

Is fungi replacing bacteria as etiological agents of community acquired pneumonia- current strategy of changing scenario?

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Abstract

Introduction: Pneumonia is one of the major infectious public health problem in developing countries. The etiologic agents causing Community Acquired Pneumonia (CAP) has been changed in the recent years. This study is conducted to determine the fungal etiologic agents causing CAP and the associated risk factors.

Materials & Methods: About 150 patients were presented with signs and symptoms of pneumonia during the one year study period. Various respiratory samples were processed and the fungal etiologic agents were identified according to standard operating procedures.

Results: Out of 150 patients, 75 were immunocompetent (IP) and rest 75 patients were immunocompromised (IC). Most commonly associated risk factor was Diabetes mellitus (48%) and haematological malignancies (18.66%). Monofungal pathogen was isolated in 6.25% of cases of IP group and in 26.78% of cases in IC group. Fungal pathogen as a part of polymicrobial infection was seen only in IC group (2 cases). *Aspergillus fumigatus* is the most common isolate in the IC patients (52.94%) followed by *Aspergillus flavus* (23.52%). *P.jerovicii* is isolated in 5.88% of cases in immunocompromised patients. Hematologic malignancies are more commonly associated with fungal infection (28.57%) followed by Diabetes mellitus (16.66%).

Conclusion: Invasive fungal lung infections are increasingly encountered in critical care and pulmonology practice. With increasing number of immunosuppressed host and emergence of drug resistant fungal pathogens, a high degree of clinical suspicion and better laboratory diagnostic methods are mandatory for prompt and effective treatment of invasive fungal infections in these high risk populations.

Keywords: Fungal pathogens, Community Acquired Pneumonia, Risk factors.

Introduction

Pneumonia was described 2,500 years ago by Hippocrates, the father of Medicine. Dr. William Osler, the founder of modern medicine, referred pneumonia as the "captain of the men of death". In the 1930s, before the advent of antibiotics, pneumonia was the third-leading cause of death in the United States. Worldwide >600,000 individuals hospitalize every year due to pneumonia with annual deaths of 45,000¹. It occurs about five times more frequently in the developing world versus the developed world². Pneumonia in adults is estimated to be prevalent in about 4% of Indian population with male to female ratio of 1.56:1.14³.

Pneumonia, which is characterized as consolidation pathologically and clinically as constellation of signs and symptoms. The potential etiological agents of Community Acquired Pneumonia (CAP) are protean with wide range of microbes from bacteria, viruses, fungi and parasites, of these fungi account for only a small portion of community-acquired pneumonias. Fungal infection occurs following the inhalation of spores or conidia, by the reactivation of a latent infection or by haematogenous spread. The prognosis depends on the severity and outcome of the underlying disease and to the patient's immune status.

The burden of opportunistic mycoses and the exact frequency of opportunistic fungal diseases in India is

not clear as there is insufficient data. A high degree of clinical suspicion is needed to direct prompt therapy, in order to avenge associated morbidity and mortality. This study is conducted to identify the fungal etiological agents of community acquired pneumonia and its associated risk factors.

Materials & Methods

The study was conducted over a period of one year, during which patients presented with signs & symptoms of pneumonia with radiologic findings were included in the study population. Patients were explained about the study and informed consent were obtained. Demographic profile of the study group along with their associated risk factors were collected by structured questionnaire. Various respiratory samples like sputum, cavity material, bronchial wash, BAL fluid and pleural fluid were collected under strict aseptic precautions and were immediately sent to the Microbiology department for further processing.

Gram stain, 10% potassium hydroxide (KOH) mount and Gomori's Methenamine silver stain was performed in all the samples. Sputum samples were homogenised with sterile glass beads. Only those sputum samples which fulfil the Bartlett scoring alone was further processed. All other respiratory fluid samples were centrifuged and the deposits were used for further processing.

For fungal culture two sets of media Sabouraud's Dextrose agar (SDA) with cycloheximide and antibiotics, were inoculated with as much sample as possible, onto the surface of the agar with one test tube, incubated at 25°C and another test tube, incubated at 37°C, for upto 4 weeks.

