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Invasive fungal infection: a visible menace

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ABSTRACT

Invasive fungal infections (IFI) are an upcoming threat in hospitalized patients. We studied the risk factors, aetiology, clinical features and outcomes (in the form of survival or death) in 30 cases displaying IFI. This was a prospective observational study. The prevalence of IFI in our study was 0.665 per 100 patients. Associated comorbidities observed included diabetes mellitus; neutropenia; chronic kidney disease; and malignancy. Therapies used included immunosuppressive therapy, including systemic steroids or chemotherapy drugs, and trauma. Some cases underwent major surgeries, some were treated using broad spectrum antibiotics. Some had sepsis or HIV infection, some were on total parenteral nutrition (TPN) and some underwent instrumentation or ICU stay. The common IFIs observed were mucormycosis, followed by candidiasis, aspergillosis and cryptococcosis. The survival rate was 73.33% of cases, while death was recorded in 26.67% of cases.

Keywords: Invasive fungal infection, risk factors, mucormycosis, asoergillosis, candidiasis, cryptococosis

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INTRODUCTION

India is a large tropical country with a monsoon season, during which heavy rains enable fungi to proliferate in many regions. Limited studies have been carried out in India, however, and hence the precise incidence of invasive fungal infection is not known.[1] Moreover, the alarming rise in fungal infections adds to the difficulty of recording the current incidence. According to the Europe-based Invasive Fungal Infection Cooperative Group (IFICG), invasive fungal infection (IFI) is defined as the existence of fungal elements – either mould or yeast – in biopsy or needle aspiration of deep tissues, established by histopathology or culture.[2] The pathogenicity of fungal infections depends upon a combination of host risk factors and fungal virulence, which in turn depends upon enzymes and toxins produced.[3] IFIs are sometimes under-reported as diagnostic cultures can lack sensitivity as well as specificity.[4] Clinical features and management depends upon the type of fungus and the organ involved.

METHODS AND MATERIALS

Aim

The aim of the study was to evaluate the clinical profile of invasive fungal infections in hospitalized patients.

Objectives

1) To determine the prevalence of invasive fungal infection in hospitalized patients.
2) To identify risk factors present with invasive fungal infections.
3) To identify fungal species involved in invasive fungal infections.
4) To determine the clinical outcomes of invasive fungal infections at the time of discharge.

This observational study was undertaken in Western Maharashtra, India, in a tertiary hospital. The first 30 patients admitted to the critical care unit and wards, above 18 years of age who met the study definition of IFI were included in the study. Patients with superficial fungal infections were excluded from the study.

Ethics Committee approval was obtained and written consent was taken from all patients. All patients suspected of having invasive fungal infections were questioned for history of symptoms and a detailed clinical examination was undertaken. Any suspected risk factors for IFI were noted carefully. Every patient suspected of having a fungal infection was subjected to a complete blood cell count, blood sugar levels, renal function test, liver function test, serum electrolytes, blood culture, urine routine and culture. Bronchoscopic alveolar lavage (BAL) routine and culture, sputum culture, tissue scrapings, KOH mount, cerebral spinal fluid (CSF) routine and culture, catheter tip culture, chest X-ray (PA View), high-resolution CT (HRCT) of the thorax, magnetic resonance imaging (MRI) of the brain, X-ray and computed tomography of the paranasal sinus cavity (CT PNS), gynaecological ultrasound (USG) of the abdomen and pelvis, electrocardiogram (ECG), and 2D-echo were carried out on indicated patients. Nasal endoscopy or surgical exploration was also carried out if needed. Probable diagnosis was made by culture from a nonsterile site such as BAL or sputum.

