Bronchiectasis is a progressive condition characterised by irreversible destruction and dilation of airways, generally associated with chronic bacterial infection.

1. Common (prevalence unknown) and underdiagnosed (29% of UK community COPD sample)
2. Substantial and unchanging morbidity and mortality
3. Predominant disease burden (mortality and morbidity) is in Maori and Pacific Islanders
4. Influences of poverty, malnutrition, immunisation, poor quality of health care, barriers to health

Pathophysiology and aetiology:
1. Pathogenesis – viscous cycle hypothesis (bacteria-provoked, host-mediated lung damage)
   a. Inciting agent (bacteria, virus) causes exfoliation → airway occlusion/obstruction
   b. Parenchyma becomes atelectatic → increased traction forces on nearby airways
   c. Impaired cough, impaired mucociliary clearance → pooling of secretions → chronic infection, PMN recruitment, further inflammation and damage
2. Pathology:
   a. Microbiology – *H. influenzae*, *S. pneumoniae*, *Pseudomonas*, *Mycobacterium avium-intracellulare* complex (MAIC), other
   b. Neutrophils recruited by IL 8 and bacterial products release proteases, free radicals
   c. CD8-positive activated T lymphocytes may modulate this process
3. Aetiology:
   a. Idiopathic
   b. Post-viral (adenovirus)
   c. Endobronchial obstruction (e.g. foreign body)
   d. Destructive pneumonia
   e. Specific aetiologies – hypogammaglobulinaemia, cystic fibrosis, allergic bronchopulmonary aspergillosis, ciliary dyskinesia syndrome

Clinical features:
1. Symptoms include productive cough with purulent sputum, dyspnoea, haemoptysis (erosion of bronchial vessels), recurrent U/LRTIs, symptoms of sinusitis/GORD, general malaise
2. Signs – chronic disease (wasting, anaemia), clubbing, coarse crackles, (cor pulmonale)
3. Investigations
   a. CXR – rings with fluid level, sinus XR (comorbid chronic rhinosinusitis)
   b. High resolution CT – ‘diamond ring’ (blood vessel on the side of a dilated airway)
   c. Others – Ig levels, sweat test (CF), aspergillus serology, AFB sputum examination

Management – note that no intervention completely prevents disease progression
1. Conservative – regular sputum clearance techniques (physiotherapy, postural drainage)
2. Medical:
   a. Inhaled DNAase or hypertonic NaCl/mannitol – alters mucus, improves clearance
   b. Antibiotics – prompt antibiotic treatment of intercurrent infections
      i. Some evidence that regular high-dose inhaled antibiotics results in less cough and sputum, improved spirometry and reduced hospitalisation
   c. NSAIDs and steroids – limited evidence (may prevent inflammation/progression)
3. Surgical – limited role for resection as bronchiectasis is typically diffuse, and even if it is limited, resection often causes distortion → bronchiectasis of the remaining lung

Community-Acquired Pneumonia

Classification
Pneumonia may be classified two ways:
1. Traditional classification
   a. Radiologic – lobar vs broncho-pneumonia
   b. ‘Typical’ (*Streptococcus pneumoniae*) vs ‘atypical’ pneumonia
2. Aetiologic
   a. Community acquired pneumonia
   b. Aspiration pneumonia
   c. Hospital-acquired (nosocomial) pneumonia
   d. Pneumonia in immune-suppressed/compromised patients
Community acquired pneumonia is a common and serious illness – it is the 6th leading cause of death. Overall mortality is less than 1-5%, but up to 25% if hospitalisation required (40% in ICU). It is increasingly common in the elderly and those with co-morbidity. In NZ (Karalus et al, Thorax 1991):

1. Microbiologic diagnosis in 72% (Pneumococcus 33%, Mycoplasma 18%)
2. 59% had significant co-morbidity (5/6 deaths >75yrs)
3. RR for death = 16, if 2 or more risk factors (age, confusion, hypotension, renal dysfunction)

Clinical, radiological and laboratory features are non-specific and do not allow reliable identification of pathogens – microbiologic diagnosis is made in <50% of cases, and therapy is best guess. ‘Atypical’ pneumonia is also undistinctive clinically, with many infections mixed (e.g. M. pneumoniae, C. pneumoniae, Legionella sp.) or due to odd pathogens (Coxiella burnetii, Hantavirus, Hendra virus).

Classification of community-acquired pneumonia involves:

1. Outpatients, no cardio-pulmonary disease, no modifying factors
   a. Pneumococcus, Mycoplasma, (Chlamydia), (Legionella), H. influenzae in smokers
   b. Macrolide (advanced generation) or doxycycline (for atypicals)

2. Outpatients with cardio-pulmonary disease (COPD, CHF) and/or modifying factors
   a. Pneumococcus, H. influenzae, Staphylococcus aureus, Gram negatives, atypical organisms (mixed), others including Moraxella catarrhalis
   b. Beta lactam (amoxicillin +/- clavulanic acid, cefuroxime) plus macrolide/doxycycline for atypicals. Alternatively, the newer oral fluoroquinolones (Moxifloxacin) have better activity against Gram-positives than older fluoroquinolones

3. Inpatients with no cardio-pulmonary disease or modifying factors
   a. Pneumococcus, H. influenzae, Mycoplasma/Chlamydia, Legionella
   b. Beta lactam plus macrolide (iv) or doxycycline; or fluoroquinolone

4. Inpatients with cardio-pulmonary disease +/- modifying factors
   a. Pneumococcus, H. influenzae, Mycoplasma/Chlamydia/Mixed, enteric Gram-negatives, Legionella, others. May be poly-microbial
   b. IV beta lactam plus macrolide/doxycycline; or fluoroquinolone