Inoculated SDA slants were inspected daily for first one week and then twice weekly for the next 3 weeks, before considering no growth. Filamentous fungi isolates were identified by LPCB mount/Scotch tape preparation, based on the hyphal and conidial arrangement and morphology.

Only the proven isolates of Invasive Fungal Infections (IFI) alone are taken into consideration as guided by EORTC/MSG criteria (i.e. direct KOH positive & culture positive).

Results

A total of 150 patients were presented with signs and symptoms of CAP during the study period majority being males (67%). Most of the patients were in the age group of 61-70yrs (26.66%) and 51-60yrs (21.33%). Out of 150 patients, 75 of them were immunocompetent (IP) and the rest 75 have one of the immunocompromised (IC) risk factors, most common being Diabetes mellitus (48%) followed by haematological malignancies (18.66%).

Culture positivity rate from all the processed respiratory samples were 104(69.33%). Pure monofungal pathogen was isolated in 6.25% of cases of IP group and in 26.78% of cases in IC group. Fungal pathogen as a part of polymicrobial infection was seen only in IC group (2 cases). Fungal etiologic agents are more common in IC patients than in IP patients with significant P value (P=0.001). (Table 1)

Table 1: Distribution of fungal culture positivity among IP and IC patients, from respiratory samples, according to the type

Type of fungal infection	Immunocompetent (n=48)		Immunocompromised (n=56)	
	No.	%	No.	%
Monomicrobial-Fungal	3	6.25	15	26.78
Polymicrobial-Fungal & Bacterial	-	-	2	3.57

Aspergillus fumigatus is the most common isolate in the IC patients (52.94%) followed by *Aspergillus flavus* (23.52%). *P.jirovecii* is isolated in 5.88% of cases in immunocompromised patients (Table 2).

Table 2: Fungal etiologic agents of CAP from respiratory samples of IP and IC patients

Sample	Immunocompetent (n=3)			Immunocompromised (n=17)			
	<i>A.fumigatus</i>	<i>A.flavus</i>	<i>A.terreus</i>	<i>A.fumigatus</i>	<i>A.flavus</i>	<i>A.terreus</i>	<i>P.jirovecii</i>
Sputum	-	1	-	5	2	1	1
Bronchialwash	1	-	1	2	1	2	-
BAL	-	-	-	1	1	-	-
Pleural fluid	-	-	-	-	-	-	-
Cavity material	-	-	-	1	-	-	-
Total	1 (33.33%)	1 (33.33%)	1 (33.33%)	9 (52.94%)	4 (23.52%)	3 (17.64%)	1 (5.88%)

Diabetes mellitus is most commonly found in association with polymicrobial infection (19.44%) followed by fungal infection (16.66%). Hematologic malignancies are more commonly associated with fungal infection (28.57%) followed by polymicrobial infection (14.28%) (Table 3)

Table 3: Correlation of immunocompromised state with fungal isolates in IC group

Immunocompromised state (75)	Fungal pathogen	
	No	%
DM (n=36)	6	16.66
Leukemia/Lymphoma (n=14)	4	28.57
Autoimmune disease (n=8)	2	25
Post renal transplant (n=8)	2	25
Prolonged steroid therapy (n=4)	-	-
Retroviral disease (n=3)	1	33.33
Solid organ malignancy (n=2)	-	-

Discussion

The potential etiological agents of CAP are protean with wide range of microbes from bacteria, viruses, fungi and parasites. The etiological agents vary from one geographic to other geographic areas due to variation in local factors, out-patient therapy practices, host and environmental factors. Fungal lung infections are being diagnosed with increasing frequency which generates great concern in the expanding population of immunosuppressed patients. The data regarding the prevalence of fungal systematic infections in India is still not clear.

In our current study out of the total etiologic isolates identified (51 in IP & 67 in IC), fungal agents comprise as a significant pathogen in 5.88% (3 isolates) of IP group and 25.37% (17 isolates) of IC group (Table 1). Study conducted by Manahil M *et al*⁴ in 2012, on identifying opportunistic respiratory fungal infections among IP and IC patients, found that the risk of acquiring fungal infections is 2-3 fold higher in IC than in IP patients (60.9%, 39.1%). Similar studies conducted by Chang GC *et al*⁵ and Pound MW *et al*⁶ also showed that patients with weakened immune system have a higher chance of acquiring fungal pneumonias which in turn increases the associated mortality in these high risk group patients.

