INVASIVE FUNGAL INFECTIONS: WHEN TO SUSPECT AND HOW TO MANAGE?

**INTRODUCTION**

There has been a considerable increase in the incidence of invasive fungal infections in clinical practice. Since invasive fungal infections are associated with very high mortality, a high degree of suspicion is required for early diagnosis which is crucial for successful outcome. Prolonged use of broad spectrum antibiotics, cancer chemotherapy, transplant immunosuppression and overall increase in the population of immune-compromised hosts are all contributing to the increasing prevalence of fungal infections. Awareness about these settings coupled with better diagnostics is ushering in a new era in the management of fungal infections. Molecular diagnostics, in-vitro susceptibility tests and availability of better, effective and less toxic anti-fungals have all helped in devising new treatment strategies. This review includes diagnosis and management of commonly encountered fungi like Candida, Cryptococcus, Aspergillus and Mucor. A summary of their clinical manifestations, diagnosis and management is given in Table 1.

**CANDIDA**

Candida is the most common opportunistic fungus causing invasive infection. Colonisation is the first step in the development of invasive candidiasis followed by invasion due to breach in skin or gut integrity. Neutropenia and prolonged use of antibiotics favour invasion and dissemination of candida. The high risk groups include neutropenics, neonates with low birth weight and non neutropenic critically ill patients with prolonged ICU stay and multiple indwelling vascular devices. Candidemia is associated with very high mortality. So it should be part of the differential diagnosis in a critically ill ICU patient with sepsis syndrome.

**Diagnosis**: The diagnosis of candidiasis in critically ill non neutropenic patients is challenging. Blood cultures have a sensitivity of only 50%. So, there is a need for other diagnostic strategies.

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<th>Risk Factors</th>
<th>Syndrome</th>
<th>Fungus</th>
<th>Treatment</th>
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<td>Sepsis Syndrome</td>
<td>Candida</td>
<td>Echinocandins if critically ill or prior azole exposure</td>
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<td>Non Neutropenic critically ill patients in ICU</td>
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<td>Amphotericin instead of echinocandins in resource limited settings</td>
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<td>HIV</td>
<td>Meningitis, Skin and Pulmonary involvement</td>
<td>Cryptococcus</td>
<td>Amphotericin + 5-Flucytosine</td>
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<tr>
<td>Prolonged Neutropenia, Prolonged steroids, Solid Organ Transplant patients(SOT), Haematopoietic stem cell transplant patients (HSCT), COPD, Liver cirrhosis</td>
<td>Pulmonary Involvement Sinus Involvement</td>
<td>Aspergillus</td>
<td>Voriconazole</td>
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<tr>
<td>Uncontrolled CKD,SOT,HSCT</td>
<td>Diabetes, Paranasal/Nose with blackish discharge/Eschar with orbital and cerebral involvement</td>
<td>Mucor</td>
<td>Amphotericin</td>
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<td></td>
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<td>Posaconazole</td>
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**Table 1: Common Fungi – Clinical Manifestations, Diagnosis and Management**
1. Colonosation Index: One way to go about is by doing surveillance cultures of blood, oropharynx, stomach, rectum, trachea, urine, catheter tip, surgical drain etc and calculate the colonisation index (CI).
   - CI = non blood cultures/total sites cultured
   - cCI is cultures with heavy growth/total culture
   Colonization may turn into invasion if CI > 0.5 or cCI > 0.4

2. Scoring Systems: Scoring systems are available based on risk factors and colonisation which predict the risk of candidemia. However the risk depends not on just the number of risk factors but what is the likelihood of alternative diagnoses. Thus, they have good negative predictive value but less positive predictive value.

Leon score is given in Table 2.
- Leon Score:\(^1\): Table 2
- Ostrosky Zeichner Score:\(^2\):
  - ICU stay for at least 4 days + Antibiotic use + Central Venous Catheter (CVC)
  Plus any 2 of the following:
  - Surgery
  - Total parenteral nutrition (TPN)
  - Hemodialysis
  - Pancreatitis
  - Steroids
  - Immunosuppression

3. Serological tests: Testing for serum Beta-D-Glucan has good sensitivity for candidemia. But it is not very specific as false positive can occur due to dialysis, gauze, TPN, cardio-pulmonary bypass, intravenous immunoglobulins and other fungi like Aspergillus, fusarium, trichosporon etc

4. Molecular tests: Fungal PCR is a new diagnostic tool for candidemia; however it is fraught with problems like what should be the optimum specimen and other issues like DNA extraction and contamination etc.

