

Third edition

Notes & Notes

By

Dr. Yousif Abdallah Hamad

Pulmonology

**Updated
2022**

Dr. Subrata

The 10 Golden Tips for MRCP written exams you will ever need

1. For MRCP, do not read hard; read smart.
2. Three to six months is usually enough for preparation.
3. Practice the best of the five questions as much as possible.
4. The few days before the exam date, stop revising questions and concentrate on your MRCP notes and top tips.
5. Remember, you are getting ideas and concepts from the questions.
6. Time factor in the exam room is the leading killer after poor preparation.
7. Manage your time wisely.
8. Read the end of the question first; if you can answer it without reading the whole scenario, it will save your time for the other tuff question (long scenario, .what is the action of imatinib?)
9. Take care for any single word in the question, e.g. (the initial test, the diagnostic test, the best test, the next step)
10. Practice, practice and practice.



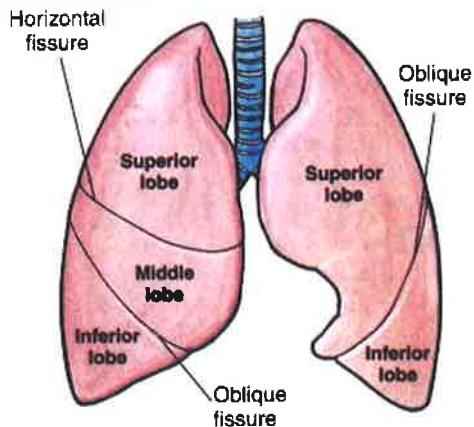
Chapter 2 Pulmonology

Lung anatomy.....	248	Pseudomonas pneumonia.....	304
Diaphragmatic paralysis (Phrenic nerve palsy)	250	Hospital-acquired pneumonia (HAP).....	305
Lung physiology.....	250	Pneumocystis Jirovecii pneumonia (PCP)	306
Oxygen Dissociation Curve.....	252	Coronavirus disease 2019 (COVID-19)	308
Pulmonary function tests.....	255	Aspergillosis: Types.....	311
Obstructive vs. Restrictive lung diseases	255	Allergic bronchopulmonary aspergillosis (ABPA)	312
Transfer factor.....	258	Aspergilloma.....	313
Transfer coefficient of carbon monoxide (KCO)	259	Invasive aspergillosis (IA).....	314
Arterial Blood Gas (ABG).....	260	Alpha-1 antitrypsin (A1AT) deficiency.....	316
Chest x-ray.....	262	Acute respiratory distress syndrome (ARDS)	318
Pleural calcification - Solitary pulmonary nodules	265	Altitude related disorders.....	321
Alveolar-arterial (A-a) oxygen gradient.....	266	Bronchiectasis.....	322
Finger clubbing.....	267	Cystic fibrosis (CF).....	325
Respiratory failure.....	268	Occupational asthma.....	331
Bronchial Asthma.....	269	Hypersensitivity pneumonitis (HP).....	332
Acute severe asthma.....	274	Pneumoconiosis.....	334
Chronic Obstructive Pulmonary Disease(COPD)	276	Asbestos and the lung.....	335
COPD: stable management.....	279	Pleural mesothelioma.....	335
Non-invasive ventilation (NIV).....	283	Silicosis.....	337
Invasive ventilation.....	285	Berylliosis.....	339
Long-term oxygen therapy (LTOT).....	285	Coal workers' pneumoconiosis (CWP)....	340
Pulmonary embolism (PE).....	286	Primary ciliary dyskinesia (PCD).....	341
Recurrent pulmonary emboli.....	291	Kartagener's syndrome.....	342
Pulmonary embolism in pregnancy: diagnosis and management.....	291	Lung cancer: General overview.....	343
Fat embolism.....	293	Lung cancer: paraneoplastic features.....	346
Community-acquired pneumonia (CAP)	294	Lung cancer: stepwise investigations.....	347
Klebsiella Pneumonia.....	298	Performance status for patient of lung cancer and COPD	349
Legionella pneumonia (Legionnaires' disease)	299	Staging lung carcinoma.....	349
Mycoplasma pneumoniae.....	300	Treatment of lung cancer.....	351
Aspiration pneumonia.....	302	Lung cancer induced superior vena cava obstruction (SVCO).....	353
Psittacosis (Chlamydia psittaci pneumonia) (Atypical pneumonia).....	303	Pancoast tumor.....	354
		Lung metastases.....	355

Chapter 2 Pulmonology

Carcinoid lung tumour.....	356	Chronic eosinophilic pneumonia.....	374
Lung fibrosis: Causes.....	357	Tropical pulmonary eosinophilia.....	375
Idiopathic pulmonary fibrosis (IPF)	358	Loffler's syndrome.....	376
Bronchiolitis obliterans (BO).....	360	Cryptogenic organising pneumonia (COP)	376
Post-extubation stridor (PES).....	362	Pulmonary hypertension (PH).....	377
Obstructive sleep apnoea (OSA).....	362	Sarcoidosis.....	379
Obesity hypoventilation syndrome (OHS)	364	Lofgren's syndrome.....	384
Pneumothorax.....	364	Yellow nail syndrome.....	384
Pleural effusion.....	368	Hepatopulmonary syndrome (HPS).....	385
Chylothorax.....	372	Pulmonary alveolar microlithiasis (PAM)	386
Haemothorax.....	372	Pulmonary Alveolar Proteinosis (PAP)	387
Eosinophilic Pulmonary Diseases.....	373	Carbon monoxide poisoning.....	388
Acute eosinophilic pneumonia.....	374	Smoking cessation.....	390

Lung anatomy



Lung lobes

- Right lung has 3 lobes; Left has less lobes (2) and lingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart
- The left lung have a part that the right lung does not have: the lingula, which is the homolog of the middle lobe of the right lung

Lung fissures

- The oblique fissure divides the superior and inferior lobes in the posterior aspect of both the right and left lungs
- Horizontal fissure is found only in the right lung

Lung bronchi

- Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:
 - While supine — usually enters superior segment of right lower lobe.
 - While lying on right side — usually enters right upper lobe.
 - While upright — usually enters right lower lobe.
- Airway resistance highest in the large-to medium-sized bronchi and least in the terminal bronchioles

Cell types in respiratory zone

- Pseudostratified ciliated **columnar cells** are found in **bronchi/early terminal bronchioles**.
- Cuboidal cells** are found in **terminal bronchioles** onward
- Simple squamous** is the primary type of epithelium present in the **alveoli**

Anatomical land marks

- Cartilage and goblet cells extend to the end of bronchi.
- The **Angle of Louis** (also known as the sternal angle or Angle of Ludwig) corresponds to **T4/T5 vertebral bodies**, which is the location at which the **trachea bifurcates to the main stem bronchi (carina)**.
- **Structures perforating diaphragm:**
 - ⇒ At T 8: IVC, right phrenic nerve
 - ⇒ At **T 10: oesophagus**, Vagus (CN10; 2 trunks)
 - ⇒ At T 12: aorta, thoracic duct, azygos vein.
- The trachea bifurcates at the level of T4 ("bi-four-cates at 4")
- Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

Azygous lobe of the lung

- An azygous lobe is a normal variant that develops when a laterally displaced azygos vein creates a deep pleural fissure into the apical segment of the right upper lobe during embryological development.
- azygous lobe is seen in about 0.5% of routine chest X-rays and is a normal variant.
- The azygous lobe is formed when the posterior cardinal vein fails to migrate over the apex.
- It is seen as a 'reverse comma sign' **behind the medial end of the right clavicle**.

Top Tips

A patient aspirates vomit. Is the right or left lung a more common site for inhaled foreign bodies and why?

- ⇒ Right lung, because the right mainstem bronchus is wider, more vertical, and shorter than the left

A patient chokes on a peanut while upright. Where exactly in the lungs do you expect to find the peanut?

- ⇒ Right lower lobe

Diaphragmatic paralysis (Phrenic nerve palsy)

Innervation

- The diaphragm is innervated by the phrenic nerve (C3,4,5).

Causes

- Unilateral diaphragmatic paralysis (more common than bilateral)
 - ⇒ Trauma e.g. Thoracic surgery,
 - ⇒ Compression: cervical spondylosis, cervical compressive tumors
 - ⇒ viral infections (eg, Herpes zoster, poliomyelitis)
- Bilateral:
 - ⇒ Guillain-Barré
 - ⇒ Infection

Features

- Unilateral paralysis: usually asymptomatic
- Bilateral : dyspnoea may progress to ventilatory failure

Diagnosis of unilateral paralysis:

- suggested by asymmetric elevation of the affected hemidiaphragm on X-ray
- Spirometry (in the supine and sitting positions)
 - ⇒ The forced vital capacity (FVC) is ↓ to 70 - 80 % of predicted and typically ↓ decreases further by 15 to 25 % in the supine position.
- Confirmed by fluoroscopy
 - ⇒ by observing paradoxical diaphragmatic motion on sniff and cough
 - ⇒ During a forced inspiratory manoeuvre (the 'sniff test'), the unaffected hemidiaphragm descends forcefully, increasing intra-abdominal pressure and pushing the paralysed hemidiaphragm cephalad (paradoxical motion)
 - ⇒ Fluoroscopy is inaccurate for the diagnosis of bilateral paralysis.

Treatment

- Unilateral diaphragmatic paralysis: do not require treatment.
- Bilateral : may require noninvasive positive pressure ventilation (NPPV) , usually a bilevel positive airway pressure device (BPAP).

Lung physiology

Pulmonary surfactant

- Surfactant is a mixture of phospholipids, carbohydrates and proteins
- first detectable around 28 weeks of gestation
- Released by type 2 pneumocytes
- The main functioning component in surfactant is dipalmitoyl phosphatidylcholine (DPPC) or lecithin, which reduces alveolar surface tension.
- as alveoli decrease in size, surfactant concentration is increased, helping prevent the alveoli from collapsing
- reduces the muscular force needed to expand the lungs (i.e. decreases the work of breathing)

- lowers the elastic recoil at low lung volumes and thus helps to prevent the alveoli from collapsing at the end of each expiration
- Because of surfactant, the pressure difference across the pleura required to inflate the lungs, is usually no more than about 4 cmH₂O.

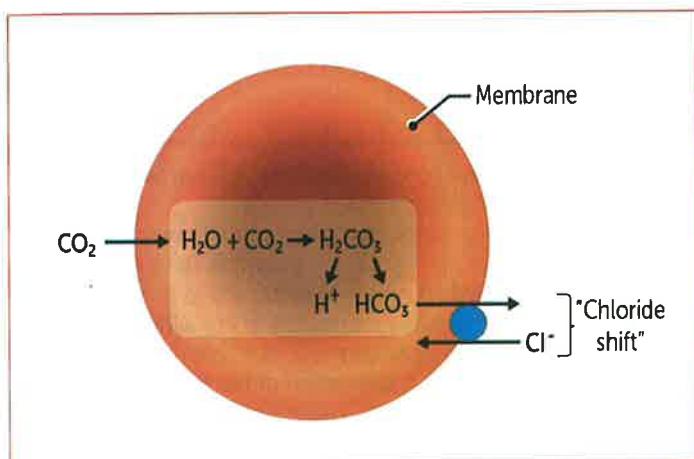
Pulmonary circulation

- The normal pulmonary circulation is characterised by:
 1. low pressures,
 2. low flow rates,
 3. high compliance vessels.
- Chronic hypoxic vasoconstriction may lead to pulmonary hypertension +/– cor pulmonale.
- A fall in the partial pressure of oxygen (pO₂) in the blood causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung and improves the efficiency of gaseous exchange.

Pulmonary arteries vasoconstrict in the presence of hypoxia

Chloride shift

- Cells metabolism → ↑CO₂ → diffuses into RBCs → CO₂ + H₂O → carbonic anhydrase → carbonic acid (H₂CO₃) → HCO₃⁻ + H⁺
- H⁺ combines with Hb
- HCO₃⁻ diffuses out of cell, - Cl⁻ replaces it
- CO₂ produced in the periphery is converted into bicarbonate inside RBCs and then shifted out with chloride replacement



Bohr Effect

- Increasing acidity (or pCO₂) means O₂ binds less well to Hb
- High CO₂ and H⁺ concentrations (from tissue metabolism) cause decreased affinity for O₂ → O₂ that is bound to Hb is released to tissue (the O₂-Hb dissociation curve is shifted to the right).

Haldane effect

- ↑ pO₂ means CO₂ binds less well to Hb
- When Hb is oxygenated (in high pO₂, for example, in the lungs):
- Oxygenated Hb has a decreased affinity for CO₂ → CO₂ that is bound to Hb is released in the pulmonary arteries to diffuse into the alveoli (the O₂-Hb dissociation curve is shifted to the left).

Acclimatisation to life at high altitudes

- Acclimatisation results in increased Hb with erythrocytosis.
- **Pulmonary artery pressure increases to oxygenate more blood.**
- **2,3-DPG increases.**
- Respiration is normal when subjects are acclimatised to altitude as is cardiac output. (Periodic respiration is a feature of non-acclimatisation).

Lung compliance is defined as change in lung volume per unit change in airway pressure

Causes of ↑ compliance	Causes of ↓ compliance
<ul style="list-style-type: none"> • Age • Emphysema 	<ul style="list-style-type: none"> • Pulmonary edema • Pulmonary fibrosis • Pneumonectomy • Kyphosis

- **Which part of the conducting zone of the respiratory tree has the least airway resistance?**
⇒ Terminal bronchioles

The **cough center** of the brain, located in the **nucleus tractus solitarius** of the **medulla of the brainstem**

Oxygen Dissociation Curve

Definition

- **Oxygen Dissociation Curve** describes the relationship between the percentage of saturated hemoglobin and partial pressure of oxygen in the blood.
- Each hemoglobin molecule has the capacity to carry four oxygen molecules.

Meaning of shifting the curve to the right or left

- Shifts to right = for given oxygen tension there is ↓ saturation of Hb with oxygen i.e. Enhanced oxygen delivery to tissues
- Shifts to left = for given oxygen tension there is ↑ saturation of Hb with oxygen i.e. ↓ oxygen delivery to tissues

Causes of shifting the curve to the right or left

Shifts to Right = Raised oxygen delivery (The R rule)	Shifts to Left = Lower oxygen delivery (The L rule)
<ul style="list-style-type: none"> Raised $[H^+]$ (acidity) Raised PCO_2 Raised 2,3-DPG Raised temperature 	<ul style="list-style-type: none"> Low $[H^+]$ (alkali) Low PCO_2 Low 2,3-DPG Low temperature HbF, methemoglobin, carboxyhaemoglobin

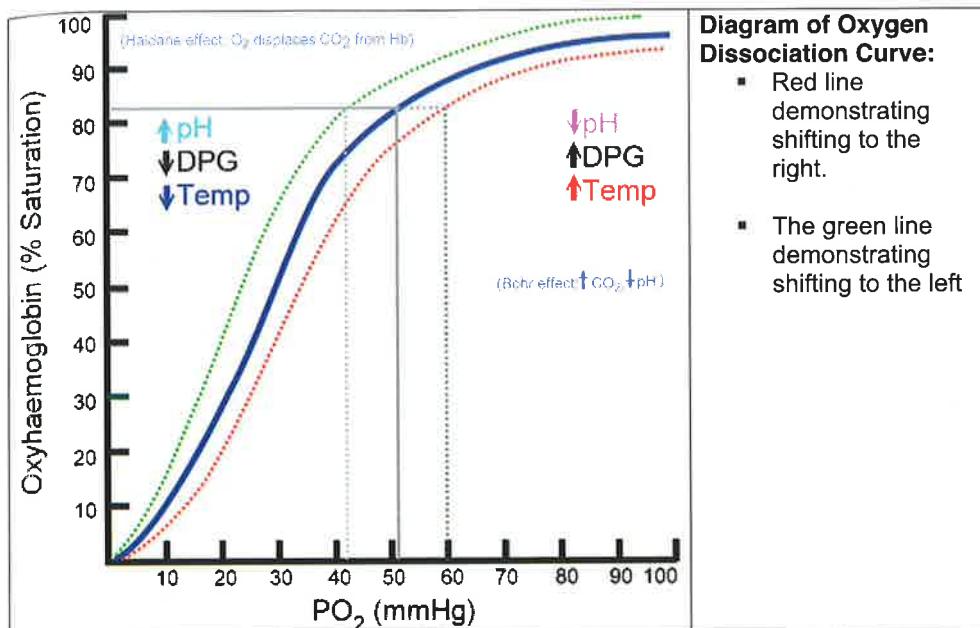


Diagram of Oxygen Dissociation Curve:

- Red line demonstrating shifting to the right.
- The green line demonstrating shifting to the left

The curve and Affinity

- Left shift of the curve is a sign of hemoglobin's ↑ affinity for oxygen (e.g. at the lungs).
- Similarly, right shift shows ↓ affinity, as would appear with an ↑ in body temperature, hydrogen ion, 2,3-diphosphoglycerate (2,3-DPG) or carbon dioxide concentration (the Bohr effect)
- Carbon monoxide has a much higher affinity for hemoglobin than oxygen does. In carbon monoxide poisoning, oxygen cannot be transported and released to body tissues thus resulting in hypoxia.

Top tips

Oxygen dissociation curve

- shifts Left - Lower oxygen delivery - Lower acidity, temp, 2-3 DPG - also HbF, carboxy/methaemoglobin
- shifts Right - Raised oxygen delivery - Raised acidity, temp, 2-3 DPG

Blood in the skeletal muscle is exposed to high temperatures, lower pH, and higher CO₂. The oxygen-hemoglobin dissociation curve shifts to the right, facilitating oxygen delivery to the tissue.

In the pulmonary vein, blood is exposed to a higher pH and lower CO₂. The oxygen-hemoglobin dissociation curve shifts to the left, facilitating oxygen binding to hemoglobin.

2,3-Diphosphoglycerate (2,3-DPG)

- 2,3-DPG is an important molecule made by tissue in response to a low pH and low oxygen environment.
- It may be helpful to think of 2,3-DPG as a help flag made by tissues in response to stress. When hemoglobin comes across higher 2,3-DPG, it "knows" that the tissue is in trouble and drops off extra oxygen. Therefore, as 2,3-DPG increases, the binding affinity of oxygen for hemoglobin decreases, which results in a rightward shift of the dissociation curve.

Question

A 24-year-old woman is evaluated before and after practice to assess oxygen delivery to her muscles. The hemoglobin-oxygen dissociation curve is shown.

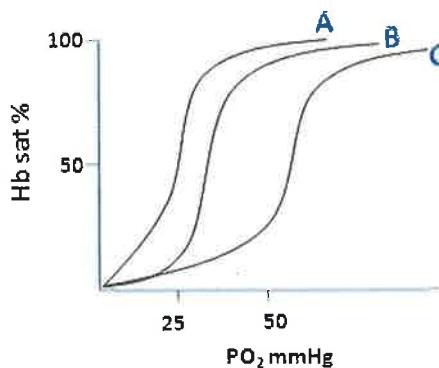
Curve B is taken before practice.

Which characteristics will most probably describe curve A?

Answer:

If curve B is taken before practice, it will be used as reference point. Curve A shows shifts to the left.

Increased pH with decreased 2,3-diphosphoglycerate concentration



Pulmonary function tests

Pulmonary function tests can be used to determine whether a respiratory disease is obstructive or restrictive.

Normal lung volumes

	Definition	Normal range
Total lung capacity (TLC)	Volume of air in the lungs after maximal inhalation [= vital capacity + residual volume].	6–6.5 L
Vital capacity (VC)	Maximum volume of air that can be expired after a maximal inspiration. [↓ with age]	4.5–5 L
Residual volume (RV)	Volume of air that remains in the lungs after maximal exhalation. [↑ with age & obstructive lung disease]	1–1.5 L
Tidal volume (TV)	Volume of air that is inhaled and exhaled in a normal breath at rest	~ 500 mL or 7 mL/kg
Inspiratory reserve volume	Maximum volume of air that can still be forcibly inhaled following the inhalation of a normal TV	3–3.5 L
Inspiratory capacity (IC)	Maximum volume of air that can be inhaled after the exhalation of a normal TV. [IC = TV + IRV]	3.5–4 L
Expiratory reserve volume (ERV)	Maximum volume of air that can still be forcibly exhaled after the exhalation of a normal TV	1.5 L
Expiratory capacity (EC)	Maximum volume of air that can be exhaled after the inspiration of a normal TV	2 L
Functional residual capacity (FRC)	Volume of air that remains in the lungs after the exhalation of a normal TV	2.5–3 L
Dead space	areas of the lung not involved in gas exchange. Anatomic dead space includes the non-respiratory airways and exists in all healthy lungs. Physiologic dead space includes the anatomic dead space plus any alveoli that are not perfused and thus cannot participate in gas exchange	150 ml

Obstructive vs. Restrictive lung diseases

	Obstructive	Restrictive
Spirometry	FEV1/FVC <0.7 (<70%)	FEV1/FVC >0.7 (> 70%)
	FEV1 - significantly reduced (<80% predicted normal)	FEV1 - reduced (<80% predicted normal)
	FVC - reduced or normal FEV1% (FEV1/FVC) - reduced	FVC - significantly reduced (<70% predicted normal) FEV1% (FEV1/FVC) - normal (>0.7) or increased

	Obstructive	Restrictive
Examples	Chronic obstructive pulmonary disease <ul style="list-style-type: none"> • chronic bronchitis • emphysema Asthma Bronchiectasis	Intrapulmonary <ul style="list-style-type: none"> • idiopathic pulmonary fibrosis • extrinsic allergic alveolitis • coal worker's pneumoconiosis/progressive massive fibrosis • silicosis • sarcoidosis • histiocytosis • drug-induced fibrosis: amiodarone, bleomycin, methotrexate • asbestos Extrapulmonary <ul style="list-style-type: none"> • neuromuscular disease: polio, myasthenia gravis • obesity • scoliosis

Forced vital capacity (FVC)

- A measure of the force, volume, and speed with which air can be maximally expelled from the lungs.
- The maneuver would be to take a deep breath, and then blow it out as hard as you can for as long as you can to maximally expel air from the lungs.
- Indications
 - ⇒ commonly done to assess patients with asthma and chronic obstructive pulmonary disease.
 - ⇒ **the best way to monitor respiratory function in any neurological disorders that can affect the respiratory muscles (e.g. GBS, myasthenia gravis). ITU admission** is recommended when FVC is less than 20 mL/kg and **intubation is recommended in most cases when FVC is less than 15 mL/kg.**

Peak expiratory flow rate (PEFR)

- **Definition** : The maximum airflow rate attained during forced expiration.
- **Normal values**
 - ⇒ PEF values are usually expressed as L/min; when measured as part of spirometry, values are expressed in L/sec. To convert, multiply L/sec x 60 sec/min = L/min.
 - ⇒ Peak flow meters are handheld devices used to measure PEFR in the ambulatory setting
 - ⇒ Normally : $\geq 80\%$ of the predicted average value
 - ⇒ Dependent upon factors such as gender, age and height. **The most accurate correlation of the peak expiratory flow rate (PEFR) is with height.** PEFR is typically higher in males than females and higher in taller patients.
- **Advantages**
 - ⇒ It is effort-independent.
 - ⇒ In patients with asthma, the PEFR % predicted correlates reasonably well with the FEV₁ and provides an objective measure of airflow limitation when spirometry is not available
 - ⇒

- **Disadvantages**

- ⇒ predominantly assesses large airway caliber and can underestimate the effects of asthma in the small airways.
- ⇒ Restrictive processes that limit full inspiration, such as chest wall disease, obesity, and muscle weakness, can lead to a reduced PEF in the absence of airflow limitation. Thus, values for PEF that are less than 80 percent of predicted should be further evaluated with spirometry before assuming that the abnormality is due to asthma.

