Moving from the Oslerian Paradigm to Post-genomic Era: Are Asthma and COPD Outdated Terms?
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Pulmonary and Critical Care Medicine
Director, Asthma Clinical Research Center
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  – National Heart, Lung, and Blood Institute, American Lung Association
  – GSK, Boehringer Ingelheim, Genentech, Sunovion, Mylan, Pearl Therapeutics, Chiesi

Outline

✓ Revisiting the Dutch Hypothesis: Do Asthma and COPD Represent a Continuum of One Disease?
✓ Similarities and Differences Between Asthma and COPD: Problems with the Traditional Approach
  ✓ Risk factors/ Clinical Presentation and Course
  ✓ Pathologic Mechanisms
  ✓ Physiology
  ✓ Management
✓ Is Asthma COPD Overlap Syndrome (ACOS) the Solution?
The “Dutch” Hypothesis

Common Disease?

Common Mechanisms

Professor Dick Orie

Groningen, NL

The “Dutch” Hypothesis

Host (Genetic) factors

Endogenous factors

Environmental factors

Bronchial Inflammation

Asthma

CNSLD

COPD

Postma DS, Boezen HM. Chest 2004; 126: 96-104


The “Dutch” Hypothesis

“one must be impressed by the very long road medicine must travel before an understanding of disease is reached, even when its clinical symptomatology is relatively simple” (Bronchitis, 1961, page 5)
The Debate Continues…

The “Dutch” Hypothesis

Common Disease?
Common Mechanisms

Professor Dick Orie
Groningen, NL


Allergies

The British Hypothesis

Different Diseases
Different Mechanisms

Professor Charles Fletcher,
London, UK

Asthma
COPD

Irritants/
Smoking

The Overlap Between Asthma and COPD

Traditional View

• A chronic inflammatory disorder of the airways in which many cells and factors play a role
• Inflammation results in
  – Recurrent symptoms
  – Variable airflow obstruction that is mostly reversible
  – Increase in existing bronchial hyperresponsiveness

What Is Asthma?

What Is COPD?

• A preventable and treatable disease
• Associated with significant extrapulmonary effects and important comorbid conditions
• Characterized by airflow limitation that is
  – Not fully reversible
  – Usually progressive
  – Associated with an abnormal inflammatory response to noxious particles or gases
Asthma and COPD Share Some Common Environmental Risk Factors

### Risk / Precipitating Factors

#### Asthma
- Genetic susceptibility
- Airway hyperresponsiveness
- Obesity
- Environmental
  - Allergen exposures
  - Viral respiratory infections
  - Tobacco smoke and air pollution
- Disease triggers
  - Exercise
  - Changes in weather
  - Exposure to cold air
  - Emotional factors
  - Endocrine factors

#### COPD
- Host factors
  - α1-Antitrypsin deficiency
  - Other genetic factors (?) not yet identified
  - Airway hyperresponsiveness
  - Lung growth: reduced maximal attained pulmonary function
- Environmental factors
  - Tobacco smoke
  - Occupational dusts and chemicals
  - Outdoor and indoor air pollution
  - Infections: history of severe respiratory infection in childhood
  - Socioeconomic factors

#### Clinical Presentation Between Asthma and COPD – Traditional View

**Asthma**
- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma

**COPD**
- Onset in mid-life
- Symptoms slowly progressive
- Long smoking history
- Dyspnea during exercise
Traditional Approach in Differentiating Asthma and COPD – Clinical Presentation

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset early/life</td>
<td>Onset after age 40</td>
<td></td>
</tr>
<tr>
<td>Often atopic</td>
<td>Usually not atopic</td>
<td></td>
</tr>
<tr>
<td>Night and early morning symptoms</td>
<td>Dyspnea with activity</td>
<td>Progressive symptoms</td>
</tr>
<tr>
<td>Variable symptoms</td>
<td>Progressive symptoms</td>
<td></td>
</tr>
<tr>
<td>Usually non-smokers</td>
<td>Smoker &gt;10 pack year</td>
<td></td>
</tr>
<tr>
<td>One phenotype</td>
<td>Blue bloater and pink puffer</td>
<td></td>
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Immunology of Asthma and COPD: Traditional View
**Inflammatory Cells / Mediators**

**Asthma vs. COPD – The Traditional View**

**Asthma**
- Eosinophils and mast cells
- Neutrophils (severe)
- CD 4+ T, 2 cells
- LTC4, D4, E4
- Cytokines
  - IL-4, IL-5, IL-13
  - RANTES, eotaxins, MCP-1

**COPD**
- Macrophages and neutrophils
- Eosinophils (exacerbations)
- CD 8+ T cells,
- LTB4, Interferon γ
- Cytokines
  - IL-8, IL-1
  - TNF-α

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**Pathology of Asthma and COPD**

