CHAPTER

18

Invasive Fungal Infections

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The four most important fungi producing invasive fungal infections (candida, cryptococcus, aspergillus and mucor) are commonly considered together. However, in reality, their clinical syndromes as well as the approach to their diagnosis and management are distinct from one another. Yet, certain management principles, that are different from those applicable to bacterial infections, remain common to them.[1]

1. Fungi generally produce disease only when the immune system of the host is compromised or mucosal or integumental barriers are disrupted. The immune system also plays an important role in expression, progression and recovery of the disease.
2. Fungal culture lacks sensitivity in some cases and specificity in others. Hence, diagnosis and its level of certainty, is often based on a combination of host factors, the particular clinical syndrome, radiological findings, non-culture based tests, histopathology and culture.
3. Fungi are eukaryotic organisms. Unlike bacteria, they possess fewer unique metabolic pathways, distinct from their mammalian hosts that may be selectively inhibited by drugs. As a result, the anti-fungal agents have in general, lesser efficacy and greater toxicity.
4. The use of antifungal combinations with different mechanisms of action, have an established place in certain invasive fungal infections (IFIs).
5. Fungi have the property of forming biofilms on various implanted medical devices which has important implications for treatment.
6. The use of adjunctive treatment in the overall management is important.
7. The duration of treatment is relatively prolonged as compared to most bacterial infections.
8. Transition to oral agents which are less toxic and expensive is attempted whenever possible.
9. Prophylactic, preemptive and empirical strategies have been proposed for IFIs as these have predictable occurrence, diagnostic difficulties and serious consequences associated with delayed treatment.

The risk factors and clinical syndromes of IFIs are given in Table 1. The diagnosis and management of IFIs is given in Table 2.

MANAGEMENT CHALLENGES IN THE INDIAN SETTING

Candidiasis

A vast spectrum of agents, (31 species) of candida has been reported from different parts of the country. The incidence of candidemia in India is 1-12 cases/1000 admissions. This is 20-30 times higher as compared to the developed world and may be attributed to sub-optimal hospital care practices, heavy patient load and high cost of disposables leading to suboptimal infection control practices.[9]

A study on ICU acquired candidemia in India found that candidemia was acquired significantly earlier after ICU admission, in patients who were considerably younger, predominantly non neutropenic and with lower APACHE scores than in other studies. Prior exposure to broad-spectrum antibiotics and use of steroids in a large number of patients were thought to be responsible for this.[10]

In contrast to data from the developed world, the commonest species of candida in our country is C. tropicalis. Features unique to this species are its predisposition to septic shock and skin emboli and its shorter time to positivity of blood cultures. A study has shown that 82% of health care worker's hands were colonised with yeast, of which 80% were C. tropicalis. The emergence of MDR C. auris in India is a matter of concern, as this fungus was isolated from 19 of 27 ICUs.[9, 10]

The lower rate of blood culture positivity in candidemia (21%) as compared to 50% elsewhere, remains a diagnostic hurdle, leading to delay in initiation of treatment and poor outcomes. Prediction models and scores are complex and require local validation. Non culture based rapid diagnostic methods such as β-D-glucan, antigen assays and PCR assays have been introduced in the country.[9]

Cryptococcosis

With the advent of HAART, the incidence of cryptococcosis has reduced considerably in the developed world. However, Indian studies show a 42-fold increase in the incidence over the past 40 years. Cryptococcus is responsible for 4% of meningitis in the HIV infected population in Eastern India. It typically presents as a sub-acute to chronic meningitis with lymphocyte predominance in CSF. If specific tests like India Ink staining and CRAG levels are not done, these cases are

Table 1: Risk Factors & Clinical Syndrome of IFIs[2,3,4,5,6,7,8]

