Asthma – 411:

What’s new
Practical tips and tricks

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Allergy and Clinical Immunology
DISCLOSURE INFORMATION SLIDE

Name: Dr. Scott Cameron M.D. Ph.D. F.R.C.P.C.

- Speaking honorariums:
  - Takeda
  - Sanofi

- AND -

I will discuss the potential off label use of a vitamin supplement in this presentation.
Sources

• Relevant Cochrane meta analysis
• Articles from 2013 and 2014
• Reports from Canadian Institute of Health Research and Statistics Canada
Objectives

1. Recognize an under-appreciated useful symptom as a sign of asthma
2. Be able to identify at least two risk factors for poorly controlled asthma
3. Identify a newer potential unconventional add on therapy for severe poorly controlled asthma
Objectives

4. Utilize a fast, simple in-clinic tool to follow your patient's asthma control

5. Utilize new techniques and technology to improve asthma medication technique, and adherence in pediatric and adult patients
What I won’t be covering:

• Overall treatment review
  – (Some specific situations will be discussed)
• Molecular diagnostics (urine testing, FeNO)
• Gene studies (GWAS)
• Low risk associations that are not modifiable*
• Things not ready to apply to your patient (asthma endotypes etc.)

* A lot of studies fall into this category. Enough with parental guilt that’s not based on good evidence!
Asthma attacks all age groups but often starts in childhood. It is a disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. In an individual, they may occur for an hour to hours and day to day.

This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. In an attack, the lining of the passages swell causing the airways to narrow and reducing the flow of air in and out of the lungs.
How to identify a child that is asthmatic?
In ¾ of these prospective cohort developed asthma prediction tools:
- Frequent wheeze
- Wheeze without colds
- Eczema
- Parental asthma

### Table III. Comparison of 4 asthma prediction tools for preschool children

<table>
<thead>
<tr>
<th>Outcome prevalence</th>
<th>Leicester (present study)</th>
<th>Tucson® (API®</th>
<th>IoWBC® (Isle of Wight Birth Cohort)</th>
<th>PIAMA® (Prevention and Incidence of Asthma and Mite Allergy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictor variables included in tool</td>
<td>1226</td>
<td>776</td>
<td>336</td>
<td>2054</td>
</tr>
<tr>
<td>Male sex, age &gt; 1 y, wheeze without colds, frequent wheeze, activity disturbance, shortness of breath, exercise-related wheeze/cough,† aeroallergen-related wheeze/cough, eczema, parental asthma or wheeze bronchitis</td>
<td>28.1%</td>
<td>13.7%</td>
<td>37.2%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Wheeze, frequent wheeze,‡ wheeze without colds, eczema, parental asthma, blood eosinophilia, allergic rhinitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of asthma, recurrent chest infections (at 2 y), skin prick test response positivity (at 4 y), nasal symptoms (at 1 y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex, postterm delivery, wheeze/dyspnea without colds, frequent wheeze, eczema, respiratory infections, inhalation medication (parents), parental education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Performance measures

<table>
<thead>
<tr>
<th>Method used to derive tool</th>
<th>Penalized logistic regression</th>
<th>Combination of predictors was chosen that yielded the highest PPV and specificity</th>
<th>Stepwise backward logistic regression</th>
<th>Stepwise backward logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance measures§</td>
<td>Score cutoff ≥5</td>
<td>Loose API</td>
<td>Score cutoff ≥5</td>
<td>Score cutoff ≥20</td>
</tr>
<tr>
<td>Youden index*</td>
<td>0.43</td>
<td>0.32</td>
<td>0.38</td>
<td>0.36</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>72</td>
<td>51</td>
<td>53</td>
<td>60</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>71</td>
<td>81</td>
<td>85</td>
<td>76</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>49</td>
<td>29</td>
<td>68</td>
<td>23</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>86</td>
<td>91</td>
<td>74</td>
<td>94</td>
</tr>
</tbody>
</table>

*NPV: Negative predictive value; PPV: positive predictive value.
*To have a prediction interval comparable with the one in our tool, we focused here on the API for prediction at 8 years.
†Wheeze or cough with moaning, playing, laughing, or crying.
‡This variable is only part of the stringent API but not of the loose API.
§Reported for cutoff where the sum of sensitivity and the specificity was maximal. It is possible that a higher sum of sensitivity and specificity exists at a cutoff point that was not explored in the respective studies.

