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Brief report

Association of mold levels in urban children's homes with difficult-to-control asthma

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Background: Mold sensitization and exposure are associated with asthma severity, but the specific species that contribute to difficult-to-control (DTC) asthma are unknown.

Objective: We sought to determine the association between overall and specific mold levels in the homes of urban children and DTC asthma.

Methods: The Asthma Phenotypes in the Inner-City study recruited participants, aged 6 to 17 years, from 8 US cities and classified each participant as having either DTC asthma or easy-to-control (ETC) asthma on the basis of treatment step level. Dust samples had been collected in each participant's home (n = 485), and any dust remaining (n = 265 samples), after other analyses, was frozen at −20°C. The dust samples (n = 265) were analyzed using quantitative PCR to determine the concentrations of the 36 molds in the Environmental Relative Moldiness Index. Logistic regression was performed to discriminate specific mold content of dust from homes of children with DTC versus ETC asthma.

Results: Frozen-dust samples were available from 54% of homes of children with DTC (139 of 253) and ETC asthma (126 of 232). Only the average concentration of the mold *Mucor* was significantly ($P < .001$) greater in homes of children with DTC asthma. In homes with window air-conditioning units, the *Mucor* concentration contributed about a 22% increase (1.6 odds ratio; 95% CI, 1.2-2.2) in the ability to discriminate between cases of DTC and ETC asthma.

Conclusions: *Mucor* levels in the homes of urban youth were a predictor of DTC asthma, and these higher *Mucor* levels were more likely in homes with a window air-conditioner. (J Allergy Clin Immunol 2021;■■■:■■■-■■■.)

Key words: *APIC, US cities, child, mold, Mucor, air-conditioner*

INTRODUCTION

Asthma is a heterogeneous disease, and individuals with asthma vary widely in their presentation of symptoms, natural history, and response to treatment.[1-3] Patients with difficult-to-control (DTC) asthma are defined as those for whom symptom control is not achieved despite high-dose inhaled corticosteroids and maximal add-on therapies.

Although patients with DTC asthma make up only a small fraction of those with asthma, they are more likely to suffer from significant asthma morbidity.[4,5] Patients with DTC asthma have more frequent exacerbations, a poorer response to medications, and lower lung function compared with those with easy-to-control (ETC) asthma.[4] DTC asthma is more prevalent in urban, non-White, and underresourced populations.[6-8] These medical and demographic characteristics describe DTC asthma, but they do not provide insights into why some patients' asthma is DTC.

Barsky et al[9] stated that understanding DTC asthma required an "assessment of medication delivery, the home environment, and, if possible, the school and other frequented locations, the psychosocial situation, and comorbid conditions." Sheehan and Phipatanakul[10] also noted the important link between DTC asthma and environmental factors. Zhang et al[11] showed that steroid

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Abbreviations used
AC: Air-conditioner
APIC: Asthma Phenotypes in the Inner-City
DTC: Difficult-to-control
ERMI: Environmental Relative Moldiness Index
ETC: Easy-to-control

resistance was associated with mold exposures. However, studies to date have not quantified mold exposures in the homes of children with DTC versus ETC asthma.

A previous analysis of the Asthma Phenotypes in the Inner-City (APIC) study demonstrated that mold sensitization, but not sensitization to dust mites, roaches, rodents, pets, pollen/peanut, or foods, was significantly more common in those participants with DTC asthma compared with those with ETC asthma.[7] In this *post hoc* analysis of APIC dust samples, we investigated whether mold exposure, assessed with the Environmental Relative Moldiness Index (ERMI) panel of 36 molds,[12] might contribute to understanding DTC asthma for urban children in the cities of Baltimore, Boston, Chicago, Cincinnati, Denver, Detroit, New York City, and Washington DC. Many studies have shown that the ERMI metric is useful in assessing the relationship between mold exposures and asthma.[13] The ERMI metric was developed in a collaboration of the US Environmental Protection Agency and the Department of Housing and Urban Development to standardize mold quantification in homes.[12]

