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MORTALITY OUTCOMES ASSOCIATED WITH INVASIVE ASPERGILLOSIS

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ABSTRACT

Prognostic variables for invasive aspergillosis (IA) are poorly recognised, despite the disease's high mortality rate. The majority of studies on clinical implications of Aspergillus species infections have focused on patients with opportunistic infection that primarily affects cancer patients and immunocompromised individuals who have prolonged neutropenia. This study was carried out prospectively in a tertiary care hospital in Navi Mumbai, India, between January 2014 and December 2015. Standard microbiological protocols were followed in the collection and processing of samples from a total of 1785 patients. Out of the 251 patients that tested positive for Aspergillus, 8 individuals (3.19%) died as a result of their infections; males were 5 (62.50%), and females were 3 (37.5%). Maximum age group for those over 50, or 5 (62.5%), is followed by those between the ages of 31 and 40, or 1 (12.5%), and 41 and 50, or 2 (25%). Five (62.5%) and three (37.5%) deaths were attributable to Aspergillus fumigatus and Aspergillus niger, respectively.The highest number of causes of mortality in cases of Aspergillosis was found to be Allergic Broncopulmonary Aspergillosis (ABPA), which accounted for 2 cases. This was followed by Chronic Pulmonary Aspergillosis, Invasive Aspergillosis in Solid Organ Transplant, HIV, Tuberculosis, Diabetes, and Lung Cancer, which each accounted for 1 case. The study assessed the variations in therapy, comorbidities, and demographics between the in-hospital mortality and survival groups. Additionally, multivariate analysis was done to find mortality risk factors. The current study displays the mortality trend for patients with IA during a two-year span. Acute renal failure, bone marrow transplantation, intubation, advanced age, male gender, and patients were on steroid use was identified as death risk factors.

KEYWORDS: Invasive aspergillosis, Allergic Broncopulmonary Aspergillosis, HIV, Aspergillus Fumigatus.

INTRODUCTION

The prevalent invasive fungal infection known as invasive aspergillosis (IA) mainly affects patients with compromised immune systems. Severe pneumonia and respiratory failure are common the outcomes of the majority of IA cases that affect the lungs (1, 2). IA is becoming more common every year (3), diabetes mellitus, chronic obstructive pulmonary disease, end-stage renal disease, and long-term steroid use are the factors for IA (4). In addition to improved diagnostic tools and antifungal therapies, identifying predictors of death may aid in identifying individuals with high mortality rates who could benefit from more aggressive therapy, resulting in patients outcome (5).

Study found that steroid use was associated with low survival of patients (6). There was no significant relationship established between patients which were on steroid and morale in invasive pulmonary aspergillosis (7). The latter authors identified respiratory failure, diabetes, and prolonged hospitalisation as independent predictors of poor prognosis. A study on ICU patients with invasive aspergillosis and discovered that older age, bone marrow transplantation, mechanical ventilation, and renal replacement therapy were found responsible for poor outcome (1).

A study conducted on the epidemiology of invasive mould infections in 5 countries of Asia, concluding that disseminated disease, rheumatic disease were predictive of mortality (8). However, some data suggest that Aspergillus species might induce invasive illness in patients in different settings, including intensive care units (9-13).

Clinical diagnosis of invasive aspergillosis is quite difficult, because standard diagnostic definitions have only been developed and validated for cancer patients

(14). IA is thought to be a rare disease among critically sick patients (15-17).

Patients acquired invasive aspergillosis; the mortality rate for these patients was 60% (18). In another study, researchers discovered that 7% of people with IA had a 91% mortality rate. Surprisingly, invasive fungal infection was not a risk factor for 70% of these patients (19). Furthermore, IA is frequently misdiagnosed and connected to poor outcomes in critical care patients, where it can affect many organs and lead to a broad disease (20).

