

Clinical Correlates and Microbiology of Invasive Fungal Disease in a Tertiary Care Hospital

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Abstract:

Background and objectives: There is a paucity of data in Indian literature regarding the risk factors, comprehensive clinical profile and treatment outcomes of Invasive fungal disease(IFD). Thus the aim of this study is to assess the frequency, type of IFD, clinical spectrum, risk factors, microbiological profile and outcome in patients with IFD.

Methods: A cross sectional descriptive study, Study duration of One and Half Years. Patients with proven and probable IFD according to EORTC/MSG criteria were selected.

Conclusion: Since elderly patients with risk factors like Type 2 diabetes, hemodialysis, prolonged ICU stay, and total parenteral nutrition were significantly associated with candidemia and mucormycosis they need to be regularly screened for these infections. Those with underlying lung disease or prolonged steroid use need to be screened for pulmonary aspergillosis. IFD specifically those needing prolonged ICU care is associated with very high mortality.

Keywords: Candidemia, Risk factors, Mucormycosis, Aspergillosis, Cryptococcus, Critical care, Opportunistic infections, Diabetes, Immunocompromised host.

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Introduction

India is a vast country of more than a billion people and spread over an area of 3.3 thousand million square kilometers. The climate of this country is well suited for a variety of fungal infections as India is located in tropics and receiving heavy monsoon. [1] Certain factors produce a fertile ground for opportunistic fungal infections to flourish in this country like solid organ and bone marrow transplantations, systemic steroids which are available over the counter in many urban and semi-urban areas, and overuse of broad-spectrum antimicrobials in most Indian hospitals. The exact frequency of opportunistic fungal infections is not known, as there are few diagnostic mycology laboratories available in India and most clinicians are unaware of the clinical manifestations of fungal infection. [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. Invasive fungal disease is a significant health problem due to extensive use of broad spectrum antibiotics, immuno-suppressive agents, increasing population of terminally ill and debilitated patients. [2] The four

most important fungi producing invasive fungal infections are *Candida* species, *Cryptococcus* species, *Aspergillus* species and *Mucorales* species. Fungi in course of time have evolved as both primary and opportunistic pathogens which have the ability to cause infection in immunocompetent and immunocompromised individuals, [3] making IFD a potential global health problem. Most untreated systemic fungal infections are associated with high rates of mortality. A significant rise has been seen in invasive fungal disease over the past few years, owing to growing number of patients with impaired immune status. Therefore there is a need to estimate the frequency of different types invasive fungal disease, associated risk factors, clinical presentation, organs affected, microbiology including antigen analysis and to correlate in-hospital outcomes with clinical parameters and microbiological profile of invasive fungal disease. Organisms once thought to be contaminants are now confirmed pathogens causing systemic fungal infections in immunocompromised patients, hence we need to have continued epidemiologic and laboratory research to better characterize these pathogens, allowing for improved diagnostic and therapeutic strategies in future. [6]

Objectives

The frequency of types of IFD.
The spectrum of clinical presentation of IFD.
The microbiological profile of IFD.
The risk factors that predisposes to IFD.
Correlate in hospital outcomes with clinical parameters, risk factors and microbiology of IFD.

Material and Methods

A cross sectional descriptive study, Total Study 130, Study duration of One and Half Years. Patients with proven and probable IFD according to EORTC/MSG criteria were selected. at Indira Gandhi Institute of medical Sciences, Patna.

Inclusion Criteria: All patients above 18 years of age with proven and probable invasive fungal infection as per revised EORTC / MSG criteria admitted to IGIMS hospital over the period of one and half years.

Exclusion Criteria: All retroviral disease positive patients were excluded from the study.

Cases were classified according to the European organization for the Research and treatment of Cancer /Mycoses Study Group (EORTC/MSG) criteria as proven, probable and possible cases. Proven invasive fungal infection required only that a fungus be detected by histological analysis or culture of a specimen of a tissue taken from a site of disease. Probable invasive fungal infection require that a host factor, clinical features, and mycological evidence be present. Possible was the presence of host factors and with sufficient clinical evidence consistent with

IFD but for which there was no mycological support.

The presence of fungal elements either as mould or yeast in deep tissues by biopsy or fine needle aspirates that is confirmed on culture and histopathological examination can be described as an Invasive Fungal Infection (IFD)

Institutional Ethical clearance was obtained for the study. Consent was obtained from the patient or their relatives. All admitted patients above the age of 18 years diagnosed as having IFD were interviewed after the diagnosis was confirmed in the hospital. Patients were examined and findings were noted as per the attached protocol. Regular contact was maintained with all clinical departments and laboratories to collect and enroll the patients for study. The investigations used for the diagnosis of IFD were also noted. Imaging records and surgical notes were noted to document extent of disease. Microscopy, fungal culture and serology collected from Department of Microbiology. Histopathology and biopsy report collected from the department of pathology. Chart review was also done for data on in-hospital stay, duration of antifungals and patient outcomes.

