Clinical spectrum and outcome of hospitalized patients with invasive fungal infections: a prospective study from a medical ward/intensive care unit of a teaching hospital in North India

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SUMMARY

The aim of the study was to determine the clinical spectrum and outcome of invasive fungal infections (IFIs) in hospitalized patients. A prospective study was conducted in a teaching hospital in North India between December 2016 and December 2018. Patients diagnosed with IFIs were enrolled. Their clinical and laboratory parameters were recorded using a pre-defined clinical report form. They were followed up till discharge or death and a 60-day outcome was recorded. A total of 110 IFI cases were identified, which included invasive aspergillosis (39%), invasive candidiasis (16%), cryptococcosis (14%) and mucormycosis (12%). Pneumonia (63%) was the most common final diagnosis in these patients. Diabetes mellitus, chronic kidney disease and chronic obstructive pulmonary disease were the most common risk factor for all four diseases. Additionally, most patients with cryptococcosis had human immunodeficiency virus infection. Mortality was observed in 73% of the patients. Overall, IFIs are an important cause of morbidity and mortality in critically ill patients admitted to medical wards and ICUs.

Keywords: aspergillosis, mucormycosis, candidiasis, cryptococcosis.

INTRODUCTION

There has been a gradual increase in the incidence of invasive fungal infections (IFIs) worldwide. This increase has been attributed to widespread use of immunosuppressive therapy and invasive devices [1]. The most common fungi causing IFIs are *Candida*, *Aspergillus* and Mucorales. *Candida* is the most frequent cause of IFI with a very high crude and attributable mortality [2]. It is most commonly seen in critically ill patients with devices-in situ. The most common species reported around the world is *Candida albicans* but the prevalence of non-albicans *Candida* species has increased in recent years [1]. This is particularly true in the Indian context where non-albicans *Candida* spp. like *Candida tropicalis* are more common [3]. Invasive aspergillosis is commonly seen in post-haematopoietic stem cell transplant (HSCT) patients or in patients with prolonged neutropenia or hematological malignancies [4]. The most common presentation is involvement

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of lungs. The most common species around the world is *Aspergillus fumigatus* but *Aspergillus flavus* has been shown to be more common in Indian settings [5]. Pulmonary mucormycosis, although not as common as the previous two is not uncommon in post-HSCT patients around the world. In Indian patients, rhino-orbital mucormycosis is more common and is traditionally reported in patients with diabetic ketoacidosis [6]. The aim of this study was to analyze the clinical and microbiological profile of IFIs along with their outcome in hospitalized patients.

PATIENTS AND METHODS

A prospective study was conducted after taking permission from the institute's ethical committee in medical ward/intensive care unit of an apex care teaching hospital in North India. All hospitalized patients (above the age of 14 years) who were diagnosed with IFI were included after taking informed consent. IFIs were diagnosed using standard definitions that use clinical presentation, radiological, histopathological and microbiological (culture, antigen) features in combination. Identification and speciation of *Aspergillus* spp. and *Mucormycetes* was done based on the micro-morphological features observed on the lacto-phenol cotton blue mount based on the subculture. *Candida* spp. were identified and speciated by Matrix assisted laser desorption ionization time of flight mass spectrometry. The demographic, clinical, biochemical and microbiological parameters were recorded using a clinical report form. The management details along with outcome in terms of death or discharge was also recorded.

The collected data was entered and analyzed using Stata v11. Results were expressed as numbers and percentages for categorical variables and as mean and standard deviation (SD) or median with interquartile range in brackets for continuous variables. Fisher's exact test or chi-square test was used for testing associations between categorical variables. Analysis of variance was used for testing the difference in mean values across fungal species. Survival distribution function was estimated using the Kaplan-Meier product-limit method. Nonparametric (Log-rank and Wilcoxon signed rank) tests were used to compare the survival functions among the different fungal species.

RESULTS

A total of 110 hospitalized patients above the age of 14-years with IFI were enrolled in this study. Pneumonia (63%) was the most common diagnosis followed by urinary tract infection (14%), meningitis (14%), sinonasal infection (9%) and infective endocarditis (3%). Out of the 110 patients with IFI, 98 patients had one or other form of underlying chronic disease. The spectrum of fungal infections responsible for IFIs were as follows: invasive aspergillosis (n=60), invasive candidiasis (n=18), cryptococcosis (n=15), mucormycosis (n=13), histoplasmosis (n=1) and infections due to *Trichosporon* species (n=2) and *Exophiala jeanselmei* (n=1). The comparative demographic, clinical and laboratory features of invasive candidiasis, invasive aspergillosis, mucormycosis and cryptococcosis has been summarized in Table 1.