5. Inpatients admitted to ICU
   a. Pneumococcus, Legionella sp., H. influenzae, enteric Gram-negatives, Staph. aureus – unknown in 50-60% of cases
   b. IV beta lactam (third-generation cephalosporins – cefotaxime, ceftriaxone) plus IV macrolide or IV fluoroquinolone

Assessment, Investigation and Diagnosis

Stratification of patients is based on:

1. Assessment of situation of therapy/severity
2. Co-morbidity (cardio-pulmonary disease)
3. Modifying factors (note that age is not a modifying factor):
   a. Drug resistant pneumococci risk factors:
      i. >65yrs, alcoholism, recent beta lactam prescription
      ii. Immune-suppression, multiple co-morbidities
      iii. Exposure to children in day care (not a strong factor)
   b. Enteric gram negatives risk factors:
      i. Nursing home resident, recent antibiotic therapy
      ii. Cardio-pulmonary disease, multiple co-morbidities

Risk factors for death (⇒ ICU admission) include:

1. On examination – age >60yrs, underlying chronic illness, confusion
   a. RR >30 breaths/min
   b. Diastolic BP <60mmHg, systolic BP <90mmHg
   c. Temperature <35 or >40°C

2. Laboratory investigations:
   a. WCC <4 or >30 x10^9/L, Hb <90gm/L
   b. PaO2 <60mmHg (8.0kPa) or PaCO2 >50mmHg (6.7kPa), arterial pH <7.35
   c. Abnormal renal function (urea >7mmol/L)

Investigations useful for diagnosis include – chest radiograph, arterial blood gases, full blood count, biochemistry, +/- blood culture. Gram stain of sputum and culture is not routine, as is serology.
Sputum examination requires an adequate sample (>25 WBC and <5-10 squamous cells per high powered field), which may be difficult. While direct staining may be diagnostic for some unexpected pulmonary infections, atypical organisms are not seen. Sputum culture has poor sensitivity and specificity. Invasive methods to obtain lower respiratory tract specimens are generally not indicated.

Specific diagnosis is found in less than 50% of cases – the initial antibiotic choice is therefore empiric. It is important that treatment is not delayed – delay increases mortality. There is no evidence that outcome is improved by establishing a specific microbiologic diagnosis.

**Management**

**General principles** of management:

1. **Supportive therapy:**
   a. IV fluids
   b. O2 therapy – target O2 saturation >90% (flat part of the O2 dissociation curve)
   c. Physiotherapy to assist removal of secretions
   d. +/- bronchodilators, +/- pain relief

2. **Specific treatment with antibiotics** – initially “best guess” (don’t delay!)
   a. Duration of therapy 7-14 days (but shorter courses may be mildly efficacious)
   b. Change to oral therapy (and discharge) if there are improved symptoms, the patient is afebrile, WCC is decreasing and the patient is able to tolerate oral therapy
   c. Do not change antibiotics in the first 48 hours

3. **Failure to respond in 72hrs** may be due to:
   a. Alternative diagnosis – check the differential
   b. Development of complication e.g. empyema
   c. Presence of underlying disease e.g. endobronchial obstruction, bronchiectasis
   d. Resistant or unusual organism or inappropriate antibiotic choice/dose

Radiological follow-up (repeat in 6-8wks) is essential – if the patient is progressing well, a repeat CXR may not be required until after discharge. Median time for clearance if young with no co-morbidity is 4 weeks, longer if older or with co-morbidity (25% clearance at 4 weeks in COPD).

**Assorted microbiological issues:**

1. *Herpes labialis* is not a specific pointer of pneumococcal pneumonia
2. Pneumococcal pneumonia is associated with positive blood cultures in 10-20%
3. *H. influenzae* is associated with chronic lung disease e.g. COPD, bronchiectasis
4. Gram negative pneumonia is more common in the elderly (oropharynx colonisation)
5. Influenza may be complicated by *Staph. pneumonia* (minor point as many antibiotics are relatively effective against *S. pneumonia*)
6. Poor dental hygiene and/or aspiration risk may indicate anaerobic infection
7. Viral pneumonia is rarely diagnosed in adults

**ASPIRATION PNEUMONIA, LUNG ABSCESS AND EMPYEMA THORACES**

Aspiration of oropharyngeal contents → aspiration pneumonia → lung abscess → para-pneumonic effusion/empyema. This occurs in conditions where there are reduced conscious level or impaired cough e.g. general anaesthesia, excess alcohol/drugs, head injury/CVA, seizures, diabetic coma.

**Lung Abscess**

A lung abscess is a localised area of destruction of lung parenchyma in which infection by a pyogenic organism results in tissue necrosis and suppurration. Tends to be a mix of organisms with anaerobes predominant (*Bacteroides, Fusobacterium, Peptostreptococcus*, micro-aerophilic *Strep.*).