Samples taken from non-sterile body locations, such as trachea and bronchi, in that case the diagnosis of invasive aspergillosis is frequently assumed (21). Because Aspergillus species are so common, it is important to exercise caution when presuming that fungus collected from these samples have a pathogenic function. Aspergillus isolated from respiratory tract samples in immunocompromised patients has been extensively researched (22,23).

A positive Aspergillus culture may be more clinically relevant if other risk factors, such as chronic lung or liver illness or general weakness, are present (20). Nonetheless, patients with acute respiratory failure or critical illness are frequently unable to undergo invasive diagnostic procedures which are required to confirm the diagnosis of Aspergillus infection (24-26). Non-invasive diagnostic assays such as galactomannan measures necessitating future research in intensive care patients (10, 27).

Therefore, the aim of this study was to obtain data on mortality associated with invasive aspergillosis in patients attending a tertiary care hospital in Navi Mumbai.

MATERIALS AND METHODS

Patients and settings: This prospective study was carried out for two years, from January 2014 to December 2015, at the Department of Microbiology, MGM Medical College, Kamothe, Navi Mumbai, India. A total of 251 patients were enrolled, and samples were collected and processed using conventional microbiological procedures. Clinical suspicion of IA prior to ICU admission was an exclusion criterion.

Sample collection: Clinical samples such as sputum, Bronchoalveolar lavage (BAL), paranasal sinuses aspirates, eye swab, ear swab, blood, and pus from suspected cases of aspergillosis in different patients were collected in a sterile container.

Identification of Aspergillus species was done using standard methods (28)

RESULT

The current investigation was started in response to an invasive aspergillosis-related fatality. 251 (14.06%) of the 1785 samples that were tested for Aspergillus species proved positive for the fungus. and eight of those fatalities were linked to invasive aspergillosis. The highest number of deaths from invasive aspergillosis, 5 (62.5%) in males and 3 (37.5%) in females, was shown to be gender-specific. Age-wise distribution, there was a maximum of 5 (62.5%) in the age group 50 years and above, 2 (25%) in the age group 41 to 50 years, and 1 (12.5%) in the age group 31 to 40 years.

Aspergillus fumigatus, accounting for 5 (62.5%) of the total Aspergillus species identified in mortality, followed by Aspergillus niger, accounting for 3 (37.5%). (Table 4)

The type of Aspergillus species recorded in mortality were maximum due to Aspergillus fumigatus i.e. 5 (62.5%) and followed by Aspergillus niger i.e. 3 (37.5%). (Table 4)

The analysis of causes of death in invasive aspergillosis cases was recorded maximum due to allergic bronchopulmonary aspergillosis (ABPA) i.e. 2 (25%) followed by chronic pulmonary aspergillosis, invasive aspergillosis in Solid organ transplant, HIV, Tuberculosis, Diabetes and Lung cancer i.e. 1(12.5%) each. (Table 5)

Fungal and Bacterial growth in various clinical samples. Out of total 1785 samples 251 showed Aspergillus species, 19 (8%) samples showed only Aspergillus species growth, 196 (78%) samples showed mixed bacterial and Aspergillus growth and 36 (14%) samples showed Aspergillus and Candida mixed growth. (Table 6 and Fig.1)

Overall Aspergillus co-infection with other fungus and bacteria were Aspergillus isolated (251), Bacterial isolate (n=194) and other fungal isolates (n=36).

Aspergillus co-infection with other fungus and bacteria were recorded in sputum samples i.e. 104. Aspergillus species isolated was Aspergillus niger 61 (58.65%), Aspergillus fumigatus 24 (23.08%), Aspergillus flavus 12 (11.54%), Aspergillus brasiliensis 5 (4.81%) and Aspergillus terrus 2 (1.92%). Bacterial isolates was recorded Streptococcus pneumoniae 39 (37.50%), Pseudomonas aeruginosa 14 (13.46%), Klebsiella pneumoniae 11 (10.58%), Acinetobacter species 9 (8.65%), Streptococcus pyogenes 7 (6.73%), Staphylococcus aureus 6 (5.77%), Escherichia coli 5 (4.81%), Enterobater species 4 (3.85%), Coagulase negative staphylococcus (CoNS) 4 (3.85%), GNNF 3

(2.88%), Enterococcus species 2 (1.92%). Other fungal isolates were Candida albicans 15 (83.33%) and Penicillium species 3 (16.67%).

