BREATHE EASY:

EVALUATION AND TREATMENT OF Difficult-to-Control and Severe Pediatric Asthma

Alfin G. Vicencio, MD

Please complete the preassessment located in your handout ***before the program begins***.

Faculty and Disclosures

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Photo Acknowledgement

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Learning Objectives

Upon completion of this activity, learners should be better able to:

- Differentiate between mild to moderate asthma and severe asthma
- Recognize the characteristics of difficult-to-control severe asthma vs treatment-refractory severe asthma and when to refer to a specialist
- Individualize maintenance strategies for patients with pediatric asthma based on current guidelines and disease severity

Asthma Epidemiology

- Most common chronic lung disease of childhood
- Approximately 6,000,000 children in the US[1]
- 2013: children with asthma ages 5 to 17 missed 13.8 million days of school per year (2.6 days/child)[2]
- 2016: half of all children with asthma had at least one asthma attack[2]

1. CDC Asthma Fast Stats. https://www.cdc.gov/nchs/fastats/asthma.htm. Accessed March 27, 2018.
2. Zahran HS, et al. *MMWR Morb Mortal Wkly Rep*. 2018;67(5):149-155 .

Imagine That…

- You are 8 years old
- You feel a weight on your chest every day – like someone wrapped it tight with duct tape
- Every breath takes an effort
- Your lungs are filled with rubber-cement–like mucus that is nearly impossible to clear out of your airways
- You wake up every night, gasping for air
- Your parents worry that you might not live to become an adult

Mild and Moderate Asthma

Option A (GINA): Retrospective assessment of level of treatment required to control symptoms and exacerbations

- Mild asthma
  - Well-controlled with PRN albuterol or low-dose inhaled corticosteroid
- Moderate asthma
  - Well-controlled with low-dose ICS/LABA

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.
GINA. Global Strategy for Asthma Management and Prevention (2018 Update). http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed June 1, 2018.

Mild and Moderate Asthma (cont'd)

Option B (NHLBI): Classification of severity at initial visit. Subsequent visits focus on control.

- Mild asthma
  - Impairments:
    - Symptoms: > 2 days/week (not daily)
    - Albuterol: > 2 days/week (not daily)
    - Nighttime awakenings: 3-4 time/month
    - Lung function: FEV1% predicted > 80%
  - Risk:
    - ≥ 2 exacerbations/year requiring oral steroids
- Moderate asthma
  - Impairments:
    - Symptoms: daily
    - Albuterol: daily
    - Nighttime awakenings: > 1 occurrence/week but not nightly
    - Lung function: FEV1% predicted 60%-80%
  - Risk:
    - ≥ 2 exacerbations/year requiring oral steroids

FEV1, forced expiratory volume in one second.
National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3). *J Allergy Clin Immunol*. 2007;120(5 Suppl):S94-S138.

What Is Severe Asthma?

- GINA classification
  - Steps 4-5 (high-dose ICS + LABA or leukotriene modifier) to achieve control
- Systemic corticosteroids ≥ 50% of previous year to achieve control
- Remains uncontrolled despite aggressive therapy

Chung KF, et al. *Eur Respir J*. 2014;43(2):343-373.

Uncontrolled Asthma in Children ≥ 6 Years

- Poor symptom control
  - ACQ score > 1.5
  - ACT score < 20
- Frequent, severe exacerbations
  - 2 or more burst systemic steroids in the previous year
  - Serious exacerbations requiring:
    - At least one hospitalization or PICU stay
    - Mechanical ventilation in the previous year
- Airflow limitation
  - FEV1 < 80% after bronchodilator

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; PICU, pediatric intensive care unit.
Chung KF, et al. *Eur Respir J*. 2014;43(2):343-373.

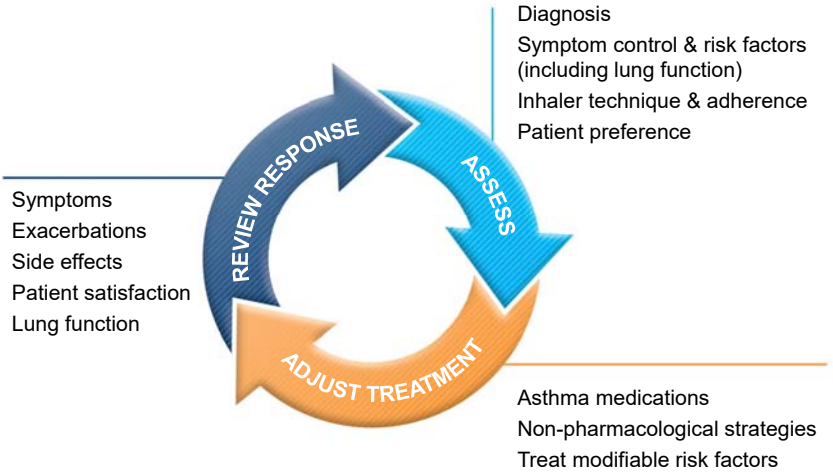
Key Questions

- Is the patient taking the medication?
- Is the patient using the medication correctly?
- Is the patient on the correct medication?
- Have all triggers been identified and removed?
- Is it really asthma?