1. Necrotizing pneumonia is more diffuse on CXR, with aerobes (*Klebsiella, Staphylococcus*)
2. Abscess also be due to haematogenous dissemination or septic emboli
3. *Staph. aureus* is the leading cause of lung abscess in children → thin-walled pneumatoceles

**Signs and symptoms** – note that it may be insidious and presentation delayed

1. +/- history of aspiration
2. General symptoms – lassitude, anorexia, weight loss
3. Usually productive cough +/- fever, sweats, fetor, dyspnoa, chest pain, haemoptysis
4. Radiologically:
Respiratory

- Parenchymal infiltrate (posterior segment of RUL, superior segments of lower lobes)
- >1 area of homogenous density where air/fluid levels develop
- Thick, irregular walled cavity +/- air/fluid levels
- Complicating empyema may be evident

Treatment:
1. Amoxycillin + clavulanic acid, plus metronidazole or clindamycin (anaerobic cover)
2. 60% of patients are clear within 4-6 weeks
3. Tube drainage/surgical drainage/resection are rarely required

Empyema
Typically, after an apparently satisfactory antibiotic response of a pneumonia, the patient remains unwell with spiking fever, clinical and radiologic signs of pleural effusion, high WCC and ESR >100mm/hr (fibro-purulent stage). May also be insidious with chronic ill health, anorexia, weight loss, lassitude, fever, and chest pain; and there may be signs of pleural effusion +/- clubbing.
1. Pneumonia ➔ exudative stage ➔ infection ➔ fibro-purulent stage ➔ organising stage
2. Organisms – mixed, anaerobes, micro-aerophilic streptococcus (similar to abscess)

Diagnosis from examination of the pleural aspirate:
1. Frank pus, turbid fluid, Gram stain, positive culture, polymorphonuclear cells
2. Low pH <7.2, low glucose <3.3, high LDH >1000 (inverse for para-pneumonic effusion)

Management – high index of suspicion, as it is important to avoid delays
1. General principles – drainage of pus, obliteration of cavity, control of infection
2. Antibiotics for 4-6 weeks (longer depending on clinical response)
3. Intercostal tube +/- irrigation, +/- intra-pleural antibiotics, +/- intrapleural streptokinase
4. Surgery for failed medical therapy

LUNG CANCER

- General Principles
Lung cancer represents 12% of registered cancer, and 20% of cancer deaths in NZ. It is the most common cause of cancer death in men, and rapidly surpassing breast cancer in women. The rate in Maori males and females is also higher than that in non-Maori males and females.

Recognised causes include asbestos exposure (dose-response relationship when controlled for smoking – RR = 1.5-13.1), radon, nickel, arsenic and others. However, smoking is estimated to cause 80% of lung cancer deaths:
1. Histologic evidence of variety of premalignant changes has been found in the airways of smokers. Normal ciliated columnar cells are replaced by squamous metaplasia, which progresses to dysplasia and carcinoma in situ.
2. There is a dose-response relationship between smoking and lung cancer
   a. Risk increases with number of cigarettes smoked
   b. Risk decreases significantly after cessation, but never falls to non-smoker levels

Screening for lung cancer has yet to have a proven benefit:
1. Four randomised trials of lung cancer screening in the 1970s showed no mortality advantage
2. Early lung cancer action project (ELCAP) using low dose spiral CT had a rate of malignant disease detected by CT was 2.7% (0.7% for CXR)
3. CT more sensitive than CXR, but mortality advantage has yet to be demonstrated

There are two major types of lung cancer – small cell (SCLC) and non-small cell (NSCLC). Treatment for NSCLC is surgery, while treatment for SCLC is chemotherapy plus radiotherapy. Prognosis for both groups depends on stage, although it is usually better for NSCLC.

- Non Small Cell Lung Cancer
Non-small cell lung cancer includes:
1. Squamous cell carcinoma (30%) – associated with cavitation, hypercalcaemia, age >45y
   a. Slow growing, prognosis predicted by stage
   b. Strong relationship with smoking
2. Adenocarcinoma (15-40%) – becoming most prevalent, fibrosis/mucin production, age <45y
Respiratory

a. Often peripheral, metastasise widely (brain, liver, bone)
b. Least relationship to smoking, most variable presentation/prognosis
c. Bronchoalveolar is a distinct clinicopathological entity with variable behaviour

3. **Large cell undifferentiated** (15%) – cerebral metastases common, very poor prognosis

Spread occurs first by local growth to contiguous structures, then by vascular/lymphatic infiltration:
1. Local lymph nodes
2. Bronchopulmonary lymph nodes (N1)
3. Mediastinal lymph nodes – ipsilateral (N2), contralateral (N3)
4. Dissemination via lymph/blood – most frequently metastasises to bone, adrenal, liver, brain

**Clinical features** depend on the type and location of the tumour, local and distant spread, and any paraneoplastic effects. Note that symptoms present late, with patients initially asymptomatic (5-10%).
1. **Local spread** (endobronchial) – cough, haemoptysis, wheeze/stridor, pneumonitis
2. **Peripheral growth** – chest/pleuritic pain, cough
3. **Regional spread** – dysphagia, hoarseness (recurrent laryngeal nerve), dyspnoea (phrenic nerve, lymphatics), Horner’s (Pancoast tumour), SVC obstruction, pericardial tamponade
4. **Metastatic effects** – fatigue, reduced activity, reduced appetite, weight loss, pain
5. **Paraneoplastic syndromes** – mix of syndromes not necessary reflecting metastatic disease:
   a. Endocrine e.g. hypercalcaemia, Cushing’s syndrome, SIADH
   b. Neurological e.g. peripheral neuropathy, Eaton Lambert Syndrome
   c. Skeletal e.g. clubbing, HPOA or other

**Diagnosis** of non-small cell lung cancer:
1. **History** – smoking, environmental exposures, family history, new symptoms
2. **Examination** – airways obstruction, atelectasis/pneumonia, pleural effusion
3. **Investigations**:
   a. Sputum cytology x3 – positive in 60-80% of central tumours, though <20% for peripheral tumours (squamous > adenocarcinoma)
   b. Abnormal CXR (abnormal in >95% of cases), CT scan
      i. Peripheral tumours – percutaneous FNA, bronchoscopy (brush/needle), thoracoscopy (wedge excision, needle aspiration, thoracotomy)
      ii. Central tumours – sputum cytology, bronchoscopy (biopsy, brush, needle), percutaneous FNA, thoracotomy

