Life-long asthma and its relationship to COPD

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Definitions

- **COPD** is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients.
- Its pulmonary component is characterized by airflow limitation that is not fully reversible.
- The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

- **Asthma** is a chronic inflammatory disorder of the airways.
  - Many cells and cellular elements play a role.
  - Chronic inflammation is associated with airway hyperresponsiveness, that leads to recurrent episodes of wheezing, breathlessness chest tightness and coughing.
  - Widespread, variable and often reversible airflow limitation.
Risk factors for COPD

- Cigarette smoke
- Occupational dust and chemicals
- Environmental tobacco smoke (ETS)
- Indoor and outdoor air pollution

- Nutrition
- Infections
- Socio-economic status

Aging Populations
Bronchial biopsy specimens of the airway mucosa.
Pathology of emphysema
Inflammatory mechanisms in COPD

Barnes PJ. Chest 2000; 117: 10-14S

CD8+/mm²

CD8⁺ lymphocyte

FeV₁, % pred.

Viruses or bacteria

Neutrophils

MCP-1

CXC chemokines (IL-8, GRO-α)

Lipid mediators (LTB₄)

Neutrophil elastase

Cathepsins

Matrix metalloproteinases

Emphysema

Mucus hypersecretion

PROTEASE INHIBITORS

α₁-At

SLPI

TIMPs

PROTEASES
Asthmatic inflammation: cells and mediators
Consequences of asthmatic inflammation

**INFLAMMATION**

*Chronic eosinophilic bronchitis*

**TRIGGERS**
- Allergens
- Exercise
- Cold air
- SO₂
- Particulates

**SYMPTOMS**
- Cough
- Wheeze
- Chest tightness
- Dyspnea

**Direct:** histamine, methacholine

**Indirect:** Allergen, exercise, cold air, hyperventilation, fog, hypertonic (mannitol, saline), bradykinin, SO₂
Overlap between asthma and COPD

- Chronic bronchitis
- Emphysema
- Asthma
- Airflow obstruction

COPD
Overlap between COPD and asthma

But none of these criteria are absolute! This where the confusion lies.
Asthma and COPD are easily confused:

CT scans of two subjects with clinical histories that are consistent with COPD

- Both patients had similar history of tobacco use, and neither had symptomatic bronchitis or bronchodilator reversibility.

- The pattern found in the right, B, panel may be indistinguishable from that of a long-term asthma patient.

66% emphysema by quantitative analysis
(FEV₁, 25% of predicted)

Minimal emphysema
(FEV₁, 23% predicted)

Sciurba FC. Chest 2004; 126 Suppl 2: 1175-245
<table>
<thead>
<tr>
<th>COPD</th>
<th>ASTHMA</th>
</tr>
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<tbody>
<tr>
<td>Onset in mid-life</td>
<td>Onset early in life (often in childhood)</td>
</tr>
<tr>
<td>Symptoms slowly progressive</td>
<td>Symptoms vary from day to day</td>
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<tr>
<td>Long smoking history</td>
<td>Symptoms at night/early morning</td>
</tr>
<tr>
<td>Dyspnoea during exercise</td>
<td>Allergy, rhinitis, and/or eczema also present</td>
</tr>
<tr>
<td>Largely irreversible airflow limitation</td>
<td>Family history of asthma</td>
</tr>
<tr>
<td></td>
<td>Largely reversible airflow limitation</td>
</tr>
</tbody>
</table>
Is it asthma?

- Recurrent episodes of wheezing.
- Troublesome cough at night.
- Cough or wheeze after exercise.

A number of these also occur in COPD!

- Cough, wheeze or chest tightness after exposure to airborne allergens or pollutants.
- Colds “go to the chest” or take more than 10 days to clear.
- Response to a short course of oral corticosteroids
Asthmatic inflammation usually responds to corticosteroids: trial of treatment

But chronic asthma can become steroid resistant
Epigenetic drivers of corticosteroid responsiveness
Chronic Obstructed ‘Fixed’ Asthma

• Decline in FEV$_1$ in non-allergic asthma over 10 years is greater (Ulrik CS et al. A 10 year follow up of 180 adults with bronchial asthma: factors important for the decline in lung function. Thorax. 1992; 47: 14-8).

