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Association of airborne *Aspergillus* with asthma exacerbation in Southern Pakistan

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Background: Exposure to airborne fungi has been related with exacerbation of asthma in adults and children leading to increased outpatient, emergency room visits, and hospitalizations. Hypersensitivity to these airborne fungi may be an important initial predisposing factor in the development and exacerbation of asthma.

Objective: This study was conducted to determine an association between fungal types and spore concentrations with the risk of asthma exacerbation in adults.

Methods: This cross-sectional study was conducted from May 2008 to August 2009 at the Aga Khan University Hospital Karachi, Pakistan. All adult (age≥16 years) patients presenting to the hospital with acute asthma exacerbation were enrolled after informed consent. A home survey was conducted for each patient to assess their environmental characteristics. Indoor air samples were also obtained from the patient's home to determine the type and spore concentration of fungi within the week of their enrollment in the study.

Results: Three hundred and ninety-one patients with an acute asthma exacerbation were enrolled during the study period. The mean age of participants was 46 years (standard deviation, ±18 years) and 247 (63.2%) were females. A trend of higher asthma enrollment associated with higher *Aspergillus* concentrations was found in two consecutive summers. A total of nineteen types of fungi were found in air samples. *Aspergillus* spp. was the most frequently isolated fungus with acute asthma exacerbation.

Conclusion: An association of higher concentration of indoor *Aspergillus* spp. with asthma exacerbation in adults was observed in this study.

Key words: Aspergillus; Asthma; Fungal spores; Pakistan

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INTRODUCTION

Aeroallergens, especially indoor allergens have been strongly associated with asthma and this risk is higher when the exposure is perennial [1-5]. Approximately 70% of asthmatics have allergic sensitization and has been reported more frequently in children [6, 7].

Indoor exposure to aerosolized fungal spores has been closely associated with sensitization and the development or exacerbation of asthma [8, 9]. The most studied fungi in relation to asthma include *Alternaria, Cladosporium, Aspergillus* and *Penicillium* spp., however these studies are mostly related to acute exposure to fungi [10-14].

The association of asthma with sensitization to common indoor allergens has been reported by Rhodes et al. [15]. Sensitization to fungal allergens has also been reported to be a risk factor in the development, exacerbation, severity and mortality associated with asthma [3, 16, 17]. *Aspergillus* spp. is now recognized to be the cause of a spectrum of allergic lower respiratory disease from asthma with fungal sensitization, severe asthma with fungal sensitization to allergic broncho-pulmonary aspergillosis [18-23].

The primary objective of this study was to determine the role of fungi in the exacerbation of asthma in adult asthmatics. The secondary objective was to determine the spectrum of fungi in relation to the characteristics of the indoor home environment.

The study was conducted in Karachi, the largest city in Pakistan, located on the southern coast with a relatively mild climate. The city enjoys mild winters and warm summers. It receives the tail end of the monsoon rains in July and August. Previous studies of outdoor fungi in Karachi have shown a high prevalence of *Aspergillus* spp. throughout the year but especially during the humid summer season [24, 25]. The presence of indoor *Aspergillus* could be a potential cause of asthma with important implications.

MATERIALS AND METHODS

Study design and settings

This cross sectional study was conducted from May 2008 to August 2009 at the Aga Khan University Hospital in Karachi, the coastal city of Pakistan. Adult patients (age≥16 years) with an acute asthma exacerbation and residents of different parts of Karachi were enrolled (Fig. 1). Written informed consent was obtained. The study was approved by the Ethical Review Committee of the Aga Khan University.

