Obstructive Airways Diseases

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Phenotypes of Obstructive Diseases

- 3 core types of obstructive disease are recognized through clinical manifestations
- Asthma COPD, ACO
- Genetics are emerging as key in our understanding of the continuum of obstructive disease.
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 2017]

COPD

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. [GOLD 2017]

Asthma-COPD overlap [not a definition, but a description for clinical use]

Asthma-COPD overlap (ACO) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Asthma-COPD overlap is therefore identified in clinical practice by the features that it shares with both asthma and COPD. This is not a definition, but a description for clinical use, as asthma-COPD overlap includes several different clinical phenotypes and there are likely to be several different underlying mechanisms.
ACOS
- Low lung function
- Episodic wheezing
- Nocturnal symptoms
- BHR
- Eosinophilia
- GERD
- Limited reversibility of airway obstruction
- Hyperinflation
- Abnormal body composition
- Coexisting cardiac conditions
- Infections
- Dyspnea

COPD
- Genetic patterns
- Aging
- Smoking
- Maternal smoking
- Exposure to smoke from biomass fuels
- Occupational hazards
- Poor nutrition
- BHR
- Emphysema
- BPD

Asthma
- Genetic patterns
- Maternal smoking
- Childhood diseases
- Allergy
- IgE
- Eosinophilia
- Exhaled nitric oxide
- Th2-related inflammation
- Rhinitis

INFLUENCE OF ENVIRONMENT AND AGING ON SEVERITY AND CHRONICITY OF DISEASE

Drazen NEJM 2015
Endotypes

• Subset of disease driven by specific molecular mechanisms
• Arising from interaction between genetic (genotypes) & environmental factors
• Characteristic course & response to therapy

Anderson Eur Respir J 2008
ASTHMA

Allergens → Ep cells → Mast cell → CD4+ cell (Th2) → Eosinophil → Bronchoconstriction

AHR

COPD

Cigarette smoke → Ep cells → Alv macrophage → CD8+ cell (Tc1) → Neutrophil → Small airway narrowing

Alveolar destruction

Airflow Limitation

Reversible

Irreversible

Peter J. Barnes
Asthma Endotypes

- Not one disease mechanism with variable presentation but several with a common clinical phenotype
  - TH2 type: Allergic disease: mast cells, eosinophils, TH2 proinflammatory proteins, NK cells ± BM thickening
  - Non TH2: EIA, smokers, elderly asthmatics, aspirin-sensitive, severe asthma: relative steroid resistance, neutrophilic or paucigranulocytic sputum profiles
Inflammatory mechanisms associated with granulocytic inflammation

**Type 2 inflammation**
- Antigens
- CRTH2
- TSLP
- IL-25
- IL-13
- IL-4, 5, and 13
- IL-4
- IgE
- KIT
- GM-CSF
- Leukotrienes
- PGD₂
- Histamine
- IL-3, 4, 5, and 9
- Th2 cell
- GATA3

**ILC2**
- GATA3
- CRTH2
- IL-5
- IL-13
- IL-17
- IL-23
- CXCL8
- IL-6
- TGF-β
- IL-25
- IL-33

**Eosinophil**
- CXCR2
- Lipoxin
- ALX
- BLT₂

**Neutrophil**
- Leukotriene B₄
- IFN-γ
- TNF-α

**Non-type 2 inflammation**
- Irritants, pollutants, microbes, and viruses
- CXCL8
- GM-CSF
- IL-6
- IL-8

**Mast cell**
- CRTH2
- IL-3, 4, 5, and 9

*Drazen NEJM 2017*
Asthma: Phenotypes

- Clinically distinct often overlapping syndromes
- Based on *clinical* characteristics including allergy, response to exercise, viral infections, smoking or other environmental factors

Phenotypes of Severe Asthma

- Early onset allergic
- Persistent eosinophilia,
- ABPA
- Obese-female
- Neutrophilic
- The future will involve personalized treatment based on biological data: genomic, proteomic and metabolic profiles

Wenzel Clin Exp Allergy 2012
Waldman Clin Transl Sci 2011
Anxiety/depression & Obesity

• Non-obese with anxiety or depression: OR 1.20 (1.00-1.45)

• Obesity without anxiety or depression OR 1.47 (1.19-1.82).

