

# Therapeutic Options Asthma COPD Overlap (ACO)

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# Disclosures

Grant support – GSK

I will be discussing off-label use of drugs as no drug is currently approved for ACO

# Objectives

Incorporate evidence to delineate therapeutic similarities and differences between asthma, COPD and ACO in clinical scenarios

# Consider this patient

## 56 year-old male with COPD

40 pack-years smoking history; current smoker

Daily cough, wheeze and shortness of breath for the past 5 years

History of childhood asthma

Seasonal allergies spring/fall

FEV<sub>1</sub> 42% predicted

FEV<sub>1</sub>/FVC 0.48

# What additional testing would you consider?

- A. Spirometry with bronchodilator challenge
- B. FeNO
- C. Blood eosinophil count
- D. All of the above

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# 56 year-old male with COPD

FEV<sub>1</sub> improved 410 ml and 16% after bronchodilator. FEV<sub>1</sub>/FVC 0.62

Blood eosinophil count 350 cells/mm<sup>3</sup>

FeNO 38 ppb

# ACO diagnostic criteria - there are many

## Consensus definition from a round table discussion

### MAJOR

- Age  $\geq 40$  years
- $\geq 10$  pack-years of smoking or equivalent air pollution exposure
- Post-BD FEV<sub>1</sub>/FVC  $< 0.70$  or LLN
- Documented history of asthma before age 40 or BDR  $>400$  ml in FEV<sub>1</sub>

### minor

- Documented history of atopy or allergic rhinitis
- BDR FEV<sub>1</sub>  $\geq 200$  ml and 12% on 2 or more visits
- Blood eosinophil count  $\geq 300$  ml

ACO = 3 major + at least 1 minor criteria

## Spanish guidelines (GesEPOC-GEMA consensus)

$\geq 35$  years  
Smoker (or former smoker)  $\geq 10$  pk-yr  
FEV<sub>1</sub>/FVC post BDT  $< 70\%^*$

Current diagnosis of asthma

No

Yes

BDT  $\geq 15\%$  and 400 mL, and/or  
Blood eosinophilia  $\geq 300$  cells/ $\mu$ L

Yes

ACO

Arch Bronconeumol 2017;53:324-35



# What would prescribe to your patient?

- A. LAMA
- B. LABA/LAMA
- C. ICS/LABA
- D. ICS/LABA/LAMA

What would prescribe to your patient?

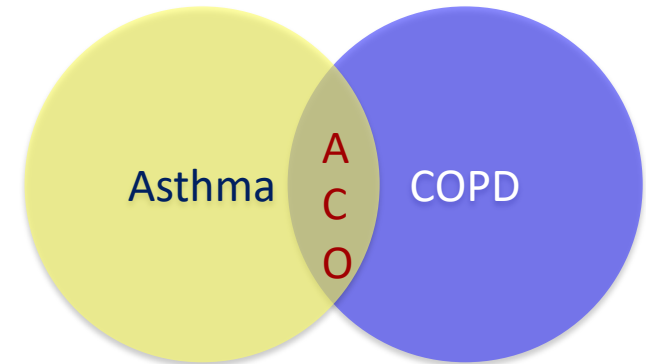
- A. LAMA
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# Management Challenges in ACO

- Lack of consensus in diagnosis/definition
- Heterogeneity – multiple endotypes
- Outcomes vary in studies but typically worse than COPD or Asthma alone
- Exclusion from clinical trials – No evidence to guide Rx

# Management principles ACO

- Evaluate
  - Symptoms, exacerbation history, physical function
  - Lung function, BD reversibility
  - Comorbidities and triggers
  - Current smoking
  - Blood eosinophils, FeNO, Atopy
- Goals
  - Symptom management
  - Exacerbation reduction
  - Disease modification