Definitive diagnosis of IFI was done either by positive culture from a sterile site like needle aspirate or tissue biopsy, pleural fluid or histopathological evidence of fungus. An aspergillus antigen test was given and galactomannan levels were tested if needed. Evidence of mucormycosis was treated with liposomal amphotericin B (Amb) or in combinations with caspifungin or anidulafungin. Aspergillosis was treated with Voricanazole. Candida infections were treated by Flucanozole, Echinocandins or Amphotericin as required, in appropriate therapeutic doses and for appropriate durations. Cryptococus was treated with Amphotericin B followed by Fluconazole. Prevalence, aetiolgy, risk factors, the organs affected and clinical outcomes were studied.

RESULTS

Patients were assigned to age groups: 6.7% of patients were under 30 years of age; 20% were 31–40 yrs; 20% were 41–50 yrs; 30% were 51–60 yrs; 16.7% were 61-70 yrs, and 6.7% were 71-80 yrs. 56.67% were male and 33.33% were female. The prevalence of IFI in our study across all groups was 66.5%.

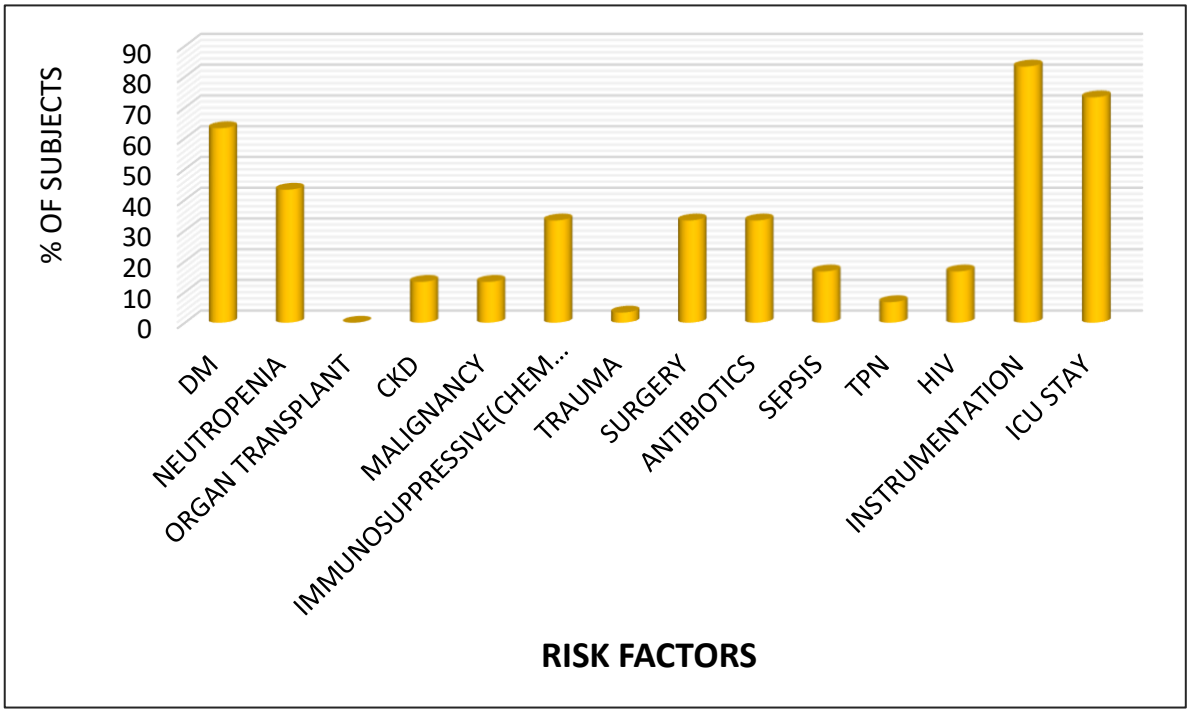

Fig 1 Risk factors associated with IFI

As far as clinical features were concerned, 50% patients had fever, 35% displayed breathlessness ,32% had a cough, 21% displayed nasal discharge and 20% nasal block, 20% had headaches, 21% reported altered senses, 18% had facial swelling, 16% had cranial nerve palsy, 13% had proptosis and 8% described abdominal pain. Weight loss and loss of vision were seen in 3% and 6% of patients respectively.

