Precision Medicine approach
And
Obstructive Airway Diseases

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Obstructive airway diseases

- Asthma and COPD
- Have a great personnel and social impact
- May share biological mechanisms (i.e. endotypes), and present similar clinical, functional, imaging and/or biological features that can be observed (i.e. phenotypes) which require individualised treatment
Precision medicine

Treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations

Final objective of precision medicine

To improve clinical outcomes for individual patients while minimizing unnecessary side effects for those less likely to respond to a given treatment
President Barack Obama launched a research initiative aimed at accelerating progress toward a new era of “precision medicine”
Asthma and COPD

- Both asthma and COPD are “complex” and “heterogeneous”
- Complex
  - They have several components with nonlinear dynamic interactions
- Heterogeneous
  - Not all of these components are present in all patients or, in a given patient, at all time points
“Oslerian diagnostic labels”

**Asthma and COPD**

- Do not consider novel genetic, molecular or imaging information
- May be valid for the “stereotypical” patients, but it may be of much less clear value in “intermediate” (and frequent) cases
- The pattern of airway inflammation even in classical cases may not be as distinct as has been assumed
“Oslerian diagnostic label” approach to airway diseases

• Fails to provide optimal care in a significant number of patients because it does not consider the biological complexity of airway diseases and does not consider the distinct endotypes present in each patient

• Does not appreciate common patterns of disease (e.g. chronic cough)
• Can increase clinical practice variability and enhance inappropriate prescription of some drugs (e.g. inhaled corticosteroids) in some patients

• Can contribute to treatment failure and high rates of hospital readmissions

• Inhibits research progress

Chakma Justin (Journal of Young Investigators, 2009)
Precision medicine approach to the diagnosis and management of chronic airway diseases

• “Label-free”
• Based on the identification of “treatable traits” in each patient
• These traits can be “treatable” based on “phenotypic” recognition or on deep understanding of the critical causal pathways (e.g. true “endotypes”)
“Oslerian diagnostic label” approach
The control-based asthma management cycle

**ASSESS**
- Diagnosis
- Symptom control & risk factors (including lung function)
- Inhaler technique & adherence
- Patient preference

**ADJUST TREATMENT**
- Asthma medications
- Non-pharmacological strategies
- Treat modifiable risk factors

**REVIEW RESPONSE**
- Symptoms
- Exacerbations
- Side-effects
- Patient satisfaction
- Lung function

**NEW!**

GINA 2014
Stepwise management – pharmacotherapy for Asthma

*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
Combined Assessment of COPD

When assessing risk, choose the highest risk according to GOLD grade or exacerbation history

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristic</th>
<th>Spirometric Classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk Less Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>0-1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>B</td>
<td>Low Risk More Symptoms</td>
<td>GOLD 1-2</td>
<td>≤ 1</td>
<td>&gt;2</td>
<td>≥ 10</td>
</tr>
<tr>
<td>C</td>
<td>High Risk Less Symptoms</td>
<td>GOLD 3-4</td>
<td>≥2</td>
<td>0-1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>D</td>
<td>High Risk More Symptoms</td>
<td>GOLD 3-4</td>
<td>≥2</td>
<td>≥2</td>
<td>≥ 10</td>
</tr>
</tbody>
</table>
Severity of Airflow Limitation in COPD

In patients with $\text{FEV}_1/\text{FVC} < 0.70$

GOLD 1: Mild \( \text{FEV}_1 \geq 80\% \text{ predicted} \)

GOLD 2: Moderate \( 50\% \leq \text{FEV}_1 < 80\% \text{ predicted} \)

GOLD 3: Severe \( 30\% \leq \text{FEV}_1 < 50\% \text{ predicted} \)

GOLD 4: Very Severe \( \text{FEV}_1 < 30\% \text{ predicted} \)

*Based on Post-Bronchodilator FEV$_1$*
Combined assessment

- Assess symptoms
- Assess degree of airflow limitation using spirometry
- Assess risk of exacerbations

