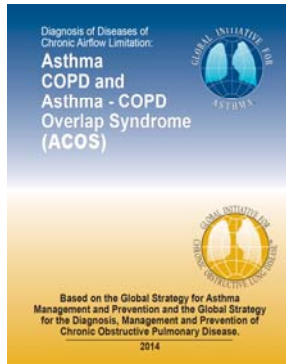


Asthma COPD Overlap Syndrome

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Diagnosis of Diseases of Chronic Airflow Limitation:
**Asthma
COPD and
Asthma - COPD
Overlap Syndrome
(ACOS)**

Based on the Global Strategy for Asthma Management and Prevention and the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease.
2014

Key points

- A step-wise approach to diagnosis is advised, comprising **recognition** of the presence of a chronic airways disease, **categorization** as asthma, COPD or the overlap between asthma and COPD (the Asthma COPD Overlap Syndrome (ACOS)), **confirmation by spirometry** and, if necessary, referral for specialized investigations.
- Although initial recognition and treatment of ACOS may be made in primary care, referral for confirmatory investigations is encouraged, as outcomes for ACOS are **worse** than for asthma or COPD alone.
- Treatment should be selected to ensure that
 - Patients with features of asthma receive adequate controller therapy including inhaled corticosteroids, but not long-acting bronchodilators alone (ie., **LABA monotherapy**), and
 - Patients with COPD receive appropriate symptomatic treatment with bronchodilators or combination therapy, but not inhaled corticosteroids alone (ie., **ICS monotherapy**).

GINA REPORT 2014
GOLD REPORT 2014

OBJECTIVE

- *Identify* patients who have a disease of chronic airflow limitation.
- *Distinguish* asthma from COPD and the Asthma-COPD Overlap Syndrome (ACOS)
- *Decide* on initial treatment and/or need for referral

Faculty/Presenter Disclosure

- **Faculty:** Alan Kaplan MD CCFP(EM) FCFP
- Chair Family Physician Airways Group of Canada
- Chair of Special Interest Focused Practice, College of Family Physicians in Respiratory Medicine.
- **Relationships with commercial interests:**
 - **Grants/Research Support:** none
 - **Speakers Bureau/Honoraria:** Astra Zeneca, Boehringer Ingelheim, Grifols, Pfizer, Purdue, Merck Frosst, Novartis, sanofi, Takeda.
 - **Consulting Fees:** Aerocrine, Novartis, Takeda, Purdue, Pfizer
 - **Other:**
 - Member of Health Canada Section on Allergy and Respiratory Therapeutics.
 - Member of Public Health Agency of Canada section on Respiratory Surveillance


Disclosure of Commercial Support

- **This program has received financial support from [none] .**
- **This program has received in-kind support from none in the form of.**
- **Potential for conflict(s) of interest:**
 - The faculty have received consultancy fees, speakers fees or been involved in research from a number of respiratory organizations
 - A) there are no organizations supporting this program
 - B) The following companies make respiratory products that we may mention in this talk including: Aerocrine, Astra Zeneca, Boehringer Ingelheim, Grifols, GSK, Merck Frosst, Pfizer, Purdue, Novartis, Sanofi, Takeda,

Mitigating Potential Bias

- I have spoken for a number of companies in the area of respiratory medicine , pain medicine, and other topics
- I do not support or speak for one Pharmaceutical organization or product solely

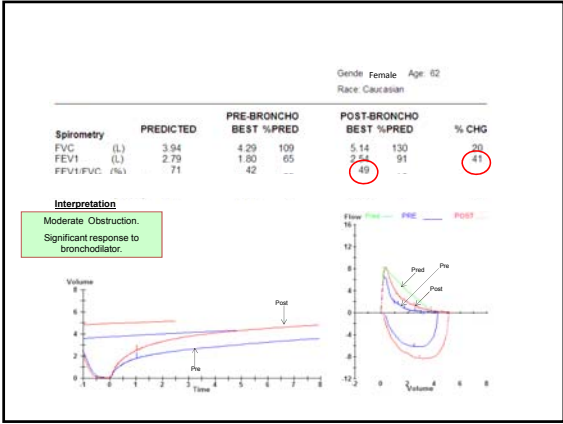
Case



- 62 year old woman
- Smoked 1/2ppd since age of 22
- Now only the occasional cigarette
- SOBOE, wheezes at night, two ER visits for her Asthma this year needing steroids and antibiotics
- CXR in ER was normal
- XST negative

What does she have?