Aspergillus co-infection with other fungus and bacteria were recorded in nasal and paranasal sinuses samples i.e. 52. Aspergillus species isolated was Aspergillus niger 32 (61.54%), Aspergillus fumigatus 13 (25%), Aspergillus flavus 5 (9.62%) and Aspergillus brasiliensis 2 (3.85%). Bacterial isolates was recorded Streptococcus pneumoniae 15 (41.67%), Klebsiella pneumoniae 6 (16.67%), Acinetobacter species 6 (16.67%), Streptococcus pyogenes 5 (13.89%), Staphylococcus aureus 4 (11.11%) Other fungal isolates was Candida species5 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in pus samples i.e. 51. Aspergillus species isolated was Aspergillus niger 31 (60.78%), Aspergillus fumigatus 13 (25.49%), Aspergillus flavus 5 (9.80%), Aspergillus brasiliensis 1 (1.96%) and Aspergillus terrus 1 (1.96%). Bacterial isolates was recorded Staphylococcus aureus 16 (47.06%), Escherichia coli 8 (23.53%), Acinetobacter species 6 (17.65%), Pseudomonas aeruginosa 4 (11.76%). Other fungal isolates was Candida species 6 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in Ear swab samples i.e. 11. Aspergillus species isolated was Aspergillus niger 5 (45.45%), Aspergillus fumigatus 3 (27.27%), Aspergillus flavus 2 (18.18%)and Aspergillus brasiliensis 1 (9.09%). Bacterial isolates was recorded Staphylococcus 3 (50%) and Escherichia coli 3 (50%). Other fungal isolates was Penicillium species 2 (100%).

Aspergillus co-infection with other fungus and bacteria were recorded in Bronchoalveolar lavage (BAL) samples i.e. 13. Aspergillus species isolated was Aspergillus niger 6 (46.15%), Aspergillus fumigatus 4 (30.77%) and Aspergillus flavus 3 (23.08%). Bacterial isolates was recorded Streptococcus pneumoniae 3 (42.86%), Klebsiella pneumoniae 2 (28.57%), Streptococcus pyogenes 1 (14.29%), Staphylococcus aureus 1 (14.29%). Other fungal isolates was Candida species2 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in Eye swab samples i.e. 10. Aspergillus species isolated was Aspergillus niger 4 (40%), Aspergillus fumigatus 3 (30%), Aspergillus flavus 3 (30%). Bacterial isolates was recorded Staphylococcus aureus 1 (50%) and CoNS 1 (50%), however no other fungal were isolated.

Aspergillus co-infection with other fungus and bacteria were recorded in blood samples i.e. 4. Aspergillus species isolated was Aspergillus niger 2 (50%) and Aspergillus fumigatus 2 (50%) Bacterial isolates was recorded Staphylococcus aureus 1 (50%) and Escherichia coli 1 (50%). Other fungal isolates was Candida species1 (100%).

Aspergillus co-infection with other fungus and bacteria were recorded in urine samples i.e. 6. Aspergillus species isolated was Aspergillus niger 1 (16.66%) and Aspergillus flavus 5 (83.34%). Bacterial isolates was recorded Escherichia coli 2 (75%) and Staphylococcus aureus 1 (25%). Other fungal isolates was Candida species 2 (100%) (Table 8).

DISCUSSION

The saprophytic, thermotolerant fungus Aspergillus species are common in the environment and air. About 20 of the 185 species in the genus Aspergillus are capable of infecting humans. Even though hundreds of Aspergillus spores are inhaled by humans every day, problems are uncommon. (28)

Aspergillus infections are more likely to occur in people who already have lung diseases like asthma, COPD, or cancer. Corticosteroids, immune suppressants, and common antibiotics are used. Invasive aspergillosis, keratitis, and other lung lesions are caused by Aspergillus species. Aspergillus infection rates are influenced by factors such as improved survival from other illnesses, pollution-induced lung disorders, and longer lifespans. (29).

