COMMONWEALTH OF AUSTRALIA

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Chronic Obstructive Pulmonary Disease (COPD)

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Learning objectives

• define COPD
• outline the burden of COPD
• list the risk factors for COPD
• explain the pathogenesis, pathology and pathophysiology of COPD
• understand relationship between COPD, asthma and other airway diseases
• understand principles of management-pharmacologic and non-pharmacologic.
Session outline

• Definition of COPD
• Burden of disease
• Pathogenesis, pathology, pathophysiology
• Relationship to other airways diseases
• Management
What is COPD?

- Group of disorders characterised by airway inflammation and airflow limitation that is not fully reversible
- A progressive condition associated with an abnormal inflammatory response to noxious stimuli
- Fully reversible asthma is not COPD
COPD in Australia

- Third leading cause of disease burden in Australia (after heart disease & stroke)
- Fourth leading cause of death in Australian men and sixth in women
- Nearly 500,000 people in Australia with moderate to severe COPD
- Mortality from COPD 10-times higher in indigenous Australians
- Among principal causes of death, only COPD continues to have a growing death rate
Pathogenesis of COPD

Noxious agent

Inflammation

Small airway disease
- Airway inflammation
- Airway remodelling

Parenchymal destruction
- Loss of alveolar attachments
- Loss of elastic recoil

Airflow limitation
• Inflammation in the airways, lung parenchyma and pulmonary vessels
• Neutrophils, macrophages, CD 8 cells
• Proteinase - antiproteinase imbalance
• Oxidative stress
Changes in Lung Parenchyma in COPD

- Alveolar wall destruction
- Loss of elasticity
- Destruction of pulmonary capillary bed
- ↑ Inflammatory cells: macrophages, CD8⁺ lymphocytes

Source: Peter J. Barnes, MD
Emphysema

- Mechanism: protease/antiprotease imbalance
  (proteases digest elastin and other structural proteins in alveolar wall; antiproteases protect against attack)
- Macrophages and T lymphocytes prominent
- Different patterns in emphysema:
  - Centriacinar (radiates from terminal bronchiole)
  - Panacinar (more generalized)
  - Bullae
Risk Factors for COPD

• Cigarette smoking is primary cause
• WHO estimates 1.1 billion smokers worldwide, increasing to 1.6 billion by 2025
• In low and middle income countries, rates are increasing at an alarming rate
• Around 50% of smokers have some degree of airflow limitation
• 15–20% of smokers develop disabling airflow limitation
• In India and China indoor air pollution from use of biomass fuels also a significant risk factor
Other Risk Factors

• Occupational exposure to irritants
• Alpha-1 antitrypsin deficiency
• Bronchial hyper-responsiveness
• Passive smoking
• Air pollution (indoor and outdoor, esp biomass fuels)
• Recurrent RTIs in childhood
• Genetic predisposition
COPD diagnosis

• Consider COPD in . . .
  – any past or current smoker
  – chronic cough
  – productive cough
  – dyspnoea
  – history of exposure to other risk factors
COPD diagnosis

• Spirometry is the best measure of airflow obstruction
• Measures time course of exhaled volume or flow
• FER = forced expiratory ratio
• FER = FEV1/FVC or FEV1/VC
  – using the larger of FVC or VC
• FER < 0.7 ⇒ airflow obstruction
  – this cut-off varies slightly with age
Spirogram
C: Volume–Time Plots

Normal

COPD

## COPD or Asthma?

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
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<tbody>
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<td>Progressive course</td>
<td>Variable course</td>
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## Clinical Features

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Overlap of Respiratory Symptoms

It may be impossible to differentiate between patients with asthma with some irreversible airflow obstruction, and between some patients with chronic bronchitis and emphysema who have partially reversible airflow obstruction.
Pathology-Asthma

- Inflammation (largely eosinophilic) affects ALL the airways (large and small) and doesn’t involve lung parenchyma
- Fibrosis is NOT a feature (sub-epithelial fibrosis may be present but is minimal compared with that seen in COPD)
Pathology-COPD

• Neutrophilic inflammation

• In contrast with asthma, most of pathologic changes are in *peripheral airways* where there is also fibrosis leading to obliterative bronchiolitis

• Mucus hypersecretion is more prominent than in asthma
Differences in Inflammation and its Consequences: Asthma and COPD