Combine these assessments for the purpose of improving management of COPD
## Manage Stable COPD: Non-pharmacologic treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Essential</th>
<th>Recommended</th>
<th>Depending on local guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Smoking cessation (can include pharmacologic treatment)</td>
<td>Physical activity</td>
<td>Flu vaccination Pneumococcal vaccination</td>
</tr>
<tr>
<td>B, C, D</td>
<td>Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation</td>
<td>Physical activity</td>
<td>Flu vaccination Pneumococcal vaccination</td>
</tr>
</tbody>
</table>
## Manage Stable COPD: Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>First choice</th>
<th>Second choice</th>
<th>Alternative choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA prn or SABA prn</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA</td>
<td>PDE4-inh. SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA</td>
<td>ICS and LAMA or ICS + LABA and LAMA or ICS + LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>
Precision medicine approach
FIGURE 1 Proposed diagnostic strategy for an adult with symptoms, signs or events suggestive of airway disease. For further explanations, see text. FeNO: exhaled nitric oxide fraction. #: smoking, allergies, sputum production, occupation, lung development and growth.
The relationships between the exposome and the genome (via complex Biological networks)

**Exposome**
Cumulative environmental exposures an individual encounters throughout life [14, 15]

**Endotype**
Subtype of a disease defined functionally and pathologically by a molecular mechanism or by treatment response [18]

**Clinical phenotype**
A single or combination of disease attribute(s) that describe differences between individuals as they relate to clinically meaningful outcomes [17]

**Genome**
Genetic material of an organism

**Biomarker**
A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or biological responses to a therapeutic intervention [19]

**Treatable trait**
Therapeutic target identified by "phenotype" or "endotype" recognition through validated biomarker(s) [7]
Treatable traits

• Pulmonary
  – Airflow limitation
  – Eosinophilic airway inflammation
  – Chronic bronchitis
  – Airway bacterial colonisation
  – Bronchiectasis
  – Cough reflex hypersensitivity
  – Pre-capillary pulmonary hypertension
  – Chronic respiratory failure

• Extrapulmonary

• Behaviour/lifestyle risk factors
Airflow limitation

\[ \text{FEV}_1 / \text{FVC} < 0.7 \text{ (or lower limit of normal)} \]

- Airway smooth muscle contraction
- Loss of elastic recoil (emphysema)
- Airway mucosal oedema
Airway smooth muscle contraction

Diagnostic criteria

- Bronchodilator reversibility
- Peak expiratory flow variability
- Positive PC20
Treatment

First choice

• Maintenance:
  – long-acting β2-adrenergic agonists/muscarinic antagonists;
• Rescue:
  – short-acting β2-adrenergic agonists/muscarinic antagonists

Second choice

• Inhaled corticosteroids
• Bronchial thermoplasty
Loss of elastic recoil (emphysema)

Diagnostic criteria

- Chest computed tomography
- DLCO, compliance

First choice

- Smoking cessation

Second choice

- Lung volume reduction surgery
- Lung transplantation
- $\alpha_{1}$-anti-trypsin replacement if deficient, valves, coils
Airway mucosal oedema

Diagnostic criteria

- Chest computed tomography
- Spirometry-induced bronchoconstriction

First choice
- Inhaled corticosteroids

Second choice
- Oral corticosteroids,
- Anti-interleukin-5, -13, -4
Eosinophilic airway inflammation

Diagnostic criteria

First choice
- Inhaled corticosteroids

Second choice
- Oral corticosteroids
- Leukotriene receptor antagonist
- Anti-IgE
- Anti-interleukin-5, -13, -4

• Sputum eosinophils
• Blood eosinophils
• FeNO, (periostin)
Chronic bronchitis

Diagnostic criteria

- Cough and sputum 3 months × 2 years (no eosinophilic airway inflammation)

First choice
- Smoking cessation

Second choice
- Carbocysteine,
- Macrolides
- Roflumilast
Airway bacterial colonisation

Diagnostic criteria

- Sputum culture,
- Quantitative PCR

First choice
- Antibiotics

Second choice
- Long-term low-dose macrolides
- Vaccination
Bronchiectasis

Diagnostic criteria

- Chest X ray
- Chest computed tomography

First choice
- Drainage

Second choice
- Macrolides, nebulised antibiotics
- Surgery
- Vaccination
Cough reflex hypersensitivity