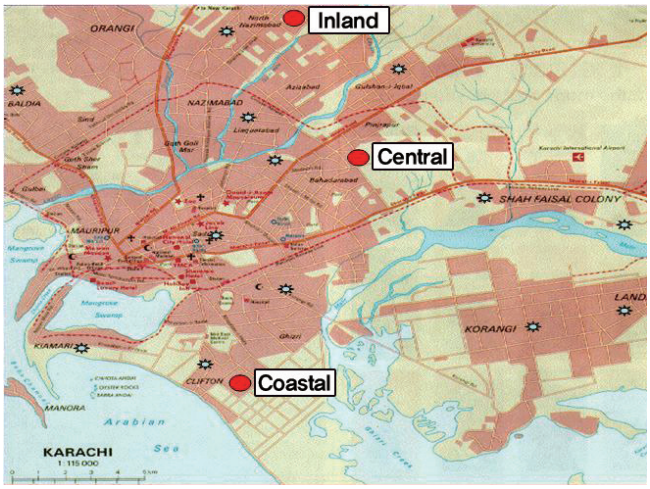

Fig. 1. Map of Karachi city showing areas of outdoor and indoor sampling. Outdoor samples. Areas of patient enrollment.

Acute asthma exacerbation

All patients of age 16 and above who presented to the Aga Khan University Hospital with acute asthma exacerbation were screened for enrollment in the study. Acute exacerbations of asthma are episodes of a progressive increase in shortness of breath, cough, wheezing or chest tightness, or a combination of these symptoms as defined by the Global Initiative for National Asthma Guidelines [26].

Data collection

A precoded, structured questionnaire was used to collect data on demographic, socioeconomic, and health-related variables. The lists of variables were:

(1) Demographic variables included age and gender

(2) Socioeconomic variables included occupation, number of family members, type of house, number of rooms and type of flooring

(3) Environmental variables included presence of indoor pets, plumbing leaks, overflowing trash can, dirty dishes and cooking pots, grease on or around stove, cockroach stains or droppings, live or dead cockroaches (or parts), standing water (in sink, on stove, in flower pots), evidence of any moisture or leaks, mildew on the ceiling, walls, window, musty smell, evidence of tobacco use like ashtrays or cigarette butts or smell of tobacco smoke in the room

(4) Health related variables included any previous episodes of asthma exacerbation, associated factors like respiratory

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tract infection, change of season, indoor smoking, allergen exposure, and site of enrollment (e.g., outpatient clinic, emergency room, or inpatient).

Home survey

A research assistant conducted a home visit within a week of enrollment. This included home inspection, environmental data collection and collection of indoor air samples.

Air sampling

Air samples were obtained by using single stage Burkard portable air sampler (Burkard Manufacturing Co., Rickmansworth, UK), which draws air through a sieve plate with 100 holes of 1-mm diameter over a petri dish containing 18 mL of agar. We used three types of media to support growth of variety of environmental fungi, named Saboraud's, cornmeal and potatodextrose agar. The plates were exposed to air sampler for a period of 60 seconds at a flow rate of 30 L per minute. Indoor air samples were collected from each patient's home within 1 week of enrollment. Outdoor air samples from three locations of the city (coastal, central and inland areas) were taken monthly during the study period.

Laboratory analysis

All specimens were submitted to Microbiology section of Clinical Laboratory at Aga Khan University. Plates were incubated at 25°C and 37°C for maximum of 7 days. Each plate was examined on daily basis. Total colony count was noted and fungal identification was performed by conventional laboratory methods including ability to grow at different temperature, rate of growth, color and morphological characteristics of colonies. Identification of fungi were further confirmed by microscopic examination by using Lactophenol cotton blue staining and biochemical reactions where required.

Meteorological data

Daily minimum and maximum ambient temperature and humidity was obtained from the Dawn newspaper (epaper.dawn.com) [27]. This newspaper gets daily information on the weather conditions of the city from Pakistan Meteorological Department located in the city center (Fig. 1).

Statistical analysis

Frequency distribution of household characteristics including type of accommodation, flooring type, cooking fuel, visible dampness, growth of mold, musty odor, indoor pets, and pest infestation were calculated. Line graphs were made by month of registration and average humidity (%), total monthly enrollment, median *Aspergillus* concentration and for other important spores as well. Descriptive statistics were computed including mean, standard deviation, minimum, maximum observations, quartiles were obtained for different fungal spore concentrations and meteorological data.

