Asthma Update 2018

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Disclosures

I have no professional or personal financial conflicts of interest to disclose.

Objectives

- Discuss important safety considerations in asthma care
- Describe asthma-COPD overlap
- Understand role of phenotyping in the care of the patient with severe asthma

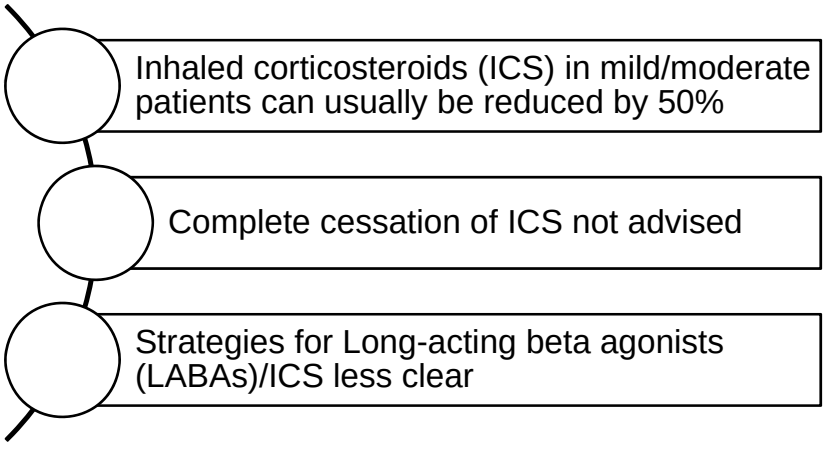
Case

- 28 year old male presents for asthma follow-up
- Denies nocturnal symptoms
- Uses albuterol 2-3 times/month prior to basketball
- No exacerbations in the past year
- Current medications
  - Beclomethasone 80 µg 2 puffs twice daily
  - Nasal fluticasone
  - As needed albuterol

Case cont.

- **Spirometry**
  - **FEV1/FVC 0.82**
  - **FEV1 82% predicted**
- **Exam unremarkable**
- **What changes would you make in his asthma therapy?**

Stepping down therapy



Hagen et al. Allergy 2014;69:510.
Rank et al. JACI 2013; 131:724.
Ahmad et al. Cochrane Database Syst Rev 2015:Cd011306.

Safety considerations for long-acting beta-agonists

December 20, 2017

Food and Drug Administration (FDA) removed the *Boxed Warning* from the drug labels of products containing both ICS and LABAs

https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm; accessed 3/7/2018

Salmeterol Multi-center Asthma Research Trial (SMART)

- Large placebo-controlled US study of salmeterol vs. placebo added to usual asthma therapy
- Increase in asthma-related deaths
  - Salmeterol group: 13 deaths in 13,176
  - Placebo: 3 deaths in 13,179
  - RR 4.4 [CI 1.2-15.3]

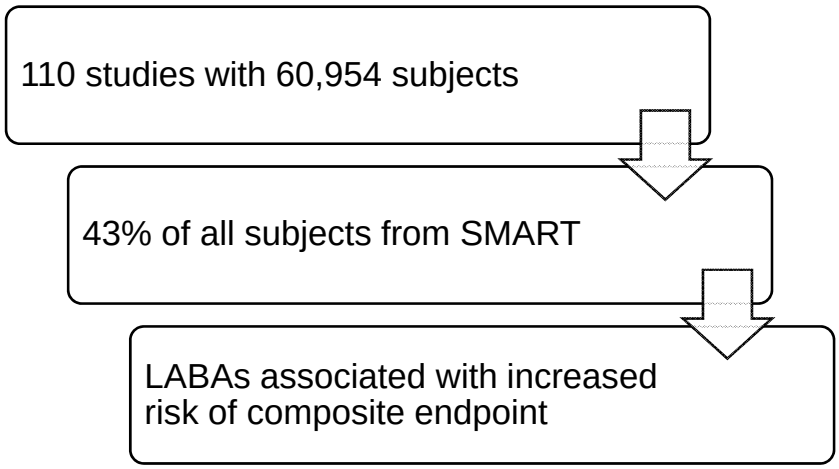
Nelson et al. Chest 2006;129:15-26.

