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Original Research Article

A study on rapid diagnosis (by PCR) and cost-effective treatment of pulmonary mycosis

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ABSTRACT

Background: Incidence of Pulmonary Mycosis is rampantly growing in critically ill patients. This study was designed to comparatively evaluate conventional and molecular method-Polymerase Chain Reaction (PCR) for detecting Candida and Aspergillus species in Brocho-Alveolar Lavage (BAL) samples and secondarily to find out the Cost-Effective treatment for Pulmonary Mycosis.
Methods: In this study 100 BAL-specimens were collected from patients suspected of Pulmonary Mycosis. These samples were examined for Aspergillus and Candida species by preparation of wet smear using potassium hydroxide, Gram staining, Culture media and Polymerase Chain Reaction (PCR). For Cost-Effectiveness analysis(CEA), a decision tree model was constructed for Anidulafungin and Fluconazole The probability of treatment success and mortality rate were extracted from published Randomized Control Trials. Incremental Cost Effectiveness Ratio (ICER) was calculated.
Results: Out of 100 samples, 22 were found to be positive for mycotic infections, 9 were detected as Candida and 13 as Aspergillus. On comparing with KOH and Culture, it was observed that all KOH positive and all Culture positive fungal infections were PCR positive. In no cases PCR negative was identified either culture or KOH positive. This establishes the superiority of PCR over conventional diagnostic methods. Anidulafungin was associated with an Incremental Cost Effectiveness Ratio (ICER) of INR 1,13,217 per LY saved, which was below the implicit ICER threshold for India.
Conclusions: PCR is a novel molecular method for early and definitive diagnosis of fungal infection and Aidulafungin appears to be the cost-effective drug for treatment of Pulmonary Mycosis.

Keywords: Anidulafungin, Cost-effectiveness, Fluconazole, ICER, PCR, Pulmonary mycosis

INTRODUCTION

In the last few decades, there has been a dramatic increase of Invasive Fungal Infections (IFI) in critically ill patients. Fungal infections of lungs i.e. Pulmonary Mycosis, are important infective processes which are being increasingly encountered in the present practice. The endemic or opportunistic fungi are most common causative organs of Pulmonary mycosis. Mortality is quite high in pulmonary mycosis, reaching upto 90% in immune-compromised patients whereas immuno-competent patients usually respond well to timely antifungal therapy.[1,2]

Pulmonary Mycosis or Fungal infections of lung often pose a difficult diagnostic challenge because, its clinical and radiological features, are very similar to that of pulmonary tuberculosis. In India this problem is further

aggravated by high prevalence of pulmonary tuberculosis and COPD.[3]

The rising rate of fungal infections in critically ill patients is mainly due to impairment of host defense mechanisms as a consequence of immunodeficiency caused by viral infections, haematological disorders, organ transplantation and more invasive and aggressive medical treatment protocols such as surgeries, use of catheters, radiation, chemotherapy, use of steroids and the indiscriminate use of broad spectrum antibiotics causing change in endogenous/commensal flora.[4,5]

Among etiological agents, Candida species and Aspergillus species are by far the most common causes of invasive fungal infections in critically ill patients, although recently a shift has been witnessed towards other non-albicans Candida species. Moreover, other yeasts and moulds, such as Zygomycetes, Cryptococcus, Fusarium and Scedosporium have also been recognized as emerging pathogens in recent years.[6,7]

The poor outcome of patients of Pulmonary Mycosis or other IFIs are explained in part by diagnosis in advanced stages of the infection due to the limitations of current diagnostic tests.

Delay in detection of fungal organisms and species identification by conventional diagnostic tests like microscopy and culture, contributes to increased mortality as well as increased length of stay in hospital, which escalates the economic burden also.[8,9]

Guidelines for the treatment of IC has been proposed by the Infectious Diseases Society of America (IDSA), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and recently by ITALIC (Italian Consensus for Invasive Candidiasis management).[10-12] All these guidelines recommend Echinocandins like Anidulafungin, Caspofungin and Micafungin as first line agents for the treatment of IFI because of their strong fungicidal activity, efficacy against strains producing biofilms, spectrum against fluconazole-resistant strains, favorable safety and tolerability and low incidence of drug-drug interactions.

