Review

Overview of Opportunistic Fungal Infections in India

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Abstract

In recent years fungi have been flourishing in immunocompromised patients of tertiary care centers. The data on the burden of opportunistic mycoses in India is not clear though the climate in this country is well suited for a wide variety of fungal infections. There are very few good diagnostic mycology laboratories and clinicians are still not aware of the emerging trends. Within the limited data available, an increased incidence of invasive candidiasis, aspergillosis, and zygomycosis are reported. The emergence of fungal rhinosinusitis, penicilliosis marneffei and zygomycosis due to *Apophysomyces elegans* is unique in the Indian scenario. Invasive candidiasis is the most common opportunistic mycosis. The global change in spectrum of *Candida* species is also observed in India; however, the higher prevalence of candidemia due to *Candida tropicalis* instead of *C. glabrata* or *C. parapsilosis* is interesting. Invasive aspergillosis is the second contender. Though due to difficulty in antemortem diagnosis the exact prevalence of this disease is not known, high prevalence is expected in Indian hospitals where construction activities continue in the hospital vicinity without a proper impervious barrier. The other opportunistic mycosis, invasive zygomycosis is an important concern as the world's highest number of cases of this disease is reported from India. The infection is commonly observed in patients with uncontrolled diabetes mellitus. Though antiretroviral therapy in AIDS patients has been introduced in most Indian hospitals, no decline in the incidence of cryptococcosis and penicilliosis has yet been observed. Thus there is need of good diagnostic mycology laboratories, rapid diagnosis, and refinement of antifungal strategies in India.

Key words : India, opportunistic mycoses, zygomycosis, candidiasis, endemic mycoses

Introduction

India is a vast country of more than a billion people and spread over an area of 3.3 thousand million square kilometers[1]. The geographical and environmental conditions in different parts of the country vary, as do uniquely different traditions. Located in the tropics, and receiving a heavy annual monsoon makes climatic conditions favorable for fungi to grow in major parts of the country. All these factors together ensure the widespread occurrence of both common and unique mycotic diseases. The human immunodeficiency virus (HIV) infected population is estimated to number anywhere between 3-6 million, and diabetes mellitus affects more than 30 million people of this country[2]. Solid organ and bone marrow transplantations are performed in tertiary care centers of urban India. Systemic steroids are available over the counter and are being misused by quacks (untrained health professionals) in several rural and semi-urban areas. Intravenous drug abuse is also quite common in large cities and very high incidence is reported from states like Manipur and Punjab[3]. Infection control practices are less than optimal and there is gross overuse of broad-spectrum antimicrobials in most Indian hospitals. These factors produce a fertile ground for opportunistic mycoses to flourish in this country.

The exact frequency of opportunistic fungal diseases is not known due to there being few diagnostic mycology laboratories in this country. Most clinicians are still unaware of manifestations of mycotic diseases. Only a handful of centers carry out routine medical autopsies. Thus what we know of these diseases is just the tip of a huge iceberg. Limited data suggests that there has been a rapid increase in the burden of invasive candidiasis, invasive aspergillosis, and cryptococcal meningitis throughout the country. Further, India is emerging as the capital of invasive zygomycosis of

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the world[4-12]. A sharp increase in the number of endemic mycoses including histoplasmosis[13-16] and penicilliosis[17-19] has been reported in the last decade in HIV infected patients. Emergence of two additional mycoses including fungal rhinosinusitis due to *Aspergillus flavus*[20-22] and zygomycosis due to *Apophysomyces elegans* are interesting developments[23, 24].