Thus diagnosis of candidemia is challenging and way forward may be by risk factor assessment coupled with knowledge of colonisation status and molecular diagnosis. On the basis of these, empirical anti-fungals can be started in critically ill patients with sepsis syndrome.

Empiric treatment choices for Candidemia:\(^3\): Echinocandins and fluconazole are the drugs of choice in candidemia. The choice between them depends upon severity of illness, previous exposure to azoles, availability of culture and drug susceptibility and local epidemiology. Epidemiology in India differs somewhat as compared to west. In India we find a higher proportion of Candida tropicalis. About 10-15% Candida albicans & Candida tropicalis are resistant to Fluconazole. Also, the proportion of Candida glabrata and Candida krusei are less; probably due to lesser use of fluconazole. On the basis of these the therapeutic options are as follows-

1. Echinocandin if moderate to severe disease or recent exposure to azoles. Echinocandins are cidal drugs and so are better in critically ill patients
2. Fluconazole in less severely ill patients with no previous azole exposure. Voriconazole not much better than Fluconazole except for C. krusei and both are static drugs. Fluconazole resistant C. glabrata is resistant to voriconazole too. Descalation to fluconazole in patients initially started on other drugs is possible if susceptibility is available & the patient has improved, or to Voriconazole if C. krusei is the pathogen.
3. Amphotericin B is an option to echinocandins in resource limited settings.

Treatment is continued till 2 weeks after 1st negative culture & resolution of signs & symptoms.

Azoles affect the liver microsomal enzymes causing various drug interactions which has clinical implications. (Table 3)

Antifungal treatment options in febrile neutropenia patients:\(^4\): In febrile neutropenics there is more emphasis on liposomal Amphotericin as it is cidal, covers moulds including mucor and has a good track record as compared to fluconazole. Also frequent use of fluconazole prophylaxis precludes its use in therapeutic settings. So the choice of antifungals in febrile neutropenics is as follows:

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### Table 3: Drug Interactions with Azoles

<table>
<thead>
<tr>
<th>Drugs whose levels are reduced by Azoles</th>
<th>Drugs which reduce the levels of Azoles</th>
<th>Drugs which increase the levels of Azoles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>Rifampicin</td>
<td>NNRTI</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Isoniacin</td>
<td>Protease Inhibitors</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terfenadine</td>
<td></td>
<td></td>
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<tr>
<td>Sirolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinca Alkaloids</td>
<td></td>
<td></td>
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<tr>
<td>NNRTI</td>
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</table>

### Table 2: Leon score

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Score</th>
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<tbody>
<tr>
<td>Sepsis</td>
<td>2</td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
</tr>
<tr>
<td>TPN</td>
<td>1</td>
</tr>
<tr>
<td>Multifocal colonization</td>
<td>1</td>
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</tbody>
</table>

A score of more than 2.5 is associated with 7 fold increase of candidemia.
**Invasive Fungal Infections: When to Suspect and How to Manage?**

- If Fluconazole prophylaxis was received consider L-AMB or Echinocandin
- If Voriconazole prophylaxis was received consider L-AMB

**ADJUVANT TREATMENT**

1. **Source Control:** CVC is often but not always the source of Candidemia. So it should be removed for adequate source control. Gut mucosa is the more likely source in neutropenic patients and so recommendation for early removal of CVC is not as strong as in non-neutropenic patients. However, CVC should be removed in neutropenic patients if clinically unstable, lack of resolution of fever in 2-3 days or if there is persistent candidemia after 2 days of treatment.

2. **Metastatic infections:** Ophthalmic evaluation and echocardiography should be done to rule out metastatic infections. Ophthalmic evaluation is done after candidemia and neutropenia resolves. This is important as ocular candidiasis needs prolonged treatment for 6-12 weeks till resolution and stabilization occurs.

**Urinary Candidiasis:** Candida in urine may be a colonizer or the first indication of fungemia. Colony counts do not help as high colony counts can be seen in the setting of colonization or contamination. Treatment depends on whether patient is symptomatic or not and also whether patient is a vulnerable host (Neutropenia, Low birth weight neonate or if urosurgical procedures planned). If candida is repeatedly isolated in urine, renal parenchymal involvement should be ruled out. Treatment strategies are as follows-

1. Renal parenchymal involvement: Fluconazole, Amphotericin B or 5-flucytosine with surgery
2. Symptomatic cystitis: Fluconazole
3. Asymptomatic vulnerable host: Fluconazole
4. Asymptomatic competent host: Remove or change catheter