Current Asthma Guidelines

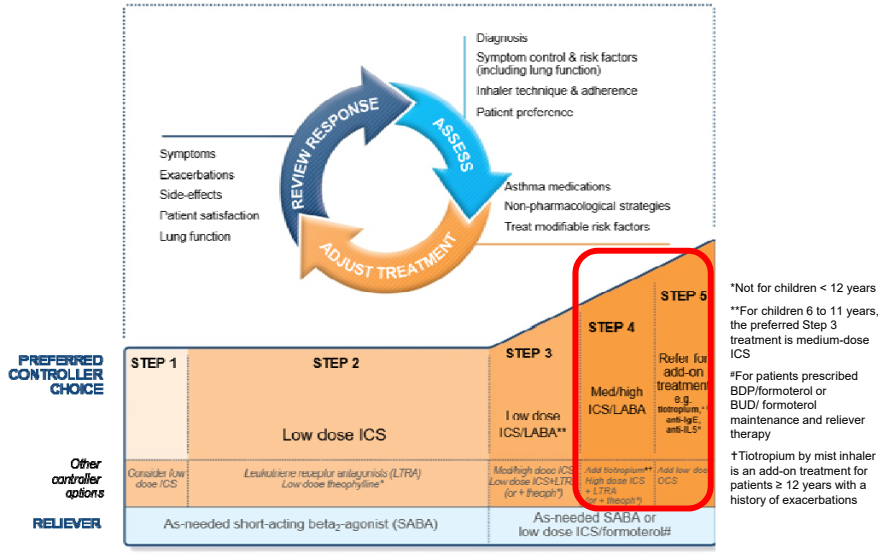
- National Heart, Lung, and Blood Institute (NHLBI)
  - Updated August 2007
  - Medication update 2011
- GINA
  - Updated 2017

The Control-Based Asthma Management Cycle



GINA. Global Strategy for Asthma Management and Prevention (2018 Update). http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed June 1, 2018.

Stepwise Management of Asthma



*Not for children < 12 years

**For children 6 to 11 years, the preferred Step 3 treatment is medium-dose ICS

#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

†Tiotropium by mist inhaler is an add-on treatment for patients ≥ 12 years with a history of exacerbations

GINA. Global Strategy for Asthma Management and Prevention (2018 Update). http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed June 1, 2018.

GINA Assessment of Asthma Control

A. Symptom control

In the past 4 weeks, has the patient had:

- Daytime asthma symptoms more than twice a week? Yes☐ No☐
- Any night waking due to asthma? Yes☐ No☐
- Reliever needed for symptoms* more than twice a week? Yes☐ No☐
- Any activity limitation due to asthma? Yes☐ No☐

Level of asthma symptom control

Well-controlled	Partly controlled	Uncontrolled
None of these	1-2 of these	3-4 of these

B. Risk factors for poor asthma outcomes

- Assess risk factors at diagnosis and periodically
- Measure FEV_1 at start of treatment, after 3 to 6 months of treatment to record the patient's personal best, then periodically for ongoing risk assessment

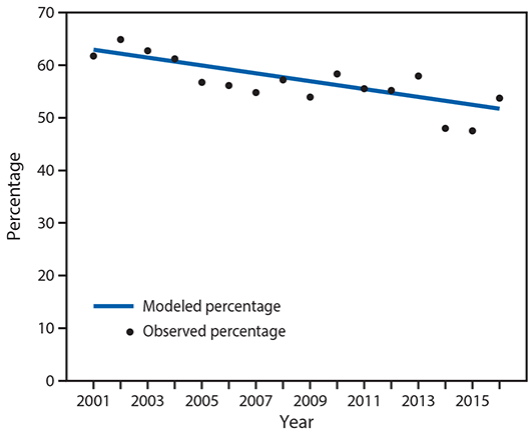
ASSESS PATIENT'S RISKS FOR:

- Exacerbations
- Fixed airflow limitation
- Medication side-effects

GINA. Global Strategy for Asthma Management and Prevention (2018 Update). http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed June 1, 2018.

Decline in Asthma Attacks, 2001-2016

National Health Interview Survey for children aged 0 to 17 years



Chung KF, et al. *Eur Respir J.* 2014;43(2):343-373.

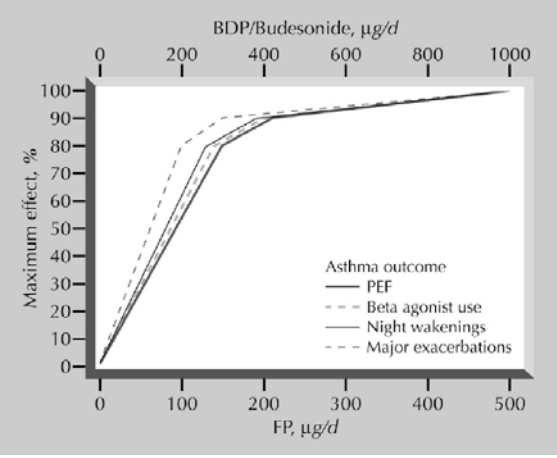
Improved Outcomes in Severe Asthma

	1993-1997* (n=65)	2003-2007* (n=164)
Chronic oral steroids	51%	28%
FEV1%	76%	84%
Albuterol inhalations/week	71	33
Leukotriene antagonist	0	76%
Combination LABA/ 2nd generation inhaled steroid	0	66%

**Comparison of two pediatric cohorts evaluated at National Jewish Health.*

Reddy MB, et al. *Allergy Asthma Proc*. 2014;35(2):119-125.

