Understanding the Relevance of School Exposure to Asthma in Children

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1. To further our understanding of community risk factors for asthma and allergies
2. To discuss community engagement and environmental disparities
3. To identify interventions to reduce risk and even prevent disease outcomes
What do we know about the home allergen exposure and asthma morbidity in children?

Home Allergen Exposure and Asthma Morbidity in Inner City Children

- Hospitalizations
  - neg skin test, low allergen exposure
  - neg skin test, high allergen exposure
  - pos skin test, low allergen exposure
  - pos skin test, high allergen exposure
  - p=0.001

- Unscheduled Medical Visits
  - neg skin test, low allergen exposure
  - neg skin test, high allergen exposure
  - pos skin test, low allergen exposure
  - pos skin test, high allergen exposure
  - p<0.001

- Change in Care Giver’s Plans
  - neg skin test, low allergen exposure
  - neg skin test, high allergen exposure
  - pos skin test, low allergen exposure
  - pos skin test, high allergen exposure
  - p=0.006

- Days Wee Changed Plans in Past Year
  - neg skin test, low allergen exposure
  - neg skin test, high allergen exposure
  - pos skin test, low allergen exposure
  - pos skin test, high allergen exposure
  - * Bla g 1 > 8 U/gram

Similar Relationships in Home Mouse Allergen

Phipatanakul et al, J Allergy Clin Immunol 2000; 106:1070-4
Phipatanakul et al, J Allergy Clin Immunol 2000; 106:1075-80
Multi-Faceted Home Intervention Works in Reducing Asthma Morbidity In Urban Kids

We have highlighted the importance of the Home Environment in Asthma Morbidity.… Where else does nearly every child in America spend the majority of his/her day?

“Required Occupation”
Exposure to common indoor allergens in the classroom will increase the risk of asthma morbidity in inner-city children with asthma, even after controlling for home allergen exposures.
School Inner-City Asthma Study
Repeating Annual Schema

350 children
38 schools

Spring

Screening & Recruitment
8-10 schools
75 Students/yr

Baseline Phenotype Survey
Spirometry
Skin testing
Blood/Nasal

Summer

Asthma Symptoms

Fall

Quarterly Parental Surveys

Winter

Class/Home Sampling Spirometry
FE(NO)

Spring

Class/Home Sampling Spirometry
FE(NO)

Allergen Skin Testing

– Molds (aspergillus, cladosporium, alternaria, penicillium)
– Indoor allergens (cat, dog, dust mite, roach, mouse, rat)
– Outdoor allergens (grass, pollen, ragweed)
Dust/Air Home/School Environmental Sample Testing

- Multiplex array for indoor allergens (MARIA™)

- Dust/Air Samples analyzed for common indoor allergens
  - Cockroach – Bla g 2
  - Dust Mite – Der f 1, Der p 1
  - Cat – Fel d 1
  - Dog – Can f 1
  - Mouse – Mus m 1
  - Rat- Rat n 1
  - Alt-a 1 (mold)

What did we find?
Is the School Environment Important in Health Even After Adjusting for Exposures at Home?

Dose Response Relation between School Mouse Allergen Levels Asthma Morbidity


P=0.02

P=0.002
School NO$_2$ Pollutant Exposure is Associated with Airflow Obstruction

Gaffin JM, et al, JACI 2018
Classroom Mold Exposure and Mold Allergy Markedly Increases Asthma Symptoms


The Journal of Allergy and Clinical Immunology

Establishing School Centered Asthma Programs

Designed Phipatanakul lab/AAAAI
We showed the school is important— but it’s not that straightforward…

Complexities in the Environment

Sheehan WJ, et al JACI Dec 2017
NO2 and Obesity Interaction

P=0.03

UNPUBLISHED
What about all this talk with the microbiome?