Results

IFD is classified into proven, probable and possible per the EORTC/MSG criteria. Out of the total number of inpatient admissions during the study period (n= 85,256) those detected to have invasive fungal disease was 150.

| | Mucormycosis | Candidiasis | Aspergillosis | Cryptococcosis | Mixed infections |
|----------|--------------|-------------|---------------|----------------|------------------|
| Proven | 40 | 45 | 21 | 2 | 9 |
| Probable | 1 | 5 | 7 | - | - |
| Possible | 2 | 3 | 15 | - | - |

Out of the total number of invasive fungal infections per the EORTC/MSG criteria(150), only the proven and probable cases(130) were considered for analysis due to lack of robust microbiological criteria to permit categorization of possible cases as invasive fungal disease. The chief fungal infections observed were candidiasis 38.5% (n =50), Mucormycosis 31.5%(n=41) aspergillosis 21.5%(n=28), cryptococcosis 1.5% (n=2) and mixed infections 6.9%(n=9). Out of the nine mixed fungal infections, *Candida* was the common co-infection for eight of them, with either *Aspergillus*(4), or *Mucormycosis* (4). The single remaining mixed infection was *Aspergillosis* with *Mucormycosis*.

The most common risk factors in invasive fungal disease is found to be the use of broad spectrum antibiotics, indwelling catheters like central venous line, arterial line, hemodialysis catheter, ryles tube and urinary catheters, prolonged ICU stay for more

than a week, uncontrolled sugars, major surgery like abdominal surgery, renal failure with hemodialysis, prolonged ventilation and long term steroid use. The most common risk factors among patients with Mucormycosis were found to be broad spectrum antibiotics, indwelling catheters, diabetes, prolonged ICU stay, renal failure etc. Among aspergillosis patients it was found to be also broad spectrum antibiotic use, indwelling catheters, steroid use, uncontrolled sugars and also newly detected diabetic patients, ICU stay, renal failure etc. In patients with candidemia it was found that indwelling catheters were the most common risk factor followed by broad spectrum antibiotic use, TPN, malignancy, chemotherapy, diabetes, steroid use, major surgery etc.

Association of risk factors and invasive fungal infections: There was a significant association between the presences of risk factors such diabetes, hemodialysis, steroid use, TPN and type of IFD. 95%

of patients with mucormycosis had diabetes (p value 0.00), and 64.43% of those with aspergillosis had concomitant steroid use (p value 0.007). There is significant association between presence of risk factors like Hemodialysis and candidiasis (60.0%) which has a p value 0.002. 34% candidiasis were also found have a significant association with TPN (

p value 0.001). Other risk factors like indwelling catheters, ICU stay, diabetes, major surgery, renal failure, prolonged ventilation, old PTB, neutropenia and chemotherapy were found to have no association with Invasive fungal disease.

Mucormycosis – Microbiological Profile

| HRCT /CT BRAIN | TOATAL (PERCENTAGE) |
|-------------------|---------------------|
| Angioinvasion | 10(24.4%) |
| Cavity | 8(19.5%) |
| Halo sign | 7(17.1%) |
| Air crescent sign | 3(7.3%) |

Radiological Findings of Mucormycosis

| MRI Brain findings | Total (PERCENTAGE) |
|----------------------------------|--------------------|
| Angio invasion | 9(22.0%) |
| Local tissue invasion | 4(9.8%) |
| Sinusitis and mucosal thickening | 3(7.3%) |

The response monitoring in patients with IFD who receives antifungal treatment has been done clinically, by assessing the improved in signs and symptoms. Patients with Mucor and Aspergillosis were monitored with repeat KOH and in possible cases with repeat imaging like MRI/CT or endoscopies like bronchoscopy or FESS. Patients with candidemia have been monitored with repeat blood cultures. Out of 50 patients with Candidiasis 22(44.0%) were improved, 19 (38.0%) were died and 9(18.0%) were lost to follow up. Among 41 patients with Mucormycosis 20(48.8%) were improved, 8(19.5%) were died and 13(31.7%) were lost to follow up. Among the 21 patients affected with invasive aspergillosis 15(53.6%) were improved, 8(19.5%) were died and 13(31.7%) were lost to follow up. Among the cryptococcosis the mortality was 2(5.6%).

