Epidemiology of Opportunist Fungal Infections in Asia

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Key Points

- Multidrug resistant *Candida auris* infection is an emerging threat in tertiary care hospitals in Asia.
- The infection has been reported from Japan, South Korea, Singapore, China, India, Pakistan, Kuwait, and Qatar.
- The burden of opportunist fungal infections is much higher in Asian countries compared to developed countries due climatic condition, over-capacity patient population in hospital, compromise in healthcare, misuse/abuse of antibiotic and steroids.
- Limited studies show distinct epidemiology of opportunist mycoses in this continent, which warrant to have more studies in each country to know local epidemiology.
- New species and new susceptible hosts for opportunist fungal infections demand awareness campaign among clinicians and development of competent diagnostic mycology laboratories in Asian countries.
- The incidence of chronic pulmonary aspergillosis and mucormycosis is very high in those countries.
- Availability and affordability of antifungal drugs are major challenges in management of opportunist fungal infections.

4.1 Introduction

Systemic fungal infections are caused by pathogenic fungi, which can adapt human body. Pathogenic fungi are few. Majority of the fungi remain as saprobes and do not cause human infections as they fail to grow at 37 °C and resist low redox potential

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in tissue. However, some of those saprobes can cause infections when the host is compromised either in immunity or due to co-morbidities. Those organisms are called opportunist that utilizes the opportunity offered by weakened defense of host to inflict damage. However, this distinction of pathogens and opportunists is getting blurred with the adaptation of more fungi on host and acquisition of virulence. Further, the global warming allows number of saprobe fungi to overcome the temperature restriction zone between host and environment. Simultaneously the understanding of host immunity clarifies that fungi may not necessarily require overt immunosuppression of host to cause invasive disease; specific defect in signal transduction pathway (like CARD 9, STAT 1) may make the host susceptible for fungal infections [1]. Underlying illness or risk factors for opportunistic fungal infections include human immunodeficiency virus (HIV) infection, hematological malignancies undergoing chemotherapy, hematopoietic stem cells and solid organ transplant recipients, burns, prematurity, and patients having indwelling devices. However, the spectrum of susceptible hosts has increased in recent years. Opportunistic fungal infections have been recorded in patients with post-influenza episode, chronic liver failure, diabetes, and obstructive pulmonary disease and staying in intensive care units (ICUs) [2].

Among opportunistic fungal infections invasive candidiasis is commonest disease, followed by aspergillosis and mucormycosis. Cryptococcosis, histoplasmosis, and talaromycosis are important in patients with HIV/AIDS. With the change of epidemiology many new fungi are gaining importance to cause infections in compromised hosts and those include *Fusarium, Scedosporium,* dematiaceous fungi, and many rare fungi. We are facing the following challenges due to emergence of rare fungi causing human infections [3, 4]:

- Epidemiology of those infections is not well understood with regard to environmental reservoirs, modes of transmission, and ways to detect them.
- Because of their relative rarity, laboratory diagnosis of these potential pathogens is challenging.
- Specific identification requires expertise.
- In vitro Antifungal susceptibility testing is difficult to perform without standard methodology, and antifungal breakpoints are not available. It is therefore difficult to choose appropriate antifungal therapy.
- Quality-assured diagnosis requires reference laboratories.
- Reference laboratory facilities are not available in all regions and countries.

The epidemiology and disease burden of opportunistic fungal infections are well studied and estimated in Western world, but the picture in Asian countries is largely unknown due to lack of study, awareness, and adequate diagnostic laboratory facilities. The available limited data indicate high incidence and unique epidemiology of opportunistic mycoses in this region due to large population at risk, broad spectrum of fungal agents, and distinct clinical entities [5, 6]. Separate chapters in the book deal with systemic and opportunist fungal disease under different risk groups. This chapter summarizes the present status of opportunist fungal infections in Asia among patients in general (Table 4.1).

Table 4.1 Opportunistic fungal infections in Asian countries

Disease	Incidence/Prevalence	Autopsy data	Epidemiology in Asia	Spectrum of agents
Candidiasis	• 1–12/1000 admission	• 0.6% of all cases • 22% of invasive fungal infections (IFIs)	• High incidence in patients admitted in ICUs. • Outbreaks due to rare yeasts and Candida auris • High hand carriage among healthcare providers (45–80%) • Intra-abdominal candidiasis especially *Candida* pancreatitis is an emerging problem • Young patients with less morbidity acquire the infection early while admitted in ICU	• 70–90% non-*albicans Candida* spp. • *C. tropicalis* commonest (35–40%) followed by C. parapsilosis and C. albicans. • Outbreak due to *Kodamaea ohmeri, Pichia anomala, C. auris.*
Aspergillosis	• No systematic data available	• 1% of all cases • 42% of IFIs	• 6–14% cases in immunocompetent hosts • Endophthalmitis, invasive fungal rhinosinusitis, and central nervous system aspergillosis are common in immunocompetent hosts • Outbreaks of endophthalmitis reported due to presumably contaminated infusion • Chronic aspergillosis in post-tuberculosis patients.	• *A. fumigatus* is common species in lung infection • *A. flavus* common in tropical climate in rhinosinusitis and endophthalmitis • *A. terreus* (amphotericin B resistant) is emerging in ICU.