Salmeterol Multi-center Asthma Research Trial (SMART)

- **Increase in asthma related deaths in African Americans**
- **"Usual asthma care" often deviated from guideline**
- **47% of participants prescribed ICS**
  - **49% Caucasians**
  - **39% African Americans**

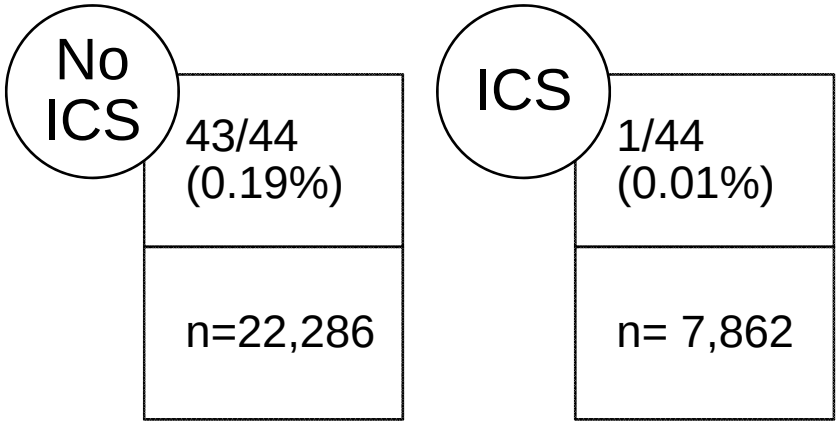
Nelson et al. Chest 2006;129:15-26.

FDA meta-analysis 2008



Levenson, M. United States Food & Drug Administration, November 12, 2008.

Deaths & intubations



Levenson, M. United States Food & Drug Administration, November 12, 2008.

FDA mandated safety studies

- **5 Randomized controlled trials**
  - **Four ages > 12 (n = 11,700 in each)**
  - **One ages 4- 11 (n = 6,200)**
- **2011-2017**
- **26 weeks duration**
- **Outcomes**
  - **Hospitalizations, intubation, death**

FDA mandated safety studies

- ICS + LABA vs. ICS—Adult
  - Fluticasone/salmeterol
  - Budesonide/formoterol
  - Mometasone/formoterol
  - Formoterol + fluticasone [individual devices]—not completed
- ICS + LABA vs ICS—Pediatric
  - Fluticasone/salmeterol

Meta-analysis of serious asthma-related events in patients ≥ 12 years

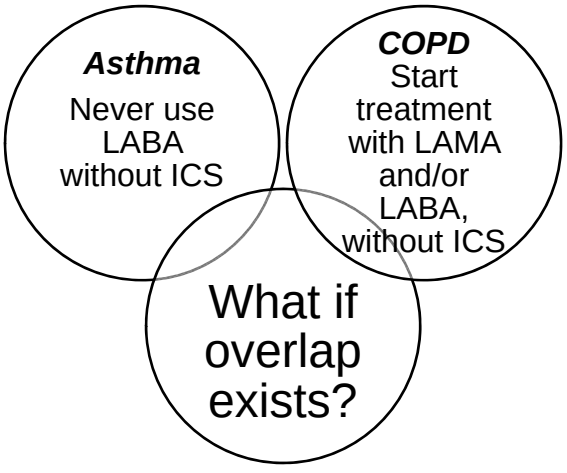
	ICS/LABA (n=17,537)	ICS (n=17,552)	ICS/LABA vs ICS Hazard Ratio (95% CI)
Serious asthma related events	116	105	1.10 (0.85, 1.44)
Asthma-related deaths	2	0	
Asthma-related intubations	1	2	
Asthma-related hospitalizations	115	105	

https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm; accessed 3/7/2018

Where does this leave us?

- **When used in combination with ICS, LABAs do not significantly increase the risk of serious asthma-related events**
- ***Boxed Warning*** **remains for single agent LABAs**

How should this influence treatment decisions?



2018 Global Initiative for Asthma; http://ginasthma.org/; accessed 3/7/2018.

Asthma-COPD overlap

Distinguishing asthma from COPD can be difficult

Not a single disease i.e. not a *syndrome*

Identified in clinical practice by features shared with both asthma and COPD

2018 Global Initiative for Asthma; http://ginasthma.org/; accessed 3/7/2018.

Clinical features assist with diagnosis

Asthma

- Before 20 years
- Variable symptoms
- Clear triggers
- Variable obstruction
- History of atopy
- No progression; variation in symptoms

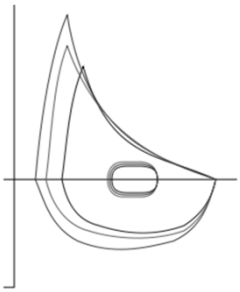
COPD

- After 40 years
- Persistent symptoms
- Cough & sputum unrelated to triggers
- Persistent obstruction
- Heavy tobacco exposure
- Slowly progressive