On considering the fungal pathogens isolated in our study, 3 cases one each of *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus terreus* (33.33% each & respectively) were isolated in IP group. In IC, group *Aspergillus fumigatus* was the most commonly isolated fungi (9 cases, 52.94%) followed by *Aspergillus flavus* (4 cases, 23.52%), *Aspergillus terreus* (3 cases, 17.64%) and *Pneumocystis jirovecii* (1 case, 5.88%, in HIV positive patient) (Table 2). Study conducted by John H Reynolds *et al*⁷ in 2012 and Spomenka Ljubic *et al*⁸ found that invasive aspergillosis is most common in immunocompromised patients than in normal controls. Study conducted by Pfaller *et al*⁹ and Spomenka Ljubic *et al*⁸ showed that *Aspergillus fumigatus* was the most common isolate causing invasive aspergillosis, which correlated with our study results. Study by Manahil *et al*⁴ showed that prevalence of aspergillus pneumonia in IP patients is 1% when compared to 4.9% in IC patients. In our study also fungal pneumonia by *Aspergillus* is more common in IC than in IP patients. A variety of data support the concept that certain opportunistic fungal infections, most notably *Aspergillus* infections, are increasing in frequency over time¹⁰.

Studies conducted by Ryan *et al*¹¹, showed that *Pneumocystis jirovecii* is more common in IC state than in IP state. Studies of Sepkowitz *et al*¹² and Phair *et al*¹³ showed that the incidence of PCP is strongly associated with CD4 count, with risk increasing to 10-100 fold with CD 4 counts < 200 cells/mm³. In our study also PCP is identified in HIV positive patient whose CD4 count is 34 cells/mm³. Study conducted by Torres A *et*

*al*¹⁴, recorded a prevalence of 11% PCP in transplant immunosuppressed individual. The reduced detection of PCP infection in our study may be due to the implementation of prophylactic cotrimoxazole therapy in high risk group.

On studying the association of immunocompromised state with the isolates of IC patients, we found that diabetes mellitus and haematological malignancies are two major factors associated with significant fungal etiologic pathogen in CAP (16.66% and 28.57% respectively) (Table 3). Similarly patients with underlying diabetes mellitus & haematological malignancies have a higher risk of developing polymicrobial infections (19.44% and 14.28% respectively). Studies conducted by Mulanovich VE *et al*¹⁵ and Pagano L *et al*¹⁶, on fungal pneumonia in haematological malignancies, showed that these malignancies pose an important threat for developing fungal pneumonia than in immunocompetent patients. Study conducted by Corinna Hahn *et al*¹⁷ in 2006, showed that the prevalence of fungal pneumonia in haematological patients vary between 2-40%, depending on their ongoing treatment protocol. This prevalence rate is similar to the positivity rate of fungal pneumonia in haematological malignancy patients in our study. Study conducted by Spomenka Ljubic *et al*⁸ showed that about 20-25% of pneumonia in diabetes patients are polymicrobial in nature and fungal pneumonias are common in these patients than with control groups.

This is in part due to increased transplantation procedures, explosion in the number of immunosuppressant agents identified and widespread implementation of antimicrobial prophylactic regimens which rendered the host at greater risk for colonization with more resistant fungal species, enhancing the increase of invasive fungal infection in these already immune-suppressed patients.

Conclusion

Systemic fungal infections are a major public health problem in both developing and developed countries and they are frequently encountered in pulmonary and critical care practice. What is currently known of these fungal infections indicates that it is just the tip of the iceberg. With the increasing number of susceptible hosts, awareness and high degree of suspicion for these invasive fungal infections with improved laboratory methods for diagnosing fungal infections is mandatory in the management of infections in these high risk group individuals. Continuous ongoing research studies are mandatory to identify this changing scenario of infectious pathogens causing Community Acquired pneumonia.

Conflicts of Interest: None

Source of Support: Nil

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