ALL THAT WHEEZES IS NOT ASTHMA: MIMICS OF ASTHMA

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- I have no conflict of interest related to this presentation
- I will not discuss off-label drug use

Objectives

- Identify the mimics of asthma
- Identify how the mimics of asthma differ from asthma
- Describe the asthma COPD overlap syndrome (ACOS)
- Describe the suggested diagnostic algorithm for ACOS

Differential Diagnoses in Infants and Children

- Upper airway diseases
  - Allergic rhinitis and sinusitis
- Large airway obstruction
  - Foreign body aspiration
  - VCD
  - Vascular rings or laryngeal webs
  - Croup or tracheal stenosis
  - Lymphadenopathy/ tumor

Differential Diagnoses in Infants and Children

- Small airway obstruction
  - Bronchioloitis
  - Cystic fibrosis
  - BPD
  - Heart disease
- Others
  - Recurrent cough not due to asthma
  - Dysphagia or GERD

Differential Diagnoses in Adults

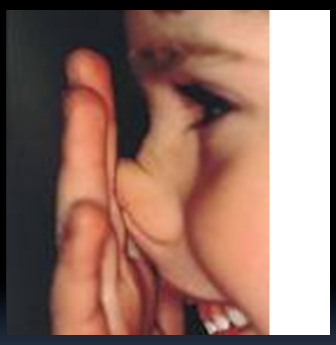
- COPD
- CHF
- Pulmonary embolism
- Airway tumors
- Pulmonary infiltrates with eosinophilia
- Drug-induced cough
- VCD
- ACOS

Allergic Rhinitis/Sinusitis

	Asthma	Allergic Rhinitis/ Sinusitis
Wheezing	X	X
Coughing	X	
Shortness of breath	X	
Chest tightness	X	
Fever		X
Sneezing		X
Itching nose and eyes		X
Rhinorrhea and nasal congestion		X
Nasal flaring/retractions	X	
Allergic shiners	X	X
Eosinophils	X	X
hypoxemia	X	

Allergic Rhinitis/Sinusitis

Allergic shiners

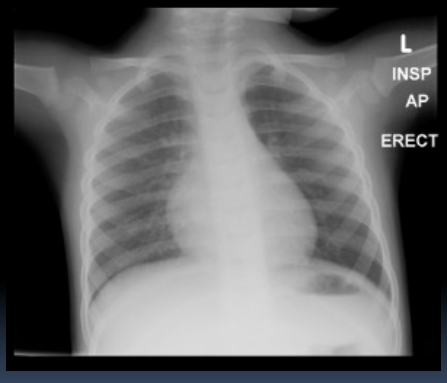


Allergic salute

Foreign body aspiration

	Asthma exacerbation	Foreign body aspiration
Age group	Any	Peaks at 1-3 years
Radiograph	Normal/hyperinflation	Identifiable object/ ipsilateral hyperinflation
		Unilateral
Wheeze	Bilateral	X
Stridor		Frequently
Asymptomatic	Rarely	Sudden
Onset of symptoms	Gradual with exposure	X
Difficulty vocalizing		X
Laryngospasm		X
Relieved by Heimlich or bronchoscopy		

Radiograph in FBA



Radiograph of 2-year-old with suspected peanut aspiration

- Radiopaque object will be seen
- I&E air trapping
- Distal atelectasis

The sensitivity of chest x-ray performed in the emergency department for foreign body aspiration was found to be only 22.6% with false-negative rates of 5% to 30% in children.

So a **NORMAL chest Xray DOES NOT rule out an airway foreign body**.

http://www.emergucate.com/2012/06/26/the-daily-educational-pearl-cxr-findings-in-suspected-inhaled-foreign-bodies/

Vocal cord dysfunction

- Abnormal adduction of vocal cords during the respiratory cycle (especially inspiration)
- Subset of patients have no organic base
  - Organic causes include GERD, neurologically based dystonia
- FVL shows flattened inspiratory loop
- Frequently mimics persistent asthma
- Lack of response to bronchodilator therapy
- Normal spirometry immediately after an attack
- Spirometric evidence of upper airway obstruction
- Negative bronchial provocation test