Role of spirometry

Reversible airflow limitation

FEV1/FVC < 0.7 post-BD



Initiate therapy based on predominant symptoms

Asthma
- Start ICS
- Add LABA and/or LAMA
- Do not use LABA without ICS

COPD
- Start LAMA and/or LABA alone or in combination
- Do not use ICS without LABA and/or LAMA

Balanced
- Initiate therapy targeted at asthma
- Start ICS and add LABA and/or LAMA as needed

2018 Global Initiative for Asthma; http://ginasthma.org/; accessed 3/7/2018.

Cases

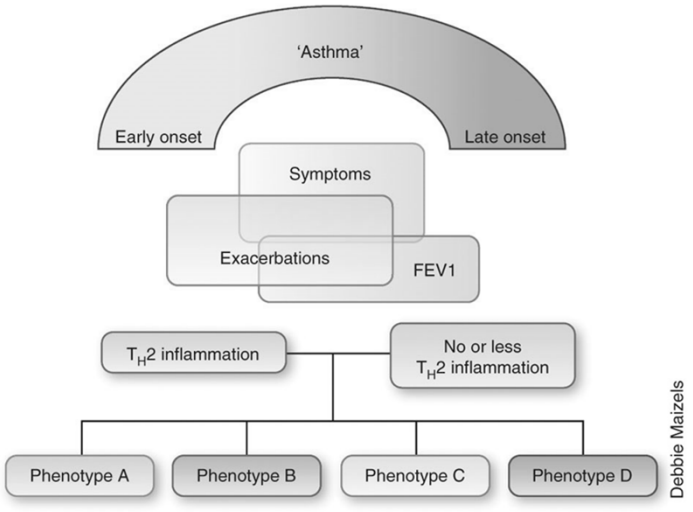
Patient 1

- 56 year old male
- Adult onset asthma
- No family history of allergies
- Nasal polyps, eosinophilic sinus disease s/p multiple surgeries
- FEV1/FVC 0.46, FEV1 51%
- Poorly controlled on LABA/ICS with multiple exacerbations

Patient 2

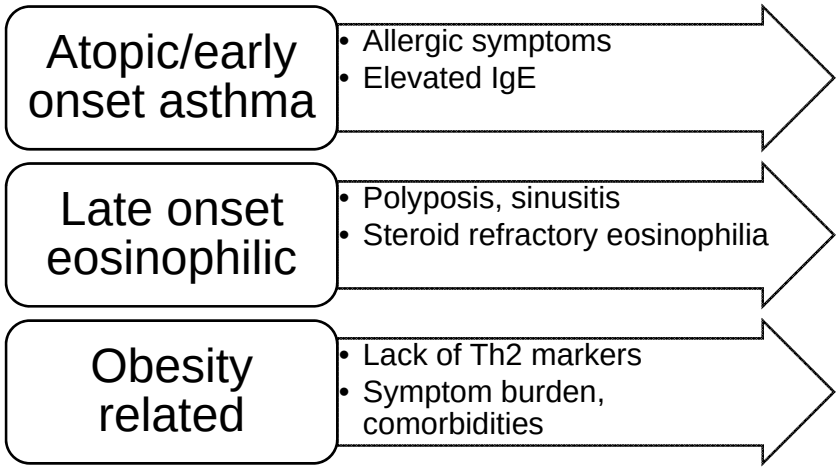
- 48 year old woman
- Adult onset asthma
- BMI 34 mg/kg^2
- No family history of allergies
- GERD, OSA
- FEV1/FVC 0.73, FEV1 74%
- Poorly controlled on LABA/ICS with multiple exacerbations

The asthma umbrella



Wenzel SE. Nature Medicine 2012; 18(5): 716-725.

