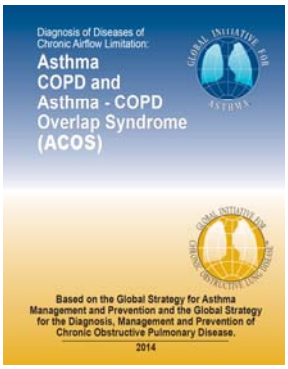
FPAGC
Family Physician Airways Group of Canada

Asthma COPD Overlap Syndrome

Alan Kaplan MD CCFP(EM) FCFP
Chair, Respiratory Medicine SIFP, CFPC
Chair, FPAGC



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 **wor**se 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, Griffols, Pfizer, Purdue, Merck Frosst, Novartis, sanofi, Takeda.
  - **Consulting Fees:** Aerocrine, GSK, 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**.

- **<u>Potential for conflict(s) of interest</u>:**
  - 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, Griffols, GSK, Merck Frosst, Pfizer, Purdue, Novartis, Sanofi, Takeda,

Mitigating Potential Bias

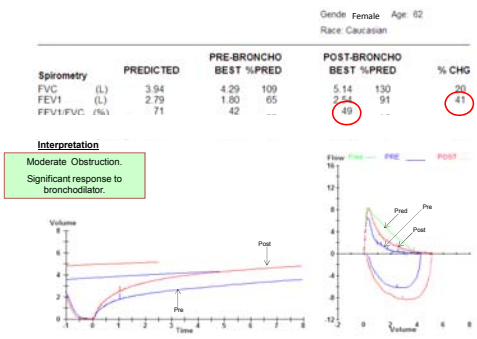
- I have spoken for a number of companies in the area of respiratory medicine , pain medicine, and other topics
- I do not support or speak for one Pharmaceutical organization or product solely

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]

1. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax 2009;64:728-35.
2. Soler-Cataluna JJ, Cosio B, Izquierdo JL, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. Arch Bronconeumol 2012;48:331-7.
3. Andersen H, Lampela P, Nevanlinna A, Saynajakangas O, Keistinen T. High hospital burden in overlap syndrome of asthma and COPD. Clin Respir J 2013;7:342-6.
4. Kauppi P, Kupiainen H, Lindqvist A, et al. Overlap syndrome of asthma and COPD predicts low quality of life. J Asthma 2011;48:279-85.
5. Weatherall M, Travers J, Shirtcliffe PM, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. Eur Respir J 2009;34:812-8.
6. McDonald VM, Simpson JL, Higgins I, Gibson PG. Multidimensional assessment of older people with asthma and COPD: clinical management and health status. Age Ageing 2011;40:42-9.
7. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. Chest 2003;124:474-81.

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

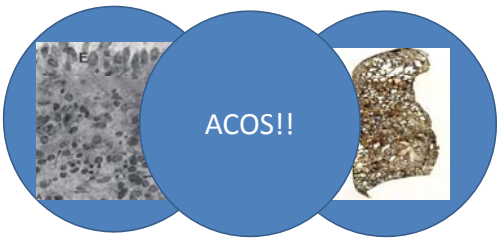
COPD is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall 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

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.

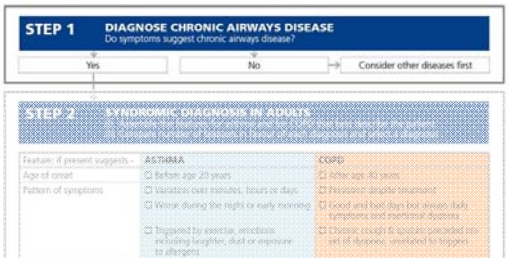
GINA 2014, Box 5-2A

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)

Step 1 – Does the patient have chronic airways disease?



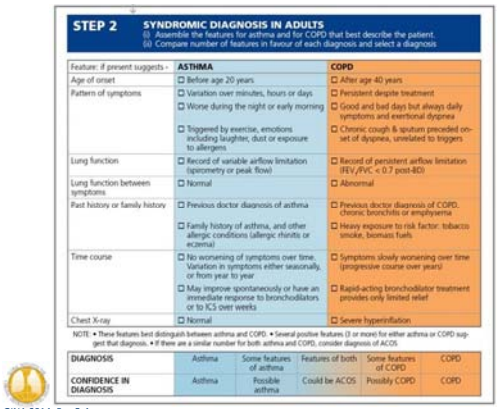
Step 1 – Does the patient have chronic airways disease?