- She is currently on Salmeterol/Fluticasone 125 MDI 2puff BID
- What is the best treatment for her?
- How should she be assessed?



Results

- She has obstruction
- It has significant reversibility
- It does not reverse to normal
- Is this asthma?
- Is this COPD?
- Is this ACOS?

What if her story was

- 50 year old marathon runner
- Smoked 20 pack years, quit x 10years
- Hx of childhood asthma, allergic rhinitis
- Family history of Asthma
- Three ER visits for asthma and one admission over last two years.
- Spirometry, exactly the same.....

Who cares?

- Patients with features of both asthma and COPD experience frequent exacerbations,¹ have poor quality of life, a more rapid decline in lung function and high mortality,^{1,2} and consume a disproportionate amount of healthcare resources.³
- The proportion of patients with features of both asthma and COPD is unclear and will have been influenced by the inclusion criteria used. However, prevalence rates between 15 and 55% have been reported.^{4,5}
- Concurrent doctor-diagnosed asthma and COPD has been reported in between 15 and 20% of patients.^{6,7}

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Definitions

Asthma
Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. [GINA 2014]
COPD
COPD is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. [GOLD 2014]
Asthma-COPD overlap syndrome (ACOS) [a description]
Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD.

GINA 2014, Box 5-1

Which one is it?



Other names:

- Asthma-COPD phenotype
- Mixed Asthma-COPD
- Mixed COPD-Asthma
- Asthma with fixed airflow limitation
- COPD with asthmatic component
- Eosinophilic COPD phenotype
- Hyper-reactive COPD phenotype

Usual features of asthma, COPD and ACOS (1)

Feature	Asthma	COPD	ACOS
Age of onset	Usually childhood but can commence at any age	Usually >40 years	Usually ≥40 years, but may have had symptoms as child/early adult
Pattern of respiratory symptoms	Symptoms vary over time (day to day, or over longer period), often limiting activity. Often triggered by exercise, emotions including laughter, dust, or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent, but variability may be prominent
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV ₁ may be improved by therapy, but post-BD FEV ₁ /FVC <0.7 persists	Airflow limitation not fully reversible, but often with current or historical variability
Lung function between symptoms	May be normal	Persistent airflow limitation	Persistent airflow limitation

GINA 2014, Box 5-2A

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Usual features of asthma, COPD and ACOS (2)

Feature	Asthma	COPD	ACOS
Past history or family history	Many patients have allergies and a personal history of asthma in childhood and/or family history of asthma	History of exposure to noxious particles or gases (mainly tobacco smoking or biomass fuels)	Frequently a history of doctor-diagnosed asthma (current or previous), allergies, family history of asthma, and/or a history of noxious exposures
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high.
Chest X-ray	Usually normal	Severe hyperinflation and other changes of COPD	Similar to COPD
Exacerbations	Exacerbations occur, but risk can be substantially reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment.

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Stepwise approach to diagnosis and initial treatment

For an adult who presents with respiratory symptoms:

1. Does the patient have chronic airways disease?
2. Syndromic diagnosis of asthma, COPD and ACOS
3. Spirometry
4. Commence initial therapy
5. Referral for specialized investigations (if necessary)

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Step 1 – Does the patient have chronic airways disease?

STEP 1 DIAGNOSE CHRONIC AIRWAYS DISEASE
Do symptoms suggest chronic airways disease?