Diagnostic criteria

- Capsaicin challenge, cough counts, cough questionnaire

First choice
- Speech and language treatment

Second choice
- Gabapentin
Pre-capillary pulmonary hypertension

Diagnostic criteria

- Doppler echocardiography,
- Brain natriuretic peptide,
- Right heart catheterisation

First choice

- Long-term (domiciliary) oxygen therapy

Second choice

- Noninvasive ventilation
- Lung transplantation
Chronic respiratory failure

- Arterial hypoxemia
- Arterial hypercapnia
Arterial hypoxemia

Diagnostic criteria

- \( \text{PaO}_2 < 55 \text{ mmHg} \)

First choice

- Long-term (domiciliary) oxygen therapy
Arterial hypercapnia

Diagnostic criteria

- $\text{PaCO}_2 > 45 \text{ mmHg}$

First choice
- Optimized medical therapy

Second choice
- Noninvasive ventilation
- Lung transplantation
Extrapulmonary treatable traits of airway diseases

- Deconditioning
- Obesity
- Cachexia
- OSA
- CVD
- GERD
- Rhino-sinusitis
- Psychiatric disorders

- Persistent systemic inflammation
- Smoking and others
- Exposure to sensitizing agents/pollution
- Symptom perception
- Inhaler device
- Adherence to treatment
- Family and social support
<table>
<thead>
<tr>
<th>Trait</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary treatable traits</strong></td>
<td></td>
</tr>
<tr>
<td>Airway smooth muscle contraction</td>
<td>Bronchodilators</td>
</tr>
<tr>
<td>Eosinophilic airway inflammation</td>
<td>Corticosteroids/Type 2 biologics</td>
</tr>
<tr>
<td>Chronic sputum production</td>
<td>Smoking cessation, macrolides, PDE4 inhibitors</td>
</tr>
<tr>
<td>Bacterial colonisation</td>
<td>Macrolides, tetracyclines</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Macrolides, tetracyclines, nebulised antibiotics/aminoglycosides</td>
</tr>
<tr>
<td>Cough reflex hypersensitivity</td>
<td>Gabapentin, P2X3, speech pathology intervention</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>Oxygen/NIV/lung transplant</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Oxygen/NIV/lung transplant</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Lung volume reduction/transplant</td>
</tr>
<tr>
<td><strong>Extrapulmonary treatable traits</strong></td>
<td></td>
</tr>
<tr>
<td>Rhinosinusitis</td>
<td>Topical steroids/surgery</td>
</tr>
<tr>
<td>Deconditioning</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td>Cachexia</td>
<td>Diet/physical activity</td>
</tr>
<tr>
<td>Obesity</td>
<td>Diet/physical activity/bariatric surgery</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>ACE inhibitors/diuretics/β-blockers</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>Speech pathology therapy</td>
</tr>
<tr>
<td>Depression</td>
<td>Cognitive and behavioural therapy</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Anxiolytics</td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>Statins?</td>
</tr>
<tr>
<td><strong>Treatable behavioural/lifestyle factors</strong></td>
<td></td>
</tr>
<tr>
<td>Poor inhalation technique</td>
<td>Education</td>
</tr>
<tr>
<td>Nonadherence to treatment</td>
<td>Reassurance/education/periodic check-up</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cessation support</td>
</tr>
<tr>
<td>Exposure to sensitising agents</td>
<td>Avoidance/desensitisation</td>
</tr>
<tr>
<td>Side-effects of treatments</td>
<td>Treatment optimisation</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Medication review</td>
</tr>
<tr>
<td>Poor family and social support</td>
<td>Family therapy education/self-management support</td>
</tr>
</tbody>
</table>
# Targeted treatments for Asthma