A simple asthma prediction tool for preschool children with wheeze or cough.
Anina M. Pescatore
JACI 2014;133:111-8.)
Posttussive emesis

• 500 patients from tertiary asthma allergy clinic
• All completed questionnaire
• 3 grps:
  – MD diagnosed asthma
  – likely asthma (based on questionnaire answers)
  – no asthma


![Image of a table with questions about asthma symptoms and responses]

Figure 1. Asthma surrogate marker questionnaire. Responses were assigned points according to the following: 0, never; 1, rarely; 2, occasionally; and 3, frequently. Respondents who did not report asthma previously diagnosed by a physician and had a total score of 5 or greater were categorized in the probable asthma group.
Table 2. Predictive Values of Asthma Surrogate Markers

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise cough</td>
<td>18 (11–29)</td>
<td>80</td>
<td>82</td>
</tr>
<tr>
<td>Family history of allergic</td>
<td>4.1 (2.7–6.0)</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night cough</td>
<td>15 (9.4–23)</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td>Posttussive emesis</td>
<td>7.9 (5.2–12)</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>31 (18–56)</td>
<td>88</td>
<td>81</td>
</tr>
<tr>
<td>Wheeze</td>
<td>59 (32–111)</td>
<td>91</td>
<td>86</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.
Asthma risk: what to blame?

BLAME

No Single Raindrop Believes It Is Responsible For The Flood
Nature vs. Nurture
Obesity: Jasmine

- Obese (BMI = 25) 8 year old female with:
  - Shortness of breath with exercise*
  - Thinks she wheezes when she exerts herself*

*Exercise challenge tests frequently demonstrate these symptoms to be due to poor cardiovascular fitness, and not asthma.
Obesity: Jasmine

- Wheezes when sick
- Parents want to start an exercise program on the advice of her doctor
- Has been told in the past she is asthmatic
Obesity: Jasmine

• Is she at increased risk for asthma just because she is obese?
  – A: Yes
  – B: No
  – C: Research isn’t yet clear on this link
<table>
<thead>
<tr>
<th>BMI status at 1-2 y of age†</th>
<th>Percent</th>
<th>No.</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BMI</td>
<td>38.9</td>
<td>347</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>High BMI</td>
<td>45.2</td>
<td>81</td>
<td>1.28</td>
<td>0.89-1.85</td>
</tr>
<tr>
<td>BMI status at 3-5 y of age†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal BMI</td>
<td>38.8</td>
<td>361</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>High BMI</td>
<td>48.1</td>
<td>67</td>
<td>1.43</td>
<td>0.97-2.12</td>
</tr>
<tr>
<td>BMI status at 6-7 y of age†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal BMI</td>
<td>38.5</td>
<td>365</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>High BMI</td>
<td>52.0</td>
<td>63</td>
<td>1.66</td>
<td>1.10-2.52*</td>
</tr>
</tbody>
</table>

*P < .05.
†Adjusted for maternal allergy, maternal education, smoking during pregnancy, smoking in the house at 8 years of age, mode of delivery, birth weight, and breast-feeding.
‡A high BMI is defined as BMI SDS >85th percentile; a normal BMI was defined as BMI SDS ≤85th percentile.
§Sensitization was defined as a specific IgE concentration of at least 0.70 IU/ml on at least 1 of the inhalant allergens.
There is evidence that obesity related asthma seems to be non-allergic and steroid resistant.
Nurture

• Exposure to traffic exhaust and ozone
• Cigarette smoke
• House dust mite sensitization
• Viral infections
• Vitamin D
It’s air pollution
FIG 3. Mean FEV$_1$ % predicted ($pred.$) values for quartiles of distance from nearest roadway in meters for the subjects with asthma ($n = 144$). The quartile means differ significantly ($F = 5.75; P < .02$).
RA Silverman et al: Age-related association of fine particles and ozone with severe acute asthma in New York City. JACI 2010

Child asthmatics are especially sensitive to Ozone

FIG 2. Estimated relative risks of asthma hospitalization per IQR increase in the average of 0-day and 1-day lagged PM$_{2.5}$ (top) and ozone (bottom) by a 5-year block of age with groups centering at the indicated age (eg, 8-12 years of age are included for the group shown as age category 10 years). Models include both pollutants, adjusting for temporal trends, day of the week, and immediate and delayed weather effects. avg, Average.
It’s Cigarette Smoke
Figure 1. Daily Hospital Admissions for Asthma among Children between January 2000 and October 2009.

The smoothing of numbers for daily hospital admissions was performed with the use of the B-spline module for the Stata statistical software package, version 10.1 (Stata). Smoke-free legislation was implemented on March 26, 2006 (vertical line). Crude numbers are for the number of admissions between the dates shown.
It’s dust mites...
House dust mite sensitization and wheeze

• Birth cohort of 620 pts, with high proportion that had family hx of atopy
• Skin tested 6 allergens at 6,12,24 mo
• Wheeze and eczema recorded 18 times in first 2 yrs
• Current wheeze recorded at 12 years of age

House dust mite sensitization in toddlers predicts current wheeze at age 12 years
House dust mite sensitization and wheeze