Of the 18 patients with invasive candidiasis, the following species were identified: *Candida parapsilosis* (7), *Candida glabrata* (4), *C. albicans* (2), *Candida guilliermondii* (2), *C. tropicalis* (1), *Candida auris* (1), *Candida krusei* (1). The following risk factors were noted in patients diagnosed with invasive candidiasis: diabetes mellitus (39%), chronic kidney disease (33%), chronic obstructive pulmonary disease (22%), chronic liver disease (28%), haematological malignancy (17%) and prior history of steroid use for more than 21 days (28%) (Table 1). Anti-fungal therapy with echinocandins could be initiated in 16 patients. In the other two patients, diagnosis of candidemia was made post-mortem. The median time between first symptom and diagnosis was 14 days (5.5-22 days). A total of 12 mortalities were observed in this group. The 60-day mortality did not significantly differ as a function of the underlying disease (p=0.909).

Of the 60 patients with invasive aspergillosis, 43 patients were culture positive. All patients had pulmonary involvement. The species wise distribution was as follows: *A. fumigatus* (26), *A. flavus* (8), *Aspergillus terreus* (7), *Aspergillus niger* (2). Rest of the 17 patients were diagnosed on the basis of clinical, radiological, microscopy and galactomannan positivity. Radiological features of lung involvement were seen in 48 patients. The following risk factors were noted in patients diagnosed with invasive aspergillosis: diabetes mellitus (65%), chronic kidney disease (60%), chronic obstructive pulmonary disease (28%), past his-

tory of tuberculosis (20%), and prior history of steroid use for more than 21 days (22%) (Table 1). The median time between onset of symptom and diagnosis of aspergillosis was 8 days. Except one individual, all patients received antifungals. Of these 59 patients, voriconazole could not be used in ten patients where amphotericin B was used. A total of 47 deaths were observed in this group. The 60-day mortality did not significantly differ as a function of underlying disease (p=0.144).

Of the 13 patients with mucormycosis, nine patients were culture positive. The most common species isolated were *Rhizopus oryzae* (n=5) followed by *Rhizopus microsporum* (n=3) and *Lichtheimia corymbifera* (n=1). The rest of the patients were diagnosed based on microscopy or histopathology alone. The most frequent localization was rhino-orbital (7/13) followed by pulmonary (5/13). Out of the 7 patients with rhino-orbital infection, three patients additionally had cerebral involvement. The following risk factors were noted in patients diagnosed with mucormycosis: diabetes mellitus (85%), chronic obstructive pulmonary disease (23%), past history of tuberculosis (23%), and prior history of steroid use for more than 21 days (23%) (Table 1). The median time for onset of symptom and diagnosis of mucormycosis was 6 days (1.5-7 days). All but one patient received amphotericin B. A total of nine mortalities were observed in this group. The 60-day mortality did not significantly differ as a function of underlying disease (p=0.144).

Of the fifteen patients with cryptococcosis, 14 patients were diagnosed with cryptococcal menin-

Table 1 - Comparison of demographic, clinical and laboratory features of invasive candidiasis, invasive aspergillosis, mucormycosis and cryptococcosis.

Parameter	*Invasive candidiasis*	*Invasive aspergillosis*	*Mucormycosis*	*Cryptococcosis*
Mean (SD) age, years	38.3 ± 17.8	44.8 ± 17.8	41.8 ± 18	34.1 ± 16
Number of patients	18	60	13	15
Male sex	10 (56%)	36 (60%)	8 (62%)	9 (60%)
Fever	18 (100%)	49 (82%)	5 (38%)	11 (73%)
Hypotension	16 (89%)	57 (95%)	8 (61%)	9 (60%)
Mechanical ventilation	11 (61%)	54 (90%)	7/13 (54%)	4 (27%)
Diabetes mellitus	7 (39%)	39 (65%)	11 (85%)	5 (33%)
Chronic obstructive pulmonary disease	4 (22%)	17 (28%)	3 (23%)	2 (13%)
Post-tubercular	3 (17%)	12 (20%)	3 (23%)	2/15 (13%)
Chronic liver disease	5 (28%)	7 (12%)	1 (8%)	0
Chronic kidney disease	6 (33%)	36 (60%)	4 (3%)	5 (33%)
Hemodialysis	6 (33%)	12 (20%)	0	0
Hematological malignancy	3 (17%)	2 (3%)	0	1 (7%)
Autoimmune disease	3 (17%)	9 (15%)	3 (23%)	0
Human immunodeficiency virus	0	4 (7%)	0	9 (60%)
Prior steroid use for >21 days	5 (28%)	13 (22%)	3 (23%)	2 (13%)
Median duration of hospital stay	29 (19.5-45.5)	18.5 (10.25-31.5)	19 (12-38)	28 (24-45)
Median duration of prior antibiotic use in days	5 (1-9)	5 (2-8)	2 (2-5)	0
Central venous catheter use	16 (89%)	60 (100%)	12 (92%)	15 (100%)
Median APACHE II score	17.5 (8-38)	39.5 (26.5-52.25)	12 (10-18)	18 (12-24)
Median SOFA score	12 (9-12)	17(12-18)	12 (12-18)	9 (5-12)
Median HbA1c	6.2 (5.8-7.1)	8.2 (6.1-9.2)	8.8 (8.1-10.2)	6.8 (5.4-8)
Median serum procalcitonin	0.8 (0.6-1.7)	1.2 (0.6-2)	0.6 (0.3-1.2)	0.4 (0.3-0.6)