4. **Staging** (note TNM system) based on:
   a. Clinical exam
   b. Investigations: LFTs (ALP), U&Es (Ca^{2+}), haematology and coags
   c. CT thorax + mediastinoscopy/otomy
   d. Others as indicated – liver ultrasound, bone scan, PET scanning (metabolic activity)

**Management** of non-small cell carcinoma:
1. **Surgery** can be curative, but only ~10% (stage I and II) are appropriate. 5-year survival:
   a. Stage I (T1/2 N0 M0) – 60-80%
   b. Stage II (T1/2 N1 M0 or T3 N0 M0) – 40%
   c. Stage IIIa (T3 N1 M0 or T1-3 N2 M0) – 10-30%
   d. Stage IIIb (T4 N0-3 M0 or T1-4 N3 M0) – <10%
   e. Stage IV (any T, any N, M1) – <2%
2. **Radiotherapy** – curative intent for stage I and II patients unfit for surgery, otherwise palliative
   a. Curative doses of 50-60Gy ± ‘hyperfractionation’, chemotherapy (but higher toxicity)
   b. Toxicity – oesophagitis, pneumonitis (7-28% three months after treatment – steroids)
   c. Very good for palliation of symptoms (e.g. haemoptysis, bone pain)
3. **Chemotherapy** – used for palliation (quality of life) of unresectable stage III or IV cancers
   a. Single agent (usually platinum) has 15% response rate, 30-50% in combination
   i. Lecture figures: median survival 25-35 months, 1-year survival 20-25%
   b. Median survival increased from 4-6 → 9-12 months, but no long-term survivors
4. **Palliative care** – hospice services for terminally ill patients
Small Cell Lung Cancer

Small cell lung cancer accounts for ~20% of lung cancers and is distinguished by its propensity for early metastases and association with cigarette smoking. It is thought to arise from Kulchitsky cells (neurosecretory core granules on EM) and secretes GRP, which acts as an autocrine growth factor.

Clinical features:
1. **Clinical signs** are limited (very rarely HPOA)
   a. 70% have demonstrable metastatic disease on presentation
   b. Often associated with paraneoplastic syndromes (SIADH, ACTH production)
2. **Staging**:
   a. Limited – tumour confined to one hemithorax and regional lymph nodes that could be encompassed in one radiotherapy field
   b. Extensive – outside the above limits
3. **Treatment** is by chemotherapy (70% overall response, 30% complete) ± radiotherapy
   a. Limited stage – treatment increases median survival 12 weeks → 12-20 months
      i. Response ~50% (80% with radiotherapy), 5-year survival 10-15%
   b. Extensive stage – treatment increases median survival 5 weeks → 7-12 months
      i. Response <20%, 5-year survival 0-3%
   c. Also evidence for better survival with radiotherapy and PCI (?) for limited disease

Other Tumours and Haemoptysis

Other tumours:
1. **Mesothelioma** – malignant tumour of the pleura
   a. Strongly associated with asbestos exposure (amphibole fibres, 20-60 year lag period)
   b. No effective treatment currently available – median survival 7-9 months
2. **Mediastinal tumours** – thymoma, germ cell, lymphoma, neurogenic, primary carcinoma
3. **Benign tumours**:
   a. Carcinoid tumour – causes bronchial obstruction (→ surgery)
   b. Others – adenoid cystic tumour, mucopidermal carcinoma, hamartomas, neuroma, fibroma, lipoma

**Haemoptysis** refers to coughing up blood – this may arise from any part of the respiratory tract, though should be distinguished from haematemesis or epistaxis. It may indicate serious underlying disease and should be investigated – massive haemoptysis (>200mL) is a medical emergency.

1. **Origin** – bronchial arteries, pulmonary veins/capillaries/arteries/arterioles, abnormal vessels
2. **Causes**:
   a. Pulmonary – embolism, neoplasm (1st and 2nd), diffuse alveolar haemorrhage syndrome, AV malformation, fistula, foreign body
   b. Cardiac – left ventricular failure, severe mitral stenosis, high pulmonary venous pressures (pulmonary venous congestion, mitral regurgitation, LA myxoma)
   c. Infectious – bronchitis (50% of haemoptysis), bronchiecasis (5%), necrotizing pneumonia, TB, fungi (*Histoplasmosis, Mucormycosis*)
   d. Inflammatory – sarcoid, Wegener’s granulomatosis, Goodpasture syndrome

**Asthma**

Asthma is characterised by hyperresponsiveness of the tracheobronchial tree to a variety of stimuli, leading to airway obstruction that presents with paroxysms of dyspnoea, wheezing and cough that range from almost undetectable to severe and unremitting (status asthmaticus).

