Clinical: Precision Therapy For ACOS

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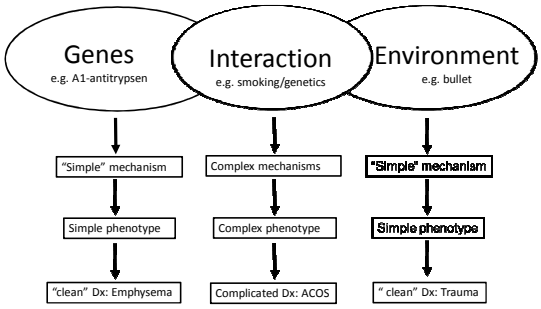
Clinical: Precision Therapy For ACOS

- Point of view: Clinical
  - Decisions must be made based on information readily available in the clinical setting
  - Predictors (e.g., genetic, phenotypic) must be verified (i.e. evidence-based) and have a high predictive value for propose therapy
- What is precision therapy?
- What is the state-of-the-art for (im)precise therapy for ACOS?
  - Genetics
  - Environment–critical element of smoking
  - Pathways
  - Overlap/interaction
  - Problem of normal aging
- What is a busy clinician to do?
  - The GINA/GOLD Recommendations

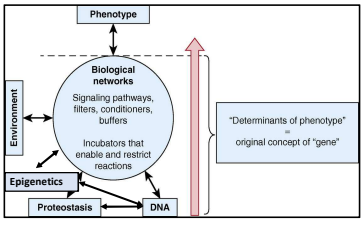
Precision Medicine

The NIH Precision Medicine Initiative Cohort Program Definition

"An approach to disease prevention and treatment based on people's individual differences in environment, genes and lifestyle."



(Complicated) Interactions Of Environment, Genes And Systems To Determine Phenotype



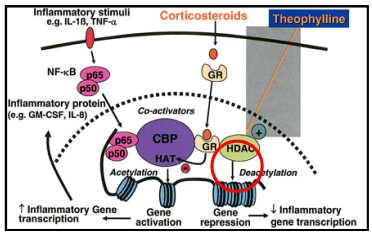
modified from Agusti A et. al. Am J Respir Crit Care Med 2014;191:391-401

Proteostasis: the concept that there are competing and integrated biological pathways within cells that control the biogenesis, folding, trafficking and degradation of proteins present within and outside the cell. The concept of proteostasis maintenance is central to understanding the cause of diseases associated with excessive protein misfolding and degradation leading to loss-of-function phenotypes, as well as aggregation-associated degenerative disorders. May be relevant in cystic fibrosis and other lung diseases.[1]

Epigenetics: the study of cellular and physiological phenotypic trait variations that result from external or environmental factors that switch genes on and off and affect how cells express genes (e.g., histone modification of T_H2 memory cells in asthma).[2]

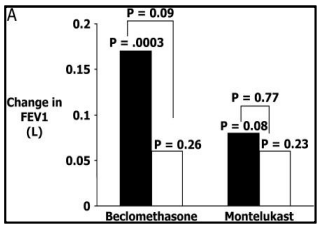
1. Balch WE, et al. Am J Respir and Crit Care Med 2014
2. Seumois G, et al. Nat Immunol 2014

Genetic/environment/pharmacologic interaction: Smoking and Corticosteroids



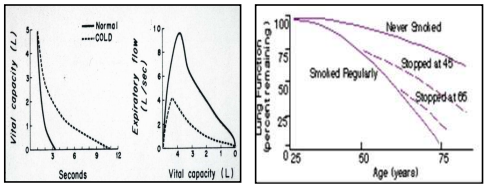
Barnes PJ. Proc Am Thorac Soc. 2005;334

Beclomethasone Not Effective In Smoking Asthmatics (but Montelukast Is)



Lazarus SC. Am J Respir Crit Care Med 2007;175:783–790

Don't Forget the Effect of Time: Smoking As Premature Aging



CHRONIC OBSTRUCTIVE PULMONARY DISEASE
NIH Publication No. 95-2020, Reprinted November 1995

Precise/Personalized Therapy

- Clean mechanism/diagnoses
- Complicated mechanism/diagnoses
- Straightforward
- Complicated

ACOS is complicated!

Is there evidence to support a precision/personalized medicine approach in ACOS treatment?

Genetics and ACOS: The COPDGene Analysis

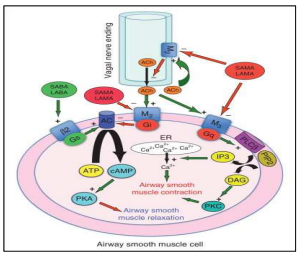
- Single nucleotide polymorphism in CSMD1 and SOX5 (important in lung development) in non-Hispanic whites
- Meta-analysis identified single nucleotide polymorphisms in the gene GPR65 (protein product important in eosinophil activation)
- Suggestive but not clinically actionable

Harden M, et al. Eur Respir J 2014; 44:341–350

Mechanistic and ACOS: Is there evidence for targeting pathways?

