Pharmacology of the Respiratory Tract: COPD and Steroids

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Lecture Overview

COPD Lecture I
- Define Lung alveolar Structure
- Define COPD - Emphysema
  - epidemiology
  - alterations in lung function
- Action of steroids

COPD Lecture II
- Define COPD – Chronic bronchitis
  - Th1 Inflammation
  - Inflammatory cells involved in COPD
  - Inflammatory mediators involved in COPD
- Actions of Anti-TNFalpha therapy
The Respiratory System

Weibel, 2009, Lung Cast

GAS EXCHANGE STRUCTURE

Blood In

CO₂Out

O₂In

Blood Out

Weibel, 2009, Lung Cast
The Lung Structure

**Conducting zone**

- Trachea
- Bronchi
- Bronchioles
- Terminal bronchioles
- Transitional bronchioles

**Respiratory zone**

- Acinar airways
  - Respiratory bronchioles
  - Alveolar ducts
  - Alveolar sacs

[Image of lung structure with labels and diagrams]
Lung parenchyma

TB = Terminal Bronchiole
RB = Respiratory Bronchiole
AD: Alveolar Duct
Lung parenchyma

TB = Terminal Bronchiole
RB = Respiratory Bronchiole
AD: Alveolar Duct
The prevalence of Asthma & COPD

COPD

- Emphysema
  - 0.2
  - 5.7
  - 5.0

- Chronic bronchitis
  - 3.2
  - 5.5
  - 5.9
  - 5.3

- Hay fever
  - 6.7
  - 10.1
  - 7.7
  - 7.4

- Asthma
  - 13.5
  - 12.0
  - 12.0
  - 10.0

- Sinusitis
  - 11.6
  - 15.6
  - 16.9
  - 13.4

Percentage among patients aged ≥18 years

Make up 90% of Health Care Costs
Chronic Obstructive Pulmonary Disease

A chronic progressive disease characterized by *airflow limitation* that is not fully *reversible*.

Triad of disease entities:
- Chronic bronchitis
- Emphysema
- COPD

Overlap leads to heterogeneity of the disease.

10% of patients also have asthma termed “wheezy” COPD.
COPD

Gas distribution images of hyperpolarized helium by MRI
Epidemiology of COPD

- Symptoms include; shortness of breath, cough and sputum production.

- COPD is the **4th** leading cause of death in the western world (2.74 million people)

- Only leading cause of death that is increasing in prevalence worldwide

- Estimated cost in 2002, $32.1 billion

- Risk factors;
  - Cigarette smoking (20% develop COPD)
  - Passive smoking
  - Exposure to biomass fuels (rural areas)
  - Genetics
Risk factors associated with COPD

- **Cigarette smoking** is the major risk factor for the development of COPD, and constitutes between 85-90% of COPD patients in developed countries.

- Cigarette smoking worsens age related decline in FEV1 (30mls - 45mls per year)

- Susceptible smokers have a faster decline in FEV1 (70-120mls per year)

- Smoking cessation reduces lung function decline to that of a non-smoker
Risk factors associated with COPD

- 30-40% of smokers actually develop COPD, thus other causal mechanisms must interact with smoking to influence disease

**Genetics**
- 1% of COPD patients have α1-antitrypsin deficiency
  - acute phase protease inhibitor which inhibits neutrophil elastase released from neutrophils
- Smoking Cessation
  - GWAS – 30 genes associated with nicotine dependence and cessation

**Environmental**
- Exposure to occupational dust, gases, fumes and air pollution
- Passive smoking - Children of smoking parents have 5% FEV1 reduction by the age of 14, compared to children of non-smoking parents

**Lung Infections**
- Latent infections of adenovirus and pneumonia may amplify inflammatory responses and increase resistance to therapy
Emphysema

- Defined as irreversible enlargement of airspaces distal to the terminal bronchiole and destruction of alveolar walls

**Normal lung architecture**

**Centrilobular emphysema**
- Proximal portion of terminal bronchiole is affected
- Most commonly associated with smoking

**Panacinar emphysema**
- Entire respiratory bronchiole is affected
- Individuals with α1-AT deficiency
Emphysema

- Alveolar and capillary walls are **destroyed** in emphysema
- Results in enlargement of airspaces
- Uncoupling of ventilation and perfusion leading to **reduced lung function**
Emphysema: Alterations in respiratory mechanics