# Management approaches in ACO

## Universal therapies

Disease education

Smoking cessation

Vaccinations

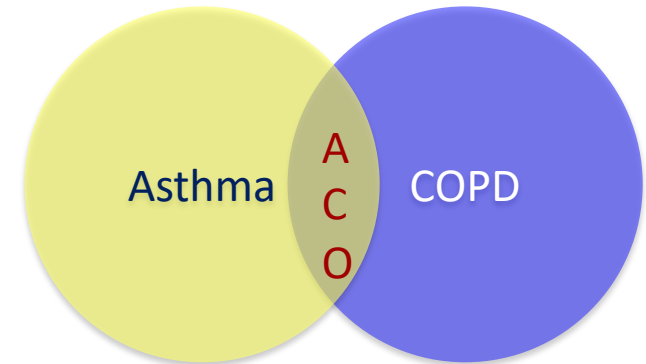
Allergen/irritant avoidance

Comorbidity management

Oxygen assessment

Adherence/technique

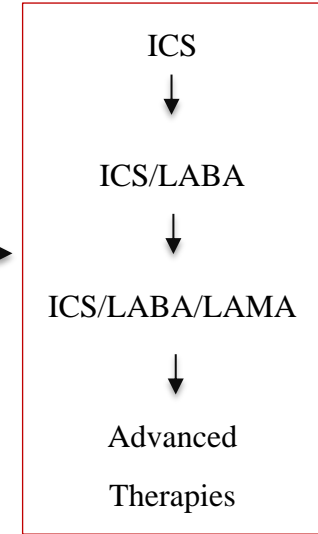
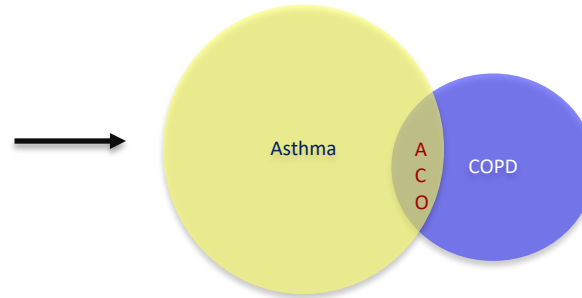
Pulmonary rehabilitation



# Management approaches in ACO

## Questions to ask:

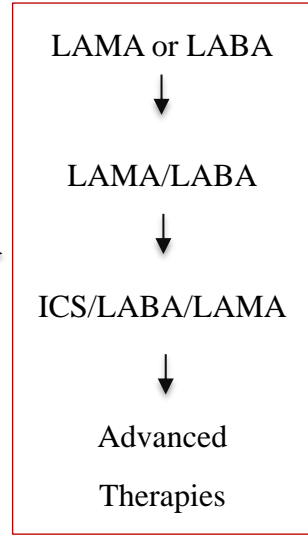
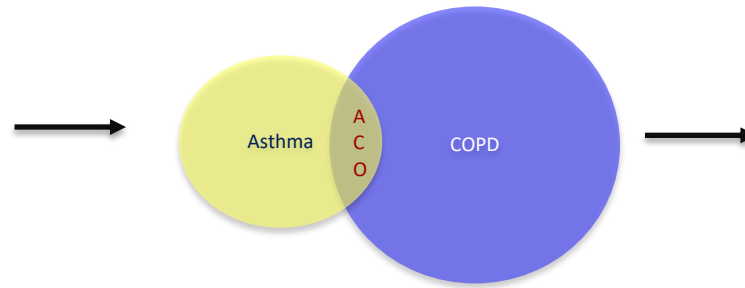
- Onset of symptoms before the age of 20 y?
- Variation of symptoms over time?
- Worsening of symptoms during the night or early morning?
- Symptoms triggered by exposure to allergens, dust, exercise?
- Documentation of variable airflow limitation?
- Previous doctor's diagnosis of asthma?
- Family history of asthma and allergy?
- Normal chest radiograph?
- Type-2 inflammation: Eos, FeNO?