Endemic mycoses in immunocompromised patients:

Among endemic mycoses frequent in India, histoplasmosis and penicilliosis marneffei are common in immunocompromised patients. Penicilliosis, caused by the dimorphic fungus, *Penicillium marneffei* is restricted to the states of Manipur (more than 500 cases so far), Nagaland (1 case) and Mizoram (1 case). Singh *et al.* in 1999 first reported it from four autochthonous patients[19]; subsequently the epidemiology of this disease with a greater number of patients was described[18]. The life cycle of the fungus in nature has not yet been elucidated clearly although association with bamboo rats, especially *Calommys badius* has been described in India[17]. Inhalation as the route of infection is predicted in penicilliosis. However, one cannot rule out the gastrointestinal tract as the route of invasion, as the population of the endemic regions has a habit of eating bamboo shoots and the meat of bamboo rats where this agent possibly exists. The cases that have been so far recorded from northeast India are all AIDS patients. Fever, weight loss, malaise, hepatosplenomegaly, lymphadenopathy and skin lesions (ranging from papules to molluscum contagiosum like) are the common manifestations[18]. The pigment produced by the fungus has been characterized in detail in India and is shown to be related to the copper-colored pigment (herquinone) produced by *Penicillium herquei* since both pigments contain the phenalene carbon framework. Unlike the latter, this pigment is dimeric and has a 1,1,3,3-tetramethyl-2,3-dihydropyrrole moiety instead of 2,3,3-trimethyl-2,3-dihydrofuran[25]. Molecular typing of *P. marneffei* from different countries including Indian strains showed that the latter are closer to the strains from Thailand than Chinese strains and the possible clonal origin of these strains was predicted[26].

Histoplasmosis is another emerging disease in India. Panja and Sen described the first case of histoplasmosis in 1954 from Calcutta, and only 38 cases were diagnosed upto 1992[14, 15]. But, at present, the disease is threatening to have serious proportions. Almost equal numbers of cases were described in the next 10 years mainly from the states of Tamil Nadu[16], and West Bengal[13]. These cases are associated with the AIDS epidemic. Similar to penicilliosis marneffei, histoplasmosis is also considered as an AIDS defining condition in endemic areas. Diabetes mellitus is the other common predisposing factor associated with histoplasmosis patients in India. Exclusively caused by *Histoplasma capsulatum* var. *capsulatum* in this country, this fungus has also been isolated from soil on the bank of the Hoogly River near Calcutta[15]. Apart from the usual acute pulmonary and chronic pulmonary disease produced by this organism, extra-pulmonary manifestations are particularly common in Indian patients. Mucocutaneous lesions, including oral or pharyngeal ulcers are common. The other common features like fever with hepatosplenomegaly may be misdiagnosed as visceral leishmaniasis in endemic areas of histoplasmosis. Adrenal involvement is seen in around 10% of the cases[13, 16].

Blastomycosis, caused by another dimorphic fungus, *Blastomyces dermatitidis*, is a rare disease reported from India. The disease often occurs in a normal host and has not yet been detected with greater frequency in immunocompromised patients; but the disease is more severe in AIDS patients or those with marked immunosuppression. Randhawa *et al.* reported the first human case from India in 1983[27]. Out of five authenticated reports of isolation of *Blastomyces dermatitidis* from India, three were human cases and one each isolation was from bat and dog[28]. One patient developed a pulmonary disease after visiting the endemic area of Milwaukee, Wisconsin, USA[28], and the other two patients had never travelled outside India[27, 29]. Two authentic cases of coccidioidomycosis were reported from India. However, both patients came from southwest America as tourists to this country[30].

Opportunistic Mycoses:

Invasive Candidiasis: This is the most common invasive mycotic infection across India. Incidence varies from 1 to 12 per thousand admissions in different hospitals across the country[31-33]. In a tertiary care hospital in northern India, systematic data on prevalence of nosocomial candidemia showed an eleven fold increase in cases with candidemia in the second half of the 1980s and a further eighteen fold rise from 1991 through to 1995[31, 32]. Candidemia is now the 4th most common cause of bloodstream infection at that institute[31, 32], most of those cases being reported from intensive care units (ICUs)[31-33]. Neonatal ICUs (NICUs) had a rate of 77 per 1000 discharges in that hospital[34]. Pediatric ICUs (PICUs) and surgical ICUs across the country also report high incidence of candidemia[35, 36]. Most studies in India identify prolonged hospitalization (>30 days), central venous access, total parenteral

nutrition, use of broad-spectrum antibiotics for a prolonged period, mechanical ventilation, major abdominal surgery and immunosuppression as risk factors for developing candidemia[33-36]. In children prematurity and low birth weight are additional risk factors[34]. Mortality in candidemia cases varies from 28% to 71.4% and attributable mortality rates between 17% and 33%[31-33]. A study on children admitted to PICUs reported that risk of death varies with pediatric risk of mortality score, presence of sepsis, isolation of non *C. albicans Candida* spp. in general and *C. tropicalis* in particular[36].

Candidal endocarditis has been reported mainly from centers that conduct autopsy studies[37,38]. Disseminated candidal infections have also been reported in such studies. Hepatosplenic candidiasis is reported occasionally[39], and candidal arthritis has also been described in neonates with candidemia[40]. Indian literature on central nervous system (CNS) candidiasis is sparse, though fungal meningitis and intracranial abscesses have been described in both HIV infected and non-HIV infected immunocompromised patients. Preterm infants and neonates seem to be at higher risk of developing CNS mycoses[41,42]. Candidal co-infections with other invasive CNS mycoses have also been described. In contrast to CNS candidiasis, candidal infections of the eye have been reported quite frequently with the diagnosis of postoperative and post-traumatic endophthalmitis. Polymerase chain reaction for early diagnosis of fungal endophthalmitis has been standardized in two centers of the country[43,44]. *Candida* spp. are important causes of fungal peritonitis[45,46]. Patients on continuous ambulatory peritoneal dialysis (CAPD) and those with severe pancreatitis have been found to be at special risk, mortality due to these infections has also been documented[45,46]. Abdominal pain and non-removal of the CAPD catheter have been found as poor prognostic markers in CAPD patients with candidal peritonitis. Patients with severe pancreatitis, especially after pancreatic necrosectomy, have higher risk of developing intra-abdominal candidal infection than patients with mild pancreatitis. Bloodstream infection has also been documented in such patients[45,46].

Life threatening infections due to rare *Candida* spp. − *C. rugosa*[47], *C. lusitaniae*[42], and *C. kefyr*[33] have been recorded. An outbreak due to *Pichia anomala* (*Candida pelliculosa*) candidemia was reported from northern India affecting 379 children over 23 months (4.2% of all admissions in a tertiary care center). The point source from a patient with fungemia due to *P. anomala* in pediatric emergency spread to other pediatric wards carried by the hand of a resident doctor. Fluconazole prophylaxis to all high-risk babies and improvement of hospital care practices helped in controlling the outbreak. Species specific and strain specific primers for *Pichia anomala* were developed targeting the intergenic spacer 1 (IGS1) region of the rDNA[48,49].

With the increase in candidemia cases a change in the spectrum of *Candida* spp. has been noticed in major hospitals in India. Non *C. albicans Candida* spp. are isolated from 30-90% cases of invasive candidiasis. In contrast to *C. glabrata* or *C. parapsilosis*, *C. tropicalis* is the most common species among non-*C. albicans Candida* isolates. *C. guilliermondii* and *C. krusei* are other frequently encountered species. The reason for this shift in distribution of *Candida* spp. is unclear as the resistance to fluconazole is seen only in <10% strains of *C. tropicalis*[31-33]. Though resistance to azoles is still low, it is rising slowly over the years and is a matter of concern[31,32].