Diminishing Returns With High-Dose Inhaled Steroid



Masoli M, et al. *Curr Allergy Asthma Rep*. 2004;4(2):144-148.

Combined ICS + LABA

- Improved lung function
- Less albuterol use compared with same ICS dose
- Compared with higher ICS dose
  - 1.2 cm more in growth over one year
  - No difference in control of asthma symptoms
- No difference in number of exacerbations requiring oral steroids
- No increase in serious side effects

Chauhan BF, et al. *Cochrane Database Syst Rev*. 2015;(11):CD007949.

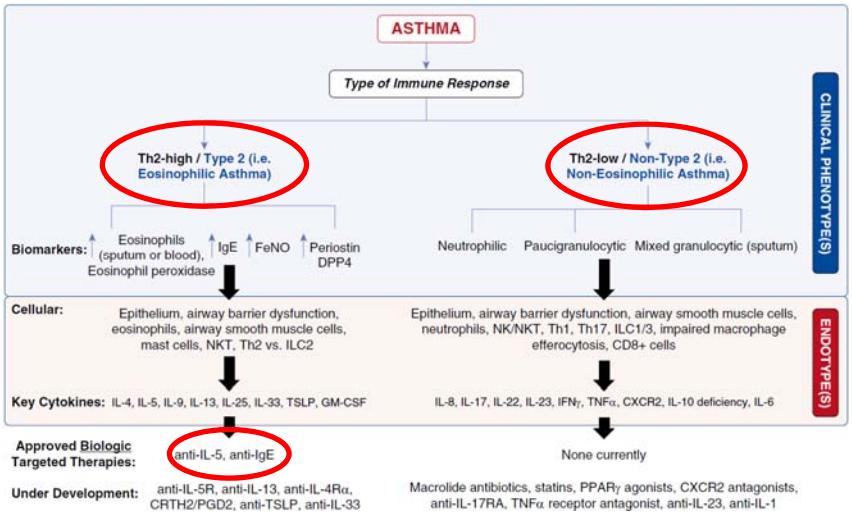
Anticholinergics

	Indication	Mechanism	Age	Comments
Tiotropium	Moderate to severe disease	Binds to muscarinic receptors Bronchodilator effect Long-acting (once-daily dosing)	≥ 6 years	Increased FEV1 in children with moderate asthma No significant change in FEV1 in 12- to 17-year-old children with severe asthma on ICS + at least one additional controller

Potential side effects: paradoxical bronchospasm, pharyngitis, sinusitis, bronchitis, and headache

Raissy HH, et al. *Paediatr Drugs*. 2017;19(6):533-538.

Precision Medicine



Carr TF, et al. *Am J Respir Crit Care Med*. 2018;197(1):22-37.

Biologic Targeting IgE

	Indication	Mechanism	Age	Comments
Omalizumab	Moderate to severe disease + Sensitization to perennial allergen	Binds to free IgE F_c receptor	≥ 6 years	**Decreases:** • Exacerbations • Symptoms • ICS dose • Seasonal asthma **Increases:** • FEV1 • QOL

Potential side effects: injection-site reactions, respiratory infections

F_c, fragment crystallizable; IgE, immunoglobulin E; QOL, quality of life.
Busse WW, et al. *N Engl J Med*. 2011;364(11):1005-1015.

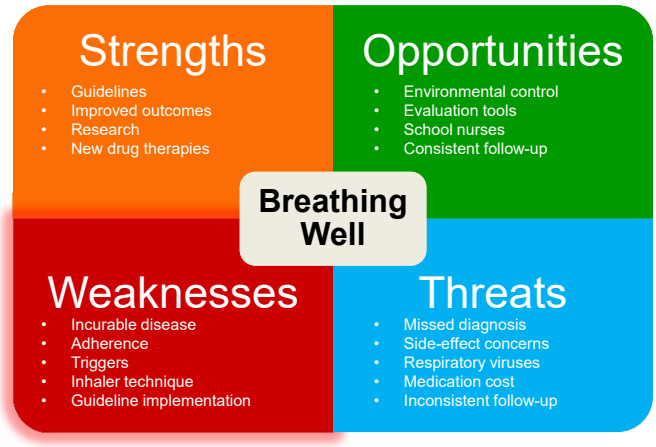
Biologic Targeting Eosinophils

	Indication	Mechanism	Age	Comments
Benralizumab[1]	Severe eosinophilic asthma	Anti-IL-5 • Binds to IL-5Rα receptor and $F_{c\gamma}$ receptor NK cells	≥ 12 years	**Decreases:** • Exacerbations • Symptoms • OCS dose **Increases:** • FEV1
Mepolizumab[2,3]	Severe eosinophilic asthma	Anti-IL-5 • Blocks IL-5 binding to eosinophils	≥ 12 years	**Decreases:** • Exacerbations • Symptoms • OCS dose **Increases:** • FEV1