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**Airway Inflammation Biomarkers**

**Asthma vs. COPD**

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Pathobiology of Asthma: Beyond TH2-Inflammation


Pathobiology of COPD: Beyond Neutrophilic Inflammation


Inflammation-Similarities

- Alveolar inflammation demonstrated in asthma
- Severe asthma / Smokers with asthma/ Elderly Asthma- BAL with neutrophils
- COPD: tissues and airway eosinophils in some patients and during exacerbations
  - Pts with eosinophils have better response to steroids

1 Kraft M. Am J Respir Crit Care Med 1996;154:1505
2 Wenzel S. Am J Respir Crit Care Med 1999;160:1001
3 Chanez P. Am J Respir Crit Care Med 1997;155:1529
Asthma with Features of COPD

Traditional Approach in Differentiating Asthma and COPD - Immunology/Pathology

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
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<tr>
<td>Airway inflammation - Eosinophil predominant</td>
<td>Airway inflammation - Neutrophil predominant</td>
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<tr>
<td>Predominantly medium airway inflammation</td>
<td>Predominant small airway inflammation and parenchymal lung destruction</td>
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<tr>
<td>Airway inflammation – Eosinophilic predominant</td>
<td>Airway inflammation - Neutrophilic predominant</td>
<td>• The presence of inflammatory cells in the airways does not differentiate asthma from COPD but their measurement may guide treatment decisions.</td>
</tr>
<tr>
<td>Predominantly medium airway inflammation</td>
<td>Predominant small airway inflammation and parenchymal lung destruction</td>
<td>• Airway inflammation in asthma often involve the small airway and parenchymal changes including lung destruction have been described.</td>
</tr>
<tr>
<td>• The presence of inflammatory cells in the airways does not differentiate asthma from COPD but their measurement may guide treatment decisions.</td>
<td>• Inflammation in COPD can involve multiple components of the lung as well as be associated with systemic inflammation.</td>
<td></td>
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Physiologic Differences: Traditional View

**Asthma**
- Reversible airway obstruction
- Normal DLCO
- Normal lung volume
- Normal elastic recoil (except in severe disease)
- Flow dominant BD response
- BHR almost always present

**COPD**
- Partially reversible obstruction
- Abnormal DLCO
- Hyperinflation
- Decreased elastic recoil
- Volume dominant BD response
- BHR only in some patients

Sources:
- Boulet L Can Respir J 1996;5:270
- Fabbri LM Am J Respir Crit Care Med 2003;167:418
- Sciurba FC CHEST 2004;117S-124S
- Gelb AF Curr Opin Pulm Med 2006;14: 24 - 30

Clinical Heterogeneity in the Severe Asthma Research Program

- Lower lung function, worse early onset
- Lower lung function, later onset
- Lower lung function, severe onset
- Lower lung function, non-severe onset
- Lower lung function, very early onset

Post classification of this group

- Group 1: Lower lung function
- Group 2: Worse early onset
- Group 3: Lower lung function, severe onset
- Group 4: Lower lung function, non-severe onset
- Group 5: Lower lung function, very early onset

10% 25% 35% 51% 72% 51% 72% 58% 87% 75%
Residual Volumes ↑
air trapping?
emphysema?

Lung Function Decline: Asthma vs. COPD

Acute Bronchodilator Response Does not Differentiate Between Asthma and COPD

Lung Function Decline: Asthma vs. COPD

Severe Asthma
Lessons Learned From the National Heart, Lung, and Blood Institute Severe Asthma Research Program

Peat JK. Eur J Respir Dis. 1987

Fletcher and Peto, 1977
Longitudinal Lung-Function Trajectories in Asthma

Factors associated with reduced lung growth:
- Lower baseline FEV1
- Smaller bronchodilator response
- AHR at baseline
- Male sex

Airway Hyperresponsiveness

- Positive Methacholine occurs in nearly all asthmatics, < 5% normals
- 63% of men and 87% of women with COPD show AHR with < 25 mg/ml of metacholine
  - Lower PFT’s associated with >AHR, decline in lung function and mortality
  - Smoking cessation has positive effect on AHR and improves FEV1 greater in those with AHR

Traditional Approach in Differentiating Asthma and COPD - Physiology

<table>
<thead>
<tr>
<th>Asthma</th>
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<tr>
<td>Reversible airway obstruction</td>
<td>Only partially reversible airflow obstruction</td>
</tr>
<tr>
<td>Normal/DLCO</td>
<td>Low (DLCO: emphysema, hyperinflation and gas trapping)</td>
</tr>
<tr>
<td>Normal lung volumes</td>
<td>No airway hyperresponsiveness (AHR)</td>
</tr>
<tr>
<td>Airway hyperresponsiveness (AHR)</td>
<td>Lung function decline</td>
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Traditional Approach in Differentiating Asthma and COPD - Physiology