Real world phenotypes

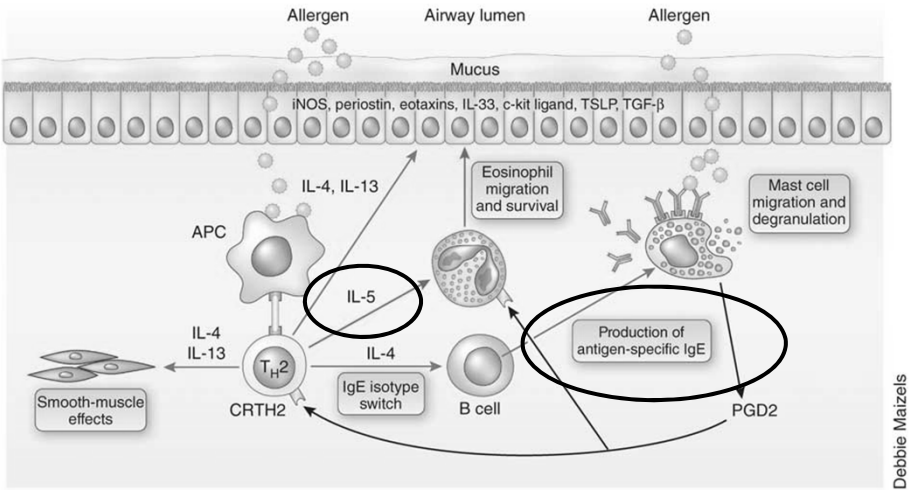


Role of tiotropium in asthma: a systematic review with meta-analysis

- **Tiotropium as add-on to ICS**
  - **Improved PEF, FEV1**
  - **Reduced exacerbations, improved control**
- **Tiotropium + ICS vs LABA + ICS**
  - **Not inferior to salmeterol**
- **Tiotropium as add-on to LABA + ICS**
  - **Improved PEF, FEV1**
  - **Reduced exacerbations, improved control**

Rodrigo et al. CHEST 2015; 147:388.

TH_2 mediated processes in airways



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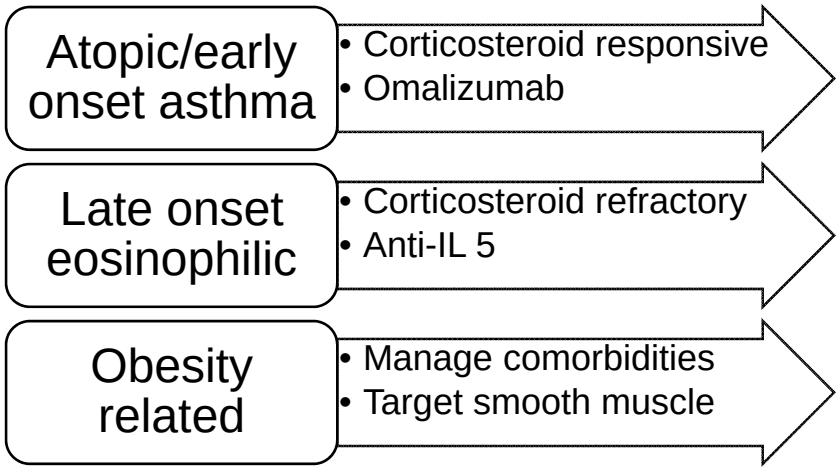
Biologics in the treatment of asthma

Agent	Target	Action
Omalizumab	Anti-IgE	Prevents binding to receptor on mast cells and basophils
Meoplizumab	Anti-IL-5	Prevents binding to eosinophils
Reslizumab	Anti-IL-5	Prevents binding to eosinophils
Benralizumab	Anti-IL-5	Binds to IL-5 receptor to cause eosinophil apoptosis

Real world phenotypes & treatment options



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Interim summary

- **Consider risk/benefit ratio of discontinuing ICS in well controlled asthma**
- **Awareness of asthma-COPD overlap can facilitate treatment decisions**
- **Evolving asthma phenotyping will guide asthma care in more severe disease**

What's New in Pediatric Asthma

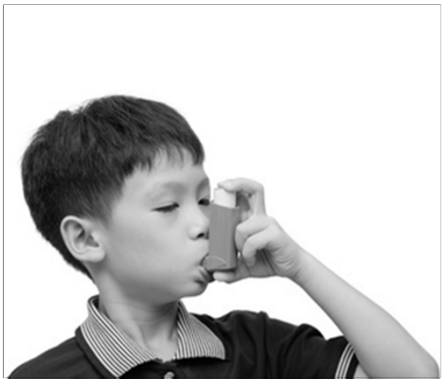
Elizabeth D. Allen, MD
Pediatric Pulmonary Medicine
Nationwide Children's Hospital

Update in Pediatric Asthma

- What's new for chronic management
- What's new for acute care
- What's new for those pesky "wheezing" infant/toddlers

Case: 7 year old with poor asthma control

- You started Jacob on low dose ICS therapy last month
- He's still having problems
- Mom (and pharmacy fill rates) vouch for good compliance



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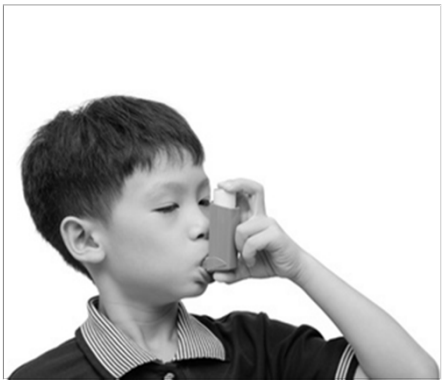

What are your options?