- **The differences between Peak Flow Meters and Spirometry**

Peak Flow Meter	Spirometry
<ul style="list-style-type: none"> ⇒ Measures ability to exhale ⇒ Will vary with lung capacity ⇒ Use with charts to detect OBSTRUCTIVE disease ⇒ Can be used by patients to monitor lung 'function' 	<ul style="list-style-type: none"> ⇒ Simultaneous measurement of flow and capacity ⇒ Can be used to diagnose both OBSTRUCTIVE and RESTRICTIVE disease (gold standard) ⇒ Costs more than peak flow meters 

Flow-volume loop

- provides additional information about the location of airway constriction
- **Best test for upper way obstruction.** the upper airway is defined as that portion of the airway extending from the mouth to the mainstem bronchi

Explanation of high FEV-1/FVC ratio in lung fibrosis

- Lung fibrosis → ↑↑high elastic recoil → most forced expiratory volume (FEV-1) will be expelled in the first second compared to full forced expiration → a relatively high FEV-1/FVC ratio.

Obesity → extra-thoracic restriction

- Obesity could show a significant restrictive defect.

Patients with respiratory muscle weakness show spirometric findings of restrictive lung disease.

- **What is the best pre-operative screen of pulmonary function for a smoker patient evaluated for a coronary artery bypass graft (CABG).?**
 - ⇒ Ratio of the forced expiratory volume in 1 second to the forced vital capacity

Flow volume loop is the investigation of choice for upper airway compression

Transfer factor (D_{LCO} or T_{LCO} (diffusing capacity or transfer factor of the lung for carbon monoxide (CO))

- The transfer factor describes the rate at which a gas will diffuse from alveoli into blood.
- Carbon monoxide is used to test the rate of diffusion.
- Results may be given as the total gas transfer (DLCO, T_{LCO}) or that corrected for lung volume (transfer coefficient, KCO).
- Diffusion capacity of carbon monoxide depends on the thickness of the alveolar wall. diffusion will be increased in healthy compared with unhealthy lungs, where the thickness is likely to increase and the surface area available for gas exchange to decrease.

Diffusing capacity of the lungs for carbon monoxide (DLCO) (also known as transfer factor for carbon monoxide or TLCO)

- DLCO measures the ability of the lungs to transfer gas from inhaled air in the alveoli to the red blood cells in pulmonary capillaries.
- Used to identify the cause of dyspnea or hypoxemia,

Factors interfere with interpretation of the Diffusing capacity (DLCO) test

- Smoking**
 - patients should avoid cigarette smoking on the day of the test
 - Carbon monoxide in cigarette smoke → ↑ carboxyhaemoglobin (COHb) (to as high as 10-15% (normal value 1-2%) → ↓ DLCO. Increasing COHb reduces DLCO
- Supplemental oxygen
 - discontinue any supplemental oxygen for at least 15 minutes prior to testing.
- Significant amount of Alcohol in the morning of the test (**not small amount**)
- Severe kyphosis (**not mild**)
- Sever scoliosis (**not mild**)

Causes of raised and lower DLCO

- Where alveolar haemorrhage occurs, the DLCO tends to increase due to the enhanced uptake of carbon monoxide by intra-alveolar haemoglobin.

Causes of a raised DLCO	Causes of a lower DLCO
<ul style="list-style-type: none"> Asthma Pulmonary haemorrhage (Wegener's, Goodpasture's) Left-to-right cardiac shunts Polycythaemia Hyperkinetic states Early left heart failure Male gender Exercise Obesity 	<ul style="list-style-type: none"> Pulmonary fibrosis Pneumonia Pulmonary emboli Pulmonary oedema Emphysema bronchiolitis obliterans Anaemia Low cardiac output Pulmonary AV malformations carboxyhemoglobinemia. hepatopulmonary syndrome lymphangioleiomyomatosis

- Transfer factor (DLCO) and transfer co-efficient (KCO) can be **normal or elevated** in patients with asthma but are always reduced in emphysema.

- **Pulmonary AV malformations cause right-to-left shunts, so reducing TLCO values and provoking hypoxaemia (\downarrow Pao₂), with a normal lung volumes** (eg FEV1 & FVC).
- **Low DLCO combined with reduced lung volumes** suggests interstitial lung disease.
- **Normal DLCO associated with low lung volumes** suggests → an extrapulmonary cause of the restriction, such as pleural effusion, pleural thickening, neuromuscular weakness, or kyphoscoliosis.

Top Tips

Transfer factor

- raised: asthma, haemorrhage, left-to-right shunts, polycythaemia
- low: everything else

Transfer coefficient of carbon monoxide (KCO)

Overview

- The transfer coefficient (Kco) represents the uptake of carbon monoxide per litre of effective alveolar volume (Va)
- KCO is a measure of the efficiency of gas exchange into the blood stream.

Causes of reduced Kco:

(It is reduced if the lungs are damaged)

- **Restrictive lung disease e.g. Interstitial lung disease**
 - ⇒ the best test - after CT- to confirm restrictive lung disease due to a **parenchymal disorder**
 - ⇒ Normal KCO may rule out significant restrictive lung disease
- **Sarcoidosis would reduce the transfer coefficient as there is damage to the alveolar cells themselves**

Causes of an increased Kco

- Increased if there is additional blood in the lungs to remove carbon monoxide (e.g. ↑blood flow, haemorrhage, or polycythaemia).
- **Extrapulmonary volume restriction**
 - ⇒ density of pulmonary capillaries is unusually high in relation to the (restricted) lung volume at which the measurement is made.
- increase with age.

Causes of an increased KCO with a normal or reduced TLCO

- Low TLCO but normal/high Kco (ie the same cardiac output is going through a smaller alveolar volume) is **characteristic of extra-thoracic restriction:**
 - ⇒ pneumonectomy/lobectomy
 - ⇒ scoliosis/kyphosis
 - ⇒ neuromuscular weakness
 - ⇒ ankylosis of costovertebral joints e.g. ankylosing spondylitis
 - ⇒ Severe thoracic skin thickening,
 - ⇒ **Pleural disease, extensive bilateral pleural thickening**
 - ⇒ **Obesity**
- In **intrapulmonary restriction**, both (TLCO & Kco) are usually decreased.

- Isolated decreases in gas transfer are typical of pulmonary vascular diseases such as vasculitis and recurrent pulmonary embolism.

Relation between DLco, VA (alveolar volume) & KCO (transfer coefficient)

- DLco is simply the product of Va and Kco
- **TLCO = KCO x Alveolar volume (VA)**

Arterial Blood Gas (ABG)

Arterial blood gases should be used for assessing respiratory failure in Critically ill Patients or those with Shock or Hypotension (Systolic blood pressure < 90mmHg)

(British Thoracic Society, 2017)

Reference ranges

- PaCO₂: 35–45 mm Hg
- SaO₂: ≥ 95%
- pH: 7.35–7.45
- HCO₃-: 21 to 27 mEq/L
- Resting PaO₂ > 80 mm Hg is considered normal.

Procedure

- A **modified Allen test must be performed before the radial artery is punctured** to assess collateral circulation in the hand.

Contra-Indications of ABG sampling

- **Absent ulnar circulation – as demonstrated by Modified Allen's Test.**
- Impaired circulation e.g. **Raynaud's Disease**
- History of arterial spasms
- Distorted anatomy/ arteriovenous fistula trauma/burns to the limb - at or proximal to the attempted arterial puncture site
- Medium or high dose anticoagulation therapy, or history of clotting disorder
- Severe coagulopathy
- Abnormal or infectious skin processes at/or near puncture site

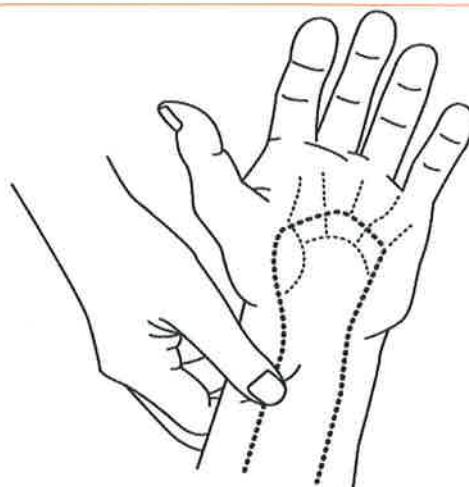
Modified Allen's test

- modified Allen test measures arterial competency, and **should be performed before taking an arterial sample.**
 - ⇒ Ask the patient to clench his fist; if the patient is unable to do this, close the person's hand tightly.
 - ⇒ Using your fingers, apply occlusive pressure to both the ulnar and radial arteries, to obstruct blood flow to the hand.
 - ⇒ While applying occlusive pressure to both arteries, have the patient relax his hand, and check whether the palm and fingers have blanched. If this is not the case, you have not completely occluded the arteries with your fingers.
 - ⇒ Release the occlusive pressure on the ulnar artery only to determine whether the modified Allen test is positive or negative.
 - If the hand **flushes within 5-15 seconds** it indicates that the ulnar artery has good blood flow → **positive test.**

- If the hand does not flush within 5-15 seconds, it indicates that ulnar circulation is inadequate or nonexistent; in this situation, the **radial artery supplying arterial blood to that hand should not be punctured.**

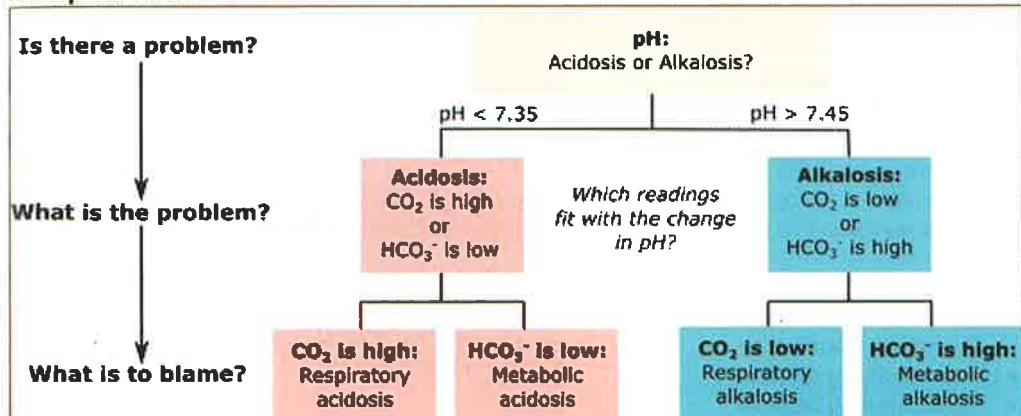


Thumbs occlude radial and ulnar arteries.
Pallor is produced by clenched fist.



Thumb occludes radial artery while ulnar artery is released and patent. Unclenched hand returns to baseline colour because of ulnar artery and connecting arches.

Interpretation of ABG



- Hypoxemic respiratory failure (type 1 respiratory failure): ↓ PaO₂
- Hypercapnic respiratory failure (type 2 respiratory failure): ↑ PaCO₂ and ↓ PaO₂
- Mixed metabolic and respiratory acidosis**
 - ⇒ pH → below 7.35
 - ⇒ PCO₂ → elevated (> 6 kPa) indicating a respiratory cause for acidosis
 - ⇒ Bicarbonate → reduced (< 20 mmol/L) which is contributing to the acidosis.
 - ⇒ **the most likely biochemical imbalance seen in fluid inhalation is → Mixed metabolic and respiratory acidosis**
 - inhalation of fluid → disordered gas exchange → respiratory acidosis.

- Metabolic acid results from intravascular volume depletion, hypotension and consequent tissue hypoxia.
- **Compensated respiratory acidosis → normal PH, high CO₂, low O₂** .
 - ⇒ The fact that the pH is normal means that there must be bicarbonate retention to compensate.
 - ⇒ In **bronchopulmonary dysplasia**, there is usually long-term CO₂ retention with compensatory increase in bicarbonate leading to a positive base excess and normal pH.
- Pathophysiological changes in case of **acute acidosis**:
 - ⇒ Occurred too quickly for metabolic compensation to occur via renal bicarbonate reabsorption, which takes 3-5 days to occur. (**bicarbonate will be normal in acute respiratory acidosis**)
 - ⇒ The oxygen dissociation curve is shifted to the right in acute acidosis, i.e. haemoglobin has a decreased affinity for oxygen.
 - ⇒ High pulmonary pressures would be expected after arrest scenario, as the **pulmonary arterioles constrict in response to hypoxia**.

Chest x-ray

Differential diagnosis of cavitating lung lesion

- abscess (Staph aureus, Klebsiella and *Pseudomonas*)
- squamous cell lung cancer
- tuberculosis
- Wegener's granulomatosis
- Progressive massive fibrosis: is a complicated coal worker's pneumoconiosis where pulmonary nodules coalesce and cavitate.
- pulmonary embolism
- Systemic embolisation: occurs in 20-50% of cases of infective endocarditis, and can involve the lungs, central nervous system, coronary arteries, spleen, bowel and extremities.
- rheumatoid arthritis
- aspergillosis, histoplasmosis, coccidioidomycosis
- Actinomycosis: is a chronic granulomatous disorder caused by a Gram-positive anaerobe.

Differential diagnosis of diffuse opacities on chest X-ray

- Pulmonary oedema
- Interstitial lung disease
- Vasculitic lung disease
- Pulmonary haemorrhage

Coin lesions on chest x-ray

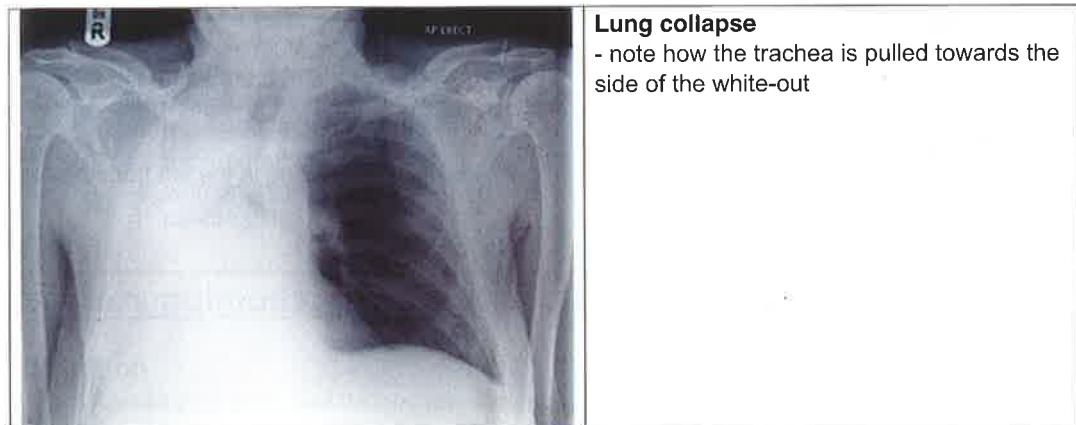
- **Coin lesions** (solitary pulmonary nodule)
 - ⇒ malignant tumour: lung cancer or metastases
 - ⇒ benign tumour: hamartoma
 - ⇒ infection: pneumonia, abscess, TB, hydatid cyst
 - ⇒ AV malformation

White lung lesions on chest x-ray

- causes of white shadowing in the lungs including:
 - consolidation
 - pneumonectomy
 - pleural effusion
 - specific lesions e.g. tumours
 - collapse**
 - fluid e.g. pulmonary oedema
- If there is a '**white-out**' of a hemithorax it is useful to assess the position of the trachea - is it central, pulled or pushed from the side of opacification.

Trachea pulled toward the white-out	Trachea central	Trachea pushed away from the white-out
Pneumonectomy Complete lung collapse (Atelectasis) e.g. endobronchial intubation Pulmonary hypoplasia	Consolidation Pulmonary oedema (usually bilateral) Mesothelioma	Pleural effusion Diaphragmatic hernia Large thoracic mass

- In the context of an acute aspiration, the most likely process is atelectasis secondary to bronchial obstruction.**
- Obstruction of the mainstem bronchus will prevent gas from entering the affected lung and will lead to the collapse of that lung.
- The collapsed lung will cause complete whiteout of the hemithorax on chest X-ray and will cause ipsilateral tension on the mediastinum leading to shifting of the trachea toward the affected lung.



Characteristics of consolidation on chest x-ray

- Consolidation in the left lower lobe** → obliterates the diaphragm.
- Lingular consolidation** → obliterates the left heart border.
- Consolidation of the right middle lobe** → obscures the right heart border (right atrial edge). More extensive consolidation also involves the right and left peri-hilar regions. The superior extent is well demarcated, due to the horizontal fissure.

- **Right upper lobe collapse** results in → displacement of the horizontal fissure upwards. The right hilum can also appear enlarged.
 - ⇒ **The classical signs of right upper lobe consolidation** → **abnormal opacity within the right upper lobe abutting the horizontal fissure.**

The loss of the left heart border is a classic sign of left lingual consolidation.

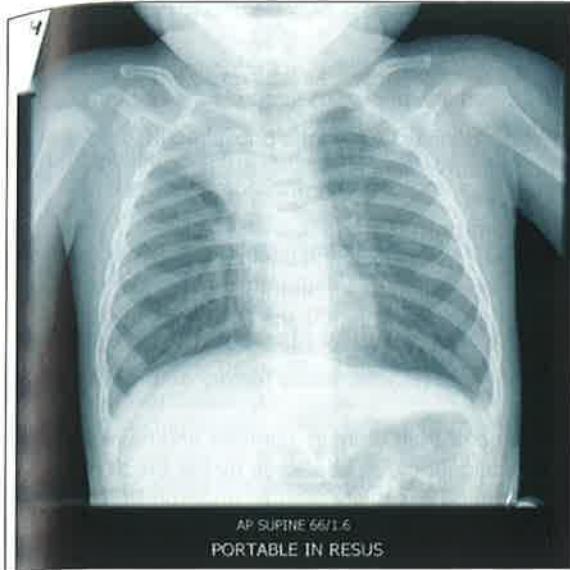
Lobar collapse on chest x-ray (Atelectasis)

- **Signs of lobar collapse on a chest x-ray**
 - ⇒ tracheal deviation towards the side of the collapse
 - ⇒ mediastinal shift towards the side of the collapse
 - ⇒ elevation of the hemidiaphragm
- **Causes**
 - ⇒ lung cancer (the most common cause in older adults)
 - ⇒ foreign body
 - ⇒ mucous plugging (e.g. in cystic fibrosis, post-operative complication , asthma)
 - **Treatment**
 - ❖ adequate hydration and chest physiotherapy.
 - ❖ Bronchoscopy with lavage may be required if this is unsuccessful.



This patient has a **left upper lobe collapse**. The following can be seen on the film to support this:

- hazy opacity projected over the left upper zone
- deviation of the trachea to the left
- elevation of the left hemidiaphragm
- loss of lung volume in the left hemithorax



Lung collapse (**Atelectasis**)

- There is increased opacity in the right upper zone. The lateral / inferior border of the shadowing actually represents the horizontal fissure which has been 'dragged' upwards.

Pleural calcification

Unilateral pleural calcification

- most commonly occurs as a chronic change secondary to:
 - ⇒ pleural infection: tuberculous empyema, pyogenic empyema,
 - ⇒ **haemothorax (post-traumatic)**

Bilateral pleural calcification

- Common
 - ⇒ calcified pleural plaques are usually considered asbestos-related.
- Other rarer causes
 - ⇒ radiation exposure,
 - ⇒ hyperparathyroidism,
 - ⇒ pulmonary infarction,
 - ⇒ pancreatitis.

