Study of the prevalence and pattern of fungal pneumonias in respiratory intensive care units

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Background Fungal pneumonia is an infectious process in the lung caused by one or more endemic or opportunistic fungi. Fungal infection occurs following the inhalation of spores, after the inhalation of conidia, or by the reactivation of a latent infection. Hematogenous dissemination frequently occurs, especially in an immunocompromised host.

Aim of the work To assess the prevalence of fungal pneumonias in a group of respiratory ICUs and identify their pattern.

Patients and methods This study was carried out on 60 patients who were admitted in respiratory ICUs of different hospitals: Ain Shams University and Military Hospitals from March 2018 till February 2019 to assess the prevalence of fungal chest infection in that group of patients and furthermore to identify their pattern. All patients were subjected to the following: history, clinical examination, radiology (plain chest radiograph and computed tomography of the chest), routine laboratory investigations and finally mycological analysis including direct microscopic examination and culture examination of the collected respiratory samples.

Results The mean age of all patients was 55.43 years. Regarding sex of the patients, the majority (76.67%) of patients were men, while 23.33% were women. Forty (66.67%) patients out of 60 patients with respiratory diseases had been culture positive for fungus and 20 (33.33%) patients had been culture-negative. The major fungal species encountered in this study were Candida species in 23 (57.5%) cases followed by Aspergillus species in 17 (42.5%) cases. *Candida albicans* was isolated in 23.33% of patients followed by Aspergillus nonfumigatus (18.33%) then Candida nonalbicans (15%), and finally *Aspergillus fumigatus* (10%).

Conclusion From the current study, we can conclude that pulmonary fungal infection appears to be an important problem in patients with respiratory diseases especially patients who are admitted in respiratory ICUs regardless of their age or sex.
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Introduction

Fungal pneumonia is an infectious process in the lungs caused by one or more endemic or opportunistic fungi. Fungal infection occurs following the inhalation of spores, inhalation of conidia, or by the reactivation of a latent infection. Hematogenous dissemination frequently occurs, especially in an immunocompromised host [1].

Endemic fungal pathogens (e.g. *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Cryptococcus neoformans*) cause infection in healthy hosts and in immunocompromised persons [2].

Opportunistic fungal organisms (e.g. *Candida* species, *Aspergillus* species, *Mucor* species) tend to cause pneumonia in patients with congenital or acquired defects in host immune defenses [2].

Among yeasts and molds, *Candida* and *Aspergillus* species are the most frequent nosocomial fungal pathogens included in the critical care setting [3].

The diagnosis of fungal pneumonias is difficult to prove and is often made on a presumptive basis. It relies on a combination of clinical, radiological, and microbiological factors [4].

Aim of the work

The aim of this study was to assess the prevalence of fungal pneumonias in a group of respiratory ICUs and to identify their pattern.

Patients and methods
Patients

This prospective cross-sectional analytical study was conducted on 60 patients who were admitted in respiratory ICUs of different hospitals: Ain Shams University and Military Hospitals (after written

consents from patients or their family) from March 2018 till February 2019; ethics committee approval was taken.

(1) Any patients with history of preexisting lung disease and immunosuppression from corticosteroids or other underlying conditions (e.g. diabetes, malnutrition and liver cirrhosis).
(2) One of the following symptoms of lower respiratory tract infection (newly developed sputum or secretions, dyspnea, hemoptysis, or pleuritic chest pain).
(3) Refractory fever after at least 3 days of appropriate antibiotics.
(4) Development of new pulmonary infiltrates on chest radiograph.
(5) Any of the following new infiltrates on computed tomography (CT) imaging: halo sign, air-crescent sign, or cavity within area of consolidation.

Exclusion criteria

(1) Patients who received systemic antifungal therapy within 3 days prior to sample collection.
(2) Patients who refused to participate in the study.

All patients were subjected to the following: full history taking, clinical examination, laboratory investigations, radiology (chest radiograph and CT chest) and mycological analysis of the collected samples as follows:

Collection of clinical samples

(1) Collection of sputum samples from the patients: sputum samples was collected in 39 patients by instructing them to cough and expectorate about 5–10 ml in a sterile container usually early in the morning.
(2) Bronchoalveolar lavage (BAL): BAL samples were collected only from 21 patients who were mechanically ventilated patients with the help of a white light flexible bronchoscope attached to a light source and digital camera.