The ERMI metric classifies 36 indicator mold species into 2 groups. Group 1 includes 26 molds indicative of water damage in the home. Group 2 includes 10 species commonly found indoors, even in homes without water damage, and originating primarily outdoors.[14] The ERMI calculation takes the results from the concentrations of each of 36 molds and mathematically converts these into a single number, as shown in the equation below.

$$ERMI = \sum_{i=1}^{26} \log_{10}(s_{1i}) - \sum_{j=1}^{10} \log_{10}(s_{2j})$$

The concentration of each of the 26 molds in group 1 is log transformed and summed to calculate the "summed logs of group 1" (s_{1i}) molds. Similarly, the concentration of each of the 10 molds in group 2 is log transformed and summed to calculate the "summed logs of group 2" (s_{2j}) molds. The arithmetic difference between the groups, $s_{1i} - s_{2j}$, determines the ERMI value for the home.[12] Therefore, the higher the ERMI value, the greater the mold contamination in the home.

Previous reviews of the scientific literature have concluded that mold exposures are associated with asthma.[15,16] Therefore, we hypothesized that mold exposures might also be associated with DTC asthma.

To test this hypothesis, we conducted a *post hoc* analysis of dust samples collected during the APIC study from the homes of children ages 6 to 17 years.[7] Samples had been collected when it was practical for the investigators, and not limited to any specific season or time of day. Therefore, the relevance of differences in season, sampling time of day, temperature, and humidity could not be distinguished in this study. In the APIC study, DTC asthma participants were defined as requiring a daily therapy of greater than or equal to 500 μg of fluticasone (with or without a long-acting β-agonist), and those with ETC asthma were defined as requiring less than or equal to 100 μg fluticasone. There were originally 485 dust samples collected in the homes of children with either DTC or ETC asthma, but a frozen-dust sample remained from only 265 of the homes. For this study, we analyzed all frozen-dust samples. The comparisons of the characteristics of the study subset of the APIC study participants (n = 265) and the full APIC cohort (n = 485) are presented in Table I.

The dust in each participant's home had been collected by wiping horizontal, above-floor surfaces, using a Swiffer cloth (Procter and Gamble, Cincinnati, Ohio) until the cloth was dark from the dust.[17] The cloth was then placed in a Ziplock (Johnson and Johnson Co, Racine, Wis) resealable plastic bag and labeled. The samples were held at −20°C until the mold analysis was completed. Each of the 36 molds included in the ERMI was quantified by quantitative PCR assays.[18] The analyses were performed by a commercial laboratory (Mycometrics LLC, Monmouth Junction, NJ).

RESULTS AND DISCUSSION

The Student *t* test was used to compare the average summed logs of group 1 or group 2 molds and the average ERMI values of homes of children with DTC versus ETC asthma. There was no significant difference in the average summed logs of group 1 or group 2 molds in homes of children with DTC versus ETC asthma (Table II). The average ERMI values in the homes of children with DTC versus ETC asthma were also not significantly different (Table II). Therefore, the total mold contamination was not a distinguishing factor in asthma-control difficulty. This finding is consistent with our earlier finding that "dampness in home" was not associated with DTC asthma.[7]

We then compared the average concentrations of each of the 36 ERMI molds in homes of children with DTC versus ETC asthma by using the Wilcoxon rank-sum test, correcting for multiple comparisons using the Holms-Bonferroni test. After Bonferroni correction, *Mucor* was the only mold with a significantly greater average concentration in homes of those with DTC versus ETC asthma, average of 295 versus 67 cell equivalents per milligram dust, respectively ($P < .001$) (Table III).

Mucor is found worldwide in soil, vegetation, and buildings.[19] In buildings, *Mucor* is known to grow in and around air-conditioner (AC) systems and ducting due to moisture from condensation.[20] If an AC unit is not cleaned, or the filter not changed regularly, dust and dampness can promote the growth of many organisms that can pose a health risk.[21] Therefore, we examined the relationship between the occurrence of window AC units in homes of children with DTC versus ETC asthma.