• Obesity plus anxiety or depression: asthma risk OR 2.93 (2.20-3.91)
COPD: Clinical phenotype

• Classical phenotypes:
  – CB: cough, sputum: goblet cell metaplasia impaired, ciliary dysfunction
  – Emphysema: progressive dyspnea, parenchymal destruction; air trapping, dynamic hyperinflation
COPD: Endotypes Inflammation

- Macrophages, PMNL, CD8 T cells, mast cells with possible systemic “spillover” of inflammation
- ECLIPSE study recognized 5 clinically & biologically different clusters with variable prognosis

Newer Phenotypes

- COPDGene cohort: 4 clusters:
  - relatively resistant smokers: heavy smoking with no/mild obstruction & minimal emphysema
  - mild upper zone emphysema-predominant
  - airway disease-predominant
  - severe emphysema

- All have COPD-related clinical characteristics eg exacerbations & dyspnea
ACO

- Growing evidence that subjects with both COPD & asthma represent an important & distinct patient population, with worse clinical features than with COPD alone
ACO Aetiology & Mechanisms

• As with COPD smoking is a critical factor in most types of ACO
• Smoke increases PMNL & eosinophils (modestly)- inflammatory response driven by TH1/TH17 cytokines; IL-8 & TNF & LTB4

Smoking

- Smoking disrupts balance between acetylated/deacetylated histones causing increased/persistent inflammation in COPD & asthma with impaired CS response.
- Aging may also be a risk factor for ACO - Increased prevalence with age associated with AHR, reduced CS response & greater asthma severity.
ACO: Endotypes

1. Asthma predominant with eosinophilic inflammation & elevated TH2 mediators
2. COPD predominant with elevated proinflammatory cytokines
3. COPD predominant: overlap group with chronic bronchitis, increased bacterial colonization, elevated sputum IL-1b and TNF-a levels & sputum neutrophilia

ACO Phenotypes

- COPD with increased reversibility
- Late onset asthma with history of smoking
- Ex smokers with asthma
- Asthma with remodelling

COPD

Mucosal and peribronchial inflammation and fibrosis (obliterative bronchiolitis)

Mucus hypersecretion

Disrupted alveolar attachments (emphysema)

FEV$_1$ (% of predicted value at 25 yr of age)

Normal

COPD

ACOS

Progressive COPD

Drazen NEJM 2015
Phenotypes of asthma, COPD & ACO

Asthma
Variable symptoms and reversible airflow limitation

COPD
Smoker and fixed airflow limitation

ACOS
Phenotypes/endotypes

Chronic airflow limitation and significant bronchodilator response

ACOS
Eosinophilic
ACOS
Asthma in smokers
ACOS
Non-smoker and biomass
ACOS
Neutrophilic
ACOS
“n”

Bateman Lancet Respir Dis 2015
Asthma Treatment: GOAL Study Design

3,416 uncontrolled asthma patients

- 3
  - > 500 – 1000 μg BDP equiv.
  - n=1155

- 2
  - ≤ 500 μg BDP equiv.
  - n=1163

- 1
  - Steroid naive
  - n=1098

Stratum

Bateman et al, AJRCCM 2004; 170: 836
Asthma Treatment


*P=0.003; **P<0.001
Stepwise management - pharmacotherapy

**GINA 2017, Box 3-5 (2/8) (upper part)**

**Other controller options**

**Low dose ICS**
- Consider low dose ICS
- Leukotriene receptor antagonists (LTRA)
- Low dose theophylline*
- As-needed short-acting beta₂-agonist (SABA)

**Low dose ICS/LABA**
- Med/high dose ICS/LABA
- Add theophylline*
- Low dose ICS+LTRA (or + theoph*)

**Med/high ICS/LABA**
- Med/high dose ICS
- Add tiotropium
- Low dose ICS+LTRA (or + theoph*)

**Step 5**
- Refer for tiotropium, * anti-IgE, ** anti-IL5*
- Add low dose OCS

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

**Asthma medications**
- Non-pharmacological strategies
- Treat modifiable risk factors
Tiotropium in Asthma

- 13 RCTs (n=4,966)
  - Add-on to ICS: Improved control; clinically significant increases in PEF & FEV1 (140-150mL); decreased rate of AE: NNT for benefit 36
  - Add on to medium-high ICS: not inferior to salmeterol
  - Add-on to ICS/salmeterol: improved control, clinically significant PFT increase, reduced AE [RR 0.70; (0.53-0.94) P<.02]; NNT for benefit 17
Biologics