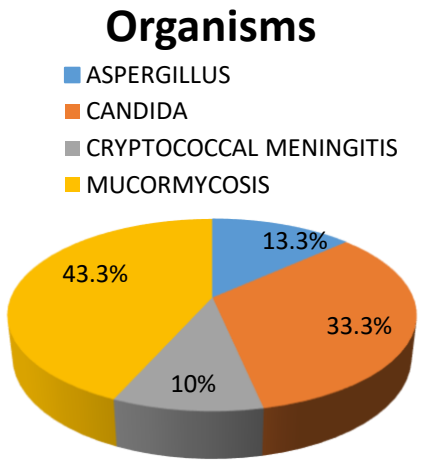

Fig 2 Distribution of organisms in the study group

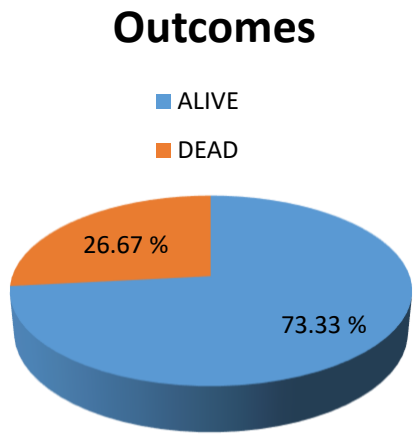

Fig 3 Distribution of outcomes in the study group

Table 1 Distribution of organs affected in the IFI in the study group

Organ Involved	Frequency	Percent
Blood	9	30
CNS-Meninges	3	10
Lungs	7	23.3
Maxillary Sinus or / with Eyes, Nasal Mucosa and Cavity	9	30%
Renal Abscess	1	3.3
CNS and Right Eye	1	3.3
Total	30	100

DISCUSSION

The incidence of IFIs in our study was 0.665 per 100 patients. There are few studies on the incidence or prevalence of IFI in different patient groups – such as patients on mechanical ventilation, haematological malignancies and in intensive care settings. Even in these studies, IFIs are not always studied separately.[5,6] There are few studies to compare incidence in general hospitalized patients, but we know that IFI is a growing challenge in hospitalized patients in India. Across our study of 30 subjects, 43.33% (13) had mucormycosis; 33.3% (10) candidiasis; 13.3 % (4) aspergillosis and 10% (3) cryptococcosis.

The prevalence of mucormycosis differs in developed and developing countries. In Europe and the United States, its prevalence is 1–2 per 100,000 population while in India it is much higher at 14 per 100,000 population[7].The commonest mucormycosis, seen in 13 cases in our study (43.33%) was rhino orbital (n=10) followed by pulmonary (n=3) and CNS involvement (n=1). Bala, in his study in North India, also found rhino orbital mucormycosis to be most common (61.5%) followed by cutaneous (31%), gastrointestinal (5%) and pulmonary involvement (2.5%).[8] In a global registry, pulmonary mucor was found to be 58.5%,

followed by rhino cerebral or rhino orbital at 19.5%. However, in an Italian study the most common infection site was rhino orbital cerebral.[9] Isolated renal mucormycosis are also known to be prevalent in India,[7] though we did not find any in our study. Mucormycosis are angioinvasive fungi, which further complicates the picture. The commonest risk factor in mucormycosis in our study was diabetes (72%), which is linked with faulty neutrophil function and microvascular insufficiency, which allows fungal growth.[9] Peterson,[10] in his study of 28 cases of mucormycosis found that 64% cases were diabetic. In another Indian study, 56.8 % were diabetic. Warning signs of rhinocerebral mucormycosis in diabetics are diplopia; cranial nerve palsy; proptosis; and swelling around the orbits. Pulmonary mucormycosis radiologically shows multiple nodules and a CT scan of the chest shows the reversed halo sign, which is more commonly seen in mucor than in aspergilosis.[7] Apart from the common risk factors, deferaxone therapy for decreasing iron load is also a risk factor, as the iron removed by it is taken by sideropores of mucous for their growth; however, this is not the case with newer iron chelators such as deferasirox.[11] In our study, no patient was taking deferaxone.