- 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

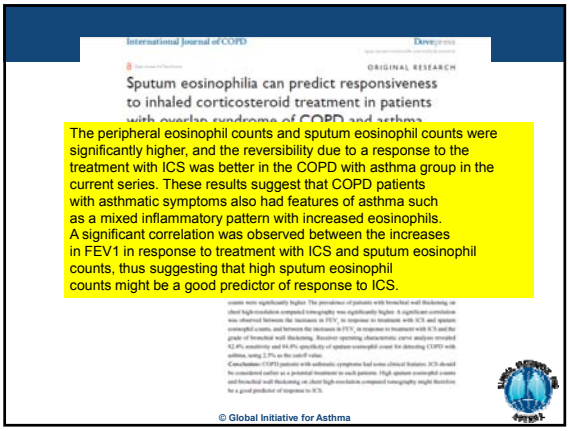
Cough and velcro like crackles = IPF

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

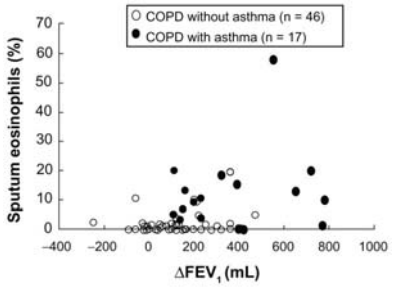


GINA 2014, Box 5-4



The peripheral eosinophil counts and sputum eosinophil counts were significantly higher, and the reversibility due to a response to the treatment with ICS was better in the COPD with asthma group in the current series. These results suggest that COPD patients with asthmatic symptoms also had features of asthma such as a mixed inflammatory pattern with increased eosinophils. A significant correlation was observed between the increases in FEV1 in response to treatment with ICS and sputum eosinophil counts, thus suggesting that high sputum eosinophil counts might be a good predictor of response to ICS.

Sputum eosinophils predict "COPD with Asthma" and thus response (FEV1 increase) to ICS



Int J Chron Obstruct Pulmon Dis. 2012; 7: 283–289.
Published online Apr 12, 2012. doi: 10.2147/COPD.S30651

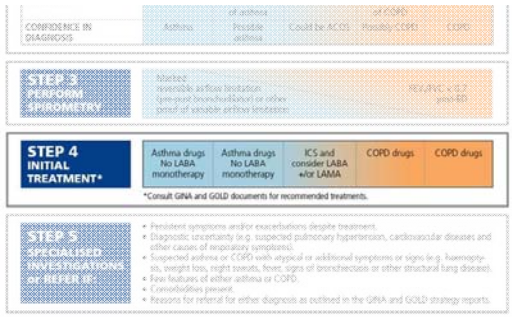
Step 3 - Spirometry

- 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

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

GINA 2014, Box 5-3



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

Step 4 – Commence initial therapy

Syndromic assessment	Initial treatment
Asthma	• Start treatment for asthma, usually low-dose ICS and as-needed SABA (see GINA report) • Avoid LABA alone (without ICS)
COPD	• 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	• 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

NACI: Asthma 2014

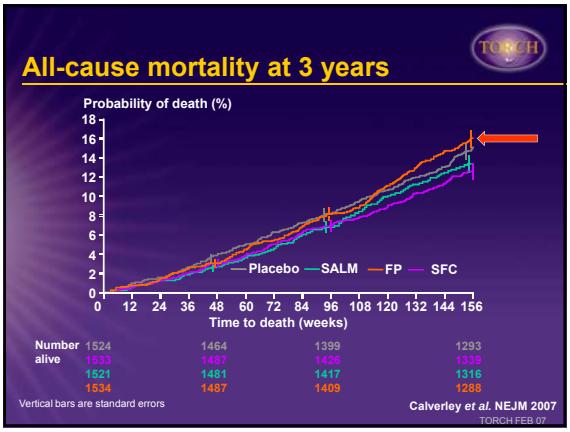
- Children 2 to 18 years of age with asthma should receive PNEU-C-13 as appropriate for their age group and an **additional dose of PNEU-P-23 at least 8 weeks after the last dose of PNEU-C-13**.
- · Adults with asthma should receive one dose of PNEU-P-23.
- At this time further booster doses of PNEU-C-13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

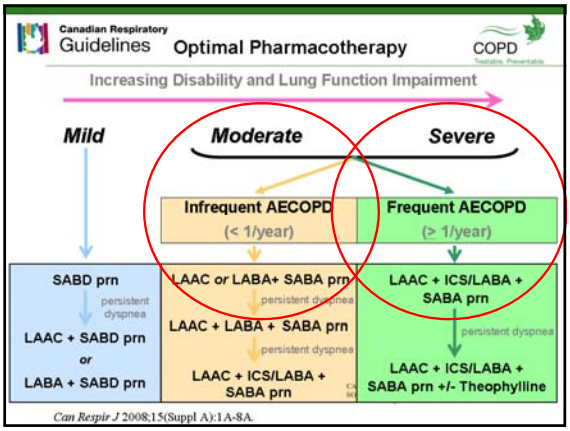
LABA monotherapy in Asthma?


CHEST Original Research

The Salmeterol Multicenter Asthma Research Trial*

A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol





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

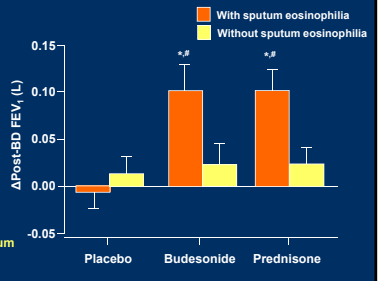
Sputum parameter	Baseline	After 4 weeks of treatment with fluticasone propionate (500 µg twice daily)
Total cell counts	1.9 (0.6-4.3)	1.4 (0.3-3.3)
Neutrophils (%)	85% (39-95%)	76% (28-95%)
Absolute neutrophils (millions/mL)	1.6 (0.3-6.9)	1.3 (0.3-2.9)
Macrophages (%)	15% (4-60%)	22% (4-69%)
Absolute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

Median and range are shown for cell data.

