Clinical: Precision Therapy For ACOS

Joe Ramsdell, M.D.
University of California, San Diego, School of Medicine
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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."

Genes e.g. A1-antitrypsin
Interaction e.g. smoking/genetics
Environment e.g. bullet

"Simple" mechanism
Complex mechanism

"Simple" phenotype
Complex phenotype

"Clean" Dx: Emphysema
"Clean" Dx: Trauma
"Clean" Dx: Trauma

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

Proteostasis: the concept that there are competing cellular and extracellular pathways that control and modulate the biogenesis, folding, trafficking, and degradation of proteins present within and outside the cell. The concept of proteostasis is essential for the maintenance of normal cellular function and for the development of disease. Proteostasis failure is associated with diseases involving protein misfolding and aggregation, leading to loss of function of proteins, as well as aggregation and accumulation of misfolded proteins. Aggregation of proteins is a hallmark of many diseases, such as cystic fibrosis and other lung diseases.

Epigenetics: the study of cellular and physiological phenotypic variation that is heritable and not associated with changes in the genetic sequence. Epigenetic mechanisms include DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA molecules. These modifications can influence gene expression and affect how genes are regulated and expressed. For example, the histone modification of H3K27me3 is associated with gene silencing and is found in various diseases.

Genetic/environment/pharmacologic interaction: Smoking and Corticosteroids

Beclomethasone Not Effective In Smoking Asthmatics (but Montelukast Is)

Don't Forget the Effect of Time: Smoking As Premature Aging
Precise/Personalized Therapy

- Clean mechanism/diagnoses
- Complicated mechanism/diagnoses

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

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
- Cigarette smoking enhances muscarinic signaling pathways in a rat model
- Mucin gene expression enhanced by cigarette smoke and down regulated by anti-muscarinic stimulation
- No definitive studies in ACOS for either, however


Phosphodiesterase Pathway Inhibitors

- PDE4 inhibitor, roflumilast, modest clinical benefit in COPD and asthma
- Theophylline effective in asthma and COPD
- No studies in ACOS

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 2021
\(^{3}\) Wenzel SE, et al, Am J Respir Crit Care Med 2009;179:549–58, and others

Antibacterial/Anti-inflammatory(?) Effect Of Antibiotics

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

\(^{17}\) Sutherland DR, et al./Allergy Clin Immunol 2010;1-6:74 7–53,

“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

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)

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 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

<table>
<thead>
<tr>
<th>Spirometric variable</th>
<th>Asthma</th>
<th>COPD</th>
<th>ACOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/FVC</td>
<td>Normal FEV1/FVC</td>
<td>Compatible with asthma</td>
<td>Not compatible with diagnostic (GOLD)</td>
</tr>
<tr>
<td></td>
<td>Pre- or post-BD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-BD FEV1/FVC &lt;50%</td>
<td>Indicates airflow limitation may improve</td>
<td>Requires for diagnosis by GOLD criteria</td>
<td>Usual in ACOS</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>Compatible with asthma (good control, or interval between symptoms)</td>
<td>Compatible with GOLD category A or B if post-BD FEV1/FVC &lt;50%</td>
<td>Compatible with mild ACOS</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>Indicates severity of airflow limitation and risk of exacerbations and mortality</td>
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</tr>
<tr>
<td>Post-BD increase in FEV1, % and mL&gt; 12% from baseline</td>
<td>Usual at some time in course of asthma, not uncommon</td>
<td>Common in COPD and more likely when FEV1 is low</td>
<td>Common in ACOS, and more likely when FEV1 is low</td>
</tr>
<tr>
<td>High probability of asthma</td>
<td>Unusual in COPD</td>
<td>Consider ACOS</td>
<td>Compatible with diagnosis of ACOS</td>
</tr>
</tbody>
</table>

Step 4 - Initial Treatment*

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
<th>ACOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LABA monotherapy</td>
<td></td>
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</tbody>
</table>

*Consult GINA and GOLD documents for recommended treatments.
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

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