In our study, there were 33.3% cases of candida fungal infections; 30% were blood stream infection while 3.33% cases had renal abscesses. Early detection of blood stream infection can reduce mortality. An important challenge in candida infection is to differentiate benign candida from deep tissue candida infection but sputum or urine testing positive for candida does not automatically mean a pulmonary or kidney infection. In our study, 30% of cases were candida albicans while 70% were non candida albicans (NCA). Initially, candida albicans was the most visited candida species but now NCA are more frequently recorded. NCA appear to be more virulent and more resistant to antifungal medications.[3] Incidence of candidaemia in India is 1–12 patients per 1000 cases, which is 20–30 times more than in developed countries. *Candida tropicalis* is also more common in India and can develop into sepsis.[4] *Candida glabrata* is commonly a commensal infection but it is now becoming a pathogen, and azole resistance is also a concern.[12] Third most common fungal involvement in our study was aspergillosis and in all cases the lungs were involved, in the form of nodules to consolidate the cavity lesions. Vaideeswar,[13] in his study of 39 cases at autopsy of invasive pulmonary aspergillosis, found lung involvement in the form of pleural fibrosis, consolidation, abscesses and cavitation, as did ours. We did not find any involvement of sinus, brain, skin, heart or eye in aspergillosis.

Out of 350 species of aspergillosis, only seven are pathogenic. A neutrophil count of less than 500/µL for longer than 21 days is the most common risk factor in aspergillosis infection. The infection has 45° dichotomous branching of hyphae, which invade tissue. Alveolar macrophages produce tnf alpha and macrophage inflammatory protein, which resist infection, but in neutropenia these are reduced, causing invasive aspergilosis.[14] Case reports record invasive paranasal aspergillosis in immunocompetent patients: one in an obese patient who had bariatric surgery and another in a case of chronic dacrocystitis which blocked the lacrimal gland and may have predisposed to aspergillosis.[15] However, in our study we did not find aspergillosis in immunocompetent patients. We do suggest, however, that physicians should try to identify predisposing factors in invasive aspergillosis, even when a patient's history of immunocompromise is unknown or unavailable.

We had three cases of cryptococcal meningitis (CSF cryptococcal antigen positive). All were HIV positive and treated with amphotericin B for two weeks followed by Flucanozole 400mg/day for eight weeks, then 200mg/day for three months. CSF culture turned sterile at the end of two weeks and all three cases improved. Early antifungal treatments, correct timing for the start of antiretroviral therapy, and proper management of raised intracranial pressure by therapeutic lumbar puncture are important aspects of management.[16] However, high mortality is seen in these infections and immune reconstitution inflammatory syndrome (IRIS) is also a complication. They all presented with fever and headache, also seen in a study undertaken by Atul Patel.[16] One patient had a sluggish course and, in such cases, we need to have a high index of suspicion: 22 (73.33%) of IFI cases survived while death occurred in 8 (26.66%) of cases.

Among patients who died, three patients displayed pulmonary aspergillosis, four had blood stream candidiasis and one patient had mucormycosis. Out of four cases of pulmonary aspergillosis, three patients died. All patients received candida Voricanazole in therapeutic doses. Aspergillosis has a mortality rate of 90%[17] but many times, the diagnosis of aspergillosis is only made at autopsy. The crude mortality of invasive candidemia is 30–81% in critical ill patients.[18]

CONCLUSION

The prevalence of IFI in our study was 0.665 per 100 patients. The most common IFI found in our study was mucormycosis followed by candida, aspergillosis and cryptococcus. All study patients had some degree of immunocompromised status, the most common being diabetes mellitus. Non candida albicans was more common than Candida albicans. Twenty-two cases (76.6%) survived, while death was seen in eight cases (26.6%). Pulmonary aspergillosis had high mortality but early diagnosis and proper treatment can reduce the mortality.