**ASTHMA**

- Allergens
- Mast cell
- Ep cells
- CD4+ cell (Th2)
- Eosinophil

**COPD**

- Cigarette smoke
- Alv macrophage
- Ep cells
- CD8+ cell (Tc1)
- Neutrophil

**Bronchoconstriction**

**AHR**

**Small airway narrowing**

**Alveolar destruction**

**Airflow Limitation**

*Source: Peter J. Barnes, MD*
GOLD Classification of COPD Severity

Stage I:  Mild  \[\text{FEV}_1/\text{FVC} < 0.70\]
\[\text{FEV}_1 \geq 80\% \text{ predicted}\]

Stage II: Moderate  \[\text{FEV}_1/\text{FVC} < 0.70\]
\[50\% \leq \text{FEV}_1 < 80\% \text{ predicted}\]

Stage III: Severe  \[\text{FEV}_1/\text{FVC} < 0.70\]
\[30\% \leq \text{FEV}_1 < 50\% \text{ predicted}\]

Stage IV: Very Severe  \[\text{FEV}_1/\text{FVC} < 0.70\]
\[\text{FEV}_1 < 30\% \text{ predicted or}\]
\[\text{FEV}_1 < 50\% \text{ predicted plus chronic respiratory failure}\]
Time Course of COPD

COPD - Current Treatment Guidelines

• Goals of therapy:
  – Control symptoms
  – Improve lung function and health status
  – Prevent exacerbations
  – Reduce hospital admissions
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## Management of COPD

### COPD-X Plan

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<th>Principle</th>
<th>Action</th>
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<tr>
<td><strong>C</strong></td>
<td>Confirm diagnosis and assess severity</td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>Optimise lung function</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>Prevent deterioration</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Develop support network and self-management plan</td>
</tr>
<tr>
<td><strong>X</strong></td>
<td>eXacerbation – manage appropriately</td>
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Stopping smoking slows the decline in lung function

Fletcher and Peto BMJ 1977; 1: 1645
Smoking cessation strategies

• Non-pharmacologic
  – Willpower alone
  – Doctor’s advice
  – Self-help materials
  – Intensive counselling
  – Smoking cessation courses

• Pharmacologic
  – Nicotine replacement therapy
  – bupropion (Zyban)
  – varenicline (Champix)
β₂ agonists

– Ventolin, Airomir = salbutamol
– Bricanyl = terbutaline
– Serevent = salmeterol
– Oxis, Foradile = eformoterol
– Onbreez = indacaterol

• Short-acting for prn use
• Long-acting for regular use
  – less symptoms, more exercise, better QOL
• Lower QOL with higher doses
• Side effects = tremor, tachycardia
Anticholinergics

– Spiriva = tiotropium
– Atrovent = ipratropium

• Long-acting more convenient, and less dyspnoea, better exercise, less exacerbations (NTT = 14), less mortality

• Side effect = dry mouth in 14 %
Inhaled corticosteroids

• Neutrophilic inflammation-steroid “resistant”
• Higher doses than in asthma
• Studies show benefit in severe COPD (FEV$_1$ < 50 %) with frequent exacerbations
Combination therapy

• Inhaled fluticasone and salmeterol (Seretide)
• Inhaled budesonide and formoterol (Symbicort)
• In moderate to severe COPD (FEV$_1$ < 60 %) may
  – reduce exacerbations
  – improve QOL
  – Improve FEV$_1$
Pulmonary rehabilitation

- Improves exercise capacity and quality of life
- May also reduce exacerbations and hospitalisations
- Patients need to be well motivated
- Two main components
  - improving fitness
  - education
- Course runs over 6-8 weeks with twice weekly visits, but the exercise needs to be maintained at home
- Usually supervised by physiotherapists
- Variable availability and cost to the patient
Theophyllines

• Rarely used in Australia
• Significant side effects
  – nausea, dysrhythmias, seizures
• Drug interactions
• Monitor blood levels
• Low dose theophylline may have anti-inflammatory and immunomodulatory effects with fewer side effects
Vaccines

• Influenza vaccine
  – Reduces mortality, hospital admissions and exacerbations
  – Local side effects only
  – It is given yearly

• Pneumococcal vaccine
  – More evidence needed about its use in COPD
  – It is given twice 5 years apart
Home oxygen therapy