Solitary pulmonary nodules

Definition

- A small (≤ 30 mm), well defined lesion completely surrounded by pulmonary parenchyma detected as an incidental finding, either on chest x-ray or CT scans.
- Lesions larger than 3 cm are considered masses and are treated as malignancies until proven otherwise.

Causes

- benign nodules (The most common)
 - ⇒ Infectious granulomas and hamartomas are the most common causes of benign nodules.
- malignant nodules
 - ⇒ The most common causes of malignant nodules are primary lung cancer, lung metastases, and carcinoid tumors.

Management

- Risk stratification of **incidental pulmonary nodules**
 - ⇒ consider the risk factors for lung cancer or metastases, as well as size and character of the nodule.
 - ⇒ surveillance according to British Thoracic Society Guidelines published in 2005.
 - Nodules < 5 mm require no further surveillance.
 - Nodules 5-6mm require CT at 1 year
 - **Nodules 6-8 mm require CT at 3 months**
 - Nodules > 8 mm require malignancy risk calculation using the Brock model and should then have CT or PET according to whether this risk is > 10%.
 - ❖ To determine risk of malignancy following CT the BTS uses the Brock model
 - ❖ The Brock model considers age, gender, family history and features of the nodule
 - ❖ Only nodules which are greater than 8mm in diameter and have a greater than 10% risk of malignancy, as assessed by the Brock model (this can be accessed on the BTS website) should undergo PET-CT and then, based on outcomes, be assessed for obtaining a histological sample.
- **Requesting a previous chest x-ray is the most appropriate first step in management of a patient with a solitary pulmonary nodule**, especially when the risk of malignancy is high (age > 40 years, history of smoking).
 - ⇒ If there are no new changes, the patient can be followed-up with yearly chest x-rays.
 - ⇒ However, if there are new changes noted (additional nodules, enlargement), or no previous chest x-ray is available, a CT scan is indicated to assess for nodule size, location, and signs of malignancy, before eventual biopsy.

Alveolar-arterial (A-a) oxygen gradient

Definition

- The difference between the partial pressure of oxygen in the alveoli (A) and the partial pressure of oxygen in the arteries (a).

Indications of uses

- Used in diagnosing the source of hypoxemia. For example,
 - ⇒ in high altitude, the arterial oxygen PaO_2 is low but only because the alveolar oxygen (PAO_2) is also low.
 - ⇒ in states of **ventilation perfusion mismatch**, such as pulmonary embolism or right-to-left shunt, oxygen is not effectively transferred from the alveoli to the blood which results in elevated A-a gradient
- in hypoxaemia it can differentiate between extrinsic and intrinsic restrictive lung disease
 - ⇒ if A-a gradient is normal → the cause is extrinsic, so exclude intrinsic lung disease

Normal range

- The normal range varies with age, altitude, and the concentration of inhaled oxygen. Normal range for a young person breathing room air at sea level is 5–10 mm Hg and increases with physical exercise.
- $A\text{-}a \text{ gradient} = \text{alveolar O}_2 (\text{PAO}_2) - \text{arterial O}_2 (\text{PaO}_2)$

Causes of increased A-a gradient

- Age
- Higher concentration of inhaled oxygen
- Right-to-left shunting (e.g. cyanotic heart disease)
- Fluid in alveoli: e.g., CHF, ARDS, pneumonia
- Ventilation/perfusion (V/Q) mismatch (due to increased dead space or shunting): e.g., pulmonary embolism, pneumothorax, atelectasis, obstructive lung disease, pneumonia, pulmonary edema
- Alveolar hypoventilation: interstitial lung disease, lung fibrosis (usually manifests with ↑ CO₂)

Causes of hypoxaemia with normal A-a gradient

- high altitude (both PAo₂ and Pao₂ are equally reduced)
- hypoventilation (except lung):
 - ⇒ higher respiratory centre (e.g. drug induced)
 - ⇒ upper air way (e.g. acute epiglottitis)
 - ⇒ chest wall (e.g. kyphoscoliosis)
 - ⇒ respiratory muscles (e.g. myasthenia gravis)
 - ⇒ haemoglobin defect
 - anaemia : normal paO₂ , normal SaO₂ , low O₂ content
 - methemoglobinemia : normal PaO₂, low SaO₂ , low O₂ content

An increased A-a gradient may occur in hypoxemia due to shunting, ventilation-perfusion mismatch, or impaired gas diffusion across the alveoli due to fibrosis or edema.

The A-a gradient remains normal with hypoventilation due to CNS and neuromuscular disorders (no diffusion defect) and in high altitude (despite a lower fraction of inhaled O₂).

Finger clubbing

Definition

- Loss of the natural angle between the nail and the nail bed.
- increased curvature of the nail

Causes

- Suppurative diseases:
 - ⇒ long-standing bronchiectasis
 - ⇒ acute lung abscesses
 - ⇒ empyema
- Malignant disease - especially carcinoma of the bronchus and pleural malignancy
- Fibrosing alveolitis
- Asbestosis
- hypertrophic pulmonary osteoarthropathy,
 - ⇒ painful osteitis of the distal ends of the long bones of the lower arms and legs.
 - ⇒ Malignancy is associated in 95% of these cases.

Finger clubbing is not seen in uncomplicated bronchitis.

Respiratory failure



Top tips

Respiratory failure

- Type 1 → hypoxaemia ($P_aO_2 < 8.0 \text{ kPa}$) without hypercapnia (P_aCO_2 normal or decreased ($<6.0 \text{ kPa}$))
- Type 2 → Hypoxemia ($PaO_2 < 8 \text{ kPa}$) with hypercapnia ($PaCO_2 > 6.0 \text{ kPa}$).

Type 2 respiratory failure with normal CXR → neuromuscular weakness

Type 1 respiratory failure

- Definition
 - hypoxaemia ($P_aO_2 < 8.0 \text{ kPa}$) without hypercapnia (P_aCO_2 normal or decreased ($<6.0 \text{ kPa}$))
- ⇒ **Causes:**
 - Low ambient oxygen (e.g. at high altitude)
 - Ventilation-perfusion mismatch (parts of the lung receive oxygen but not enough blood to absorb it, e.g. pulmonary embolism)
 - Alveolar hypoventilation (decreased minute volume due to reduced respiratory muscle activity, e.g. in acute neuromuscular disease); this form can also cause type 2 respiratory failure if severe
 - Diffusion problem (oxygen cannot enter the capillaries due to parenchymal disease, e.g. in pneumonia or ARDS)
 - Shunt (oxygenated blood mixes with non-oxygenated blood from the venous system, e.g. right-to-left shunt)

Type 2 respiratory failure

- Definition: Hypoxemia ($PaO_2 < 8 \text{ kPa}$ (**60 mmHg**)) with hypercapnia ($PaCO_2 > 6.0 \text{ kPa}$ (**45 mmHg**))).
- **Causes:**
 - ⇒ Increased airways resistance (COPD, asthma, suffocation)
 - ⇒ Reduced breathing effort → hypoventilation:
 - **acutely** due to drug overdose and brain stem lesion
 - **chronically** due to: gross obesity, kyphoscoliosis (and similar musculoskeletal disorders)
 - **Hypoventilation, where inadequate alveolar ventilation results in low alveolar PO_2 , is the only cause of hypoxia that inevitably causes raised $PaCO_2$.**
 - ⇒ A decrease in the area of the lung available for gas exchange (such as in chronic bronchitis)
 - ⇒ Neuromuscular problems (**respiratory muscle weakness**) (Guillain-Barre syndrome, motor neuron disease)
 - ⇒ Deformed (kyphoscoliosis), rigid (ankylosing spondylitis), or flail chest.
 - ⇒

Bronchial Asthma

Immunological response involved in atopic asthma:

- Immediate response: type I hypersensitivity
 - ⇒ immunomodulators involved: mast cells , histamine
 - ⇒ Result in immediate bronchoconstriction reaction
 - ⇒ Usually subsides within two hours
 - ⇒ Reversible with bronchodilators.
- Late phase:
 - ⇒ type IV hypersensitivity response
 - ⇒ Results in bronchoconstriction, airways inflammation, hyper-responsiveness and oedema.
 - ⇒ This typically occurs three to 12 hours after the immediate response
 - ⇒ Less susceptible to bronchodilators.

Pathogenesis of asthma:

- Asthma occurs due to a combination of airway hyper-responsiveness, airflow limitation and airway inflammation
- The alveolar functional structure is preserved in asthma.

Near fatal asthma

- The British Thoracic Society defines near fatal asthma as an attack with raised PaCO_2 and/or requiring mechanical ventilation with raised inflation pressures.
- A raised PaCO_2 is an important sign that intubation may be required if the patient is not responding to maximum medical management.

Features

- wheeze, cough or breathlessness, and any daily or seasonal variation in these symptoms, any triggers that make symptoms worse
- a personal or family history of atopic disorders.

Asthma diagnosis (NICE guidelines 2017)

NICE guidelines

- Do not use symptoms alone without an objective test to diagnose asthma.
- Empirically inhaled corticosteroids may affect the results of spirometry and FeNO tests

- Step 1: Exclude occupational asthma by asking if their symptoms are better on days away from work/during holidays.
- Step 2: Test for airway inflammation → Fractional exhaled nitric oxide (FeNO) test
 - ⇒ If > 40 ppb → positive
- Step 3: test for obstructive airway disease → Spirometry
 - ⇒ FEV1/FVC ratio < 70% → positive (obstructive spirometry).
- Step 4: test for Bronchodilator reversibility (BDR) → bronchodilators + Spirometry
 - ⇒ improvement in $\text{FEV1} \geq 12\%$, + ↑ volume $\geq 200 \text{ ml}$ → positive

- **Step 5: If there is diagnostic uncertainty** (e.g. positive BDR with borderline FeNO **OR** obstructive spirometry + negative BDR) → Peak expiratory flow variability for 2 to 4 weeks
⇒ **value ≥ 20% variability is a positive test.**
- **Step 6: If there is diagnostic uncertainty** (positive FeNO ≥ 40 BUT normal spirometry and no variability in peak flow readings **OR** borderline FeNO with obstructive spirometry BUT negative BDR and no variability in peak flow readings) → **Airway hyperreactivity measures** → Direct bronchial challenge test with histamine or methacholine
⇒ PC₂₀ value ≤ 8 mg/ml is a positive test.

NICE quality statement : **Adults with new onset asthma are assessed for occupational causes.**

- ➡ Are you better on days away from work?
- ➡ Are you better on holiday?

All patients with suspected B. Asthma should have spirometry with a bronchodilator reversibility (BDR) test and FeNO test

Diagnosis of asthma (NICE guidelines 2017)

Patients ≥ 17 years:

- ☞ Exclude occupational asthma (by asked if their symptoms are better on days away from work/during holidays).
- ☞ Do spirometry with a **bronchodilator reversibility (BDR) test** + **Fractional exhaled nitric oxide (FeNO)** for all patients
 - book obstructive spirometry → FEV1/FVC ratio $< 70\%$
 - book positive BDR test → improvement in FEV1 $\geq 12\%$, together with an increase in volume ≥ 200
 - book positive FeNO test ≥ 40
- ☞ monitor **Peak expiratory flow variability:** for 2 to 4 weeks, if there is **diagnostic uncertainty:**
 - book normal spirometry OR
 - book obstructive spirometry, positive BDR but a FeNO ≤ 39
⇒ **Regard a value > 20% variability as a positive test.**

Patients 5-16 years:

- ☞ Do spirometry with a **bronchodilator reversibility (BDR) test**
- ☞ Do a FeNO test if there is:
 - book normal spirometry OR
 - book obstructive spirometry with a negative BDR test
⇒ **Regard a value of FeNO test ≥ 35 as a positive test.**

In asthma diagnosis:

- ☞ Positive spirometry with a **bronchodilator reversibility (BDR) test** → improvement in FEV1 of $\geq 12\%$
- ☞ Positive peak flow meter → $> 20\%$ variation

Positive tests in Asthma	
Test	Positive result
Fractional exhaled nitric oxide (FeNO)	40 ppb or more
FeNO	35 ppb or more
Obstructive spirometry	Forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio less than 70% (or below the lower limit of normal if this value is available)
Bronchodilator reversibility (BDR) test	Improvement in FEV1 of 12% or more and increase in volume of 200 ml or more
BDR test	Improvement in FEV1 of 12% or more
Peak flow variability	Variability over 20%
Direct bronchial challenge test with histamine or methacholine	Provocative concentration of methacholine causing a 20% fall in FEV1 (PC ₂₀) of 8 mg/ml or less

Management of asthma (NICE guidance 2017).

One of the key changes is in 'step 3' - patients on a SABA + ICS whose asthma is not well controlled should be offered a leukotriene receptor antagonist, not a LABA

Step	Notes
1 Newly-diagnosed asthma	Short-acting beta agonist (SABA)
2 Not controlled on previous step OR Newly-diagnosed asthma with symptoms \geq 3 / week or night-time waking	SABA + low-dose inhaled corticosteroid (ICS)
3	SABA + low-dose ICS + leukotriene receptor antagonist (LTRA)
4	SABA + low-dose ICS + long-acting beta agonist (LABA) Continue LTRA depending on patient's response to LTRA
5	SABA +/- LTRA

	Switch ICS/LABA for a maintenance and reliever therapy (MART), that includes a low-dose ICS
6	SABA +/- LTRA + medium-dose ICS MART OR consider changing back to a fixed-dose of a moderate-dose ICS and a separate LABA
7	SABA +/- LTRA + one of the following options: <ul style="list-style-type: none"> • increase ICS to high-dose (only as part of a fixed-dose regime, not as a MART) • a trial of an additional drug (for example, a long-acting muscarinic receptor antagonist or theophylline) • seeking advice from a healthcare professional with expertise in asthma

Drugs used in asthma

Drug	Mechanism of action	Notes
Salbutamol	Beta receptor agonist	<ul style="list-style-type: none"> • Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle through effects on beta 2 receptors • Used in asthma and chronic obstructive pulmonary disease (COPD). • Salmeterol has similar effects but is long-acting
Corticosteroids	Anti-inflammatory	<ul style="list-style-type: none"> • Inhaled corticosteroids are used as maintenance therapy • Oral or intravenous corticosteroids are used following an acute exacerbation of asthma or COPD
Ipratropium	Blocks the muscarinic acetylcholine receptors	<ul style="list-style-type: none"> • Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle • Used primarily in COPD • Tiotropium has similar effects but is long-acting
Methylxanthines (e.g. theophylline)	Non-specific inhibitor of phosphodiesterase resulting in an increase in cAMP	<ul style="list-style-type: none"> • Given orally or intravenously • Has a narrow therapeutic index
Montelukast, zafirlukast	Blocks leukotriene receptors	<ul style="list-style-type: none"> • Usually taken orally • Useful in aspirin-induced asthma

Steroid inhalation

- Fluticasone is more lipophilic and has a longer duration of action than beclomethasone
- Hydrofluoroalkane is now replacing chlorofluorocarbon as the propellant of choice.
 - ⇒ Only half the usual dose is needed with hydrofluoroalkane due to the smaller size of the particles
- **Table showing examples of inhaled corticosteroid doses**
-

Dose	Example
low dose	≤ 400 micrograms budesonide or equivalent
moderate dose	400 micrograms - 800 micrograms budesonide or equivalent
high dose	> 800 micrograms budesonide or equivalent

- **Side effects:**

- ⇒ Inhaled corticosteroids → ↓↓ skin collagen synthesis → skin fragility → ↑↑ tendency for bruising & vascular changes
- ⇒ Cushing's syndrome: Interaction with potent cytochrome P450-3A4 inhibitor → elevations in plasma fluticasone concentrations (even nasal or inhaled preparations) → suppress endogenous cortisol levels and produce Cushing's syndrome. eg: a patient with HIV and asthma, C/O tiredness, lethargy and weight gaining → suspect Cushing's syndrome produced by Ritonavir, a protease inhibitor which is an extremely potent cytochrome P450-3A4 inhibitor.

Long acting B2-agonists

- Action:
 - ⇒ acts as bronchodilators but also inhibit mediator release from mast cells.
 - ⇒ The duration of action of salmeterol is around 12 hours
- **Side effects: Salmeterol → may cause paradoxical bronchospasm**

Leukotriene receptor antagonists

- Action
 - ⇒ Montelukast, zafirlukast
 - CysLT1 antagonist; it **blocks the action of leukotriene on cysteinyl leukotriene receptor CysLT1** by binding to it.
 - ⇒ Zileuton → blocks leukotriene **synthesis** by **inhibiting 5-lipoxygenase**,
 - inhibits 5-lipoxygenase pathway, **blocking the conversion of arachidonic acid to leukotrienes**.
 - ⇒ have both anti-inflammatory and bronchodilatory properties
- Inductions
 - ⇒ **should be used when patients are poorly controlled on high-dose inhaled corticosteroids and a long-acting b2-agonist**
 - ⇒ have been shown to be as effective as doubling the dose of inhaled steroid.
 - ⇒ asthma with allergic rhinitis
 - ⇒ aspirin-induced asthma
 - ⇒ **exercise-induced asthma**
- Side effects
 - ⇒ associated with the development of Churg-Strauss syndrome

Asthma drugs: leukotriene inhibitor action:

- ⇒ Zafirlukast → Inhibitor of LT receptor
- ⇒ Zileuton → Antagonist of lipoxygenase

Omalizumab

- **Action:** monoclonal antibody that **binds to IgE**.
- **Indications:** severe refractory, persistent confirmed **allergic IgE-mediated asthma** (e.g. positive skin test to a recognised respiratory allergen)
- **Administration:** given subcutaneously every 2 or 4 weeks.
- **Side effects:** injection site pain, swelling, erythema, pruritus, and **headaches**

Non-pharmacological management

- Stop smoking.
- **Weight-loss interventions**
- **Breathing exercise** programs (including physiotherapist-taught methods) can be offered to people with asthma as an adjuvant to pharmacological treatment to improve quality of life and reduce symptoms
 - ⇒ **Diaphragmatic breathing**, (as opposed to thoracic breathing which is practised by many asthmatics); reduce symptoms
 - ⇒ **Buteyko technique**: a breathing technique which can 'improve asthma symptoms, quality of life and reduce bronchodilator (blue reliever inhaler) requirement

Omalizumab

- anti-IgE monoclonal antibody
- used for **resistant asthma** with evidence of **raised IgE** and **allergic symptoms**.

Mepolizumab

- anti-IL5 monoclonal antibody
- used for **resistant asthma** with **raised eosinophils**

B-blockers, including eye drops, should be avoided in patients with asthma. They are not however absolutely contraindicated.

Acute severe asthma

Classification of acute severe asthma

- Patients with acute severe asthma are stratified into moderate, severe or life-threatening.
- Note that a patient having any one of the life-threatening features should be treated as having a life-threatening attack.

Moderate	Severe	Life-threatening
<ul style="list-style-type: none"> • PEFR 50-75% best or predicted • Speech normal • RR < 25 / min • Pulse < 110 bpm 	<ul style="list-style-type: none"> • PEFR 33 - 50% best or predicted • Can't complete sentences in one breath • RR > 25/min • Pulse > 110 bpm 	<ul style="list-style-type: none"> • PEFR < 33% best or predicted • Oxygen sats < 92% • PaO₂ < 8 kPa • Normal PaCO₂ (4.6-6.0 kPa) • Silent chest, cyanosis or feeble (Poor) respiratory effort • Bradycardia, dysrhythmia or hypotension • Exhaustion, confusion or coma

Management of acute severe asthma

Magnesium sulphate - monitor reflexes + respiratory rate

- **β_2 -agonists should be administered as soon as possible, preferably nebulised driven with high flow oxygen.**
 - ⇒ salbutamol administration can rapidly worsen the V/Q mismatch which is the cause of hypoxia in asthma. They can therefore cause reduction in arterial oxygen tension unless supplemental oxygen is given
- **Nebulised ipratropium bromide.** It's addition produces significantly greater bronchodilation than a β_2 -agonist alone.
- **Oxygen:** Targeted oxygen in asthma → SpO₂ level of 94–98%.
- **Steroids:**
 - ⇒ steroids reduce mortality, relapses, subsequent hospital admission and requirement for β_2 -agonists1.
 - ⇒ This should be continued for five days, and can then be stopped abruptly.
- **Magnesium sulphate** recommended as next step for patients who are not responding (e.g. 1.2 - 2g IV over 20 mins) .
 - ⇒ Mechanism: low magnesium levels in bronchial smooth muscle favour bronchoconstriction.
 - ⇒ reduce rates of admission to intensive therapy units
- **Intensive care** is indicated for patients with severe acute or life threatening asthma who are failing to respond to therapy.
 - ⇒ **Strongest indicator of a need for intubation and ventilation → PH 7.31**

Asthmatic patient with + PaCO₂ at the upper limit of normal. What would be the most appropriate next step?

- ⇒ A normal or elevated pCO₂ in an asthmatic indicates impending respiratory failure
- ⇒ review by an anaesthetist/intensivist is the next immediate step.
- ⇒ Hypercapnia and signs of fatigue are indications for immediate intubation and ventilation.

Management of Asthma in pregnancy

- In general, the medicines used for asthma are safe during pregnancy.
- The British Thoracic Society (BTS) guidelines make it clear that short-acting /long-acting beta 2-agonists, inhaled and oral corticosteroids should all be used as normal during pregnancy.
- The BNF advises that 'inhaled drugs, theophylline and prednisolone can be taken as normal during pregnancy and breast-feeding'.

Chronic Obstructive Pulmonary Disease(COPD)

Definition: airflow obstruction that is not fully reversible.