# Management approaches in ACO

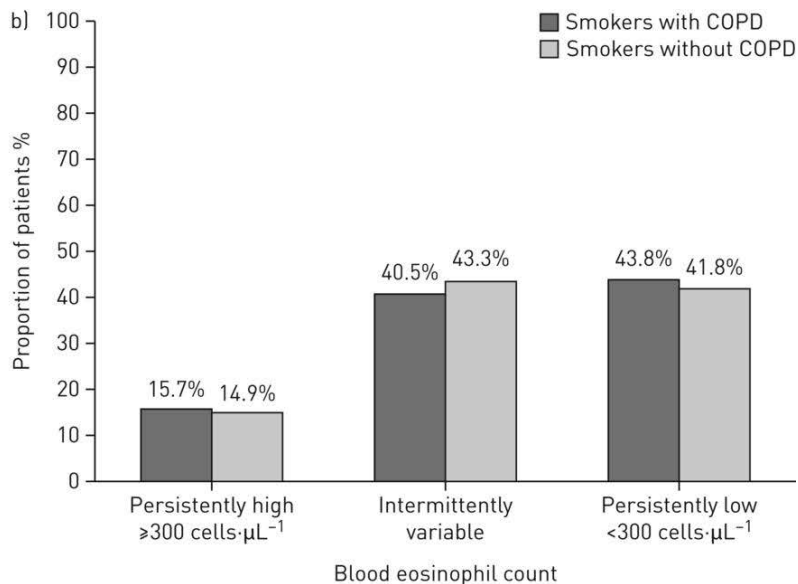
## Questions to ask:

- Onset of symptoms after the age of 40 y?
- Persistence of symptoms despite treatment?
- Good and bad days, but always some degree of symptoms?
- Chronic cough and sputum unrelated to triggers?
- Documentation of persistent airflow limitation?
- Previous doctor's diagnosis of COPD?
- Previous noxious inhalation exposure?
- Hyperinflation on chest radiograph?
- Absent type-2 inflammation?