Logistic regressions were performed for the log odds of finding a child with DTC in homes with and without a window AC unit. Mold concentrations were used as candidate cutoff points to discriminate between DTC and ETC asthma. The resulting points of true-positive (sensitivity) versus false-positive rates (1 – specificity) were plotted to produce empirical receiver-operating characteristics curves for homes with or without a window AC unit.[22]

For homes with window AC units, the log-transformed *Mucor* concentrations were found to be a significant ($P = .007$) predictor of the probability of DTC asthma but not for homes without

TABLE I. Comparison of the characteristics of the study subset (n = 265) of APIC participants and the full APIC cohort (N = 485)

Characteristic	Study subset of APIC (n = 265)	Overall APIC population (N = 485)
Site city		
Baltimore	53 (20.00)	81 (16.70)
Boston	32 (12.08)	65 (13.40)
Chicago	29 (10.94)	58 (11.96)
Cincinnati	29 (10.94)	49 (10.10)
Dallas	24 (9.06)	43 (8.87)
Denver	29 (10.94)	51 (10.52)
Detroit	24 (9.06)	44 (9.07)
New York	33 (12.45)	59 (12.16)
Washington DC	12 (4.53)	35 (7.22)
Sex		
Female	104 (39.25)	205 (42.27)
Male	161 (60.75)	280 (57.73)
Age (y)		
Mean ± SD	11.0 ± 3.05	10.9 ± 3.04
Median	11.0	11.0
Q1, Q3	8.0, 13.0	8.0, 13.0
Range	(6.0-17.0)	(6.0-17.0)
Participant race		
Missing	0	1 (0.21)
Black (non-Hispanic)	168 (63.40)	311 (64.12)
Hispanic	78 (29.43)	137 (28.25)
Other/mixed	15 (5.66)	26 (5.36)
White (non-Hispanic)	4 (1.51)	10 (2.06)
BMI percentile at screening		
Number	265	485
Mean ± SD	75.1 ± 27.64	75.1 ± 27.40
Median	88.2	87.3
Q1, Q3	58.0, 97.5	58.0, 97.6
Range	(0.0-99.9)	(0.0-99.9)
Income <$15,000		
Missing	2 (0.75)	2 (0.41)
No	122 (46.04)	222 (45.77)
Yes	141 (53.21)	261 (53.81)
Family history of asthma		
Missing	6 (2.26)	13 (2.68)
No	67 (25.28)	126 (25.98)
Yes	192 (72.45)	346 (71.34)
Eczema diagnosis		
No	123 (46.42)	218 (44.95)
Yes	142 (53.58)	267 (55.05)
Allergic rhinitis diagnosis		
Allergic	179 (67.55)	333 (68.66)
Nonallergic	86 (32.45)	152 (31.34)
Age (mo) asthma first diagnosed by doctor		
Number	264	483
Mean ± SD	42.9 ± 37.48	40.7 ± 37.34
Median	36.0	24.0
Q1, Q3	12.0, 60.0	12.0, 60.0
Range	(1.0-180.0)	(1.0-192.0)
Controller treatment step		
Number	265	485
Mean ± SD	3.3 ± 2.12	3.4 ± 2.06
Median	3.0	4.0
Q1, Q3	2.0, 5.0	2.0, 5.0
Range	(0.0-6.0)	(0.0-6.0)
No. of hospital stays (12 mo)		
Number	265	485
Mean ± SD	0.2 ± 0.53	0.2 ± 0.55
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Range	(0.0-5.0)	(0.0-5.0)
Any steroid courses (in previous year)		
No	137 (51.70)	257 (52.99)
Yes	128 (48.30)	228 (47.01)
eNO (ppb) at enrollment		
Number	243	448
Mean ± SD	29.2 ± 27.34	29.2 ± 27.90
Median	19.0	19.0
Q1, Q3	11.0, 35.5	11.0, 35.5
Range	(2.5-137.0)	(2.5-179.0)
Baseline (results of best effort)		
FEV_1 (% predicted) at enrollment		
Number	264	484
Mean ± SD	95.1 ± 16.70	93.7 ± 16.44
Median	94.5	94.0
Q1, Q3	84.3, 106.0	82.8, 104.6
Range	(44.0-136.5)	(39.7-136.5)
FEV_1/FVC at enrollment		
Number	259	476
Mean ± SD	80.1 ± 9.43	79.3 ± 9.25
Median	80.9	80.7
Q1, Q3	75.0, 87.0	74.3, 85.6
Range	(47.3-97.8)	(45.0-99.9)
Total IgE (kUA/L)		
Number	263	478
Mean ± SD	551.7 ± 754.12	625.0 ± 860.31
Median	213.0	248.0
Q1, Q3	80.0, 719.0	91.0, 766.0
Range	(1.0-3852.0)	(1.0-5001.0)
No. of allergen sensitivities (panel of 22; skin test OR IgE; at least 1 nonmissing)		
Number	265	485
Mean ± SD	8.2 ± 6.02	8.7 ± 6.23
Median	8.0	8.0
Q1, Q3	2.0, 13.0	3.0, 14.0
Range	(0.0-21.0)	(0.0-21.0)
sIgE ≥0.35 to any aeroallergen		
Missing	2 (0.75)	4 (0.82)
No	60 (22.64)	111 (22.89)
Yes	203 (76.60)	370 (76.29)
sIgE ≥0.35 to any food allergen		
Missing	3 (1.13)	6 (1.24)
No	138 (52.08)	238 (49.07)
Yes	124 (46.79)	241 (49.69)
Final protocol classification		
DTC	139 (52.45)	253 (52.16)
ETC	126 (47.55)	232 (47.84)