Epidemiology:

- worldwide prevalence of 10%
- COPD is the third leading cause of death worldwide

Subtypes of COPD

1. **Chronic bronchitis:** defined as chronic cough and sputum production for at least three months of two consecutive years in the absence of other disease which could explain these symptoms.
2. **Emphysema**

Pathophysiology

- Inflammatory changes → ciliary dysfunction and **increased goblet cell size and number**, → excessive mucus secretion.
- **Increased airway resistance** is the physiological definition of COPD.
- Decreased elastic recoil, fibrotic changes in lung parenchyma, and luminal obstruction of airways by secretions all contribute to increased airways resistance.
- Progressive hypoxia → vascular smooth muscle thickening → pulmonary hypertension
- **Which mechanism is most likely responsible for the increased mean arterial pulmonary pressure in COPD?**
 - ⇒ Hypoxic induced pulmonary vasoconstriction

Causes

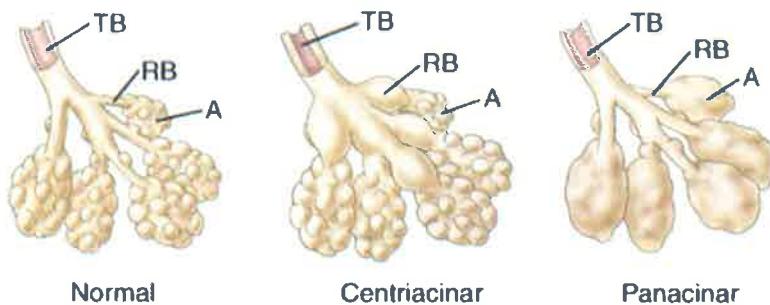
- Smoking
- Alpha-1 antitrypsin deficiency
- Using open fires at homes for cooking or heating (patients from the developing world present with a COPD-like history without smoking history)
- Occupational exposures, such as harmful dust and chemicals
 - ⇒ **cadmium (used in smelting) (recognised cause of emphysema specifically)**
 - ⇒ coal, cotton, cement, grain

Emphysema

- **Definition**
 - ⇒ emphysema is a term that refers to the actual damage to the air sacs in the lung, called the alveoli. In other words, emphysema is a pathological term.
- **Pathophysiology**
 - ⇒ destruction of alveolar air sacs due to an **imbalance between protease and anti-protease action**.
 - ⇒ **loss of elastic recoil, which drives airflow limitation.**
- **Types**
 - ⇒ **Panlobular (panacinar) pulmonary emphysema**
 - Rare
 - Associated with **α1-antitrypsin deficiency**
 - Characterized by destruction of the entire acinus
 - Usually affects the **lower lobe**
 - ⇒ **Centrilobular or proximal acinar pulmonary emphysema**
 - Common
 - Classically seen in **smokers**

- Characterized by destruction of the respiratory bronchiole (central portion of the acinus)
- Usually affects the **upper lobe**
- most severe at the apex of the lung.

Types of Emphysema



Types of emphysema

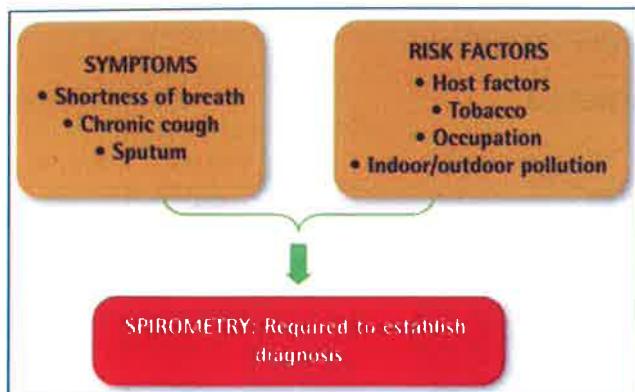
Type	Centriacinar (centrilobular)	Panacinar
Prevalence	the most common type	Less common
destruction	focal destruction mainly localized to the proximal respiratory bronchioles	destroys the entire alveolus uniformly
Location	upper lung zones.	lower half of the lungs.
causes	smoking & dust	alpha 1-antitrypsin (AAT) deficiency

MRCPUK-part-1-september-2017: What is the most important factor in airflow limitation in severe emphysema?

⇒ **Loss of elastic recoil**

Features and complications

- Chronic cough , SOB and recurrent infection
- **extensor plantar response is common in (COPD)** due to carbon dioxide retention, which results in carbon dioxide narcosis.
- Cor pulmonale
 - ⇒ features include peripheral oedema, raised jugular venous pressure, systolic parasternal heave, loud P2
 - ⇒ use a loop diuretic for oedema, consider long-term oxygen therapy
 - ⇒ ACE-inhibitors, calcium channel blockers and alpha blockers are not recommended by NICE
- Polycythaemia

COPD - Investigation and diagnosis**Who should be suspected of COPD?**

- NICE recommend considering a diagnosis of COPD in patients over 35 years of age who are smokers or ex-smokers and have symptoms such as exertional breathlessness, chronic cough or regular sputum production.

Investigations recommended in patients with suspected COPD:

- spirometry**
 - Post-bronchodilator spirometry to demonstrate airflow obstruction: FEV1/FVC ratio less than 70%
- Chest x-ray**
 - hyperinflation, bullae, flat hemidiaphragm.
 - Also, important to exclude lung cancer
- Full blood count:** exclude secondary polycythaemia
- Body mass index (BMI) calculation
- methacholine challenge**
 - useful in differentiating between asthma and chronic obstructive pulmonary disease (COPD).
 - methacholine utilizes the M3 receptor for bronchoconstriction.
- ABG**
 - In long standing COPD the bicarbonate is likely to be normal, or raised if the patient has chronic hypercapnia. (a low pH, low pO₂, high pCO₂ and a high HCO₃)

Severity of COPD: categorised by using the FEV1:

Post-bronchodilator FEV1/FVC	FEV1 (of predicted)	Severity
< 0.7	> 80%	Stage 1 - Mild
< 0.7	50-79%	Stage 2 - Moderate
< 0.7	30-49%	Stage 3 - Severe
< 0.7	< 30%	Stage 4 - Very severe

COPD: causes of acute exacerbations

- Infective exacerbation of COPD is **the most common cause of haemoptysis in UK patients**
- bacterial organisms
 - ⇒ *Haemophilus influenzae* (**most common cause of COPD exacerbation**)
 - ⇒ *Streptococcus pneumoniae*
 - ⇒ *Moraxella catarrhalis*
- Respiratory viruses : account for around 30% of exacerbations, with the **human rhinovirus** being the most important pathogen.

COPD: management of acute exacerbations

- **Bronchodilator**
- **Steroids:** prednisolone 30 mg daily for 7-14 days. Prolonged courses offer no additional benefit
- **Antibiotics:** It is common practice for all patients with an exacerbation of COPD to receive antibiotics. NICE do not support this approach. They recommend giving oral antibiotics 'if sputum is purulent or there are clinical signs of pneumonia'
- **Oxygen management of COPD patients**
 - ⇒ **If the patient have an individual target range:** Oxygen should be given to maintain SaO₂ within the **patient's individual target** range, if available
 - ⇒ **If the individual target is not known:**
 - prior to availability of blood gases (pCO₂ is unknown):
 - ❖ saturations should be maintained at 88-92% to avoid risk of hypercapnia
 - after availability of blood gases (**pCO₂ is normal**): adjust target range to 94-98%
- **Non-invasive ventilation**
- **Respiratory stimulants (e.g. Doxapram)**
 - ⇒ **In COPD exacerbations, respiratory stimulants (e.g. Doxapram) should only be used when Non-invasive ventilation is either unavailable or considered inappropriate**

COPD: stable management

COPD - reason for using inhaled corticosteroids - reduced exacerbations

COPD - still breathless despite using inhalers as required?

- FEV₁ > 50%: LABA or LAMA
- FEV₁ < 50%: LABA + ICS or LAMA

COPD - LTOT if 2 measurements of pO₂ < 7.3 kPa

General management

- smoking cessation advice
- annual influenza vaccination
- one-off pneumococcal vaccination

Pharmacological therapy

- first-line:
 - ⇒ short-acting beta₂-agonist (SABA) or short-acting muscarinic antagonist (SAMA)
- second-line:
 - ⇒ for patients who remain breathless or have exacerbations despite using short-acting bronchodilators the next step is determined by the FEV₁
 - FEV₁ > 50%
 - long-acting beta₂-agonist (LABA), for example salmeterol, or:
 - long-acting muscarinic antagonist (LAMA), for example tiotropium
 - FEV₁ < 50%
 - LABA + inhaled corticosteroid (ICS) in a combination inhaler, or:
 - LAMA
- Third-line:
 - ⇒ For patients with persistent exacerbations or breathlessness
 - if taking a LABA then switch to a LABA + ICS combination inhaler
 - otherwise give a LAMA and a LABA + ICS combination inhaler

Factors to consider when initiating inhaled corticosteroids (ICS) for COPD (GOLD guidelines January 2021)

Strong support	Consider use	Against use
 <ul style="list-style-type: none"> History of hospitalization for exacerbation of COPD ≥ 2 moderate exacerbation of COPD per year Blood eosinophils > 300 cells/ml History of, or concomitant asthma 	 <ul style="list-style-type: none"> 1 moderate exacerbation of COPD per year Blood eosinophils 100 – 300 cells/ml 	 <ul style="list-style-type: none"> Repeated pneumonia events Blood eosinophils < 100 cells/ml History of mycobacterial infection

PassOnExam

Other pharmacological therapies

- Oral theophylline**
 - ⇒ NICE only recommends theophylline after trials of short and long-acting bronchodilators or to people who cannot use inhaled therapy
 - ⇒ the dose should be reduced if macrolide or fluoroquinolone antibiotics are co-prescribed
- Mucolytics:** should be 'considered' in patients with a chronic productive cough and continued if symptoms improve
- LTOT :** should be offered to:
 - ⇒ patients with a pO₂ of < 7.3 kPa or
 - ⇒ patients with a pO₂ of 7.3 - 8 kPa and one of the following:

- secondary polycythaemia
- nocturnal hypoxaemia
- peripheral oedema
- pulmonary hypertension
- **Roflumilast**
 - ⇒ **Indication:**
 - recommended by NICE for patients who have suffered two or more exacerbations in a year, despite triple inhaled therapy, where FEV1 is less than 50% of predicted.
 - ⇒ Mode of action:
 - selective long-acting phosphodiesterase-4 inhibitor.
 - It is orally administered.

Management of side effect of steroid inhaler (Oro-pharyngeal and oesophageal candidiasis)

- the patient should be taught adequate inhaler technique. **Advise him to rinse his mouth each time he uses his inhaler and use a spacer device and review him in a month.**
- Resistant symptoms can be managed with oral nystatin or a course of fluconazole.

Pulmonary rehabilitation

- Definition: a programme of aerobic lower-extremity training combined with education.
- Indication: Patients with very limited exercise tolerances
- **Effects**
 - ⇒ **It leads to improvements in exercise capacity (walking distance should improve after the rehabilitation programme)**
 - ⇒ The improvement in walking distance would not be a long-lasting improvement
 - Decline in exercise tolerance and health status tends to occur 6–12 months after the completion of a course.
 - The effect of sustained improvement with ongoing rehabilitation has yet to be evaluated.
 - ⇒ **does not improve lung function.**
 - ⇒ **does not decrease hospital admissions because of chest problems**, but their hospital stays are likely to be shorter.

Lung volume reduction surgery

- Is a palliative treatment which can be used in advanced COPD to remove the least functional part of the lungs.
- there are **3 groups of patients that tend to benefit**:
 - ⇒ **Group 1: Upper lobe emphysema and low exercise capacity.**
 - These patients show improvement in both functional outcomes and survival after lung volume reduction surgery compared to medical therapy.
 - ⇒ **Group 2: upper lobe emphysema and high exercise capacity.**
 - These patients have improved functional outcomes but no difference in survival compared to medical therapy.
 - ⇒ **Group 3: non-upper lobe emphysema and low exercise capacity.**
 - These patients have improved survival after surgery but there is no difference in survival compared to medical therapy.
- **patients with emphysema that are unlikely to do well from lung volume reduction surgery** and have a high risk of death includes:
 1. **non-upper lobe emphysema and high exercise capacity.**
 2. **extremely poor pulmonary function** (forced expiratory volume in 1 second (**FEV1**) **20% or less** than predicted) and either homogenous distribution of emphysema on

computed tomography scan or extremely poor carbon monoxide diffusing capacity (20% or less than predicted).

- **Indications:**

- ⇒ CO₂ retention: **The upper cut off for referral for lung reduction surgery for pCO₂ is 7.3**
 - ⇒ Severe limitation of exercise capacity despite maximal therapy
 - ⇒ predominant upper lobe emphysema, and persistent symptoms despite a period of pulmonary rehabilitation.

- **selection criteria:** used when assessing suitability for treatment:

- ⇒ Age <75 years
 - ⇒ Emphysema by clinical evaluation
 - ⇒ Ex-smoker of more than 4 months
 - ⇒ Clinically stable on no more than 20mg prednisolone daily
 - ⇒ Significant functional limitation after 6-12 weeks of pulmonary rehabilitation on optimal medical therapy
 - ⇒ Demonstrated compliance with medical regimen
 - ⇒ FEV-1 >20% predicted
 - ⇒ Post-bronchodilator FEV-1 >45% predicted and >15% if >70 years
 - ⇒ Hyperinflation demonstrated by TLC >100% predicted and RV >150% predicted
 - ⇒ Carbon monoxide lung transfer factor greater than 20% predicted
 - ⇒ Post rehabilitation 6-minute walk distance >140 m
 - ⇒ Low post rehabilitation exercise capacity
 - ⇒ HRCT demonstrating bilateral severe emphysema, ideally with upper-lobe predominance

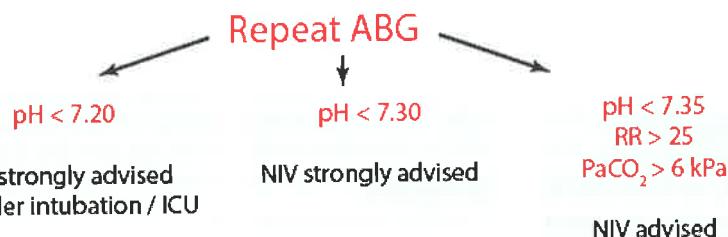
Symptomatic relief of breathlessness in end-stage COPD (DNR cases)

- **opioid or benzodiazepine medications for symptomatic relief of breathlessness is appropriate.**

Non-invasive ventilation (NIV)

Patient presenting with acute exacerbation of COPD

Institute standard medical therapy. Once O₂ sats > 92%, change non-re-breathing reservoir O₂ supply to controlled oxygen therapy - either using a 24% or 28% Venturi oxygen mask or nasal cannulae and a flow rate targeted to keep an oxygen saturation 88 to 92%



Indications of NIV

1. COPD with respiratory acidosis (**pH 7.25-7.35**) who have not improved despite immediate maximum standard medical treatment on controlled oxygen for no more than one hour.
 - ⇒ patients with a pH in the range of 7.25-7.35 achieve the most benefit.
 - ⇒ If the pH is < 7.25 then invasive ventilation should be considered if appropriate.
2. Type II respiratory failure secondary to chest wall deformity, neuromuscular disease or Obstructive sleep apnoea
3. Cardiogenic pulmonary oedema
4. Weaning from tracheal intubation

Advantage of NIV

- reduce intubation rates
- lower hospital mortality rates and
- lead to shorter hospital stays

Recommended initial settings for bi-level pressure support in COPD

- **Inspiratory Positive Airway Pressure (IPAP):** RCP advocate 10 cm H₂O whilst BTS suggest 12-15 cm H₂O.
- **Expiratory Positive Airway Pressure (EPAP):** 4-5 cm H₂O
- back up rate: 15 breaths/min
- back up inspiration: expiration ratio: 1:3

Monitoring and setting adjustment

- ABGs should be repeated after 1 hour of NIV therapy, and 1 hour after subsequent change in settings or 4 hours in stable patients.
 - ⇒ **If gas exchange is not significantly improved:**
 - the **IPAP** can be gradually increased at a rate of approximately 5 cms (2-5cm) H₂O every 10 minutes with a usual target of 20cm H₂O or until a response has been achieved or patient tolerability has been reached.
 - Increases in **EPAP** are not recommended without specialist advice.

- If the patient struggle to tolerate the NIV mask, what is the most appropriate method to help him settle him?
 - ⇒ **haloperidol or morphine**
 - Decreasing the IPAP or stopping NIV would be more comfortable but would be inappropriate as treatment is then likely to fail with greater hypoxia and acidosis.
 - Diazepam is contraindicated
 - Increasing EPAP without increasing IPAP would reduce the amount of ventilatory support and would be inappropriate.

Complication of NIV

- ventilation associated pneumothorax is (most important complication of NIV → present acutely)
- Ventilator associated pneumonia → present in patients who have been ventilated for long period of time and would not present so acutely).

Contraindications to NIV

- Absolute contraindications:
 - ⇒ inability to fit the NIV mask appropriately,
 - ⇒ cardiopulmonary arrest, and need for urgent intubation
- Relative contraindications
 - ⇒ **haemodynamically unstable** requiring inotropes/pressors (unless in a critical care unit)
 - ⇒ **confusion/agitation**

NIV modes

- **Continuous positive airway pressure (CPAP)**
 - ⇒ As this mode only provides a continuous pressure, CPAP is a spontaneous mode of ventilation that requires patient initiation and respiratory muscle effort. Therefore, no respiratory rate or minute ventilation is targeted or guaranteed.
 - ⇒ **The clinical benefit of CPAP is most evident in hypoxicemic respiratory failure** as the positive airway pressure predominately augments oxygenation with the goal of recruiting alveoli, increasing functional residual capacity, and decreasing shunting.
 - ⇒ **Inspiration during IPPV** → ↑↑ intrathoracic pressure → ↑↑ right atrial pressure → ↓↓ venous return → ↓↓ cardiac output
- **Bilevel positive airway pressure (BiPAP)**
 - ⇒ in contrast to CPAP, provides both an expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP).
 - ⇒ BiPAP has utility in both hypoxicemic and hypercarbic respiratory failure.

Minute ventilation

- Minute ventilation is equal to tidal volume (volume of air moved in normal breathing) multiplied by the respiratory rate.
- In metabolic alkalosis, one could increase CO₂ content by decreasing the minute ventilation (volume of air moved per minute).
- Reducing either one of these variables (↓tidal volume or ↓ respiratory rate) will decrease minute ventilation and lead to increased CO₂ retention.
-

Invasive ventilation

Indications

- unconscious patient
- if the **pH is below 7.25**.
 - ⇒ Patients with a pH <7.26 should be managed with a low threshold for intubation.
 - ⇒ give NIV whilst waiting for intensive care.
- in Guillain Barre syndrome with respiratory involvement → the parameter used to assess whether a patient needs ventilator support is an **FVC <15-20ml/kg**.

Ethics in decision to ventilate

- If the patient had a written advanced directive, properly witnessed, **while he was well**, then it would not be possible to consider intervention if he wished for it not to happen.
- **If he has significant hypoxia, he might not be able to give a rational decision** with respect to his further treatment.
- **if significantly hypoxic patient refused intubation during acute exacerbation → Intubate and act on the best interests of the patient, while informing the relatives**
- The family should not have the final decision with respect to intubation.

Long-term oxygen therapy (LTOT)

COPD - LTOT if 2 measurements of $\text{pO}_2 < 7.3 \text{ kPa}$

Which patients should be assessed for and offered (LTOT)?

- Assess patients if any of the following:
 - ⇒ Very severe airflow obstruction ($\text{FEV}_1 < 30\%$ predicted).
 - ⇒ cyanosis
 - ⇒ polycythaemia
 - ⇒ peripheral oedema
 - ⇒ raised jugular venous pressure
 - ⇒ oxygen saturations less than or equal to 92% on room air

How to assess patient for LTOT?

- ⇒ Assessment is done by measuring arterial blood gases on 2 occasions at least 3 weeks apart in patients with stable COPD on optimal management.
- ⇒ Blood gases should be performed in a stable state, which should be at least four weeks after an exacerbation of the disease.

Indications for LTOT in COPD:

- **patients with pO_2 of $< 7.3 \text{ kPa}$**
- **patients with pO_2 of $7.3 - 8 \text{ kPa}$ and one of the following:**
 - ⇒ secondary polycythaemia
 - ⇒ nocturnal hypoxaemia
 - ⇒ peripheral oedema
 - ⇒ pulmonary hypertension

Duration of LTOT

- Patients who receive LTOT should breathe supplementary oxygen for at least **15 hours** a day including at night time.

Contraindications

- Continued cigarette smoking should be a relative contraindication to long-term oxygen therapy.

In patients with chronic hypoxaemia, LTOT should be prescribed after assessment, when the PaO₂ is consistently at or below 7.3 kPa (55 mm Hg) when breathing air during a period of clinical stability. Clinical stability is defined as the absence of exacerbation of chronic lung disease for the previous five weeks.

The level of PaCO₂ (which may be normal or elevated) does not influence the need for LTOT prescription.

The only treatment that improves the long-term prognosis in patients with (COPD) is LTOT, given for at least 15 hours per day.

Patients who develop a respiratory acidosis and/or a rise in PaCO₂ of >1 kPa (7.5 mmHg) during an LTOT assessment on two repeated occasions, while apparently clinically stable, should only have domiciliary oxygen ordered in conjunction with nocturnal ventilatory support.

How will you manage this patient?

- ⇒ **LTOT with nocturnal BiPAP**
 - BiPAP is the modality of choice for treating CO₂ retention.