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Biomarkers</th>
<th>Targeted treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin-sensitive asthma/AERD</td>
<td>Elevated FeNO</td>
<td>Leukotriene modifier</td>
</tr>
<tr>
<td></td>
<td>Elevated uLTE4</td>
<td>Anti-IgE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-interleukin 5/α</td>
</tr>
<tr>
<td>T2 allergic severe asthma</td>
<td>High serum periostin</td>
<td>Anti-IgE</td>
</tr>
<tr>
<td></td>
<td>High serum IgE</td>
<td>Anti-interleukin 13</td>
</tr>
<tr>
<td></td>
<td>High FeNO</td>
<td>Anti-interleukin 4α</td>
</tr>
<tr>
<td>Eosinophilic severe asthma</td>
<td>Recurrent exacerbations</td>
<td>Anti-interleukin 5/α</td>
</tr>
<tr>
<td></td>
<td>High serum IgE</td>
<td>Anti-interleukin 4α</td>
</tr>
<tr>
<td></td>
<td>High FeNO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High blood eosinophils</td>
<td></td>
</tr>
<tr>
<td>Chronic airflow obstruction</td>
<td>Airway remodelling</td>
<td>Bronchial thermoplasty</td>
</tr>
<tr>
<td></td>
<td>Increased airway wall thickness</td>
<td>Other biologicals</td>
</tr>
</tbody>
</table>

FENO, Fractional exhaled Nitric Oxide

- A reliable indicator of corticosteroid-responsive (Th2 driven) airway inflammation
- Monitor anti-inflammatory treatment effectiveness
- FeNO* testing of asthma patients or suspected asthma measures allergic airway inflammation
FeNO IS A BIOMARKER OF INFLAMMATION

Exhaled air

Allergen exposure

FeNO

Eosinophils

STAT-6

Mucus, AHR

IL-5

IL-4/IL-13

Th2 cells

Corticosteroid-sensitive mechanism

*Airway hyperresponsiveness

Ludviksdottir 2012
FeNO* Test: Initial Patient Visit

*Fractional exhaled Nitric Oxide

Help reveal if ICS will benefit patient

Assessment of inflammation
Is it steroid responsive inflammation?

Example values
FeNO 18 ppb, FeNO 54 ppb
Unlikely, Likely

Follow-up Visit

Help optimise ICS dose

Monitor treatment
Is anti-inflammatory therapy working?

Example values
FeNO 12 ppb, FeNO 62 ppb
Likely, Unlikely

Follow-up Visit

Help detect Non-adherence to ICS

Meaningful patient dialogue
Is the patient possibly not adhering to therapy?

Example values
FeNO 15 ppb, FeNO 78 ppb
Unlikely, Likely
Bronchial Thermoplasty

• A non-drug procedure for severe persistent asthma in patients 18 years and older whose asthma is not well-controlled with inhaled corticosteroids and long-acting beta-agonists.

U.S. Food and Drug Administration (FDA) approved bronchial thermoplasty on April 27, 2010.
Basic principle

• Delivers thermal energy to the airway wall, in a precisely controlled manner, in order to reduce excessive airway smooth muscle.

• Reducing airway smooth muscle decreases the ability of the airways to constrict, thereby reducing the frequency of asthma attacks.
Procedure

- Minimally invasive bronchoscopic procedure
- Performed in three outpatient procedure visits,
- Each treating a different area of the lungs
- Scheduled approximately three weeks apart.
- Should never be applied without proper anti-inflammatory pharmacotherapy in these patients.
Phenotypes of COPD

1. Non-exacerbator phenotype
   - (< 2 exacerbations/year)

2. Mixed phenotype COPD-asthma

3. Exacerbator phenotype with chronic bronchitis

4. Exacerbator phenotype with emphysema
   - (£ 2 exacerbations/year)

Spanish Guideline for COPD (GesEPOC). Update 2014
Pharmacological treatment of COPD according to phenotypes

<table>
<thead>
<tr>
<th>No exacerbator</th>
<th>Overlap COPD-asthma</th>
<th>Exacerbator with emphysema</th>
<th>Exacerbator with chronic bronchitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Long-acting bronchodilators</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhaled corticosteroids</td>
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<td></td>
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<td></td>
<td>Mucolytics</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PDE$_4$ inhibitors</td>
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<tr>
<td></td>
<td></td>
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<td>Macrolides</td>
</tr>
</tbody>
</table>
COPD heterogeneity

Faner R, Agustí Á.
Ann Am Thorac Soc 2016
Phenotyping Construct for the Development of Companion Diagnostics

Validation of molecular marker or determination of therapeutic response in population

Clinical Phenotype

Physiological and/or Radiological Characterization of phenotype

Biologic or molecular characterization of phenotype

+/− Development of therapy
Physicians always try to be as precise as possible in relation to the needs of individual patients - Best care for patients
Thank You for Your Attention!

Questions?