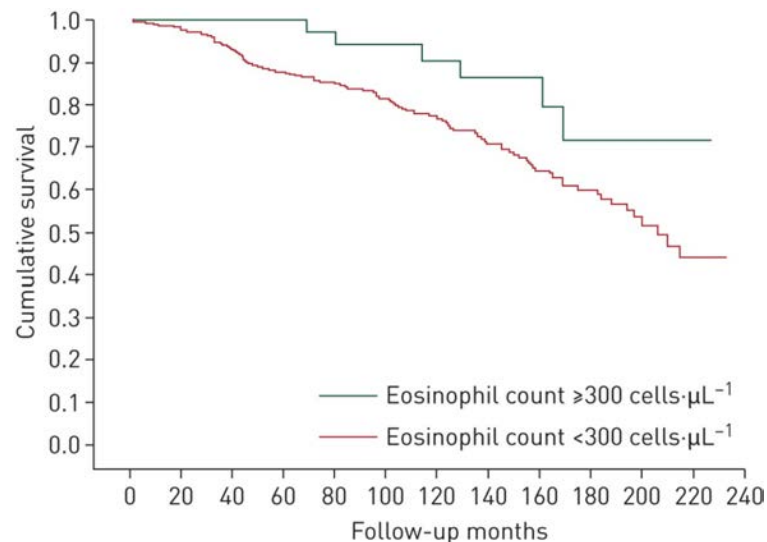


# COPD & Eosinophils

## Blood eosinophils in COPD vary over time



## Blood eosinophils in COPD are associated with worse survival



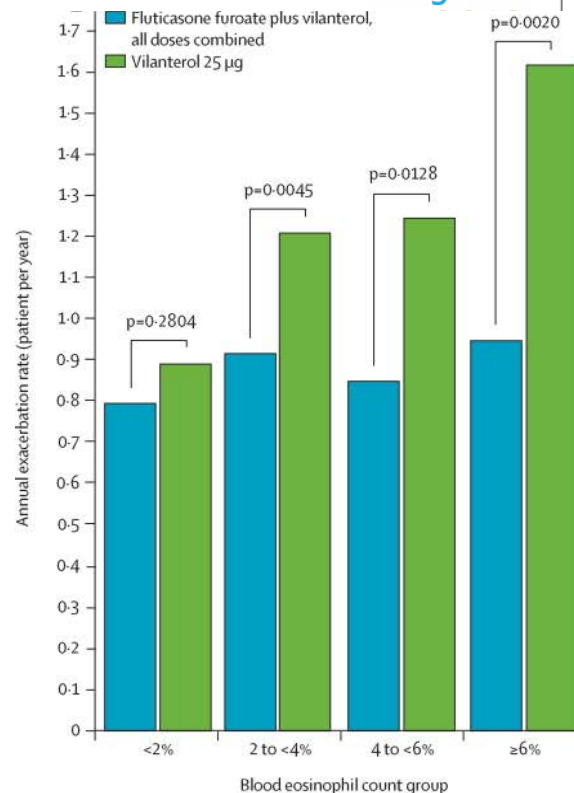


# ICS/LABA in ACO

- Ontario, CN, population based longitudinal study of 38,266 patients newly prescribed LABA or ICS/LABA therapy
- Median 2.5 years follow-up
- COPD + asthma, > 65 years old
- 28% of population studied
- In COPD + Asthma: ICS/LABA resulted in lower risk of all-cause mortality and COPD hospitalization (HR 0.84)
- COPD w/o Asthma: No benefit

# ICS in COPD – Effect by Eos

- *Post hoc* analysis of two replicate RCTs
- 3177 patients followed over 12 months
- Mod-severe COPD with at least 1 exacerbation in the last year
- ICS vs. ICS/LABA
- Effect size stratified by blood eosinophils



# LAMA add-on therapy in ACO

- 472 patients with COPD + asthma
- 12-week randomized, controlled trial
- LAMA added to usual therapy. ICS use required per inclusion criteria
- Percent of patients with COPD exacerbations:
  - Tiotropium: 5.7 %
  - ICS only: 10.7 %

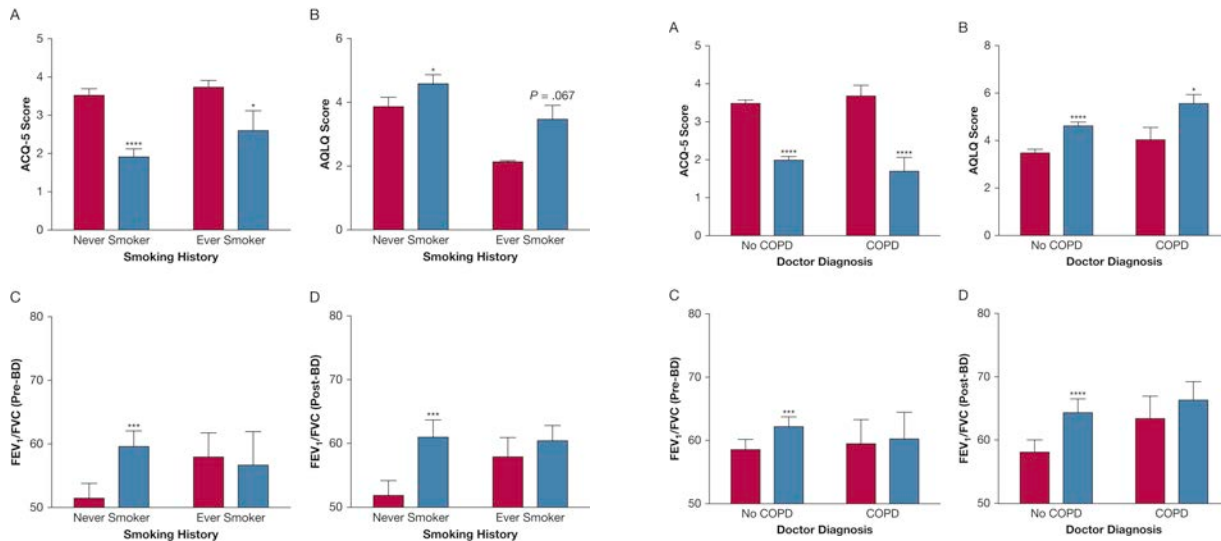
# Omalizumab in ACO

Data from Australian Xolair Registry

Severe asthma vs. ACO (diagnosis of COPD or FEV<sub>1</sub> <80%/ever smokers)