Prognosis of COPD

- Once respiratory failure criteria have been met, the 5-year survival rate is only around 25%.
- Prognostic indicators in COPD**
 - ⇒ The strongest predictors of survival in patients with (COPD) are FEV1
- Factors, which may improve survival in patients with stable COPD**
 - ⇒ **smoking cessation**, the single most important intervention in patients who are still smoking
 - ⇒ **long term oxygen therapy** in patients who fit criteria
 - ⇒ lung volume reduction surgery in selected patients

Pulmonary embolism (PE)

Pathophysiology

- PE → ↓ lung blood flow → ventilation- perfusion mismatches (**Decreased perfusion + normal ventilation**) → ↑ physiologic dead space.

Risk factors

The Virchow triad pathophysiological components of thrombus formation:

- Hypercoagulability**: thrombophilia (e.g., factor V Leiden mutation), use of oral contraceptives, pregnancy.
- Endothelial damage**: inflammatory or traumatic → activation of clotting factors through contact with exposed subendothelial collagen.
- Stasis** (e.g. varicosis, immobilization)

Major risk factors	Minor risk factors
<ul style="list-style-type: none"> • lower limb problems including a fracture or varicose veins • postoperative intensive care • hospitalisation • abdominal/pelvic or advanced malignancy • previous VTE, and • pregnancy. 	<ul style="list-style-type: none"> • occult malignancy • long distance travel • hypertension • congestive cardiac failure • thrombotic disorder • use of the oral contraceptive pill

Features

Sudden shortness of breath, pleuritic chest pain with haemoptysis and tachypnoea are the commonest features. (triad of pleuritic chest pain, dyspnoea and haemoptysis)

- Tachypnea (respiratory rate >16/min) - 96% (Sudden shortness of breath)
- **Pleuritic chest pain (worse on deep breathing)**
- haemoptysis
- Tachycardia (heart rate >100/min) - 44%
- Fever (temperature >37.8 C) - 43%.

Diagnosis

- If a patient presents with signs or symptoms of pulmonary embolism (PE)
 - ⇒ performed chest x-ray to exclude other pathology
 - ⇒ estimate the clinical probability of PE by two-level PE **Wells score**

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1

Clinical probability simplified scores

PE <i>likely</i>	More than 4 points
PE <i>unlikely</i>	4 points or less

- PE likely (> 4 points):
 - ⇒ arrange an immediate computed tomography pulmonary angiogram (**CTPA**).
 - If there is a delay in getting the CTPA then give low-molecular weight heparin until the scan is performed.
 - If the patient has an allergy to contrast media or renal impairment a Ventilation-perfusion (V/Q) scan should be used instead of a CTPA.
- PE unlikely (≤ 4 points):
 - ⇒ arranged a D-dimer test:
 - If this is **positive** arrange an immediate (**CTPA**).
 - If there is a delay in getting the CTPA then give low-molecular weight heparin until the scan is performed.

It is interesting to note that the Well's criteria for diagnosing a PE use tachycardia rather than tachypnoea.

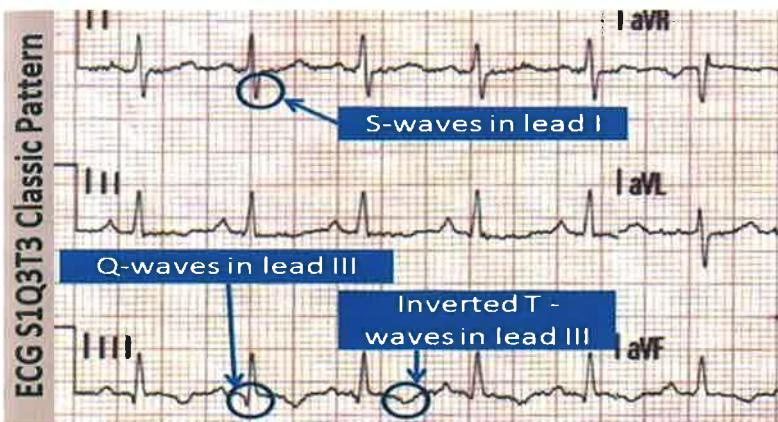
Pulmonary embolism - normal CXR

Investigations

Pulmonary embolism - CTPA is first-line investigation

- **Chest x-ray**
 - ⇒ Should be performed in all patients with symptoms or signs suggestive of PE
 - ⇒ **to exclude other pathology**
 - ⇒ **usually normal in PE**
- **Computed tomographic pulmonary angiography (CTPA)**
 - ⇒ **the first-line diagnostic test**
 - ⇒ If the CTPA is negative then patients do not need further investigations or treatment for PE
 - ⇒ Disadvantages of CTPA:
 - Contrast induced nephropathy
 - **Low sensitivity for detecting pulmonary emboli in sub-segmental pulmonary arteries**
- **Ventilation-perfusion (V/Q) scans**
 - ⇒ Indication? → If CTPA is contra-indicated
 - renal impairment (as the contrast media used during CTPAs is nephrotoxic).
 - allergy to contrast media
 - ⇒ Sensitivity = 98%; specificity = 40% → high negative predictive value, i.e. if normal virtually excludes PE
 - ⇒ In pregnancy → Radiation to the fetus is small.
- **D-dimers**
 - ⇒ Should be performed ONLY when the probability of PE is low, so the normal value would be taken as reassuring and further investigation would not be pursued.
 - ⇒ High sensitivity (95-98%), but poor specificity

- A negative d-dimer is useful for excluding PE in patients who are clinically thought to be at low risk, but a 'positive' result does not establish the diagnosis.
- The negative predictive value is greater than the positive predictive value
- ⇒ D-dimers can be positive in:
 - hospitalised patients
 - obstetric patients
 - patients with peripheral vascular disease, cancer and inflammatory conditions
 - increasing age
- ⇒ D-Dimer measurements should not be performed if:
 - an alternative diagnosis is likely,
 - the clinical probability is high or
 - there is a probable massive PE.
- ECG
 - ⇒ sinus tachycardia
 - **the most common abnormality**; seen in 44% of patients.
 - ⇒ **the classic ECG changes → S1Q3T3** (seen in no more than 20% of patients)
 - large S wave in lead I
 - large Q wave in lead III
 - inverted T wave in lead III
 - ⇒ Right bundle branch block
 - seen in 18% of patients.
 - associated with increased mortality;
 - ⇒ Right axis deviation (seen in 16% of patients).



- **Elevated cardiac troponin levels also occur in patients with pulmonary embolism** because of right ventricular dilation and myocardial injury

Management

Start low molecular weight heparin and request CT pulmonary angiography if the symptoms and findings clearly point towards pulmonary embolism (PE).

Fluid resuscitation is **the most appropriate immediate measure** before further investigations confirm the presence of a pulmonary embolism (PE).

Massive PE + hypotension - thrombolysis

- **Anticoagulant**

- ⇒ First-line: apixaban or rivaroxaban
- ⇒ Second-line: (if apixaban or rivaroxaban are not suitable)
 - LMWH for at least 5 days followed by dabigatran or edoxaban **OR**
 - LMWH concurrently with a vitamin K antagonist (warfarin) for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
- ⇒ For patients with positive antiphospholipid syndrome → the 1st line is LMWH concurrently with a VKA.
- ⇒ **Duration of anticoagulant:**
 - For most patients → 3 months
 - with active cancer → 3 to 6 months.
 - For unprovoked DVT or PE → Consider continuing anticoagulation beyond 3 months (6 months for people with active cancer) → use the HAS-BLED score for major bleeding risk → stop anticoagulation if the HAS-BLED score is 4 or more and cannot be modified.
- ⇒ **Heparin**
 - When should be started?
 - ❖ For patients with a high or intermediate probability of a non-massive PE → **low molecular weight heparin should be given before imaging**
 - ❖ For patient with low probability of non-massive PE → immediately after diagnosis.
 - Which type?
 - ❖ For **non-massive PE** → Low molecular weight heparin (LMWH) or fondaparinux.
 - ❖ For patients with **severe renal impairment** ([eGFR] <30 ml/min/1.73 m²) offer either:
 - ─ unfractionated heparin (UFH) with dose adjustments based on the APTT **or**
 - ─ LMWH with dose adjustments based on an anti-Xa assay.
 - ❖ For patients with an **increased risk of bleeding** consider UFH.
 - ❖ For **massive PE** where **thrombolysis** is being considered, → **unfractionated heparin** should be used.
 - Benefit of heparin?
 - ❖ Heparin reduces risk of further embolism (anticoagulant) and reduces pulmonary vasoconstriction.

- **Thrombolysis**

- ⇒ Indication?
- **Massive PE** where there is haemodynamic instability demonstrated by hypotension, right ventricular strain on an ECG or signs of right heart failure.
- Cardiac arrest situation for suspected PEs. However, it can take 90 minutes to be effective and therefore must only be used if it is appropriate to continue CPR for this duration.
- ❖ **Cardiac arrest for suspected PEs** → **Intravenous thrombolysis followed by CPR for 90 minutes**
- ⇒ Which drug?

- Alteplase 100 mg over 1.5 hours peripherally.
- **Thrombolysis administered through a peripheral vein is as effective as through a pulmonary artery catheter**
- Percutaneous insertion of **Inferior vena cava (IVC) filter**
- ⇒ Indication?
 - If anticoagulation is a contraindicated (eg PE following a recent haemorrhagic stroke)
 - if anticoagulation alone fails
 - ⇒ Benefit of **IVC filter?**
 - may be as effective as anticoagulation.

Recurrent pulmonary emboli

- Recurrent pulmonary emboli should always be considered in cases of progressive shortness of breath with no obvious cause.
- **Predisposing factors for recurrent pulmonary embolism include:**
 - ⇒ Antithrombin III deficiency
 - ⇒ Protein C deficiency
 - ⇒ Factor V Leiden mutation
- **Possible clues** include pulmonary hypertension, right ventricular enlargement, hypoxia with a low PaCO₂ and a low transfer factor.
- **Widening of the alveolar-arterial (A-a) gradient on exercise is likely to be found.**
- Mismatched defects are classic features of pulmonary embolus.
- Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as:
 - ⇒ increasing target INR to 3–4 for long-term high-intensity oral anticoagulant therapy **or**
 - ⇒ switching treatment to LMWH.

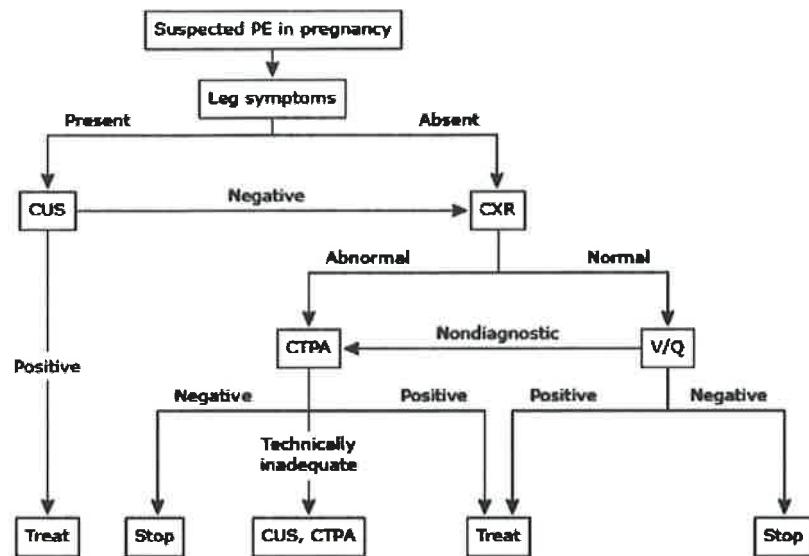
Pulmonary embolism in pregnancy: diagnosis and management

Diagnosis

- Chest x-ray and ECG to look for an alternative diagnosis such as pneumonia and pneumothorax.
- If the chest x-ray is normal:
 - ⇒ In women with **suspected PE** who also have **symptoms and signs of DVT** → consider a **compression duplex doppler of both legs to exclude a DVT**.
 - this may provide indirect evidence of a pulmonary embolism and negate the need for further radiation exposure
 - If this is positive, the patient is treated with full dose low molecular weight heparin (LMWH) (warfarin is of course teratogenic).
 - ⇒ In women with suspected PE **without symptoms and signs of DVT** → ventilation/perfusion (V/Q) lung scan **or** a computerised tomography pulmonary angiogram (CTPA) should be performed.
- When the **chest X-ray is abnormal** and there is a **clinical suspicion of PE**, CTPA should be performed in preference to a V/Q scan. [New 2015]

- CTPA vs V/Q scan
 - ⇒ CTPA → ↑risk of maternal breast cancer
 - ⇒ V/Q scanning → ↑risk of childhood cancer
- D-dimer is of limited use as it often raised in pregnancy.

Diagnostic algorithm for suspected pulmonary embolism in pregnancy



PE: pulmonary embolism; CUS: compression ultrasound; CXR: chest radiography; CTPA: computed-tomographic pulmonary angiography; V/Q: ventilation-perfusion.

Treatment of PE in pregnancy

- In clinically suspected DVT or PE, treatment with low-molecular-weight heparin (LMWH) should be commenced immediately until the diagnosis is excluded by objective testing
- 1st line: **low-molecular-weight heparin (LMWH)** should be employed during the remainder of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total.
- 2nd line: In pregnant women who are unable to tolerate heparin (LMWH or unfractionated heparin) or danaparoid and who require continuing anticoagulant therapy → use the newer anticoagulants (fondaparinux, argatroban or r-hirudin)
- Unfractionated heparin (UFH)
 - ⇒ UFH is the preferred, initial treatment in massive PE with cardiovascular compromise.

- ⇒ platelet count monitoring should be performed every 2–3 days from days 4 to 14 or until heparin is stopped.
- Warfarin should not be used for antenatal VTE treatment.
- Postpartum warfarin should be avoided until at least the fifth day and for longer in women at increased risk of postpartum haemorrhage.

Post-thrombotic syndrome (PTS)

- Develop in nearly 50% of all patients who experience a DVT.
- Features: chronic leg pain, swelling, redness, and ulcers.
- Prevention: **prolonged use of LMWH (more than 12 weeks).**

References

- Royal College of Obstetricians and Gynaecologists guidelines (Update August 2018)

Fat embolism

The classic triad of presentation is:

- **Eosinophilia**
- **Acute renal failure and**
- **Livedo reticularis.**

Definition

- Entry of fat particles usually from bone marrow, in the pulmonary circulation.

Causes

- Traumatic (95%):
 - ⇒ **most commonly associated with long bone (especially femur) and pelvic fractures.**
 - ⇒ typically manifests 24 to 72 hours after the initial insult.
- Non-traumatic (Rare): Sickle cell crisis, pancreatitis, osteomyelitis.

Features

- The classic **triad of hypoxemia, neurologic abnormalities** (eg, confusion, altered consciousness, seizure), and a **petechial rash**.
- Less common: anemia, thrombocytopenia, fever, lipiduria, and coagulation abnormalities;
- Rare: myocardial depression and shock

Diagnosis

- Presence of clinical triad
- Exclusion of other possible causes
 - ⇒ embolization syndromes (thrombus, amniotic fluid, tumor, foreign body, air),
 - ⇒ acute alveolar filling diseases (eg, heart failure, pneumonia, and ARDS) and
 - ⇒ cutaneous vasculitic disorders (eg, systemic lupus erythematosus).

Treatment

- **Supportive**
 - ⇒ **Intravenous (iv) fluids** to maintain high right ventricular filling pressures.
 - ⇒ High flow oxygen
 - ⇒ Diuretic treatment would be strongly contraindicated in this case. This is because right ventricular output is dependent on elevated filling pressures. Reducing the preload is therefore not a good idea.
- Steroids are reserved for severe or refractory cases.
- Most patients fully recover spontaneously.

The diagnosis of cholesterol embolism should be considered in any patient with atherosclerotic disease presenting with deteriorating renal function, multisystem disease or distal ischaemia developing after an invasive arterial procedure.

Community-acquired pneumonia (CAP)

Definition

- Pneumonia acquired outside hospital or healthcare facilities.

Streptococcus pneumoniae is associated with cold sores

Preceding influenza predisposes to **Staphylococcus aureus** pneumonia

Both **Klebsiella** and **Staphylococcus** are associated with empyema formation and cavitating lung lesions.

Causes

- **Streptococcus pneumoniae**
 - ⇒ the most common cause of CAP & single lobar pneumonia (80%)
 - ⇒ Streptococcus pneumoniae commonly causes reactivation of the herpes simplex virus resulting in 'cold sores' → herpes labialis
 - ⇒ **S. pneumoniae is the most important cause of fulminant sepsis in patients with hyposplenism.**
- **Haemophilus influenzae**
 - ⇒ more likely to be associated with exacerbations of COPD
- **Staphylococcus aureus**
 - ⇒ commonly **after the 'flu'**.
 - ⇒ It's an organism often found on the skin. It is therefore commonly associated with systemic infections in **intravenous drug users**, this may hint in questions by the presence of track marks.
 - ⇒ It also causes a **bibasal pneumonia** as opposed to *Streptococcus pneumoniae* that is the most common cause of a single lobar pneumonia.

- ⇒ seen most frequently in the **elderly** and in **intravenous drug users or patients with underlying disease**.
- ⇒ It can result in a cavitating pneumonia.
- ⇒ **Carries a high mortality, and therefore if suspected treatment should initially be for a severe CAP.**
- ⇒ Capable of production of Panton-Valentine-Leucocidin toxin , associated with severe illness and high mortality.
- ⇒ Pneumothorax, pleural effusion and empyema are common in staphylococcal pneumonia.
- ⇒ the BNF advises the co-prescription of flucloxacillin.
- ⇒
- **Atypical pneumonias** due to:
 - ⇒ *Mycoplasma pneumoniae* ,
 - ⇒ *Legionella pneumophila* .
 - ⇒ *Coxiella burnetii* (Q fever) → relation to animal sources (usually sheep).
 - ⇒ *Chlamydophila psittaci* → bird contact (eg, poultry or duck workers)
 - ⇒ *Chlamydophila pneumoniae*
- **Viruses**
 - ⇒ Some studies have found that influenza virus is the most common cause of CAP in adults.
- ***Klebsiella pneumoniae***
 - ⇒ **Classically occurs in alcoholics** (Friedlander's pneumonia) and immunosuppressed individuals
 - ⇒ can cause cavitating pneumonia
 - ⇒ usually affects the upper lobes
 - ⇒ Chest x-ray features may include abscess formation in the middle/upper lobes and empyema.
 - ⇒ The mortality approaches 30-50%.

Features

- Respiratory symptoms (e.g. cough, often with increasing sputum production, expectoration, dyspnoea, pleuritic pain, and haemoptysis)
- Signs of infection (fever or chills and leukocytosis)
- Non-specific symptoms such as myalgia and arthralgia.
- Specific features of some causes of pneumonia:
 - ⇒ Legionellosis can present with headache, confusion, digestive manifestations such as diarrhoea, and clinical manifestations of hyponatraemia.
 - ⇒ *Mycoplasma pneumoniae* may present with extrapulmonary manifestations such as myringitis, encephalitis, uveitis, iritis, and myocarditis
- **Elderly** patients may present **atypically**, often **afebrile**, with **confusion** and **worsening of underlying diseases**.

Investigations

- Chest x-ray

Organism	Characteristic chest x-ray
<i>Streptococcus pneumoniae</i>	lobar consolidation
<i>Legionella</i>	bibasal consolidation
<i>Staphylococcus aureus</i>	bilateral cavitating bronchopneumonia,

- Leukocytosis.
- Biomarkers (useful for predicting inadequate host response.)
 - ⇒ C-reactive protein (CRP) >100 mg/L makes pneumonia likely.
 - ⇒ Procalcitonin (PCT)
 - Elevated PCT are correlated with bacterial pneumonia whereas lower values are correlated with viral and atypical pneumonia.
 - PCT is especially elevated in cases of pneumococcal pneumonia.

Management

Mild community acquired pneumonia (CURB 0-1) should be treated with oral penicillin therapy alone assuming no allergies and no other complicating factors

- Assessed the severity of pneumonia using (CURB-65 score)

⇒ **CURB-65 score criteria**

1. Confusion (abbreviated mental test score \leq 8/10)
2. Urea $>$ 7 mmol/L
3. Respiratory rate \geq 30 / min
4. BP: systolic \leq 90 or diastolic \leq 60 mmHg
5. age \geq 65 years

⇒ CURB-65 score of 0 – 1 can be managed in the community.

⇒ CURB-65 score of 2 or more should be managed in hospital as this represents a severe community acquired pneumonia.

- Empirical antibiotics

⇒ A summary table of empirical antibiotics as suggested by the BTS is shown below.

Pneumonia Severity (based on clinical judgement and CURB score)	Treatment Site	First line	Second line
Low Severity (CURB65 = 0-1)	Home	Amoxicillin orally	Doxycycline or clarithromycin orally
Moderate severity (CURB65 = 2)	Hospital	Amoxicillin plus clarithromycin orally (IV if oral administration not possible)	Doxycycline, Levofloxacin or moxifloxacin orally
High Severity (CURB65 = 3-5)	Hospital	Co-amoxiclav plus clarithromycin IV	Benzylpenicillin plus levofloxacin or ciprofloxacin IV OR Cefuroxime plus clarithromycin IV

- BNF advice: add flucloxacillin if staphylococci suspected (e.g. In influenza)
- Pneumonia possibly caused by atypical pathogens → Clarithromycin
- If Staphylococcus aureus is identified, treatment should be altered:

- ⇒ **Non-MRSA** organisms should be treated with flucloxacillin and/or rifampicin; an alternative for penicillin-allergic patients is teicoplanin and rifampicin.
- ⇒ **MRSA** should be treated with vancomycin.