Invasive Aspergillosis: Invasive pulmonary[50], paranasal sinus[20-22], and cerebral[51] aspergillosis are common presentations of the disease in India, though the exact prevalence of invasive aspergillosis is not known. Classical risk factors for invasive pulmonary disease have been shown to be prolonged antibiotic therapy, steroid therapy, ICU stay, mechanical ventilation and renal transplantation. AIDS patients also have been reported to acquire the disease[10,50]. However, this fatal disease has also been shown to occur with increasing frequency in immunocompetent hosts. Frequent dissemination to the cerebrum, even in immunocompetent persons, has been documented. Sino-cranial extension of disease to the brain is the most common cause.

Aspergillus endocarditis is often diagnosed post-mortem in most centers due to lack of clinical suspicion. Primary cutaneous aspergillosis has been documented in 12 cases from a single tertiary care center in northern India. Burn wounds are the most common sites of such disease in that center[52-54]. Definite *Aspergillus* fungemia has been documented in a single case from Delhi[55]. The most interesting aspect of the disease in India is the overwhelming causative role of *A. flavus*[20-22]. Unlike the western world and temperate countries, where *A. fumigatus* is the foremost pathogen, *A. flavus* is the common etiological agent in India. Preponderance of *A. flavus* isolates is even more skewed in paranasal sinus disease. A cluster of cases with *Aspergillus* endogenous endophthalmitis without any underlying illness was reported from a center in northern India. The patients were from villages in the state of Haryana; they had a history of 5% dextrose infusion

by village quacks for some trivial illness. While investigating the outbreak, the same *Aspergillus* species was isolated from 5% dextrose bottles procured from chemists of the same rural area. This study had tremendous impact on health practices in rural India[56].

Cryptococcosis: Cryptococcosis is encountered frequently throughout the country. The first case was reported by Reeves *et al.*, 1941 from Calcutta in a patient with interlobar empyema and draining chest sinuses[57-59]. This was followed by a handful of reports (eight cases) in the late 1940s and 1950s[58]. Due to increased awareness and probably the increased use of immunosuppressive agents, the disease has been reported with increasing frequency since the 1960s[58]. Incidence was high in places like Calcutta, Mangalore and Delhi. Disease frequency increased drastically in the 1980s and 1990s with the emergence of the AIDS epidemic[58]. Though global incidence of cryptococcosis has decreased with introduction of antiretroviral therapy, incidence is still on the rise in India[59, 60]. It may be due to the increasing number of AIDS cases reporting to the hospital and incomplete coverage of antiretroviral therapy. From systematic data from a center in northern India, the incidence of cryptococcosis was 0.8 cases per year during 1970 through 1982[61]. A 15 fold rise with incidence of 11.6 cases/year was recognized between 1995 and 1999[62]. A further three fold rise (34 cases/year) has been documented between 2000 and 2007 (unpublished observation). Thus, a 42-fold rise in the incidence of cryptococcosis has been witnessed since 1970[61, 62]. Carefully conducted studies have estimated that the incidence of cryptococcosis in AIDS patients varies from 4% to 26% but is as low as 2.97% in HIV-infected children[63-65]. Figures from such studies are comparable to data from other Southeast Asian countries. Mortality rate due to cryptococcosis varies from 18.3% to 40% in different centers[59-62]. Interestingly, increased MIC against fluconazole has also been observed among *Cryptococcus neoformans* strains isolated in recent years[66].

Cryptococcus grubii (serotype A) is the most prevalent (>90%) of the Cryptococci isolated in India. *Cryptococcus gattii*, serotype B strains have occasionally been reported. Serotype AD strain has also been isolated from northern India[58]. In an interesting case report, serotype A and serotype B strain was isolated simultaneously from the same patient in New Delhi[58]. Other species of *Cryptococcus* are rarely isolated. Three cases due to *C. laurentii* and one due to *C. albidus* were recorded from Chandigarh and Madras, respectively[58].