1. **Epidemiology** – 10-20% of children, 10% adults (prevalence and severity increasing)
   a. May be broadly classified as childhood and adult asthma:
      1. Childhood – 70% mild episodic, 20% frequent episodic, 5% persistent
         1. 2/3 have spontaneous remission, but some relapse in adulthood
      2. Adult asthma may become chronic with irreversible airways remodelling
      3. Occupational asthma accounts for ~5% of adult asthmatics
   b. Mortality is rare – only 2 epidemics in NZ in the 1960-70s (overuse of β-agonists)
Respiratory

1. Risk factors – excessive \( \beta \)-agonist use, inadequate long-term care, socioeconomic factors, previous ICU admission, recurrent hospitalisation, non-compliance, self-management errors, psychological factors

2. Symptoms (note persistent Vs episodic)
   a. Recurrent wheeze, cough (especially dry cough at night), breathlessness
   b. Exercise-induced wheeze or chest tightness
   c. Response to bronchodilator

3. Diagnosis:
   a. Careful history and exam
   b. Positive family history, personal history of atopy
   c. Confirmation – post-bronchodilator spirometry (>15-20% improvement in PEFR/FEV\(_1\))
   d. Differential – COPD, bronchiectasis, CF, endobronchial lesion, hyperventilation

Pathophysiology:
1. General principles:
   a. External stimuli \( \rightarrow \) activation of macrophages, dendritic, mast, epithelial cells
   b. Eosinophil recruitment \( \rightarrow \) airway obstruction, hyperresponsiveness, asthma
   c. Large and small airway obstruction \( \rightarrow \) ↑ resistance, ↓ flow rate, ↓ FEV\(_1\), premature closure of airways, static and dynamic hyperinflation, ↑ work of breathing
   d. Diffuse but non-uniform impairment of gas exchange \( \rightarrow \) V/Q mismatch

2. Asthma pathology:
   a. Mast cells are the key factor in acute inflammation:
      i. Preformed mediators (histamine, tryptase) activate enzymes \( \rightarrow \) leukotrienes C\(_4\), D\(_4\), E\(_4\) \( \rightarrow \) smooth muscle contraction, ↑ vascular permeability, oedema
      ii. Allergen challenge \( \rightarrow \) expression of adhesion molecules (E-selectin, ICAM-1) \( \rightarrow \) recruitment of neutrophils and inflammatory cells \( \rightarrow \) potentiation
   b. T-lymphocytes are the key factor in chronic inflammation:
      i. Release TH2 \( \rightarrow \) cytokines \( \rightarrow \) modulate eosinophil, endothelium, B-cell and mast cell functions, also modulates survival of inflammatory cells
      ii. Airway remodelling:
         1. Matrix cells – fibroblasts, myofibroblasts, smooth muscle cells
         2. Subepithelial fibrosis – irreversible basement membrane thickening 2° to collagen deposition and smooth muscle hyperplasia

3. Bronchial hyperresponsiveness:
   a. Excessive airways narrowing when challenged with a non-specific stimulus
   b. Characteristic of asthma, but not seen in all asthmatics and may be isolated
   c. Tested by histamine/methacholine challenge – good indication of asthma in the absence of variable PEFR

Management:
1. Medications – see next section
   a. 1\(^{st}\) line – inhaled \( \beta \)-agonist or anticholinergic (use 5-10min before exercise)
   b. 2\(^{nd}\) line – inhaled corticosteroids 400-800\( \mu \)g/day, DSCG may be used in children
   c. 3\(^{rd}\) line – high dose inhaled steroids (1000-2000\( \mu \)g/day)
   d. 4\(^{th}\) line – long-acting inhaled \( \beta \)-agonist or theophylline

2. Education should be realistic, relevant, repeated and reviewed
   a. Goals – nature, triggers, treatment goals, means of achieving control, individual plans
   b. Reality – knowledge/self-management improve, little change in behaviour/morbidity

3. Peak flow monitoring allows an objective measure of severity
   a. Early detection allows control to be maintained (alerts patients of exacerbations)
   b. Note diurnal variations of PEFR

Asthma Medications

\[ \beta \]-adrenergic agonists act primarily by relaxation of airways smooth muscle via \( \beta \(_2\) \) receptors (also present on epithelium, endothelium and mast cells) and may also increase mucociliary clearance and inhibit mast cell degranulation.

1. Types:
   a. Isoprenaline – first available \( \beta \)-selective agent used for asthma
Salbutamol, terbutaline (1970s) – relatively β₂-selective, not degraded by catechol-o-methyltransferase (so longer duration of action)

Salbutamol, terbutaline (1970s) – relatively β₂-selective, not degraded by catechol-o-methyltransferase (so longer duration of action)

Fenoterol – withdrawn in 1989 (? Increased asthma mortality)

Administration is usually by inhalation (quicker onset, fewer systemic effects).

- MDI dose = 100μg/puff, higher nebulised doses acutely = 2.5-5mg (up to half-hourly)
- IV/IM β-agonists are reserved for severe/life-threatening attacks (anecdotal evidence)
- 80% of total effect is seen within 5 min, peaking at 15-20 min and lasting 4-6hrs.
- Oral preparations were used for nocturnal asthma and children

Adverse effects include tremor and sinus tachycardia (worst with oral preparations), but tachyphylaxis develops rapidly with use (no tachyphylaxis to bronchodilator effects).

Long-acting inhaled β-agonists (salmeterol, eformeterol) provide 12 hour bronchodilatation

- Slower acting than salbutamol (eformeterol > salmeterol) – used as a preventer
- Effective in helping control asthma when used regularly
- Only available for patients not controlled on 1500μg beclomethasone or equivalent

Anticholinergic agents act by blocking acetylcholine released from vagal nerve endings, which usually contracts airways smooth muscle (note there is no direct sympathetic innervation) by acting on M3 muscarinic receptors. Other mediators (histamine, PGD₂) stimulate sensory nerve endings, leading to a reflex increase in resting vagal tone.

- Administration – most are inappropriate for inhalation due to systemic side effects, except for ipatropium bromide (quaternary ammonium compound) which is poorly absorbed
- Efficacy – less effective, slower onset than β-agonists for asthma but longer duration (6-8hrs)
- No additive effect with β-agonists in asthma
- Often used in COPD – equal efficacy with β-agonists

Theophylline is a methylxanthine (same class as caffeine), and while its mode of action is unclear, it appears to act as a phosphodiesterase inhibitor to inhibit breakdown of cAMP. Used as 3rd line therapy for asthma as an alternative to long-acting inhaled β-agonists.