Potential side effects: common cold symptoms, headaches, fever, upper abdominal pain, pharyngitis, ear discomfort, intestinal infection causing abdominal pain, nausea and vomiting, and nosebleeds

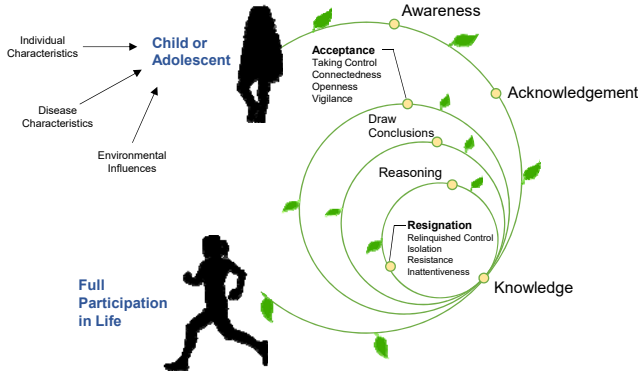
IL, interleukin; OCS, oral corticosteroid.

1. FitzGerald JM, et al. *Lancet*. 2016;388:2128-2141.
2. Bel EH, et al. *N Engl J Med*. 2014;371:1189-1197.
3. Ortega HG, et al. *N Engl J Med*. 2014;371(13):1198-1207.



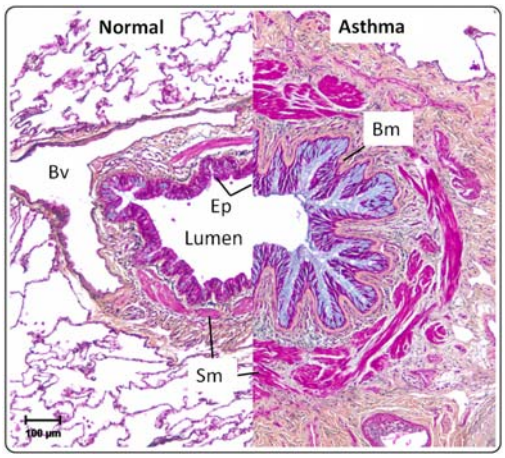
No Curative Treatments

Parents and children move through gradual process from knowledge to acceptance at own pace



Kinter E. *J Asthma*. 1997;34(6):547-561.

Chronic Airway Remodeling



BM, basement membrane; BV, blood vessel; EP, epithelium; SM, smooth muscle.

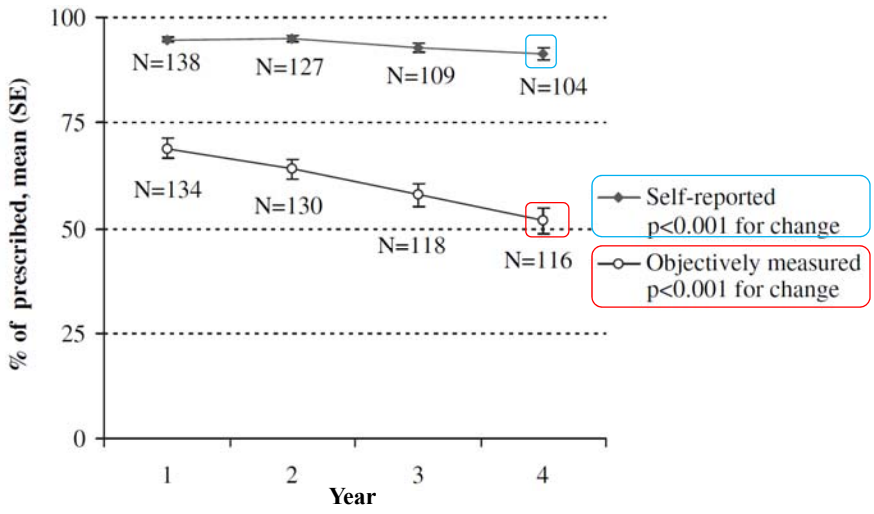
Wadsworth SJ, et al. IL-13, Asthma and Glycosylation in Airway Epithelial Repair. *InTech*. Published 2012. https://www.intechopen.com/books/carbohydrates-comprehensive-studies-on-glycobiology-and-glycotechnology/il-13-asthma-and-glycosylation-in-airway-epithelial-repair. Accessed July 31, 2018.

Adherence

- 4-year study – Childhood Asthma Management Program (CAMP)
- Measurements
  - Subjective: diary cards
  - Objective: dose counter inhaler

Krishnan JA, et al. *J Allergy Clin Immunol*. 2012;129(1):112-118.

Objective Adherence Much Lower Than Self-Reported Adherence



Krishnan JA, et al. *J Allergy Clin Immunol*. 2012;129(1):112-118.

