ASTHMA & ALLERGY IN 2016: THE ENVIRONMENT MATTERS – WE JUST HAVE TO UNDERSTAND IT & WE GENERALLY DON’T

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Peds Asthma Statistics

- 9 million children diagnosed with asthma
- 75% increase in prevalence from 1980-1994
- 160% increase in prevalence in children <5 yo
- 12.8 million missed school days annually
- 12.7 million physician office visits
  - 5000 deaths annually (8-10/day in U.S.), ~40 per year in Utah.
  - 1.9 million ER visits
- Direct Health care costs >$11.5 billion
- Indirect costs $4.6 billion
Too many people have asthma

- 1:12 (25 million, 8% have asthma) in 2009 compared to 1:14 (7%) in 2001
- 10% kids, 8% adults – asthma 2009
  - 17% African American kids w/ asthma 2009
- 51% asthmatic adults – asthma attack
- 57% asthmatic kids – asthma attack 2008
- 185 kids, 3262 adults died asthma 2007
17 million have asthma – a serious allergic disease caused by inflammation of the lung airways.

Between 1980 and 1998, reported cases of asthma doubled.

The epidemic is most serious in children.

Why is there so much more asthma?

- Leading theory is **Hygiene Hypothesis** – we are too clean and do not have enough exposure to bacteria/virus, etc. Diversity seems to be good.

- What can I do to potentially reduce the risk of asthma in my kids?
  - Grow up on a farm with large animals.
  - Have a large family
  - Clean your kids pacifier in your mouth

- Most of these risk factors are modestly viable options, what can be done?
  - Allergy shots, new homes for pets, identify early, no smoking, PEAK study failed but showed meds work.
Atopic March theory — independent variables

- Sensitization with RR 6 by 14 yo but generally one disease does not depend on another.

**FIG 1.** Prevalence of asthma, eczema, and allergic sensitization during childhood.
Cat & Dog allergy overtime

Overlap in IgE reactivity

4 years
- Cat only: n=57 (7%)
- Dog only: n=13 (2%)
- Cat+dog: n=15 (2%)

8 years
- Cat only: n=67 (9%)
- Dog only: n=18 (2%)
- Cat+dog: n=46 (6%)

16 years
- Cat only: n=82 (11%)
- Dog only: n=27 (3%)
- Cat+dog: n=88 (11%)

Allergic sensitization increases with age typically. Dog & cat allergy with time noted here.

A Asarnoj 2015 JACI; in press
The intrauterine environment is powerfully Th2 – this imprints Th2 dominance upon the neonate.
Delayed maturation of Th1 capacity

- Few serial infections – hygiene, small family size etc
- Longer period of time in which to make and establish Th2 responses to environmental antigens (i.e. allergens)

Unbalanced Th1/Th2 Th2 dominance at ~2yr
What does not prevent asthma: PEAK showed early ICS do not alter the natural history of asthma.

Aims: To determine if early tx with ICS could alter the course of asthma.

Methods: ID high risk kids (API) then tx/placebo and compare.

Results: Kids did well on tx (Flut 44 mcg 2p bid) but worsened off med. No lasting effect of ICS on the natural history of the disease.
Mycoplasma in susceptible host increases risk of asthma – azithromycin not effective tx however.

Yeh JACI 2015; in press
Dimensions of the Microbial World

- Standard medical culture techniques fail to document the presence of up to 99% of environmental microbes.
- Even under growth conditions thought to mimic environmental conditions, ~ 80% of organisms do not grow in culture.