Table II. Dust mite sensitization at 2 time points and 12-year wheeze

<table>
<thead>
<tr>
<th>Dust mite sensitivity</th>
<th>Proportion of wheeze at 12 y (n)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 y 2 y</td>
<td>28% (88/315)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- -</td>
<td>19% (45/236)</td>
<td>1</td>
<td>.81</td>
<td>1.15 (0.20-6.69)</td>
<td>.88</td>
</tr>
<tr>
<td>+ -</td>
<td>22% (2/9)</td>
<td>1.21 (0.24-6.03)</td>
<td>.81</td>
<td>1.15 (0.20-6.69)</td>
<td>.88</td>
</tr>
<tr>
<td>- +</td>
<td>48% (20/42)</td>
<td>3.86 (1.94-7.67)</td>
<td>&lt;.001</td>
<td>4.52 (2.08-9.83)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>+ +</td>
<td>75% (21/28)</td>
<td>12.73 (5.10-31.79)</td>
<td>&lt;.001</td>
<td>10.50 (3.62-30.40)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

OR, Odds ratio.

House dust mite sensitization in toddlers predicts current wheeze at age 12 years
Caroline J. Lodge et al. J Allergy Clin Immunol 2011;128:782
Hospital admissions and emergency rooms visits for asthma are highest in the month of:

a) April  
b) May  
c) September  
d) October
What is the September Asthma Epidemic?

Peak of pediatric asthma hospitalization of children occurred in week 38 (September 17-23) in 8/10 years

The September epidemic of asthma exacerbations in children: A search for etiology, Johnston et al. JACI 2005 V115 pg 132
They’re back to School...
Infections

• Which Virus is most likely to cause a viral exacerbation, especially during the September asthma epidemic?:
  – A: Influenza
  – B: Rhinovirus
  – C: RSV
  – D: Parvovirus
Rhinovirus

PDB 1RYN
Olivera et al.
The structure of human rhinovirus 16.
Structure 1 pp. 51 (1993)
• 412 patients admitted with LRTI, 216 assessed 3 years later
• Those that wheezed with a rhinovirus infection were the most likely to be wheezy 3 years later

It’s because we don’t get enough sunshine
Epidemiological studies demonstrating a role for Vitamin D in asthma

Age 5-13
Mild-moderate asthma

2093 Patients were assessed for eligibility

1052 Were excluded owing to asthma that was too severe or too mild, other reasons for ineligibility, nonadherence during run-in period, or lack of interest

1041 Underwent randomization

200mg BID

311 Were assigned to receive budesonide

312 Were assigned to receive nedocromil

418 Were assigned to receive placebo

30 Were lost to follow-up

27 Were lost to follow-up

41 Were lost to follow-up

281 Had measurement of adult height
271 Had measurement at age 
≥18 yr (women) or 
≥20 yr (men)
10 Grew <1 cm per year

285 Had measurement of adult height
274 Had measurement at age 
≥18 yr (women) or 
≥20 yr (men)
11 Grew <1 cm per year

377 Had measurement of adult height
368 Had measurement at age 
≥18 yr (women) or 
≥20 yr (men)
9 Grew <1 cm per year

-RDBPCT
-Treated 4 years
-Then open label as per family MD based on Sx and control
-Followed growth
-Exacerbations
-Blood samples
-Followed into adulthood

Figure 1.
Enrollment and Outcomes.
Risk of severe exacerbation over four years by combination of inhaled corticosteroid use and vitamin D status

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>%</th>
<th>Odds ratio&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>On inhaled steroids, sufficient vitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On inhaled steroids, insufficient vitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on steroids, sufficient vitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on steroids, insufficient vitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> Odds ratios are for each stratum in reference to a subject on inhaled corticosteroids with sufficient vitamin D. The Cochran-Armitage two-sided P-value for trend over the four strata is .0009.

J. M Brehm et al.: Serum Vitamin D Levels and Severe Asthma Exacerbations in the Childhood Asthma Management Program Study. JACI 2010
Vitamin D and corticosteroids:

• Vitamin D level (25-hydroxyl vitamin D) from 100 asthmatic children measured, and then its level compared with lung function and steroid use.

• Correlation:
  – Higher FEV1 (p=0.004)
  – Higher FEV1/FVC (p=0.01)

• Inverse correlation:
  – Use of inhaled steroids (p=0.0475)
  – Oral steroids (p=0.02)
  – Total steroid dose (p=0.001)

D.A. Searing Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. JACI 2010
Proposed mechanism of Vitamin D’s role in steroid sensitivity

D.A. Searing Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. JACI 2010

FIG 3. VitD augments DEX’s effect on TSST-1–stimulated lymphocyte proliferation in human PBMCs. PBMCs from healthy control subjects were treated with DEX and VitD, as indicated in the Methods section. Tritiated thymidine was added to the medium 18 hours before collecting the cells. Cell division was estimated based on tritiated thymidine incorporation (n = 4).
Correlation

I used to think correlation implied causation.

Then I took a statistics class. Now I don't.