• Mean loss FEV$_1$ in males with asthma 50ml/yr vs 35ml/yr normals (Peat et al, Rate of decline of lung function in subjects with asthma. Eur J Respir Dis. 1987; 70: 171-9).

• Associated with severe asthma in children and late-onset asthma.

• Older patients and smokers have more fixed airflow obstruction.

• Accelerated decline in lung function over time partially responds to better asthma control with corticosteroids.
Severe exacerbations and lung function decline in asthma

- 93 moderate-severe non-smoking asthmatics followed for 5 years after starting ICS.
- 56 recorded at least 1 severe exacerbation.
- Frequent exacerbations associated with larger annual decline in FEV$_1$ (median $\Delta$ 17 ml/yr).

Exacerbations are associated with excess lung function decline in asthma.

Bai TR et al Eur Respir J 2007; 30: 452-6
Quality of life and economic features in elderly asthmatics.

- To compare the characteristics of asthma between elderly (≥65 years) and adult (<65 years) asthma patients with regard to asthma severity, health-related quality of life, and direct expenditures for medical care generated by the disease in Barcelona, Spain.

- Asthma was more severe in the elderly group (mild 10%, moderate 35%, severe 55%) than in the adult group (mild 47%, moderate 35%, severe 18%).

- Asthma-derived direct costs in the elderly (mean USD $1,490 vs. $773) were double those in adult asthmatics, due to higher costs of hospitalization and medication.

- Asthma in older people more severe and was associated with a worse health-related quality of life, and significantly higher expenditures for medical care.

Asthma in the elderly: mortality rate and associated risk factors for mortality

• To compare mortality rates of elderly people with and without asthma and to identify mortality risk factors in those with asthma. 1,233 ambulatory patients aged ≥ 65 years with a diagnosis of asthma (n = 210) or chronic non-respiratory conditions (n = 1,023) enrolled.

• Spirometry and multidimensional assessment and followed up for a mean of 57.9 months.

• The 5-year mortality rate in people with asthma was 24.3% vs 16.3% in control subjects (p < 0.01), but asthma per se did not explain the excess risk of death.

• The main causes of death among people with and without asthma were cardiovascular diseases (36.4% and 21.3%, respectively), non-neoplastic lung diseases (28.8% vs 5.4%), and neoplasms (7.6% vs 22.6%).

Other disorders confused with asthma/COPD

- Eosinophilic bronchitis (cough++ with sputum eosinophils, no BHR).
- Broncho-pulmonary aspergillosis.
- Occupational asthma.
- Churg-Stauss syndrome.
- Bronchial neoplasm.
- Endobronchial sarcoid.
- Bronchiectasis.
- *Bronchiolitis obliterans*
Life-course of asthma

The contribution of EMTU components to asthma inception, persistence and chronicity
Similarities and differences in asthma and chronic obstructive pulmonary disease exacerbations.


- Time course of an exacerbation similar between asthma and COPD.
- Decrease in PEF is more pronounced in asthma than in COPD.
- Frequency of exacerbations is linked to disease severity in both asthma and COPD.
- Common causes are viral infections and increased environmental air pollution, whereas allergen exposure and bacterial infections are more specific for asthma and COPD exacerbations, respectively.
- Few data are available about the airway pathology of asthma or COPD exacerbations. Eosinophilia and/or neutrophilia associated with exacerbations in both diseases.
Overcoming gaps in the management of asthma in older patients: new insights.

• Distinguishing asthma from COPD is important to allow appropriate management of disease.

• The two conditions are usually differentiated by clinical features: age at onset, variability of symptoms and nocturnal symptoms in asthma, supported by the results of reversibility testing. Gas transfer factor is characteristically reduced in COPD and usually normal or high in asthma.

• Methacholine challenge tests previously mainly used in research are now used widely and safely to confirm asthma.