Pulmonary disease exclusively due to *Cryptococcus neoformans* has seldom been documented in India. However, asymptomatic and symptomatic colonization of airways has been described. Association with pulmonary tuberculosis was an interesting observation in an earlier study from New Delhi. Involvement of sites other than central nervous system and lung is occasionally reported and that included primary involvement of skin, osteolytic lesions in bones, hepatic and peritoneal involvement in chronic liver disease patients and generalized lymphadenopathy. A few cases of ocular infections due to *Cryptococcus neoformans* are reported. Ocular involvement has been specially noted in immunocompetent individuals. Other uncommon presentations reported from India include cryptococcal granulomas in the brain, cryptococcal retinal cyst, cryptococcoma in the left ventricle without any CNS involvement, cryptococcal prosthetic valve endocarditis, ventriculoperitoneal shunt (VP) shunt infection, and infection of the genitourinary system[58].

Among the underlying diseases leading to cryptococcosis, AIDS is most common[58]. The proportion of HIV positive patients among those with cryptococcosis increased from 9.3% in 1983-94 to 57.4% in 1995-99 in a hospital in northern India[62]. Renal transplant recipients, hematologic malignancies including acute lymphocytic leukemia, systemic steroid therapy, diabetes mellitus, systemic lupus erythematosus and pulmonary tuberculosis are the other predisposing diseases for the development of cryptococcosis[58, 62].

In India, *Cryptococcus neoformans* var. *neoformans* has been isolated from droppings of pigeons, munia birds and canaries, as well as from soil contaminated with pigeon excreta. Vegetables and fruits have also been shown to harbor *Cryptococcus neoformans* var. *neoformans*. *Cryptococcus gattii* has been isolated from *Eucalyptus camaldulensis* trees in the flowering season from northern India. Recently both varieties have been isolated from *Ficus religiosa*, *Syzigium cumini* and *Tamarind indica* trees of Delhi. Antifungal resistance among environmentally isolated strains however, seems to be rare, but serotype B has higher MICs to polyenes than serotype A[58, 67].

Zygomycosis: Balasubramanyam *et al.* for the first time reported zygomycosis from India in 1963[4]. Despite the lack of diagnostic mycology facilities, India contributes about 40% of the global burden of the disease. More than 300 such cases have been reported from a single tertiary care center in northern India[6]. Alarmingly, incidence of this disease in that center increased rapidly from 12.9 cases/year during 1991 through 2000 to 35.6 cases per year during 2001 through 2005[6, 8]. Nevertheless, the disease is also reported frequently from other parts of the country[5].

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However, a large number of cases are identified at autopsy, as the disease is difficult to diagnose ante-mortem unless a high index of clinical suspicion is maintained. Another interesting development in this country is recognition of renal zygomycosis as a separate clinical form. Renal involvement occurs in 22% cases with disseminated zygomycosis especially in patients with intravenous drug abuse or corticosteroid therapy, but isolated renal disease has rarely been documented. In contrast, isolated renal zygomycosis is a common occurrence in India; nearly 50 cases were reported over the last 2 decades from a single center in northern India. These patients usually present with fever, flank pain, hematuria, pyuria or anuria with infarction of the kidney unilaterally or bilaterally but without any predisposing factor[11, 12]. Cerebral zygomycosis is also reported frequently from a tertiary care center in South India. Surprisingly, cerebral disease due to zygomycosis has also been detected in the immunocompetent host[9, 10].