(continued)

Table 4.1 (continued)

Disease	Incidence/Prevalence	Autopsy data	Epidemiology in Asia	Spectrum of agents
Mucormycosis	• 1.6/1000 diabetics • 0.14/1000 population (very high incidence)	• 0.6% of all cases • 23% of IFIs.	• High incidence is associated with uncontrolled diabetes (diabetes with high number in adults of India, China, Japan) • Renal failure, a new risk factor • Isolated renal mucormycosis in apparently healthy individual, a new clinical entity in India and China. • Cutaneous mucormycosis due *to Mucor irregularis* among farmers in South-East China and India—a new clinical entity.	• *Rhizopus oryzae* commonest. *Apophysomyces variabilis* next common species in India. • Comparatively antifungal resistant *R. microsporus* emerging • *Rhizopus homothallicus,* a new pathogenic agent. • Susceptibility variation among isolates under same species.
Cryptococcosis	• 1–9% of AIDS patients (very high incidence in Chiang Mai, Thailand and Ho Chi Minh city in Vietnam)	• 0.1% of all cases • 5% of IFIs	• Second most common AIDS defining illness in Chiang Mai, Thailand and fifth most common in Ho Chi Minh City of Vietnam. • The incidence has reduced after introduction of HAART therapy, but reduction is not substantial. • Incidence in immunocompetent host rising	• *C. neoformans* var. grubii commonest • *C. gattii* predominantly in immunocompetent host, reported from India, Malaysia, Hong Kong, China. • *C gattii* infection—more serious with high intracranial pressure. • *C. gattii*—hetero-resistance to fluconazole
Scedosporiosis and fusariosis	• Rarely reported	• No data available	• Post-tsunami *S. apiospermum* infection reported. • Post-transplantation fusariosis recorded in China and India. • Low incidence of both diseases may be due to lack of awareness and difficulty in diagnosis.	• *S. prolificans* (resistant to almost all antifungal agents—Voriconazole and terbinafine combination may be used) • The reports of these infections are increasing.

Disease	Incidence/Prevalence	Autopsy data	Epidemiology in Asia	Spectrum of agents
Pneumocystosis	• 5–69% of patients with AIDS. • 6.5% in NHL undergoing chemotherapy. • <1% of renal transplant recipients after chemoprophylaxis (6–12 months post transplant)	• 0.03% of all cases • 1% of IFIs.	• The incidence is low compared to western world—reason may be difficulty in diagnosis. • New risk groups emerged—pediatric population at risk.	• *Pneumocystis jiroveci*
Pythiosis	• No data	• No data	• Large number of cases reported from Thailand • Keratitis cases are reported from India in recent years • Localized keratitis, cutaneous, disseminated, and vascular form reported. • Vascular form commonly occurs in extremities of patients with underlying hemoglobinopathies	• *Pythium insidiosum*

4.1.1 Incidence/Prevalence

The global estimates indicate >700,000 cases of invasive candidiasis, >200,000 cases of invasive aspergillosis, >220,000 cases of cryptococcosis in HIV/AIDS, ~500,000 cases of *Pneumocystis jiroveci* pneumonia, ~100,000 cases of disseminated histoplasmosis occurring annually [6]. Though such estimates are not available in Asian countries, invasive candidiasis and mucormycosis rate appear very high in this region [7–9] and it relates to large patient load, compromise in healthcare, unabated construction activities in the hospital without covering the site from patient area, and largely tropical environment that helps fungi to thrive [7, 10–12].