Yes No Consider other diseases first

STEP 2 SYNDROMIC DIAGNOSIS IN ADULTS
Compare number of features for asthma and for COPD that best describe the patient. Compare number of features in favour of each diagnosis and select a diagnosis.

Feature: if present suggests...	ASTHMA	COPD
Age of onset	<input type="checkbox"/> Before age 20 years	<input type="checkbox"/> After age 40 years
Pattern of symptoms	<input type="checkbox"/> Variations over minutes, hours or days	<input type="checkbox"/> Persistent despite treatment
	<input type="checkbox"/> Worse during the night or early morning	<input type="checkbox"/> Good and bad days but always daily symptoms and exertional dyspnea
	<input type="checkbox"/> Triggered by exercise, emotions including laughter, dust or exposure to allergens	<input type="checkbox"/> Chronic cough & sputum preceded on-set of dyspnea, unrelated to triggers
Lung function	<input type="checkbox"/> Record of variable airflow limitation (apnoeometry or peak flow)	<input type="checkbox"/> Record of persistent airflow limitation (FEV ₁ /FVC < 0.7 post-BD)
Lung function between symptoms	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal
Past history or family history	<input type="checkbox"/> Previous doctor diagnosis of asthma	<input type="checkbox"/> Previous doctor diagnosis of COPD, chronic bronchitis or emphysema
	<input type="checkbox"/> Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	<input type="checkbox"/> Heavy exposure to risk factor: tobacco smoke, biomass fuel
Time course	<input type="checkbox"/> No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year	<input type="checkbox"/> Symptoms slowly worsening over time (progressive course over years)
	<input type="checkbox"/> May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	<input type="checkbox"/> Rapid acting bronchodilator treatment provides only limited relief
Chest X-ray	<input type="checkbox"/> Normal	<input type="checkbox"/> Severe hyperinflation

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Step 1 – Does the patient have chronic airways disease?

- Clinical history: consider chronic airways disease if
 - Chronic or recurrent cough, sputum, dyspnea or wheezing, or repeated acute lower respiratory tract infections
 - Previous doctor diagnosis of asthma and/or COPD
 - Previous treatment with inhaled medications
 - History of smoking tobacco and/or other substances
 - Exposure to environmental hazards, e.g. airborne pollutants
- Physical examination
 - May be normal
 - Evidence of hyperinflation or respiratory insufficiency
 - Wheeze and/or crackles

Cough and velcro like crackles = IPF

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Step 1 – Does the patient have chronic airways disease?

- Radiology (CXR or CT scan performed for other reasons)
 - May be normal, especially in early stages
 - Hyperinflation, airway wall thickening, hyperlucency, bullae
 - May identify or suggest an alternative or additional diagnosis, e.g. bronchiectasis, tuberculosis, interstitial lung disease, cardiac failure
- Screening questionnaires
 - Designed to assist in identification of patients at risk of chronic airways disease
 - May not be generalizable to all countries, practice settings or patients
 - See GINA and GOLD reports for examples

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STEP 2 SYNDROMIC DIAGNOSIS IN ADULTS

Compare number of features for asthma and for COPD that best describe the patient. Compare number of features in favour of each diagnosis and select a diagnosis.

