ORIGINAL RESEARCH PAPER

Pulmonary Medicine

INVASIVE FUNGAL INFECTIONS IN RESPIRATORY INTENSIVE CARE UNIT: EPIDEMIOLOGY AND RISK FACTORS

KEY WORDS: Invasive Fungal infections, Candidemia, Aspergillus, Respiratory intensive care unit

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ABSTRACT

Background: Invasive fungal infections (IFA) are a growing problem in critically ill patients and these infections carry a high attributable mortality and morbidity. The incidence of fungal infections has increased considerably over the last several years.

Aims: The present study was intended to describe the epidemiology and risk factors associate with fungal infections/ colonization in a respiratory intensive care unit (ICU) of a tertiary care teaching hospital.

Settings and Design: All consecutive adult patients (≥ 18 years) admitted to respiratory ICU of the institution from January 2015 to December 2016 were surveilled for fungal infection or fungal colonization.

Material and methods: All patients with positive fungal isolates from any of the biological samples viz. blood, body fluids, respiratory samples, urine, pus, fine needle aspiration cytology and surgical drain fluid, either on admission or during stay were enrolled. For every positive fungal isolates the information pertaining to demographics, clinical, radiological and microbiological data was collected on a predesigned structured performa.

Results: During this period a total of 3140 patients were admitted to respiratory ICU. Positive fungal isolates from any of the biological samples was there in 156 patients, of which 72 (46.2%) had invasive fungal infection, and 84 (53.8%) had fungal colonization. The incidence of fungal infections in our intensive care units was 22.9 cases per 1,000 admissions in our study. The risk factors significantly ($p<0.05$) associate with IFI included use of broad spectrum antibiotics, mechanical ventilation, central venous catheterization, diabetes mellitus and malignancy.

The most common fungus isolated in patients with invasive fungal infections was Candida spp. in 54 (75%) patients, followed by Aspergillus spp. (22.2%). Among the Candida isolates C. tropicalis (38.9%) was most common and among the molds A. flavus (59.1%) was most common The most common specimens yielding IFI were blood (58.3%) followed by tissue cultures (26.4%) from various sites

Conclusion: Candidemia was the most frequent IFI in respiratory ICU patients. Candida non albicans were the most frequent isolates with C. tropicalis being the most common. Broad spectrum antibiotic use, diabetes mellitus, mechanical ventilation and malignancy were significantly associated with invasive fungal infections.

INTRODUCTION

Invasive fungal infections (IFI) are a growing problem in critically ill patients and these infections carry an attributable mortality and morbidity that is much higher than bacterial infections. The incidence of fungal infections has increased considerably over the last several years. Rampant and inappropriate use of antibiotics, widespread use of immunosuppressant drugs and improved knowledge of fungal diseases has led to the increased incidence of fungal infections.

Systemic fungal infections have become a major issue in intensive care settings both in developed and developing nations. National nosocomial infections surveillance from United States reported an increased incidence of nosocomial fungal infections from 2 to 3.8 per 1000 from 1980-1990. [1]

The fungi most commonly associated with infections in the critically ill patients include Candida and Aspergillus. [2] Less common causes include Zygomycetes, Histoplasma, Cryptococcus, Blastomyces, and Coccidioides. Mortality from candidemia has remained high in spite of advances in diagnosis, treatment, prophylaxis, and infection control. A multicentric study from Indian intensive care units reported a 30-day crude mortality of about 45% for candidemia. [3] There is limited data on the incidence and pattern of fungal infections from India especially in the intensive care setting. [4] The present study was intended to describe the surveillance of fungal infections/ colonization and its associated risk factors in respiratory ICU settings.

MATERIAL AND METHODS

This observational study was carried out at in a 1400-bed tertiary care teaching hospital in Northwest India. All consecutive adult patients (≥ 18 years) admitted to respiratory ICU of the institution from January 2015 to December 2016 were surveilled for fungal infection or fungal colonization. During this period a total of 3140 patients were admitted and treated in all the ICUs of which 156 patients had fungal colonization/ infections. The ethical clearance was taken from the institutional ethics committee.