Values are n (%) unless otherwise indicated.

BMI, Body mass index; *eNO*, exhaled nitic oxide; *FVC*, forced vital capacity; *kUA/L*, kilo units of allergen per liter; *ppb*, parts per billion; *Q*, quartile; *sIgE*, specific IgE.

TABLE II. The average and SD of the summed logs of group 1 and summed logs of group 2 molds and the ERMI values for the homes of children with DTC vs ETC asthma

	Difficult		Easy		
Metric comparison	Average	SD	Average	SD	Student *t* test, *P* value
No. of homes	n = 139		n = 126		
Group 1	17.01	8.1	16.53	7.4	>.2
Group 2	12.29	4.2	11.46	3.7	>.2
ERMI	4.72	6.4	5.07	6.0	>.2

TABLE III. Comparison of average concentrations in cell equivalents (CEs) per milligram dust for each of the 36 molds in homes of children with DTC vs ETC asthma using the Wilcoxon rank-sum test, corrected for multiple comparisons using the Holms-Bonferroni test

	Average CE/mg dust		Wilcoxon test,
Molds	Difficult	Easy	*P* value
Group 1			
Aspergillus flavus	5.29	3.32	.06
Aspergillus fumigatus	1.95	3.15	.36
Aspergillus niger	173.67	162.70	.12
Aspergillus ochraceus	9.04	27.39	.89
Aspergillus penicillioides	1505.66	572.73	.97
Aspergillus restrictus	1.57	5.42	.99
Aspergillus sclerotiorum	1.65	21.07	.94
Aspergillus sydowii	98.95	42.78	.13
Aspergillus unguis	59.70	6.80	.34
Aspergillus versicolor	86.06	326.56	.71
Aureobasidium pullulans	698.88	441.93	.45
Chaetomium globosum	9.03	4.15	.002
Cladosporium sphaerospermum	40.12	36.95	.82
Eurotium amstelodami	2078.36	503.92	.44
Paecilomyces variotii	6.17	4.65	.57
Penicillium brevicompactum	178.70	8.54	.59
Penicillium corylophilum	19.05	5.22	.39
Penicillium crustosum	30.27	16.40	.08
Penicillium purpurogenum	4.12	0.15	.03
Penicillium spinulosum	0.34	0.02	.17
Penicillium variabile	6.19	4.96	.38
Scopulariopsis brevicaulis	370.39	4.51	.02
Scopulariopsis chartarum	4.17	10.31	.39
Stachybotrys chartarum	1.73	1.76	.49
Trichoderma viride	3.60	24.55	.08
Wallemia sebi	579.76	792.05	.98
Group 2			
Acremonium strictum	5.19	9.71	.92
Alternaria alternata	245.57	133.27	.19
Aspergillus ustus	6.58	2.99	.03
Cladosporium cladosporioides type 1	1246.83	882.09	.65
Cladosporium cladosporioides type 2	13.66	16.19	.67
Cladosporium herbarum	787.84	449.30	.32
Epicoccum nigrum	113.32	83.31	.68
***Mucor* group**	**294.72**	**67.16**	**<.001**
Penicillium chrysogenum type 2	694.65	80.38	.01
Rhizopus stolonifer	70.64	12.94	.09