Feature: if present suggests...	ASTHMA	COPD
Age of onset	<input type="checkbox"/> Before age 20 years	<input type="checkbox"/> After age 40 years
Pattern of symptoms	<input type="checkbox"/> Variations over minutes, hours or days	<input type="checkbox"/> Persistent despite treatment
	<input type="checkbox"/> Worse during the night or early morning	<input type="checkbox"/> Good and bad days but always daily symptoms and exertional dyspnea
	<input type="checkbox"/> Triggered by exercise, emotions including laughter, dust or exposure to allergens	<input type="checkbox"/> Chronic cough & sputum preceded on-set of dyspnea, unrelated to triggers
Lung function	<input type="checkbox"/> Record of variable airflow limitation (apnoeometry or peak flow)	<input type="checkbox"/> Record of persistent airflow limitation (FEV ₁ /FVC < 0.7 post-BD)
Lung function between symptoms	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal
Past history or family history	<input type="checkbox"/> Previous doctor diagnosis of asthma	<input type="checkbox"/> Previous doctor diagnosis of COPD, chronic bronchitis or emphysema
	<input type="checkbox"/> Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	<input type="checkbox"/> Heavy exposure to risk factor: tobacco smoke, biomass fuel
Time course	<input type="checkbox"/> No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year	<input type="checkbox"/> Symptoms slowly worsening over time (progressive course over years)
	<input type="checkbox"/> May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	<input type="checkbox"/> Rapid acting bronchodilator treatment provides only limited relief
Chest X-ray	<input type="checkbox"/> Normal	<input type="checkbox"/> 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	Possible asthma	Could be ACOS	Possible COPD	COPD

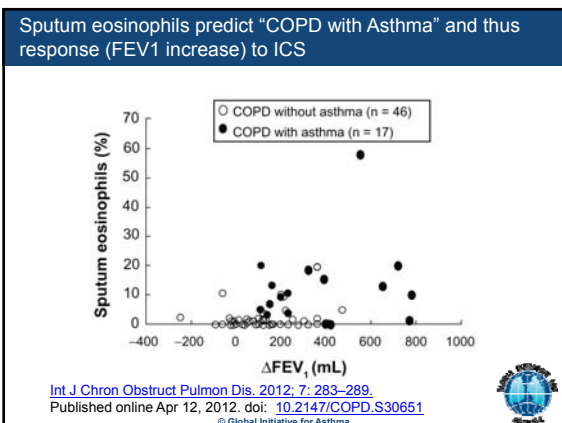
GINA 2014, Box 5-4

How to identify patients with ACOS

Persistent airflow limitation (essential) PLUS

- The presence of 3 or more features of both asthma and COPD (from table)
- The presence of some features may be more important e.g. Childhood asthma, cigarette smoking
- The absence of some features is also important e.g. cigarette smoking, reversible airflow obstruction

Asthma → ACOS ← COPD

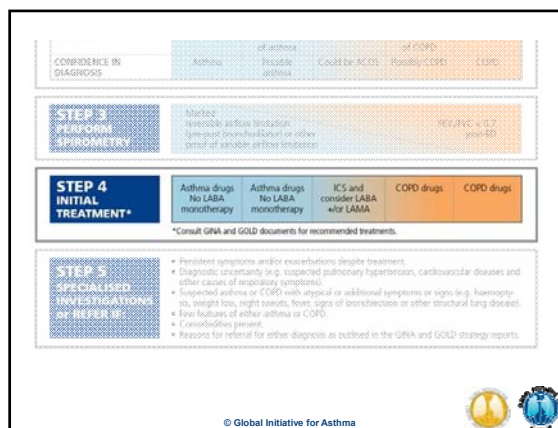


- Step 3 - Spirometry**
- Essential if chronic airways disease is suspected
 - Confirms chronic airflow limitation
 - More limited value in distinguishing between asthma with fixed airflow limitation, COPD and ACOS
 - Measure at the initial visit or subsequent visit
 - If possible measure before and after a trial of treatment
 - Medications taken before testing may influence results
 - Peak expiratory flow (PEF)
 - Not a substitute for spirometry
 - Normal PEF does not rule out asthma or COPD
 - Repeated measurement may confirm excessive variability, found in asthma or in some patients with ACOS
- © 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, but consider ACOS	Common in ACOS, and more likely when FEV ₁ is low
Post-BD increase in FEV ₁ >12% and 400mL from baseline (marked reversibility)	High probability of asthma	Unusual in COPD. Consider ACOS	Compatible with diagnosis of ACOS