Inhaler Technique

- Prevalence of correct technique only 31%[1]
- Appropriate age for inhaler devices[2]

Age	Device	Notes
< 3 years	MDI: spacer + mask	Nebulizer if intolerant MDI
≥ 3 years	MDI: spacer + mask	Consider mouthpiece
≥ 5-6 years	Dry powder	Evaluate patient for readiness

Clinical Pearl: Include reminder in written asthma plan to bring medications and spacer to each visit

MDI, metered-dose inhaler.

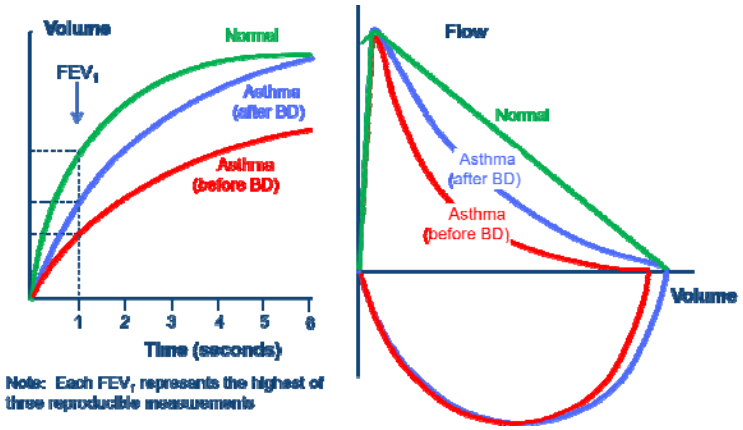
1. Sanchis J, et al. *Chest*. 2016;150(2):394-406.
2. Laube BL, et al. *Eur Respir J*. 2011;37(6):1308-1331.

Evaluation Tools

- History
  - Important tool
  - Reflects patient's experience of disease and impact on QOL
- Spirometry
  - Supports diagnosis
  - Important in assessing response to changes in therapy and exacerbations
- Positive test for airway reactivity:
  - Post-bronchodilator FEV1% change > 12% or 200 mL
  - > 8% likely significant in children

Pellegrino R, et al. *Eur Respir J*. 2005;26(5):948-968.

Typical Spirometric Tracings



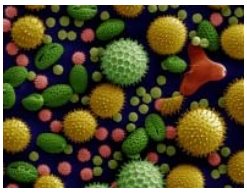
*GINA. Global Strategy for Asthma Management and Prevention (2018 Update). http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed June 1, 2018.

Asthma Control Questionnaires

	Age	Recall Window	Number of Questions	Comments
TRACK	0-5 years	1-12 months	5	Includes number of oral steroid courses
C-ACT	4-11 years	4 weeks	4 by child 3 by parent	Children report lower control
CASI	> 6 years	2 weeks	5	*Includes:* FEV1% Medication level Number of exacerbations
ACQ	≥ 12 years	1 week	6 + FEV1%	
ACT	≥ 12 years	4 weeks	5	

C-ACT, Childhood Asthma Control Test; CASI, Composite Asthma Severity Index; TRACK, Test for Respiratory and Asthma Control in Kids.

HEPA Air Filters Might Reduce Some Triggers



Sublett JL, et al. *J Allergy Clin Immunol*. 2010;125(1):32-38.

Indoor Triggers

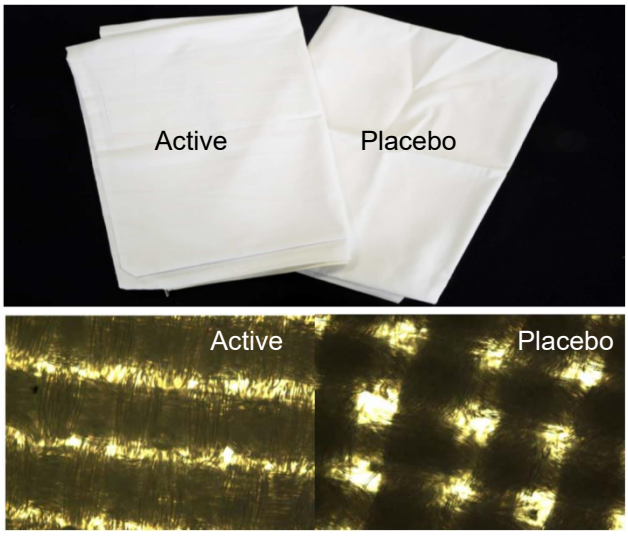


Preventing Severe Asthma Exacerbations

- Kids screened for dust mite sensitivity after asthma attacks in ER
- 284 sensitized kids randomized
- Outcome: Asthma attacks over 12 months
  - ER visits, hospitalization, or oral steroids

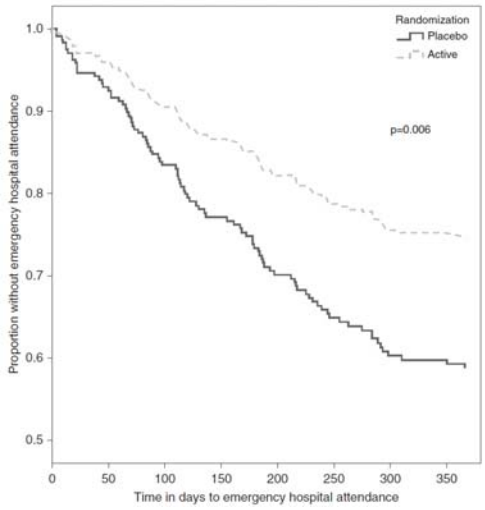
ER, emergency room
Murray CS, et al. *Am J Respir Crit Care Med*. 2017;196(2):150-158..