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

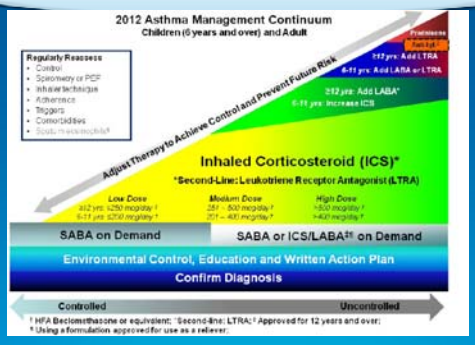
35

Sputum eosinophilia and response to budesonide in COPD: does work in COPD with eosinophilia (ACOS?)



Leigh et al. ERJ 2006;27:964-971

What about Asthma: CTS Asthma Continuum

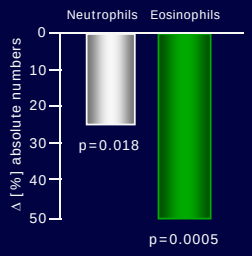


MD Lougheed, C Lemiere, FM Ducharme, et al; Canadian Thoracic Society Asthma Clinical Assembly. Canadian Thoracic Society 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults. Can Respir J 2012;19(2):127-164.

Novel treatment?

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

Phosphodiesterase-4 inhibitors for the treatment of COPD-specific inflammation



- 38 Patients
- FEV_1 61% predicted
- 4 Weeks treatment
- 500 µg roflumilast
- Lung function improvement 70 mls

Grootendorst DC, Gauw SA, Verhoosel RM, et al. *Thorax* 2007;62:1081-1087.

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

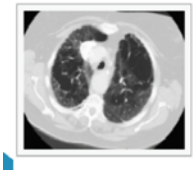
Investigation	Asthma	COPD
Lung function tests		
DLCO	Normal or slightly elevated	Often reduced
Arterial blood gases	Normal between exacerbations	In severe COPD, may be abnormal between exacerbations
Airway hyperresponsiveness	Not useful on its own in distinguishing asthma and COPD. High levels favor 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	

GINA 2014, Box 5-1

Maybe you do not have to be fancy???

Blood Eosinophilia in COPD

The reliability and utility of blood eosinophils as a marker of disease burden, healthcare resource utilisation and response to treatment in COPD

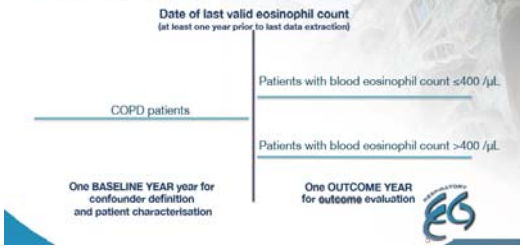


Lead Investigator: David Price
Working Group:

- Alvar Agusti, Spain
- Antonio Anzueto, USA
- Ian Pavord, UK
- Claus Vogelmeier, Germany
- Nicolas Roche, France
- Dirkje Postma, The Netherlands
- Emillio Pizzichini, Brazil
- Todor Popov, Bulgaria
- Daryl Freeman, UK
- Dermot Ryan, UK
- Rupert Jones, UK
- Alberto Papi, Italy

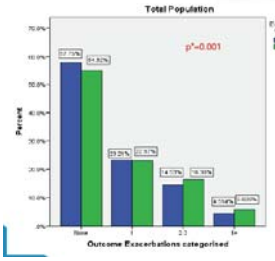
Study design

- A retrospective database analysis of COPD patients consisting of:
  (i) a one-year baseline period, (ii) a one-year outcome period and
  (iii) an index date, defined as the date of the last valid eosinophil count.
- Patients were categorised by blood eosinophil count as: ≤400/µL OR >400/µL



Severe exacerbations: total population

	TOTAL	≤400 /µL	>400 /µL
N (%)	37,112 (100)	33,473 (90.2)	3,639 (9.8)
Rate Ratio unadjusted (95% CI)	1.00	1.13 (1.07,1.94)	



The incidence rate of outcome COPD exacerbations is estimated to be **13% higher** in the group of patients with raised eosinophil counts (p<0.001).

What would an ACOS action plan look like?

- Green zone:
- LABA/ICS
- Beta 2 prn
- Yellow zone:
- Prednisone
- +/- Antibiotic
- Add second LABD like a LAMA
- Red Zone:
- ER and Beta-2 on way
- Prednisone if available

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!

GOOD ADVICE: WHEN YOU ARE IN DEEP TROUBLE, LOOK STRAIGHT AHEAD,

KEEP YOUR MOUTH SHUT & SAY NOTHING.