A comparison of incidence of candidemia shows 1 to 12 cases/1000 admission in India [7] compared to 0.05 to 0.36/1000 admission, 0.8/1000 discharges, and 0.2–0.5/1000 discharges in Australia [13], United States [14], and European countries [15, 16], respectively; this means that the rate of candidemia in India is 20–30 times higher as compared to the developed world. In a cross-sectional study at 25 tertiary care centers of six Asian countries, the overall incidence of candidemia was 1.22 episodes per 1000 discharges and varied among the hospitals (range 0.16–4.53 per 1000 discharges) and countries (range 0.25–2.93 per 1000 discharges) [17]. Neonatal candidemia rate was ~46 cases/1000 admission in a tertiary care center in North India, which is nearly three times higher than the incidence reported by National Nosocomial Infection Surveillance in the USA. Multi-center prospective study on ICU acquired candidemia covering 27 ICUs across India, reported 6.5 candidemia cases/1000 ICU admission [8].

Similarly, a very high incidence of mucormycosis has been reported in diabetics (1.6 cases/1000 diabetics) from India [18]. Rhinocerebral mucormycosis is most common presentation. In one center, gastrointestinal mucormycosis has been reported at a rate of 20% of all operated cases of enterocolitis in neonates [19]. All cases autopsy data reported mucormycosis at the rate of 0.6% (23% of all invasive fungal infections) in India (personal communication with Dr. Ashim Das, Professor of Pathology at our Center) which is six times higher than national registry from Japan [20]. Analyzing the reported literature and development of a computational model, the prevalence rate of mucormycosis was estimated at 0.14 cases per 1000 population in India, which is 70 times higher than the incidence of western world [21].

However, such projected data is not possible for invasive aspergillosis as reported case series are limited. A recent multi-center ICU data from India reported 9.5 cases of invasive mold infection per 1000 ICU admission and majority are due to invasive aspergillosis [22]. All cases autopsy data from our center reflects invasive aspergillosis at a rate of 1% (42% of all invasive mycosis). Though majority cases of invasive aspergillosis are known to occur in immunosuppressed patients, 6–14% of Indian patients are apparently immunocompetent especially with clinical presentation of central nervous system aspergillosis, endophthalmitis, and invasive fungal rhinosinusitis [23]. Post-tuberculosis chronic pulmonary aspergillosis (CPA) is a common disease in Asian countries and significantly higher than other continents. Among Asian countries, the highest burden of CPA is from India (209,147) followed by Pakistan (72,438), Philippines (77,172), and Vietnam (55,509) [6].

Before AIDS era, the prevalence of cryptococcosis was nearly equal in immunocompetent and immunosuppressed patients. The balance shifted to immunosuppressed patients with the advent of AIDS. Cryptococcosis is the second most common AIDS defining illness in Chiang Mai Province of Thailand and has been reported at a rate of 1–2% of HIV infected population. Despite the availability of generic fluconazole and highly active antiretroviral therapy, the incidence of cryptococcosis has not decreased substantially in Asian AIDS population. The reason may be poor affordability and compliance to therapy [5].

Pneumocystis pneumonia is a well-known disease in patients with AIDS. Though HIV infection is a major public health problem in Asian Countries, the reported incidence of pneumocystis pneumonia is not as high as developed countries. This low to moderate incidence may be due to difficulty to diagnose this infection rather than actual low prevalence of the organism in this geographical region [24]. A rise in talaromycosis and histoplasmosis cases was recorded during HIV epidemic in restricted geographic regions of Asia. However, the incidence is going down with the introduction of antiretroviral therapy [25].

Many emerging fungi caused outbreaks in Asian countries. Several unusual yeast species (*Pichia anomala*, *P. fabianii,* and *Kodamaea ohmeri*) were isolated in outbreaks in India affecting large number of patients [26, 27]. *C. africana*, a cryptic species of *C. albicans*, has recently been reported to cause infection in China [28]. Trichosporonosis due to multidrug resistant *Trichosporon asahii* is frequently encountered in China, India, Japan, Taiwan, and Thailand [29, 30]. Other uncommon yeasts reported from Asia include *Geotrichum, Malassezia, Rhodotorula,* and *Saccharomyces* species [30, 31]. The emergence of multidrug resistant *C. auris* is the latest threat in Asia. It started from Japan in 2009, spread to South Korea, then India and Pakistan. The infection is also reported from China and Singapore [32, 33]. The magnitude of the infection can only be accessed from the study conducted in India covering 27 ICUs. *C. auris* accounted for 5.3% of 1400 *Candida* blood isolates [8]. *Saccharomyces* fungemia related to use of probiotics has raised concern in critically ill patients of India [34]. Among the black fungi, *Cladophialophora bantiana* is an emerging fungus in Asia and causes brain abscess even in immunocompetent patients. More than 50% cases reported from the world are from Asia, especially India [35].