- Administration – oral preparation or IV (as theophylline ethylenediamine – aminophylline)
- T 1/2 is 8hrs, but slow-release preparations allow od/bd dosing
- Adverse effects – narrow therapeutic index → nausea, vomiting, headache, palpitations, supraventricular arrhythmias (tachycardia and seizures at very high doses)
- Metabolism is highly variable:
  - Smoking, phenytoin, rifamycin increase clearance
  - Heart failure, cimetidine, erythromycin decrease clearance
- Therapeutic drug monitoring is useful.

Anti-inflammatories

Inhaled corticosteroids reduce airway inflammation and hence lead to better asthma control.

- Types:
  - Beclomethasone dipropionate (90% FPM) – 200μg bd or more
  - Budesonide (90% FPM) – 200μg bd or more
  - Fluticasone propionate (99% FPM) – 100μg bd
- Administration – note that most of the dose is actually swallowed
  - Mild asthma may be controlled with od, while severe asthma may need up to qid
  - Most adults controlled with 400-800μg, while some need 1000-2000μg
- Adverse effects are minimal due to very high first-pass metabolism by the liver
  - Local – oral candidiasis, hoarseness (laryngeal muscle myopathy)
  - Reduced by gargling and use of a spacer
  - Long term high doses may lead to skin thinning and bruising
- Oral corticosteroids are rarely used for long-term treatment due to adverse effects (requires specialist follow-up) but are very useful for acute exacerbations
- 20-40mg/day for 1-2 weeks, then stop (as safe as a tapering dose)
- Never stop long term steroids suddenly!

Disodium cromoglycate and nedocromil have some anti-inflammatory action (unclear mechanism) but are not as effective as 400μg of beclomethasone. They are not widely used in adults, but may be used as an alternative to steroids in children.

- Only 2/3 of patients respond – requires a 4-6 week trial to determine response
- Administration:
Respiratory

a. Disodium cromoglycate – inhalation qid, may drop to bd once well controlled
b. Nedocromil – bd
3. Adverse effects are virtually absent, although the taste of nedocromil is not tolerated by some

• Delivery Devices

Metered dose inhalers are most commonly used and are relatively cheap. They use CFCs as propellants, although this accounts for <1% of all CFCs in the atmosphere and a newer propellant (HFA 134a) is being phased in presently.
1. Only 5-10% reaches the lung, the rest is deposited in the oropharynx or swallowed
2. Use requires coordination – poor technique
3. Spacers – coordination not required, large particles deposited (fewer systemic effects)
   a. Tube or pear shaped – pear shapes more effective but less portable/compatible

The only available breath activated MDI is the Autohaler. This device is triggered by inhalation, so there is no problem with coordination.

Dry powder devices (spinhaler, turbuhaler, diskhaler) do not have CFS and are also breath activated so do not need coordination – however, children <4yrs cannot generate enough inspiratory flow rate.
1. Diskhaler (8 doses) – salbutamol, beclomethasone, fluticasone, salmeterol
2. Turbuhaler (200 doses) – budesonide, terbutaline, eformeterol
3. Spinhaler – originally used for disodium cromoglycate

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Impact of COPD:
1. Source of immense morbidity and mortality (2.2 million deaths in 1990)
2. Often undiagnosed in the 75% with mild/moderate disease
3. Correlation between COPD and socio-economic status (Asia-Pacific, 3rd world)
4. Greater susceptibility of women

Smoking-related airways disease:
1. Chronic bronchitis (mucus hypersecretion)
   a. Productive cough most days for at least 3/12 in two consecutive years
   b. Mainly large airways – goblet cell hyperplasia, mucus gland hyperplasia/hypertrophy
2. Emphysema – permanent abnormal enlargement of any or all of the acinus with destructon
   a. Centracinar and panacinar
   b. Not simple correlation with clinical, radiologic or physiologic abnormalities
3. Small airways disease – inflammation and narrowing (bronchiolitis) with peribronchiolar fibrosis and inflammation. Note the ‘silent zone’ – physiologic abnormalities are usually late.

• Pathogenesis and Diagnosis

Risk factors for chronic fixed airflow obstruction:
1. Cigarette smoke is the largest single risk factor
2. Airway hyper-responsiveness (Dutch hypothesis)
3. Early childhood lower respiratory infection
4. Ambient air pollution probably has a limited role
5. Occupational dust and fumes may → both acute obstruction and chronic fixed obstruction
   a. Possible occupational exposures include cotton grain, wood dust (western red cedar), coffee beans, isocyanates, gases and inorganic dusts
6. Demographic characteristics
7. Alpha-1-antitrypsin deficiency

While low levels of alpha-1-antitrypsin are commonly used as a marker, it is probably not the main antiprotease – others are not detectible clinically. Serum leukocyte protease inhibitor (SLIPI) is probably the most important – pathogenesis involves protease vs antiprotease balance/imbalance.
1. Excess levels of proteases cause elastolysis of emphysema
2. Airflow obstruction is mediated by mucus plugging, oedema, smooth muscle contraction
3. Loss of elastic recoil with airflow obstruction → hyperinflation, increased work
4. Resulting dyspnoea → less exercise and fitness → weaker muscles, often V/Q mismatch
Respiratory

Clinical manifestations include:
1. Symptoms – dyspnoea, cough, fatigue
2. Signs – hyperinflation, tachypnoea, reduced breath sounds, wheeze, cyanosis

Spirometry is useful for diagnosis/prognosis:
1. PEF is highly effort-dependent and more variable, with a wide normal range
2. Correlation between FEV\textsubscript{1} and PEF is poor – it is not possible to predict one from the other
3. PEF may grossly under-estimate the degree of airflow obstruction
4. Use of FEV\textsubscript{1}:
   a. Reproducible and objective measure with well defined normal ranges (+/- 170mL)
   b. Relatively effort-independent, measured relatively easily and quickly
   c. FEV\textsubscript{1} is predictor of mortality, most closely correlated with level of dyspnoea
   d. Serial measures document disease progression

• Therapy

Goals of therapy in COPD are to prevent disease progression, relieve symptoms, improve exercise tolerance, improve health status, prevent and treat complications and ultimately reduce mortality.