L Weng, EM Rubin, J Bristow. Genome Research, 2006;16:316
16S rRNA-based tools characterize microbial ecology in human niches

Structure of bacterial communities are associated with states of health or disease:

- Periodontitis (Sakamoto, 2004)
- Inflammatory bowel disease
- Obesity (Ley, Nature 2006)
- Cystic fibrosis (Harris, PNAS 2007)
- Ventilator-associated pneumonia (Flanagan, JCM 2007)

Major bacterial phyla identified in human niches.
(Dethlefsen et al., Nature 2007)
Healthy vs. Asthma, Bacterial burden, and Airway hyperresponsiveness

- Higher bacterial burden observed in asthmatics compared to healthy control (16S rRNA amplicon concentration as proxy)
- Generally higher bacterial burden in those with "more hyperresponsive" vs. "less hyperresponsive" airways by methacholine challenge

_Huang Y, J Allergy Clin Immunol 2011_
Airway Microbiome in Mild-Moderate Asthma

Higher baseline bacterial diversity in asthmatics with improved bronchial reactivity after 6 weeks of clarithromycin

Huang Y, J Allergy Clin Immunol 2011

Slide taken from talk by Dr Monica Kraft
Airway Bacterial Microbiota – Healthy vs. Asthma or COPD

24 adults: asthma (11), COPD (5), healthy (8). Traditional 16S rRNA clone library-serial sequencing approach (34-63 sequenced clones/subject)

Proteobacteria

LUL brushings (adults)

BAL (children)

Asthma patients: more pathogenic Proteobacteria, e.g. *Haemophilus* spp.
Healthy controls: more Bacteroidetes, esp. *Prevotella* species

_Hilty et al., PLoS One 2010_

Slide taken from talk by Dr Monica Kraft
You see the same problem in sinus disease

- Loss of bacterial richness, evenness, and diversity in CRS

Sinus Mucosal Pathogenesis and Protection

**Microbial Diversity, Living on a Farm, and Asthma**

**A Bacteria (PARSIFAL)**

![Graph showing relationship between microbial exposure and the probability of asthma for bacteria.](image)

**B Fungi (GABRIELA)**

![Graph showing relationship between microbial exposure and the probability of asthma for fungi.](image)

*Figure 3. Relationship between Microbial Exposure and the Probability of Asthma.*

In both the PARSIFAL study and GABRIELA, the range of microbial exposure was inversely associated with the probability of asthma.

Maternal exposure to farm life decreases asthma risk (ORs)

TABLE I. Mutually adjusted ORs for associations of farm-related exposures with health outcomes

<table>
<thead>
<tr>
<th></th>
<th>Atopic sensitization (≥3.5 kU/L) (n = 285/2086)</th>
<th>Rhinoconjunctivitis symptoms (n = 507/8174)</th>
<th>Physician’s diagnosis of rhinoconjunctivitis (n = 343/8130)</th>
<th>Wheezing (n = 552/8169)</th>
<th>Diagnosis of asthma (n = 656/8080)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current farm exposure*</td>
<td>0.96 (0.63-1.46), P = .854</td>
<td>0.63 (0.45-0.88), P = .007</td>
<td>0.66 (0.41-1.07), P = .900</td>
<td>0.88 (0.65-1.19), P = .403</td>
<td>0.82 (0.62-1.09), P = .172</td>
</tr>
<tr>
<td>Regular contact with</td>
<td>0.76 (0.51-1.15), P = .194</td>
<td>0.87 (0.67-1.14), P = .321</td>
<td>0.69 (0.47-1.00), P = .049</td>
<td>0.97 (0.75-1.26), P = .822</td>
<td>0.94 (0.75-1.19), P = .629</td>
</tr>
<tr>
<td>farm animals ever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farm milk consumption</td>
<td>0.76 (0.52-1.11), P = .162</td>
<td>0.77 (0.58-1.03), P = .079</td>
<td>0.63 (0.42-0.93), P = .022</td>
<td>0.77 (0.58-1.02), P = .065</td>
<td>0.76 (0.59-0.99), P = .038</td>
</tr>
<tr>
<td>ever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable exposure in</td>
<td>0.58 (0.39-0.86), P = .007</td>
<td>0.74 (0.50-1.09), P = .126</td>
<td>0.77 (0.44-1.36), P = .371</td>
<td>0.76 (0.54-1.07), P = .120</td>
<td>0.86 (0.63-1.16), P = .325</td>
</tr>
<tr>
<td>pregnancy†</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

ORs are given with 95% CIs in parentheses and P values. The models are adjusted for age, sex, family, tobacco smoking, maternal smoking during pregnancy, number of older siblings, contact with pets ever presented in the table.