Dust Mite-Proof Bedding



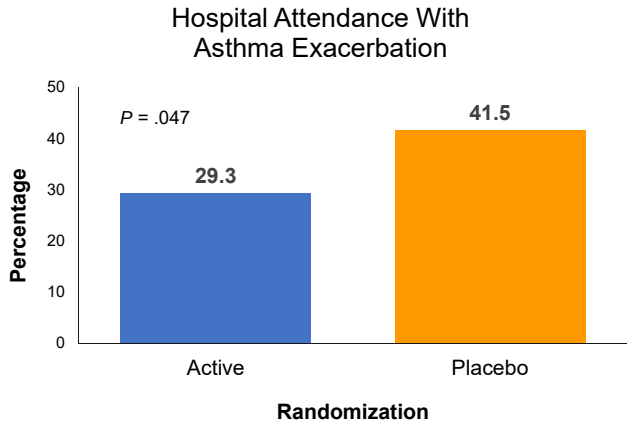
Murray CS, et al. *Am J Respir Crit Care Med*. 2017;196(2):150-158.

45% Lower Risk of ER Visits



Murray CS, et al. *Am J Respir Crit Care Med*. 2017;196(2):150-158.

Fewer Severe Exacerbations



Murray CS, et al. *Am J Respir Crit Care Med*. 2017;196(2):150-158.

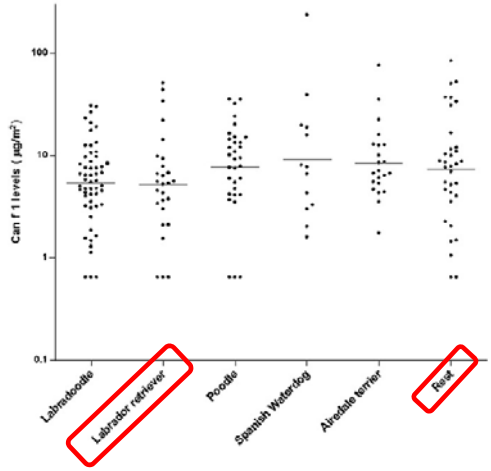
Decreasing Pet Allergens

- Takes 20 to 24 weeks to reduce cat allergen after removing the animal from home
- Washing pets not effective in decreasing allergens
  - Cats – washing benefits not sustained beyond 1 week
  - Dogs – benefits only sustained if dog washed twice a week

Wright LS, et al. *Curr Allergy Asthma Rep*. 2014;14(3):419.

Hypoallergenic Dogs

No difference in airborne antigen between hypoallergenic and regular breeds



Vredegoor DW, et al. *J Allergy Clin Immunol*. 2012;130(4):904-909.

Humidifiers

- South Korea: cluster of severe lung disease due to humidifier disinfectant
- No evidence for benefit in asthma
- Can promote mold growth

Kim KW. *Am J Respir Crit Care Med*. 2014;189(1):48-56.

School-Based Administration of ICSs

- 48 urban students on Medicaid (grades K-8)
- Randomized controlled trial
- 60-day treatment period
- Intervention group
  - 92% received morning ICS at school
  - Decrease in asthma symptoms
  - More sleep
- Despite improvements in intervention group, parents in control group reported same number of ICS treatments, suggesting parental over-reporting

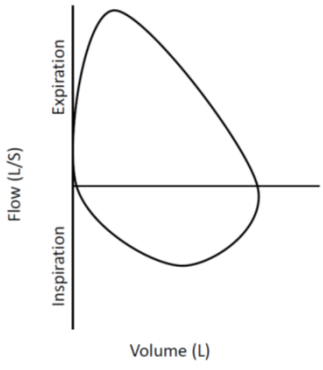
Harrington CB, et al. *J Asthma*. 2018;55(2):145-151.

Red Flags for Missed Diagnosis

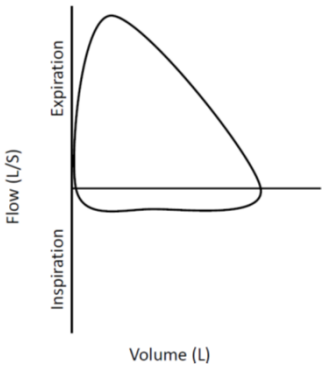
- No response to standard asthma therapy
- Chronic productive cough
- Poor weight gain and growth
- Recurrent pneumonia
- Chronic sinusitis
- Sudden onset

Expert Opinion.

Normal and Abnormal Flow-Volume Loop



Normal flow-volume loop

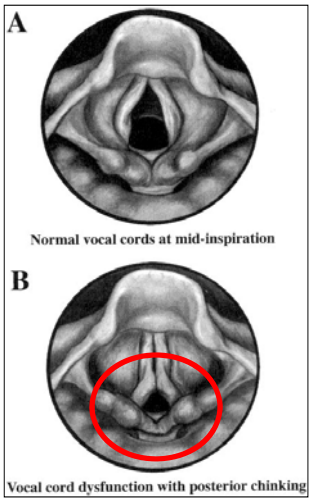


Inspiratory flow-volume loop limitation as seen in vocal cord dysfunction

Link HW. *Pediatr Rev*. 2014;35(7):287-298.