COPD Therapy:
1. Prevention, early diagnosis and intervention
   a. Smoking cessation:
      i. Behavioural stages of smoking cessation – “How do you feel about your smoking?”
         1. “Not ready to change” (precontemplative) – 60%
         2. “Unsure” (contemplative) – 30%
         3. “Ready to change” (preparation) – 10%
      ii. Nicotine therapy and agents such as Zyban have cumulative benefits
   b. Immunisation (influenza, pneumococcal)
2. Symptomatic relief – bronchodilators can be used regularly for symptomatic relief
   a. Inhaled beta agonists vs ipratropium (non-selective antimuscarinic)
      i. No evidence of tachyphylaxis to beta agonists
      ii. Equal proportions of patients respond – response to one does not predict response to the other (try one, then other)
      iii. Combination has additional benefits (sub-maximal dose e.g. Combivent)
      iv. There is limited data for long-acting agents in COPD, but efficacy is likely
   b. Theophylline has a limited role, as it has little/no clinical effect on respiratory muscles and requires monitoring of serum levels (narrow therapeutic range)
   c. The role of inhaled corticosteroids in COPD is still undefined – however, it is clear that they are grossly overused in this condition. There is some evidence that those with the most severe disease and most frequent exacerbation might benefit.
3. Long-term oxygen therapy – note that dyspnoea does not equate hypoxaemia
   a. If a patient has an FEV\textsubscript{1} > 1.0L, and O\textsubscript{2} saturation is over 92%, there probably isn’t much point doing blood gases to see if they require oxygen therapy
   b. Requires arterial blood gas estimation – absolute:
      i. PaO\textsubscript{2} <7.3kPa
      ii. PaO\textsubscript{2}<8.0kPa if cor pulmonale, polycythemia, or nocturnal desaturation
   c. About 9 months before a demonstrable survival benefit, with saturation of >90% required for >16hrs/day from an oxygen concentration device (nasal prongs)
4. Rehabilitation programmes are conducted by a respiratory physiotherapist (without medical supervision) – in those with severe disease, this has probably the greatest impact on QOL
   a. Groups of 6-8 patients after optimisation of pharmacologic management
   b. Seven 2-hour sessions over one month, concentrating on improving strength and endurance of limb and respiratory muscles – unclear if this improves mortality
   c. Other aspects:
      i. Secretion removal, breathing/relaxation exercises, rehabilitation
      ii. Limited role for mucolytics/expectorants (starting to be re-evaluated)
      iii. Unknown if this nutritional supplements affect outcome
      iv. Psychological support
5. Lung volume reduction surgery – very limited role, only in rare cases
Acute Management

Management of an acute exacerbation:

1. Exclude other conditions – pulmonary emboli, LVF, arrhythmias, GORD, respiratory depression (high inspired O2, sedatives, obstructive sleep apnoea)
2. History to be obtained:
   a. Exercise tolerance, usual and during exacerbation
   b. Treatment (ongoing and for exacerbation). Include specifically nebulisers and LTOT
   c. Time course of acute exacerbation
   d. Patient’s social circumstances, QOL, social support, hospitalisations, smoking
   e. Previous lung function test results
3. Treatment
   a. Bronchodilators – ipratropium bromide, beta agonist, few cases use IV theophylline
   b. Antibiotics (amoxycillin/doxycycline) – *S. Pneumoniae, H. influenzae, M. catarrhalis*
   c. Corticosteroids
   d. Reverse hypoxaemia (target saturation >90% – 20 + 4 x flow = equivalent oxygen %)
      i. Patients with severe COPD may be dependent on hypoxic drive – oximeter only measures O2 saturation (not PaCO2 or pH).
      ii. O2 therapy may maintain satisfactory O2 saturation, at the expense of worsening respiratory acidosis – must use arterial blood gases to manage
      iii. Use FiO2 of <0.28 (or 2L via nasal prongs) initially
4. Non-invasive positive pressure may be used in acute respiratory failure (pH <7.3, rising PaCO2) in patients who:
   a. Fail to respond to conventional therapy
   b. Have acceptable QOL or habitual level of activity
   c. Lack severe morbidities
   d. Are able to tolerate mask/treatment
5. Prevention:
   a. Stop smoking
   b. Vaccination (Fluvax, Pneumovax)
   c. Domiciliary O2
   d. Mixed evidence for mucoactive and immunostimulatory agents, regular ipratropium

Miscellaneous (Not Lectured On)

Hypoxia, Oxygen Therapy and Pulmonary Function Tests

Hypoxia is defined as a lack of oxygen regardless of cause or site. Its effects are at a tissue level, characterised by increased cardiac/respiratory rates, mental deterioration and sometimes cyanosis.