Healthy alveolus

Emphysematus alveolus

Prevents airflow out of the alveolus
**Diagnosis of disease severity**

- Normal lung function \( \text{FEV1/FVC} > 70\% \)
- GOLD guidelines for COPD diagnosis \( \text{FEV1/FVC} < 70\% \)

| GOLD 1 | Mild | Mild airflow limitation  
|        |      | \( \text{FEV1} \geq 80\% \) predicted |
| GOLD 2 | Moderate | Moderate airflow limitation  
|        |       | \( 50\% \geq \text{FEV1} < 80\% \) predicted |
| GOLD 3 | Severe | Severe airflow limitation  
|        |       | \( 30\% \geq \text{FEV1} < 50\% \) predicted |
| GOLD 4 | Very Severe | Very severe airflow limitation  
|        |       | \( \text{FEV1} < 30\% \) predicted |
How can smoking be good??

Before

After
Emphysema disease mechanisms: Protease / Antiprotease imbalance

- **α1-Antitrypsin deficiency**
- Serine protease inhibitor produced in liver
- Innate inhibitor of neutrophil elastase
- Imbalance of proteases leads to tissue destruction
Emphysema disease mechanisms: Oxidant / Antioxidant Balance

- Smoking alters the protease and oxidant balance within the lung.
- Oxidation of anti-proteases leads to inactivation.
- Increased inflammatory cell recruitments increases protease burden.

Matrix metalloproteinases (MMP-9 and MMP-12)
Tissue Inhibitors of MMPs (TIMPs)
Principles of COPD therapy

- **Smoking cessation**
  - Target therapy with buropion (antidepressant) and nicotine replacement therapy

- **Corticosteroids**
  - Reduce inflammation in the lungs of COPD patients to treat symptoms getting worse
  - Once lung function is lost it cannot be replaced!

- **Oral corticosteroids (Budesonide)**
  - **short-term use Side effects**: Weight gain and fluid retention, Mood changes, Increased blood sugar level (type II diabetes), more lung infections.
  - **long-term use Side effects**: Osteoperosis, recurrent infections, stomach ulcers.

- **Inhaled steroids (Fluticasone)**
  - Side effects: Sore mouth or throat, voice changes, such as hoarseness.
Corticosteroids

Corticosteroid binds GC receptor complex which:
1) Up-regulate anti-Inflammatory proteins **TRANSLOCATION**
2) Prevent translocation of inflammatory transcription factors from cytosol into nucleus **TRANSREPRESSION**

![Diagram of corticosteroid action](image-url)

- Anti-Inflammatory Cytokines
- Anti-Proteases
- Anti-oxidants
- Inflammatory Cytokines
- Proteases
- ROS
Corticosteroids

- Formulation is important in pulmonary deposition
  - Inhaled drug particle size
  - Aerosol vehicle
  - Inhaler technique
- Proper pulmonary deposition impacts efficacy and safety

<table>
<thead>
<tr>
<th>Particle Size</th>
<th>Location of Deposition</th>
<th>Efficacy</th>
<th>Safety</th>
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</thead>
<tbody>
<tr>
<td>&gt;5 μm</td>
<td>Mouth/esophageal region</td>
<td>No clinical effect</td>
<td>Absorption from GI tract if swallowed</td>
</tr>
<tr>
<td>2–5 μm</td>
<td>Upper/central airways</td>
<td>Clinical effect</td>
<td>Subsequent absorption from lung</td>
</tr>
<tr>
<td>&lt;1 μm</td>
<td>Peripheral airways/alveoli</td>
<td>Clinical effect</td>
<td>Subsequent absorption from lung</td>
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Particle size of corticosteroids depend on inhalation medium

<table>
<thead>
<tr>
<th>Mass Medium Aero diameter (µm)</th>
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<tbody>
<tr>
<td>Dry Powder Inhaler</td>
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<tr>
<td>Metered Dose Inhalers</td>
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- Dry Powder Inhaler
- Metered Dose Inhalers Propellant Based (Chlorofluorocarbon)
- Metered Dose Inhalers Propellant Based (Hydrofluoroalkane)
Formulation: Pulmonary Deposition

1) Higher pulmonary Deposition seen in HFA solutions

2) Reduced oropharyngeal deposition with HFA formulations may reduce local side effects