Panton-Valentine Leukocidin-producing *Staphylococcus aureus* (PVL-SA)

- a rare cause of high severity pneumonia , associated with rapid lung cavitation (necrotising pneumonia) and multiorgan failure.
- empirical antibiotic combination of IV **linezolid** 600 mg twice daily, IV **clindamycin** 1.2 g four times a day and IV rifampicin 600 mg twice daily

Prognostic factors

- **Factors associated with a poor prognosis include:**
 - ⇒ ↑ CURB-65 score
 - CURB-65 score of 4 → mortality rate at 30 days = 30%.
 - ⇒ Co-morbidity such as renal disease, DM, chronic lung disease, heart failure
 - ⇒ hypoxaemia ($pO_2 < 8 \text{ kPa}$) independent of FiO_2
 - ⇒ White cell count less than $4 \times 10^9/\text{L}$ or greater than $20 \times 10^9/\text{L}$
 - ⇒ Multi-lobar involvement on CXR
 - ⇒ Temperature less than 35°C or more than 40°C .
 - ⇒ **Thrombocytosis** is associated with increased mortality compared to thrombocytopaenia or normal platelet levels.
- **The risk of mortality increases as the CURB score increases**

Score	Risk of death at 30 days
0 to 1	<5% mortality
2 to 3	< 10% mortality
4 to 5	15-30% mortality

- **How quickly their symptoms should resolve?**
 - ⇒ NICE recommend that the following information is given to patients with pneumonia in terms of how quickly their symptoms should resolve:

Time	Progress
1 week	Fever should have resolved
4 weeks	Chest pain and sputum production should have substantially reduced
6 weeks	Cough and breathlessness should have substantially reduced
3 months	Most symptoms should have resolved but fatigue may still be present
6 months	Most people will feel back to normal.

Follow up

- **What review policy should be adopted in patients managed in the community?**
 - ⇒ Review is recommended after 48 h or earlier if clinically indicated for disease severity assessment

- ⇒ Those who fail to improve after 48 h of treatment should be considered for hospital admission or chest radiography.
- C-reactive protein should be re-measured, and a chest radiograph repeated in patients who are not progressing satisfactorily after 3 days of treatment.
- **Chest x ray in six weeks to ensure complete resolution.**
 - ⇒ What arrangements should be made for follow-up after hospital discharge?
 - Clinical review should be arranged for all patients at around 6 weeks.
 - **radiological changes can take up to 6 weeks to improve.**
 - ⇒ This is to exclude any underlying cause especially malignancy.
 - ⇒ those who have persistent shadowing on the lung need referral to a respiratory physician.

Klebsiella Pneumonia

Pneumonia in an alcoholic - Klebsiella

Overview

- Klebsiella is a **Gram-negative rod** (bacillus) encapsulated, non-motile bacterium that is part of the normal gut flora.
- It can cause many infections in humans including pneumonia (typically following aspiration) and urinary tract infections.
- Most frequently causes infection in hospitalized patients and in those with impaired host defenses, including patients with diabetes mellitus, alcoholism, malignancy, hepatobiliary disease, chronic obstructive pulmonary disease, and renal failure,
- It is an uncommon cause of community-acquired pneumonia. is a common cause of nosocomial pulmonary infections

Pathophysiological mechanism

- Colonization of the oropharynx followed by microaspiration of upper airway secretions in the setting of decreased consciousness (due to heavy alcohol drinking).

Features

- **more common in alcoholic** and diabetics
- may occur following aspiration
- **'red-currant jelly'** sputum
 - ⇒ One stark difference between Streptococcus pneumonia and Klebsiella pneumonia is the type of sputum produced. The sputum produced by S. pneumoniae is described as "blood-tinged" or "rust-colored," however, the sputum blood-tinged by those infected by K. pneumoniae is described as "currant jelly."
- **Cavitating lesions**, often affects upper lobes.
- Typically causes a lobar infiltrate that is in the posterior aspect of the right upper lung.
- Another non-specific sign of K. pneumoniae on a chest radiograph is the **bulging fissure sign**. This is related to the large amount of infection and inflammation that the organism can cause.
- commonly causes empyema and less commonly lung abscess

Treatment

- Community-acquired K. pneumoniae pneumonia → third-generation cephalosporins or quinolones
- Extended-spectrum beta-lactamase (ESBL) K. pneumoniae → carbapenem therapy

Prognosis

- mortality is 30-50%

History of alcoholism and cavitations are suggestive of Klebsiella as the etiology.

Legionella pneumonia (Legionnaires' disease)

Legionella pneumophila is best diagnosed by the urinary antigen test

Aetiology

- Legionella bacteria are aerobic, **gram-negative rod**, intracellular pathogens that are commonly found in water and soil. Human infection is typically acquired through inhalation of aerosols from these substances.
- L. pneumophila* serotype 1 is the most common cause of human *Legionella* infections.

Epidemiology

- Cause 2-5% of community-acquired pneumonia admitted to hospital.
- Incubation period 2-10 days
- More common in males and age of > 50 years.
- Can cause outbreaks** in large facilities such as hospitals, hotels, or apartment buildings due to **contaminated communal water supplies**

Source infections

- It is typically **colonizes hot water tanks** and hence questions may hint at air-conditioning systems or foreign holidays.
- Factors that encourage colonisation and multiplication are temperature (20-45 °C) and stagnation.

Transmission

- By inhalation of contaminated water droplets (aerosol)**
- Person-to-person transmission is not seen**

Features

- Flu-like symptoms (present in > 95% of patients), dry cough
- Gastrointestinal symptoms such as nausea, vomiting, and diarrhea
- Elevated hepatic transaminases
- Relative bradycardia**
- Lymphopaenia**
 - ⇒ A marked **neutrophil leukocytosis** may be associated with concomitant **lymphopenia**.
- Hyponatraemia**
 - ⇒ Secondary to syndrome of inappropriate antidiuretic hormone secretion (**SIADH**)

The **classic features** of Legionnaires' disease are:

- Recent foreign travel**
- Relative bradycardia**
- prominent headache**
- Hyponatraemia**

Diagnosis

- Urinary antigen
 - ⇒ the most useful diagnostic test
 - ⇒ Sensitivity 80%; specificity >99%.
 - ⇒ Rapid test
 - ⇒ Only detects *L. pneumophila* serotype 1, so a negative result does not exclude the diagnosis of *Legionella* infection.
 - ⇒ results are positive during early infection and remain positive for several weeks or months and it is, therefore, not a test for cure.
- Polymerase chain reaction (PCR) using sputum or bronchoalveolar lavage specimen
 - ⇒ has high diagnostic accuracy (if available) and detects all *Legionella* species and serogroups
- The organism does not show up on Gram-staining.
- Cultures
 - ⇒ on buffered charcoal yeast extract (BCYE) agar.
 - ⇒ Sensitivity 20% to 95%; specificity 100%
- Chest x-ray: Diffuse reticular opacities are commonly seen

Management

- First line: fluoroquinolones or macrolides
 - ⇒ Fluoroquinolones: levofloxacin (preferred), ciprofloxacin, or moxifloxacin.
 - ⇒ Macrolides: Azithromycin (preferred), clarithromycin or erythromycin.
- Second line
 - ⇒ Tetracyclines; doxycycline

Pontiac fever

- Non-pneumonic *Legionella* infection
- causes a mild, self-limiting course of legionellosis without pneumonia.
- flu-like symptoms (e.g. fever, headache, and muscle ache)
- Not require antibiotic.

Mycoplasma pneumoniae

Pathogen

- *Mycoplasma pneumoniae* is a cause of atypical pneumonia, more closely related to gram positive bacteria.
- Because it lacks a cell wall, it is not visible on Gram stain and is not susceptible to antibiotics that inhibit cell wall synthesis, such as penicillins.

Epidemiology

- Most commonly affects younger patients (15-30 years).
- Accounts for 7% of all community-acquired pneumonias.
- Can occurs epidemic outbreaks, most commonly among persons living in close quarters, such as households, schools, and military facilities

Features

- URI and acute bronchitis are the most common (flu-like symptoms classically precede a dry cough)
- Systemic upset (arthralgia, haemolytic anaemia, erythema multiforme, Neurological, pericarditis/myocarditis, GIT, renal)
- Bilateral consolidation on x-ray

Complications → (Extra-pulmonary manifestations occur in ~10% of cases)

- Rash → **Erythema multiforme**, erythema nodosum
- Neurological : meningoencephalitis, Guillain-Barré syndrome, transverse myelitis
- Cardiac: Myocarditis, Pericarditis
- Renal failure: acute glomerulonephritis
- **Hepatitis**
- **Haemolytic anaemia** (found in up to 50% of cases)
 - ⇒ the most common extra-pulmonary manifestations and is typically mild and self-limited.
 - ⇒ Presence of IgM antibodies (**cold agglutinins**) directed against the I antigen of the erythrocyte membrane → **Spherocytes** → **Haemolysis** → **Features of haemolysis (direct Coombs' test, ↑reticulocyte counts, ↑unconjugated bilirubin, ↑LDH, ↓haptoglobins, fragmented red blood cells)**

Mycoplasma pneumoniae → Serology is diagnostic

Diagnosis

- **Mycoplasma serology**
 - ⇒ the "gold standard" diagnostic test
 - ⇒ 92% sensitivity and 95% specificity
 - ⇒ more sensitive than culture for detecting acute infection
- **Positive cold agglutination test**
 - ⇒ occur in only half of patients
- **Chest X-ray**
 - ⇒ might not correlate with the patient's condition → much worse than would be suggested by the clinical examination
 - ⇒ the commonest chest x-ray abnormality is bilateral interstitial infiltrate (90%)
- **Nucleic acid amplification test (NAAT), such as polymerase chain reaction (PCR)**
 - ⇒ Sensitivity is very high
 - ⇒ Faster than serology
 - ⇒ Cannot distinguish between active infection and asymptomatic carriage
 - ⇒ Causes of Positive PCR but negative serology tests
 - Asymptomatic carriage of *M. pneumoniae* (after disease, or during incubation period)
 - Immunocompromised patients, → no diagnostic antibody response.
 - Early successful antibiotics therapy.
- **Culture**
 - ⇒ rarely used for routine diagnosis
 - ⇒ sensitivity may be no more than 60%, but when positive, its specificity is 100%,
- WBC can be normal

Mycoplasma pneumonia if allergic/intolerant to macrolides → doxycycline

High titer of **cold** agglutinins (**IgM**), which can agglutinate RBCs. *Mycoplasma* gets **cold** without a **coat** (no cell wall).

Management

- **First line** → macrolides (eg, azithromycin), tetracyclines (eg, doxycycline), and respiratory fluoroquinolones (eg, levofloxacin or moxifloxacin).
- Second-line → Tetracyclines such as doxycycline.

Prognosis

- Most cases resolve **spontaneously** within a few weeks.

Indolent onset, concurrent URI symptoms (eg, rhinorrhea, pharyngitis, ear ache), and the presence of non-respiratory tract manifestations (eg, hemolysis) are suggestive *Mycoplasma pneumoniae*

Aspiration pneumonia

Definition

- a type of pneumonia that occurs as a result of oropharyngeal secretions and/or gastric contents aspiration
- also known as Mendelson syndrome

Risk factors

- ↓ level of consciousness (e.g. seizure, Alcohol use, stroke, **post-anaesthesia**) → impaired gag or swallowing reflex → aspiration occurred several weeks earlier.
- Gastroesophageal reflux disease, esophageal motility disorders, dysphagia.
- poor oral hygiene

Features

- Immediate symptoms: **bronchospasms**, crackles on auscultation, hypoxemia with cyanosis
- Late symptoms: fever, shortness of breath, cough with foul-smelling sputum

Site of aspiration

- which lung?
 - ⇒ Due to the angle of the bronchi, the **right lung** is more commonly affected by aspiration than the left lung.
 - ⇒ The right mainstem is more vertical and wider than the left mainstem bronchus.
- Which lobe?
 - ⇒ Depends on patient's position during aspiration:
 - in a patient who aspirates while **recumbent** (lying down):

- ❖ **superior segment of the right lower lobe** (most common site of aspiration)
- in a patient who aspirates while **sitting upright**:
 - ❖ posterior basal segment of the right lower lobe

Organisms

- Anaerobes and Gram-negative organisms are the usual organisms in abscesses following aspiration.
- Sputum or tracheal Gram stain reveals mixed flora.

Complications

- lung abscess and empyema
 - ⇒ **air-fluid level is characteristic of a lung abscess.**

Treatment

- **Combination of antibiotics → Cefuroxime + Metronidazole**
- If the patient is allergic to penicillin or cephalosporin→ Vancomycin + Metronidazole



The slide shows an abscess in the right mid-zone.

Psittacosis (Chlamydia psittaci pneumonia) (Atypical pneumonia)

Exposure to an ill bird and a rash (Horder's spots) are pathognomonic

Definition

- Psittacosis is a disease caused by *Chlamydia psittaci*, an obligate intracellular organism, transmitted to humans from birds., induces prominent systemic manifestations and some respiratory.

Pathogenesis

- Humans are usually **infected by inhalation of organisms** in dried feces or in bird feather dust.
- Pet owners, vets and zoo keepers are most at risk.
- The incubation period is usually 5 to 14 days.

Diagnosis

- typical clinical features (fever, headache, myalgias, dry cough) **in a patient with a history of bird contact**
- In a patient presenting with pneumonia, severe headache, splenomegaly, and failure to respond to beta-lactam antibiotics may be other clues to the diagnosis.
- Serology:** (e.g. microimmunofluorescent antibody testing, or complement fixation assay) **the most useful diagnostic test**
- Abnormal LFTs in up to 50%.
- Chest X-ray: segmental or diffuse multi-lobar consolidation.
- Culture is discouraged since *C. psittaci* is highly infectious when cultured and is only performed in specialized laboratories.

Complications

- Respiratory failure, hepatitis, endocarditis, and encephalitis.

Treatment

- 1st line : tetracyclines e.g. doxycycline**
- 2nd line: macrolides e.g. erythromycin or azithromycin**

Pseudomonas pneumonia

Overview

- P. aeruginosa* is a common cause of gram-negative hospital-acquired pneumonia
- Community-acquired *P. aeruginosa* pneumonia occurs mainly in
 - immunocompromised patients (eg, HIV, post-transplant, or neutropenic hosts)
 - structural lung abnormalities (e.g. cystic fibrosis, bronchiectasis, COPD)
- Nosocomial or **hospital-acquired infections** should be suspected in patients with an onset of symptoms at least 48 hours after admission to the hospital.

Treatment

- Antibiotics used for the treatment of *Pseudomonas aeruginosa* infections

Class	Agent
Penicillin-beta-lactamase combinations	Piperacillin-tazobactam
Cephalosporins	Ceftazidime or Cefepime
Fluoroquinolones	Ciprofloxacin or Levofloxacin
Carbapenems	Meropenem, Imipenem

- Fluoroquinolones are the only class of antibiotics with antipseudomonal activity that have an oral formulation.
- The only antipseudomonal penicillin is piperacillin.

Hospital-acquired pneumonia (HAP)

Definition

- Hospital-acquired pneumonia (HAP): nosocomial pneumonia, with onset > 48 hours after admission

Prevalence

- The third most common hospital-acquired infection after urinary tract infections and wound infections.

Causes

- **Gram-negative organisms** are the most common causes, especially aerobic gram-negative bacilli, such as:
 - ⇒ *Pseudomonas aeruginosa*,
 - ⇒ *Escherichia coli*,
 - ⇒ *Klebsiella pneumoniae*, and
 - ⇒ *Acinetobacter* species.

Diagnosis

- A new and/or persistent alveolar shadowing on chest x-ray or CT scan confirms the diagnosis.

Treatment

- most commonly as combination therapy. A third generation cephalosporin with an aminoglycoside is the current British Thoracic Society (BTS) recommendation.

Choice of antibiotic

Antibiotics for adults aged 18 years and over (NICE guidelines, September 2019)

Treatment	Antibiotic
First-choice oral antibiotic if non-severe symptoms or signs, and not at higher risk of resistance (guided by microbiological results when available)	Co-amoxiclav
Alternative oral antibiotics if non-severe symptoms or signs, and not at higher risk of resistance, for penicillin allergy or if co-amoxiclav unsuitable.	Doxycycline Cefalexin (caution in penicillin allergy) Levofloxacin
First-choice if severe symptoms or signs (e.g. sepsis) or ↑ risk of resistance.	Piperacillin with tazobactam Ceftazidime Ceftriaxone Cefuroxime Meropenem Ceftazidime with avibactam Levofloxacin
If suspected or confirmed methicillin resistant <i>Staphylococcus aureus</i> infection (dual therapy with a first-choice intravenous antibiotic)	Vancomycin Teicoplanin Linezolid (if vancomycin cannot be used)

Pneumocystis Jirovecii pneumonia (PCP)

Pneumocystis jiroveci pneumonia - pneumothorax is a common complication

Pathogen

- *Pneumocystis jiroveci* is an ubiquitous, yeast-like fungus unicellular eukaryote.

Association

- PCP is the most common opportunistic infection in AIDS
 - ⇒ **Pneumocystis jirovecii pneumonia is unlikely in a patient who has had a CD4 count above 200 cells/mm³** in the preceding 2 months in the absence of other HIV-associated symptoms.
- Immunosuppressed patients, particularly after organ transplantation

Pathophysiology

- The organism is confined to the alveolar space of the lung and produces debris and cysts in the alveolar space with interstitial infiltration of lymphocytes and plasma cells. As a result, it can cause profound disturbance of oxygen exchange and fatal hypoxaemia if left untreated.
- **The morphological appearance of *Pneumocystis jirovecii* infection in the lung → An interstitial pneumonitis with foamy intra-alveolar exudate**

Features

- Dyspnoea, dry cough, fever
- **Exercise-induced desaturation**
- **Very few chest signs: The lungs are commonly clear on auscultation**
- **Pneumothorax is a common complication of PCP.**

Investigation

- **Lymphopenia is very suggestive of PCP with AIDS** (and therefore low CD4 lymphocyte count).
- Lactate dehydrogenase raised in 90% of patients with PCP (but this can occur with other pulmonary diseases).
- **Chest x-ray**
 - ⇒ Typically shows **bilateral interstitial pulmonary infiltrates** (diffuse ground-glass opacities)
 - ⇒ 30% have non-specific or inconclusive findings.
 - ⇒ 10-15% of patients with PCP have normal chest radiographs
- **Bronchoalveolar lavage (BAL)**
 - ⇒ often needed to demonstrate PCP
 - ⇒ **silver stain shows characteristic cyst** phase of the organism
 - ⇒ Spontaneously expectorated sputum should not be used for diagnostic studies because it has poor sensitivity for PCP. Use induced sputum instead

Pneumocystis jiroveci pneumonia → Definitive diagnosis is by bronchial alveolar lavage with silver staining

Management

- 1ST line : Co-trimoxazole
 - ⇒ should be given for 21 days in HIV, but can be shorter in other causes of immunosuppression.
 - ⇒ **the preferred initial therapy during pregnancy**
 - ⇒ Glucose 6-phosphate dehydrogenase deficiency (G6PD) levels should be checked prior to TMP-SMX, dapsone or primaquine use
- 2ND line: in severe cases or in patients who are intolerant of co-trimoxazole → IV **pentamidine**
- Steroids
 - ⇒ Reduces mortality and prevent lung damage in people with moderate-to-severe PCP.
 - ⇒ a **21-day** tapering course has been shown to be safe and effective.
 - ⇒ The severity is determined on the basis of arterial blood gas results.
 - **severe PCP is defined by a room air arterial oxygen pressure (pO₂) of less than 9 kPa** (70 mmHg) or an arterial-alveolar O₂ gradient that exceeds 4.5 kPa (35 mmHg).

Any patient with PaO₂ <70 and A-a gradient >35 should be started on steroid therapy.

Prophylaxis

- All patients with a CD4 count < 200/mm³ should receive PCP prophylaxis (Co-trimoxazole is the preferred agent. Dapsone and inhaled pentamidine are also used.)
- Primary *Pneumocystis* prophylaxis should be discontinued if the patient responded to ART with an increase in CD4 counts ≥200 cells/mm³ for ≥3 months.

MRCPUK-part-1-January 2016 exam

HIV positive but poorly compliant with his antiretroviral therapy (ART). CD4 : 180 cells/ml. oxygen saturations 97% on room air with a temperature of 38.1°C. He has coarse crackles on the right side of his chest. A **chest x-ray shows consolidation of the right mid zone**. What is the most likely causative organism?

- ⇒ ***Streptococcus pneumoniae***
- (Whilst *Pneumocystis jirovecii* is of course associated with HIV, patients who are immunocompromised are more likely to develop infections due to the common pathogens which affect immunocompetent individuals. *Streptococcus pneumoniae* is therefore the most likely cause of community-acquired pneumonia in this patient. *Pneumocystis jirovecii* tends to present with very few chest signs and bilateral interstitial pulmonary infiltrates on chest x-ray)

Coronavirus disease 2019 (COVID-19)

Overview

- Caused by coronaviruses, SARS-CoV-2
- The transmission occurs mainly through respiratory droplets (particles are greater than 5-10 micrometers in diameter) from coughing and sneezing.
- The incubation period is 2-14 days.
- Host cell entry occurs by attachment of viral spike protein to angiotensin-converting enzyme 2 receptor on cell membranes.

Features

- Most common: Fever, Fatigue, Dry cough
- Common: Shortness of breath, Loss of smell and/or taste
- Less common: Thromboembolic events (e.g., pulmonary embolisms)
- Complications include respiratory failure, hypercoagulability, shock, organ failure.