Independent samples *t*-test was used to observe the mean age difference between those who refused or did not refuse to participate in the study. Similarly, chi-square test was used to observe the association between participation status and gender as well as area of residence. Pearson correlation was also computed to observe the relationship between average humidity (%) and asthma exacerbation.

Data was analyzed in PASW ver. 18.0 (SPSS Inc., Chicago, IL, USA). A *p* value less than 0.05 was considered as statistically significant.

RESULTS

Four hundred and seventy-six patients with acute asthma

Table 1. Household characteristics of patients (n = 391)

Characteristic	No. (%)
Type of accommodation	
Apartment	194 (49.6)
House	197 (50.4)
Indoor environmental observation	
Flooring type*	
Carpeted	170 (35.7)
Noncarpeted	306 (64.3)
Gas cooking stove or range	389 (99.7)
Cockroach stains (dead or live)	113 (28.9)
Stagnant water/moisture	71 (18.2)
Indoor pets	51 (13.1)
Mildew on walls/windows/ceilings	49 (12.5)
Dirty dishes/stoves	42 (10.7)
Ashtray or cigarettes butts	34 (8.7)
Tobacco smell	26 (6.9)
Musty smell	18 (4.6)
Overflowing trash can	14 (3.6)

*Multiple responses.

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Table 2. Summary statistics for indoor fungal spore concentrations (CFU) and other environmental factors

Variable	No.	1st Quartile	Median	3rd Quartile	Mean	SD
Total colony count	391	14	21	33	27.37	23.39
Aspergillus flavus	354	3	6	11	9.15	14.01
Aspergillus niger	374	5	8	15	12.08	15.20
Aspergillus fumigatus	246	2	3	5	4.32	4.02
Aspergillus terreus	100	1	2	3	2.11	1.44
Aspergillus glaucus	11	2	2	3	2.63	1.12
Aspergillus nidulans	7	2	2	3	2.57	1.27
Penicillium	78	2	3	4	4.17	5.62
Fusarium	61	1	2	3	2.83	2.67
Drechslera	99	2	3	5	4.05	3.89
Mucor	78	2	2	4	3.65	5.23
Alternaira	28	2	2	5	4.14	4.88
Rhizopas	41	2	2	4	3.26	3.39
Curvalaria	15	2	2	3	2.26	0.88
Cladosporin	9	2	3	4	4.00	3.50
Syncephalastrum	7	2	2	3	3.00	2.70
Min. temperature (℃)		20.7	26	28	23.7	5.1
Max. temperature (℃)		31.0	33	35	32.8	3.5
Humidity (%)		43	61	68	54.6	18.8

SD, standard deviation.

exacerbations were identified, out of which 391 agreed to participate in the study (Fig. 2). The mean age of the patients was 46 years (standard deviation, ±18 years) and 247 (63.2%) were females. Characteristics of patients who refused to participate were not significantly different from participants; i.e., age ($p = 0.58$), gender ($p = 0.34$) and area of residence ($p = 0.64$).

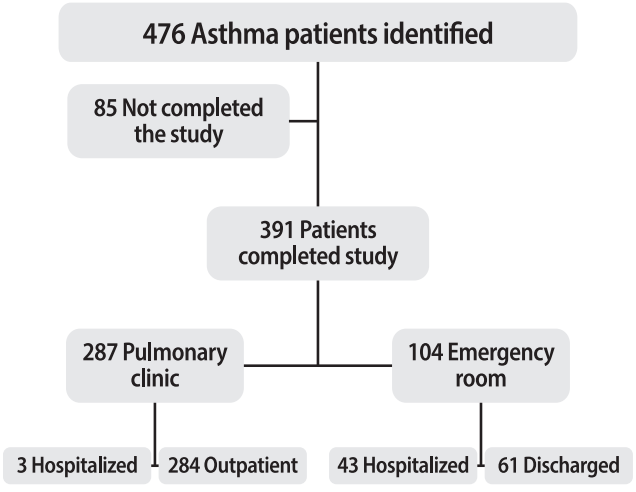

Fig. 2. Flow chart of the study.