Sounds like the class helped.

Well, maybe.

From http://xkcd.com/552/
Vitamin D can prevent influenza A?

- RDBPCT comparing Vit D3 (1200IU/D) with placebo in school children (n=167/grp)
- Primary outcome: influenza infection(nasal swab) during single influenza season
- Secondary outcome: number of asthma exacerbations in previously identified asthmatics

Vitamin D can prevent influenza A?

**TABLE 2**
Influenza A as a primary outcome, subgrouped by factors

<table>
<thead>
<tr>
<th>Subjects with influenza A</th>
<th>Vitamin D&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Placebo</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>P value</th>
<th>P value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/total n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Influenza A</strong></td>
<td>18/167 (10.8)</td>
<td>31/167 (18.6)</td>
<td>0.58</td>
<td>0.34, 0.99</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Additional vitamin D&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>None</td>
<td>8/140 (6.0)</td>
<td>22/140 (16.5)</td>
<td>0.36</td>
<td>0.17, 0.79</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>At least once per week&lt;sup&gt;3&lt;/sup&gt;</td>
<td>10/34 (29.4)</td>
<td>9/34 (26.5)</td>
<td>1.11</td>
<td>0.52, 2.39</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Starting age of nursery school</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>&lt;3 y</td>
<td>10/59 (16.9)</td>
<td>7/49 (14.3)</td>
<td>1.19</td>
<td>0.49, 2.88</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>&gt;3 y</td>
<td>8/107 (7.5)</td>
<td>24/117 (20.5)</td>
<td>0.36</td>
<td>0.17, 0.78</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> We compared the null hypothesis of equality of risk ratios between demographic groups by using a chi-square test.

<sup>2</sup> Vitamin D supplement other than the study drug.

<sup>3</sup> Frequencies: 200–400 IU/wk (n = 7), 600–800 IU/wk (n = 7), 1000–1200 IU/wk (n = 46), and >1400 IU/wk (n = 8).

Vitamin D can prevent influenza A?

Effect of Vitamin D Supplementation on Moderate to Severe Bronchial Asthma (RDBPCT)

• Randomized 100 pts:
  – 60,000IU Vit D3/mo
  – Placebo powder

• Followed for 6 months
Effect of Vitamin D Supplementation on Moderate to Severe Bronchial Asthma (RDBPCT)

Primary outcome measure was change in the level of severity of asthma according to GINA guidelines. Secondary outcome measures were

- Number of exacerbations during treatment period
- Change in the PEFR
- Change in the Steroid dosage
- Level of control
- Emergency visits
Effect of Vitamin D Supplementation on Moderate to Severe Bronchial Asthma (RDBPCT)

Table 3  Number of exacerbations during treatment period

<table>
<thead>
<tr>
<th>Number of exacerbations during treatment period</th>
<th>Placebo group $(n=50)$ (%)</th>
<th>Vitamin D group $(n=50)$ (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20 (40.0)</td>
<td>36 (72.0)</td>
<td>0.011 (S)</td>
</tr>
<tr>
<td>1</td>
<td>17 (34.0)</td>
<td>9 (18.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (8.0)</td>
<td>3 (6.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 (16.0)</td>
<td>2 (4.0)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Effect of Vitamin D Supplementation on Moderate to Severe Bronchial Asthma. Madhu Yadav & Kundan Mittal, Indian J Pediatr 2013
Vitamin D in Pediatric Asthma: a Randomized Controlled Open-label Pilot Trial (D-Asthma)

This study is currently recruiting participants.
Verified February 2014 by Nationwide Children's Hospital
Sponsor:
Nationwide Children's Hospital
Collaborator:
Ohio State University
Information provided by (Responsible Party):
Barbara Gracious, Nationwide Children's Hospital

ClinicalTrials.gov Identifier:
NCT02054975
First received: February 3, 2014
Last updated: NA
Last verified: February 2014
History: No changes posted

Purpose

This is a pilot randomized controlled trial of lower vs. higher dose vitamin D supplementation in D-deficient asthmatic children, to determine necessary sample sizes for outcome measures in a larger multisite study, and to examine possible relationships and effect sizes between various biological markers that may be important to the pathophysiology of childhood asthma.

