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# Association of Mold Levels in Urban Children's Homes with Difficult-to-Control Asthma

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Conflict of Interest

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## Abstract

**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:** 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 (APIC) study recruited participants, 6 to 17 years of age, from eight US cities and classified each participant as having either DTC asthma or easy-to-control (ETC) asthma based on 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, were frozen at  $-20^{\circ}$ C. The dust samples (n=265) were analyzed using qPCR to determine the concentrations of the 36 molds in the Environmental Relative Moldiness Index (ERMI). 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 (139/253) and ETC asthma (126/232). Only the average concentration of the mold *Mucor* was significantly (p<0.001) 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% confidence interval = 1.2 to 2.2) in the ability to discriminate between cases of DTC versus ETC asthma.

**Conclusion:** *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.

## **Capsule Summary**

Previously, we reported that mold sensitization was significantly greater for children with difficultto-control asthma. Now we have shown that higher levels of the mold *Mucor* in home dust samples were specifically associated with difficult-to-control asthma.

#### Keywords

APIC; US cities; child; asthma treatment; 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.<sup>1–3</sup> 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.<sup>4,5</sup> Patients with DTC asthma have more frequent exacerbations, a poorer response to medications, and lower lung function compared to those with easy-to-control (ETC) asthma.<sup>4</sup> Difficult-to-control asthma is more prevalent in urban, non-white, and under-resourced populations.<sup>6–8</sup> These medical

and demographic characteristics describe DTC asthma, but they do not provide insights into why some patients' asthma is DTC.

Barsky et al.<sup>9</sup> 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<sup>10</sup> also noted the important link between DTC asthma and environmental factors. Zang et al<sup>11</sup> showed that steroid 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 to those with ETC asthma.<sup>7</sup> 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,<sup>12</sup> 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.<sup>13</sup> 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.<sup>12</sup>

The ERMI metric classifies 36 indicator mold species into two 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.<sup>14</sup> 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 equation below.

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

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

Prior reviews of the scientific literature have concluded that mold exposures are associated with asthma.<sup>15, 16</sup> 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 6–17 years.<sup>7</sup> 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 APIC, DTC asthma participants were defined as requiring a daily therapy of 500  $\mu$ g of fluticasone (with or without a long acting  $\beta$ -agonist), and those with ETC asthma were defined as requiring 100  $\mu$ g 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 APIC participants (n=265) and the full APIC cohort (n=485) are shown in Table 1.

The dust in each participant's home had been collected by wiping horizontal, above floor surfaces, using a Swiffer  $\operatorname{cloth}^{TM}$  (Procter and Gamble, Cincinnati, OH) until the cloth was dark from the dust.<sup>17</sup> The cloth was then placed in a Ziplock<sup>TM</sup> (Johnson and Johnson Co., Racine, WI) re-sealable, plastic bag and labeled. The samples were held at  $-20^{\circ}$ C until the mold analysis was completed. Each of the 36 molds included in the ERMI was quantified by quantitative PCR (qPCR) assays.<sup>18</sup> 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 the Group 1 or Group 2 molds in homes of children with DTC versus ETC asthma (Table 2). The average ERMI values in the homes of children with DTC versus ETC asthma were also not significantly different (Table 2). 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.<sup>7</sup>

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 mg dust, respectively (p<0.001) (Table 3).

*Mucor* is found worldwide in soil, vegetation and buildings.<sup>19</sup> In buildings, *Mucor* is known to grow in and around air-conditioning (AC) systems and ducting due to moisture from condensation.<sup>20</sup> 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.<sup>21</sup> 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 air conditioner. Mold concentrations were used as candidate cut-off points to discriminate between DTC versus ETC asthma. The resulting points of

true positive (sensitivity) versus false positive rates (1 - specificity) were plotted to produce empirical Receiver Operating Characteristics (ROC) curves for homes with or without a window AC unit.<sup>22</sup>

For homes with window AC units, the log transformed *Mucor* concentrations were found to be a significant (p=0.007) predictor of the probability of DTC asthma but not for homes without window AC units (p=0.148). Based on the ROC curve in those homes with window AC units (Figure 1), the *Mucor* concentration contributed about a 22% increase (1.6 odds ratio, 95% confidence interval = 1.2 to 2.2) in the ability to discriminate between cases of DTC versus 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 5 to 15 years of age 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.<sup>23</sup> Data for both adults and children suggests that severe asthma with fungal sensitization (SAFS) is associated with worse asthma control and greater susceptibility to asthma attacks than in non-sensitized patients.<sup>24</sup> 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, as the homes we sampled were from cities across the US. Therefore, 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 the full APIC cohort (Table 1). 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.<sup>25</sup> 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.

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## Abbreviations used

AC	Air-conditioner
APIC	Asthma Phenotypes in the Inner City
DTC	Difficult-to-control
eNO	exhaled nitic oxide
ERMI	Environmental Relative Moldiness Index
ETC	Easy-to-control
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
kUA/L	Kilo units of allergen per liter
Q	Quartile
qPCR	Quantitative polymerase chain reaction
ROC	Receiver Operating Characteristic
SD	standard deviation
slgE	specific IgE
US	United States

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## **Clinical Implications**

Quantifying molds, especially *Mucor* levels, in the dust in homes of children with difficult-to-control asthma might be helpful in guiding mitigation efforts.