Discussion

In our present study done over a period of one and half year, the number of IFD cases among the in-patients admitted was 130 which includes the proven and probable IFD. [3-5] Out of 130 patients the most common invasive fungal infection found to be candidiasis 50(38.5%), followed by mucormycosis 41(31.5%), aspergillosis 28(21.5%), mixed infections 9(6.9%) and cryptococcosis 2(1.5%). The organ systems most predominantly involved in Mucor are rhino cerebral which includes 34(82.92%), pulmonary 5(12.19%), skin (deep seated wound infection and proven by tissue biopsy) 1(2.43%) and fungal keratitis 1(2.43%). Among the aspergillosis 5(17.85%) had rhino cerebral involvement and 23(82.14%) has pulmonary involvement. Candida species were isolated from different body fluids and cryptococcosis was proven from CSF India ink and cryptococcal antigen test.

Age group and invasive fungal infections

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The age ranges from 16 to 88 years with mean age of 52.2 years among patients admitted with IFD. Sixty three percentage (63%) were male patients and thirty six percentage (36%) were female patients .A study including five Asian countries shows the median age is 54 years with 74(47.7%) were males out of 155 cases which is done in 2017(5). Gurmaet Singh *et al* (83), also shows age between 18 to 79 years with mean age of 58 years and majority were males(52.7%) and in Singh T *et al*¹⁰ has an age range between 18 to 80 years with mean age of 43.5 years.

The most common risk factor in most of the Indian studies regarding IFD is diabetes (28.6%) and the current study shows 66.7% of IFD had diabetes. The study done in

Asian countries also shows the most common risk factor for IFD as diabetes (n=60, 38.7%), study done in ICU with a sample size of 155(5). [6]

Association of risk factors

In this study there was a significant association between the presence of risk factors such as diabetes, hemodialysis, steroid use, TPN etc. [7,8] 95% of patients with mucormycosis had diabetes, 60% of those with candidiasis were undergoing hemodialysis, and 64.43% of those with aspergillosis have concomitant steroid use. Study done in Asian countries shows risk factors like diabetic (p value .002), prolonged use of steroids and recent onset neutropenia has significant association(5) with invasive fungal disease. Diabetes mellitus has significant association between invasive fungal disease (p value .000) as compared to other Indian studies (p < 0.25) (83). Possibly the decreased functional activity of macrophages in patients with diabetes mellitus predisposes to invasive fungal infections. 9,10]

Out of 90 patients in ICU 32(38.88%) patients died of IFD, in which 16(50.0%) were stayed in ICU for one week, 11(34.3%) patient stayed in ICU for 2 weeks and 5(15.6) patients stayed in ICU for 3 weeks. In this study all patients who died of IFD had a prolonged stay in ICU for more than a week. Mortality with candidiasis 19(38.0%), mucormycosis is 8 (19.5%), aspergillosis 8(28.6%), Cryptococcus is 2(5.56%) and mixed infections 2(22.2%). Mortality with candidemia is similar to the other studies from India and other IFD has a lower mortality rate in this study. The lower mortality rate in this study is probably due to the majority of patients who has not received treatment as they were discharged at request due to various reasons. [11,12]

Out of 130 patients who had IFD in which 90(69.23%) were in ICU and all patients had indwelling catheters like central venous line 32(100.0%), 31(96.87%) had foleys catheter, 30(93.75%) had arterial line, 25(78.12%) had hemodialysis catheter and 6(18.75%) had tracheostomy. This is similar to a study done by Tirath Singh from Ludhiana (84), which shows the risk of IFD and the high mortality among 91 patients with urinary catheterization 78(85.7%), central venous line 74(81.3%), prolonged ventilation 48(52.7%) [13] etc.

As per our study the mortality is found to be 27.69% in IFD, 46.15% survived after treatment with antifungal drugs and about 26.16% lost to follow up. Ravikant et al (9) shows mortality associated with IFD among patients hospitalized in critical care has reached up to 67%. The mortality in the current study is low, probably due to the patients that were lost to follow up.

Conclusion

The total number of patients diagnosed to have Invasive Fungal Disease for a period of one and half year among all the admitted patients was 150. The most common invasive fungal infections were found to be candidiasis (38.5%), followed by Mucormycosis (21.5%), Aspergillosis (6.9%) and Cryptococcosis(1.5%) . The most common organ systems involved were rhino cerebral and pulmonary and the most common Invasive fungal diseases affecting these organs were found to be Mucormycosis in rhino-cerebral is 82.9% and pulmonary is 12.2% Aspergillus affecting pulmonary system is 82.1% and rhino cerebral is 17.9%. Candidiasis is most commonly found in age group of 50 to 59 years, which is about 14(28.0%) and Candidemia is found to the most common blood stream infections which is 88.0%. Out of 90 patients in ICU 32(38.9%) patients died of IFD, of which 16(50.0%) were stayed in ICU for one week 11(34.3%) patient had ICU stay for 2 weeks.

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