Of the 251 patients whose samples in our study contained Aspegillus species, 8 deaths were ascribed to invasive aspergillosis. (Table 1).

Males had the highest mortality rate from invasive aspergillosis (56.2%), while females had the highest mortality rate (37.5%). (Table 2)

The age-wise distribution was highest in the group 50 and older, which was 5 (62.5%), followed by 2 in the age group 41 to 50, which was 2 (25%) and 1 in the age group 31 to 40, which was 12.5%. (Table 3)

The type of Aspergillus species recorded in mortality were maximum due to Aspergillus fumigatus i.e. 5 (62.5%) and followed by Aspergillus niger i.e. 3 (37.5%). (Table 4)

The analysis of causes of death in invasive aspergillosis cases was recorded maximum due to allergic bronchopulmonary aspergillosis (ABPA) i.e. 2 (25%) followed by Chronic Pulmonary Aspergillosis, Invasive Aspergillosis in Solid organ transplant, HIV, Tuberculosis, Diabetes and Lung cancer i.e. 1(12.5%) each. (Table 5)

Fungal and Bacterial growth in various clinical samples. Out of total 1785 samples 251 showed Aspergillus species, 19 (8%) samples showed only Aspergillus species growth, 196 (78%) samples showed mixed bacterial and Aspergillus growth and 36 (14%) samples showed Aspergillus and Candida mixed growth. (Table 6 and Fig.1)

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Aspergillus co-infection with other fungus and bacteria were recorded in nasal and paranasal sinuses samples i.e. 52. Aspergillus species isolated was Aspergillus niger 32 (61.54%), Aspergillus fumigatus 13 (25%), Aspergillus flavus 5 (9.62%) and Aspergillus brasiliensis 2 (3.85%). Bacterial isolates was recorded Streptococcus pneumoniae 15 (41.67%), Klebsiella pneumoniae 6 (16.67%), Acinetobacter species 6 (16.67%), Streptococcus pyogenes 5 (13.89%), Staphylococcus aureus 4 (11.11%) Other fungal isolates was Candida species5 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in pus samples i.e. 51. Aspergillus species isolated was Aspergillus niger 31 (60.78%), Aspergillus fumigatus 13 (25.49%), Aspergillus flavus 5 (9.80%), Aspergillus brasiliensis 1 (1.96%) and Aspergillus terrus 1 (1.96%). Bacterial isolates was recorded Staphylococcus aureus 16 (47.06%), Escherichia coli 8 (23.53%), Acinetobacter species 6 (17.65%), Pseudomonas aeruginosa 4 (11.76%). Other fungal isolates was Candida species 6 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in Ear swab samples i.e. 11. Aspergillus species isolated was Aspergillus niger 5 (45.45%), Aspergillus fumigatus 3 (27.27%), Aspergillus flavus 2 (18.18%)and Aspergillus brasiliensis 1 (9.09%). Bacterial isolates was recorded Staphylococcus 3 (50%) and Escherichia coli 3 (50%). Other fungal isolates was Penicillium species 2 (100%).

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Aspergillus co-infection with other fungus and bacteria were recorded in Eye swab samples i.e. 10. Aspergillus species isolated was Aspergillus niger 4 (40%), Aspergillus fumigatus 3 (30%), Aspergillus flavus 3 (30%). Bacterial isolates was recorded Staphylococcus aureus 1 (50%) and CoNS 1 (50%), however no other fungal were isolated.

Aspergillus co-infection with other fungus and bacteria were recorded in blood samples i.e. 4. Aspergillus species isolated was Aspergillus niger 2 (50%) and Aspergillus fumigatus 2 (50%) Bacterial isolates was recorded Staphylococcus aureus 1 (50%) and Escherichia coli 1 (50%). Other fungal isolates was Candida species1 (100%).