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<th>COPD</th>
<th>Problem with the approach</th>
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</thead>
<tbody>
<tr>
<td>Reversible airflow obstruction</td>
<td>Only partially reversible airflow obstruction</td>
<td>A subgroup of patients with long-standing asthma do not demonstrate reversible airflow obstruction. A subgroup of chronic obstructive pulmonary disease (COPD) does not demonstrate reversible airflow obstruction.</td>
<td></td>
</tr>
<tr>
<td>Normal/DLCO</td>
<td>Low DLCO (emphysema)</td>
<td>Hyperinflation and gas trapping</td>
<td>Some patients with severe asthma have physiologic abnormalities seen in COPD (reduced RV/TLC, low DLCO)</td>
</tr>
<tr>
<td>Airway hyperresponsiveness (AHR)</td>
<td>No airway hyperresponsiveness (AHR)</td>
<td>Some patients with asthma fail to demonstrate AHR. AHR is common in COPD patients with emphysema (correlates with poor outcomes)</td>
<td></td>
</tr>
<tr>
<td>Lung function decline</td>
<td>Lung function decline</td>
<td>In a subgroup of asthma, lung function decline may result in airflow obstruction that resembles COPD</td>
<td></td>
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</tbody>
</table>

Similar Goals of Management

- Reducing Impairment
- Reducing Risk
- Reducing Hospital Admissions and Mortality

Treatment Guidelines

- GINA
- GOLD

- Two different sets of guidelines
- Two different treatment paradigms
- Similar pharmacologic agents
Medications for Asthma and COPD

Asthma
- Anti-inflammatory drugs
  - Corticosteroids
  - Antileukotrienes
  - Theophylline (?)
- Bronchodilators
  - Short and Long-acting ß-agonists
  - Short-acting and Long-Acting Anticholinergics
- ICS/LABA combination
- Anti IgE
- Anti IL-5

COPD
- Bronchodilators
  - Short and Long-acting ß-agonists
  - Short and Long-acting Anticholinergics
  - Theophylline
- Anti-inflammatory drugs
  - Corticosteroids
  - PDE4 inhibitor (Roflumilast)
- ICS/LABA Combination
- Anti IgE
- Anti IL-5
- Antibiotics
- Vaccination

Asthma and COPD Pharmacological Treatment Options: Current Guidelines

Adapted from: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

Traditional Approach in Differentiating Asthma and COPD - Response to Therapy

<table>
<thead>
<tr>
<th>Asthma</th>
<th>COPD</th>
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<tbody>
<tr>
<td>Steroid-responsive</td>
<td>Relative steroid-resistant</td>
</tr>
<tr>
<td>Marked response to bronchodilators</td>
<td>Partial response to bronchodilators</td>
</tr>
<tr>
<td>LABA monotherapy unsafe</td>
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Traditional Approach in Differentiating Asthma and COPD- Response to Therapy

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<th>COPD</th>
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</table>
| Steroid-responsive | Relative steroid resistant | - A moderate proportion of COPD patients have eosinophilic airway inflammation which predict response to inhaled steroids.  
- Asthma patients with Low T2 airway inflammation or no inflammation do not respond to steroids. |
| Marked response to bronchodilators | Partial response to bronchodilators | - Variable according to disease severity and duration.  
- COPD patient demonstrate volume response |
| LABA monotherapy unsafe | LABA monotherapy safe | - Same patients with COPD have asthma component |

Pathways to Chronic Airflow Obstruction

- No Asthma  
  - No allergies  
  - No family history  
  - Smoking  
  - Risk factors

- Asthma  
  - Allergies  
  - Family history  
  - No Smoking  
  - No Risk factors

- No Asthma  
  - No allergies  
  - No family history  
  - Smoking  
  - Clinical features of asthma  
  - Risk factors

- Asthma  
  - Allergies  
  - Family history  
  - Smoking  
  - Clinical features of asthma  
  - Risk factors

- Asthma  
  - Allergies  
  - Family history  
  - No Smoking  
  - No Risk factors
The Overlap Between Asthma and COPD
Emerging View: Is this ACOS??

Other Asthma Phenotypes
- Smoker with asthma
- Late-onset Asthma
- Neutrophilic Asthma

Other COPD Phenotypes
- Eosinophilic COPD
- Emphysema

Prevalence of Overlap Syndrome Increases with Age

What do we know about ACOS?

- Complex interaction between genetic predisposition and the environment
- Inflammation plays a key role for both, neutrophilic and eosinophilic inflammation can be seen in both
- Heterogeneous (variable) natural history & clinical course
- Airway obstruction and hyperresponsiveness underly pathophysiology and is associated with progressive loss of lung function
- The presence or absence of reversibility of FEV1 does not distinguish one from the other
- Approach to management for both involves risk factor modifications, self management education and pharmacotherapy