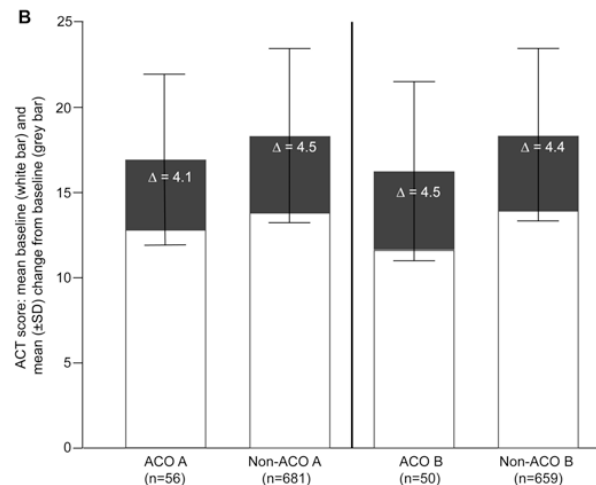
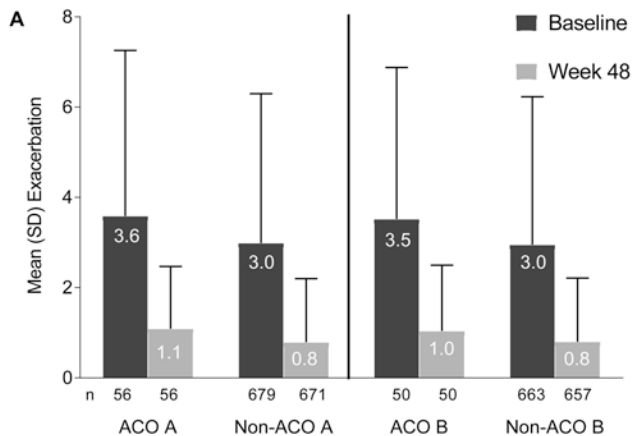
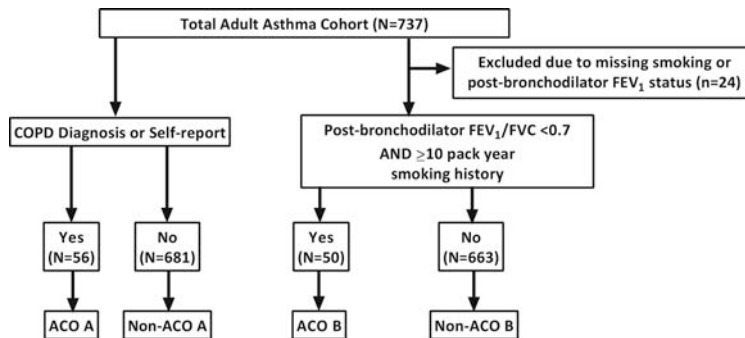
177 participants