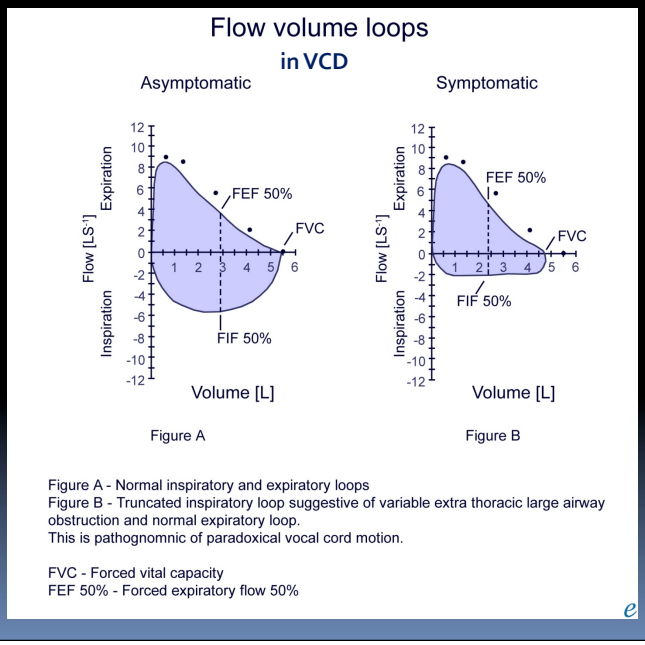


Figure A - Normal inspiratory and expiratory loops
Figure B - Truncated inspiratory loop suggestive of variable extra thoracic large airway obstruction and normal expiratory loop.
This is pathognomnic of paradoxical vocal cord motion.

FVC - Forced vital capacity
FEF 50% - Forced expiratory flow 50%

VCD

- Paradoxical vocal cord motion can be confirmed with laryngoscopy during an episode
- Episodic dyspnea and wheezing in response to irritant triggers
- Often refractory to treatment
- Absence of hypoxemia
- Exact cause is unknown. Thought to be related to mediation of vagus nerve that alters laryngeal tone and decreases threshold for vocal cord spasm
- Treatment includes exercises to help patient relax vocal cords during episodes
- Associated with GERD and postnasal drip

Figure 2. Normal and abnormal laryngoscopy results. Adapted with permission from Perkner JJ, Fennelly KP, Balkissoon R, et al. Irritant-associated vocal cord dysfunction. J Occup Environ Med. 1998;40:136-143.

Normal
Mid-Inspiratory Glottis

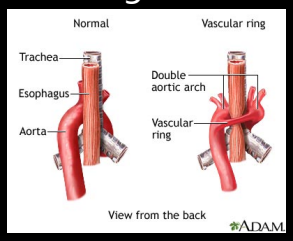
Closed
Mid-Inspiratory
Vocal Cord Adduction

Mid-Inspiratory
Vocal Cord Adduction
with Posterior Chinking

Mid-Inspiratory Prolapse
of Periglottic Structures
into Glottic Airway

Vascular rings

- Rare congenital malformations of the great vessels surrounding the airways



Laryngeal webs

- Failure of complete recanalization of the larynx in the embryo
- Abnormal cry and stridor

Croup

	Asthma	Croup
Wheezing	X	
Cough	X	
Shortness of breath	X	
Chest tightness	X	
Stridor		X
Hoarseness		X
Barking cough		X
Age	All ages	< 2 yoa
High fever		X
Tripod posturing		X
Drooling		X
Relieved with racemic epinephrine		X

Lymphadenopathy/ Tumor

- Swollen lymph nodes in the mediastinum
- Tumor of the upper airway
- Stridor
- Flattened flow-volume loop
- Bacterial infection from otitis media or pharyngitis
- Congenital or acute

Bronchiolitis

	Asthma	Bronchiolitis
Age	All	Most often in infants < 6 mos.
Viral etiology		X (RSV)
Allergic etiology	X	
Cough	X	X
Wheeze	X	X
Tachypnea	X	X

TABLE 1

A CLINICAL INDEX TO DEFINE ASTHMA RISK*

Major Criteria	Minor Criteria
1. Parental MD asthma†	1. MD allergic rhinitis§
2. MD eczema‡	2. Wheezing apart from colds
	3. Eosinophilia (≥ 4%)

* Loose index for the prediction of asthma: Early wheezer plus at least one of two major criteria or two of three minor criteria. Stringent index for the predication of asthma: Early frequent wheezer plus at least one of two major criteria or two of three minor criteria.

† History of a physician diagnosis of asthma.

‡ Physician diagnosis of atopic dermatitis as reported in questionnaires at ages 2 or 3.