REFERENCES

1. Chakrabarti A, Chatteerjee SS, Shivaprakash MR. Overview of Opportunistic Fungal Infections in India. Jpn J.Med.Mycol. 2008; Vol.49. (3).
2. Ramana, K V, et al. "Invasive Fungal Infections: A Comprehensive Review." American Journal of Infectious Diseases and Microbiology .2013; 1(4): 64-69.
3. Enoch DA, Ludlam HA, Brown NM. Invasive fungal infections: a review of epidemiology and management options. Journal of medical microbiology. 1 July 2006; 55(7): 809-18.
4. Sunavala AJ, Soman R. Invasive Fungal Infections. The association of physicians of India.76-80
5. Hsu.L.Y,Lee D.G , Yeh.S.P, Bhurani D, etall Epidemiology of Invasive Fungal Diseases among patients with haematological disorders in the Asia – Pacific : a prospective observational study. Clin Microbiol infect 2015 ; 21:59 4e7594e11
6. Chakraboti A, Jaiswal A, Verma .P.K Singhal R. A Prospective study of fungal colonization and Invasive Fungal Diseases in Long term Mechanically Ventilated patients in a Respiratory Intensive Care Unit. Indian J Criti Care Med.2018; 22(8):597-601.
7. Skiada A, Lass-Floerl C,. Klimko N et al. Challenges in the diagnosis and treatment of mucormycosis .Medical Mycology,.2018; 56, S93–S101
8. Bala K, Chander J, Handa U, Punia RS, Attri AK. A prospective study of mucormycosis in north India: experience from a tertiary care hospital. Med Mycol. April 2015; 53 (3): 248-57.
9. Carlos Rodrigo Camara-Lemarroy, Emmanuel Irineo González-Moreno, Rene Rodríguez-Gutierrez, et al., "Clinical Features and Outcome of Mucormycosis," Interdisciplinary Perspectives on Infectious Diseases. 2014; 5.
10. K. L. Peterson, M. Wang, R. F. Canalis, and E. Abemayor, "Rhinocerebral mucormycosis: evolution of the disease and treatment options," Laryngoscope.1997;7(107) : 855–862.
11. Prakash A, Chakrabarti A Global epidemiology of mucormycosisJ, Fungi. 2019; 5(26):
12. Bhattacharjee P, Epidemiology and antifungal susceptibility of candida species in a tertiary care hospital, Kolkata, India curr, Med Mycol. June 2016; 2(2):20-27.
13. Vaideeswar P,Prasd S ,Deshpande JR, Pandit SP.Invasive pulmonary aspergilosis :A study of 39 cases at autopsy .Journal of postgraduate medicine.Jan 2004;50 (1):21.
14. Ana María Garcia-Giraldo, Barbara Lucia Mora, Jorge Mario Loaiza-Castaño, Jorge Andrés Cedano, Fernando Rosso. Diagnosis and treatment of invasive pulmonary aspergillosis in neutropenic patients. Med Mycol Case Rep.March 2019 ; 23: 12–15.
15. Invasive fungal infections by Aspergillus in Immunocompetent hosts: A case series and literature review.
16. Patel AK, Patel KK, Ranjan R, Shah S, Patel JK. Management of cryptococcal meningitis in HIV-infected patients: Experience from western India. Indian J Sex Transm Dis AIDS. 2010;31(1):22–26.
17. David W.Denning Invasive fungal infection by Aspergillus flavus in immunocompetent hosts: A case series and literature review .Aspergilosis,.Harrisons principles of Internal Medicine chapter 212,1536
18. Tak V, Mathur P, Varghese P, Gunjiyal J, Xess I, Misra MC. The epidemiological profile of candidemia at an Indian trauma care center. J Lab Physicians. 2014;6(2):96–101.