Cross-Canada Rounds

Danielle Adam, PGY5
Pediatric Respirology Fellow
December 20th, 2018
Case

How far have we gone? Ten miles? Ten kilometers? 20 klicks?

Almost to the end of the driveway!

Lung distance running

theAwkwardYeti.com
14yo male: referred for poorly controlled asthma and persistent Xray changes

Diagnosed at age 3 (recurrent cough and wheezing)

Previous treatment: Flovent and Symbicort PRN

Present treatment (for the last year): Zenhale 100mcg 2 puffs BID, Singulair 5mg once daily, and Nasonex, no Ventolin use last year

Ventolin has helped in the past
Case

- Present symptoms: chest tightness and SOB with exercise (5min of running)
- Exercises 4 times a week
- Chronic dry cough every night
- Only sick once this winter with a cold
- Previous illnesses: LUL pneumonia – treated with abx with incomplete resolution (persistent x-ray changes). Repeated abx and prednisone
Case: Past Medical History

- Adopted as a baby, no neonatal respiratory distress
- No hospitalizations, surgeries
- Several childhood visits to the ER for asthma and received steroids multiple times (last oral steroids for asthma was 5 years ago)
- Suspected allergies to cats, dogs, dust
- Family history: limited known about biological family except for history of CF
Case: Review of Systems

- Chronic nasal congestion, no polyps
- No history of choking or coughing with eating
- Normal bowel movements
- No eczema history
- No snoring
- Growing well
- Multiple ear infections in early childhood but otherwise no history to suggest immunodeficiency
Any additional investigations you want to do?
**SPIROMETRY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ref</th>
<th>Pre Meas</th>
<th>% Ref</th>
<th>Pre</th>
<th>Post Meas</th>
<th>% Ref</th>
<th>% Chg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>4.13</td>
<td>4.88</td>
<td>118</td>
<td>4.67</td>
<td>115</td>
<td>115</td>
<td>-3</td>
</tr>
<tr>
<td>FEV1</td>
<td>3.81</td>
<td>3.81</td>
<td>100</td>
<td>3.69</td>
<td>97</td>
<td>97</td>
<td>-3</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>86</td>
<td>78</td>
<td>91</td>
<td>78</td>
<td>90</td>
<td>90</td>
<td>-1</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>4.19</td>
<td>3.32</td>
<td>79</td>
<td>3.26</td>
<td>78</td>
<td>78</td>
<td>-2</td>
</tr>
<tr>
<td>FEF50%</td>
<td>4.73</td>
<td>4.56</td>
<td>96</td>
<td>4.45</td>
<td>94</td>
<td>94</td>
<td>-2</td>
</tr>
<tr>
<td>FEF75%</td>
<td>2.63</td>
<td>1.57</td>
<td>60</td>
<td>1.38</td>
<td>52</td>
<td>52</td>
<td>-12</td>
</tr>
<tr>
<td>PEF</td>
<td>7.91</td>
<td>8.41</td>
<td>106</td>
<td>8.88</td>
<td>112</td>
<td>112</td>
<td>6</td>
</tr>
<tr>
<td>FIVC</td>
<td>3.70</td>
<td>2.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIF</td>
<td>5.11</td>
<td>5.56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LUNG VOLUMES**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ref</th>
<th>Pre Meas</th>
<th>% Ref</th>
<th>Pre</th>
<th>Post Meas</th>
<th>% Ref</th>
<th>% Chg</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>4.13</td>
<td>5.19</td>
<td>126</td>
<td>5.19</td>
<td>126</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>TLC</td>
<td>5.27</td>
<td>6.67</td>
<td>127</td>
<td>6.67</td>
<td>127</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td>1.08</td>
<td>1.48</td>
<td>137</td>
<td>1.48</td>
<td>137</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>RV/TLC%</td>
<td>20</td>
<td>22</td>
<td>108</td>
<td>22</td>
<td>108</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>FRC PL</td>
<td>2.49</td>
<td>3.56</td>
<td>143</td>
<td>3.56</td>
<td>143</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>3.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERV</td>
<td>2.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DIFFUSION CAPACITY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ref</th>
<th>Pre Meas</th>
<th>% Ref</th>
<th>Pre</th>
<th>Post Meas</th>
<th>% Ref</th>
<th>% Chg</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO</td>
<td>28.5</td>
<td>28.5</td>
<td>100</td>
<td>28.5</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>DL Adj</td>
<td>28.5</td>
<td>28.5</td>
<td>100</td>
<td>28.5</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td>5.27</td>
<td>5.70</td>
<td>100</td>
<td>5.70</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>DLCO adj for VA</td>
<td>28.5</td>
<td>27.6</td>
<td>97</td>
<td>27.6</td>
<td>97</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>IVC</td>
<td>4.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**AIRWAYS RESISTANCE**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ref</th>
<th>Pre Meas</th>
<th>% Ref</th>
<th>Pre</th>
<th>Post Meas</th>
<th>% Ref</th>
<th>% Chg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw</td>
<td>2.28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaw</td>
<td>0.119</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eRaw</td>
<td>5.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sGaw</td>
<td>0.168</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COMMENTS:**
The patient provided good effort, however, was unable to meet end of test criteria for flow volume loops. ATS criteria were not met. Lung volumes and DLCO testing met ATS criteria. 4 puffs of bronchodilator - Salbutamol, were administered via space chamber.
Case: Next steps