Mycological analysis of clinical samples
Direct microscopic examination
Direct smears from sputum samples and BAL samples were prepared and examined by direct microscopy using Lactophenol Cotton Blue stain. The slides were examined under a light microscope on power ×40 and ×100, magnification.

Culturing of samples
The samples were streaked on Sabouraud's glucose agar medium and examined.

Statistical analysis
The data collected were tabulated and statistically analyzed using the following methods:

(1) Descriptive statistics: continuous data was represented as mean and SD, while nonnumerical data as number and percentage.
(2) Analytic statistics:
  (a) One-way analysis of variance test for rank (Kruskal–Wallis): this test was used to compare between more than two groups of numerical origin.
  (b) Person's χ^2 test: the test was used to test the association between categorical variables.
All statistical tests were two sided, P considered significant if less than 0.05.

Ethics committee approval
Study was done after ethics committee approval and written consents were taken from the patients.

Results
The examined specimens had been collected from patients by two methods: sputum (65%) and BAL (35%), and the results showed that the prevalence of fungal infection was 66.67%. The most common fungus present was *Candida albicans* (23.33%) and Aspergillus nonfumigates (18.33%) (Table 1).

There was an insignificant statistical difference between the median age of patients infected by Candida or Aspergillus in comparison with others without fungal infection, $P=0.4$. Also, there were insignificant association of specific sex type or smoking activity with fungal infection, $P=0.3$ and 0.5, respectively (Table 2).

Table 1 Specimen analyzed and final diagnosis

Specimen analyzed and final diagnosis	N=60 [n (%)]
Specimen	
BAL	21 (35)
Sputum	39 (65)
Result	
Aspergillus fumigates	6 (10)
Aspergillus nonfumigates	11 (18.33)
Candida albicans	14 (23.33)
Candida nonalbicans	9 (15)
Nil	20 (33.33)

BAL, bronchoalveolar lavage.

Table 2 Demographic characteristics in correlation with fungal infection

Variables	Without fungal infection (N=20)	With Candida infection (N=23)	With Aspergillus infection (N=17)	P
Age (years)	56.5 (49.25–58.75)	59 (44–66)	56 (52–62)	0.4[a]
Sex (male)	13 (65)	19 (82.61)	46 (76.67)	0.3[b]
Smoking (yes)	12 (60)	8 (47.06)	30 (50)	0.5[b]
MV	7 (35)	12 (52.17)	2 (11.76)	0.02

Continues; none normally distributed data represented as median and IQR, categorical data as *n* (%). MV, mechanical ventilation. [a]Kruskal–Wallis test. [b]χ^2 test. *P* value considered significant if less than 0.05.

Table 3 Comorbidity impact in patients with fungal infections

Comorbidities	Without fungal infection (N=20)	With Candida infection (N=23)	With Aspergillus infection (N=17)	P
DM	6 (30)	9 (39.13)	1 (5.88)	0.03[a]
Renal disease	1 (5)	0 (0)	2 (11.76)	[b]
Liver disease	3 (15)	2 (8.7)	2 (11.76)	0.8[a]
Malignancy	1 (5)	1 (4.35)	1 (5.88)	[b]
CVD	3 (15)	2 (8.7)	1 (5.88)	0.6[a]
Blood disease	0 (0)	2 (8.7)	0 (0)	[b]

[a]χ^2 test. [b]No test of significant. CVD, cardiovascular disease; DM, diabetes mellitus. *P* value considered significant if less than 0.05.

Table 4 Impact of medication used with fungal infection

Medication risks	Without fungal infection (N=20)	With Candida infection (N=23)	With Aspergillus infection (N=17)	P
Antibiotics	18 (90)	18 (78.26)	14 (82.35)	0.5[a]
Steroids	6 (30)	16 (69.57)	3 (17.65)	0.002[a]
Immunosuppressive drugs	1 (5)	2 (8.7)	0 (0)	[b]

[a]χ^2 test. [b]No test of significance. *P* value considered significant if less than 0.05.

There was significant association of diabetes mellitus (DM) with Candida infection, *P*=0.03, while the other comorbidity showed an insignificant association with Candida or Aspergillus infection (Table 3).