**Antifungal Toxicity:** Antifungal toxicities affect patient management and it is important to be aware of them. Clinically important toxicities are described in Table 5

### Table 4: Choice of Antifungals in neutropenia patients

<table>
<thead>
<tr>
<th>Liposomal Amphotericin</th>
<th>= Echinocandin</th>
<th>&gt; Voriconazole</th>
<th>&gt; Amphotericin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covers Candida, For those not at high risk of Aspergillus, Zy- risk of zygomyces aspergillus. Presence of respiratory, sinus and CNS symptoms. Galactomannan positive</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### Table 5: Toxicity of Antifungals

<table>
<thead>
<tr>
<th>Amphotericin</th>
<th>Nephrotoxicity, Hypokalemia, Hypomagnesemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Flucytosine</td>
<td>Myelotoxicity, Colitis</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Hepatitis, Drug interactions</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Drug interactions</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Retinal toxicity, Drug interactions, Accumulation of cycloextrin in renal toxicity (IV preparation), Skin Rash</td>
</tr>
<tr>
<td>Echinocandin</td>
<td>Flushing and Drug interactions</td>
</tr>
</tbody>
</table>

**CRYPTOCOCCUS**

Cryptococcal infection occurs in patients with impaired T cell function; however it can occur in immunocompetent individuals rarely. It is an important cause of meningitis in HIV positive patients. Other common sites of cryptococcal infection include skin and lung; although it can affect any organ systems.

**Diagnosis:** Cryptococcal meningitis should be suspected in HIV patients presenting with headache. Neck stiffness may or may not be present. It occurs at CD4 below 100. So in HIV patients with low CD4, serum cryptococcal antigen should be done even if they are asymptomatic. CSF tap is required for diagnosis as well as therapeutic purpose. CSF will reveal lymphocytic pleocytosis with high protein and low sugar. CSF India ink sensitivity is around 50-80%. Cryptococcal antigen has a sensitivity of 95%. However, false positive is seen in trichosporon and false negative in early disease or due to prozone effect of high titre. Titre of more than 1:1024 is suggestive of high burden of Cryptococcus with poor host response and likely failure. CSF culture for Cryptococcus is less sensitive (around 70%) and so needs to be incubated for a prolonged time (upto 21 days). In HIV patients, blood culture can be positive for Cryptococcus due to high burden of organisms.

**Treatment:** Treatment includes induction with Amphotericin B 0.7 mg/kg with 5-flucytosine 100mg/kg/daily for 2 weeks. This is followed by consolidation with fluconazole-800mg daily for 2 days and then 400mg daily for 8 weeks. After consolidation, maintenance therapy with 200-400mg fluconazole should be continued till CD4>100 for 6 months. The minimum duration of treatment should be 1 year. During induction if fluconazole is not available, high dose fluconazole (800-1200mg) or Amphotericin B 1mg/kg/daily or liposomal Amphotericin 4-5mg/kg/daily can be used. Repeated CSF drainage is required during induction phase to lower the intracranial pressure. HAART is initiated only after induction treatment is over; generally between 2 to 10 weeks.

**ASPERGILLUS**

Invasive Aspergillus infection is increasing in incidence due to increasing population of immunosuppressed hosts. Awareness of risk factors is the most important aspect in diagnosis of invasive aspergillosis. Pulmonary aspergillosis...
is the most common manifestation of invasive disease and Aspergillus fumigatus the commonest organism responsible. Other sites include paranasal sinuses and brain. Diagnosis is challenging and delayed treatment is associated with high mortality.

Invasive pulmonary aspergillosis should be suspected in a susceptible host presenting with cough, fever and breathlessness. The high risk group includes

- Febrile neutropenics with prolonged neutropenia (ANC<500 for more than 10 days)
- Patients on prolonged steroids (0.3mg/kg/daily prednisone for >3 weeks)
- HSCT patients
- Treatment with T cell immunosuppressants
- Inherited immunodeficiency syndromes
- SOT patients
- COPD
- Liver cirrhosis

**Diagnosis**: The European organization for research and treatment of cancer-Mycoses study group (EORTC-MSG) has devised criteria for the diagnosis of IPA. Accordingly, IPA is suspected if in a susceptible host there is compatible clinical and radiological syndrome.

1. The radiological features include dense consolidation, nodule with halo sign or air-crescent sign or cavity. Such patients should be investigated to establish an etiological diagnosis by biopsy and culture or by molecular methods.