*APACHE- acute physiological and chronic health evaluation score, SOFA- sequential organ function assessment score.

gitis based on cryptococcal antigen positivity in cerebrospinal fluid. One patient was diagnosed based on culture positivity of lymph node biopsy. The following risk factors were noted in patients diagnosed with cryptococcosis: human immunodeficiency virus infection (60%), diabetes mellitus (33%) and chronic kidney disease (33%) (Table 1). The median time between onset of symptoms and diagnosis of cryptococcosis was 6.5 days. All of the fifteen patients received amphotericin in combination with flucytosine/ fluconazole. Overall 12 deaths were observed. Patients without HIV had better probability of survival compared to HIV patients (p=0.025).

DISCUSSION

In our patients, the most common IFI was invasive pulmonary aspergillosis followed by candidemia. This was unlike other epidemiological studies where candidaemia was more common [7]. This may have been because ours was a medical ward/intensive care unit with pneumonia being the commonest cause of admission and most of our patients required mechanical ventilation. Also, DM and COPD were amongst the commonest co-morbidities and many of our patients were on steroids. These are established risk factors for invasive aspergillosis [5]. The demographic and clinical features in our study was similar to other studies done in past. *A. fumigatus* followed by *A. flavus* were the commonest species noted in our study unlike other Indian studies [5].

Candidemia was also seen in our study, albeit not as commonly. Use of broad-spectrum antibiotics and presence of central venous catheter (CVC) was common in patients who developed invasive candidiasis which have been found to be independent risk factors for candidemia in studies. Long duration of hospital stay such as in our study has been established as one of the most important risk factor for invasive candidiasis in non-neutropenic adults [3]. In most studies around the world, *C. albicans* is the most common species causing invasive candidiasis [8]. However, in Indian ICUs, non-albicans Candida are more common with the most common species being reported is *C. tropicalis* [5]. In our study, non-albicans candida were more common as well. *C. parapsilosis* was noted to be the most common species. This is mostly because most of the patients who developed invasive candidiasis had CVC *in situ* and *C. parapsilosis* is notorious for the ability to form biofilms on catheters and its potential for nosocomial spread by the hands of healthcare workers due to its ability to persist in the hospital environment [9].

Mucormycosis involving the rhino-orbital site was the commonest clinical type followed by pulmonary in our study. This was in concordance with previous studies from India [10]. However, the time period between onset of symptoms and diagnosis was 6 days which was lesser than other studies. Uncontrolled type 2 diabetes is known to be the most significant risk factor for mucormycosis in most India studies [10]. Similar result was observed in our study.

Cryptococcosis was noted more commonly in patients with HIV. This in concordance with most other studies as HIV is the most important risk factor for cryptococcosis [11]. Surprisingly, six out of 15 patients diagnosed with cryptococcosis were HIV negative. Understandably, the survival in HIV negative group was better. The demographic and clinical features in our study was similar to other studies done in past [11].

Mortality rate was probably higher because ours is an apex care referral institute with most patients that get admitted are critically ill. This is reflected by the very high baseline APACHE and SOFA score in all the four groups.

IFIs are largely under-reported in low- and middle-income countries due to lack of proper diagnostic facilities. With advent of better infrastructure and diagnostics, the true burden of fungal infections is now being realized [12-15]. IFIs should be suspected in critically ill patients admitted in medical wards and ICUs, especially if they have concurrent DM and/or CKD. Heightened suspicion will decrease the time to diagnosis and may decrease the considerable mortality associated with these diseases.

Conflict of interest: none

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