Also, there was significant association of steroid use with Candida infection (*P*=0.002), while neither antibiotics nor immunosuppressive drugs were significantly associated with fungal infection, *P*=0.5 (Table 4).

Our results showed insignificant statistical difference between patients with fungal infection (Candida and

Table 5 Length of stay in ICU and mechanical ventilation use in correlation with fungus infection

Variables	Without fungal infection (N=20)	With Candida infection (N=23)	With Aspergillus infection (N=17)	P
LOS (days)	7 (5–8)	5 (4–8)	7 (4.5–8)	0.3[a]
MV	7 (35)	12 (52.17)	2 (11.76)	0.02[b]
Neutropenia	2 (10)	1 (4.35)	0 (0)	[c]

Continues; non-normally distributed data represented as median and IQR, categorical data as *n* (%). [a]Kruskal–Wallis test. [b]χ^2 test. LOS, length of stay; MV, mechanical ventilation. *P* value considered significant if less than 0.05. [c]No test of significance.

Table 6 Effect of the underling chest disease on fungal infection

Variables	Without fungal infection (N=20)	With Candida infection (N=23)	With Aspergillus infection (N=17)	P
Asthma	2 (10)	6 (26.09)	4 (23.53)	
Bronchiectasis	1 (5)	3 (13.04)	1 (5.88)	
COPD	12 (60)	10 (43.48)	7 (41.18)	
ILD	2 (10)	1 (4.35)	2 (11.76)	*
Pneumonia	2 (10)	2 (8.7)	2 (11.76)	
TB	1 (5)	1 (4.35)	1 (5.88)	

Categorical data as *n* (%). *No test of significance. COPD, chronic obstructive pulmonary diseases; ILD, interstitial lung disease; TB, tuberculosis. *P* value considered significant if less than 0.05.

Table 7 Clinical presentation of patients

Clinical presentation	N=60
Cough	60 (100)
Expectoration	56 (93.33)
Dyspnea	60 (100)
Chest pain	13 (21.67)
Hemoptysis	9 (15)
Wheeze	39 (65)
Constitutional symptoms	50 (83.33)

Aspergillus) as regards the median length of stay in ICU, *P*=0.3, while mechanical ventilation (MV) use was significantly associated with Candida infection (*P*=0.02) (Table 5).

Statistically there was an insignificant association of specific underling chest disease with fungal infection either by Candida or Aspergillus (Table 6).

All of the patients presented by cough and dyspnea (100%), 93.33% of the patients presented by expectoration, and 83.33% with constitutional symptoms. Finally, the less frequent symptoms were hemoptysis and chest pain (15 and 21.67%, respectively) (Table 7).

Table 8 Radiological aspect of fungal infection

Radiological finding	Without fungal infection (N=20)	With Candida infection (N=23)	With Aspergillus infection (N=17)	P
Radiography				
Bronchiectatic changes	1 (5)	3 (13.04)	Any patients with a history of preexisting lung disease and immunosuppression from corticosteroids or other underlying conditions (e.g. diabetes, malnutrition, and liver cirrhosis). 0 (0)	
Cavities	1 (5)	1 (4.35)	1 (5.88)	*
Consolidation	2 (10)	2 (8.7)	2 (11.76)	
Hyperinflation	12 (60)	11 (47.83)	7 (41.18)	
Normal	2 (10)	4 (17.39)	7 (41.18)	
Reticulonodular	2 (10)	2 (8.7)	0 (0)	
CT				
Air crescent	1 (5)	2 (8.7)	0 (0)	
Bronchiectatic changes	1 (5)	3 (13.04)	1 (5.88)	
Cavities	1 (5)	1 (4.35)	1 (5.88)	*
Consolidation	2 (10)	2 (8.7)	2 (11.76)	
Halo sign	1 (5)	1 (4.35)	1 (5.88)	
Hyperinflation	12 (60)	9 (39.13)	7 (41.18)	
Normal	0 (0)	3 (13.04)	3 (17.65)	
Reticulonodular	2 (10)	2 (8.7)	2 (11.76)	

Categorical data as n (%). *No test of significance. $^b\chi^2$ test. P value considered significant if less than 0.05.

Hyperinflation was the most common radiological features in both radiograph and CT in the three groups of patients (Table 8).