Baseline data and at 6 months of anti-IgE therapy



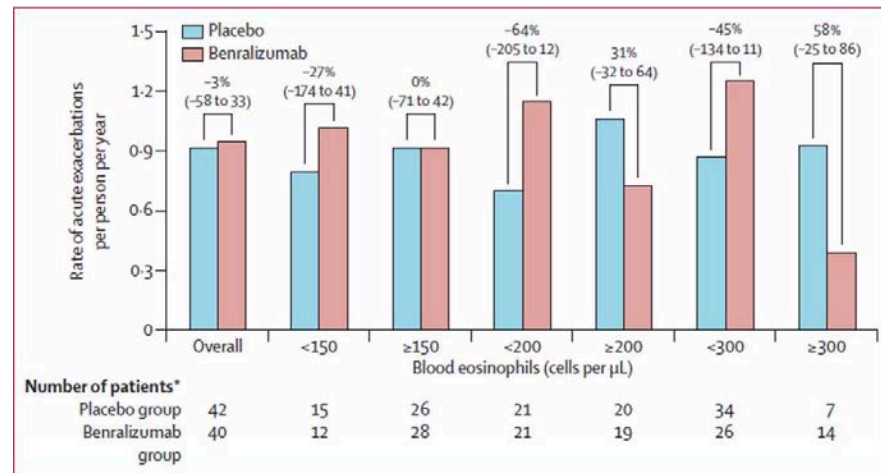
# Omalizumab in ACO

post hoc analysis from Prospero



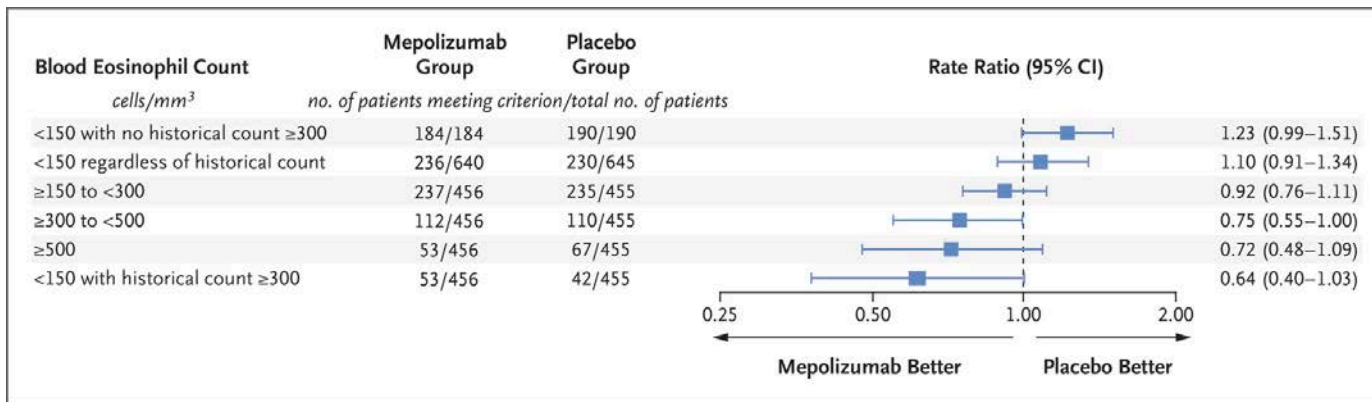
# Benralizumab in Eosinophilic COPD

- Phase 2a study of 101 patients
- Mod-severe COPD
- At least 1 acute exacerbation in the previous year
- sputum eosinophils  $\geq 3\%$
- Placebo vs. benralizumab
- 48 weeks
- No effect overall
- Pre-specified analysis by blood eos



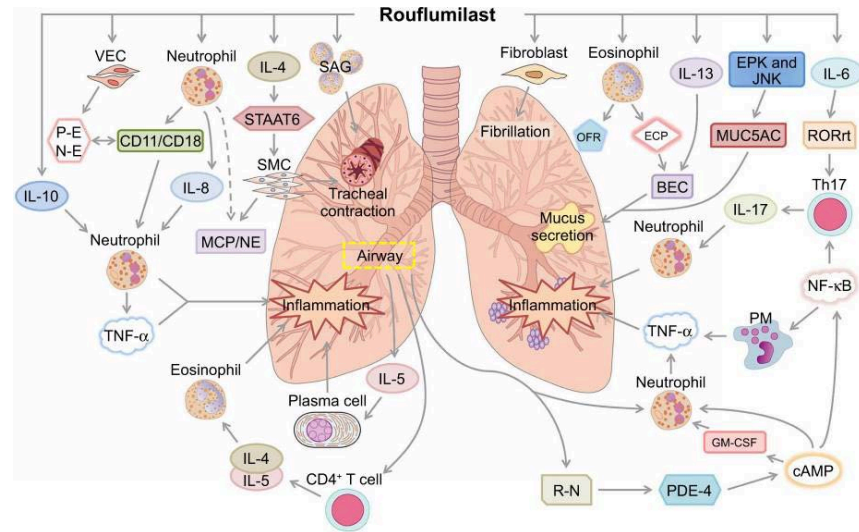
# Mepolizumab in Eosinophilic COPD

Two phase 3 trials of mepolizumab vs placebo for 52 weeks  
Mod-Severe COPD with h/o exacerbations