## Figure 1.

Receiver Operating Characteristic analysis (black, jagged-curved line) and area under the curve (AUC=0.6143) for homes with window air-conditioning units. Every potential *Mucor* concentration cut-off point plotted as a step function of the respective sensitivity (1-specificity) for difficult- versus easy-to-control asthma.

## TABLE 1

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

Site city	Study subset of APIC (N=265)	Overall APIC Population (N=485)
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%)
Gender		
Female	104 (39.25%)	205 (42.27%)
Male	161 (60.75%)	280 (57.73%)
Age (years)		
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		

Site city	Study subset of APIC (N=265)	Overall APIC Population (N=485)
No	123 (46.42%)	218 (44.95%)
Yes	142 (53.58%)	267 (55.05%)
Allergic rhinitis diagnosis		
Allergic	179 (67.55%)	333 (68.66%)
Non-allergic	86 (32.45%)	152 (31.34%)
Age (months) 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)
Number of hospital stays - 12 months		
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 - FEV1 (% 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)
Baseline - Results of Best Effort - FEV1/FVC at Enrollment		
Number	259	476
Mean (SD)	80.1 (9.43)	79.3 (9.25)
Median	80.9	80.7

Site city	Study subset of APIC (N=265)	Overall APIC Population (N=485)
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)
Number of all ergen sensitivities (panel of 22) -skin test OR IgE - at least 1 non-missing		
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 aero allergen		
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 classi fication		
Difficult-to-control	139 (52.45%)	253 (52.16%)
Easy-to-control	126 (47.55%)	232 (47.84%)

## TABLE 2

The average and standard deviation of the summed logs of the Group 1 and summed logs of the Group 2 molds and the Environmental Relative Moldiness Index (ERMI) values for the homes of children with difficult- versus easy-to-control asthma.

(Number homes)	Difficult Average (n=139)	SD	Easy Average (n=126)	SD	Student T-test p-value
Group 1	17.01	8.1	16.53	7.4	>0.2
Group 2	12.29	4.2	11.46	3.7	>0.2
ERMI	4.72	6.4	5.07	6.0	>0.2

## TABLE 3

Comparison of average concentrations in cell equivalents (CE) per mg dust for each of the 36 molds in homes of children with difficult- versus easy-to-control asthma using the Wilcoxon rank sum test, corrected for multiple comparisons using the Holms–Bonferroni test. (Significant differences are bolded.)

Molds	Difficult Average	Easy Average	Wilcoxon Test
Group 1	CE/mg dust	CE/mg dust	p-value
Aspergillus flavus	5.29	3.32	0.06
Aspergillus fumigatus	1.95	3.15	0.36
Aspergillus niger	173.67	162.70	0.12
Aspergillus ochraceus	9.04	27.39	0.89
Aspergillus penicillioides	1505.66	572.73	0.97
Aspergillus restrictus	1.57	5.42	0.99
Aspergillus sclerotiorum	1.65	21.07	0.94
Aspergillus sydowii	98.95	42.78	0.13
Aspergillus unguis	59.70	6.80	0.34
Aspergillus versicolor	86.06	326.56	0.71
Aureobasidium pullulans	698.88	441.93	0.45
Chaetomium globosum	9.03	4.15	0.002
Cladosporium sphaerospermum	40.12	36.95	0.82
Eurotium amstelodami	2078.36	503.92	0.44
Paecilomyces variotii	6.17	4.65	0.57
Penicillium brevicompactum	178.70	8.54	0.59
Penicillium corylophilum	19.05	5.22	0.39
Penicillium crustosum	30.27	16.40	0.08
Penicillium purpurogenum	4.12	0.15	0.03
Penicillium spinulosum	0.34	0.02	0.17
Penicillium variabile	6.19	4.96	0.38
Scopulariopsis brevicaulis	370.39	4.51	0.02
Scopulariopsis chartarum	4.17	10.31	0.39
Stachybotrys chartarum	1.73	1.76	0.49
Trichoderma viride	3.60	24.55	0.08
Wallemia sebi	579.76	792.05	0.98
Group 2			
Acremonium strictum	5.19	9.71	0.92
Alternaria alternata	245.57	133.27	0.19
Aspergillus ustus	6.58	2.99	0.03
Cladosporium cladosporioides Type 1	1246.83	882.09	0.65
Cladosporium cladosporioides Type 2	13.66	16.19	0.67
Cladosporium herbarum	787.84	449.30	0.32
Epicoccum nigrum	113.32	83.31	0.68
Mucor group	294.72	67.16	<0.001
Penicillium chrysogenum Type 2	694.65	80.38	0.01

C	CE/mailent	CE/mailent	
Group 1	70.64	<b>CE/mg dust</b>	<b>p-value</b>
Rhizopus stolonifer		12.94	0.09