LABA and LAMA Non-disease Specific Mechanisms Relevant To Bronchodilation in ACOS

- Both effective in patients with asthma and COPD[1,2]
- Cigarette smoking enhances muscarinic signaling pathways in a rat model[3]
- Mucin gene expression enhanced by cigarette smoke and down regulated by anti-muscarinic stimulation[3]
- No definitive studies in ACOS for either, however

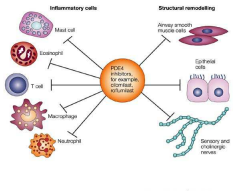


Montuschi, et al. Drug Disc Today 2014;19:1928-35

1. Mangnusen H, et. al. Respir Med. 2008 Jan;102(1):50-6
2. Peters SP et al. N Engl J Med 2010;363:1715-1726
3. Chiba Y. et. al. Am J Respir Cell Mol Biol. 2005; 33:574 – 581
4. Cortijo J, et.al. Eur Respir J. 2011 Feb;37(2):244-54.

Phosphodiesterase Pathway Inhibitors

- PDE4 inhibitor, roflumlast, modest clinical benefit in COPD[1,2] and asthma
- Theophylline effective in asthma and COPD[3]
- No studies in ACOS



1 Martinez FJ, et al. Lancet 2015; 385:85 7–66,
2 Azam MA, et al. Sci Pharm 2014; A2: 45 3–81
3 Barnes P.J. J Allergy Clinic Immunol 2015;136:531–45

Targeted Anti-inflammatory Mediator Therapy

- Anti-IL5 (benralizumab) not effective in COPD (even with increased eosinophils)[1]
- Anti-TNF antibodies ineffective in COPD or severe asthma[2,3]
- Anti-IL17 ineffective in asthma[4]
- No studies in ACOS

1. Brightling CE, et al, Lancet Respir Med 201
2. Rennard SI, et al, Am J Respire Crit Care Med 2007;175: 926–34
3. Wenzel SE, et al, Am J Respire Crit Care Med 2009;179:549–58, and others
4. Busse WW, et al. Am J Respire Crit Care Med 2013;188:1294–302

Antibacterial/Anti-inflammatory(?) Effect Of Antibiotics

- Macrolides (clarithromycin): No clear improvement in asthma but may reduce exacerbations and COPD
- Not studied in ACOS

Sutherland ER, at all J Allergy Clinic Immunol 2010; 1-6:74 7–53,
Ni W, et al. PLoS One 2015; 10:e 012-1257

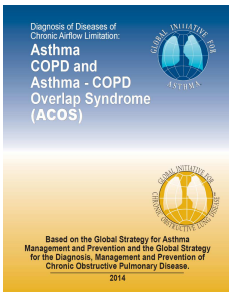
"Untargeted" Anti-inflammatory Therapy: Corticosteroids and ACOS

- A retrospective study found no benefit to the use of inhaled corticosteroids on FEV_1 decline, incidence of severe exacerbations or overall mortality in 125 patients with ACOS
- No definitive evidence in ACOS

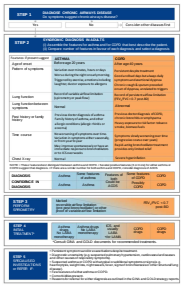
Lim HS, et al. Annals of **Allergy, Asthma & Immunology**. 2014;113:652-657.

Where Are We Now: What The Guidelines Say.

UPDATED!



Stepwise approach to diagnosis and initial treatment of ACOS based on *PHENOTYPE*.



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)

GINA 2015, Box 5-4

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

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

Step 2 – Syndromic diagnosis of asthma, COPD and ACOS

- Assemble the features that, **when present**, most favor a diagnosis of typical asthma or typical COPD
- Compare the number of features on each side
  - If the patient has ≥3 features of either asthma or COPD, there is a strong likelihood that this is the correct diagnosis
- Consider the level of certainty around the diagnosis
  - Diagnoses are made on the weight of evidence
  - The absence of any of these features does not rule out either diagnosis, e.g. absence of atopy does not rule out asthma
  - When a patient has a similar number of features of both asthma and COPD, consider the 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

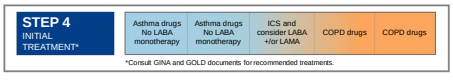
DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Asthma	Could be ACOS	Possibly COPD	COPD

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

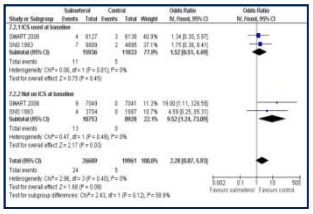
Spirometric variable	Asthma	COPD	ACOS
Normal FEV_1/FVC pre- or post-BD	Compatible with asthma	Not compatible with diagnosis (GOLD)	Not compatible unless other evidence of chronic airflow limitation
Post-BD FEV_1/FVC <0.7	Indicates airflow limitation; may improve	Required for diagnosis by GOLD criteria	Usual in ACOS
FEV_1 ≥80% predicted	Compatible with asthma (good control, or interval between symptoms)	Ccompatible 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



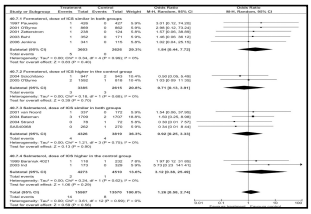
Step 4 – Commence initial therapy

- Initial pharmacotherapy choices are based on both efficacy and safety
  - SABA as needed for symptom relief
- 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

The ("official") Effects of LABA on Asthma Mortality with and without ICS



Cates CJ, Cates MJ Cochran Database Syst Rev. 2008



Jaeschke R. et.al. Am J Respir Crit Care Med. 2008

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
- See GINA and GOLD reports for details

Can we use precision medicine to do better than the guidelines?

Not yet