- CT
- Allergy test: Positive for horse, trees, indoor and outdoor molds, house dust mites and cat
- CBC: normal
Follow-up

- His Singulair was optimized to 10mg once daily and he was given a Ventolin discus to take with exercise. He was told to remain on the Zenhale.
- He returned to clinic 4-6 weeks later and is very happy with the improvement.
- He is now completely asymptomatic.
### SPIROMETRY

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref</th>
<th>Pre Meas</th>
<th>% Ref</th>
<th>Post Meas</th>
<th>% Ref</th>
<th>Post % Chg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>Liters</td>
<td>4.27</td>
<td>4.99</td>
<td>4.95</td>
<td>115</td>
<td>-1</td>
</tr>
<tr>
<td>FEV1</td>
<td>Liters</td>
<td>3.94</td>
<td>3.78</td>
<td>3.86</td>
<td>99</td>
<td>3</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>%</td>
<td>86</td>
<td>76</td>
<td>88</td>
<td>79</td>
<td>92</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>L/sec</td>
<td>4.32</td>
<td>3.10</td>
<td>72</td>
<td>3.51</td>
<td>81</td>
</tr>
<tr>
<td>FEF50%</td>
<td>L/sec</td>
<td>4.89</td>
<td>3.96</td>
<td>81</td>
<td>4.33</td>
<td>89</td>
</tr>
<tr>
<td>FEF75%</td>
<td>L/sec</td>
<td>2.74</td>
<td>1.42</td>
<td>52</td>
<td>1.63</td>
<td>59</td>
</tr>
<tr>
<td>PEF</td>
<td>L/sec</td>
<td>8.14</td>
<td>8.55</td>
<td>105</td>
<td>8.42</td>
<td>103</td>
</tr>
<tr>
<td>FET100%</td>
<td>Sec</td>
<td>4.86</td>
<td>6.46</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>Liters</td>
<td>4.45</td>
<td>4.56</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIF</td>
<td>L/sec</td>
<td>8.39</td>
<td>8.42</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVV</td>
<td>L/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COMMENTS:**
Last used Zentale approximately 16 hours prior to testing, has not used Ventolin over past month.
4 puff of bronchodilator - Salbutamol, were administered via space chamber.
The patient provided adequate effort, flow volume loop testing met ATS criteria.
Case – more details

- Sweat chloride: 59 (repeat 58)
- IgE: 8981
- Bronch: lipid laden macrophages, no bacterial growth, scant secretions
Outline

- To review the criteria and suggested workup for difficult to treat asthma.
- To review normal sweat chloride levels, and what it could mean to have an indeterminate sweat chloride level.
- To outline the possible relationship of elevated sweat chloride levels and difficult to treat asthma.
Difficult to Treat Asthma
Severe asthma

Asthma which requires treatment with high-dose ICS as outlined in Table 1 (adults and children) and a second controller for the previous year, or systemic corticosteroids for 50% of the previous year to prevent it from becoming “uncontrolled”, or which remains “uncontrolled” despite this therapy is defined as severe asthma.