### Classroom Microbial Diversity differs from Home and is Associated with Asthma Symptoms

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Odds Ratio [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male vs. female</td>
<td>0.89 [0.26 - 3.00]</td>
<td>0.85</td>
</tr>
<tr>
<td>Age in years</td>
<td>1.35 [0.74 - 2.47]</td>
<td>0.33</td>
</tr>
<tr>
<td>Hispanic vs. black race</td>
<td>1.55 [0.38 - 6.42]</td>
<td>0.54</td>
</tr>
<tr>
<td>Other vs. black race</td>
<td>0.97 [0.17 - 5.49]</td>
<td>0.97</td>
</tr>
<tr>
<td>Classroom microbial diversity</td>
<td>1.91 [0.99 - 3.70]</td>
<td>0.04</td>
</tr>
<tr>
<td>Home microbial diversity</td>
<td>0.65 [0 - 7183.18]</td>
<td>0.93</td>
</tr>
<tr>
<td>Season b</td>
<td>0.94 [0.07 - 12.56]</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Lai PS, Phipatanakul W. JACI 2018
Integrated pest management intervention associated with classroom microbiome

<table>
<thead>
<tr>
<th></th>
<th>$R^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPM</td>
<td>0.03499</td>
<td>0.002</td>
</tr>
<tr>
<td>HEPA filtration</td>
<td>0.01781</td>
<td>0.27</td>
</tr>
<tr>
<td>Classroom ID</td>
<td>0.38837</td>
<td>0.001</td>
</tr>
</tbody>
</table>

PERMANOVA on Bray-Curtis dissimilarity of sequenced vacuum dust samples

Some lessons learned from SICAS-1

- School environment is important in asthma morbidity even after adjusting for home
- School and home microbiomes are different
- Classroom microbiome associated with asthma symptoms
- ↑ diversity → ↑ symptoms
- Classroom microbiome may be modifiable IPM
- School Inner-City Asthma Intervention Study (SICAS-2) (U01 AI110397) Completes this next school year– Stay tuned!
Is there a Gene x Environment Interaction that Could Explain our Findings?

An asthma associated IL4R polymorphism Increases Airway Inflammation by Conversion of regulatory T cells to Th_{17}-like Cells

- IL-4Rα-Q576R polymorphism
  - R allele frequency 68% (blacks); 20% (whites)
  - R allele associated with severe asthma
  - Unique among IL4R polymorphisms, directly drives T_{reg} to T_{H17} response

Massoud et al, Nat Med 2016; 22(9):1013-22
Mixed Endotoxin Signals and Th17 skewing may be explained by GxE Interactions

- High endotoxin exposure
  - Found in urban homes with lowest SES
  - Associated with ↑ Th17 skewing
  - Associated with asthma symptoms in schools but has been considered “protective” in asthma development (i.e. farming communities) and differs by setting
  - Endotoxin's differing effects on asthma morbidity could potentially be explained by these mixed mechanisms


Distribution of the IL-4Rα-Q576R genotypes amongst the School Inner City Asthma Study

- Q576/Q576
- Q576/R576
- R576/R576
- Total=337
IL4Rα-R576R Variant Allele is Associated with Increased Asthma Exacerbation Rates in SICAS

Asthma Symptoms Differ by Genotype and School Specific Exposure

Q/Q wild type: Protective

Lai PS, et al JACI 2017 In PRESS
Asthma Symptoms Differ by Genotype and School Specific Exposure

Q/Q wild type: Protective
Q/R heterozygous mutant: Equivocal
R/R homozygous mutant: Harmful

Lai PS, et al JACI 2017 In PRESS
Preliminary Similar Genotype Relationships with Atopic Dermatitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$Q/Q$ variant</th>
<th>$Q/R + R/R$ variant</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>58</td>
<td>178</td>
<td>0.861</td>
</tr>
<tr>
<td>Age in years (mean ± sd)</td>
<td>8.00 (1.84)</td>
<td>7.95 (1.94)</td>
<td>0.452</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>27 (46.6%)</td>
<td>95 (53.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Self-reported race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (15.5%)</td>
<td>3 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>11 (19.0%)</td>
<td>73 (41.0%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>26 (44.8%)</td>
<td>56 (31.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (19.0%)</td>
<td>31 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (1.7%)</td>
<td>15 (8.4%)</td>
<td></td>
</tr>
<tr>
<td>Annual income &lt; $25,000</td>
<td>30 (51.7%)</td>
<td>74 (41.6%)</td>
<td>0.230</td>
</tr>
<tr>
<td>Physician diagnosis of eczema, n (%)</td>
<td>19 (32.8%)</td>
<td>89 (50.0%)</td>
<td>0.033 a</td>
</tr>
<tr>
<td>Allergic sensitization b (%)</td>
<td>40 (69.0%)</td>
<td>119 (66.9%)</td>
<td>0.891</td>
</tr>
</tbody>
</table>