Vocal Cord Dysfunction

- Poor response to standard asthma therapy
- Acute onset and resolution
- Symptoms disappear during sleep
- Patients often point to throat when asked to locate tightness

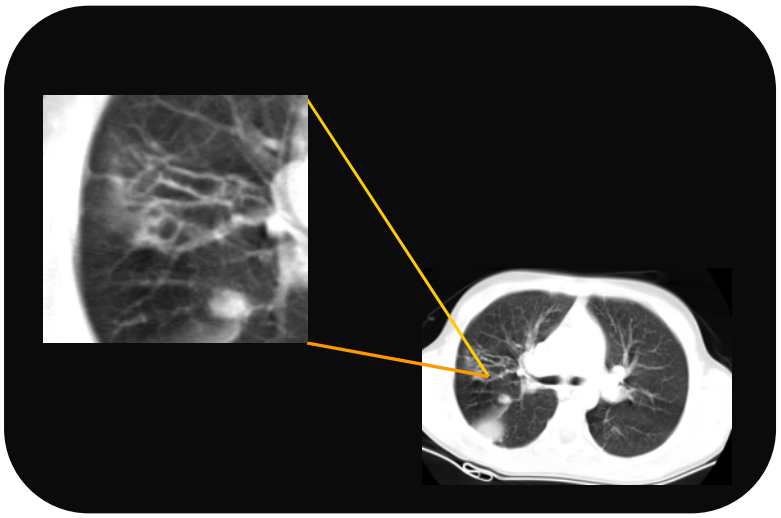


Perker JJ, et al. *J Occup Environ Med*. 1998;40(2):136-143.

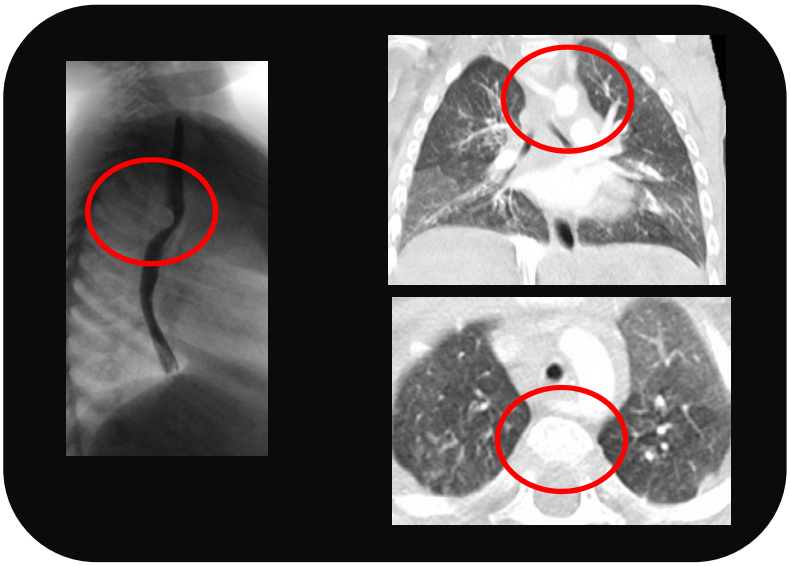
Hilar Adenopathy From *Mycobacterium Avium*