Aims of the study are to:
1. Evaluate effect sizes for relationships between serum 25OH-vitD and omega-fatty acid (FA) biomarkers, before and after supplementation with lower or higher dose vitamin D, on immune function, and asthma severity.
2. Characterize changes in innate and adaptive immune function and inflammatory responses in asthmatic D-deficient youth at baseline and after vitD supplements, by dietary O6:O3FA status and vitD dose.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Drug: Vitamin D + vitamin D3</td>
</tr>
<tr>
<td>Vitamin D Deficiency</td>
<td>Drug: Vitamin D3</td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Randomized
Endpoint Classification: Safety Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment
Current Canadian Study:

Participants:
- age 1-5 years
- healthy
- attending a TARGet Kids! practice site for a well-child visit

Randomize (September-November):
- Standard Dose: 400 IU Vitamin D₃ daily
- High Dose: 2000 IU Vitamin D₃ daily

Baseline (September-November):
- Questionnaire
- Anthropometrics
- Vitamin D serum level

Viral nasal swabs and symptom checklists through the winter

Follow-up (April-May):
- Primary Outcome:
  - Laboratory confirmed URTI rate
  - Time to first URTI
- Secondary Outcomes:
  - Parent reported URTI symptoms
  - Wheezing episodes among children with asthma
  - Influenza, adenovirus and RSV
  - 25-hydroxyvitamin D serum level
  - Physician diagnosed acute otitis media
  - Physician diagnosed pneumonia

Randomization:
- Stratified by practice site
- Varying sized blocks

DO IT Trial: vitamin D Outcomes and Interventions in Toddlers - a TARGet Kids! randomized controlled trial

My suggestions:

• No evidence to suggest regular measurement of Vitamin D levels in someone suspected to be deficient

• *Might* be worth measuring in severe, poorly controlled asthmatic who is not responding to steroids (academic interest only)

₁http://www.bcguidelines.ca/pdf/vitamind.pdf
My suggestions:

• Supplementation recommendations (not for asthma specifically):

  **Recommendation**

  3.3 For children aged 1–18 yr who are vitamin D deficient, we suggest treatment with 2000 IU/d of vitamin D$_2$ or vitamin D$_3$ for at least 6 wk or with 50,000 IU of vitamin D$_2$ once a week for at least 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml followed by maintenance therapy of 600-1000 IU/d (2⃣⃣⃣⃣⃣⃣⃣⃣).
Practical Duct Tape Projects

1. Pencil Case
2. Wallet with Optional Change Purse
3. No-Sew Tote
4. Tablet Folio Case
5. Hammock

Instructables.com
Practical tips and tricks:

- How to provide timely efficient education for your asthmatic patients
- Providing an asthma action plan
- Getting patients to be adherent
- A simple tool to Recognize which patients have poor asthma control
- Treatment suggestions: what not to do
How good are we at educating?
<table>
<thead>
<tr>
<th>Topics of Asthma Education</th>
<th>Community pediatric group practice</th>
<th>County hospital-based pediatric asthma clinic (reference)</th>
<th>General pediatrics clinic at academic medical center</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past, (if parent) has your child’s doctor ever...? (if child) has your doctor ever...?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Reviewed with you how to use a metered dose inhaler</td>
<td>75.9%</td>
<td>75.0%</td>
<td>76.7%</td>
</tr>
<tr>
<td>2. Discussed with you how to manage an asthma attack</td>
<td>69.0%</td>
<td>86.1%</td>
<td>71.7%</td>
</tr>
<tr>
<td>3. Advised you regarding the effects of smoking</td>
<td>51.7%</td>
<td>72.2%</td>
<td>43.3%**</td>
</tr>
<tr>
<td>4. Asked you about problems taking asthma medications</td>
<td>34.5%*</td>
<td>63.9%</td>
<td>41.7%*</td>
</tr>
<tr>
<td>5. Discussed with you what happens during an asthma attack</td>
<td>58.6%*</td>
<td>83.3%</td>
<td>66.7%</td>
</tr>
<tr>
<td>6. Provided you with take-home educational materials</td>
<td>44.8%*</td>
<td>69.4%</td>
<td>50.0%</td>
</tr>
<tr>
<td>7. Discussed with you how different medications work</td>
<td>51.7%</td>
<td>69.4%</td>
<td>48.3%*</td>
</tr>
<tr>
<td>8. Reviewed with you peak flow meter use</td>
<td>34.5%</td>
<td>44.4%</td>
<td>48.3%</td>
</tr>
<tr>
<td>9. Asked you about worries you have about medications</td>
<td>31.0%*</td>
<td>61.1%</td>
<td>50.0%</td>
</tr>
<tr>
<td>10. Taught you how to recognize a change in asthma symptoms</td>
<td>31.0%**</td>
<td>63.9%</td>
<td>55.0%</td>
</tr>
<tr>
<td>11. Discussed with you the difference between asthmatic and normal Airways</td>
<td>41.4%*</td>
<td>69.4%</td>
<td>53.3%</td>
</tr>
<tr>
<td>12. Discussed with you allergen control</td>
<td>41.4%</td>
<td>63.9%</td>
<td>50.0%</td>
</tr>
<tr>
<td>13. Provided you with a written medication plan</td>
<td>24.1%***</td>
<td>77.8%</td>
<td>48.3%**</td>
</tr>
<tr>
<td>14. Discussed with your child/you the child’s feelings about asthma</td>
<td>13.8%***</td>
<td>61.1%</td>
<td>25.0%***</td>
</tr>
<tr>
<td>15. Talked with you about goals in management</td>
<td>34.5%**</td>
<td>66.7%</td>
<td>46.7%</td>
</tr>
<tr>
<td>16. Provided you with written guidelines on when to call the doctor or when to go to the emergency department</td>
<td>44.8%**</td>
<td>77.8%</td>
<td>50.0%**</td>
</tr>
</tbody>
</table>