Risk factors associated with the disease in Indian patients include uncontrolled diabetes mellitus, diabetic ketoacidosis, hematological malignancy, systemic steroid therapy, burn wounds, organ transplant recipients, HIV, trauma, intramuscular injection, intravenous drug abuse, endotracheal intubation, malnourishment, premature newborn and alcoholism[4 – 12]. Majority of the patients are immunocompromised and only 12% cases are immunocompetent[8]. Also, a preponderance of the disease in males has been noticed. In the western literature, different clinical forms are often associated with particular underlying conditions e.g.; rhino-orbito－cerebral（ROC）type in individuals with diabetic ketoacidosis; pulmonary disseminated infection in patients with hematological malignancies and bone marrow transplantation; gastrointestinal zygomycosis in patients with malnutrition; central nervous system infection in intravenous drug abusers; and cutaneous lesions following trauma/burns. The rise in the number of patients with zygomycosis in developed countries has been particularly evident in hematopoietic stem cell transplant recipients and patients with hematological malignancies. However, in India overwhelming association of uncontrolled diabetes was seen in all forms of zygomycosis[5, 6, 8]. The disease has also been described without any underlying conditions[5, 6, 8]. Among the species of zygomycotic agents causing human disease, *Rhizopus arrhizus* is the most frequent agent followed by *Rhizopus microsporus*, *Absidia corymbifera*, *Rhizomucor pusillus* and *Mucor circinelloides*. These 5 agents account for 80% of culture proven cases of zygomycosis[5, 6, 8]. Interestingly, *Apophysomyces elegans* is an emerging zygomycotic agent in India. Besides cutaneous or subcutaneous zygomycosis, this agent has also been isolated from Indian patients with rhino-orbito-cerebral and renal zygomycosis[5, 6, 8].

Pneumocystis jiroveci **Pneumonia**（**PCP**）: PCP was for the first time reported in India by Desai *et al.*, 1971 in a 2.5 year old child from Ahmedabad. Lung biopsy showed interstitial plasma cell pneumonia with PAS positive cysts of the fungus[68]. Thereafter cases were reported from renal transplant recepients[69]. PCP pneumonia in AIDS patients was first reported in 1987. Simultaneous reports from northern[70] and souther India[71] in 1995 showed that the incidence of PCP pneumonia in AIDS patients varies between 10-15%. Other reports since then have confirmed similar rates. However, lower rate（1.1%）in AIDS patients has been reported from Manipur[72]. Thus, unlike high rate during the pre HAART and pre-prophylaxis era in the western world, Indian cases are less frequent. A few reasons for this lower incidence have been proposed. These include earlier death of Indian AIDS patients due to tuberculosis before severe immunosuppression sets in, tropical climate, differing virulence of strains, prevalence of different genotypes in different regions, and most importantly lack of awareness and diagnostic expertise[70]. Without laboratory confirmation, provisional diagnosis based on clinical features and radiology has been reported frequently[73]. In a recent study enhanced detection rate from 3.4% to 12% in AIDS patients was reported by use of PCR technology[74]. Recently large numbers of cases have been reported from two centers in southern and western regions of the country[75, 76].

Phaeohyphomycosis: Subcutaneous and systemic（especially cerebral and pulmonary）phaeohyphomycosis in immunocompromised hosts with high mortality are reported from different centers in India. However, the disease in immunocompetent individuals is also reported. Phaeohyphomycosis consists of a group of mycotic infections characterized by the presence of dematiaceous（dark-walled）septate hyphae and sometimes yeast or a combination of both in tissue. Sporadic cases of phaeohyphomycosis have been reported across India. Agents associated with case reports from India include *Cladophialophora bantiana*, *Bipolaris hawaiiensis*, *Exserohilum rostratum*, *Phialophora richardsiae*, *Phialophora dermatitidis*, *Phialophora verrucosa*, *Cladosporium cladosporioides*, *Exophiala spinifera* and *Fonsecea pedrosoi* [77, 78].

Conclusion:

Opportunistic fungal infections are important chal-

lenges in the progress of modern medicine. Early diagnosis and prompt therapy are the important tools for effective management against those opportunistic fungal infections. Lack of clinical awareness and few diagnostic mycology facilities in India are major drawbacks against this threat of opportunistic fungal diseases. Still, the limited data of devastating fungal infections in tertiary care hospitals has drawn the attention of clinicians and medical mycologists towards this field. Regular training courses at the national reference laboratory at Chandigarh, frequent continuing medical education programme and conferences in this field are playing significant role in improvement of facilities in India.

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