Cytokine storm:

- an excessive release of proinflammatory cytokines that causes hyperactivation of immune system and exaggerated immune response leading to multiorgan dysfunction.
- Initial treatment with tocilizumab plus a glucocorticoid

Risk factors for severe illness

- Increasing age,
- Obesity,
- Diabetes, hypertension, chronic kidney disease, and severe cardiopulmonary illness.

Pathogenesis

- In the normal lung, type II pneumocytes secrete pulmonary surfactant; this phospholipid coats the alveoli and keeps them open and available for gas exchange. The initial lung injury in COVID-19 infection may occur via loss of surfactant and alveolar collapse.
- A cytokine storm occurs when white blood cells (WBCs) release large numbers of inflammatory cytokines (eg, interleukin [IL]-1, IL-6) in response to the virus, leading to further WBC activation

Diagnosis

- RT-PCR (most common)
 - ⇒ The nucleic acid amplification test (NAAT) is the diagnostic test of choice for COVID-19. NAAT is performed using RT-PCR.
- Antigen and antibody tests are available (less accurate)
- **Chest x-ray** may be normal in early or mild COVID-19. Findings in COVID-19 pneumonia include bilateral or peripheral consolidation or opacities
- **CT scan** findings may include ground glass opacities and consolidations, especially in the lung periphery

Management

- **Cough**
 - ⇒ Avoid lying on the back
 - ⇒ Use simple measures first, e.g. honey.
 - ⇒ If it is distressing → Consider short-term use of codeine linctus, codeine phosphate tablets or morphine sulfate oral solution in people 18 years and over to suppress coughing

- **Breathlessness**

- ⇒ Identify and treat reversible causes of breathlessness, for example, pulmonary oedema, pulmonary embolism, chronic obstructive pulmonary disorder and asthma.
- ⇒ encouraging relaxation and breathing techniques, and changing body positioning
- ⇒ If hypoxia is the likely cause of breathlessness: consider a trial of oxygen therapy
- ⇒ **Consider continuous positive airway pressure (CPAP) when:**
 - hypoxaemia not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, and escalation to invasive mechanical ventilation would be an option but it is not immediately needed, or it is agreed that respiratory support should not be escalated beyond CPAP.
- ⇒ Consider using high-flow nasal oxygen for people having continuous positive airway pressure (CPAP) when they need:
 - a break from CPAP, such as at mealtimes
 - humidified oxygen
 - weaning from CPAP.

- **Corticosteroids**

- ⇒ Indication: people with COVID-19 who need supplemental oxygen.
- ⇒ 1st choice : dexamethasone. Hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable.

- **Combination of casirivimab and imdevimab**

- ⇒ to people aged 12 and over hospitalised because of COVID-19 who have no detectable SARS-CoV-2 antibodies (**seronegative**).
- ⇒ Not recommended for patients who have detectable SARS-CoV-2 antibodies (**seropositive**)

- **Remdesivir**

- ⇒ Indication: hospitalised patient who are > 12 year old and weight ≥ 40 kg and need low-flow supplemental oxygen.
- ⇒ Not recommended for patient who need NIV or invasive mechanical ventilation.

- **Tocilizumab: (Single dose)**

- ⇒ Indications
 - hospitalised with severe COVID-19 (need O₂ and CRP ≥ 75 mg/litre)
 - no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.
- ⇒ Consider sarilumab if tocilizumab is unavailable or cannot be used

- **Medication not recommended to treat COVID-19.**

- ⇒ Azithromycin, budesonide, colchicine, doxycycline

- **Venous thromboembolism (VTE) prophylaxis**

- ⇒ only for in hospital patients, consider a prophylaxis dose of low molecular weight heparin (LMWH) if the risk of VTE outweighs the risk of bleeding.
- ⇒ Do not base prophylactic dosing of heparin on levels of D-dimer.

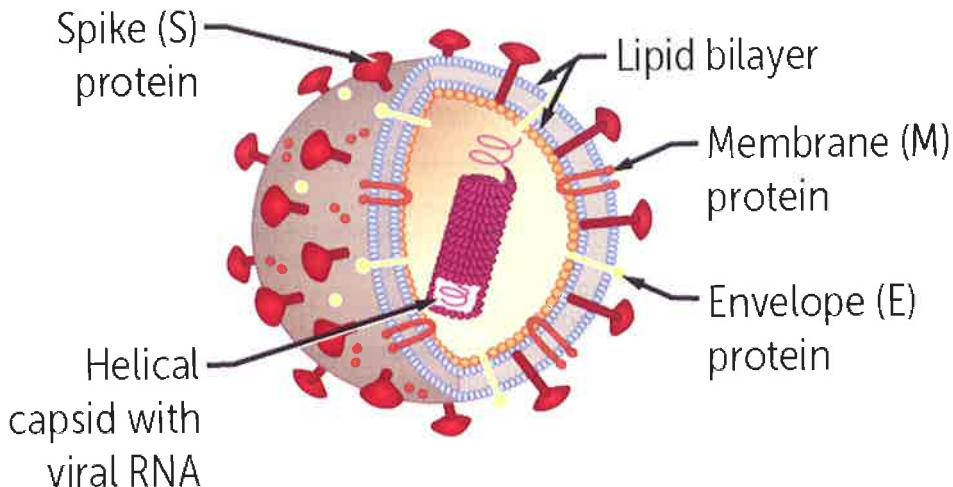
- **Antibiotics:** Should not be used unless there is clinical suspicion of additional bacterial co-infection.

- ⇒ Procalcitonin tests could be useful in identifying whether there is a bacterial infection.
- ⇒ High C-reactive protein levels do not necessarily indicate whether pneumonia is due to bacteria or SARS-COV-2.
- ⇒ Low C-reactive protein level indicates that a secondary bacterial infection is less likely.
- ⇒ Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.

- Medicines for end-of-life care:** opioid and benzodiazepine combination.

Remdesivir

- Remdesivir is a nucleotide prodrug of an adenosine analog.
- It binds to the viral RNA-dependent RNA polymerase
- It inhibits viral replication by terminating RNA transcription prematurely.
- Adverse Effects: ↑ transaminase levels & prothrombin time (Liver function tests and prothrombin time tests should be performed for all patients before they receive remdesivir).



COVID-19 enters the lungs via type II pneumocytes.

Tocilizumab

- Mode of action
 - Antagonizes the IL-6 receptor, which leads to a reduction in cytokine and acute phase reactant production.
- Common adverse effects (>10%)
 - Neutropenia
 - ↑ liver enzyme
 - ↑ serum cholesterol
 - Constipation

Treatment of COVID-19 in pregnant patients

Initial management

- Oxygen – titrate supplemental oxygen to keep sats >94%
- Thromboprophylaxis – prophylactic LMWH dose according to weight
- Corticosteroids – if oxygen dependent give for a total of 10 days
 - Oral prednisolone 40mg OD; or
 - IV hydrocortisone 80mg BD
- If steroids used for fetal lung maturation use Dexamethasone 12mg IM 24 hourly (2 doses) followed by either (a) or (b) above for 10 days

Clinical deterioration

- Increased O₂ requirements : O₂ sat<93 , RR > 22
 - ⇒ Give tocilizumab (or sarilumab if unavailable) if needing escalation of care and/or if CRP>75
 - ⇒ Check COVID-19 antibodies, if negative consider 2.4g Ronapreve IV once (RONAPREVE contains the active ingredients casirivimab and imdevimab.)

Discharge

- Thromboprophylaxis for at least 10 days
- Encourage COVID19 vaccination: can be given 28 days following recovery
- Advise: if given tocilizumab/sarilumab, be aware of an increased risk of infection without typical signs for several months.

Aspergillosis: Types

Overview

- Aspergillosis is the collective term for diseases caused by mold species in the genus Aspergillus.
- Most common: ***Aspergillus fumigatus*** and ***Aspergillus flavus***
- Transmission:** airborne exposure to mold spores

	ABPA	Chronic pulmonary aspergillosis (e.g. Aspergilloma)	Invasive aspergillosis
Main features	Asthmatic symptoms	Hemoptysis, shortness of breath	Dry cough, septic shock, multi-system involvement
Laboratory tests	<ul style="list-style-type: none"> ↑ IgE levels Eosinophilia ↑ ESR Positive Aspergillus antigen skin test 	Positive Aspergillus IgG serology	<ul style="list-style-type: none"> Positive galactomannan antigen test: (galactomannan is a protein found in Aspergillus cell wall). Positive 1,3-β-D glucan test Septate hyphae on tissue biopsy
Chest x-ray and CT	<ul style="list-style-type: none"> Bronchiectasis Pulmonary infiltrates 	<ul style="list-style-type: none"> Mobile fungus ball (demonstrated by moving the patient from a supine position to a prone or lateral recumbent position) Monod sign: a peripheral air crescent around a fungus ball in a preexisting lung cavity The upper lobe is mostly 	<ul style="list-style-type: none"> Multiple nodules Halo sign: hemorrhagic ground glass opacities around nodules

Treatment	<ul style="list-style-type: none"> Oral prednisone if severe Itraconazole if recurrent 	<ul style="list-style-type: none"> Surgical resection (e.g., lobectomy) Itraconazole OR voriconazole (should be used preoperatively and postoperatively) 	IV voriconazole
-----------	--	--	-----------------

The most important diagnostics for the different aspergillosis types are:

- ABPA:** increased IgE and eosinophil count.
- Aspergilloma:** positive culture or serology and fungus ball seen on chest imaging.
- Invasive aspergillosis:** positive culture or biopsy showing septate hyphae.

Allergic bronchopulmonary aspergillosis (ABPA)

In the exam questions often give a history of bronchiectasis and eosinophilia.

Definition

- ABPA results from an allergy to Aspergillus spores (**Type I hypersensitivity to Aspergillus fumigatus**).
- a hypersensitivity reaction caused by exposure to Aspergillus that mostly occurs in patients with cystic fibrosis or asthma
- Aspergillus fumigatus is the most common airborne fungus causative organism for ABPA.

Risk factors

- Preexisting bronchopulmonary conditions (e.g., **asthma, cystic fibrosis**)

Features

- Bronchoconstriction: wheeze, cough, dyspnoea (clinical deterioration in asthma symptoms)
- Bronchiectasis (**proximal**)

Investigations

- Serum **eosinophilia**
- Raised IgE: helpful test, but **not specific** enough to establish the diagnosis.
- Aspergillus skin-prick test (the most specific investigation)**
 - Positive radioallergosorbent (RAST) test to Aspergillus.
 - Immediate (type I) reactions occur in virtually all patients with ABPA following intradermal injections of *Aspergillus fumigatus* extracts, with only 16% developing delayed (type IV) reactions.
 - An early positive skin-prick test for Aspergillus fumigatus is the most specific to (ABPA).**
 - Positive skin-prick tests reflect antigen-specific IgE.
- Positive IgG precipitins** (not as positive as in aspergilloma) in 70% of patients.
 - Precipitins (IgG) are more usual with an aspergilloma**, but may be positive in ABPA or in up to 10% of patients with asthma.
- Pulmonary infiltrates on CXR. Lobar collapse can also occur, due to mucus plugging.

Allergic bronchopulmonary aspergillus: both of the following must be present to confirm the diagnosis:

- ❑ Aspergillus skin test positivity or detectable IgE levels against aspergillus fumigatus and
- ❑ Elevated total serum IgE concentration.

Management

- First line → steroids (prednisone)
- **Second line → add itraconazole** or voriconazole
 - ⇒ Itraconazole leads to significant reductions in corticosteroid dose, decreases IgE levels, greater resolution of pulmonary infiltrates, and improves exercise tolerance.

Aspergilloma

The clue can be a lack of improvement with broad spectrum intravenous antibiotics, haemoptysis and chest X-Ray findings.

Definition

- An aspergilloma is a mycetoma (**mass-like fungus ball**) which often colonises an existing lung cavity (e.g. secondary to tuberculosis, lung cancer, cystic fibrosis or emphysema)

Feature

- often asymptomatic
- cough
- **haemoptysis** in up to three quarters of patients (may be severe and fatal)
- Systemic symptoms of weight loss, lethargy and fever are less common.

Investigations

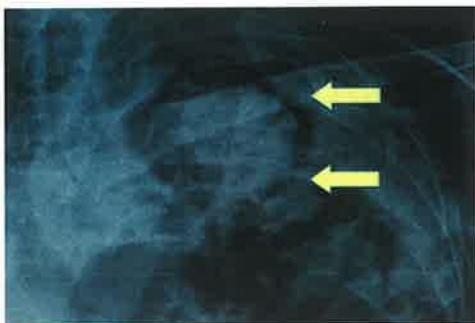
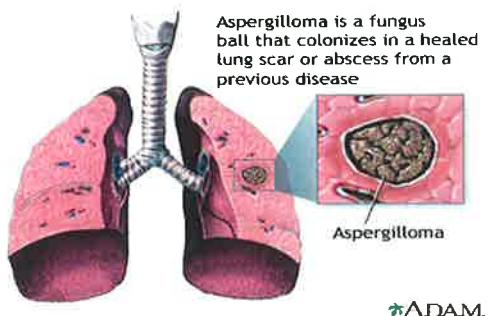
- chest x-ray containing a rounded opacity within a cavity often associated with a rim of air. These features are seen more clearly on **CT**.
- High titres Aspergillus precipitins (**IgG antibodies**) present in 95% of cases.

Treatment

- **Surgery should be considered as a first-line** option where erosion into a major vessel and massive haemoptysis is a possibility
- **In case of massive haemoptysis the next appropriate management – after transfusion and resuscitation- is → Angiography and embolisation, after that → lobar resection as the intervention of next resort**

Aspergilloma should be considered in patients with chronic lung disease and radiographs showing intracavitary mass lesions.

Images



Invasive aspergillosis (IA)

Definition

- a severe form of *Aspergillus* infection with severe pneumonia and septicemia, most commonly occurs in immunocompromised individuals.

Risk factors

- **immunosuppression** (e.g., due to HIV/**chemotherapy**, after organ transplantation) or neutropenia (e.g., due to chronic granulomatous infection).

Features

- Symptoms of active infection & haemoptysis.

Investigations

- the classical signs on CT scanning the '**halo sign'** **air crescent sign**
- galactomannan test:
 - ⇒ Galactomannan is a component of the cell wall of the *Aspergillus* and is released during growth.
 - ⇒ Detection of galactomannan in blood by ELISA is used to diagnose invasive aspergillosis
- Silver staining shows → hyphae.
 - ⇒ **Haematoxylin and eosin (H&E) stain** does not stain most of the fungi, except the **Aspergillus** species.

Treatment

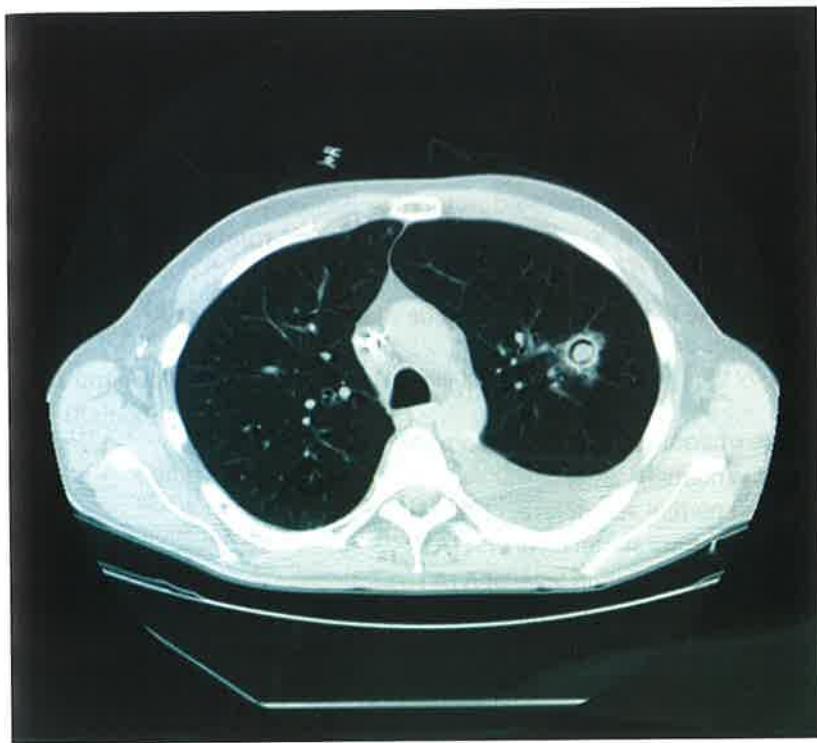
- 1st line **voriconazole**: start iv before oral (as oral 10 days to get therapeutic levels).
- 2nd line (If voriconazole is not tolerated): **amphotericin B**

Prognosis

- Mortality vary from 40-90%



Typical morphology of *Aspergillus fumigatus*.



CT chest showed Aspergilloma

A slightly thick-walled left upper lobe cavity contains a rounded mass. A crescent-shaped airspace, termed the air crescent sign, separates the mass from the cavity wall. An aspergilloma can often be shown to move to the dependent position within its cavity

Invasive aspergillosis

- Invasive aspergillosis should be suspected in someone who is immunocompromised (neutropenia, steroids, HIV) with severe chest pain, high-grade fevers, and haemoptysis.
- The treatment of choice for invasive aspergillosis is voriconazole

Voriconazole → ↑risk of developing skin malignancy (malignant melanoma, squamous cell carcinoma)

Alpha-1 antitrypsin (A1AT) deficiency**Alpha-1 antitrypsin deficiency - autosomal recessive / co-dominant****Definition**

- Alpha-1 antitrypsin (A1AT) deficiency is a common inherited genetic disorder characterized by the accumulation of defective alpha-1 antitrypsin enzyme

Genetics & Pathophysiology

- Alpha-1 antitrypsin: a **protease inhibitor** that is synthesized in the liver and protects cells from breakdown by neutrophil elastase (AAT neutralises neutrophil elastase, thereby preventing lung destruction.)
- The mode of inheritance: autosomal **co-dominant**
- Mutations in **SERPINA1 gene**, located on the long arm of **chromosome 14** → **dysfunctional (or absent) AAT**
- **A1AT deficiency is the most prevalent genetic disease in patients of finnish/scandinavian origin**
- Alleles classified by their electrophoretic mobility - **M** for normal, **S** for slow, and **Z** for very slow
- **The serum levels of some of the common genotypes are:**
 - ⇒ PiMM: 100% (normal)
 - ⇒ PiMS: 80% of normal serum level of A1AT
 - ⇒ PiSS: 60% of normal serum level of A1AT
 - ⇒ PiMZ: 60% of normal serum level of A1AT
 - ⇒ PiSZ: 40% of normal serum level of A1AT
 - ⇒ PiZZ: 10-15% (severe alpha 1-antitrypsin deficiency).
- Patients who manifest disease usually have **PiZZ genotype**
- Effect on the lungs: deficient AAT → uninhibited neutrophil elastase activity → destruction of the pulmonary parenchyma → panacinar emphysema
- Effect on the liver: accumulation of AAT in hepatocellular endoplasmic reticulum → hepatocyte destruction → hepatitis and liver cirrhosis

Features

- **Pulmonary**
 - ⇒ **Panacinar emphysema**, most marked in **lower lobes** (2% of cases of emphysema)
 - ⇒ The interplay between the **environmental** and **genetic** factors determine its onset.
 - ⇒ Patients usually present with increasing dyspnoea.
- **Hepatic**
 - ⇒ Hepatitis
 - ⇒ Cirrhosis (15%)
 - ⇒ Increased risk of hepatocellular carcinoma (HCC)

Investigations

- Serum: decreased antitrypsin protein levels
- Electrophoresis: decreased alpha-1 peak
- Chest x-ray
 - ⇒ Low and flat diaphragm
 - ⇒ Widened intercostal spaces
 - ⇒ Hyperinflation and increased basilar radiolucency of both lungs with rarification of peripheral pulmonary vessels
- Chest CT
 - ⇒ Panacinar emphysema (in contrast to centriacinar emphysema in smoking-related emphysema)
 - ⇒ Bronchiectasis
 - ⇒ Bullae
- Liver biopsy
 - ⇒ PAS-positive, spherical inclusion bodies in periportal hepatocytes
 - ⇒ Signs of cirrhosis

Management

- Avoid smoking
 - ⇒ smoking is harmful to those with A1AT deficiency and can accelerate the progression of emphysema by 10 years.
- Supportive
 - ⇒ Preventive vaccination (e.g., influenza vaccine, pneumococcus vaccine)
 - ⇒ Symptomatic treatment (bronchodilators)
 - ⇒ Pulmonary rehabilitation (Physiotherapy)
- Intravenous alpha1-antitrypsin protein concentrates
- Surgery
 - ⇒ Volume reduction surgery
 - ⇒ Lung transplantation
 - ⇒ Liver transplantation → Results in correction of AAT deficiency (Considered for end-stage liver disease)

Which form of lung disease develops typically in people with α1-antitrypsin deficiency?

⇒ **Emphysema**

The diagnosis of AAT deficiency should be considered in all patients with emphysema under the age of 50 years.

Acute respiratory distress syndrome (ARDS)

Definition

- acute respiratory failure characterized by hypoxemia and bilateral pulmonary infiltrates that cannot be explained by heart failure or fluid overload.