All patients with positive fungal isolates from any of the biological samples viz. blood, body fluids [ascitic fluid, pleural fluid, cerebrospinal fluid (CSF)], respiratory samples [sputum, endotracheal aspirate, bronchoalveolar lavage (BAL) fluid], urine, pus, fine needle aspiration cytology and surgical drain fluid, either on admission or during stay were enrolled. For every positive fungal isolates the information pertaining to demographic data [age, gender], clinical data [risk factors viz. presence of central venous catheter (CVC), urinary catheterization, steroid therapy, total parenteral nutrition, mechanical ventilation, diabetes mellitus, alcohol use, recent major surgery, malignancy, peritoneal dialysis, concomitant bacterial infections and antibiotic therapy, antifungal prophylaxis and treatment], microbiological data (etiological agents, ICU stay before the isolation of fungus), radiological and/or histological findings and outcome was collected on a predesigned structured performa. The blood sample and body fluids were collected under aseptic conditions in BACTEC culture vials. All biological samples were cultured on two Sabouraud chloramphenicol dextrose agar plates, incubated at 36 ± 1 and 28° C (for yeasts and molds isolation), and examined daily until 4 weeks. Yeasts identification was performed with sugar assimilation profiles. Filamentous fungi were identified at the levels of genera and species using macro- and micromorphology observations, according to standard methods [5]. The galactomannan (GM) antigen test was performed in patients with clinical signs and/or symptoms suggestive of invasive aspergillosis (development of pulmonary infiltrates on chest X-ray, fever refractory to at least 3 days of appropriate antibiotics, pleuritic chest pain). GM in serum was measured using a sandwich ELISA. An optical density ratio ≥ 0.5 in serum was considered to be positive. Samples that yielded positive results, in which interference was known to have occurred, were excluded.

Criteria for diagnosis of invasive fungal infection (IFI)

- Isolation of Candida species from blood, sterile body fluids (ascitic fluid, pleural fluid, CSF) pus or FNAC culture
- Isolation of Aspergillus species/Mucor from a normally sterile or non-sterile body site, in conjunction with suggestive clinical manifestations and other lab test findings (like Galactomanin, HRCT Chest)

Criteria for diagnosis of fungal colonization

- Isolation of Candida species on sputum, endotracheal aspirate, BAL or surgical drain fluid culture.
- Isolation of Aspergillus species from non-sterile body site without clinical manifestations and other lab test findings suggestive of invasive fungal infection.

STATISTICAL ANALYSIS

The data collected were expressed in numbers and percentages. Mean and standard deviation were computed. The difference between the two groups was compared using the Z-test for proportion. A p-value less than or equal to 0.05 was considered statistically significant.

The analysis was performed using Statistical Package for Social Sciences (SPSS) version 20.0.

RESULTS

Amongst the 156 positive fungal isolates 72 (46.2%) had invasive fungal infection, and 84 (53.8%) had fungal colonization. The incidence of fungal infections in our intensive care unit was 22.9 cases per 1,000 admissions. The median age of patients with fungal infection and fungal colonization were 58.5 and 58 years, respectively. The demographic details and underlying risk factors in patients with fungal infection and colonization is given in Table 1.

Table1: Demographic details and Underlying Risk factors in patients with invasive fungal infection and fungal colonization

Risk factors	Fungal infection (n=72)	Fungal colonization (n=84)	p value
Age (years)	51.8 ± 18.6	50.88 ± 19.3	0.6187
Males	46 (63.9)	52 (61.9)	0.7948
Age (years)	51.8 ± 18.6	50.88 ± 19.3	0.6187
Males	46 (63.9)	52 (61.9)	0.7948
Broad spectrum antibiotics	72 (100)	80 (95.26)	0.0301
Urinary catheterization	50 (69.4)	46 (54.8)	0.7113
Invasive Mechanical ventilation	47 (65.3)	30 (35.7)	0.0002
Sepsis	45 (62.5)	42 (50.0)	0.2040
Central venous catheterization	34 (47.2)	32 (38.1)	0.0046
Diabetes Mellitus	30 (41.7)	20 (23.8)	0.0063
Alcohol	18 (25.0)	26 (30.9)	0.2891
Corticosteroid use	14 (19.4)	19 (22.6)	0.4593
Malignancy	14 (19.4)	6 (7.1)	0.0220
Major surgery	8 (11.1)	10(11.9)	0.8807
Peritoneal dialysis	4 (5.6)	21 (25.0)	0.0394
Total Parental nutrition	5 (6.9)	6 (7.1)	0.9601
Organ transplant	2 (2.8)	0	--
HIV/AIDS	2 (2.8)	3 (3.5)	0.7794

In 4 cases (5.6 %), IFI was present at the time of ICU admission, while in 68 (94.45 %) it occurred during ICU stay. The mean ICU stay before the isolation of fungus in the fungal infection and colonization groups were 10.3 (range 4- 41) days and 6.7 (range 1-14) days respectively.