2. The availability of serum galactomannan has greatly revolutionized the diagnosis of IPA especially in neutropenics. It is a product of budding hyphae and its levels are high in neutropenics. The sensitivity of this test in serum is low in non-neutropenia patients but 93% in neutropic patients. The specificity is around 86%. In non-neutropenic patients, a negative serum galactomannan does not rule out the disease due to low sensitivity in them. But the positive predictive value in a susceptible non-neutropenic host with compatible syndrome is around 70%. The sensitivity of broncho alveolar lavage (BAL) galactomannan is up to 100% in neutropenics and around 90% in non-neutropenics.

As per EORTC-MSG criteria, IPA is proven if positive Aspergillus culture is obtained from a sterile site or a positive culture from unsterile site along with evidence of tissue invasion on histopathology. Probable IPA is when there is a positive mycological criterion like serum galactomannan in a susceptible host with compatible radiological features.

**Treatment**: Voriconazole is the drug of choice for management of IPA. Amphotericin B is the alternative treatment. The minimum inhibitory concentration of amphotericin for Aspergillus is creeping up and can be associated with treatment failure. Higher dose or loading dose of amphotericin is not more effective and associated with higher toxicity. Echinocandins are not cidal for Aspergillus and hence not primary therapy but may have a role in salvage therapy or if there is intolerance to amphotericin or if prior voriconazole prophylaxis was taken. It is important to exclude mucormycosis before starting echinocandin. Combination treatment is used commonly in patients at the highest risk of poor outcome but is of unproven incremental value. The duration of treatment is for at least 3 months.

**MUCORMYCOSIS**

Mucor is an important invasive fungus causing disease in diabetics, chronic kidney disease patients, SOT and HSCT patients. The commonest manifestation is a rhino-orbito-cerebral disease or sino-rhino-orbito-cerebral involvement. It should be a clinically suspected in a diabetic presenting with invasive sinusitis with nasal or orbital involvement causing blackish discharge or eschar. It is important to recognize this entity early as it can progress rapidly due to angio-invasion. Extensive involvement and intracranial spread is associated with high mortality.

**Diagnosis**: Swabs are not adequate for diagnosis. Scrapings and biopsy with histopathological examination using PAS or GMS stains are required for identification and diagnosis. Mucor is difficult to culture from homogenized tissue so it is important to instruct the lab to process culture for mucor without tissue homogenization.

**Treatment**: The principles of successful management of mucor are

- Timely diagnosis
- Reversal of the underlying predisposing factors
- Early and wide surgical debridement of infected tissue
- Rapid initiation of effective systemic antifungal therapy

**Antifungal Therapy**: Amphotericin therapy is the drug of choice. Amphotericin B 1mg/kg/daily or Liposomal Amphotericin 3 mg/kg/daily. Posaconazole is a newer extended spectrum triazole which has activity against mucor. It is oral treatment and achieves therapeutic levels only after 7-8 days of starting it. So, posaconazole can only be considered in patient intolerant to amphotericin or as salvage therapy and not as initial therapy.

**Adjunctive therapy**: Various adjunctive strategies are used along with Amphotericin and surgical management. They are as follows-
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- Itraconazole for *Absidia*, Caspofungin for *R. oryzae* along with Amphotericin B
- Hyperbaric oxygen: By producing free radicals it helps in the antimicrobial effect and helps in tissue healing. It is particularly useful in diabetic patients with rhinocerebral disease
- IFN γ, GCSF: These agents help by augmenting the polymorphonuclear cells mediated hyphal damage
- Deferiprone, Deferasirox: Chelating agents exert antimucor activity by iron deprivation of the fungus and can be used along with Amphotericin with good results.

**SUMMARY**

Invasive fungal infections chiefly affect immunocompromised hosts. Recognizing various symptom complexes in these high risk group individuals can give a clue to diagnosis of the fungal pathogen. This in turn helps in early initiation of appropriate anti-fungals.

It is especially important to differentiate colonisation from invasion while managing fungal infections. Application of various scoring systems and diagnostic criteria in high risk population aid in early diagnosis of invasive fungal infections. Whenever possible clinical material should be obtained for culture and histopathological diagnosis. If obtaining samples is difficult, molecular methods can help in diagnosis.

Correct etiological diagnosis and availability of culture with speciation and susceptibility helps in planning effective treatment strategies. Treatment should be individualized as per the type of fungus, extent of disease, risk factors and response to therapy. Adjunctive treatment strategies like surgery, source control methods, immune-modulation and control of underlying disease should be incorporated in treatment regime for successful outcome.

**REFERENCES**