Hence it is imperative to switch over to new proteomic and molecular diagnostic tools like PCR, that carry the advantage of rapid analysis and increased sensitivity for species identification and detection of invasive fungal pathogen, so that clinically befitting and cost-effective antifungal therapy could be initiated at the earliest.[13,14]

The focus of interest in this paper is limited to comparatively evaluate the conventional and novel molecular techniques like PCR for detection of Candida and Aspergillus species in critically ill patients of suspected Pulmonary Mycosis and to further assess the cost-effectiveness of Anidulafungin versus Fluconazole.

METHODS

This study was carried out in the Department of Microbiology and Pharmacology in the Intensive care unit of Rohilkhand Medical College and Hospital, Bareilly. Specimens for isolation of fungi were collected from 100 subjects who were admitted to ICU and were suspected to have Pulmonary Mycosis. Cases taken from ICU were suffering from different diseases, which are grouped in five classes -COPD, Malignancy, Pulmonary Tuberculosis, Septicaemia and Other (Diabetes mellitus, Hypertension, Liver diseases, Renal failure, Head injury, CVA etc). Bronchoscopy was performed according to the standard guidelines and Broncho-Alveolar Lavage (BAL) samples were obtained. In this study we used BAL fluid as sample of choice because the isolation rate of fungus from BAL is more accurate as compared to other non-invasive samples like sputum or tracheal aspirate. Moreover, in BAL sample there are lesser chances of contamination with normal flora of the throat.

Exclusion criteria

- The patients, excluded from the study, were < 14 yrs of age, as they were admitted to PICU.
- Patients who were on antifungal treatment, as this can affect our study results.
- Patients who were already diagnosed to have fungal infections, because there is no need to perform culture /microscopy or PCR.

Conventional microbiological investigations

Direct microscopic examination at x40 magnification, of the BAL samples was performed with 10% KOH wet mount and by Gram's staining for demonstration of fungal elements. Another portion of the collected sample was inoculated directly on Culture Media such as Blood agar (BA), MacConkey agar (MA), Sabouraud's dextrose agar (SDA) and SDA with chloramphenicol. These inoculated plates were incubated at 37ºC and were examined daily and discarded after 48 hrs, if no growth was seen on BA and MA. SDA was incubated at 25ºC and 37ºC for 3 weeks. Cultures were checked daily during the first week and twice a week for the subsequent 2 weeks. After standardization with ATCC Strains PCR was done on clinical samples with same Pan fungal primers and primer specific for Candida and Aspergillus.

Cost-effectiveness analysis (CEA)

Health economic studies are important in the clinical scenario where decision-makers face constant pressure to balance out cost and quality of care. The aim of this study was to determine the cost-effectiveness of Anidulafungin versus Fluconazole in the treatment of Invasive Fungal Infections. The analysis was conducted from the perspective of the medical payer. A decision analytic model was constructed in Microsoft Excel to estimate the potential treatment costs of anidulafungin versus

comparator agent Fluconazole. The model was pooled with data derived primarily from the study by Reboli et al.[15] The data included outcome probabilities, mortality rates, dose and duration of initial antifungal therapies, as shown in Table 1 An expert panel was appointed to determine if data from Reboli et al, were generalizable to the INDIAN setting, as well as for validating the decision tree model. The panel also provided local data related to diagnosing and treatment of fungal infections. Antifungal drug-acquisition costs were recorded from the pharmacy of our hospital (pfizer and cipla brand). In accordance with the Infectious Diseases Society of America and European Society for Clinical Microbiology and Infectious Diseases guidelines patients remained on antifungal therapy for 14 days after their first negative blood culture.[10,11] All the patients were followed for a period of atleast 3 weeks. The cost per successfully treated patient was calculated as the cost of a full course of I.V. Anidulafungin or Fluconazole therapy. To avoid double counting, the costs of pharmacy, pathology, imaging and intensive care management were excluded from hospitalization costs. In the current model, the incremental cost per an additional treatment success and LYs saved was calculated using the formula:

$$\text{ICER} = \frac{C1-C2}{E1-E2}$$

C1 and E1 were the cost and efficacy of Anidulafungin

C2 and E2 were the cost and efficacy of the Fluconazole.