The most common risk factor in patients with invasive fungal infection was use of broad spectrum antibiotics (100%). Other risk factors included urinary catheterization (69.4%), invasive mechanical ventilation (65.3%), sepsis (62.5%), central venous catheterization (47.2%), diabetes mellitus (41.7%), alcohol (25.0%), corticosteroid use (19.4%), malignancy (19.4%), abdominal surgery (11.1%), total parentral nutrition (6.9%), peritoneal dialysis (5.6%), organ transplant (2.8%) and HIV/AIDS (2.8%). Broad spectrum antibiotics, invasive mechanical ventilation, central venous catheterization, diabetes mellitus and malignancy were significantly ($p<0.05$) more in patients with IFI than in colonizers.

The preference of empirical antibiotics in the critically ill patients was at the judgment of the treating clinician, which was modified during the course of stay depending on bacterial culture sensitivity reports. The most common antibiotic group used in patients with invasive fungal infections was ureidopenicillins (57.2%) followed carbapenems (48.6%), glycopeptides (48.6%), cephalosporins (47.2%), and nitroimidazole (44.4%). The use of cephalosporins was observed in 76.2%, fluroquinolones in 45.2%, aminopenicillins in 42.9%, macrolide in 28.6%, oxazolidine in 23.8% and lincosamide in 21.4% of the patients with the fungal colonization. (Table 2)

Table 2: Various classes of antibiotics used in patients with invasive fungal infections and fungal colonization

Antibiotic class	Fungal infection (n=72)	Fungal colonization (n=84)	p value
Uriedopenicillins	39 (57.2)	18 (21.4)	0.0001
Carbapenems	35 (48.6)	22 (26.2)	0.0037
Glycopeptides	35 (48.6)	8 (9.5)	0.0001
Aminoglycosides	20 (27.8)	14 (16.7)	0.0929
Cephalosporins	34 (47.2)	64 (76.2)	0.0002
Flouroquinolones	18 (25.0)	38 (45.2)	0.0085
Aminopenicillins	16 (22.2)	36 (42.9)	0.0063
Lincosamide	6 (8.3)	18 (21.4)	0.0238
Oxazolidine	6 (8.3)	20 (23.8)	0.0096
Macrolides	4 (5.5)	24 (28.6)	0.0002

The most common fungus isolated in patients with invasive fungal infections was Candida spp. in 54 (75%) patients, followed by Aspergillus spp. (22.2%) (Table 3). Among the 54 Candida isolates C. tropicalis (38.9%) was most common followed by C. albicans (31.4%). Other candida isolates were C. krusei (9.3%), C. parasilosis (7.4%), C. lusitaniae and C. glabrata (3.7%; each), C. guilliermondii, C. kefyr and C. lipolytica (1.8%; each). Among the molds, A. flavus (55.6%) was most common isolate followed by A. fumigates (33.3%) and Mucor spp. (11.1%).

The most common fungus isolated in patients with fungal colonization was Candida spp. in 62 (73.8%) patients (Table 3). Among the 62 patients with Candida colonization, C. tropicalis (29.0%) was most common isolate followed by C. albicans (25.8%). Other candida isolates observed were C. parasilosis (9.7%), C. krusei (8.1%), C.lusitaniae (6.5%), C.glabrata and C. kefyr (4.8%; each), C. guilliermondii, C. lipolytica and C. stellatoides (3.2%; each) and C. rugosa(1.6%). Among the molds A. flavus (59.1%) was most common isolate followed by A. fumigates (40.9%).

Table3: Distribution of fungal isolates in patients with invasive fungal infection and fungal colonization

Fungus	Fungal infection (n=72)	Fungal colonization (n=84)	p value
Candida spp.	**54 (75.0)**	**62 (73.8)**	0.8650
C. albicans	17 (31.4)	16 (25.8)	0.4965
C. tropicalis	21 (38.9)	18 (29.0)	0.2627
C. krusei	5 (9.3)	5 (8.1)	0.8181
C. parasilosis	4 (7.4)	6 (9.7)	0.6672
C. lusitaniae	2 (3.7)	4 (6.5)	0.5028
C. glabrata	2 (3.7)	3 (4.8)	0.7641
C. guilliermondii	1 (1.8)	2 (3.2)	0.6383
C. kefyr	1 (1.8)	3 (4.8)	0.3788
C. lipolytica	1 (1.8)	2 (3.2)	0.6383
C. rugosa	-	1 (1.6)	--
C. stellatoides	-	2 (3.2)	--
Molds	**18 (25.0)**	**22 (26.2)**	0.8650
Aspergillus spp.	16 (88.9)	22 (100.0)	0.0001
A.flavus	10 (55.6)	13 (59.1)	0.1498
A.fumigatus	6 (33.3)	9 (40.9)	0.6100
Mucor species	2 (11.1)	-	--