Poor Control in a Compliant Patient – Check Inhaler Technique

- Standard: Spacer Use with HFA Inhaler

- New: Consider Breath Actuated Inhaler?
- Now with multiple drug options
- Pitfalls?
- Age limits?

Poor Control in Compliant Patient – Check Exposures

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Poor Control in Compliant Patient – Increasing ICS Step-Up Option

Poor Control in Compliant Patient – Increasing ICS Step-Up Option

- **Potential for height growth suppression by ICS therapy remains a uniquely pediatric concern**
  - **Cochrane Review 2014 regarding ICS growth effects in prepubescent children**
  - **Small but significant decrease in growth velocity noted in those using low-medium dosed versus low-dose ICS**

Poor Control in Compliant Patient – Adding Montelukast Option

Poor Control in Compliant Patient – Adding Montelukast Option

- **Montelukast and neuropsychiatric reactions**
  - **European Respiratory Journal 2017 published study of children starting montelukast in "real-life"**
  - **>10% stopped medication due to issues such as irritability, aggressiveness or sleep disturbances**

Poor Control in Compliant Patient – Medication Step-Up Options

- ICS/LABA products no longer carry Black Box warning
  - ICS/LABA products are approved down to age 6 years
  - Especially effective for reducing day to day symptoms
- Add-on LAMA therapy for asthma control now FDA approved for ages 6 years and older
  - Consider in those failing ICS/LABA or intolerant to LABA
  - Appears to work despite underlying asthma "type"

Poor Control in Compliant Patient – Medication Step-Up Options

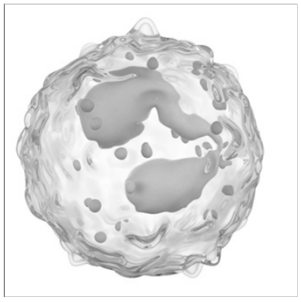
- Allergen immunotherapy
  - Option when asthma is inadequately controlled despite standard medications and allergen avoidance
  - Single aeroallergen therapy to mite or pollen most helpful – efficacy of allergen mixes less clear
- Biologic therapies
  - Omiluzimab (age 6 and older)
  - Mepolizumab (age 12 and older)
  - Benralizumab (age 12 and older)

These therapies warrant specialist referrals

What about Fraction of Exhaled Nitrous Oxide (FeNo) Testing?

- Asthma diagnosis and medication adjustment traditionally hinges on symptoms/signs & spirometry
- FeNo (inflammatory marker elevated in allergic asthma) increasingly used as additional tool

So What is FeNO?



- Nitric oxide is produced by the airway epithelium of bronchial wall
- Production increases in eosinophilic airway inflammation, and can be measured in exhaled air
- In children, levels defined as:
  - Low <20 ppb
  - Intermediate 20-35 ppb
  - High >35 ppb
- Elevation suggests eosinophilic airway disease, and predicts likely corticosteroid responsiveness

What role does FeNO have in Pediatric asthma management?

- Issues:
  - Eosinophilic inflammation is seen in most, but not all childhood asthma
  - Levels can also be elevated in atopy & allergic rhinitis
  - Levels are suppressed by ICS therapy

What role does FeNO have in Pediatric asthma management?

- For Diagnosis:
  - Potentially helpful if asthma diagnosis is unclear following initial history, exam & spirometry testing
  - Need to remember low values may be due to non-eosinophilic disease
- For Management:
  - Elevation suggests ICS non-compliance (or oncoming flare)
  - Medication adjustment per FeNO in addition to usual strategies has limited impact on outcomes

Case: 9 year old with acute exacerbation

- 2 days into a cold, Robert woke with cough and wheeze that didn't respond to albuterol
- His family brought him to the Emergency Department

What's new in acute asthma management?