RESULTS

In this study, 100 Broncho-Alveolar Lavage (BAL) specimens were evaluated for fungal infections from ICU. The isolation rate of fungus from invasive specimen like BAL is more accurate in comparison to other non-invasive specimens like sputum as well as from tracheal aspirate, as there are lesser chances of colonization of fungus at the lower most portion of respiratory tract.

It has been very well seen that the chances of fungal infection increase when the patients stay in ICU for more than 48 hours, hence in this study we have taken the BAL fluid sample from those patients who had a stay of >48 hours. Our finding was further strengthened by the study of Pasqualatu et al, who found that the duration of ICU stay was >48 hours in 66.7% of patients detected with fungal infection in his study.[16]

Gender-wise distribution of cases reveal that out of 100 cases enrolled for BAL, 77 were male and 23 were females. (Figure 1) Age wise distribution of cases depicted in Table 2, showed 15 cases between age of 14-30 yrs, 22 cases of 31-50 yrs, 50 cases of 51-70 yrs and 13 cases of age >70 yrs. Hence maximum number of cases were seen in the age-group between 51-70 years (Table 2).

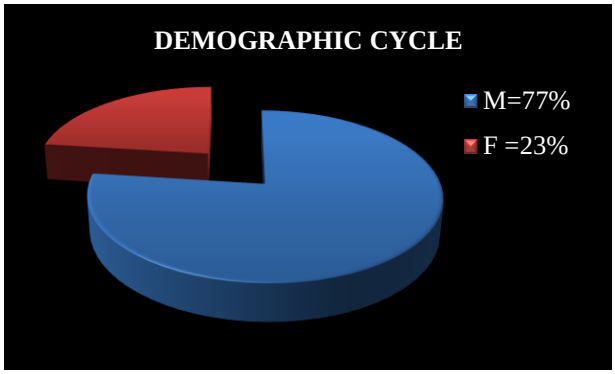

Figure 1: Gender distribution of cases.

Table 1: Probability of clinical success and mortality rate.[15]

Drug	Clinical success	Mortality
Anidulafungin	77.5%	20.8%
Fluconazole	63.0%	28.4%

Table 2: Age-wise distribution of cases.

Age groups (yrs)	Number of cases
14 -30	15
31 -50	22
51-70	50
>70	13

Out of 100 samples, 22 were found to be positive for mycotic infections, out of these 9 samples were confirmed as Candida, 13 were confirmed as Aspergillus. Incidence of fungal infections in various clinical ailment groups shown in table 3. Out of 17 cases (17%) of Pulmonary TB, 7 cases (41.4%) were positive for fungal infections. Out of 7 detected cases of fungal infections, 5 were positive for Aspergillus and 2 were positive for Candida. 14 cases (14%) of COPD cases were taken in the study. Out of these 14 cases, 3 cases (21.4%) found to be positive for fungal infections. Out of 3 detected cases, 2 cases were positive for Aspergillus and 1 for Candida.21 patients (21%) of malignancy were included in this study, out of these 21 cases, 4 cases (19.04%) were found to be fungal positive. In 4 cases of fungal infections, 3 (75%) were identified as Candida and 1 (25%) identified as Aspergillus. 21 patients (21%) of septicaemia were taken in this study, out of these 21 cases 4 cases (19.04%) were found to fungal positive. In 4 cases of fungal infections, 3 were identified as Aspergillus and 1 identified as Candida.27 patients belong to other groups, who were not belonging to above described diseases included in the study. Out of these 27 patients, 4 cases (14.8%) were found positive for fungal infections, in these cases 2 (50%) were positive for Candida and 2 (50%) for Aspergillus. In the present study we have considered that all PCR positive results as diseased one and compared with different conventional methods (Table 3).