*Current regular exposure to stable or barn or regular participation in haying.
†Mother worked regularly in stable during pregnancy.

JACI 2006;117:817-23
Early-life Exposure to Dogs and Cats Protects Against Childhood Allergic Sensitization

Analysis of Microbial Content of House Dust

Fujimura, K. et al., JACI. 2010 126(2):410-2

Slide taken from talk by Dr Monica Kraft
First Year Pet Exposure And Allergic Sensitivity

Ownby DR et al. JAMA 2002;288:963-972
Do hypoallergenic pets exist?

Dog/ cat allergen is in saliva, parotid and perianal glands primarily

<table>
<thead>
<tr>
<th>Characteristics of cat and dog allergen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common name</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Cat</td>
</tr>
<tr>
<td>Dog</td>
</tr>
</tbody>
</table>

- Bathing can help as deposited on hair/ fur through licking, works better in dog and studies show minimum twice a week to help with allergy.
- Modest benefit at best with bathing/ HEPA filters/ etc.

Big picture if someone has an allergy to pets and asthma both, the only way to help control their asthma in regards to the pet allergy is: 1. getting rid of the pets, 2. increased medication: more ICS/ omalizumab (Xolair) or 3. allergy immunotherapy (allergy shots) and very rarely does anyone get rid of their pets (<10%).
Pacifier cleaning & risk of allergy

- Notably allergic group with 80% having one parent with allergy.

- Pacifier cleaning practices
Pacifier cleaning & risk of allergy

Oral microbiota diversity

Children whose parents sucked their child’s pacifier were less likely to get asthma (OR 0.12), eczema (OR 0.37). Vaginal delivery provided additional benefit.

Peds 2013;131:1-9
Raw farm milk protective against asthma/ atopy

Note greatly increased diversity of bacteria/ yeast in raw milk.

Results

- No improvement with boiled milk & certainly not with pasteurized.
- Asthma aOR 0.59
- Atopy aOR 0.71
- Hay fever aOR 0.51

Not saying that we should all drink non-pasteurized farm milk as we do that for a reason but this does teach a concept that diversity in immune exposure matters.
Asthma more common with swimmers

Tech & Asthma: Another Step in Personalized Medicine

- Phone based app that uses the GPS on a phone to correlate asthma status with environmental data and better understand how the environment impacts asthma and communicates that information to doctor and patient to better manage disease.

Pilot study noted PM2.5 and grass pollen were the 1st and 2nd drivers of asthma exacerbations respectively.
Treatment: What about worms???

Appears to be effective at preventing disease but not treating.

- 3 studies in humans at treating failed to work.
- My experience (n=3) in my practice, not at my encouragement, failed too.

TABLE II. Animal models with live helminth infections: protection against established allergy

<table>
<thead>
<tr>
<th>Protective effect</th>
<th>Helminth</th>
<th>Allergy model</th>
<th>Host</th>
<th>Notes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection protected against pre-existing allergy:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td><em>Heligmosomoides polygyrus</em></td>
<td>AHR</td>
<td>BALB/c and C57BL/6 mice</td>
<td>Infected mice had reduced numbers of total cells and eosinophils in BALF.</td>
<td>50</td>
</tr>
<tr>
<td>Yes</td>
<td><em>Strongyloides venezuelensis</em></td>
<td>AHR</td>
<td>Wistar rats</td>
<td>Infection reduced AHR 48 h after challenge, even though larvae were migrating through the lungs at this time.</td>
<td>53</td>
</tr>
<tr>
<td>Infection did not protect against pre-existing allergy:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td><em>Nippostrongylus brasiliensis</em></td>
<td>Local and systemic anaphylaxis</td>
<td>Hooded Lister rats</td>
<td>Allergic reactions were exacerbated by helminth infection. Parasite-induced IgE is not responsible for host protection from allergy.</td>
<td>51</td>
</tr>
<tr>
<td>No</td>
<td><em>N brasiliensis</em></td>
<td>AHR and local anaphylaxis</td>
<td>BALB/c and C57BL/6 mice</td>
<td>Mice infected for 1 wk before challenge had high eosinophil numbers and high IL-5 levels in BALF. Mice were also not protected from local anaphylaxis.</td>
<td>48</td>
</tr>
</tbody>
</table>