IFI	Predisposing Conditions	Clinical Syndrome
Candidiasis	1. Critically ill- ICU stay 2. Central venous catheter 3. Broad spectrum antibiotics 4. Total parenteral nutrition 5. Hemodialysis 6. Pancreatitis 7. GI perforation, surgery 8. Steroids 9. Immunocompromised host	1. Candidemia- sepsis, septic shock 2. Acute disseminated candidiasis-cutaneous manifestations 3. Endovascular infection – infective endocarditis, infection of implantable cardiac devices 4. Osteomyelitis, arthritis 5. Endophthalmitis 6. Chronic disseminated candidiasis (hepatosplenic candidiasis)
Cryptococcosis	1. HIV 2. Transplant recipients 3. Idiopathic CD4 lymphocytopenia Emerging Risk Factors: DM, ESRD, CLD, TB, SLE, malignancy, steroid use	1. Chronic meningitis, cerebral cryptococcoma 2. Pulmonary nodules, infiltrates, cavities, mediastinal adenopathy 3. Other commonly involved sites: skin, eye, prostate
Aspergillosis	1. Prolonged/profound neutropenia 2. Prolonged steroids, T-cell immunosuppressants 3. Hematopoietic & solid organ transplant recipients 4. Primary immunodeficiency states: CGD Emerging Risk Factors: COPD, liver cirrhosis critically ill, mechanical ventilation	1. Pulmonary aspergillosis 2. Acute rhinosinusitis 3. Tracheobronchitis in lung transplant recipients, AIDS 4. Cerebral aspergillosis 5. Osteomyelitis 6. Cutaneous aspergillosis 7. Disseminated aspergillosis
Mucormycosis	Clinical Syndromes associated with specific risk factors 1. Poorly controlled DM (type1 and type 2), DKA : rhinocerebral, sino-orbital, cutaneous 2. Hematological malignancy, HSCT, SOT recipient,: pulmonary, sino-orbital, cutaneous, disseminated, rhinocerebral 3. Penetrating trauma, burns: cutaneous, ocular 4. Chelation therapy with deferoxamine: disseminated, rhinocerebral, pulmonary, gastrointestinal, cutaneous 5. IV drug user: cerebral, endocarditis, cutaneous, disseminated 6. Malnutrition, premature infants: gastrointestinal, disseminated 7. Nosocomial acquisition/pseudo-outbreaks- linked to contaminated dressing, splints for IV cannulation etc.: cutaneous 8. Unknown etiology: isolated renal mucormycosis	

*DM: diabetes mellitus, ESRD: end- stage renal disease, CLD: chronic liver disease, SLE: systemic lupus erythematosus, CGD: chronic granulomatous disease, COPD: chronic obstructive pulmonary disease, DKA: diabetic ketoacidosis, HSCT: hematopoietic stem cell transplant, SOT: solid organ transplant

often treated with empiric AKT leading to inordinate delays in diagnosis of this life threatening condition. Latex agglutination –based antigen tests have a good sensitivity but are still not widely available in India due to high cost, need for expertise, and maintenance of cold chain. Recently introduced lateral flow assay for CRAG is easy to perform, economical and has reagents which are stable at room temperature. This has major indications for preemptive management of cryptococcal meningitis in patients with advance HIV infection in resource-poor environments.

Studies from India have identified that C. neoformans var grubii and C. gattii prevail all through the year in the environment with the highest prevalence in autumn months. There has been a rise in incidence of cryptococcosis in immunocompetent hosts in India with a reported association with pulmonary TB. [11]

Table 2: Diagnosis & Management of IFIs.[2,3,4,5,6,7,8]