The most common specimens yielding IFI were blood (58.3%) followed by tissue cultures (26.4%). (Table 4) Various other specimens yielding of IFI were BAL (8.3%), ascetic fluid (4.2%), pus and pleural fluid (1.4%; each). In patients with blood stream fungal infections, the most common fungus isolated was C. tropicalis (42.8%), followed by C. albicans (33.3. %), C. krusei (7.1 %), C. parasilosis (4.8%), C. lusitaniae, C. glabrata, C. guilliermondii, C. kefyr and C. lipolytica (2.4%; each). Among patients with fungal culture positive from various tissues sites the most common isolate was A. flavus (36.8%) followed by A. fumigates and C. tropicalis (15.8%; each), C. albicans and Mucor spp. (10.5 %; each), C. krusei and C. parasilosis (5.3%; each)

The most common specimens yielding fungal colonization was urine (36.9%) and sputum (26.2%) cultures. Various other specimens yielding fungal colonization were endotracheal aspirate (21.4%), BAL (9.5%), surgical and chest drain (5.9%). (Table 4)

Table 4: Specimen-wise distribution of isolates amongst patients with Fungal infections and Fungal Colonization

Fungal infections	Number (%age)	**Fungal Colonization**	Number (%age)
Blood	**42 (58.3)**	**Urine**	**31 (36.9)**
C. albicans	14 (33.3)	C. albicans	5 (16.1)
C. tropicalis	18 (42.8)	C. tropicalis	7 (22.6)
C. krusei	3 (7.1)	C. krusei	4 (12.9)
C. parasilosis	2 (4.8)	C. parasilosis	4 (12.9)
C. lusitaniae	1 (2.4)	C. lusitaniae	3 (9.7)
C. glabrata	1 (2.4)	C. glabrata	2 (6.5)
C. guilliermondii	1 (2.4)	C. guilliermondii	1 (3.2)
C. kefyr	1 (2.4)	C. kefyr	2 (6.5)
C. lipolytica	1 (2.4)	C. lipolytica	1 (3.2)
Tissues	**19 (26.4)**	C. rugosa	1 (3.2)
C. albicans	2 (10.5)	C. stellatoides	1 (3.2)
C. tropicalis	3 (15.8)	**Bronchoalveolar lavage**	**8 (9.5)**
C. krusei	1 (5.3)	C. albicans	2 (25.0)
C. parasilosis	1 (5.3)	C. tropicalis	2 (25.0)
A. fumigates	3 (15.8)	A. fumigates	2 (25.0)
A. flavus	7 (36.8)	A. flavus	2 (25.0)
Mucor Spp.	2 (10.5)	**Sputum**	**22 (26.2)**
Bronchoalveolar lavage	**6 (8.3)**	C. albicans	4 (18.1)
A. fumigates	3 (50.0)	C. tropicalis	5 (22.7)
A. flavus	3 (50.0)	C. krusei	1 (4.5)
Ascitic fluid	**3 (4.2)**	C. parasilosis	1 (4.5)
C. albicans	1 (33.3)	C. lusitaniae	1 (4.5)
C. krusei	1 (33.3)	A. fumigates	5 (22.7)
C. parasilosis	1 (33.3)	A. flavus	5 (22.7)
Pus	**1 (1.4)**	**Endotracheal aspirate**	**18 (21.4)**
C. lusitaniae	1 (100.0)	C.albicans	3 (16.7)
Pleural fluid	**1 (1.4)**	C. tropicalis	3 (16.7)
C. glabrata	1 (100.0)	C. parasilosis	1 (5.5)
		C. guilliermondii	1 (5.5)
		C. kefyr	1 (5.5)
		C. lipolytica	1 (5.5)
		A. fumigates	2 (11.1)
		A. flavus	6 (33.3)
		Chest tube Drain	**2** (2.4)
		C. albicans	1 (50.0)
		C. tropicalis	1 (50.0)
		Surgical drains	**3** (3.6)
		C. albicans	1 (33.3)
		C. stellatoides	1 (33.3)
		C. glabrata	1 (33.3)

DISCUSSION

Despite the advances in diagnostic and therapeutic interventions, infections continue to be an integral part of ICU across the globe. The last few years have witnessed an increase in the incidence of invasive fungal infection which has coincided with an increase number of immunosuppressed patients, inappropriate and wide spread use of antibiotics and antifungals.