- **Omalizumab**: (weight & IgE based dose) Anti-IgE; binds free IgE Fc receptor (IgE ≥30 IU/ml; atopic; Feno ≥20ppb): Reduces AE; ± symptoms & FEV1
- **Mepolizumab**: Anti-IL-5: Best response ≥ 2 AE/year & ≥300 EOS/μl: Reduces AE, symptoms, ± FEV1
- **Reslizumab**: Anti-IL-5 ≥ AE & ≥400 EOS/μl. Reduces AE & symptoms, small effect FEV1
- **Benralizumab**: Anti-IL-5 efficacy with ≥2 AE & ≥300 EOS/μl; Reduced AE, symptoms, moderate FEV1
- **Dupilumab**: Anti- IL4 & 13 via common receptor ≥1 AE & ≥300 EOS/μl: Reduced AE improved FEV1

Drazen NEJM 2017
COPD Treatment Goals

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent disease progression
- Prevent & treat exacerbations
- Reduce mortality

Reduce symptoms

Reduce risk

Symptoms: LABA/LAMA

- LABA and Tiotropium
  - increase exercise duration, reduce lung volumes and reduce exercise associated dyspnoea
  - Improve quality of Life (SGRQ)
  - Reduce exacerbations
LABA/LAMA Combinations

- COPD not controlled on 1 bronchodilator should be given 2 with different mechanisms of action
- May allow lower doses, decrease adverse effects, simplify regimens & improve compliance
- LABA/LAMA induces larger bronchodilation & improves many patient-reported outcomes

Cazzola Clin Chest Med 2014
van der Molen Prim Care Respir J 2012
Inhaled corticosteroids in Stable COPD

- ICS/LABA improve PFT & health status & reduce AE in patients with exacerbations & moderate-very severe COPD > LABA or ICS alone (Evidence A)
- ICS increase CAP esp in severe disease (A)
- ICS/LAMA/LABA improve PFT, symptoms, health status (A) & reduce AE (B) > ICS/LABA or LAMA

**Oral glucocorticoids:** Long-term have numerous side effects (A) & no evidence of benefit (C)

Roflumilast (RFT) & AE in severe COPD & Appropriate Combination Therapy (REACT)

- 1-year DBPCT, parallel group, phase 3-4 study: n=1945; chronic bronchitis & ≥ 2 AE in past year
- RFT 500μg vs placebo + (ICS/LABA ± tio)
- Moderate/severe AE: 13.2% < placebo: RR 0.868 [0.753-1.002] p=0.0529: (Poisson progression analysis) but 14.2% lower with negative binomial regression: RR 0.858 [0.740-0.995] p=0.0424
- Adverse events: RFT 67%; placebo 59%
- Withdrawals: RFT 11%; placebo 5%

Martinez Lancet 2015
GOLD 2017

Spirometrically confirmed diagnosis → Assessment of airflow limitation → Assessment of symptoms/risk of exacerbations

Post-bronchodilator FEV₁/FVC < 0.7

| GOLD 1 | ≥ 80 |
| GOLD 2 | 50-79 |
| GOLD 3 | 30-49 |
| GOLD 4 | < 30 |

Exacerbation history

≥ 2 or ≥ 1 leading to hospital admission

0 or 1 (not leading to hospital admission)

Symptoms

mMRC 0-1
CAT < 10

mMRC ≥ 2
CAT ≥ 10
Treatment Algorithms by GOLD Grade

(highlighted boxes and green arrows indicate preferred treatment pathways)

Am J Respir Crit Care Med 2017 [E-Pub]
ACO: Therapy

• More problematic
  – Asthmatics mostly excluded from COPD trials
  – Asthma guidelines exclude smokers

• Given the role of ICS in asthma & COPD & effects of cigarettes on steroid responsiveness choices are difficult
ACO: Therapy

• Uncertainties regarding LABAs alone in ACOS led to recommendation ICS should always be used as well

• Thereafter consensus recommends triple therapy  ICS, LABA & LAMA

Soler Curr Allergy Asthma Rep 2014;14:484.