4.1.2 Risk Factors/Underlying Illness

Considerable variations of underlying disease/risk factors have been observed in opportunistic mycoses from Asian countries. In the hospitals, outbreaks have been reported due to sub-optimal hospital care practices and contaminated environment [26, 36], whereas outbreaks in the community is related to spurious practices by untrained healthcare providers [37]. Easy availability of antibiotics and steroids over the counters, intravenous drug abuse, and contaminated infusion bottles contribute further in the rise of these infections [7]. Other than classical risk factors like hematological malignancies, transplant recipients, and immunosuppressive therapy,

opportunistic fungal infections are also recorded in critically ill patients with tuberculosis, chronic liver failure, diabetes, chronic obstructive pulmonary diseases, and renal failure. Invasive aspergillosis is also recorded in patients with H1N1 influenza infections [38]. Nearly 10–14% of the patients with opportunistic fungal infections have no predisposing factor. The risk factors for opportunistic fungal infections are tabulated in Tables 4.2 and 4.3. During the suppression of cell-mediated immunity (HIV infection) cryptococcosis, histoplasmosis, pneumocystis pneumonia, and mucosal candidiasis are prevalent, while in neutropenic patients (hematological

Table 4.2 Fungi causing opportunistic fungal infections in different risk groups

Risk groups	Fungi and diseases	Comments
HIV infected patients	• Oropharyngeal candidiasis (up to 75%) • Esophageal candidiasis (10–15%) • Cryptococcosis • PCP pneumonia • Talaromycosis • Histoplasmosis	• Cryptococcosis—second most common AIDS defining illness in Chiang Mai Province, Thailand. • Talaromycosis—third most common AIDS defining illness in the same area. • Histoplasmosis incidence increased in India with the advent of AIDS. • PCP pneumonia incidence seems to be lower in Asian countries (may be due to lack of diagnosis)
Transplant patients • H*SCT (3–20% IFIs)*	• Invasive candidiasis (30–70%) • Aspergillosis (20–45%) • Mucormycosis (8%)	• Fusariosis and scedosporiosis are emerging in developed countries, no large series reported from Asian countries • The incidence of invasive aspergillosis is rising
• *Kidney (0–20%)*	• Invasive candidiasis (50%), cryptococcosis (10–20%) • Aspergillosis (10–15%) • Mucormycosis (2%) • Hyalohyphomycosis, phaeohyphomycosis (rare to 3%)	• The incidence of cryptococcosis was higher before tacrolimus use (cyclosporine was used) • PCP pneumonia after 1 year post-transplant when prophylaxis stopped • Rare dematiaceous fungal infections reported
• *Liver (5–40%)*	• Candidiasis (70%) • Aspergillosis (10%) • Mucormycosis (2%) • Other fungal infections rarely	• Invasive fungal infections common when MELD score > 30 • Complexity of surgery and duration • Intra-operative transfusion • Renal and hepatic failure
• *Lung (8–35%)*	• Aspergillosis (40–60%) • Candidiasis (20–25%) • Mucormycosis (3%) • Other fungal infections rarely.	• Rate of lung transplantion is rising in Asian countries, but data on invasive fungal infections is still limited.

Table 4.2 (continued)

Risk groups	Fungi and diseases	Comments
• *Heart (5–20%)*	• Candidiasis (50–60%) • Aspergillosis (25%) • Mucormycosis (3%) • Other fungal infections rarely.	• Rate of Heart transplantation is rising in Asian countries, but data on ivasive fungal infectios is still limited.
• *Small bowel (12–60%)*	• Candidiasis (80%) • Aspergillosis (2%) • Other fungal infections rarely.	• Small bowel transplantation is rare in Asia.
• *Pancreas (3–35%)*	• Candidiasis (75%) • Aspergillosis (10–15%) • Other fungal infections rarely.	• Pancreas transplantation is rare in Asia
Hematological malignancy undergoing chemotherapy (5–30%)	• Aspergillosis (45–55%) • Candidiasis (25–50%) • Mucormycosis (9–10%) • Cryptococcosis (5%) • Trichosporonosis (5%) • Other fungal infections are rare.	• AML patients have highest rate of IFIs followed by ALL and CML.
Chronic granulomatous disease (20–40%)	• Aspergillosis (40%) • Candidiasis (10–15%) • Other fungal infection rarely	
Exogenous steroid therapy	• Aspergillosis • Candidiasis • Mucormycosis • Other fungal infections are rare	
Diabetes	• Candidiasis (most common) • Mucormycosis (1.6/1000 diabetics)	• Very high incidence in India and China
Anti-TNF therapy	• Histoplasmosis (30%) • Aspergillosis (24%) • Candidiasis (23%) • Cryptococcosis (10%) • Mucormycosis (1.5%)	• Figures are from western world • No data from Asian countries.

malignancies under chemotherapy, transplant recipients) invasive candidiasis, aspergillosis, and mucormycosis are common diseases. Invasive candidiasis and aspergillosis may be seen occasionally in patients with AIDS when CD4 count goes <50 cells/cm and neutropenia develops [2, 5].