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- Step 4 – Commence initial therapy**
- Initial choices based on syndromic assessment and spirometry
 - If features are consistent with asthma, treat as asthma
 - If features are consistent with COPD, treat as COPD
 - If syndromic assessment suggests ACOS, or there is significant uncertainty about the diagnosis of COPD, start treatment as for asthma pending further investigation
 - Consider both efficacy and safety
 - If any features of asthma, do not prescribe LABA without ICS
 - If any features of COPD, give symptomatic treatment with bronchodilators of combination therapy, but not ICS alone
 - If ACOS, give ICS and consider LABA and/or LAMA
 - Other important strategies for ACOS and COPD
 - Smoking cessation, pulmonary rehabilitation, vaccinations, treatment of comorbidities
- © Global Initiative for Asthma

Step 4 – Commence initial therapy

Syndromic assessment	Initial treatment
Asthma	<ul style="list-style-type: none"> • Start treatment for asthma, usually low-dose ICS and as-needed SABA (see GINA report) • Avoid LABA alone (without ICS)
COPD	<ul style="list-style-type: none"> • Start treatment as for COPD, with as-needed SABA, and regular LABA and/or LAMA if needed (see GOLD report) • Avoid ICS alone as monotherapy • Other therapeutic strategies including smoking cessation, pulmonary rehabilitation, vaccinations, treatment of comorbidities
ACOS, or significant uncertainty about diagnosis of COPD	<ul style="list-style-type: none"> • Start treatment for asthma (low/moderate dose ICS), given the pivotal role of ICS in preventing asthma exacerbations/death • Add LABA and/or LAMA, but avoid using LABA without ICS if there are any features of asthma • Other therapeutic strategies as for COPD, including smoking cessation, pulmonary rehabilitation, vaccinations, treatment of comorbidities

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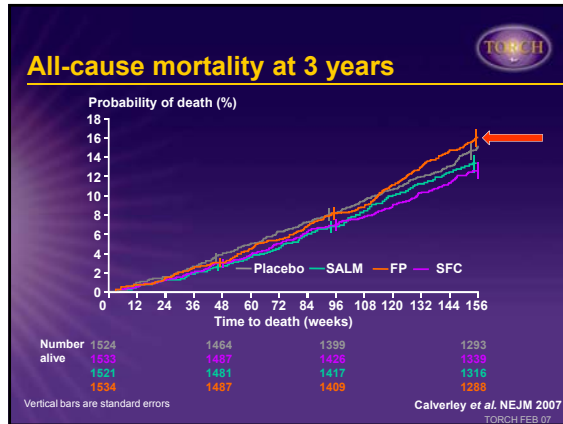
LABA monotherapy in Asthma?

CHEST Original Research

The Salmeterol Multicenter Asthma Research Trial*
A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol

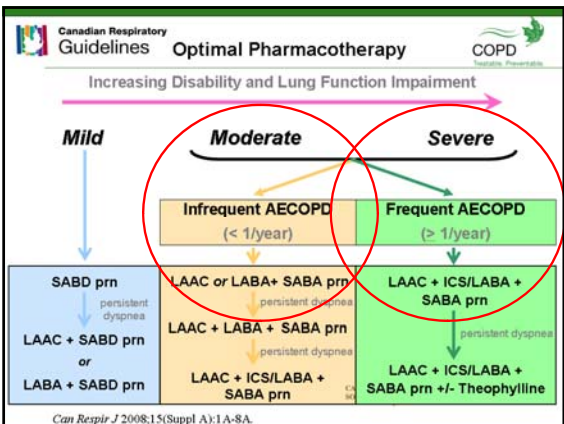
Harold A. Nelson, MD, Scott F. Wise, MD, MS, Eugene B. Blumenthal, MD, Steven W. Young, MD, and Paul M. Cherniack, MD, and the SMART Study Group