1. Hypoxia (PAO2 <8.0kPa) and/or hypercapnoea (PaCO2 >6kPa) = respiratory failure
2. Oxygen passes to the mitochondria down a partial pressure gradient (oxygen cascade):
   a. PIO2 (20kPa) – influenced by FIO2 and atmospheric pressure
   b. PAO2 (13.3kPa) – influenced by alveolar ventilation and O2 consumption
   c. PaO2 (12.9kPa) – influenced by venous admixture, gas diffusion, mixed venous O2
   d. Tissue capillary PO2 (12.9-5.3kPa) – influenced by O2 delivery and consumption
   e. Intracellular PO2 (low, <2.0kPa)
3. Intracellular PO2 can be increased by increasing the driving pressure for the O2 cascade (i.e. increased PIO2) – in practise, this means delivery O2-enriched air to the patient.

Note that oxygen is a drug as should be charted (concentration, flow rate, mode of administration)

1. Methods of delivery:
   a. Mask (>4L/min) – variety of types available (use diluter jets, Venturi principle)
   b. Nasal prongs (<4L/min) – % inspired O2 = 20 + (4 x flow rate in L/min)
   c. Hudson mask – used with a humidifier to give humidified O2
   d. Intubation and assisted ventilation – used for patients in respiratory failure
2. Indications – O2 should be given to all acutely hypoxic patients, giving 50% O2 if they are cyanosed and 30-40% if they are not. However:
   a. COPD patients may have CO2 retention and a hypoxic drive for respiration
   b. Initially use low inspired O2 concentrations (~30%) to avoid abolishing hypoxic drive
Pulmonary function tests in routine use include arterial blood gases, spirometry (FEV₁/FVC – normal is >70%) and peak expiratory flow rate. Note that a quantitative assessment of pulmonary function (i.e. spirometry) is essential in the management of patients with pulmonary disease:

1. Obstructive disease – FEV₁/FVC reduced (i.e. FEV₁ is reduced more than FVC)
2. Restrictive disease – FEV₁/FVC is normal (i.e. both are reduced equally)
3. PEFR is a cheap and easy test for monitoring obstructive disease

Lung Defence Mechanisms

The lungs are an ideal environment for growing bacteria – hence it uses several defence mechanisms to get rid of inhaled particles. Note that inhaled particle retention depends on size (>10μ nose, 5-10μ trachea, <2μ alveoli), density, shape, charge, aggregation, water solubility and respiratory pattern.

Lung defence mechanisms:

1. Large airways – mechanical filtration (nose) and reflexes:
   a. Sneeze (URT)
   b. Cough (LRT) – effective down to 17th generation of airway branching 2° to inflammatory, mechanical, chemical, thermal or psychogenic stimuli
      i. Forced expiration against a closed glottis \( \rightarrow \) increased intrathoracic pressure
      ii. High velocity linear airflow when glottis opened
   c. Cough centre in medulla, travels via cranial nerves

2. Smaller airways – mucociliary clearance escalator
   a. Mucus – viscous gel made of mucin, proteoglycans, proteins and DNA
      i. Produced by mucosal glands and goblet cells under the influence of inflammatory mediators, nerves and hormones
      ii. Absorbs gas, dilutes chemicals, traps particles and has antimicrobials
   b. Cilia (>2000 per cell) – effective and recovery strokes, continuous/coordinated action
      i. Periciliary fluid volume is critical for ciliary function (modifies mucus layer)
      ii. Produced from Clara and epithelial cells, regulated by active ion transport
      iii. Amenable to drug modulation

3. Peripheral airways – cellular and immunologic mechanisms
   a. Phagocytic – PMNs, alveolar macrophages
   b. Lymphoid – bronchus-associated lymphoid tissue (BALT)
   c. Immunoglobulins – IgA
   d. Complement
   e. Surfactant

Defects in defence mechanisms:

1. Mechanical – large foreign body (too large to remove)
2. Cough – due to reduced airflow or high mucus viscosity (e.g. mucus/goblet cell hyperplasia)
   \( \rightarrow \) mucoid, serous, purulent, mucopurulent and/or blood tinged sputum
   a. Abnormal cilia – ciliary dyskinesia syndrome, infection or inflammation
   b. Slow cilia – inflammatory mediators can slow beat frequency
   c. Cellular – immune deficiency 2° to congenital selective IgA deficiency, AIDS, infection

Pathophysiology of Respiratory Symptoms

Dyspnoea is an uncomfortable sensation of the need for increased respiratory effort, inappropriate for the level of exercise.

1. Subjective sensation resulting from integration of CNS and peripheral signals:
   a. Respiratory muscle activity – afferent information carried by the vagus
   b. Chemoreceptors – changes in arterial blood gases (↑ pCO₂, ↓ PaO₂)
   c. Cortical motor neurones – stimulated during anxiety, nervous tension

2. Causes:
   a. Narrowing of upper airways – croup, epiglottitis
   b. Narrowing of lower airways – asthma, foreign body, emphysema
   c. Lung parenchyma disease – pneumonia, fibrosing alveolitis
   d. Pleural disease – effusion, pneumothorax
   e. Chest wall changes – pregnancy, obesity, fatigue, muscular dystrophy
   f. Cardiovascular – pulmonary oedema, PE, decreased O₂ carrying capacity (anaemia)
   g. Increased respiratory drive – pregnancy, chronic liver disease, thyrotoxicosis
Wheeze is a continuous high-pitched sound which occurs in narrowed airways, but may disappear completely when gas flow is reduced further.

1. Airflow resistance is mediated by narrowing – halving diameter → 16x increase in resistance
2. Causes:
   a. Luminal narrowing – foreign body, secretions
   b. Airway wall thickening – inflammatory oedema, smooth muscle contraction
   c. Outside pressure – tumour, destruction of elastic tissue

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