Table 4 depicts the comparison of PCR and other conventional diagnostic methods. All the PCR positive cases are considered as diseased.

Table 3: Isolation of Candida and Aspergillus in different cases.

Fungus isolated	Pulmonary TB (n=17)	COPD (n=14)	Malignancy (n=21)	Septicaemia (n=21)	Others (n=27)
Candida	2	1	3	1	2
Aspergillus	5	2	1	3	2

PCR versus KOH smear results

Of the total 22 cases diagnosed positive by PCR, 11 were also positive for KOH as well, but another 11 specimens were negative for KOH. The sensitivity of fungal KOH identification was 50% with 95% CI (28.22-71.28%). The specificity of fungal KOH identification was 100% with 95% CI (95.38-100%). The PPV and NPV for KOH were 100% and 87.65% respectively. On applying Chi square test the p value is <0.0001 which is statistically highly significant.

Table 4: Comparison between PCR and conventional methods of diagnosis.

	PCR +ve	PCR +ve	P value
KOH +ve	11	0	<0.001
KOH -ve	11	78	
Culture +ve	14	0	< 0.001
Culture -ve	8	78	
	PCR +ve	PCR +ve	
Gram Stain +ve	7	0	<0.001
Gram Stain +ve	15	78	

P<0.001 is considered highly significant

PCR versus culture results

It also shows that there are 14 specimens which were positive for culture as well as for PCR, but another 8 specimens were PCR positive but negative for culture. The sensitivity of fungal culture identification was 63.64% with 95% CI (40.66-82.80%). The specificity was 100% with 95% CI (95.38-100%). The PPV and NPV for culture were 100% and 90.69%. On applying Chi square test, the p value is 0.0001 which is statistically significant.

PCR versus gram stain results

There are 7 specimens which were positive for Gram's staining as well as for PCR, but another 15 specimens were PCR positive, but cannot be detected by Gram's staining. The sensitivity of fungal identification with Gram's stain was 31.81% with 95% CI (13.86 - 54.87%). The specificity was 100% with 95% CI (95.38-100%). The PPV and NPV value was 100% and 83.87% respectively. On applying Chi square test the p value is <0.0001 which is statistically significant.

Table 5: Calculation of ICER for cost-effectiveness analysis.

Drug	Cost per loading dose IV	Cost per maintenance IV	Oral	Total cost	Incremental cost	Total no. of life years	Incremental no. of life years	ICER
Anidulafungin	Day 1 200mg 10,528	14 days 100mg 5264	Nil	84224		7.23		
Fluconazole	Day 1 800mg 480	14 days 400mg 3360	Nil	3840	80384	6.52	-0.71	1,13,217

CEA

The patients enrolled in this study were being treated either with Anidulafungin or with Fluconazole for Pulmonary Mycosis. Anidulafungin had a higher total cost (Rs.84224) than fluconazole (Rs.3840) per successfully treated patient, primarily due to its higher acquisition cost. One vial of 200mg of Anidulafungun costs Rs. 10,528 (Inj. Eraxis by Pfizer) whereas One vial of 400mg of Fluconazole costs Rs.240 (Inj. Forcan by Cipla). Table 5 shows that when the rates of mortality in both treatment arms were considered, treatment with

anidulafungin was expected to save an additional 0.71 life-years, with an incremental cost-effectiveness ratio (ICER) of Rs.1,13,216 per life-years saved, which was below the implicit ICER threshold value for India. Hence Anidulafungin can be considered cost-effective as compared to Fluconazole for the treatment of Invasive Fungal Infections (Table 5).

DISCUSSION

Invasive fungal infections are becoming increasingly prevalent and are associated with considerable morbidity and mortality. Traditional diagnostic methods, such as histopathology and culture, which are still considered the gold standards, have low sensitivity, specificity and are time consuming. This often leads to considerable delay in adequate therapeutical management, which ultimately leads to significant increase in mortality and hospitalization costs.[17,18] A study by Morrell et al, and colleagues evaluated the delay in treatment due to the time required for diagnosis as a mortality risk factor for invasive Candida infection.[19] In order to combat these difficulties, novel serologic and molecular diagnostic methods like PCR are in the spotlight.

