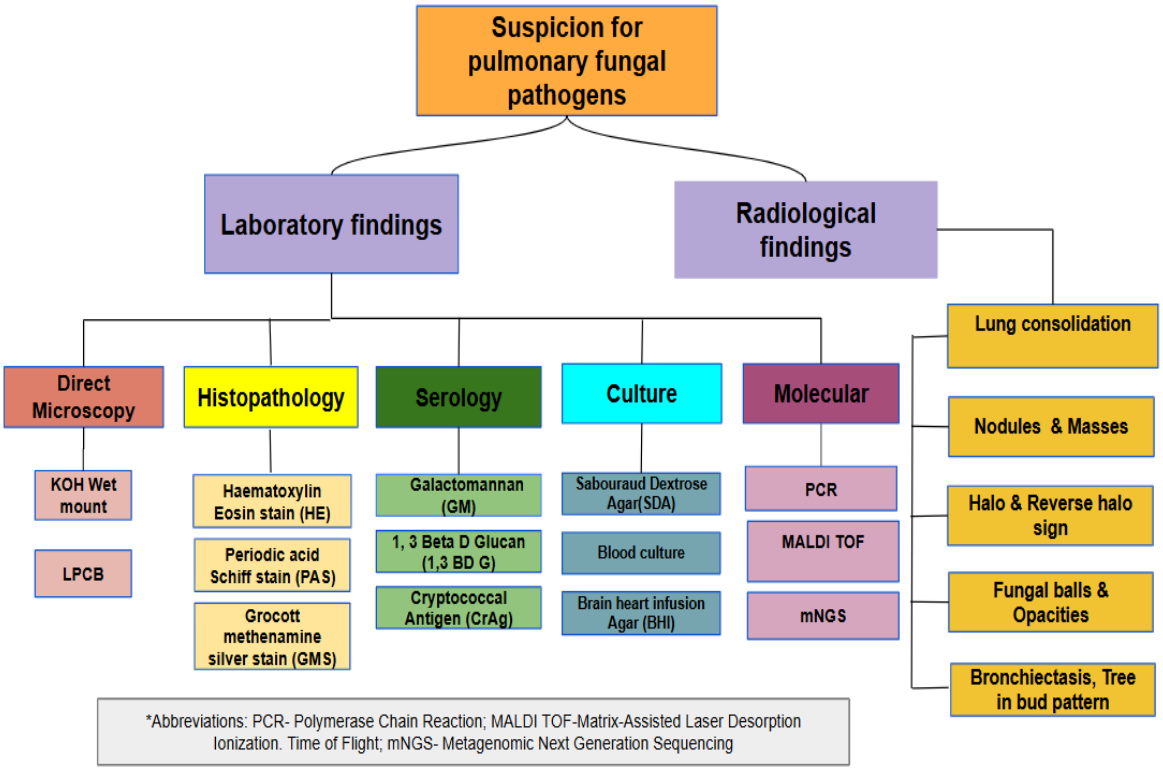

Figure 1. Diagnostic tools for fungal infections in patients with pulmonary diseases.

3.1. Direct microscopy & Histopathological Examination

Histopathological examination can be carried out by staining methods using Haematoxylin Eosin stain (HE), periodic acid Schiff stain (PAS), or Gomori's methenamine silver stain (GMS) [96]. An evaluation study carried out to detect fungal infections in post-COVID-19 patients by Baxi et al. from Gujarat compared the efficacies of histopathological, culture, and KOH wet mount methods, of which the histopathological diagnosis by Haematoxylin and Eosin staining was found to be the most sensitive and rapid technique for mycological identification [97]. Another retrospective study from a tertiary care hospital in Jammu & Kashmir stressed the potential misdiagnosis in the microbiological examination as it cannot differentiate between pathogenic fungi and contamination. Further, they

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suggested that histopathology could be more reliable for fungal diagnosis as it can distinguish between contamination, colonization, or actual infection [98]. Seth et al. from AIIMS New Delhi reviewed the diagnostic progress of fungal infections and concluded that diagnostic tools need to be validated in younger children. They also admitted that histopathological examination remains the gold standard while galactomannan assay or PCR techniques can be employed for pediatric populations [99].

3.2. Radiology

Radiological diagnosis includes the utility of X-rays, CT scans, radiofrequency (MRI), and sound waves (ultrasound) for pathogen identification [100]. High-Resolution Computed Tomography (HRCT), though insensitive, can be utilized as a screening tool initially in highly suspected cases, and an empirical therapy could be started when microbiological diagnosis takes up more time [101]. It has been documented that PJP by *Pneumocystis* in HIV/AIDS patients can be suspected with radiological evidence. Similarly, lung consolidation, nodules, and masses can be used to suspect cryptococcosis and blastomycosis [102]. Garg et al. from PGIMER, Chandigarh, studied the imaging spectrum of CPA and summarised that a patient's immune status plays a significant role in radiological diagnosis as clinical presentation is often not specific and leads to misdiagnosis [37].