Barua P, O’Mahony MS  Drugs Aging. 2005;22(12):1029-59
Differences in inflammatory mechanisms between asthma and COPD

<table>
<thead>
<tr>
<th>Chronic obstructive pulmonary disease</th>
<th>Asthma</th>
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<tbody>
<tr>
<td>CD8 type 1 T lymphocytes</td>
<td>CD4 T&lt;sub&gt;+&lt;/sub&gt;2 lymphocytes</td>
</tr>
<tr>
<td>↓ CD4/CD8</td>
<td>↑ CD4/CD8</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Mast cells</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>Eosinophils (exacerbation)</td>
<td>Neutrophils (severe asthma)</td>
</tr>
<tr>
<td>IL-8, IL-1</td>
<td>IL-4, IL-5, IL-13</td>
</tr>
<tr>
<td>Leukotriene B4, interferon γ</td>
<td>RANTES, eotaxins, MCP-1</td>
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IL, interleukin; MCP-1, monocyte chemoattractant protein 1; RANTES, regulated on activation, normal T-cell-expressed and secreted.
Symptom-based questionnaire for differentiating COPD and asthma.

- Symptom-based questionnaires could identify persons likely to need spirometry.

- A prospectively tested questions derived from a comprehensive literature review and an international Delphi panel to help identify chronic OLD (COPD) in persons with prior evidence of OLD.

- Participants answered 54 questions covering demographics and symptoms and underwent spirometry with reversibility testing.

- The ability of individual questions in a multivariate framework to discriminate between persons with and without the study diagnosis of COPD was examined.

Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over

- Among subjects with a spirometry-based study diagnosis of COPD, 51.5% reported prior diagnosis of asthma without concurrent chronic bronchitis and emphysema (CBE), 37.9% a prior diagnosis of CBE, and 10.6% no prior diagnosis of obstructive lung disease.

- Despite the availability of consensus guideline diagnostic recommendations, diagnostic confusion between COPD and asthma appears common.

- Increased awareness of the differences between the two conditions is needed to promote optimal patient management and treatment.

Tinkelman DG et al   J Asthma. 2006 Jan-Feb;43(1):75-80
Symptom-based questionnaire for differentiating COPD and asthma.

- 597 persons completed all investigations and proceeded to analysis. The list of 54 questions yielded 52 items for analyses, which was reduced to 19 items for entry into a multivariate regression model.

- Nine items had significant relationships with the study diagnosis of COPD, including increased age, pack-years, worsening cough, breathing-related disability or hospitalization, worsening dyspnea, phlegm quantity, cold going to the chest, and receipt of treatment for breathing. Individual items yielded odds ratios ranging from 0.33 to 20.7.

- This questionnaire demonstrated a sensitivity of 72.0 and a specificity of 82.7.

The course and prognosis in subjects with chronic airflow obstruction selected from general population in a longitudinal study.

Subjects with symptoms and signs of asthma had higher survival rate and a much lower rate of decline in lung function than the subjects whose clinical characteristics were compatible with emphysematous COPD.

The 10-year mortality among subjects in non-atopic smokers without a history of asthma was 60% vs 15% for atopic subjects or non-smokers with known asthma.

Mean rate of decline in FEV₁ 70 ml/yr in COPD, but < 5 ml/yr in asthma.

Patients in Group II who did not clearly fit into either Group I or III had intermediate values for survival and decline in pulmonary function.

Better control of progression of “asthmatic bronchitis” with therapy may explain its more favourable prognosis.
Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex


- Median follow-up of 23 yrs: after ICS, men had 21 ml/yr less decline in FEV₁ c.f. 3.2 ml/yr for women.

- A higher dose of ICS was associated with a smaller decline in lung function in men, but not in women.

- 1 severe exacerbation/yr → 30 ml greater decline in FEV₁

Dijkstra A et al  Thorax  2006; 61: 105-10
Asthma in the elderly: mortality rate and associated risk factors for mortality

- In people without asthma, death was associated with age, gender, smoking, cardiovascular diseases, worse performance on a 6-min walking test, cognitive impairment, depression, and worse respiratory function.

- In people with asthma, only the association between death and age, smoking, and depression was confirmed.

- In asthmatics: inverse correlation between being overweight and death (hazard ratio [HR], 0.35; and a trend toward a higher mortality rate in people with a body mass index < 22 kg/m$^2$ (HR, 2.21; 95% CI, 0.94 to 5.18).

- Asthma in the elderly was associated with higher mortality rate, although this condition was not an independent risk factor. Causes of death and factors associated with death were somewhat different between people with and without asthma.