Significant differences are **bolded**.

window AC units ($P = .148$). Based on the receiver-operating characteristics curve in those homes with window AC units (Fig 1), the *Mucor* concentration contributed about a 22% increase (1.6 odds ratio; 95% CI, 1.2-2.2) in the ability to discriminate between cases of DTC asthma and ETC asthma.

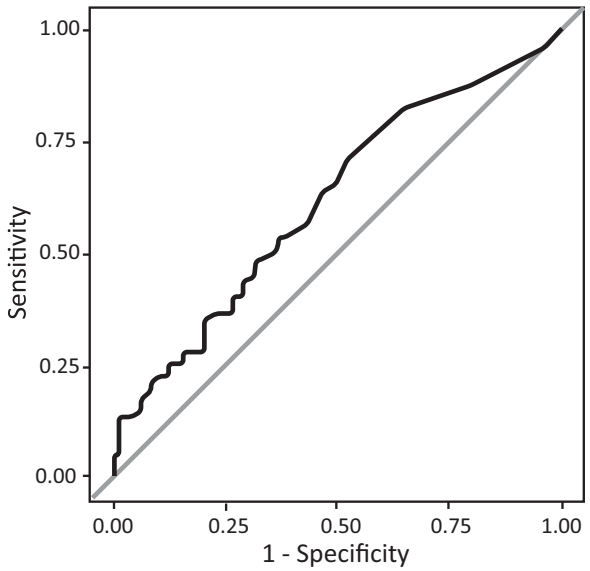

FIG 1. Receiver-operating characteristic analysis (black, jagged-curved line) and area under the curve (0.6143) for homes with window AC units. Every potential *Mucor* concentration cutoff point plotted as a step function of the respective sensitivity (1 − specificity) for DTC vs ETC asthma.

Mold exposures have been linked to poorly controlled asthma for children in other studies. For example, a prospective, cross-sectional study of children aged 5 to 15 years with poorly controlled asthma showed that allergic bronchopulmonary aspergillosis was diagnosed in 11.3% and aspergillus sensitization in 61.3% of children with poorly controlled asthma.[23] Data for both adults and children suggest that severe asthma with fungal sensitization is associated with worse asthma control and greater susceptibility to asthma attacks than in nonsensitized patients.[24] Therefore, our results are consistent with these studies in identifying mold exposures as relevant to the difficulty of controlling asthma.

Limitations to our study include the relatively small number of homes studied. However, because the homes we sampled were from cities across the United States, the findings have wide geographic application. Although frozen-dust samples were not available from all APIC homes, homes of children with DTC and ETC asthma were equally represented and the characteristics of the study subset of participants were comparable to those of the full APIC cohort (Table I). Another limitation was that only the 36 ERMI-panel molds were quantified. We did not quantify other potential exposures, including other molds in the home, and other contaminants both inside and outside the home. Therefore, we are not suggesting there is a causal relationship between *Mucor* levels and DTC. Rather, a high concentration of *Mucor* in the home may be an "indicator" of higher levels of home contamination.

Standard treatments alleviate symptoms for most children with asthma, but new approaches are needed to help children who suffer from uncontrolled asthma.[25] Cases of DTC asthma were more likely in homes with higher *Mucor* levels in dust samples, and eliminating the conditions that contribute to high levels of *Mucor* might be appropriate to reduce DTC asthma.

We are grateful to the APIC study participants and their families.

Clinical implications: Quantifying molds, especially *Mucor* levels, in the dust in homes of children with DTC asthma might be helpful in guiding mitigation efforts.

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