§ Physician diagnosis of allergic rhinitis as reported in questionnaires at ages 2 or 3.

Castro-Rodriguez, et.al. AJRCCM 2000;162:1403-1406.

Cystic Fibrosis

	Asthma	Cystic Fibrosis
Wheeze	X	X
Cough	X	X
Sputum production	X	X
Recurrent infections		X
Persistent abnormal CXR		X
Clubbing		X
Positive sweat test		X
Failure to thrive		X
GI symptoms		X

Other Causes of Recurrent Cough

- Recurrent cough at age 2 clears in 50% by age 6
  - Often leads to overdiagnosis of asthma
  - Cough with positive methacholine challenge and reversibility: cough variant asthma
  - These atypical cough presentations often respond to asthma therapy
- Increased cough receptor sensitivity
  - Not asthma

deBenedictis et.al. Pediatr Allergy Immunol 2004;15:386-393.

Gastroesophageal Reflux

	Asthma	GERD
Wheeze	X	X
Resolved by histamine-2 blockers		X
Retrosternal burning		X
Frequent burping		X

Mimics in Adults: COPD

	Asthma	COPD
Age	Often younger	Often older
Smoking		X
Allergies	X	
Inflammatory	X	X
Reversible obstruction	Fully-partially	Partially-non
Radiograph	Normal between exacerbations	Abnormal
Hyperinflation	With exacerbation	Increases with severity
ABGs	Hypoxemia with exacerbation	Resting hypercapnia and hypoxemia increasing with severity
DL_{CO}	Normal to increased	Decreases with severity
Obstructive spirometry	In exacerbation	Chronic

Heart Failure (untreated)

	Asthma	Heart Failure
Dyspnea	X	X
Orthopnea		X
PND		X
Wheezing	X	X "cardiac asthma"
Crackles		X
Cardiomegaly		X
Hepatomegaly & ascites		X
Peripheral edema		X
Elevated BNP		X

Pulmonary embolism

- Nontransient, acute, refractory hypoxemia
- Clear or minimally changed CXR
- Tachypnea
- Clinical history of immobility and DVT

Tumors

- Stridor
- Fixed obstructive defect on PFT

Pulmonary Infiltration with Eosinophilia

- Chest pain
- Dry cough
- Fever
- General ill feeling
- Rapid respiratory rate
- Rash
- Shortness of breath
- Wheezing

Drug-Induced Cough

- Induced by angiotensin-converting enzyme inhibitor (-pril), vasodilators
- Dry cough
- Tickling or scratching sensation
- Incidence of 5-35% in patients on ACE inhibitor
- More common in women, nonsmokers and persons of Chinese origin
- Hours-weeks in onset from first dose

Dicpinigaitis. Chest 2006;129(1);169s-173s.

Asthma-COPD Overlap Syndrome (ACOS)

- Why is this needed?
  - Frequent presentation with chronic respiratory symptoms; ICD-10 may be J44.9
  - Often in older adults
  - Features of asthma and COPD
  - Chronic airflow obstruction, not completely reversible
  - Frequent exacerbations
  - Low QOL
  - Rapid decline in lung function
  - High mortality
  - Disproportionate use of health resources (2-6x)
  - Often excluded from clinical trials

ACOS

- Reported prevalence of 15-55%
- Criteria vary
- Description from GINA
  - ACOS is characterized by persistent airflow limitation with features associated with asthma and COPD; identified by the features it shares with asthma and COPD
  - Cannot be specifically defined until mechanisms and phenotypes are identified

GINA 2015:75.

ACOS

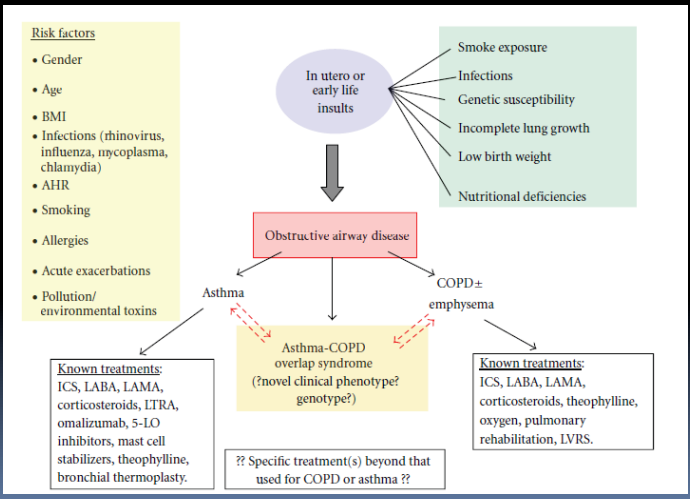
- "syndrome in which older adults with a significant smoking history have asthmatic features to their COPD"
- Share risk factors
- Is this a coexistence of asthma and COPD?
- Is there a common pathogenic mechanism?