The characteristics of the households of the study subjects are summarized in Table 1.

A total of nineteen genuses of fungi were isolated from the indoor samples. The common fungi were *Aspergillus* (99.7%), *Drechslera* (25.3%), *Penicillium* (19.9%), *Mucor* (19.9%), *Fusarium* (15.6%), and *Rhizopus* (10.4%). Spore counts of fungi other than *Aspergillus* were <100 and are summarized in Table 2. There was no association seen between the concentrations of fungi and the household characteristics.

The commonest indoor fungi were *Aspergillus* spp. The most frequent isolates were *Aspergillus flavus* and *Aspergillus niger*. The concentration of *Aspergillus* was directly proportional to the number of enrollments from May to November 2008. A weak relationship was observed between number of asthma exacerbation and *Aspergillus* concentration ($r = 0.22$). The concentration of *Aspergillus* was lowest from December 2008 till March 2009 which coincided with relatively low humidity. During the study period, two peaks of asthma exacerbation enrollments were observed, one in January and the second noticed both years, in the month of June and

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July (Fig. 3). This trend was observed in months of 2 consecutive summers where high *Aspergillus* concentration was found with high humidity. Association of asthma exacerbation with any other fungi was not observed, albeit their concentrations were much lower than *Aspergillus* spp. (Fig. 4). There was no relationship observed between average monthly humidity and enrollment of asthma exacerbation ($r = 0.01$, $p > 0.99$).

Aspergillus was seen throughout the year while certain fungi like *Curvalaria* were seen exclusively in autumn. The concentration of *Rhizopas* and *Drechslera* peaked in low humidity season (Fig. 4).

In the outdoor samples, nine fungi were isolated; *Aspergillus*, *Drechslera* and *Penicillium* outnumbered the rest on the basis of their spore concentration. The average spore concentrations were similar for the three outdoor locations (Fig. 1). The meteorological data was divided into three categories; hot and dry (April, September till October), hot and humid (May to August) and cold and dry weather (November to March). Increased enrollment in cold and dry season did not correlate with *Aspergillus* concentration.

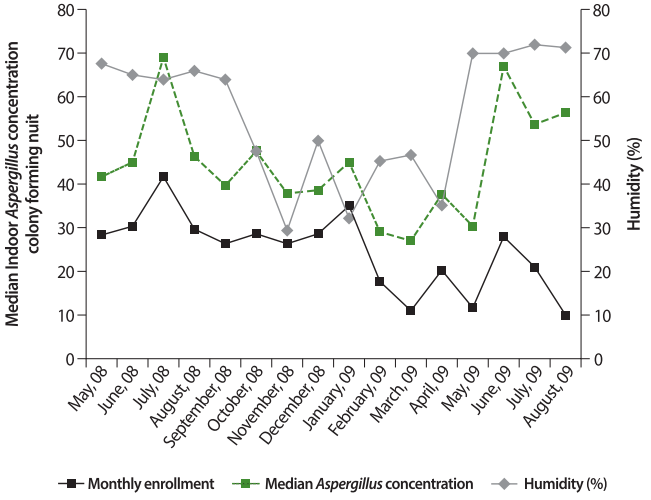

Fig. 3. Relationship between enrollment of asthma exacerbation, humidity and indoor *Aspergillus* concentration.