# Roflumilast in ACO?

Asthma	COPD
1. Reduces airway inflammation	1. Reduces airway inflammation
2. Reduces bronchoconstriction	2. Improves airway remodeling
3. Enhances mucociliary clearance	3. Improves pulmonary ventilation function
4. Improves airway remodeling	4. Reduces oxygen free radical release
5. Relieves airway hyperresponsiveness	5. Inhibits pulmonary fibrosis





# Azithromycin in ACO with exacerbations?

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### Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

### Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial



*Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson*

Lancet 2017; 390: 659-68

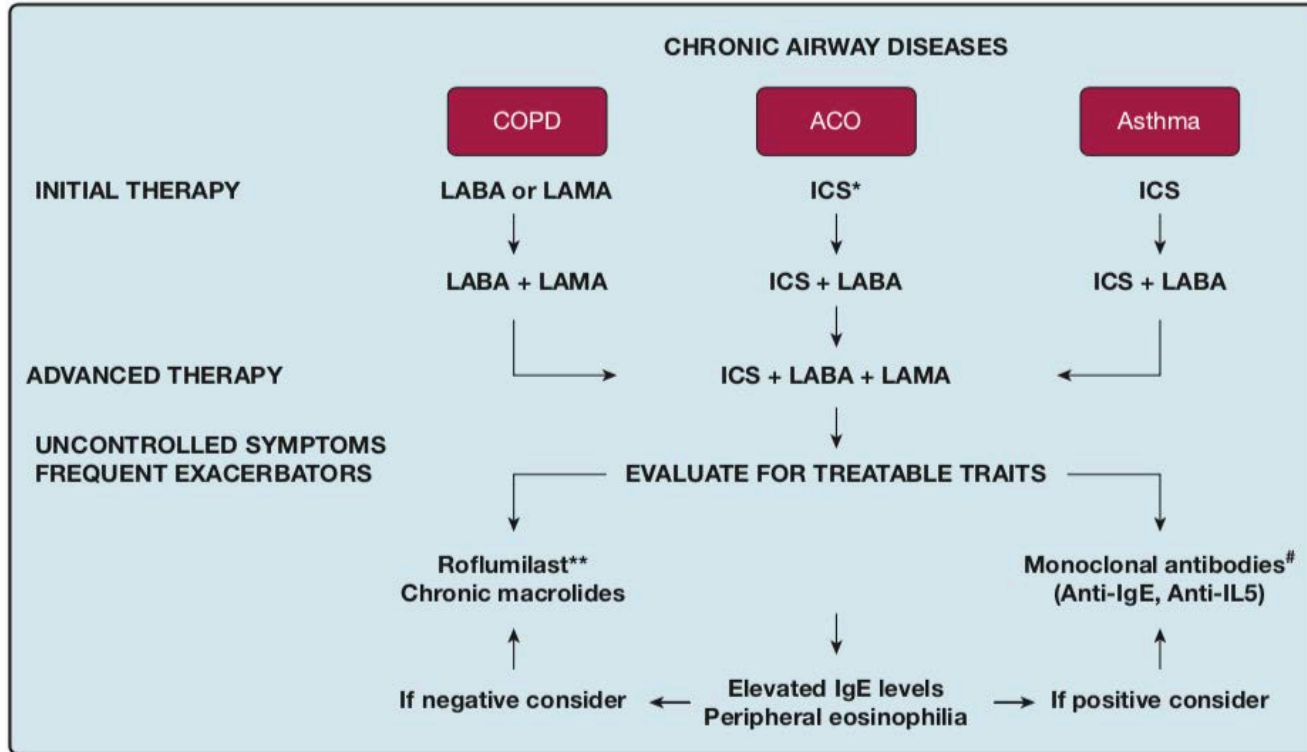
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# Summary

- The key goals of management of airways disease include identification of specific treatment targets, optimize symptom control and reduce risk for patients
- Best practices are based on evidence from robust clinical trials
- Unfortunately, with ACO, we are in an ‘evidence free’ zone as these patients have been systematically excluded from such clinical trials.
- Real life studies focusing on pheno-endo-types of ACO and efficacy of targeted therapies are urgently needed

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