IFI	Diagnosis	Management
Candidiasis	1. Candida colonisation index 2. Scoring systems: Leon, Ostrosky Zeichner 3. Blood culture- gold standard but sensitivity-50% 4. β-D-Glucan: pan-fungal marker with sensitivity & specificity of 80% for invasive candidiasis 5. MALDI-TOF- requires pure growth of an organism on artificial media 6. PNA FISH- performed directly on positive blood culture 7. T2Candida (PCR)–based assay -uses magnetic resonance detection to identify presence of candida in whole blood	Empiric Treatment: 1. Echinocandins: cidal drugs preferred for critically ill or recent azole exposure. Recent data showing improved survival with echinocandins even in azole susceptible candidemia. Poor penetration into eye, CNS, and urine. 2. Triazoles: static drugs Fluconazole- in less severely ill patients with no previous azole exposure. 3. Amphotericin B- option to echinocandins in resource limited settings. Duration of treatment: 14 days of effective antifungal therapy following the first negative blood culture & resolution of illness Adjuvant treatment: 1. Source Control: removal of CVC in non neutropenic host 2. Metastatic infections: Ophthalmic evaluation and 2D echo to rule out metastatic infections.
Cryptococcosis	CSF: 1. Lymphocytic pleocytosis with high protein and low-normal glucose 2. India Ink: sensitivity 80% in non-AIDS patients, 50% in patients with AIDS 3. CSF CRAG: sensitivity of 95% (Titre > 1:1024 suggestive of high burden with poor host response and likely failure) 4. CSF culture: less sensitive (around 70%), needs prolonged incubation (up to 21 days) 5. Serum CRAG: positive in meningeal & non-meningeal infection, may be positive long before symptom onset. Positive S. CRAG should prompt LP to rule out meningeal disease.	Induction (2 weeks) 1. Amphotericin B + 5 Flucytosine 2. Amphotericin B + Fluconazole Consolidation (8 weeks):Fluconazole Maintenance (≥6 months): Fluconazole Duration: at least 1 yr on maintenance therapy + asymptomatic from cryptococcal infection + CD4 ≥100cell/µl for ≥3 months + suppressed HIV viral load in response to effective ART Therapeutic CSF drainage required during induction to lower raised intra cranial pressure. HAART to be initiated only after induction treatment is over; generally between 2 to 10 weeks
Aspergillosis	EORTC-MSG criteria: Proven IPA: Positive aspergillus culture obtained from a sterile site/ positive culture from an unsterile site along with evidence of tissue invasion on histopathology. Probable IPA: Positive non culture-based test like galactomannan in a susceptible host with compatible radiological features. Possible IPA: Presence of compatible clinical and radiological features in a susceptible host. Radiological features: dense consolidation, nodule surrounded by area of low attenuation (halo sign), nodular cavitation giving rise to the air-crescent sign Serum Aspergillus Galctomannan: sensitivity 70% in neutropenics, as low as 20% in non-neutropenic population. BAL galactomannan: sensitivity >70% in all risk groups including patients on mold active prophylaxis	Drug of choice: Voriconazole Alternative agents: 1. Amphotericin B 2. Echinocandins- not cidal for aspergillus and hence not primary therapy but may have a role in salvage therapy/ intolerance to amphotericin or if prior voriconazole prophylaxis was taken. Combination treatment is used commonly in patients at the highest risk of poor outcome but is of unproven incremental value Duration of treatment: ≥ 3 months

Table 2: Diagnosis & Management of IFIs.[2, 3, 4, 5, 6, 7, 8]

IFI	Diagnosis	Management
Mucormycosis	1. Direct microscopy: calcofluor stain 2. Culture: • Mucor is difficult to isolate from homogenized tissue, lab to be instructed to mince sample with sterile scissors to prevent damage to fungal hyphae. 3. Histopathology: to differentiate mucor from other molds, to document evidence of angio invasion Radiological features suggestive of pulmonary mucormycosis: 1. >10 nodular infiltrates 2. Reverse halo sign 3. Pleural effusion	Drug of choice: Polyenes Alternative treatment: Posaconazole only as salvage therapy • Requires 7-8 days to achieve therapeutic concentrations. • Absorption maximized when taken with high fat food Adjuvant therapy: Deferasirox, hyperbaric oxygen, G CSF, IFN ɣ Duration of treatment: Until near normalization of radiographic imaging, negative biopsy specimens, and cultures from the affected site and recovery from immunosuppression

Aspergillosis

Aspergillus is capable of surviving and thriving in all the diverse environmental conditions in India. The tropical climate allows greater dispersal of the hydrophobic spores. It produces a variety of infectious and allergic syndromes, the diagnosis of which requires invasive and hi-tech procedures.

Plain chest x-rays have limited diagnostic utility in IPA. Even CT radiological criteria for IPA are not as specific for the non-neutropenic host and closely resemble findings of pulmonary TB leading to diagnostic confusion and empiric anti-tubercular treatment (ATT). Rifampicin is an enzyme inducer which reduces the action of voriconazole by 95% when these drugs are used together. This interaction persists for up to 2 weeks even after the withdrawal of rifampicin thus reducing the efficacy of voriconazole.

Although, the availability of serum galactomannan levels has greatly revolutionalised the diagnosis of IPA in neutropenics, it has several limitations in our setting like cost and false positive results seen with the use of generic brands of certain antibiotics such as piperacillin tazobactam and in penicilliosis, an opportunistic endemic mycosis in northeast India.