Aspergillus co-infection with other fungus and bacteria were recorded in urine samples i.e. 6. Aspergillus species isolated was Aspergillus niger 1 (16.66%) and Aspergillus flavus 5 (83.34%). Bacterial isolates was recorded Escherichia coli 2 (75%) and Staphylococcus aureus 1 (25%). Other fungal isolates was Candida species 2 (100%) (Table 8).

The epidemiology of Influenza Acute (IPA) is unknown and affected by case mix, environmental factors, and diagnostic techniques. Geographic region influences IPA rates, but European studies show comparable rates (10%) to Asia (11%). Lack of knowledge in other regions could contribute to low rates. (30-33).

Chronic lung disease, such as asthma or COPD, increases the risk of developing IPA because of impaired respiratory function and increased corticosteroid use. A study discovered multiple comorbidities, higher mortality, longer hospital stays, and higher costs among invasive aspergillosis patients

Species wise	Total death	Percentages
Aspergillus Fumigatus	**5**	**62.5%**
Aspergillus niger	3	37.5%
Aspergillus flavus	0	0%
Aspergillus brasiliensis	0	0%
Aspergillus terrus	0	0%
Total	8	100%

Table 1: Showing type of Aspergillosis

Number of death	Complications and Causes of death
2	**Allergic Bronchopulmonary Aspergillosis (ABPA)**
1	Chronic Pulmonary Aspergillosis
1	Invasive Aspergillosis in Solid organ transplant
1	HIV
1	Tuberculosis
1	Diabetes
1	Lung cancer

Table 2: Analysis of causes of death in Aspergillosis cases.

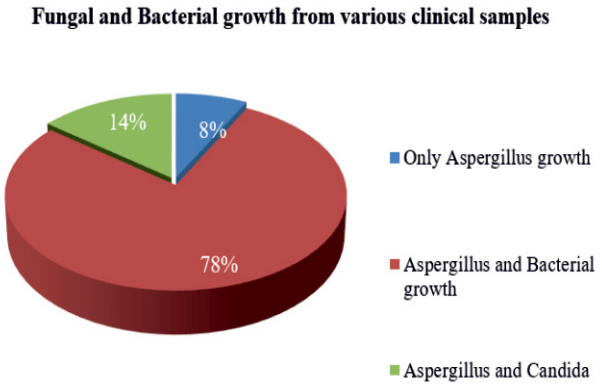

Fig.1: Fungal and Bacterial growth from various Clinical Samples

Parameter	Value
No. of isolates	251
No. of patients	1785
Sample origin	
Sputum	104/251 (41.43%)
Nasal and Paranal Sinuses	52/251 (20.72%)
Pus	51/251 (20.32%)
Ear swab	11/251 (4.38%)
Bronchoalveolar lavage fluid	13/251 (5.18%)
Eye swab	10/251 (3.98%)
Blood	04/251 (1.59%)
Urine	06/251 (2.39%)
Clinical diagnoses	
Invasive pulmonary aspergillosis	85/1785 (4.76%)
Chronic pulmonary aspergillosis except simple aspergilloma	59/1785 (3.31%)
Simple aspergilloma	41/1785 (2.30%)
Allergic bronchopulmonary aspergillosis	34/1785 (1.90%)
Colonization	32/1785 (1.79%)

Table 4: Clinical Correlation of Patients and Isolates

Total No. of samples	Total Aspergillus	Only Aspergillus growth	Aspergillus and Bacterial growth	Aspergillus and Candida
1785	251	19	196	36

Table 3: Showing Fungal and Bacterial growth in various Clinical Samples.