Uncontrolled asthma is defined as at least one of the following:

1) Poor symptom control: as per Canadian Thoracic Society asthma control criteria or other standardized questionnaires: Asthma Control Questionnaire (ACQ) consistently > 1.5, Asthma Controlled Test (ACT) < 20, or child Asthma Controlled Test (cACT) < 20.
2) Frequent severe exacerbations: two or more courses of systemic corticosteroids (≥3 days each) in the previous year.
3) Serious exacerbations: at least one hospitalization, intensive care unit (ICU) stay or mechanical ventilation in the previous year.
4) Airflow limitation: after appropriate bronchodilator withhold forced expiratory volume in one second (FEV₁) <80% of personal best (or < the lower limit of normal (LLN), in the face of reduced FEV₁/forced vital capacity (FVC) defined as less than the LLN).

*Not meeting the criteria described in Table 2."
CTS Position Statement

- “A diagnosis of asthma using **objective measures**, the assessment of **domestic and work environment** along with the **verification of adherence to medication and co-morbidities** is key”

- Non-adherence to treatment = major challenge

- Another issue: incorrect use of inhalers

- Consider co-morbidities during initial assessment esp if:
  - Lack of response to ICS with another controller
  - Usual management of the most frequent reasons for poor control
A Practical Approach to Severe Asthma in Children

Emily E. Barsky¹,², Lauren M. Giancola¹, Sachin N. Baxi²,³, and Jonathan M. Gaffin¹,²

¹Division of Respiratory Diseases and ²Division of Allergy and Immunology, Department of Medicine, Boston Children’s Hospital, Boston, Massachusetts; and ³Harvard Medical School, Boston, Massachusetts

- Step 1: Diagnosis Confirmation
- Step 2: Evaluation and Optimization of Difficult to Treat Asthma
- Step 3: Assessment and Management of Severe Asthma Refractory to Traditional Therapy
- Step 4: Efficacy Assessment
Step 1: Diagnosis Confirmation

- 30% of referrals for severe asthma = misdiagnosed
- History, physical and spirometry
- Atypical presentations
- Consider: lung volumes, sweat test, bronchoscopy, CT
Step 2/3: Evaluation and Optimization of Difficult to Treat Asthma & Asthma refractory to traditional therapy

- Adherence, technique and optimizing delivery
- Use of technology
- Environment
- Management (refractory disease)
  - Steroids (oral)
  - Anticholinergics
  - Biologics
Emerging therapeutic considerations:

- Increased inhaled steroids during exacerbations
- Theophylline
- Additional biologics
- Antimicrobial drugs
- Immunosuppressants
- Allergen immunotherapy
- Surgical Intervention
Sweat Chloride

THE INDETERMINATE LEVEL IS THERE A LINK TO DTT ASTHMA?
### FALSE-POSITIVE

- Adrenal insufficiency
- Eczema
- Ectodermal dysplasia
- Nephrogenic diabetes insipidus
- Hypothyroidism
- Fucosidosis
- Mucopolysaccharidosis
- Dehydration
- Malnutrition

### FALSE-NEGATIVE

- Edema
- Poor technique/inadequate sweat collection
### Sweat Chloride Ranges

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Intermediate</th>
<th>Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &gt;60mmol/L</td>
<td>• 30-59mmol/L</td>
<td>• &lt;30mmol/L</td>
</tr>
</tbody>
</table>

+ NBS
+ Clinical history
+ Family history

Consider extended CFTR genetic analysis

CF is unlikely

---


Guidelines (CF Foundation)
Diagnostic Definitions

**CF**
- clinical presentation and CFTR dysfunction

**CFMS/CFSPID**
- Infants with positive NBS AND EITHER:
  - Sweat chloride <30 + 2 CFTR mutations
  - Indeterminate sweat chloride and 1 or 0 mutations

**CFTR-related**
- Symptoms that related to CFTR dysfunction but not full CF criteria

---

Guidelines (CF Foundation)
Indeterminate Sweat – Thoughts?