3.3. Culture

Sabouraud's Dextrose agar or Potato Dextrose agar with certain antibiotics or Brain Heart Infusion agar enriched with blood is generally used for growing fungal pathogens [103]. The culture of clinical specimens is considered more efficient in determining the specific fungal etiological agent if the sample is positive and susceptibility patterns can be determined. A retrospective study by Ghosh et al. from PGIMER stated that around 50% of direct microscopy-confirmed cases of fungal keratitis yielded positive results on culture, with *Aspergillus* being the predominant among isolated spectrum [104]. When culture is challenging to identify using tease mounts, the slide culture technique has to be used alternately, states the ICMR SOP for Fungal Identification and Detection of Antifungal Resistance, Edition 2 [105].

3.4. Immunology

Serum Galactomannan (GM) testing can be recommended for IPA suspects initially, and they can be subjected to tissue biopsy only when a GM negative result is obtained if there is still high clinical suspicion for IPA. Consequently, false positive serum GM can be avoided with a BAL GM confirmation [106]. Another biomarker, B, D glucan, can identify different fungi in clinical specimens. However, in the case of ABPA, Aspergillus-specific IgG has proven higher sensitivity and specificity than IgE [107] GM and B, D glucan [108]. Point of care identification of Aspergillus in corneal samples was demonstrated by Gunasekaran et al. in Tamil Nadu, using a Lateral flow device for microbial keratitis, and they have achieved prominent results for the same [109]. Other serological assays with significant diagnostic ability for fungal detection include immunodiffusion (ID), counter-immunoelectrophoresis (CIE), enzyme-linked immunosorbent assays (ELISA), complement fixation (CF), radio-immunosorbent assays (RIA) and agglutination assays [110].

3.5. Molecular Diagnosis

Nucleic acid-based molecular diagnostics include PCR, loop-mediated isothermal amplification, nucleic acid sequence-based amplification (NABSA), and rolling circle amplification. Gudisa et al. from PGIMER, Chandigarh, reviewed the evolution of molecular diagnostics for fungal infection over the years and elucidated the significance of RT-PCR, the role of Sanger sequencing, and next-generation sequencing in the detection and speciation of fungal pathogens [111]. A study from North India by Srinivas et al. from Maharashtra evaluated GenoSen's panfungal RT PCR kit. It depicted the utility of panfungal PCR in a resource-limited country like India [112].

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3.6. Metagenomic Next Generation Sequencing (mNGS)

Molecular methods such as mNGS will greatly help diagnosis but require strong validation and standardization for better utility [113]. Moreover, metagenomic next-generation sequencing is a fast-growing diagnostic technique with the subsequent advantage of rapid and broad detection [114]. Different studies have demonstrated the efficiency of the NGS technique in detecting fungal pathogens such as Pneumocystis, Histoplasma, Aspergillus, and Candida [115]

3.7. Matrix Assisted Laser Desorption Ionisation-Time of Flight Mass Spectrometry (MALDI TOF MS)

Ghosh et al. tried to evaluate the utility of MALDI-TOF MS in diagnosing bloodstream yeasts. They also added the need for extensive studies to be carried out to validate the potential of MALDI-TOF as a diagnostic technique for effective patient care and management [116]. Paul et al. standardized the MALDI-TOF method with different protocols and concluded it could be used for routine diagnosis of pathogenic molds [117].

3.8. Antifungal Therapy

Traditional antifungals available for treating pulmonary mycoses were previously limited, but the therapeutic potential has increased substantially with new azole compounds. Further, initiating newer treatment options has established wider options for clinicians to assist in treating fungal infections [118]. Some antifungals and newer biologic agents utilized in treating pulmonary fungal infections are listed in Table 7.

Table 7. Antifungal and biologic agents used for treatment of pulmonary mycoses.

Pulmonary Mycosis	**Antifungal Agents**	**Biological Agents**
Aspergillosis	Voriconazole, Amphotericin B, Caspofungin, Posaconazole [119]	Omalizumab, Mepolizumab, Benralizumab, Dupilumab, Tezepelumab [120] , Echinocandins [121]
Cryptococcosis	Fluconazole, Amphotericin B, Amphotericin B with flucytosine [122]	3-Bromopyruvate - Anticancer agent with excellent fungicidal activity [123]

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Pneumocystis pneumonia	Trimethoprim-sulfamethoxazole, pentamidine, & Atovaquone [124]	Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab- these anti-tumor necrosis factor alpha agents used for Rheumatoid arthritis patients have been involved in Pneumocystis development [125]
Endemic mycoses	Itraconazole, Fluconazole, Voriconazole, Posaconazole, Isavuconazole and Corticosteroids [126].	Promising research is currently underway to develop biological agents for the treatment of endemic mycoses.

4. Conclusions

This review has summarised distinct studies conducted in India concerning the concrete connection between tuberculosis and pulmonary mycoses. It is worth noting that the incidence of misdiagnosis documented in this review explains the poor clinical suspicion for pulmonary mycosis among TB cases. Hence, we suggest clinical suspicion of pulmonary mycoses among TB cases and ATT non-responders could help in timely prognosis and patient care. Further, it emphasizes the urgent necessity to develop differential diagnostics for TB and pulmonary mycoses, as most of the available tools have been exposed to either cross-reactivity or low specificity.

Conflicts of Interest: All authors declare no conflicts of interest.

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