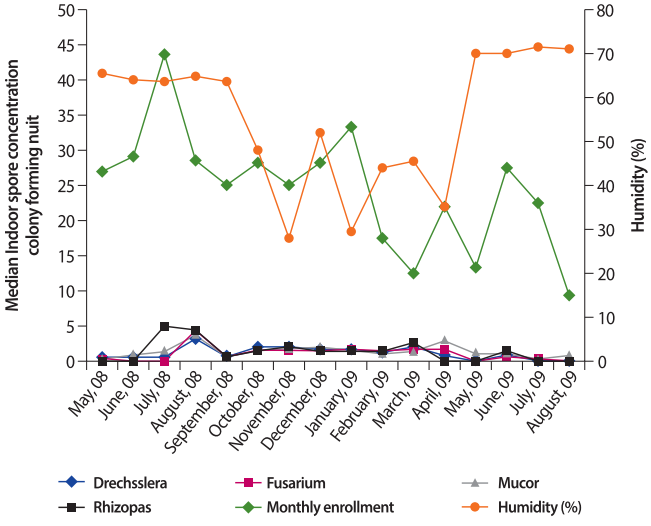

Fig. 4. Relationship between enrollment due to asthma exacerbation and indoor spores concentration.

DISCUSSION

In this study we found that patients with an acute exacerbation of asthma had corresponding high spore counts of *Aspergillus* in indoor air sampled from their homes.

We observed the trend of asthma exacerbation in adult asthmatics with increasing levels of indoor *Aspergillus* spp. A study by Shendell et al. [28] found a trend of association between total fungal DNA with decreased forced vital capacity and forced expiratory volume in 1 second in adults with asthma and chronic bronchitis. Similarly, Alternaria has been reported to be associated with asthma in the northern hemisphere [10].

Long-term studies of adult asthma in association with fungi are limited. Dales et al. [29] reported that higher concentrations of *Alternaria, Caldosporium, Aspergillus, Epicoccum,* and *Ganoderma* were associated with increased emergency room visits in children in Canada because of asthma. A study conducted in London from June to October (1992–93) looked at the association of outdoor fungi with asthma exacerbation in children [30]. This study showed the association of increased emergency visits and hospitalizations in children with various fungi including *Alternaria, Epicoccum, Agrocybe, Basidiospores,* and *Ascospores*. Similarly, a study by Rosas et al. [31] on environmental factors in relation to asthma hospitalization in Mexico City concluded that elevated hospital asthma admissions in children were associated with *Leptospheria* spp.

The winter peak enrollment seen in December 2008 and January 2009 in this study was most likely due to increased respiratory tract infection resulting in asthma exacerbations. Previous studies suggested that 50–60% of adult asthma exacerbation is associated with upper respiratory tract infections [32]. Johnston [33] showed the predictable seasonal epidemics of asthma exacerbations in winter in adults and early September in children in Canada, were mostly caused by an increase in seasonal viral infections in both

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children and adults.

The secondary study objective of the study was to determine the spectrum of fungi in relation to the characteristics of the indoor home environment and the effect of temperature, humidity and seasonal variation. There is evidence of an association between respiratory tract symptoms like cough and wheezing with damp indoor environment [34]. In this study, *Aspergillus* spp. was found in most homes of asthmatic patients in all seasons with relatively high concentration in summers, while other fungi were found in certain seasons in low concentration. The presence of such high levels of air-borne *Aspergillus* spp. in adult asthmatic homes has not been reported previously. Previous data of fungi in Karachi has shown high levels of outdoor *Aspergillus* spp. during the hot and humid summer season [24, 25].

Previous studies, mostly in the United States, United Kingdom, and Northern Europe have shown the association of dampness and molds in homes with adverse respiratory effects among adults and children [35]. We did not find any association between particular home characteristic or dampness with any fungus in this study in Southern Pakistan.

The role of indoor allergens as a constant source of exposure, sensitization and development of asthma is considered important in the case of house dust mite, cockroach and pet allergy. The association of constant exposure to fungi as a causal agent of asthma has not been well studied but could be important in regions with high indoor fungi prevalence. The finding of *Aspergillus* spp. all year round in the homes of adult asthmatics could have important implications. This study looks at the spatial relationship of *Aspergillus* spp. with asthma exacerbation.