Mean % children reporting adequate education

\[
\begin{align*}
\text{Mean} & \pm \text{SD} \\
(\pm SD) & (\pm 15.9) & (\pm 10.0) & (\pm 12.2) \\
\text{Number of topics discussed adequately} & 42.5\% & 69.1\% & 51.6\% \\
\text{Mean} \pm \text{SD} & 6.8 \pm 4.2\% & 11.1 \pm 4.8\% & 8.3 \pm 4.8\% \\
\text{Median (IQR)} & 6 (4–10) & 13 (10–14) & 8 (4–13) \\
\end{align*}
\]

Note: *\( p \leq .05 \), **\( p \leq .01 \), ***\( p \leq .001 \).
ASThma Action Plan

Goals

Signs of poor control

How to manage an exacerbation

How to manage an acute attack

Where to go for more info

Visit www.asthma-education.com
Asthma action plans

• I am happy to email you:
  – Pre-prepared asthma action plans for most drugs and doses in PDF and MSWord format for printing or use in your EMR
  – Blank Asthma action plan (PDF and MSWord)
  – Accuro-compatible drop down auto fill form
  – Send an email requesting it to sbcameron@gmail.com
Use of iPad in clinic

- Educational videos (Buzz player)
- ACT and C-ACT scoring
- Form completion for EMR (Waiting Room app)
- Educational games
- Videos for distraction during painful procedures
Factors contributing to the September Asthma epidemic

• High period of summer allergen exposure
• Return to school stress
• Viral infections

• Non adherence to medications over the summer

**Adherence: a modifiable factor?**
Non-adherence: evidence based on prescription data

The September epidemic of asthma exacerbations in children: A search for etiology, Johnston et al. JACI 2005 V115 pg 132

Lowest amount of prescription renewals for asthma control medication prior to week 38
How can I get my patient to be % adherent?
How bad is the problem?

- Covert medication monitoring for 24 weeks
- Recruited from a database of asthmatics that had been in previous asthma studies
- Told them they were seeing which medication worked better, but they were really secretly checking to see if they took it

K Perrin et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. JACI 2010
How bad is the problem?

• Because recruited from previous study subjects, an expected higher than normal adherence

• Because they were in study, would have higher than normal adherence compared to real life usage

K Perrin et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. JACI 2010
What percent of patients were adherent (80% of days took medication)?

• A) 10%
• B) 30%
• C) 50%
• D) 70%

K Perrin et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. JACI 2010
Decreased Adherence over time

K Perrin et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. JACI 2010

FIG 3. Percentage of adherent days in the four 6-week periods of the study in the subjects prescribed FP/salmeterol (SM; ▲), SM (■), and FP (●). The symbols show the mean and the error bars the SEM.
TABLE III. Proportion of subjects with >50%, >80%, and >90% adherence during the final 6-week period of study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Single inhaler n/N (%)</th>
<th>Combination inhaler n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence &gt;50%</td>
<td>FP 40/49 (81.6)</td>
<td>51/54 (94.4)</td>
</tr>
<tr>
<td></td>
<td>SM 40/47 (85.1)</td>
<td>51/54 (94.4)</td>
</tr>
<tr>
<td>Adherence &gt;80%</td>
<td>FP 24/49 (50.0)</td>
<td>32/54 (59.3)</td>
</tr>
<tr>
<td></td>
<td>SM 26/47 (55.3)</td>
<td>32/54 (59.3)</td>
</tr>
<tr>
<td>Adherence &gt;90%</td>
<td>FP 18/49 (36.7)</td>
<td>24/54 (44.4)</td>
</tr>
<tr>
<td></td>
<td>SM 21/47 (44.7)</td>
<td>24/54 (44.4)</td>
</tr>
</tbody>
</table>

SM, Salmeterol.

