An Update on Pediatric Asthma in 2012-2013
Learning Objectives

- To understand the most recent clinical research findings in pediatric asthma and allergies
- To briefly discuss recent evidence on herbal and alternative medication therapy in asthma
How it goes...
The Natural Course of Asthma Activity

- Ontario health data, 15-year follow-up study of 613,394 patients
- Primary outcome: active asthma (any physician claim ICD9 493; ICD 10 J 45, J 46)
- Secondary outcome: gap in asthma activity of 2 years or more
- Persistent asthma: 2 year gap between asthma claims not present

The natural course of asthma

- 82.3% had active asthma during follow-up, with a median of 4 asthma-related claims per person.
- 74.6% had at least a 2-year gap between claims.
- Factors associated with increased asthma activity:
  - higher number of previous asthma claims
  - older and younger age, particularly >65yo
  - presence of chronic obstructive pulmonary disease.
Asthma remissions and the return of asthma

- Study limitations: individuals may or may not use healthcare when disease is active (or inactive)
- asthma definition; potential misclassification
- Most patients have active asthma
- periods of "remission" occur and are prolonged
- 3/4 of patients had a gap of at least 2 years in their asthma activity
- The natural course of asthma is to wax and wane--but that it doesn't really resolve.
GERD
Yes or No in Asthma
GERD in Asthma

- Study of Acid Reflux in Children with Asthma (SARCA)
- Lansoprazole vs placebo with poorly controlled asthma
- Masked, PC RCT N=306
- 19 USA academic centers f/u for 24 weeks

GERD and asthma

- Primary outcome: ACQ (asthma control questionnaire)
- Secondary outcome measures: FEV1, asthma related quality of life, or rate of episodes of poor asthma control
- N=115 with esophageal ph studies, GER =43%
- ↑AE: ↑ resp infections in lansoprazole group (RR: 1.3)
GERD and asthma

- No Rx effect in positive ph probe sub-group
- No statistically significant difference in primary and secondary outcomes
- No difference in activity related fractures
- ↑ URTI, sore throats and bronchitis
- ? Non-acid reflux worsening asthma
- Does not evaluate GER and cough
## Adverse Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n = 150)</th>
<th>Lansoprazole (n = 147)</th>
<th>Relative Risk (95% CI)</th>
<th>( P ) Value(^{a} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>74 (49)</td>
<td>93 (63)</td>
<td>1.3 (1.1-1.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Sore throat</td>
<td>59 (39)</td>
<td>77 (52)</td>
<td>1.3 (1.0-1.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Group A Streptococcus</td>
<td>11 (7)</td>
<td>6 (4)</td>
<td>0.8 (0.5-1.1)</td>
<td>.23</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (2)</td>
<td>10 (7)</td>
<td>2.2 (0.8-6.1)</td>
<td>.04</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (3)</td>
<td>4 (3)</td>
<td>0.9 (0.5-1.6)</td>
<td>.76</td>
</tr>
<tr>
<td>Otitis media</td>
<td>10 (7)</td>
<td>12 (8)</td>
<td>1.1 (0.7-1.8)</td>
<td>.62</td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td>17 (11)</td>
<td>16 (11)</td>
<td>1.0 (0.7-1.4)</td>
<td>.90</td>
</tr>
</tbody>
</table>
Growth and asthma! AGAIN!!!
Ok here’s the growing stuff again!

Effect of Inhaled Glucocorticoids in Childhood on Adult Height

H. William Kelly, Pharm.D., Alice L. Sternberg, Sc.M., Rachel Lescher, M.D., Anne L. Fuhlbrigge, M.D., Paul Williams, M.D., Robert S. Zeiger, M.D., Ph.D., Hengameh H. Raissy, Pharm.D., Mark L. Van Natta, M.H.S., James Tonascia, Ph.D., and Robert C. Strunk, M.D., for the CAMP Research Group*
ICS and Final Adult Height

- Transient decrease in height 1-4 yrs after initiation of ICS Rx in pre-pubertal children; not thought to decrease final adult height
- Continuation of the CAMP study; adult height of participants measured
- Subjects were given budesonide 400 mcg, nedocromil 16 mg or placebo daily starting at age 5-13 yrs
- 943/1041 (96%) had final adult ht. measured at ~ 25 yrs
- Adjusted for demographic variables, initial height and asthma features at trial entry
Affect of ICS on adult height

Mean adult ht was 1.2 cm lower in the budesonide group than placebo (p=0.001; CI -1.9 to -0.5) and not stat. sig. different in Nedocromil group