An incidental finding was a dominance of female asthmatics in the study. Although this is consistent with previous data on the gender preponderance in asthma, no specific environmental factor causing this phenomenon was identified. The women in this region are usually housewives, spending more time at home, where dampness could be associated with increased fungal concentrations leading to asthma exacerbation [34, 35]. Respiratory symptoms have been associated with wood smoke exposure in women in Southern Pakistan [36] while in urban population natural gas is a source of fuel for cooking. Previous studies have suggested both hormonal and environmental influences are possible causes of this predilection among females [37, 38].

The strength of the study is that it provides data on a region, which has been under studied in the past. This study provides new information on the possibility of *Aspergillus* spp. as an important trigger of asthma and enabled us to correlate the climatic effect on the concentration of *Aspergillus* and asthma exacerbations in two consecutive summer months of June and July.

A limitation of this study is the lack of specific sensitization data of the patients such as allergy skin tests and specific immunoglobulin E levels. Another limitation of study was the lack of objective laboratory confirmation of the possibility of upper respiratory tract infections as a cause of increased patient enrollment in winter season. The lack of a control group is also a limitation of the study, which is an important criteria to observe the risk factors related to the disease.

In conclusion, in this study population an association between higher concentration of indoor *Aspergillus* spp. and asthma exacerbation in adults was found. We suggest that future studies need to be conducted to see the contributing role of dust mite, cockroach and other air pollutants.

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REFERENCES

1. Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, Greenberger PA, Kariuki B, Kita H, Kurup VP, Moss RB, Niven RM, Pashley CH, Slavin RG, Vijay HM, Wardlaw AJ. Fungi and allergic lower respiratory tract diseases. J Allergy Clin Immunol 2012;129:280-91.
2. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, Malveaux F. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 1997;336:1356-63.
3. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, Sachs MI. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N Engl J Med 1991;324:359-63.
4. Targonski PV, Persky VW, Ramekrishnan V. Effect of environmental molds on risk of death from asthma during the pollen season. J Allergy Clin Immunol 1995;95(5 Pt 1):955-61.
5. Black PN, Udy AA, Brodie SM. Sensitivity to fungal allergens is a risk

