President Forum: Preventing Asthma and the Atopic March

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Disclosures/Objectives

• Funding NIH
• Advisory Genentech, Novartis, Teva, Regeneron, GSK
• Goal: To Discuss Strategies for Prevention and Logical Next Steps

Typical Patient Seen in Our Allergy Clinic

• JB is a 2 year old male with history of eczema and milk allergy
• He was just evaluated in the ER with a bad case of wheezing
• Family History:
  – Father and brother with moderate persistent asthma and allergies
  – Mom has bad “hay fever”
• Mom is very concerned—“Dr. P, will my child develop asthma like my husband and my older son? Can I do anything to stop this process??”
Is this child at risk for persistent asthma?

Is there anything we can do about it?

What are some logical approaches and considerations?

- Targeting allergies and atopy?
- Modification of exposures?
- Infection-directed approaches?
- Medications and Antibiotics?
- Microbial Modifications?
- Vitamins and Supplements?
- Early identification of at-risk individuals?
- Timing, Effectiveness, Feasible?

Let's Review the Natural History of the Allergic/Asthma March
Relative Prevalence of Allergic Diseases by Age and the Atopic March

Atopic Dermatitis
Food Allergy
Asthma
Allergic Rhinitis

Prevalence (%)
0            1yr         3yr          5yr        7yr                 15yr
0 2 4 6 8 10 12

Age
0 1yr 3yr 5yr 7yr 15yr

Eczema Interventions

Application of Moisturizer to High Risk Neonates Prevents Development of AD

Study of the Atopic March - Prevention
Study Tacrolimus versus Control
DIDN'T WORK

Environment

Schneider LC, et al – Pediatric Dermatology 2016
### Randomized Primary Prevention

**Environmental HMD Studies - Mixed Bag**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Intervention</th>
<th>N</th>
<th>Years Follow-up</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isle of Wright, England</td>
<td>Dust mite/food avoidance</td>
<td>220</td>
<td>1-18</td>
<td>Asthma and atopy all ages</td>
</tr>
<tr>
<td>Manchester Asthma and Allergy</td>
<td>Stringent Dust Mite Control Infancy</td>
<td>391</td>
<td>1-16 (published only age 1 and 3)</td>
<td>Severe wheezing (infancy) and lung function (age 3 years) and mite sensitization (age 3 years)</td>
</tr>
<tr>
<td>Canadian Asthma Primary Prevention</td>
<td>Dust mite, diet</td>
<td>545</td>
<td>1-15</td>
<td>Asthma (up to age 7) and age 15 in females only</td>
</tr>
<tr>
<td>Prevention of Incidence of Asthma and Mite Allergy Netherlands</td>
<td>Mattress Covers</td>
<td>319</td>
<td>1-8</td>
<td>Asthma at age 2. and NO effect at other ages.</td>
</tr>
<tr>
<td>Australia: Childhood Asthma Prevent</td>
<td>Mites, Covers, Diet</td>
<td>616</td>
<td>18 months-5</td>
<td>Asthma, wheezing, or atopy and Eczema</td>
</tr>
</tbody>
</table>

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### Complexities in the Environment

- Shesahan WJ, et al. JACI Dec 2017

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### Cat Exposure in Early Life Decreases Asthma Risk by 17q21 high risk variant

- Stockholm J, Bisgaard H, JACI May 2018
Allergen Immunotherapy

Open Label Allergy Shots in School age Kids, Reduces Allergen Specific IgE Response and Asthma Risk


7 years off Therapy

Coseasonal Grass Sublingual IT In Elementary Kids Reduces Reported Asthma

Consideration of Primary Prevention of Allergy with Dust Mite OIT in Babies

DBPC Grass SLIT Prevention Study Helped Symptoms in the Winter but Failed Prevention

Infection Approaches RSV
Antibiotics and Antipyretics
Azithromycin Prevents LRI in Preschool Wheezers


Early Azithromycin Alters Airway Microbiome—Possible Prevention?


Rise in Asthma Has Coincided with the Rise in Acetaminophen Use

MMWR Surveill Summ. 2007; 56(8):1-54

Paracetamol or Ibuprofen in the Primary Prevention of Asthma in Tamariki (PPPPA Tamariki).

- Randomised controlled trial of Paracetamol or Ibuprofen, as required for fever and pain in the first year of life, for prevention of asthma at age six years.
- Universal Trial Number (UTN) U1111-1203-1961
- Enrolling nearly 4000 infants with primary outcome of wheeze last year at age 6
When to Feasibly and Effective Intervene? Pregnancy or Early Childhood?