ACOS phenotypes

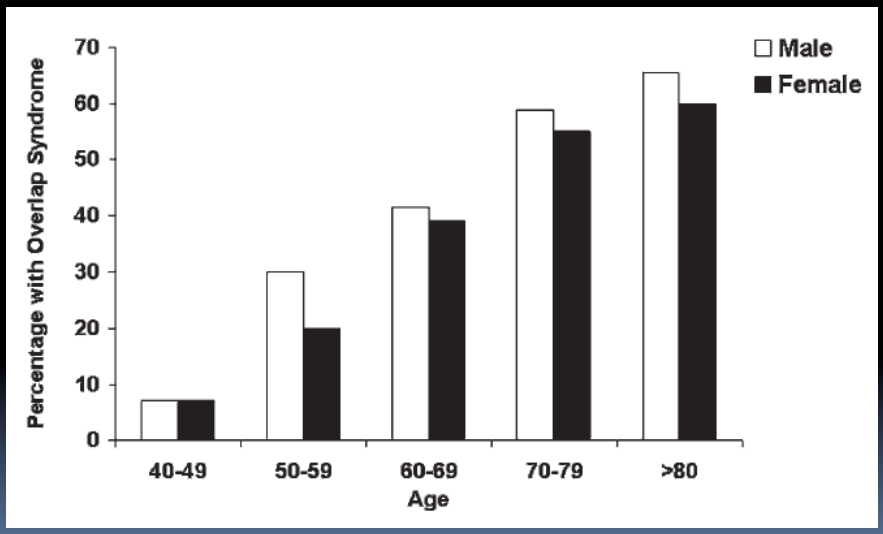
- Allergic disease consistent with asthma with variable airflow obstruction or AHR that is incompletely reversible (with or without emphysema or reduced DL_{CO})
- COPD with emphysema accompanied by reversible or partially reversible airflow obstruction (with or without an allergic syndrome or reduced DL_{CO})

Zeki AA et. al. J Allergy 2011;article ID 861926

ACOS Risks and Therapy



ACOS Prevalence Increases with Age



Gibson & Simpson. Thorax 2009;64:728-735.

Features of ACOS

Age of Onset	Usually ≥ 40 years; may have had symptoms in childhood or early adulthood
Pattern of respiratory symptoms	Symptoms including DOE are persistent; may be prominent
Lung function	Not fully reversible, often with current or historical variability
Lung function between symptoms	Persistent airflow limitation
Past or family history	Dr. diagnosed asthma, allergies, family hx of asthma and/or noxious exposures
Time course	Sx partly but significantly reduced by tx; usual progression; high tx needs
Radiograph	Similar to COPD
Exacerbations	More common than in COPD, reduced by tx; comorbidities may contribute
Airway inflammation	Eosinophils or neutrophils in sputum

Stepwise Approach to Diagnosis of Patients with Respiratory Symptoms

- Step 1. Does the patient have chronic airways disease?
  - History
    - Cough, sputum, dyspnea, diagnosis, tobacco, exposures
  - Physical examination
    - Hyperinflation, adventitious breath sounds
  - Radiography
    - Hyperinflation, retrosternal air, flat diaphragms, hyperlucency
  - Screening questionnaires
    - ACT, CAT, something new?

Stepwise Approach to Diagnosis of Patients with Respiratory Symptoms

- Step 2: Syndromic diagnosis of asthma, COPD and ACOS in adults
  - Assemble the features that favor a diagnosis of asthma or COPD
  - Compare the number of features in favor of a diagnosis of asthma or COPD
  - Consider the level of certainty around the diagnosis, or whether there are features of both, suggesting a diagnosis of ACOS

STEP 2 — **SYNDROMIC DIAGNOSIS IN ADULTS**
(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