Study objective: To compare the safety of add-on salmeterol to placebo added to usual asthma care. **Design:** A 3-year, randomized, double-blind, placebo-controlled trial. **Setting:** Study subjects were recruited to the study physician's office for screening and were provided all medical study medication for the entire study period. Follow-up by telephone was scheduled every 4 weeks. **Participants:** Subjects (>12 years old) with asthma as judged by the study physician were eligible. Individuals with a history of long-acting β_2 -agonist use were excluded. **Interventions:** Subjects (>12 years old) were randomized to placebo (SALM) and placebo plus LABA. **Measurements and results:** During an interim analysis at 96 weeks, the study was terminated due to findings in African Americans and differences in compliance. The compliance of the primary outcome, respiratory-related deaths, on the observational requirement was low and not significantly different for salmeterol vs placebo (59 vs 55, relative risk [RR] = 1.06, 95% confidence interval [CI], 0.51 to 2.15). There was a small, significant increase in respiratory-related deaths (19 vs 11, RR, 1.76, 95% CI, 1.04 to 2.97) and asthma-related deaths (17 vs 8, RR, 2.12, 95% CI, 1.20 to 35.41), and no difference in total deaths or life-threatening respiratory events (27 vs 20, RR, 1.35, 95% CI, 0.74 to 2.49) in subjects receiving salmeterol vs placebo. The findings observed largely in the African American group suggest a potential racial difference in the effectiveness of salmeterol. **Conclusion:** For the primary end point, the observational findings suggest no significant differences between treatment. Plans were made, but statistically significant increases in respiratory-related and asthma-related deaths and overall add-on-related deaths on the observational requirement in the total population receiving salmeterol suggest the risk may be greater in African Americans compared with Caucasian subjects. Whether this risk is due to factors including but not limited to a pharmacologic treatment effect, genetic factors, or patient behavior needs to be further examined.



- ### NACI: Asthma 2014
- Children 2 to 18 years of age with asthma should receive PNEU-C-13 as appropriate for their age group and an **additional dose of PNEU-P-23 at least 8 weeks after the last dose of PNEU-C-13.**
 - Adults with asthma should receive one dose of PNEU-P-23.
 - At this time further booster doses of PNEU-C-13 or PNEU-P-23 are not recommended.

- ### How do you treat COPD?
- Bronchodilators
 - Steroids in which patients



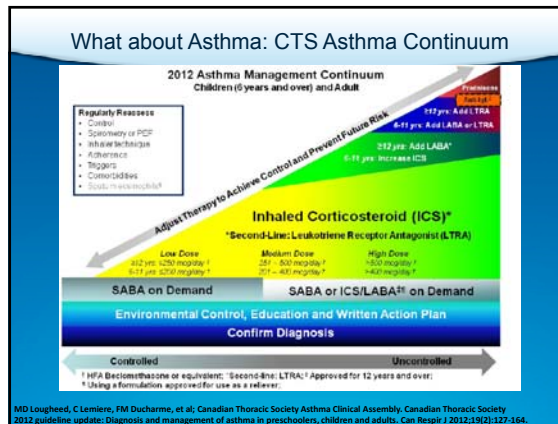
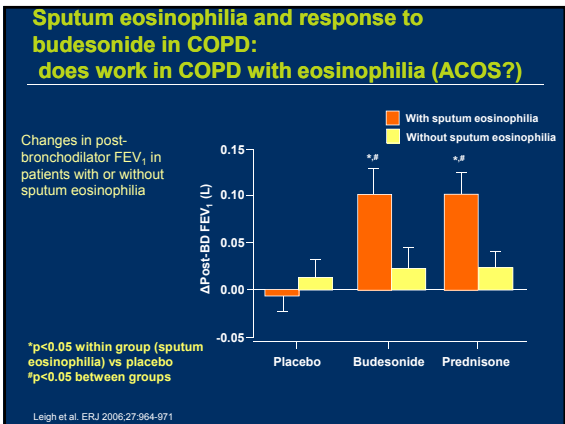
Anti-inflammatory Action of The ICS Fluticasone: does not work in COPD!