• Oxygen concentrator: 2-4 L/min via nasal prongs for >16 hours/day IF
  – when at his/her best and stable
  – $PO_2$ on air at rest < 55 mmHg OR
  – $PO_2$ < 60 if evidence of hypoxic damage
    i.e. cor pulmonale, pulmonary hypertension, polycythaemia
  – AND no cigarettes for 3 months

• This oxygen improves mortality, and usually has no effect on symptoms
Portable oxygen

• This is designed to improve symptoms and increase exercise
  – No cigarettes for 3 months
  – SpO₂ < 88 % with exercise AND
  – Supplemental O₂ prevents this desaturation
  – AND Exercise is improved

• Recent trial suggested mainly placebo benefit!
Other treatments

• Chronic antibiotics
  – Generally not recommended;
  – Some benefit from low dose macrolides in recent studies (selected patients-? antibacterial or immunomodulatory effect?); AE’s: deafness, resistance

• Mucolytics
  – small benefit
  – may help selected patients

• Non-invasive ventilation
  – unproven for chronic use, so only used for selected patients
Other treatments

• Lung volume reduction surgery
  – Improves symptoms
  – Improves quality of life
  – No clear survival advantage
  – Consider lung transplantation

• Other experimental devices eg endobronchial valves
Therapy at Each Stage of COPD

I: Mild
- FEV₁/FVC < 70%
- FEV₁ ≥ 80% predicted

II: Moderate
- FEV₁/FVC < 70%
- 50% ≤ FEV₁ < 80% predicted

III: Severe
- FEV₁/FVC < 70%
- 30% ≤ FEV₁ < 50% predicted

IV: Very Severe
- FEV₁/FVC < 70%
- FEV₁ < 30% predicted or FEV₁ < 50% predicted plus chronic respiratory failure

Active reduction of risk factor(s); influenza vaccination

**Add** short-acting bronchodilator (when needed)

**Add** regular treatment with one or more long-acting bronchodilators (when needed); **Add** rehabilitation

**Add** inhaled glucocorticosteroids if repeated exacerbations

**Add** long term oxygen if chronic respiratory failure.

**Consider** surgical treatments
An exacerbation of COPD is defined as:

“An event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.”

GOLD Exec Summary 2007
Acute COPD exacerbation

- The cause is often unknown
- Respiratory infections
  - bacterial, viral
  - URTI, bronchitis, pneumonia
- Heart failure, arrhythmia
- Systemic infection, fever
- Anaemia
- Anxiety
- Anything that increases metabolic rate
Exacerbations of COPD

- Costly
  - decline in HRQOL
  - more rapid loss of lung function
  - mortality
  - economic terms (hospitalisations, medications, time off work, carer costs)
COPD exacerbation features

- **Anthonisen criteria:**
  - increased dyspnoea
  - increased sputum production
  - sputum becoming discoloured

- **Antibiotics to cover Strep and Gram negatives have been shown to be useful if all three criteria are present**

- **CXR to look for pneumonia, and cover atypical bacteria if there is pneumonia**
Exacerbation management

• Supplemental $O_2$
  – Aim to keep $SpO_2 > 90%$
    and/or $PaO_2 > 60$ mmHg
  – Do not give high doses of $O_2$ too quickly

• Consider the $O_2$ concentration, flow rate
  and patient’s inspiratory flow rate
Caution

• A high dose of O2 in COPD with chronic hypercapnia may lead to a further rise in pCO₂ due to:
  – Reduced ventilatory drive
  – Worsening V/Q mismatch due to high PO₂ in parts of the lung overcoming hypoxic vasoconstriction
  – Haldane effect
    • O2 displacing CO₂ from Hb
Other therapy

• Bronchodilators
  – anticholinergics and $\beta_2$ agonists
• Corticosteroids (oral, rarely intravenous)
  – some benefit, but not great
  – must be balanced with side effects
• Antibiotics
  – if there is evidence of infection
• Physical activity
  – to prevent deconditioning
• Non-invasive ventilation (BiPAP, VPAP)
How do we prevent exacerbations?

- Smoking cessation
- Vaccinations
- Tiotropium (antimuscarinic)
- Long-acting beta agonists
- Theophylline
- Inhaled corticosteroids (ICS)
- Combination of ICS and LABA (+Tio)
- Pulmonary rehabilitation
- Mucolytics