The median age of patients with invasive fungal infection in the present study was 58 years (range 18 to 88 years), this is similar to that reported in various other studies. A multicenter Italian survey (AURORA Project) reported a median age of 60 (44.5–71) years in patients with invasive fungal infections.[5] In another study from Indonesia, the median age of patients with invasive fungal disease in critically ill patients was 58 years (range, 18–79 years).[6]

There was male (60.2%) predominance of patients with invasive fungal infections in our cohort of patients admitted to respiratory ICU which is consistent with other studies. [5, 6] However, gender is not a predisposing factor of IFI.

Our study shows that IFIs represent an important infectious complication in critically ill patients with an overall incidence of 22.9 cases per 1,000 admissions. In our cohort, Candida sp. was the most common fungus isolated (75%) and amongst the various specimens for IFI Candida BSI was the most common. The incidence of Candida BSI in our study was13.4 cases per 1,000 admissions which is in coherence with various other studies. In an Italian study, Tortorano et al. [7] found an incidence of 10.08 per 1,000 admissions for Candida BSI. A multicenter Italian survey (AURORA Project) reported an incidence of 16.5 cases per 1,000 admissions for Candida BSI [6]. However, Dimopoulos et al.[8] and Jorda`-Marcos et al.[9] reported a higher incidence of 35.7 and 54 cases per 1,000 admissions, respectively. The differences among various studies may be due to several factors, including diversity in patient age, variations in clinical and microbiological practices and differences in drugs usage.

Although C. albicans is still regarded as the most common species [10] however, some studies have demonstrated an increasing incidence of Candida non- albicans candidemia, with C. glabrata and C. parapsilosis[11-14] being the commonest. In our study

candida non albicans were the most frequent etiologic agent for candidemia, with C. tropicalis ranking the topmost (38.9%). The reason for this change in the distribution pattern of Candida species is not known, but certain predisposing factors such as indwelling, catheters and parenteral nutrition, neutropenia and previous exposure to azoles may contribute to it.

In the present study the risk factors significantly ($p<0.05$) associate with IFI included use of broad spectrum antibiotics, mechanical ventilation, central venous catheterization, diabetes mellitus and malignancy which is consistent with other studies. In a study by Singh et al [5] from Indonesia diabetes mellitus and mechanical ventilation were significantly more in patients with IFI. Observations on central venous catheter (CVC), as a risk for IFI have yielded mixed results. Few studies [15, 16] have reported that CVC is a risk factor for IFD in critically ill patients while others [11, 17] could not find any such relationship. The difference might be caused by varying methods of CVC insertion and care of patients with CVC.

There was no significant association between sepsis and IFD in the present study. Similar observations have been made by Singh et al.,[18] Paswan et al.,[17] Fraser et al.,[15] and Pittet et al.[19] however, Chow et al.[11] reported a significant association between sepsis and IFI.

Major surgery was reported as a risk factor in IFI by Chow et al.[11] however, we could not find any such association. The present study could not find a significant association between parenteral nutrition and IFI. Various studies [11, 15, 16] have reported parenteral nutrition as a risk factor of IFI. This difference might be caused by early institution of enteral nutrition in our study which is a routine protocol. All the patients having IFI were on broad-spectrum antibiotics. The most common antibiotic group used in patients with fungal infections was ureidopenicillins, carbapenems, glycopeptides, cephalosporins and nitroimidazole. Studies by Pittet et al.,[19] and Wey et al.,[20] reported that type and duration of antibiotic treatment affects the occurrence of IFI.

In our study, the mold infections were less common than yeast infections (ratio 1:4). The incidence of invasive pulmonary aspergillosis (IPA) was 5.1/1,000 admissions. This is higher than the multicenter Italian survey [6] which reported an incidence of 2.3 cases per 1,000 admissions. Now a day's IPA has gained importance in the ICU setting, causing IFI ranging from 0.3 to 6.9 % [21, 22] In the present study most of the cases of IPA occurred in patients with acute exacerbation of chronic obstructive pulmonary disease, diabetes, and in those on corticosteroids.

In conclusion, candidemia was the most frequent IFI in ICU patients. Candida non albicans were the most frequent isolates with C. tropicalis being the most common. Diabetes mellitus, mechanical ventilation and malignancy were significantly associated with invasive fungal infections.

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