6-19% don’t take even half the time

41-50% are not taking it 80% of the time

K Perrin et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. JACI 2010
How bad is the problem

• Only 50% of patients miss only 1 day/week of their medication
• If when you ask, you are not getting this stat from your patients, you are asking wrong
How bad is the problem

• Ask in a way that normalizes non-adherence
  – (patients want to please their doctor)
• Obtain pharmanet data on those with poor control, record when you give samples (and mention in your referral letters)
Reasons for poor medication adherence are:

a) Insufficient patient education  
b) Fear of medication side effects  
c) Busy lives  
d) Poor perception of symptoms  
e) All of the above
Growth Suppression
Growth Suppression

- Current data from CAMP study indicates that there is as much as 0.8-1.8cm difference in height in those on long term inhaled corticosteroids
- By most MD’s (not parents) this is considered a minimal difference
- This must be a fear we address with parents
- Ask parents: “Do you have any concerns with this medication?”
Suppression happens in first few months on ICS
# CAMP study and growth

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Adult Height</th>
<th>Difference in Height</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Budesonide (N = 281) cm</td>
<td>Nedocromil (N = 285) cm</td>
</tr>
<tr>
<td>All participants</td>
<td>171.1</td>
<td>172.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>162.8</td>
<td>163.9</td>
</tr>
<tr>
<td>Male</td>
<td>176.8</td>
<td>177.6</td>
</tr>
<tr>
<td>P value for interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–8 yr</td>
<td>170.7</td>
<td>171.8</td>
</tr>
<tr>
<td>9–13 yr</td>
<td>171.4</td>
<td>172.4</td>
</tr>
<tr>
<td>P value for interaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean values for adult height have been adjusted for age, race or ethnic group, sex, clinic, duration of asthma, asthma severity, presence or absence of skin-test reactivity, and height at trial entry. In the analysis of mean adult height according to sex, 385 participants were female and 558 were male. In the analysis of age at study entry, 489 participants were 5 to 8 years of age and 454 were 9 to 13 years of age.
So use intermittent steroids right?

- Cochrane meta-analysis
- Primary outcomes:
  - Number of patients with one or more exacerbations requiring oral steroids
- Secondary outcomes:
  - Exacerbations
  - Lung function tests
  - Asthma control
  - Inflammatory markers
  - Withdrawal rates
  - Adverse effects
Daily vs Intermittent ICS:

- Primary outcomes:
  - No difference

Daily vs Intermittent ICS:

- Secondary outcomes:
  - Daily ICS had more growth suppression*
  - Daily ICS had improved:
    - markers of lung function
    - airway inflammation
    - asthma control
    - reliever use

*note that growth suppression with intermittent ICS use has not been well studied

Daily vs Intermittent ICS:

• Conclusion: low quality evidence that they were similarly effective \( \therefore \) cannot assume equivalence

Black Box Warnings
Black Box BS

• Both studies that resulted in Singuair and LABA black box warnings had significant methodological flaws

• Numerous papers\textsuperscript{1,2} published over the last two years have demonstrated good long term safety of both medications

• Currently ongoing LABA safety study, unlikely to be of benefit\textsuperscript{3}

\textsuperscript{1}Nelson et al JACI 2010
\textsuperscript{2}Holbrook and Harik-Khan JACI 2010
Life is sooo busy...
Phones are GOOD for something other than Facebook updates?
Their Phones are GOOD for something other than Facebook updates?

- At least 75% of Canadian Teens have cell phones
- >85% of adults have cell phones
- ALL of them can set reminder alarms
- Music players (Ipods etc.) can do the same
Take home:

• have your patients set a medication alarm on their phone before they leave your office
Poor recognition of symptoms
Asthma control Test (ACT)

- 471 patients
- Administered 22 questions
- Correlated answers with MD’s assessment of asthma control after spirometry
- Honed down to 5 questions that best matched
- Score ranges from 5-25
- ≤19 is considered poor asthma control
- Numerous studies have validated it
- Minimal important difference: 2

Development of the Asthma Control Test: A survey for assessing asthma control. Robert A. Nathan et al. JACI 2004 V113 pg 59
The lower the score, the more likely the asthma is poorly controlled.

<table>
<thead>
<tr>
<th>Cut point score</th>
<th>Odds ratio</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>7.41</td>
<td>9.0</td>
<td>98.7</td>
</tr>
<tr>
<td>≤11</td>
<td>7.04</td>
<td>14.3</td>
<td>97.7</td>
</tr>
<tr>
<td>≤12</td>
<td>9.11</td>
<td>21.8</td>
<td>97.0</td>
</tr>
<tr>
<td>≤13</td>
<td>7.96</td>
<td>29.3</td>
<td>95.1</td>
</tr>
<tr>
<td>≤14</td>
<td>7.58</td>
<td>36.1</td>
<td>93.1</td>
</tr>
<tr>
<td>≤15</td>
<td>9.27</td>
<td>44.4</td>
<td>92.1</td>
</tr>
<tr>
<td>≤16</td>
<td>9.41</td>
<td>52.6</td>
<td>89.4</td>
</tr>
<tr>
<td>≤17</td>
<td>7.68</td>
<td>57.9</td>
<td>84.8</td>
</tr>
<tr>
<td>≤18</td>
<td>6.72</td>
<td>62.4</td>
<td>80.2</td>
</tr>
<tr>
<td>≤19</td>
<td>7.20</td>
<td>69.2</td>
<td>76.2</td>
</tr>
<tr>
<td>≤20</td>
<td>6.31</td>
<td>75.9</td>
<td>66.7</td>
</tr>
<tr>
<td>≤21</td>
<td>5.01</td>
<td>82.7</td>
<td>51.2</td>
</tr>
<tr>
<td>≤22</td>
<td>4.35</td>
<td>87.9</td>
<td>37.3</td>
</tr>
<tr>
<td>≤23</td>
<td>5.32</td>
<td>94.0</td>
<td>25.4</td>
</tr>
<tr>
<td>≤24</td>
<td>3.31</td>
<td>94.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Continuous</td>
<td>0.78</td>
<td>44.4</td>
<td>92.01</td>
</tr>
</tbody>
</table>