NEJM 2012; 367; 904-12
A larger daily ICS does in first 2 yrs was associated with lower adult ht (p=0.007)
The reduction in adult ht in budesonide group was similar to placebo after first 2 yrs (-1.3 cm)
During first 2 years decreased growth velocity occurred primarily in pre-pubertal children

NEJM 2012; 367; 904-12
The final say on how tall you’ll be

- The initial decrease in height associated with ICS use in pre-pubertal children persisted as a reduction in attained adult height of approximately half an inch, though the decrease was not progressive nor cumulative.
An alternative treatment and way to monitor things
Hypertonic saline and wheezing

- Rhinovirus: main cause of acute wheezing episodes in preschool children; associated with decreased mucus clearance
- RCT evaluated inhaled hypertonic saline as a treatment option
- 41 children, mean age 32 months, seen in ED for wheezing
- X 1 albuterol, then 4 mL of inhaled hypertonic 5% saline, or normal saline
- Both Rx given with 0.5 mL albuterol: x2 q 20 minutes, then x 4 in the ED daily if the child was hospitalized.
Hypertonic Saline and Wheezing

- Primary Outcome: Length of stay (LOS)
- Secondary outcomes: admission rate and clinical severity score
- LOS: Median length of stay: 2 (HS group) vs 3 days (NS group) (p=0.027)
- Hospital admission rates were 62% versus 92%, respectively
- Improvements in clinical severity scores but not between the groups.
- Majority needed hospitalization (92%)- higher rate than before; greater disease severity; milder severity improved after pre-randomization albuterol
- Groups were younger (less than 4 years)
- Inhaled hypertonic saline can improve outcomes in preschool-aged children with acute wheezing.

Good old spiro....

**Best Data**

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Ref</th>
<th>Pre</th>
<th>% Ref</th>
<th>Post</th>
<th>% Ref</th>
<th>% Chg</th>
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<tbody>
<tr>
<td>FVC Liters</td>
<td>2.02</td>
<td>1.63</td>
<td>81</td>
<td>2.14</td>
<td>106</td>
<td>31</td>
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<tr>
<td>FEV1 Liters</td>
<td>1.78</td>
<td>1.19</td>
<td>67</td>
<td>1.70</td>
<td>96</td>
<td>43</td>
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<tr>
<td>FEV1/FVC %</td>
<td>91</td>
<td>73</td>
<td>79</td>
<td></td>
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<tr>
<td>FEF25-75% L/sec</td>
<td>2.14</td>
<td>0.88</td>
<td>41</td>
<td>1.44</td>
<td>67</td>
<td>64</td>
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<tr>
<td>PEF L/sec</td>
<td>3.73</td>
<td>3.05</td>
<td>82</td>
<td>4.44</td>
<td>119</td>
<td>46</td>
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<tr>
<td>PIF L/sec</td>
<td>2.27</td>
<td>3.30</td>
<td>45</td>
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<tr>
<td>FVL Time</td>
<td>15:15</td>
<td>15:28</td>
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</table>

**Flow Volume**

**Best Data**

**Volume/Time Graph**

**All Trials**

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Pre</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Trial 4</th>
<th>Trial 5</th>
<th>Trial 6</th>
<th>Trial 7</th>
<th>Trial 8</th>
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<tbody>
<tr>
<td>FVC Liters</td>
<td>1.63</td>
<td>1.46</td>
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</tr>
<tr>
<td>FEV1 Liters</td>
<td>1.19</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>PEF L/sec</td>
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<tr>
<td>PIF L/sec</td>
<td>2.27</td>
<td>2.54</td>
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</table>

**COMMENTS**

**INTERPRETATION**

PF Reference: Knudson (1983)
ENOSources:

- Establish baseline FeNO level during clinical stability for subsequent monitoring of chronic, persistent asthma
- Monitor airway inflammation levels in patients with asthma
- Account for persistent and/or high allergen exposure as a factor associated with elevated FeNO levels
- Assist in evaluation of adherence to ICS treatment
- Assess whether airway inflammation is contributing to poor asthma control

Where can ENO play a role

- Help to Differentiate asthma from other conditions
- Help to Identify likelihood of response to ICS therapy
- Help to Predict loss of control and adherence
- Help to Predict asthma relapse
- Help to Guide and optimize ICS therapy
# Clinical Guide to Interpretation of FeNO Values

## Management of Patients with Ongoing or Recent Asthma-Like Symptoms, Not Treated with ICS or Combination Therapy

<table>
<thead>
<tr>
<th>FeNO value (ppb), patients ≥12 years of age</th>
<th>LOW</th>
<th>INTERMEDIATE</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>25-50</td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>20-35</td>
<td>&gt;35</td>
<td></td>
</tr>
</tbody>
</table>

In the case of a >40% increase from previously stable levels, interpret as high FeNO.