Features: if present suggest -	ASTHMA	COPD
Age of onset	❑ Before age 20 years	❑ After age 40 years
Pattern of symptoms	❑ Variation over minutes, hours or days ❑ Worse during the night or early morning ❑ Triggered by exercise, emotions including laughter, dust or exposure to allergens	❑ Persistent despite treatment ❑ Good and bad days but always daily symptoms and exertional dyspnea ❑ Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	❑ Record of variable airflow limitation (spirometry or peak flow)	❑ Record of persistent airflow limitation (FEV_1/FVC < 0.7 post-BD)
Lung function between symptoms	❑ Normal	❑ Abnormal
Past history or family history	❑ Previous doctor diagnosis of asthma ❑ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	❑ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ❑ Heavy exposure to risk factor: tobacco smoke, biomass fuels
Time course	❑ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year ❑ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	❑ Symptoms slowly worsening over time (progressive course over years) ❑ Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	❑ Normal	❑ Severe hyperinflation

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Asthma	Could be ACOS	Possibly COPD	COPD

GINA 2015, Box 5-4 © Global Initiative for Asthma

Step 3 - Spirometry

Spirometric variable	Asthma	COPD	ACOS
Normal FEV_1/FVC pre- or post-BD	Compatible with asthma	Not compatible with diagnosis (GOLD)	Not compatible unless other evidence of chronic airflow limitation
Post-BD FEV_1/FVC <0.7	Indicates airflow limitation; may improve	Required for diagnosis by GOLD criteria	Usual in ACOS
FEV_1 ≥80% predicted	Compatible with asthma (good control, or interval between symptoms)	Compatible with GOLD category A or B if post-BD FEV_1/FVC <0.7	Compatible with mild ACOS
FEV_1<80% predicted	Compatible with asthma. A risk factor for exacerbations	Indicates severity of airflow limitation and risk of exacerbations and mortality	Indicates severity of airflow limitation and risk of exacerbations and mortality
Post-BD increase in FEV_1 >12% and 200mL from baseline (reversible airflow limitation)	Usual at some time in course of asthma; not always present	Common in COPD and more likely when FEV_1 is low	Common in ACOS, and more likely when FEV_1 is low
Post-BD increase in FEV_1 >12% and 400mL from baseline	High probability of asthma	Unusual in COPD. Consider ACOS	Compatible with diagnosis of ACOS

GINA 2015, Box 5-3 © Global Initiative for Asthma

Step 4 – Commence initial therapy

- Initial pharmacotherapy choices are based on both efficacy and safety
- If syndromic assessment suggests asthma as single diagnosis
  - Start with low-dose ICS
  - Add LABA and/or LAMA if needed for poor control despite good adherence and correct technique
  - Do not give LABA alone without ICS
- If syndromic assessment suggests COPD as single diagnosis
  - Start with bronchodilators or combination therapy
  - Do not give ICS alone without LABA and/or LAMA
- If differential diagnosis is equally balanced between asthma and COPD, i.e. ACOS
  - Start treatment as for asthma, pending further investigations
  - Start with ICS at low or moderate dose
  - Usually also add LABA and/or LAMA, or continue if already prescribed

Step 4 – Commence initial therapy

- For all patients with chronic airflow limitation:
  - Treat modifiable risk factors including advice about smoking cessation
  - Treat comorbidities
  - Advise about non-pharmacological strategies including physical activity, and, for COPD or ACOS, pulmonary rehabilitation and vaccinations
  - Provide appropriate self-management strategies
  - Arrange regular follow-up
  - Oxygen therapy as needed
- See GINA and GOLD reports for details

Case Study

H&P

- 55 y.o. M with a diagnosis of acute bronchitis, 6’ 2”, 286 lbs.
- Occasional wheeze and chest tightness, DOE, no chronic cough or mucus production; BS clear
- 40 pk/yr smoking
- Allergies: pollen, mold, cat
- Meds: albuterol MDI 2 puffs QD