*Specialist’s rating of not controlled at all, poorly controlled, or somewhat controlled.
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

2. During the past 4 weeks, how often have you had shortness of breath?

- More than once a day
- Once a day
- 3 to 6 times a week
- Once or twice a week
- Not at all

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

- 4 or more nights a week
- 2 or 3 nights a week
- Once a week
- Once or twice
- Not at all

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

- 3 or more times per day
- 1 or 2 times per day
- 2 or 3 times per week
- Once a week or less
- Not at all

5. How would you rate your asthma control during the past 4 weeks?

- Not controlled at all
- Poorly controlled
- Somewhat controlled
- Well controlled
- Completely controlled

Very important question to identify poor perceivers (Especially teens)

http://www.asthma.com/resources/asthma-control-test.html
Child-Asthma control test (C-ACT)

• Validated for ages 4-11
• 7 items
• Summed score 0-27
• $\leq 19$ indicates inadequately controlled asthma (specificity 74%, sensitivity 68%, although varies depending on study)
• Minimal important difference: 2

Development and cross-sectional validation of the Childhood Asthma Control Test. Andrew H. Liu et al. JACI 2007 V 119 pg817
Have your child complete these questions.

1. How is your asthma today?
   - Very Bad
   - Bad
   - Good
   - Very Good

2. How much of a problem is your asthma when you run, exercise or play sports?
   - It's a big problem, I can't do what I want to do.
   - It's a problem and I don't like it.
   - It's a little problem but it's okay.
   - It's not a problem.

3. Do you cough because of your asthma?
   - Yes, all of the time.
   - Yes, most of the time.
   - Yes, some of the time.
   - No, none of the time.

4. Do you wake up during the night because of your asthma?
   - Yes, all of the time.
   - Yes, most of the time.
   - Yes, some of the time.
   - No, none of the time.

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?
   - Not at all
   - 1-3 days
   - 4-10 days
   - 11-18 days
   - 19-24 days
   - Everyday

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?
   - Not at all
   - 1-3 days
   - 4-10 days
   - 11-18 days
   - 19-24 days
   - Everyday

7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?
   - Not at all
   - 1-3 days
   - 4-10 days
   - 11-18 days
   - 19-24 days
   - Everyday
Advantages of ACT and C-ACT use in the clinic

• Fast to administer
• Follow changes over time as you make changes to management
• Can predict severe exacerbations
Advantages of ACT and C-ACT use in the clinic

• Motivational tool - goals for families
• Encourages parent child discussion
• allows more child input
• Catch a miss
C-ACT can identify poorly controlled asthmatics that you’ll miss:

- 354 parents and children (4–11)
- moderate-severe asthma
- C-ACT scoring done at pediatrician or respirologist visit

C-ACT can identify poorly controlled asthmatics that you’ll miss:

• Of the 229 who’s asthma was not controlled (C-ACT ≤19)
  – 41.9% MD’s thought it controlled (GINA guidelines)
  – 72.9% of parents thought it controlled

C-ACT can identify poorly controlled asthmatics that you’ll miss:

- “Listening solely to the parents’ description may therefore give a false impression of the child’s complaints. This discordance may have led physicians to underestimate the asthma’s control and hence prescribe suboptimal treatment, and could be a reason why in so many children (about half of those studied) asthma was uncontrolled.”

Quick note on therapy:

- Can Respir J. 2010 Jan-Feb; 17(1): 15–24.
*Personal opinion:

• Consider not starting a very young (less than age 5), mild asthmatic with no ED visit history on ICS, trial Singulair first
• If no improvement in symptoms, daily low dose ICS as a trial
• Growth data may support this strategy especially for those under 3 years old and 15kg.
*Personal opinion:*

- Don’t start with combo therapy in children or adults. Start with daily ICS first
  - Otherwise these patients end up using combo therapy as PRN treatment
- A child that is using ICS PRN and is subsequently hospitalized for asthma has failed ICS PRN: put them on daily ICS
Clinic resources

• Asthma control test website: www.asthma.com
• Asthma education website: www.asthma-education.com
• www.teen-asthma.com
• If you want the asthma action plans: email me at sbcameron@gmail.com
Questions?