Discussion

The incidence of pulmonary mycosis has increased over the past few decades due to the wide use of broad-spectrum antibiotics, immunosuppressive and chemotherapy agents as well as the increased incidence of respiratory diseases, including chronic obstructive pulmonary disease (COPD), lung cancer, and tuberculosis [5].

This cross-sectional study was done to assess the prevalence of fungal chest infection in patients at different RICUs and to identify their pattern.

The demographic features of the studied 60 patients demonstrated that the majority of patients were men presenting 76.67% while women were 23.33%. The mean age of these participants was 55 years. Furthermore, 50% of patients in our study had positive smoking history. There were insignificant statistical difference between the median age of patients infected by Candida or Aspergillus in comparison with others without fungal infection, $P=0.4$. Also, there were insignificant associations of specific sex type or smoking activity with fungal infection, $P=0.3$ and 0.5, respectively.

The current study showed that 66.67% (40 out of 60 patients) of the patients with respiratory diseases were culture positive for fungal agents and 20 (33.33%) patients only were negative. The major fungal species encountered in this study were Candida species in 23 (57.5%) cases, followed by Aspergillus species in 17 (42.5%) cases. *C. albicans* was isolated in 23.33% of patients, followed by Aspergillus nonfumigatus (18.33%), then Candida nonalbicans (15%), and finally *Aspergillus fumigatus* (10%).

Our results came in accordance with the Farghaly and colleagues study in which the major fungal species encountered in 114 (46.3%) cases were Candida species followed by Aspergillus species in 82 (33.3%) cases, pencillium species in 10 (4.1%) cases, and fusarium spp. in seven (2.8%) cases, while combined Candida and Aspergillus infection was present in eight (3.3%) cases. *C. albicans* was the most predominant versus Candida nonalbicans. However, Aspergillus nonfumigatus percentage exceeded that of *A. fumigatus* [6].

Again, our results came in accordance with another study of fungal culture of 60 patients with respiratory diseases, by Biswas *et al.* [7] which reported *Aspergillus* sp. in 13 patients (including *Aspergillus flavus* in six patients, *A. fumigatus* in four patients, and *Aspergillus niger* in three patients) and *Candida* sp. in 14 (*C. albicans* and *C. tropicalis* being isolated from 12 and two patients, respectively). One patient, with chronic

interstitial lung disease, showed growth of *Cryptococcus neoformans*.

The most common comorbidity of respiratory ICU patients at risk of pulmonary fungal infections were uncontrolled DM (26.67%) and it was also found to be the most common comorbid disease associated with high fungal recovery rates; 10 (62.5%) out of 16 diabetic patients had positive fungal culture. DM was followed by liver disease and cardiovascular disease (11.67 and 10%, respectively); finally, the least common comorbidity was blood disease (3.33%).

There was a significant association of DM with Candida infection, $P=0.03$, while the other comorbidities including cardiovascular, liver, renal diseases, and malignancies showed insignificant association with either Candida or Aspergillus infection.

Regarding the drugs used 83.33% of patients studied were on antibiotic therapy, 41.67% on steroid therapy, and only 5% of patients used immunosuppressive drugs. About 35% of RICU patients were on MV support with a mean length of stay in ICU of about 6 days. Finally, only 5% of patients were suffering from neutropenia.

Statistically, this study demonstrated significant association of steroid use with Candida infection ($P=0.002$), while neither antibiotics nor immunosuppressive drugs were significantly associated with pulmonary fungal infection, $P=0.5$. Also, in mechanically ventilated patients, there was a significant association between MV and Candida infection, $P=0.02$. Furthermore, there were insignificant statistical differences between patients with fungal infection (Candida and Aspergillus) as regards the median length of stay in ICU, $P=0.3$.

Our study results came in agreement with the results of Biswas *et al.* [7] who screened 60 patients with chronic respiratory diseases for the presence of pulmonary fungal infections which reported that among the different comorbid conditions and risk factors, the common associations included DM, severe anemia (hemoglobin <9%), use of steroids, alcoholism, and chronic carrier state of HBV. Moreover, this study also reported that DM was found to be the most common risk factor associated with isolation of *Candida albicans* [7].

Our study results also came in accordance with the results of Schnabel *et al.* [8] which revealed that the use of steroids and prior antibiotic use have been linked to

increased colonization with Candida species at various anatomical sites.