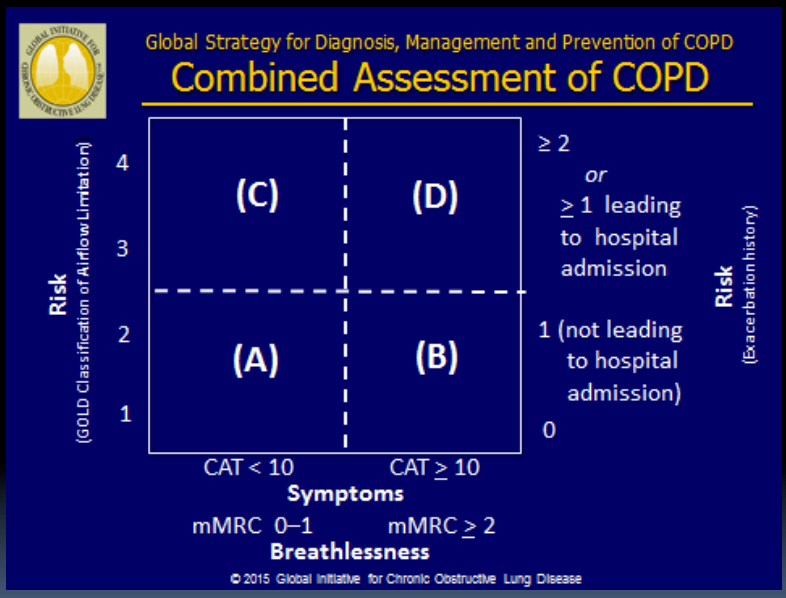
PA radiograph

Lateral Radiograph

PFTs

Parameter	Pretest best	Pred	% Pred	Post best	% Pred	% change
FVC	4.67	5.62	83	5.39	95.9	15
FEV1	2.24	4.3	52	2.74	63.7	22
FEV1/FVC%	48			50.8		

Interpreted as moderate obstruction with reversibility
Old GOLD: Moderate COPD
If Asthma: Severe persistent
CAT: 11



GOLD 2015: category B

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Lung function	❑ Record of variable airflow limitation (spirometry or peak flow)	Record of persistent airflow limitation ($FEV_1/FVC < 0.7$ post-BD)
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Time course	❑ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	❑ Symptoms slowly worsening over time (progressive course over years) ❑ Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	❑ Normal	Severe hyperinflation

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CONFIDENCE IN DIAGNOSIS	Asthma	Asthma	Could be ACOS	Possibly COPD	COPD

GINA 2015, Box 5-4 © Global Initiative for Asthma

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Post-BD increase in FEV_1 >12% and 400mL from baseline	High probability of asthma	Unusual in COPD. Consider ACOS	Compatible with diagnosis of ACOS

GINA 2015, Box 5-3

Case Study

Plan of care:

- Albuterol HFA, 2 puffs PRN; Advair 250/50 1 puff BID
- Smoking cessation, pulmonary rehab, vaccines

Follow-up

- Wheezing last 2 days due to mold abatement, new onset cough, DOE
- Daily Albuterol MDI

Plan:

- Continue present meds, add Spiriva 1 puff daily
- F/U 1 month

Step 5 – Refer for specialized investigations if needed

- Refer for expert advice and extra investigations if patient has:
  - Persistent symptoms and/or exacerbations despite treatment
  - Diagnostic uncertainty, especially if alternative diagnosis (e.g. TB, cardiovascular disease) needs to be excluded
  - Suspected airways disease with atypical or additional symptoms or signs (e.g. hemoptysis, weight loss, night sweats, fever, chronic purulent sputum). Do not wait for a treatment trial before referring
  - Suspected chronic airways disease but few features of asthma, COPD or ACOS
  - Comorbidities that may interfere with their management
  - Issues arising during on-going management of asthma, COPD or ACOS

Step 5 – Refer for specialized investigations if needed

Investigation	Asthma	COPD
DLCO	Normal or slightly elevated	Often reduced
Arterial blood gases	Normal between exacerbations	In severe COPD, may be abnormal between exacerbations
Airway hyperresponsiveness	Not useful on its own in distinguishing asthma and COPD. Higher levels favor asthma	
High resolution CT scan	Usually normal; may show air trapping and increased airway wall thickness	Air trapping or emphysema; may show bronchial wall thickening and features of pulmonary hypertension
Tests for atopy (sIgE and/or skin prick tests)	Not essential for diagnosis; increases probability of asthma	Conforms to background prevalence; does not rule out COPD
FENO	If high (>50ppb) supports eosinophilic inflammation	Usually normal. Low in current smokers
Blood eosinophilia	Supports asthma diagnosis	May be found during exacerbations
Sputum inflammatory cell analysis	Role in differential diagnosis not established in large populations	

Summary

- Wheezing in infants is commonly associated with bronchiolitis
- Half of children who wheeze at age 2 resolve by age 6
- COPD and heart failure in adults causes wheezing and may occur in addition to asthma
- ACOS and its diagnostic pathway are described
- All that wheezes is not asthma!