*Note: *Heligmosomoides polygyrus* was formerly known as *Nematospiroides dubius*. References that have used the former nomenclature have been updated to *H polygyrus* in this review.
Local honey compared to corn syrup & national honey made no difference in allergy.
Treatment – anti-IgE affects seasonal variation w/o seasonal allergy - ICAC

Is it virus, is it fall allergy, is it something else???
Potential Role of Probiotics

- Commensal gut flora play a role in induction of oral tolerance and the importance of the intestinal microbiota in the development of food allergy is essential in early ages, when the mucosal barrier and immune system are still immature.

- Probiotics interact with the mucosal immune system by the same pathways as commensal bacteria.

- Recent study show that probiotic bacteria induced \textit{in vivo} increased plasma levels IL-10 and total IgA in children with allergic predisposition.

- Many clinical studies report significant benefits by probiotics supplementation in food allergy prevention and management. However, the effectiveness can be affected by patient age, patient diet, and variety of strains of probiotics use.
Treatment: AIT & Asthma

- SCIT (allergy shots) vs SLIT (allergy drops n=245) have proven efficacy.
- Seasonal/Native allergens have a greater impact on asthma.
- >3 years duration is a little more effective.

J. Schmitt, JACI 2015; 136:1511-6
PREVALENCE — PEANUT ALLERGY

• Australian Capital Territory — incidence by 5 years old.
  -0.73% born in 2001
  -1.15% born in 2004
  Mullins, RJ JACI 2009; 123:689-693

Quadrupled in U.S. in 13 years.
0.4% in 1997
2% in 2010

• Montreal School children
  -2000-2002, 1.5% (95% CI, 1.2-1.9%)
  -2005-2007, 1.63% (95% CI, 1.3-2%)
  Ben-Shoshan, M. JACI 2009; 123:783-788

• Israel vs UK Jews
  -0.17% vs 1.85%

FIG 1. FA and PA diagnostic time trends. The number of patients diagnosed with FA, PA, PAA, and PS increased more than 10-fold between 1995 and 2007. Data are shown according to year of diagnosis.
PEANUT ALLERGY - HISTORY

Prevalence and natural history of specific food allergies in children

– Peanut

• 2% in 2010 - 22% develop tolerance (CAP-RAST <3)

• 2000 in response to rising peanut allergy – AAP recommended no peanut until 3 years of age. Based on eczema study.

• 2008 the growing evidence indicated this was not helping and AAP reversed that recommendation. Subsequent studies showed early consumption of milk and egg decreased risk of those food allergies as well.

• 2015 – LEAP study published.
Household exposure especially peanut butter increased the risk of peanut allergy, but early oral exposure greatly decreased the risk of peanut allergy.

- Skin exposure is sensitizing (controlling eczema important?).
- Oral exposure is tolerizing, negating the effect of environmental exposures.
- Delayed introduction might be counterproductive.

Fox et al. JACI 2009; 123:417-423
Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy.

Note the risk of peanut allergy increases with time and severity of atopic dermatitis.

Likely sensitization comes through skin and tolerance is achieved through GI tract.
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

Figure 1 (facing page). Enrollment and Randomization. Baseline visits occurred when participants were at least 4 months of age but younger than 11 months of age. Participants randomly assigned to peanut consumption who had a positive response to the oral food challenge administered at baseline were instructed not to eat peanuts but were included in the intention-to-treat analysis. Only participants who adequately adhered to treatment were included in the per-protocol analysis. Adequate adherence to treatment was defined in the peanut-avoidance group as consumption of less than 0.2 g of peanut protein (the equivalent of one peanut) on any occasion and less than 0.5 g over a single week in the first 2 years of life. In the peanut-consumption group, adequate adherence was defined as consumption of at least 2 g of peanut protein on at least one occasion in both the first and second years of life and of at least 3 g of peanut protein (25 g of Bamba [a snack food made from peanut butter and puffed maize] or 12 g of peanut butter) per week for at least 50% of the weeks during which data were recorded. SPT denotes skin-prick test.