### Interpretable with respect to steroid response

- **Unlikely to respond to corticosteroids** (interpreted cautiously in clinical context)
- **May respond to corticosteroids**
- **Highly likely to respond to corticosteroids**

### Other causes to consider

- Anxiety/Hyperinflation
- Cardiac disease
- COPD
- GERD
- Non-asthmatic asthma
- Rhinosinusitis
- Vocal cord dysfunction
- Cystic Fibrosis
- Primary ciliary dyskinesia (FeNO <5 ppb)

### Smoking has been shown to reduce FeNO levels.

## Possible alternative diagnoses

- Asthma
- Asthma with concomitant COPD
- Allergic rhinitis
- Obstructive sleep apnea
- Chronic obstructive pulmonary disease

### FeNO tests using NOx MIN® are reimbursable: CPT 85812

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**References:**
1. Ouellet KA, Boggs PE. American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications. An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FeNO) for clinical applications.  Am J Respir Crit Care Med. 2011;184:902-915.

NOX MIN®, NOX®, and Aerocrine are registered trademarks of Aerocrine AB. CPT coding to NOX MIN® is final authority for indications.
Big medicine and Christmas
Omalizumab and the risk of malignancy: Results from a pooled analysis

William Busse, MD,a Roland Buhl, MA, PhD,b Carlos Fernandez Vidalurre, MD, MPH,c Martin Blogg, BSc (Hons), CStat,d Jin Zhu, PhD,e Mark D. Eisner, MD, MPH,e and Janice Canvin, MD, FRCPCd Madison, Wis; Mainz, Germany; East Hanover, NJ; Horsham, United Kingdom; and South San Francisco, Calif

Previous pooled data (2003) from phase I to III studies of omalizumab showed a numeric imbalance in malignancies arising in omalizumab recipients (0.5%) compared with control subjects (0.2%)

Data from 67 phase I to IV clinical trials
Prespecified primary analysis: incidence of primary malignancy in 32 RDBPC trials
Xolair and malignancy

- Incidence rates per 1,000 patient-years were omalizumab (4.14; 95% CI, 2.26-6.94), placebo (4.45) (95% CI, 2.22-7.94)
- No association was observed between Omalizumab treatment and malignancy; the rate was below unity (0.93)

<table>
<thead>
<tr>
<th>TABLE 1. Patients’ demographics and baseline characteristics</th>
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<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Sex, no. (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Race, no. (%)</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Age (y),‡ no. (%)</td>
</tr>
<tr>
<td>&lt;12</td>
</tr>
<tr>
<td>12-17</td>
</tr>
<tr>
<td>18-64</td>
</tr>
<tr>
<td>≥65</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>IgE (IU/mL)</td>
</tr>
</tbody>
</table>

JACI 2012; 129; 983-9
Allergies at Christmas!

- New onset of alder pollen allergies in 15-yr old children attending a school in Grabs, a village in n Switzerland
- They had symptoms during the winter, a time when runny noses are typically attributed to viral infections
- The genesis of this unusual occurrence was the serendipitous planting of 96 hybrid trees with winter resistance about 10 years ago along a commonly commuted boulevard
- This resulted in exposure to alder pollen in December (the geographical flowering season) and development of IgE antibodies causing symptoms

Grassnner M et al. NEJM 368;4:393.
Allergies at Christmas!
Take home messages

• While some patients with asthma have periods of clinical remission, the majority continue to have active disease
• There is an initial decrease in height of about 1/2 inch associated with ICS use in pre-pubertal children, though not progressive or cumulative
• There is no increased risk of malignancy with use of Xolair
• Consider administration of inhaled hypertonic saline, along with albuterol, in preschool-aged children with acute wheezing
• Be aware of ‘out of season’ seasonal allergic rhinitis due to geographical and climate changes
Can herbal therapies save us?
Are herbal therapies legit?

- Several studies in both adults and children have suggested a role for herbal or homeopathic therapies for asthma and other allergic diseases
- Several reviews have evaluated the current herbals being studied
- The general consensus is that the current studies promoting herbal therapies are not fully rigorous, but there is some evidence that herbal preparations do have true biological effects
Several homeopathic treatments are on the market.
A little common sense may help clear the air.
Openly discussing these treatments with families is important, but don’t be “biased” or “condescending”.
Ingredients?