Our study revealed that 29 (48.33%) patients of a total 60 patients were COPD, 17 (42.5% out of the positive cases) of them had positive culture for fungal infection, 10 (43.48%) of them with Candida infection, and seven (41.18%) with Aspergillus infection. Also, there were 20% with bronchial asthma; 10 (25% out of the positive cases) of them had positive culture for fungus, six (26.09%) of them with Candida infection, and four (23.53%) with Aspergillus infection. Moreover, the study group included bronchiectasis in 8.33%, pneumonia in 10%, interstitial lung diseases in 8.33%, and tuberculosis in 5% of patients.

On comparing culture positivity for fungal infection among different pulmonary diseases we found that culture-positivity rate was statistically significantly higher in asthma and bronchiectasis than other pulmonary diseases ($P<0.05$).

The Egyptian study of Farghaly and colleagues showed that 177 (45.5%) of a total of 389 patients were COPD and114 (46.3% out of the positive cases) of them had positive culture for fungal infection. Also, there were 38 (9.8%) patients with bronchial asthma; 26 (10.6% out of the positive cases) of them had positive culture for fungus. Moreover, the study group included 36 (9.3%) patients, 35 (9.0%) patients and 34 (8.7%) patients with tuberculosis, suppurative lung diseases and pneumonia, respectively. On comparing culture positivity for fungal infection among different pleuropulmonary diseases, culture-positivity rate was statistically significantly higher in COPD patients compared with pneumonia ($P<0.05$). Also, culture-positive rate was statistically significantly higher in bronchial asthma patients in comparison with pneumonia patients ($P<0.05$). However, the culture-positive rate was statistically significantly lower in pneumonia patients compared with patients with pleural diseases ($P<0.05$). On the other hand, there was no statistically significant difference between COPD in comparison with asthma, tuberculosis, or suppurative lung diseases ($P>0.05$) [6].

All of patients presented by cough and dyspnea (100%), 93.33% of patients presented by expectoration and 83.33% with constitutional symptoms. Finally, the less frequent symptoms were hemoptysis and chest pain (15 and 21.67%, respectively).

Luo and colleagues in their study on pulmonary mycosis among 68 patients in China showed that

the main symptoms of the patients were as follows: cough in 51 (75.0%) cases; expectoration in 38 (55.9%) cases, with blood in sputum in 18 cases, white phlegm in 12 cases, and purulent sputum in eight cases; hemoptysis in 25 (36.8%) cases; fever in 20 (29.4%) cases; chest pain and shortness of breath in five cases; headache, nausea, and vomiting in three cases. Only six (11.1%) patients were asymptomatic [9].The present study revealed that the most frequent radiographic manifestations in patients at risk of pulmonary fungal infection in chest radiograph and CT, respectively, were hyperinflation (50 and 46.67%). Other radiological presentations were consolidation (10 and 10%), bronchiectasis (6.67 and 8.33%), reticulonodular infiltrations (6.67 and 10%), and cavities (5 and 5%). Moreover, CT chest revealed halo sign (5%) and air crescent (5%) in patients with Aspergillus infections. Interestingly, normal chest radiograph and CT chest were found in some patients at risk of pulmonary fungal infections (21.67 and 10%). Our study reported that there was no significant association between any radiological presentation and Candida or Aspergillus infection.

This results came in accordance with those of Biswas *et al.* [7] in which none of the radiological patterns showed significantly higher association with fungal recovery ($P=0.7$) and normal radiography was associated with fungal growth in five of 10 patients [7].

Luo *et al.* [9] showed that radiographic characteristics were masses or nodule lesions in 52 (76.5%) cases, patchy lesions in 10 (14.7%) cases, cavity formation in 15 (22.0%) cases, and diffuse miliary nodules in one case.

Limitations of the study were the small number of cases collected, thus our findings may not be representative of the entire population of Egypt, relatively short period during which patients selected from different respiratory ICUs and finally making nonmolecular diagnosis only, thus recommending more informative studies in the future.

Conclusion

From the current study, we can conclude that pulmonary fungal infection appears to be an important problem in patients with respiratory diseases especially in patients who are admitted to the medical respiratory ICU regardless of their age or sex.

Among different respiratory diseases, COPD is the most common disease among patients at risk of pulmonary fungal infection. DM is the most common comorbid disease associated with high fungal recovery rates especially Candida.

Conflicts of interest
There are no conflicts of interest.

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