Our study data shows that the fungal infection is more common in age group of 51-70 yrs of age i.e. this group is most vulnerable for fungal infections. This data is supported by study of Hajjah et al, who reported a characteristic age distribution among cases of fungal infections, with majority i.e. 72% cases at age >45 yrs.[20]

This study results as well as data from other studies have shown that the epidemiology of IFI like Pulmonary Mycosis has shown a shifting trend from those traditionally considered at risk i.e. immune-compromised to non-immuno-compromised but critically ill subjects i.e. patients with Pulmonary TB and chronic COPD.[21] Rate of fungal infection in TB and COPD patients was quite high in this study being 41% and 21.4% respectively. Similar results depicting Aspergillus and Candida species causing secondary infection i.e. Pulmonary Mycosis in patients of Pulmonary TB have been reported recently by Mathavi S et al, and Al-Khalidi AA et al.[22,23] The reason for increased prevalence are lowering of immune status due to tuberculosis , impaired lung architecture, prolonged use of corticosteroids, frequent hospitalization, broad spectrum antibiotics, impaired mucociliary clearances and co-morbid conditions.

Authors have also drawn a comparison between the Sensitivity, Specificity, Positive Predictive Value (PPV) and the Negative Predictive Value(NPV) of PCR and Conventional methods for diagnosis of invasive fungal infections. In the present study we have considered all PCR positive results as diseased ones and compared with different conventional methods.

On comparing with KOH and Culture, it was observed that all KOH positive and all Culture positive fungal infections are PCR positive. In no cases PCR negative was identified either culture or KOH positive. Our results are consistent with previous studies in suggesting that PCR performed on BAL has high positive and negative predictive values.[21,24] The high negative predictive value of the PCR test reflects a low probability for fungal infection, hence a clinician can withhold the unjustified anti-fungal therapy in such cases, whereas a positive PCR result will lead to prompt and early administration of targeted antifungal treatment. E Hardak et al, found sensitivity of Candida PCR assay to be 95% as compared to Candida Elisa which showed a sensitivity of 75%. Similarly M Kousha et al, estimated the sensiyivity and specificity of PCR of BAL fluid to be 75-100% and 65-95% but for serum sample it was 70-80% and 65-85% only.[21,24] All these findings are in line with the results of our study. This shows the superiority of PCR over conventional methods.

Another important aspect of our study was to determine the cost-effective therapy for treating invasive fungal infections. To the best of our knowledge, this is the first economic evaluation to comprehensively assess the cost-effectiveness of echinocandin- Anidulafungin versus non-echinocandin- Fluconazole in North India. According to World Health Organization's recommendations, the treatment is considered as cost-effective if the cost of one Life Year (LY) gained was less than a certain pre-defined threshold, which is calculated as three times the per capita national gross domestic product (GDP).[25] India's per capita GDP was INR 90,688 as per 2015 estimates, so the implicit cost-effectiveness threshold was calculated to be INR 2,72,064 per LY gained.[26]

Anidulafungin was associated with an Incremental Cost Effectiveness Ratio (ICER) of INR 1,13,217 per LY saved, which was below the implicit ICER threshold for India. (INR 1,13,217per LY saved <INR 2,72,064 per LY gained) The considerable decrease in the ICER per LY saved was due to the lower mortality rate in the Anidulafungin arm. Our results indicate that despite its higher acquisition cost than Fluconazole, Anidulafungin could potentially be a cost-effective option in the treatment of Pulmonary Mycosis. Other authors around the globe who have compared the cost-effectiveness of Anidulafungin with Fluconazole for Invasive Fungal Infections, provided findings that are in concordance with our results, suggesting Anidulafungin as a Cost-effective agent over Fluconazole.[27-30]

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