Tin
Arsenic
Antimony
Sulfuric acid
Chlorine
FAQ’s about this product

- **Q: Can Respitrol replace my inhaler?**  
  A: Respitrol is indicated to relieve asthma symptoms including, chest tightness, shortness of breath, wheezing and coughing. Asthma is an inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. **Respitrol is not intended to cure chronic asthma, nor is it intended to replace the emergency inhaler prescribed by your physician.**

- **Q: How safe is Respitrol?**  
  A: Respitrol is made with natural ingredients and is, first and foremost, formulated to be safe. Respitrol has no reported side effects or drug interactions, and may be used with other prescription or OTC medications. Respitrol is safe for both adults and children 2 years of age and up.

- **Q: Has Respitrol been clinically tested?**  
  A: The individual ingredients in Respitrol have claims based on the Homeopathic Materia Medica. As a composite formulation, however, Respitrol has not been clinically tested.
Why warnings if so safe?

- Ask a doctor before use if
  - you are taking other medications
  - you have a medical condition
  - When using this product, use only as directed.
  - Stop use and ask a doctor if symptoms persist or worsen.
  - If pregnant or breast-feeding, use only on the advice of a physician.
  - Keep out of the reach of children.
### Summary of current TCM in Pediatric asthma

<table>
<thead>
<tr>
<th>Publication Date</th>
<th>2005</th>
<th>2005</th>
<th>2006</th>
<th>2006</th>
<th>2007</th>
<th>2004</th>
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<tbody>
<tr>
<td>Number of Herbs</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Type of study</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Sample size</td>
<td>n = 45 ASHNI n = 46 Placebo</td>
<td>n = 40 mMMDT 10mg n = 40 mMMDT 40mg n = 20 Placebo</td>
<td>n = 28 DCT n = 24 Placebo</td>
<td>n = 50 STA-1 n = 50 STA-2 n = 20 Placebo</td>
<td>n = 8 RIA + Prob n = 9 NIA + Placebo</td>
<td>n = 33 AA n = 33 SA</td>
</tr>
<tr>
<td>Ages (years)</td>
<td>12-65</td>
<td>5-18</td>
<td>8-15</td>
<td>8-15</td>
<td>6-12</td>
<td>6-21</td>
</tr>
<tr>
<td>Indication</td>
<td>Moderate-to-severe persistent asthma</td>
<td>Mild-to-moderate persistent asthma</td>
<td>Mild-to-moderate persistent asthma</td>
<td>Intermittent or mild persistent asthma</td>
<td>Persistent Allergic rhinitis</td>
<td></td>
</tr>
<tr>
<td>Length of Study</td>
<td>4 weeks</td>
<td>4 months</td>
<td>3 months</td>
<td>6 months</td>
<td>16 wks</td>
<td>8 week</td>
</tr>
<tr>
<td></td>
<td>Combined formula of mMMDT without the herb #8 with Lai Wei Di Huang Wan (6 herbs)</td>
<td>Combined formula of mMMDT without the herb #8 with Lai Wei Di Huang Wan (6 herbs)</td>
<td>Combined formula of mMMDT without the herb #8 with Lai Wei Di Huang Wan (6 herbs)</td>
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<td>Combined formula of mMMDT without the herb #8 with Lai Wei Di Huang Wan (6 herbs)</td>
</tr>
<tr>
<td>Improved FEV1</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Li XM, Curr Opin Allergy Clin Immunol. 2009 Apr;9(2):161-7
Twenty-seven studies (29 experimental groups) met the review entry criteria, randomising a total of 1925 participants.

The studies identified assessed the effects of 21 different herbal preparations. Study quality varied considerably, and the sample sizes were often small.

For primary outcomes (exacerbations, steroids use and lung function measurements): Two out of six studies reporting change in FEV1 were positive, with very few data available on the frequency of exacerbations.

One study which did report these data was negative.

Health-related quality of life was only measured in one trial.
The evidence base for the effects of herbal treatments is hampered by the variety of treatments assessed, poor reporting quality of the studies and lack of available data.

The data that are available from the studies provide only a small insight into the long-term efficacy and harm profiles of these treatments.

The absence of common endpoint measurements limits the validity of our findings further.

Positive findings in this review warrant additional well-designed trials in this area.

Questions?