http://dx.doi.org/10.5415/apallergy.2014.4.2.91

factor for life-threatening asthma. Allergy 2000;55:501-4.
6. Cruz AA, Bousquet J, Khaltaev NG. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. Geneva: World Health Organization; 2007.
7. Kalliel JN, Goldstein BM, Braman SS, Settipane GA. High frequency of atopic asthma in a pulmonary clinic population. Chest 1989;96:1336-40.
8. Institute of Medicine (US), Committee on Damp Indoor Spaces and Health. Damp indoor spaces and health. Washington, DC: National Academies Press; 2004.
9. Douwes J, Pearce N. Invited commentary: is indoor mold exposure a risk factor for asthma? Am J Epidemiol 2003;158:203-6.
10. Salo PM, Arbes SJ Jr, Sever M, Jaramillo R, Cohn RD, London SJ, Zeldin DC. Exposure to Alternaria alternata in US homes is associated with asthma symptoms. J Allergy Clin Immunol 2006;118:892-8.
11. Bush RK, Prochnau JJ. Alternaria-induced asthma. J Allergy Clin Immunol 2004;113:227-34.
12. Pulimood TB, Corden JM, Bryden C, Sharples L, Nasser SM. Epidemic asthma and the role of the fungal mold Alternaria alternata. J Allergy Clin Immunol 2007;120:610-7.
13. O'connor GT, Walter M, Mitchell H, Kattan M, Morgan WJ, Gruchalla RS, Pongracic JA, Smartt E, Stout JW, Evans R, Crain EF, Burge HA. Airborne fungi in the homes of children with asthma in low-income urban communities: The Inner-City Asthma Study. J Allergy Clin Immunol 2004;114:599-606.
14. Bernton HS. Asthma due to a mold-aspergillus fumigatus. JAMA 1930:95:189-91.
15. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. Am J Respir Crit Care Med 2002;165:176-80.
16. Singh AM, Busse WW. Asthma exacerbations. 2: aetiology. Thorax 2006;61:809-16.
17. Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F; European Community Respiratory Health Survey. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. BMJ 2002;325:411-4.
18. Hinson KF, Moon AJ, Plummer NS. Broncho-pulmonary aspergillosis; a review and a report of eight new cases. Thorax 1952;7:317-33.
19. Schwartz HJ, Greenberger PA. The prevalence of allergic bronchopulmonary aspergillosis in patients with asthma, determined by serologic and radiologic criteria in patients at risk. J Lab Clin Med 1991;117:138-42.
20. Maurya V, Gugnani HC, Sarma PU, Madan T, Shah A. Sensitization to Aspergillus antigens and occurrence of allergic bronchopulmonary aspergillosis in patients with asthma. Chest 2005;127:1252-9.
21. Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. Eur Respir J 2006;27:615-26.
22. Kauffman HF, Tomee JF, van de Riet MA, Timmerman AJ, Borger P. Protease-dependent activation of epithelial cells by fungal allergens leads to morphologic changes and cytokine production. J Allergy Clin Immunol 2000;105(6 Pt 1):1185-93.
23. Agarwal R, Gupta D. Severe asthma and fungi: current evidence. Med Mycol 2011;49 Suppl 1:S150-7.
24. Rao TA, Shaikh AH, Ahmed M. Airborne fungal flora of Karachi, Pakistan. Pak J Bot 2009;41:1421-8.
25. Afzal M, Mehdi FS. Atmospheric fungi of Karachi city. Pak J Biol Sci 2002;5:707-9.
26. The Global Initiative for Asthma. GINA report: global strategy for asthma management and prevention. Updated 2012 [Internet]. The global initiative for asthma; c2012 [cited 2012 Dec 10] Available from: http://www.ginasthma.org/documents/4.
27. Pakistan Meteorological Department, Government of Pakistan [Internet]. Islamabad: Pakistan Meteorological Department, Government of Pakistan; c2012 [2012 Dec 10]. Available from: http://www.pmd.gov.pk/.
28. Shendell DG, Mizan SS, Yamamoto N, Peccia J. Associations between quantitative measures of fungi in home floor dust and lung function among older adults with chronic respiratory disease: a pilot study. J Asthma 2012;49:502-9.
29. Dales RE, Cakmak S, Burnett RT, Judek S, Coates F, Brook JR. Influence of ambient fungal spores on emergency visits for asthma to a regional children's hospital. Am J Respir Crit Care Med 2000;162:2087-90.
30. Atkinson RW, Strachan DP, Anderson HR, Hajat S, Emberlin J. Temporal associations between daily counts of fungal spores and asthma exacerbations. Occup Environ Med 2006;63:580-90.
31. Rosas I, McCartney HA, Payne RW, Calderon C, Lacey J, Chapela R, Ruiz-Velazco S. Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. Allergy 1998;53:394-401.
32. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. BMJ 1993;307:982-6.
33. Johnston NW. The similarities and differences of epidemic cycles of chronic obstructive pulmonary disease and asthma exacerbations. Proc Am Thorac Soc 2007;4:591-6.
34. Fisk WJ, Lei-Gomez Q, Mendell MJ. Meta-analyses of the associations

of respiratory health effects with dampness and mold in homes. Indoor Air 2007;17:284-96.

35. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. Environ Health Perspect 2011;119:748-56.
36. Siddiqui AR, Lee K, Gold EB, Bhutta ZA. Eye and respiratory symptoms among women exposed to wood smoke emitted from indoor cooking: a study from southern pakistan. Energy Sustain Dev 2005;9:58-66.
37. Chen Y, Stewart P, Johansen H, McRae L, Taylor G. Sex difference in hospitalization due to asthma in relation to age. J Clin Epidemiol 2003;56:180-7.
38. Schatz M, Clark S, Camargo CA Jr. Sex differences in the presentation and course of asthma hospitalizations. Chest 2006;129:50-5.

http://dx.doi.org/10.5415/apallergy.2014.4.2.91