- Sweat chloride = good discriminating test but **normal adults can have values as high as 50 and 60**
- Sweat chloride values increase with age higher with normal adolescents and adults
- Does lowering the borderline cut-off for sweat chloride impact the diagnostic process?

1. Hodson et al. (1983). Sweat test used to diagnose CF in adults, BMJ
2. Leigh, M (2004). Diagnosis of CF despite normal or borderline sweat chloride. Paeds Resp Reviews
CFTR mutation analysis and borderline sweat chloride concentration

The mean value in the DNA negative subjects was significantly lower than in those with at least one CFTR mutation.

Subjects with a sweat value <39 mEq/l are unlikely to carry variant/mutation in the CFTR gene and genetic analysis may be performed only in subjects with chloride values >39 mEq/l.
Elevated Sweat Chloride Levels and Asthma

IS THERE AN ASSOCIATION?
Sweat Chloride Levels and Asthma

- Research suggests there could be a link between higher sweat chloride levels in asthmatics compared to healthy controls
  - Generally, these values are still under 40mmol/L
- Others have not found a difference between healthy controls and those with asthma
- A history of several asthma exacerbations and recurrent pneumonia should prompt consideration of a sweat test

Mandal et Kabra, Sweat Chloride Levels in Asthma Indian J Pediatr (February 2015) 82(2):103–104
Sweat Chloride Levels and Asthma

- Related to Ventolin use (selective beta-2 agonist)
  - Hypokalemia → increased chloride levels
- Asthmatics are more likely to receive steroids
  - Associated with sodium retention which directly correlates with increased level of chloride in sweat.

~10% of individuals with asthma have severe disease

Heterozygosity for CF has been associated with increased airway reactivity → airflow obstruction

Heterozygosity for CFTR gene mutations → ?predisposition to the development of asthma

Possible association between CFTR mutations and asthma severity
Some studies suggest an association between being heterozygous for a CFTR gene mutation and forms of pulmonary diseases, including asthma and ABPA.

- Others have suggested CFTR mutations may be protective against bronchial asthma (or no relationship at all)

- ATS/ERS and CTS recommend screening for CF in cases of severe asthma

The risk of asthma was significantly higher in people heterozygous for CF than in non-carriers.

Is asthma a CFTR-related disorder?
- reduction of CFTR function vs interaction
CF-like symptoms with inconclusive CFTR genotype and sweat chloride concentrations → non-allergic asthma

Childhood history of obstructive lung disease and recurrent airway infections.

The sweat chloride: **normal to borderline range**

A CFTR-related disorder may manifest in childhood with obstructive lung disease that is classified as an intrinsic or non-allergic asthma.
Case: Additional Results

- common CF genetic mutations - pending
- cough swab: negative
- fecal elastase: indeterminate range
- liver enzymes, glucose and iron studies - normal
- repeat immunoglobulins and vaccine titres - normal
- nasal brush biopsy – pending
- Vitamin A level: low
Take Home Points

- If the "asthma" doesn’t fit like asthma, trust your gut
- Consider the broad differential for asthma and if suspected, include additional investigations such as lung volumes, sweat test, bronch with BAL, HRCT, PCD
- Children with asthma have been found to have higher sweat chloride levels than their "non-asthma" peers, although this is still usually in the normal range
- Sweat chloride levels tend to increase with age, so normal adolescents and adults may have a sweat chloride over 50-60
References

- CF Foundation
- Barsky et al. Practical approach to severe asthma in children (2017). Focused Review
- Hodson et al. (1983). Sweat test used to diagnose CF in adults, BMJ
- Leigh, M (2004). Diagnosis of CF despite normal or borderline sweat chloride. Paeds Resp Reviews
- Mandal et Kabra, Sweat Chloride Levels in Asthma Indian J Pediatr (February 2015) 82(2):103–104
References

- Riolo. Severe asthma and CF: Overlapping phenotypes
- Schulz et al. Non-allergic asthma as a CFTR related disorder
- Noone et al. ‘CFTR-opathies’: disease phenotypes associated with cystic fibrosis transmembrane regulator gene mutations