* Fish exact test
b Allergic sensitization was defined as any positive skin prick test to 14 common allergens or specific IgE level ≥ 0.35 kU/L on serologic testing

Implications and Clinical Implications for the Future

• G×E (IL4Ra-Q576R × School endotoxin) interaction
• May contribute to asthma disparities
• May explain previous disparate effects of endotoxin on asthma
• Suggests that reducing harmful school specific exposures such as endotoxin exposure should be targeted
• Inner-city schools with high proportion of black/mixed race children also have a higher prevalence RR genotype and could be targets for intervention, including precision intervention trials
Dupilumab® Blocks Signaling Through the IL-4/IL-13 Receptor/Ligand System

**Type I Receptor**
- IgE responses, Th2–mediated inflammation, reduced antimicrobial peptides

**Type II Receptor**
- Reduced skin barrier function, increased Th2 responses
IL-4Rα-R576 variant drives mixed T\(_H2/T\_H17\) cell inflammation in the airways by subverting allergen-specific induced T regulatory (iT\(_{reg}\)) cell responses into the T\(_H17\) cell lineage, and that pediatric age asthmatics harboring this variant will manifest a particular favorable response to Dupilumab associated with the acquisition of favorable long-term tolerance.

**Effect of IL-4RαR576 polymorphism on response to Dupilumab in children with Asthma, a Genotype stratified, randomized-placebo controlled trial (I-DAG Study)**

NIH U01 AI143514 – Phipatanakul/Chatila
We are working on Community-Based Interventions to Reduce Morbidity in Children with Asthma…

What about Prevention?

Allergen Sensitization (IgE) Begins in Early Childhood and then Takes Off

Sheehan/Phipatanakul 2010; Clin Pediatrics. 49(6): 579-585
Triple Threat: Important in the Development of Asthma

ATOPY

VIRUS

EXPOSURE

What is a feasible agent that could be used in young children that:

• Blocks allergic process
• Helps fight viruses
• Blocks response to exposure
• Holds promise in PREVENTION by blocking the “triple threat”
Could Early IgE Blockade Prevent or Modify the Course of Asthma?

- Aeroallergen sensitization
- IgE-mediated allergic inflammation
- Recurrent wheezing
- Atopic march
- Childhood asthma
- Impaired Epithelial Barrier
- Impaired Antiviral Response
- Viral infections/Airway Damage

Omalizumab
Preventing Asthma in High Risk Kids - PARK
U01AI126614 - Principal Investigator Phipatanakul

Randomized, multicenter, DBPC Trial in 250 allergic wheezing 2-4 year olds who are at high risk for developing established, persistent asthma

Screening/ Eligibility
Run-in
1 month
Randomize
Treatment – Anti-IgE or Placebo
Observation

Years 1 & 2
Health Outcomes
Wheezing, Rhinitis, Food Allergy
Mechanistics

Co-Primary Outcome

Years 3
Year 4

In Summary…

• School environment is important in asthma morbidity, where nearly every child spends their day
• We can intervene on relevant school specific exposures
• Future impact may enable us to benefit communities through a school a school-based intervention, as opposed to individuals in the home, where prior to this most of the efforts have been home focused
• Decade of community relationships allow us to expand our work into understanding of microbial exposure and genex environment interactions in a home/school setting and its effects on disease
• Future trial building on targeted interventions based on genotype is planned
• Prevention is on the Horizon

clinical trials.gov NCT02570984
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