4.1.2.1 Spectrum of Agents

The spectrum of fungal agents causing opportunistic fungal infections has widened in Asia over the years. Many new agents have been reported only from this continent. The spectrum varies from other continents and even between the countries in

Table 4.3 Opportunistic fungal infections associated with different risk factors

Disease	Underlying disease	Healthcare-related facts
Candidiasis	Prematurity, neutropenia due to any disease, burn (>50%), APACHE SEORE II >20, diabetes, renal failure, extremes of age, pancreatitis	Colonization at multiple sites, antibiotics, major abdominal injury, total parenteral nutrition, hemodialysis, central venous catheters, multiple transfusion, immunosuppressive therapy, ICU stay.
Aspergillosis	Acquired/primary neutrophil defect, neoplastic diseases with persistent neutropenia, transplant recipients, chronic granulomatous diseases, Job's syndrome, aplastic anemia/ myelodysplastic syndrome/ myelofibrosis, rheumatoid arthritis **Non-neutropenic causes** Chronic obstructive pulmonary disease, chronic and acute liver disease, post-influenza, alcoholism, sepsis, diabetes, burns.	High dose of steroid, immunosuppressive therapy, surgery, ICU stay, building construction.
Mucormycosis	Uncontrolled diabetes with or without ketoacidosis, hematological malignancies under chemotherapy, transplant recipients, prematurity, protein-calorie malnutrition, renal failure, trauma	Deferoxamine therapy, intravenous drug abusers, intramuscular injection, adhesive tapes, tongue depressor, building construction, natural disasters steroid, voriconazole/echinocandins therapy.
Cryptococcosis	HIV infection, transplant recipients, hematological malignancies Immunocompetent host may also acquire the disease	Anti-TNF factor use.
Pneumocystosis	HIV infection, renal transplant recipients, non-Hodgkin lymphoma, premature neonates	
Scedosporiosis and fusariosis	Transplant recipients, hematological malignancy, trauma, burn.	Surgery

Asia. Among *Candida* species causing invasive candidiasis, the prevalence of infections caused by *C. albicans* drastically has come down in certain countries like India, though it is still >40% in 13 of 25 tertiary care centers studied in six countries in Asia [17]. *C. tropicalis* is commonest species in India, Malaysia, Singapore, Thailand, and the countries situated in tropical region. In ICU study in India, 31 yeast species were found to cause fungemia [8]. Besides, multidrug resistant *C. auris* is an emerging species in many Asian countries. The major challenge is that those rare Candida species can not be identified by phenotypic methods commonly practiced in laboratories in Asian countries [32]. Contrary to *A. fumigatus, A. flavus* is the commoner agent causing infection in some of the Asian countries [23]. Though *Aspergillus* spp. are the common mycelial fungi causing infection in critically ill patients, in a recent multi-center study mucormycosis has been recorded in

24% of invasive mold infections [22]. Among *Mucorales, R. arrhizus* is the commonest species isolated. *Apophysomyces variabilis, R. microsporus, R. homothallicus, and Rhizomucor variabilis* are the emerging agents in Asian countries [22, 38–40]. The details of the fungal species prevalent in Asian countries are provided in Table 4.1. Like other countries, antifungal resistance to *Candida* spp. is evolving. Even azole resistance has been noted in so-called susceptible *C. albicans* and *C. tropicalis* [8]. However, azole resistance in *A. fumigatus* is still not a major problem in Asian countries [41].

4.2 Conclusions

Opportunistic fungal infections are serious problem in the management of immunocompromised and seriously ill patients in Asian countries. While managing a patient with systemic infection, a low threshold to include opportunistic fungal infections in differential diagnosis is desirable due to its high incidence in those countries. Study on local epidemiology is essential, as the risk factors and spectrum of agents vary in those countries. The available literature shows several unique features in epidemiology of opportunistic mycoses in Asian countries: a) high incidence, b) high yeast carriage rate in the hands of healthcare providers, c) high fungal spore burden in the air in the vicinity of susceptible patients, d) emergence of new risk factors, e) systemic fungal infections even in apparently healthy hosts, f) unique spectrum of etiological agents and resistance pattern. The epidemiology also indicates the need of adequate understanding of disease, source limitation, and early diagnosis to control opportunistic fungal infections in Asian countries.

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