Ciliary Dyskinesia

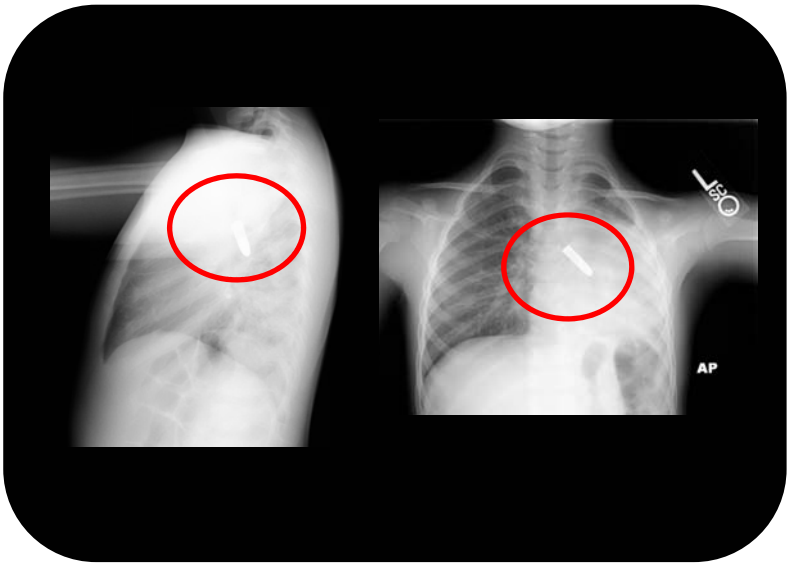
Bronchiectasis



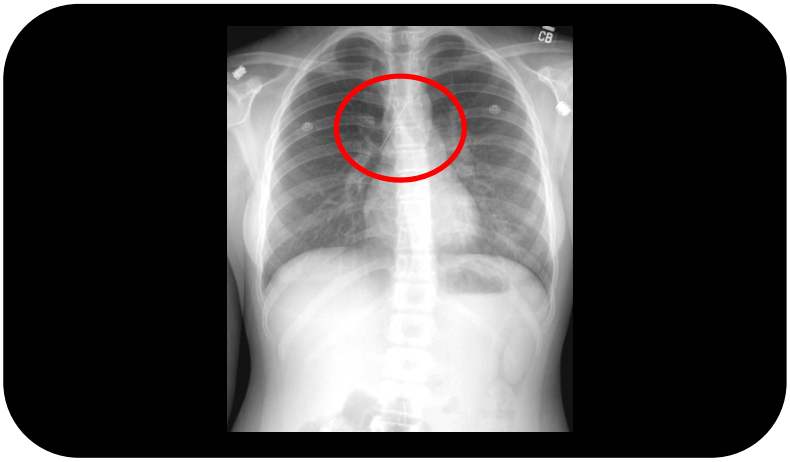
Aberrant Right Subclavian Artery



Foreign Body



Foreign Body



Side Effects of ICSs

- Local
  - Oral candidiasis
    - Higher risk with high-dose ICSs
    - Preventable with mouth rinsing immediately after dose
- Systemic
  - Growth suppression
    - Effect on final adult height likely negligible (1 cm to 0.7% total height)
  - Adrenal suppression
    - Children on moderate- to high-dose ICSs at highest risk

Clinical Pearl: Asthma control should be periodically evaluated to determine if dose can be reduced

Hossny E, et al. *World Allergy Organ J.* 2016;9:26.

Clinical Pearl: Exacerbations

- No data supporting increase of inhaled steroids to treat asthma exacerbations
- Increasing inhaled steroids may be associated with diminished linear growth

Jackson DJ, et al. *N Engl J Med*. 2018;378(10):891-901.
Kew KM, et al. *Cochrane Database Syst Rev*. 2016;(6):CD007524.

Medication Costs

- Asthma medications are expensive
  - Combination ICS/LABA: $400-$600/month
- Inconsistent drug coverage between insurance plans
- High drug copays

Rosenthal E. "The Soaring Cost of a Simple Breath." *New York Times.* October 12, 2013.

Reducing Inconsistent Follow-Up

- Partner with parents
- Pay attention to parents' concerns
- Explore barriers to consistent follow-up
  - Health literacy (12% of adults are proficient)[1]
  - Transportation
  - Taking time off work
  - Not understanding why follow-up needed
  - Benefits and goals of therapy not clear
- Population management
  - Patient registry to proactively manage patients

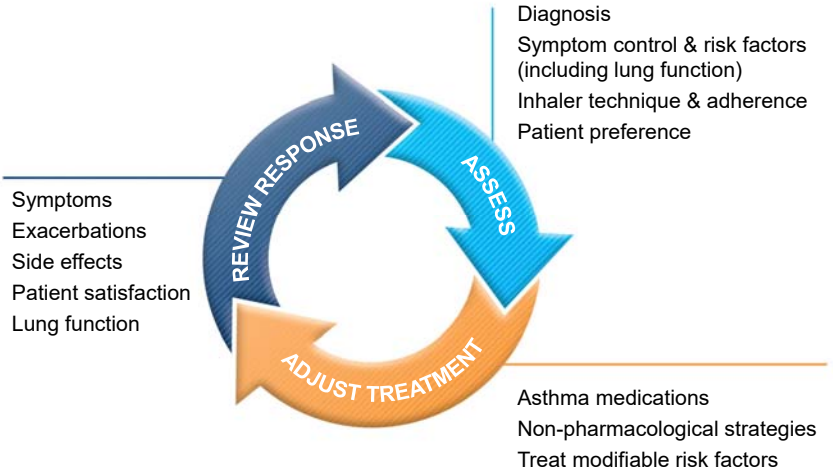
Expert Opinion.

1. U.S. Dept of Education. NCES 2006-483. https://nces.ed.gov/pubs2006/2006483.pdf. Accessed March 27, 2018.

When to Refer to a Pulmonary Specialist

- Need for ≥ step 4 level therapy
- Not responding to standard asthma therapy
- Atypical presentation and diagnosis not clear
- High-risk patients
  - History of hospital admissions
- Need for parent and patient education

The Control-Based Asthma Management Cycle



GINA. Global Strategy for Asthma Management and Prevention (2018 Update). http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention. Accessed June 1, 2018.

Take-Home Messages

- Proactively manage difficult-to-control asthma with recurring assessments, treatment adjustments, and review of response
- If patients don't respond to therapies, systematically explore for barriers, triggers, adherence, and consider different diagnosis
- Newer therapeutics are targeted to specific asthma phenotypes
- Acknowledge patient's difficulty accepting the chronic illness

Questions?

Thank You

Please complete the
postassessment and evaluation
located in your meeting handout.