Sino-orbital-cerebral aspergillosis is a condition reported almost exclusively from the Indian subcontinent and the Middle East. This occurs typically in males involved in agricultural work in moldy environments and presents as an indolent granulomatous condition with intracranial and cerebral extension. Most cases are due to A. flavus.[12]

Voriconazole, the recommended primary therapy for invasive aspergillosis must be used with adequate caution due to its narrow therapeutic window and interactions with other drugs, notably immunosuppressants like tacrolimus. It is metabolized by the hepatic CYP2C19 isozyme and polymorphisms in the CYP2C19 gene, influence the drug levels. Studies have shown a higher frequency of CYP2C19 poor-metabolizer genotype among Indians, thus increasing the potential for drug toxicity in this population. Therapeutic drug monitoring although not widely available in our setting plays an important role in the management of this challenging condition.[13, 14]

Mucor

A review of several Indian studies has revealed a prevalence rate of 0.14 cases/1000 population of mucormycosis, which is 70 times the worldwide rate. Uncontrolled diabetes is a strong risk factor; however in India this association is overwhelming. Data shows that 16-23% of patients were unaware of underlying DM and mucormycosis was in fact a diabetes-defining illness in these patients.[9]

As a result of poor access to healthcare and diagnostic facilities, most patients present with advanced orbital and intracranial extension.

There is a distinct entity of isolated renal mucormycosis seen in India and China. This typically affects young, immunocompetent individuals and has a fulminant course with high mortality.[15, 16]

Due to favourable weather conditions in our country, many species of mucor thrive in the environment. They may contaminate open soil injuries and lead to invasive disease.

SUMMARY

Invasive fungal infections are diseases of medical progress, closely following the evolution of various diagnostic and therapeutic strategies. Broad management principles include recognizing characteristic symptom complexes in high risk individuals, differentiating colonisation from invasion and timely initiation of appropriate antifungal agents. Individualized antifungal treatment based on host factors, organism, extent of disease as well as the incorporation of adjunctive methods such as source control, surgical debridement and immunomodulation are essential for optimal outcomes.

REFERENCES

1. Soman R, Sunavala A. Principles of Management of Invasive Fungal Infections. In: Chakrabarti A, editor. Fungal

Infections in Asia- The Eastern Frontier of Mycology. New Delhi: *Elsevier* 2013; 221–7.

2. Pappas PG, Kauffman CA, Andes DR et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 62:e1.
3. McCarty, Todd P. et al. Invasive Candidiasis. *Infectious Disease Clinics* 2016; 30:103-124.
4. Maziarz, Eileen K. et al. Cryptococcosis. *Infectious Disease Clinics* 2016; 30:179-206.
5. Perfect, JR, Dismukes, WE, Dromer, F et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2010; 50:291–322.
6. Patterson, T.F., Thompson, G.R. 3rd, Denning, D.W. et al, Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 63:e1–e60.
7. Cadena, Jose et al. Invasive Aspergillosis. *Infectious Disease Clinics* 2016; 30:125-142.
8. Farmakiotis, Dimitrios et al. Mucormycosis. *Infectious Disease Clinics* 2016; 30:143-163.
9. Chakrabarti A. Opportunistic Fungal Infections in Asia. In: Chakrabarti A, editor. The Eastern Frontier of Mycology. New Delhi: *Elsevier* 2013; 11–21.
10. Chakrabarti A, Sood P, Rudramurthy S.M. et al. *Intensive Care Med* 2015; 41:285. doi:10.1007/s00134-014-3603-2.
11. Shivaprakash M, Rudramurthy H. Cryptococcosis in Asia. In: Chakrabarti A, editor. The Eastern Frontier of Mycology. New Delhi: *Elsevier* 2013; 120-134.
12. Panda, N.K., Balaji, P., Chakrabarti, A., Sharma, S.C. & Reddy, C. E. (2004). Paranasal sinus aspergillosis: its categorization to develop a treatment protocol. *Mycoses* 47; 277–283.
13. Chawla P, Nanday S, Dherai A et al. Correlation of CYP2C19 genotype with plasma voriconazole levels: a preliminary retrospective study in Indians. *International Journal of Clinical Pharmacy* 2015; 37:925-930.
14. Ashbee HR, Barnes RA, Johnson EM et al. Therapeutic drug monitoring (TDM) ofantifungal agents: guidelines from the British Society for Medical Mycology. *JAC* 2014; 69:1162-76.
15. Chakrabarti A, Das A, Sharma A et al. Ten years Experience in Zygomycosis at a tertiary care centre in India. *J Infect* 2001; 42:261-6.
16. Yu J, Li RY. Primary renal zygomycosis due to *Rhizopus oryzae*. *Med Mycol* 2006; 44:461-66.