Same key drugs – different delivery options

Short Acting Beta-agonists (SABA)

- Can be delivered by nebulizer OR MDI/Spacer
- 2.5 mg albuterol by nebulizer typically matched to 4-8 puffs via valved holding chamber

Systemic Corticosteroids

- Timing is important – goal < 60 minutes from presentation
- Dexamethasone (1 or 2 doses, 0-3-0.6 mg/kg) may be as effective as prednisone (3-5 days, 1-2 mg/kg/day)

Additional Therapies

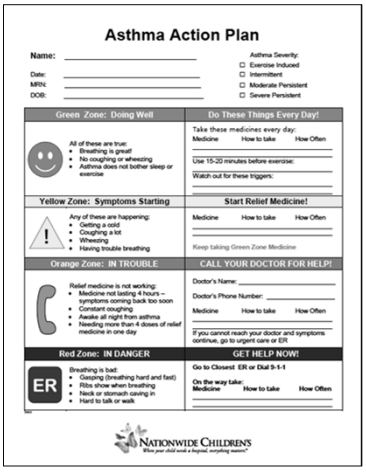
- Oxygen (of course)
- Ipratropium
  - Helpful when added to albuterol *in the ED*
  - Dosing 250-500 µg by nebulizer OR 2-3 puffs of 17µg/puff inhaler up to 3 doses
- Magnesium (IV)
  - Considered if suboptimal response to albuterol/ipratropium plus systemic steroids
  - Smooth muscle relaxant, reduces hospitalization rates

For those with persistent severe air exchange difficulty

- Heliox
- BiPAP
- Continuous albuterol
- Rarely
  - IV beta-agonists (discouraged due to side effects)
  - IV theophylline (discouraged due to side effects)
  - Intubation (High risk for complications)
  - Extra-Corporeal Membrane Oxygenation (ECMO)

Role of Follow-up

- Confirm improvement
- Critically, adjust plan to help avoid repeat event
  - Review adherence
  - Start or adjust controller therapy*
  - Construct an asthma action plan
  - Make referrals if needed



*** Increasingly, controller refills or changes may occur in ED setting as well**

Case: 12 month old with persistent cough and noisy breathing

- Otherwise healthy child developed bronchiolitis at age 7 months, and has remained symptomatic ever since
- Chronic cough, "wheeze" with rattling quality
- Albuterol helps somewhat. Steroids "don't do anything."

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What's new for noisy infant/toddlers?

The Special Challenges of Wheezing Infants and Toddlers

- Recurrently wheezing infants and toddlers is challenging to manage
- Even in infants with proven airway reactivity, eosinophilic inflammation typically isn't present
- Family history, personal signs of atopy increase likelihood of asthma by school age

When to worry it's NOT just episodic airway inflammation/"Asthma"

- Symptoms present from birth
- Poor growth
- Stridor component
- Failure to respond to asthma medications
- Recurrent severe episodes
- Symptoms rarely resolve

Potential Causes of Unremitting Symptoms

- **Large airway narrowing or obstruction**
  - **Vascular rings**
  - **Tracheal stenosis or malacia**
  - **Foreign body**
  - **Mediastinal masses**
- **Small airway infection or secretions**
  - **Aspiration**
  - **Cystic fibrosis**
  - **Primary Ciliary Dyskinesia**
  - ***Protracted Bacterial Bronchitis***

Protracted (Persistent) Bacterial Bronchitis: Presentation

- **Increasing recognized cause of persistent (over 4 weeks) wet/productive sounding cough**
- **In toddlers/older infants may also present with parent reported "wheeze" with wet/rattling quality**
- **May be semi-responsive to albuterol, and mistaken for "asthma"**
- **PBB patients otherwise appear well with normal growth & development, lack of systemic symptoms**

Protracted Bacterial Bronchitis: Test Results

- CXR:
  - Normal to nonspecific airway changes
- Bronchoscopy/BAL findings*:
  - Frequently, some degree of airway malacia
  - Marked increase in neutrophils
  - Bacteria: H. influenza, S. pneumoniae, M. catarrhalis (Often in combination)

Protracted Bacterial Bronchitis: Diagnosis and Management

- Diagnosis can be based on symptoms – and response to trial of antibiotic therapy
- If symptoms improve within 2 weeks, complete 4-6 weeks of continuous therapy
- Bronchoscopy & BAL are not necessary if presentation and therapy response are straightforward
- Consider specialist referral if no response to initial antibiotics, or rapid recurrence off therapy

- **New agents to complement ICS therapy**
- **New delivery device/inhaler options**
- **Evolving use of FeNO in outpatient management**
- **Oral steroid options for acute management**
- **New differential possibility – protracted bacterial bronchitis – for young patients with chronic ”rattling” and cough**