Sr. No.	Nature of samples	Aspergillus isolated (251)	Bacterial Isolate (n=194)	Other fungal isolates (n=36)
1	Sputum (n=104)	Aspergillus niger 61 (58.65%)	Streptococcus pneumoniae 39 (37.50%)	Candida albicans 15 (83.33%)
		Aspergillus fumigatus 24 (23.08%)	Pseudomonas aeruginosa 14 (13.46%)	Penicillium species 3 (16.67%)
		Aspergillus flavus 12 (11.54%)	Klebsiella pneumoniae 11 (10.58%)	
		Aspergillus brasiliensis 5 (4.81%)	Acinetobacter species 9 (8.65%)	
		Aspergillus terrus 2 (1.92%)	Streptococcus pyogenes 7 (6.73%)	
			Staphylococcus aureus 6 (5.77%)	
			Escherichia coli 5 (4.81%),	
			Enterobater sp. 4 (3.85%)	
			CoNS 4 (3.85%)	
			GNNF 3 (2.88%)	
			Enterococcus sp. 2 (1.92%)	
2	Nasal and Paranasal sinuses (n=52)	Aspergillus niger 32 (61.54%)	Streptococcus pneumoniae 15 (41.67%)	Candida species 5 (100%)
		Aspergillus fumigatus 13 (25%)	Klebsiella pneumoniae 6 (16.67%)	
		Aspergillus flavus 5 (9.62%)	Acinetobacter species 6 (16.67%)	
		Aspergillus brasiliensis 2 (3.85%)	Streptococcus pyogenes 5 (13.89%)	
			Staphylococcus aureus 4 (11.11%)	
3	Pus (n=51)	Aspergillus niger 31 (60.78%)	Staphylococcus aureus 16 (47.06%)	Candida species 6 (100%)
		Aspergillus fumigatus 13 (25.49%)	Escherichia coli 8 (23.53%)	
		Aspergillus flavus 5 (9.80%)	Acinetobacter species 6 (17.65%)	
		Aspergillus brasiliensis 1 (1.96%)	Pseudomonas aeruginosa 4 (11.76%)	
		Aspergillus terrus 1 (1.96%)		
4	Ear swab (n=11)	Aspergillus niger 5 (45.45%)	Staphylococcus 3 (50%)	Penicillium species 2 (100%)
		Aspergillus fumigatus 3 (27.27%)	Escherichia coli 3 (50%)	
		Aspergillus flavus 2 (18.18%)		
		Aspergillus brasiliensis 1 (9.09%)		
5	BAL (n=13)	Aspergillus niger 6 (46.15%)	Streptococcuspneumoniae 3 (42.86%)	Candida species2 (100%)
		Aspergillus fumigatus 4 (30.77%)	Klebsiella pneumoniae 2 (28.57%)	
		Aspergillus flavus 3 (23.08%)	Streptococcus pyogenes 1 (14.29%)	
			Staphylococcus aureus 1 (14.29%)	
6	Eye swab (n=10)	Aspergillus niger 4 (40%)	Staphylococcus aureus 1 (50%)	-
		Aspergillus fumigatus 3 (30%)	CoNS 1 (50%)	
		Aspergillus flavus 3 (30%)		
7	Blood (n=4)	Aspergillus niger 2 (50%)	Staphylococcus aureus 1 (50%)	Candida albicans 1 (100%)
		Aspergillus fumigatus 2 (50%)	Escherichia coli 1 (50%)	
8	Urine (n=6)	Aspergillus niger 1 (16.66%)	Escherichia coli 2 (75%)	Candida albicans 2 (100%)
		Aspergillus flavus 5 (83.34%)	Staphylococcus aureus 1 (25%)	
	Total (n=251)	251 (100%)	194 (100%)	36 (100%)

Table 5: Aspergillus Co-infection with other Fungus and Bacteria.

with aspergillosis. The most common host factor associated with IA was previous corticosteroid use for autoimmune disease. (34-37).

CONCLUSION

This study shows trends in mortality in IA patients over a 2-year period. Male gender, allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, invasive aspergillosis in solid organ transplant, HIV, tuberculosis, diabetes and lung cancer were identified as risk factors for death. Compared with Aspergillus-colonized patients, IA patients were more likely to have sepsis or respiratory failure on admission, and more often had underlying medical conditions such as immunocompromised states.

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