What does peanut consumption mean?

Du Toit et al; NEJM 2015
What is going on immunologically?
1. Stable skin test & blood IgE
2. Dramatically increased IgG & IgG4.
Take home message:

- Class 1 evidence that introducing peanut between 4-11 months decreases the risk of peanut allergy dramatically in a high risk population (eczema, egg allergy, 1st degree family member with FA).
- Those that are high risk (egg allergy, moderate to severe eczema) would likely benefit from evaluation by a specialist in food allergy between 4-6 months (skin test, challenge, etc.). Of note skin testing was more accurate in the LEAP study.
- Adherence was great (92%)
- Peanut soup, peanut butter in milk yogurt were used. Goal 1 tsp peanut butter 3 times per week.
-22% resolved (CI 14-31%) by 4 years old

-Decreasing skin test size predicted tolerance.

-Predictors of persistent peanut allergy @ 1 year old was:
-SPT > 13 mm
-CAP-RAST > 5

No difference was how allergic the child was or what his prior reaction were.
Summary & Review

• Prevention 1st:
  • Ideally a mother eats milk, wheat, peanut and nuts during pregnancy & breast feeding
  • Ideally a mother breast feeds until 4-6 months of age
  • If she cannot breast feed then hydrolyzed formula currently recommended.
  • If high risk get PST at 4-6 months of age and work with specialist.
  • Treat eczema as sensitization comes through skin it appears.
  • Ideally introduce peanut, tree nuts, milk, wheat and variety of foods at 4-6 months old.

• Diagnosis:
  • Always get diagnosed by specialist in food allergy,
  • Recognize PPV/ NPV in doing PST and sIgE (CAP-RAST) testing.
  • Never rely on IgG testing or other forms of testing.

• Treatment:
  • Standard of care – avoidance, 1% risk of anaphylaxis per year, 0.01% risk EoE
  • Likely safe and appropriate now: milk and egg OIT starting with milk or egg baked cooked into things.
  • Peanut and then tree nut OIT or SLIT then OIT is emerging therapy, still a little higher risk than avoidance and SLIT then OIT is getting really close.
  • Near future & my opinion:
    • Prevent and Dx appropriately, SLIT or patch @ 4 yo, then OIT with Xolair and/ or probiotics, none of this is permanent in 90% of cases, treatment is lifelong.
Question 1:

1. What environmental treatment options have proven efficacy?
   1. Local honey
   2. Probiotics
   3. Parasitic worms
   4. Allergy immunotherapy — allergy shots
   5. Growing up on a farm using a pacifier cleaned by the parents mouth.

2. Answer: Allergy immunotherapy & growing up on a farm.
Question 2:

What is the primary mechanism responsible for increasing risk of allergy in the environment.

1. Decreased biodiversity of exposures.
2. Increased biodiversity of exposures.
3. Increased proteobacteria.
4. Increased bacteroidetes.

Answer: 1 and 4 - diversity is good and the right kind of bacteria matters.
Question 3:

What is one of the barriers to understanding the microbiome?

1. Culturing gut bacteria is successful 50% of the time.
2. Culturing gut bacteria is successful 20% of the time.
3. Culturing gut bacteria is successful 1% of the time.
4. Even under ideal situations reproducing the gut microenvironment only 20% of bacteria are culturable.

Answer: 3 & 4 – 16s RNA analysis has helped the above problems.
Conclusions:

- Environment interacts with allergic disease including asthma.

- It appears timing, dose, genetics, route of exposure all matter.

- Progress is being made but treatment options are limited in their efficacy and 'devil is in the details'.