- Fluticasone showed no anti-inflammatory action in **stable** COPD in an analysis of induced sputum
 - No clinical benefit in terms of lung function or symptom scores
 - No change in induced sputum inflammatory cells, percentage neutrophils, and IL-8 levels

Sputum parameter	Baseline	After 4 weeks of treatment with fluticasone propionate (500 µg twice daily)
Total cell counts	1.9 (0.6-4.3)	1.4 (0.3-3.3)
Neutrophils (%)	85% (39-95%)	76% (28-95%)
Absolute neutrophils (millions/mL)	1.6 (0.3-6.9)	1.3 (0.3-2.9)
Macrophages (%)	15% (4-60%)	22% (4-69%)
Absolute macrophages (millions/mL)	0.27 (0.11-1.71)	0.23 (0.02-2.49)

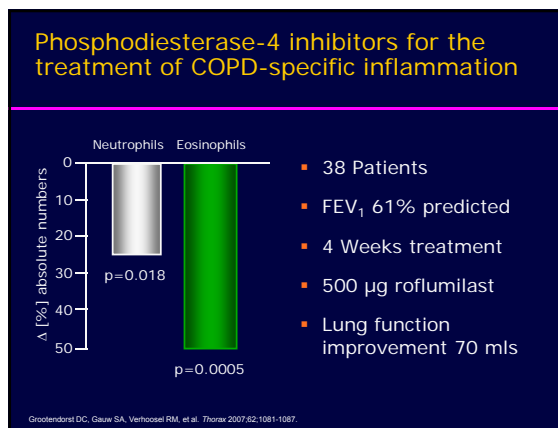
Median and range are shown for cell data.

Culbert SV, et al. Am J Respir Crit Care Med. 1999; 160(5 Pt 1):1635-1639.



Novel treatment?

- Roflumilast treats both neutrophilic and eosinophilic inflammation
- Once daily pill, 500 µg po daily
- GI side effects
- Weight loss



Diagnosis of Asthma, COPD and Asthma-COPD Overlap Syndrome

STEP 1	Diagnose Chronic airways disease Do symptoms suggest chronic airways disease?				
STEP 2 Syndromic diagnosis (from case)	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
Confidence in diagnosis?	Asthma	Possible asthma	Could be ACOS	Possibly COPD	COPD
STEP 3 Perform spirometry	Marked reversible airflow limitation (pre-post bronchodilator) or other proof of variable airflow limitation FEV ₁ /FVC <0.7 post-BD				
STEP 4 INITIAL TREATMENT*	Asthma drugs No LABA monotherapy	Asthma drugs No LABA monotherapy	ICS & consider LABA +/-or LAMA	COPD drugs	COPD drugs
STEP 5 Specialized investigations or refer if ...	Persistent symptoms and/or exacerbations in spite of treatment; diagnosis uncertain; atypical symptoms or signs; Few features of either asthma or COPD; co-morbidities present; other reasons as per GINA or GOLD report				

*Consult GINA & GOLD documents for recommended treatments for asthma and COPD *www.ginasthma.org & www.goldcopd.org

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

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Step 5 – Refer for specialized investigations if needed		
Investigation	Asthma	COPD
Lung function tests		
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. High levels favor asthma	
Imaging		
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
Inflammatory biomarkers		
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 airway inflammation	Usually normal. Low in current smokers
Blood eosinophilia	Supports asthma diagnosis	May be present during exacerbations
Sputum inflammatory cell analysis	Role in differential diagnosis not established in large populations	
<small>GINA 2014, Box 5-1 © Global Initiative for Asthma</small>		

- ### Summary
- Asthma and COPD Overlap: This is a source of confusion still!
 - Treat what is obvious
 - No isolated bronchodilators for Asthma
 - No isolated ICS for COPD
 - Still need the basics (vaccination, smoking cessation, healthy lifestyle, even pulmonary rehabilitation!)
 - Five steps to try to work out the optimal therapy
 - Step six, review efficacy of what you have done!