Interventions During Pregnancy

Vit-Kids
Asthma or Recurrent Wheeze-Free Proportion by Vitamin D Treatment - US

HR, 0.8 (95% CI 0.6-1.0, P=0.051)

Chawes JAMA 2016

Copenhagen Study: 700 Pregnant Women 2400 IU/D vs. STD 400 IU

HR, 0.76 (95% CI 0.52-1.12, P=0.16)

Chawes JAMA 2016

Strongest Fish Oil Effect in Moms with low EPA and DHA Pre Intervention

HR= 0.47 (95% CI, 0.26-0.84)  P=0.01

HR= 0.81 (95% CI, 0.44-1.5)  P=0.51

Bisgaard H, NEJM 2016
Managing Asthma in Pregnancy by \( F_{\text{ENO}} \) and ICS use

- 179 pregnant moms
- 140 children followed to age 4-6
- Intervention: \( F_{\text{ENO}} \) guided ICS use during Pregnancy
- Results mediated in \( F_{\text{ENO}} \) guided group by increased ICS use during pregnancy


Why do we keep striking out on prevention?

- I do NOT apologize for a deliberate and passionate display of fandom. Yes the choice of a Yankee picture to illustrate this point was deliberate. Go Sox.

Weaknesses in the Studies so far...

- Environment: Impossible to fully intervene/microbiome-complicates
- Sublingual or SCIT: only open label trials- Immunology? Only targets specific allergens, early on child still developing allergies
- SLIT FDA approved only single allergens even mixes, immunologic efficacy questionable- didn’t meet primary outcome-
- RSV specific time window certain kids- Rhinovirus associated more with asthma- no effective treatment
- Vitamins- too weak/ Antibiotics/Antipyretics conflicting effects/benefit
- Timing: Pregnancy Management-Hard to implement-
- Do we start genotyping everyone? 17q21?
- Fish Oil conflicting and high doses- Long term effects? No effect on allergic outcomes
Two NIH Funded Approaches/Interventions

Microbial Diversity, Living on a Farm and Lower Rates of Asthma

Figure 1: Relationship between microbial exposure and the probability of asthma.

Fungal and Bacterial Dysbiosis and Risk of Atopic Asthma

BronchoVaxom®

- BronchoVaxom® is made up of lyophilized fractionated alkaline extracts of H. influenzae, D. pneumoniae, K. ozaenae, K. pneumoniae, S. aureus, S. pyogenes, S. viridans, and N. catarrhalis grown on vegetal substrate
- It is a powder mixture of acidic proteins, peptides and amino acids, with minor components of detoxified LPS and lipoteichoic acids
- No live bacteria
- Marketed in the EU for the prevention of respiratory illness for over 25 years

What about allergy?? Could we block the atopic march to persistent asthma?
Allergen Sensitization (IgE) Begins in Early Childhood and then Takes Off

Sheehan/Phipatanakul 2010; Clin Pediatrics. 49(6): 579-585

Which Came First— the Chicken or the Egg in the Asthma Pathway?

Virus Allergy

Allergen-specific IgE Production Precedes Viral Wheeze in Pivotal Causal Pathway for Asthma

Jackson/Lemanske 2012; AJRCCM 185:281-85
Timing and Degree of Atopy Markedly Increases Risk of Asthma by School Age with Clusters of Impaired Viral/Allergen Responses

Predominant Risk:
- Recurrent wheeze/severe exacerbations by age 3
- At least one positive skin test by age 3
- Exposure to environmental tobacco smoke

Rhinovirus Interacts with Mouse/Dust IgE in Severity and Rise in IgE levels

Kantor GB, Phipatanakul W, Hirschorn J. Allergy Clin Immunol 2016
Early Allergy and Viral Wheeze Markedly Increases Risk of Asthma

What is a feasible agent that could be used in young children that blocks IgE/allergic processes related to exposures and may be the logical next step in targeting atopy in the prevention of asthma?

Preseasonal Treatment with Anti-IgE reduces seasonal exacerbations

Omalizumab is Associated with a Reduction in Acute Severity of RV+ Asthma Exacerbation

Could Early IgE Blockade Prevent or Modify the Course of Asthma?

Preventing Asthma in High Risk Kids-PARK

U01AI126614- Principal Investigator Phipatanakul- NCT02570984

Randomized, multicenter, DBPC Trial in 250 allergic wheezing toddlers who are at high risk for developing established asthma

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

1 month  Years 1 & 2  Year 3  Year 4

Randomize  Asthma/Allergic Outcomes Mechanistics

*Adapted Prevention of Early Asthma in Kids using ICS Guilbert TW et al. NEJM 2006;354:1985-97
Strategies and Approaches

• Targeting allergies and atopy?
• Modification of exposures?
• Infection-directed approaches?
• Medications and Antibiotics?
• Microbial Modifications?
• Vitamins and Supplements?
• Early identification of at-risk individuals?
• Timing, Effectiveness, Feasible?

Prevention: the Holy Grail: What will work if anything?

• Complete Blockade of Atopy?
• Killed Bacterial Lysate?
• Future?
• We should have major advancements in our understanding of what may really work in prevention and modifying asthma/allergies the next decade

Preventing Asthma in High Risk Kids (PARK)
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