Causes

- Sepsis (most common cause)
- Trauma
- Shock
- Massive transfusion (TRALI)
- Acute pancreatitis
- Hematopoietic stem cell transplantation
- Medication (e.g., salicylic acid, tricyclic antidepressants, bleomycin)
- Recreational drug overdose (e.g., cocaine)
- Primary damage to the lungs (Pneumonia, Aspiration, Inhaled toxins)

Pathophysiology

- Tissue damage (pulmonary or extrapulmonary) → release of inflammatory mediators (e.g., interleukin-1) → inflammatory reaction → migration of neutrophils into alveoli → excessive release of neutrophilic mediators (e.g., cytokines, proteases, reactive oxygen species) → injury to alveolar capillaries and endothelial cells (diffuse alveolar damage)

Phases: diffuse alveolar damage lead to:

- Exudative phase:**
 - excess fluid in interstitium and on alveolar surface → pulmonary edema with normal pulmonary capillary wedge pressure (noncardiogenic pulmonary edema)
 - decreased lung compliance and respiratory distress
- Hyaline membrane formation:**
 - exudation of neutrophils and protein-rich fluid into the alveolar space → formation of alveolar hyaline membranes → impaired gas exchange → hypoxemia
 - Hypoxemia → compensation through hyperventilation → respiratory alkalosis
 - Hypoxemia → chronic hypoxic pulmonary vasoconstriction → pulmonary hypertension and right-to-left pulmonary shunt (increased shunt fraction)
 - Damage to type I and type II pneumocytes → decrease in surfactant → alveolar collapse → intrapulmonary shunting
- Organizing phase (late stage):**
 - proliferation of type II pneumocytes and infiltration of fibroblasts → progressive interstitial fibrosis

What would one expect to see on a histological specimen of a lung from a patient who died of ARDS?

☞ The presence of hyaline membranes is a hallmark of ARDS.

Features

- Symptoms: Acute dyspnea. Fever, cough, and chest pain may also be present.
- Signs: Tachypnea, cyanosis, diffuse crackles

What is the most consistent finding you would expect to see on arterial blood gases taken from patients with ARDS?

☞ **increased arterial-alveolar oxygen gradient.**

ARDS is associated with:

- **Increased elastic recoil.**
- **Low pulmonary artery wedge pressure.**
- **Low compliance.**
- **Restrictive lung disease**

Berlin criteria for ARDS

- The Berlin criteria are the criteria most commonly used to define ARDS.
- All four of the following conditions must be met:
 - 1) **Acute onset:** respiratory failure within one week of a known predisposing factor (e.g., sepsis, pneumonia)
 - 2) **Bilateral opacities** (on chest x-ray or CT)
 - Similar appearance to pulmonary oedema
 - Not sufficiently explained by pleural effusions, lobar or lung collapse, or nodules
 - 3) **Hypoxemia:** $\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$ (measured with a minimum of 5 cm H₂O PEEP)
 - Mild ARDS: $\text{PaO}_2/\text{FiO}_2 = 201\text{--}300 \text{ mm Hg}$
 - Moderate ARDS: $\text{PaO}_2/\text{FiO}_2 = 101\text{--}200 \text{ mm Hg}$
 - Severe ARDS: $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$
 - 4) **Respiratory failure cannot be fully accounted for by heart failure or fluid overload.**
 - **Patients with ARDS have normal pulmonary capillary wedge pressure (PCWP) (<18 mmHg).**

Management

- **Admit all patients with ARDS to the ICU.**
- **Oxygenation**
 - ⇒ Noninvasive ventilation: for hemodynamically stable, alert patients with mild ARDS.
 - ⇒ Endotracheal intubation: respiratory failure or rapid deterioration
- **Lung-protective ventilation:** to decrease the risk of ventilator-induced lung injury
 - ⇒ General initial settings include:
 - Low tidal volume ($V_t 6\text{--}8 \text{ mL/kg}$): prevents alveolar distention
 - Low plateau pressure ($P_{Plat} \leq 30 \text{ cm H}_2\text{O}$): prevents barotrauma
 - PEEP > 5 cm H₂O: allows for alveolar recruitment
 - ⇒ PEEP and FiO_2 can be adjusted to recruit collapsed alveoli and improve oxygenation.
 - Oxygenation goal: $\text{PaO}_2 55\text{--}80 \text{ mm Hg}$ or $\text{SpO}_2 88\text{--}95\%$
 - Avoid oxygen toxicity: use lowest FiO_2 possible
- **Identify and treat the underlying cause**

- If the patient is on maximal ventilatory therapy but is still hypoxic & hypercapnic?
 - **Extracorporeal membrane oxygenation (ECMO)** (connecting a patient's circulation to an external oxygenator and pump, via a catheter placed in the right side of the heart).
- **Diuretics** are NOT particularly effective, because the infiltrate of ARDS is primarily inflammatory.
- **Glucocorticoids** have NOT been shown to help patients in the acute phase of ARDS.

Acute respiratory distress syndrome (ARDS) diagnostic criteria:

- Abnormal x-ray,
- Respiratory failure < 1 week after a known or suspected trigger,
- Decreased $\text{PaO}_2/\text{FiO}_2$,
- Should exclude CHF or fluid overload as a potential cause of respiratory distress.

ARDS patient on mechanical ventilation

If the patient's blood gases reflect hypoxaemia and a slight respiratory alkalosis, (despite high FiO_2 settings and sufficient ventilation, his arterial oxygenation remains inadequate). **What is the best next step?**

⇒ **Adding positive end-expiratory pressure (PEEP)**

- The ventilator strategy should employ a relatively high level of PEEP.
- Generally, oxygenation may be improved by further increasing the FiO_2 or by adding PEEP.
- High FiO_2 is contraindicated due to the risk of pulmonary oxygen toxicity. Thus, the goal in managing mechanically ventilated patients should be to keep the FiO_2 below 40% at all times.
- The patient's FiO_2 may need to be reduced soon- if more than 40% - in order to avoid pulmonary oxygen toxicity, but this should be accomplished by first increasing oxygenation by another means, such as by increasing PEEP.
- PEEP prevents alveolar collapse, directly counteracting the means by which ARDS causes hypoxaemia. It may also reopen some alveoli that have already collapsed.

- Which therapies has been shown to most likely decrease overall mortality of ARDS?

⇒ **Implementing a low tidal volume ventilation protocol (6 mL/kg based upon ideal body weight)**

- The target tidal volume is based on ideal, rather than actual body weight. Fat has no alveoli !
- A target tidal volume of 6 ml/kg ideal body weight should be set maintaining plateau pressures of less than 30 cmH₂O

The two main ventilator methods used in the management of ARDS are:

- **High positive end-expiratory pressure (PEEP)**
- **Low tidal volume ventilation (LTVV)**

Altitude related disorders

Response to high altitude

- The arterial partial pressure of oxygen (PaO_2) decreases with altitude, resulting in progressive tissue hypoxia. The normal compensatory response to hypobaric hypoxia is termed acclimatization. Its main feature is increased ventilation.
- ↓atmospheric oxygen (PiO_2) → ↓ PaO_2 → ↑ventilation → ↓ Paco_2 → respiratory alkalosis → altitude sickness (headaches, nausea, fatigue, lightheadedness, sleep disturbance).
- Chronic ↑ in ventilation.
- ↑Erythropoietin → ↑Hct and Hb (due to chronic hypoxia).
- ↑2,3-bisphosphoglycerate (2,3-BPG) (binds to Hb → shifts the oxygen-hemoglobin dissociation curve to the right → ↑O₂ release).
- Cellular changes (↑mitochondria).
- ↑Renal excretion of HCO₃⁻ to compensate for respiratory alkalosis (can augment with acetazolamide).
- Chronic hypoxic pulmonary vasoconstriction → ↑pulmonary vascular resistance → pulmonary hypertension, RVH.

Types

- There are three main types of altitude related disorders:
 1. **acute mountain sickness (AMS)**, which may progress to
 2. **high altitude pulmonary edema (HAPE)** or
 3. **high altitude cerebral edema (HACE)**.
- All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes

Acute mountain sickness (AMS)

- AMS start to occur above 2,500 - 3,000m, developing gradually over 6-12 hours and potentially last a number of days.
- **Features**
 - ⇒ Headache
 - ⇒ Nausea
 - ⇒ Fatigue
- **Treatment**
 - ⇒ descent
 - ⇒ generally a self-limiting condition. usually resolves by day 3 with rest and gradual acclimatization to the high altitude.
- **Prevention**
 - ⇒ gain altitude at no more than 500 m per day
 - ⇒ acetazolamide (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base

High altitude cerebral oedema (HACE)

- Generally occur above 4,000m
- HACE presents with headache, ataxia, papilloedema
- **Management**
 - ⇒ descent
 - ⇒ dexamethasone

High altitude pulmonary oedema (HAPE)

- Generally occur above 4,000m
- **Presents with classical pulmonary oedema features**
- **Management** (after descent)
 - ⇒ **1st line → High concentration O₂**
 - ⇒ **2nd line → Nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors**
 - All seem to work by reducing systolic pulmonary artery pressure

Acetazolamide

- Carbonic anhydrase inhibitor
- Causes HCO₃⁻ wasting (prevents HCO₃⁻ reabsorption in the proximal tubule) metabolic acidosis, and subsequent diuresis.
- Metabolic acidosis → hyperventilation (physiological response) → ↑ oxygenation → prevent altitude sickness

Bronchiectasis

Bronchiectasis should be suspected in a patient with chronic cough producing large amounts of sputum

Definition

- Permanent dilatation of the airways secondary to chronic infection or inflammation.

Causes

- Post-infective: (i.e., bacterial, viral, fungal)
 - ⇒ tuberculosis, measles, pertussis, pneumonia
 - ⇒ **A history of previous whooping cough suggests bronchiectasis.**
- Disorders of secretion clearance, mucous plugging or bronchial obstruction
 - ⇒ Cystic fibrosis (CF)
 - ⇒ Primary ciliary dyskinesia (PCD)
 - ⇒ **Allergic bronchopulmonary aspergillosis (ABPA)**
 - ⇒ Kartagener syndrome
 - ⇒ α1-antitrypsin deficiency
 - ⇒ Smoking; associated with poor ciliary motility
 - ⇒ Lung cancer/foreign body
- Immunodeficiency (e.g., common variable immunodeficiency, hypogammaglobulinemia, HIV)
- Chronic inflammatory diseases (e.g., rheumatoid arthritis, Sjogren syndrome, Crohn disease)
- Yellow nail syndrome

Features

The most common findings on examination are crackles (75%) and wheeze (22%). Clubbing is only found in 2%.

- Chronic productive cough, with **copious amounts of sputum** (expectorating phlegm on most days)

- Dyspnea
- frequent chest infections
- haemoptysis
- Post nasal drip - common (chronic sinusitis in around 30%)
- Tiredness - many patients find this more troublesome than the productive cough
- Low Ventilation perfusion ratio leading to hypercapnia → Respiratory acidosis, and the body compensate by increasing heart rate and vasodilatation.

Diagnosis

- Chest X-ray
 - ⇒ The best **initial** test
 - ⇒ can be normal in 50% of patients (**Bronchiectasis cannot be ruled out with a chest x-ray**)
 - ⇒ Findings:
 - thickened and dilated bronchi, which produce **tramline opacities** and **ring shadows** "**tram track**" lines due to Inflammation and fibrosis of bronchial walls
 - Retained mucus might be seen as tubular opacities,
 - volume loss of the affected lobe.
 - Thin-walled cysts (i.e., dilated bronchi forming sacs), possibly with air-fluid levels
 - Late-stage bronchiectasis: honeycombing
- High-resolution computed tomography scan of the lungs (HRCT)
 - ⇒ **The gold standard** for diagnosis of bronchiectasis.
 - ⇒ Findings
 - **'tram track lines and honeycombing'**
 - **'signet ring' sign**
 - ❖ increased broncho-arterial ratio (bronchus larger than neighboring pulmonary artery). The bronchus and artery should be the same size, whereas **in bronchiectasis, the bronchus is markedly dilated.**

Differential diagnosis

- Carcinoma of the lung:
 - ⇒ Lung cancer can present with non-resolving respiratory infection with productive cough due to endobronchial obstruction by tumour, **but there would be a much shorter duration of symptoms**. Without treatment **most patients would be dead within a year** of the onset of lung cancer.



Chest x-ray showing tramlines, most prominent in the left lower zone



CT chest showing widespread tram-track and signet ring sign

Subtypes of Bronchiectasis

- **Cylindrical** bronchiectasis
 - ⇒ bronchi have a uniform calibre, do not taper and have parallel walls (tram track sign and signet ring sign)
 - ⇒ **commonest form** (47%)
- varicose bronchiectasis
 - ⇒ relatively uncommon (9.9%)
 - ⇒ beaded appearances where dilated bronchi have interspersed sites of relative narrowing
- cystic bronchiectasis (45.1%)
 - ⇒ severe form with cyst-like bronchi that extend to the pleural surface
 - ⇒ air-fluid levels are commonly present
- multiple types: ~ 24.3%

Management

Symptom control in non-CF bronchiectasis → inspiratory muscle training + postural drainage

The mainstay of therapy for bronchiectasis is antibiotics and chest physiotherapy.

After assessing for treatable causes (e.g. immune deficiency) management is as follows:

- physical training (e.g. inspiratory muscle training) - has a good evidence base for patients with non-cystic fibrosis bronchiectasis
- postural drainage
- antibiotics for exacerbations + long-term rotating antibiotics in severe cases
- bronchodilators in selected cases
- Immunisations: Influenza and pneumococcal vaccinations are strongly recommended.
- surgery in selected cases (e.g. Localised disease that fails to resolve after I.V antibiotic)

Most common organisms isolated from patients with bronchiectasis

Bronchiectasis: most common organism → *Haemophilus influenzae*

- *Haemophilus influenzae* (most common)
- *Pseudomonas aeruginosa*
- Klebsiella spp.
- *Streptococcus pneumoniae*

Prevention

- Primary prevention:
⇒ antibiotic control of bronchial and pulmonary infections in predisposed individuals
- Secondary prevention:
⇒ long-term low-dose macrolide treatment (e.g., azithromycin) in patients with two or more bronchiectasis exacerbations within one year.

Cystic fibrosis (CF)

Genetics

- Autosomal recessive; defect in *CFTR gene* on chromosome 7; commonly a deletion of Phe508.
- The defective gene inhibits the body's ability to move salt and water in and out of cells → Deranged chloride transport → thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract.

Children whose parents are both heterozygous carriers of cystic fibrosis have a 25% chance of being affected by the condition.

Epidemiology

- Occurs in 1 in 2500 live births.
- The carrier frequency in white populations is 1 in 25.
- the most common genetically inherited diseases in Caucasian individuals.
- Rare in patients of Afro-Caribbean and Asian origin.
- 10% of people with cystic fibrosis are not diagnosed until adult life.

Features

- Failure to thrive and delayed puberty (100%)
- Infertility
 - ⇒ Male infertility occurs in 98% due to failure of development of the vas deferens (congenital bilateral absence of the vas deferens (CBVAD); therefore, the anatomic duct through which spermatozoa pass from the testes to the urethra is absent, resulting in obstructive azoospermia)
 - ⇒ Patients may have CBVAD and cystic fibrosis transmembrane conductance regulator gene (CFTR) mutation without symptoms of CF.
 - ⇒ Female subfertility secondary to viscous cervical secretions. (only a 20% will be infertile)

- **Pancreatic insufficiency**
 - ⇒ **The most common (85%) almost always present in adult patients**
 - ⇒ Due to obstruction of the pancreatic ductules by thickened secretions.
 - ⇒ Diabetes mellitus: occurs in > 65% of patients by age 25
 - treatment of choice is subcutaneous insulin. Calorie intake should not be restricted in CF patients, who are prone to malnutrition due to their pancreatic insufficiency.
 - ⇒ Malabsorption (30%): steatorrhoea
 - ⇒ Fat-soluble vitamin deficiencies (including vitamins A, D, E and K)
- **Respiratory**
 - ⇒ Recurrent chest infections (40%)
 - **Clues to a diagnosis of cystic fibrosis rather than an alternative immunodeficiency would be manifestations in other organ systems (pancreatic disease or infertility).**
 - ⇒ **Allergic bronchopulmonary aspergillosis (ABPA) is a recognised complication, occurring in 15% of adult CF patients**
 - ⇒ Pneumothorax is seen in up to 5% of patients over 10 years of age and approximately 50% recur.
- **Liver disease**
 - ⇒ By young adulthood, CF-associated liver disease develops in 30 % of those affected.
 - ⇒ **Cholestasis due to defective CFTR protein on bile duct epithelial cells**
- **Nasal polyps**
 - ⇒ While nasal polyps occur in adults secondary to recurrent episodes of rhinitis, **nasal polyps in children should always raise the suspicion for cystic fibrosis.**
- **Gastro-intestinal**
 - ⇒ **Distal intestinal obstruction syndrome :**
 - **most common bowel complication** in cystic fibrosis after **Gastroesophageal reflux disease (GERD)**
 - Occurs in 10-20% of patients with cystic fibrosis and incidence increases with age. About 80% of cases present for the first time in adults.
 - ⇒ Rectal prolapse (in children) due to bulky stools
 - ⇒ Constipation is common
- **Renal**
 - ⇒ Urinary stress incontinence
 - ⇒ Renal calculi (incidence increases with age and 1 in 20 adults are affected).

Distal intestinal obstruction syndrome is the most common bowel complication in cystic fibrosis after Gastroesophageal reflux disease (GERD)

Diagnosis

- **Sweat chloride test**
 - ⇒ The most important diagnostic test
 - ⇒ Sweat chloride **>60 mmol/L** is abnormal. The patient should undergo **CFTR gene mutation testing to confirm the diagnosis** (false negative in 1-2% of patients).
 - ⇒ Sweat chloride **≤29 mmol/L** is normal. **This is sufficient to rule out CF.**

- ⇒ Sweat chloride 30 to 59 mmol/L is intermediate. These patients should have repeat sweat chloride testing and *CFTR* sequencing.
- ⇒ sweat test is conducted using **pilocarpine iontophoresis.(a direct acting muscarinic agonist)**
- ⇒ **Causes of false negative sweat test**
 - nephrotic syndromes.
- ⇒ **Causes of false positive sweat test**
 - malnutrition
 - adrenal insufficiency
 - glycogen storage diseases
 - nephrogenic diabetes insipidus
 - hypothyroidism, hypoparathyroidism
 - G6PD
 - ectodermal dysplasia
- **Genetic test (DNA analysis) → CFTR gene mutation → confirm the diagnosis**
 - ⇒ Should be performed for patients with intermediate or positive sweat chloride results.

Management

Management of pulmonary disease

- **Airway clearance techniques**
 - ⇒ Chest physiotherapy and postural drainage, regular (at least twice daily)
 - ⇒ An airway clearance session generally begins with SABA therapy to open the airways, followed by mucolytics to thin the mucus, then airway clearance techniques.
 - ⇒ high-frequency chest wall oscillation is not recommended by NICE.
- **Mucoactive agents**
 - ⇒ 1st line: rhDNase (dornase alfa; recombinant human deoxyribonuclease)
 - ⇒ 2nd line: rhDNase and hypertonic sodium chloride or hypertonic sodium chloride alone.
 - ⇒ 3rd line: mannitol dry powder for inhalation
- **Anti-inflammatory agents (e.g., macrolide antibiotics, ibuprofen, corticosteroids) are used to control inflammation in the airway**
- **Lumacaftor-Ivacaftor Combination**
 - ⇒ Used by NHS but not recommended by NICE
 - ⇒ specifically targets the most common *CFTR* mutation, the ΔF508 mutation.
 - ⇒ Ivacaftor potentiates the opening of the *CFTR* chloride ion transport channel,
 - ⇒ Lumacaftor improves the conformational stability of ΔF508-*CFTR*, resulting in increased processing and trafficking of mature protein to the cell surface.

Lung transplant

- **Indications**
 - ⇒ Evidence of pulmonary hypertension
 - ⇒ **FEV1 <50% predicted and rapidly declining (eg, >20% relative decline in FEV1 within 12 months)**
 - ⇒ **FEV1 <40% predicted and BMI <18 (while working to improve nutritional status)**
 - ⇒ **FEV1 <40% predicted and any of the following markers of shortened survival:**
 - >2 exacerbations per year requiring intravenous antibiotics

- Massive hemoptysis (>240 mL) requiring intensive care unit admission or bronchial artery embolization.
- Pneumothorax
- ⇒ **FEV₁ <30% predicted**
- ⇒ **Any of the following, regardless of FEV₁:**
 - 6-minute walk test <400 meters
 - Hypoxemia (SpO₂ <88% or PaO₂ <55 mmHg, at rest or with exertion)
 - Hypercarbia (PaCO₂ >50 mmHg, confirmed on arterial blood gas)
 - Pulmonary artery systolic pressure >50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of tricuspid regurgitant jet
 - Any exacerbation requiring positive pressure ventilation
- **Factors that warrant earlier consideration for transplant referral**
 - ⇒ Female sex, especially those who are younger
 - ⇒ Short stature (height <162 cm)
 - ⇒ Liver cirrhosis or chronic kidney disease (may require consideration of multiple organ transplantation and may affect timing or choice of transplant center)
- **Absolute contraindications include**
 - ⇒ Sepsis
 - ⇒ multiple organ dysfunction,
 - ⇒ documented history of non-adherence to treatment,
 - ⇒ patients colonised with *Burkholderia cepacia*
 - ⇒ class III obesity (body mass index [BMI] 40 or above), and
 - ⇒ refractory gastro-oesophageal reflux.
- **Recipient criteria**
 - ⇒ Age under 60 years
 - ⇒ Life expectancy of less than 18 months
 - ⇒ No underlying cancer or serious systemic disease
- **Donor characteristics**
 - ⇒ The donor should have been under the age of 40.
 - ⇒ The chest of the donor should be slightly smaller than that of the recipient.
 - ⇒ A double lung transplant is usually performed because of the risk of chronic infection in the remaining lung.

Management of extra-pulmonary disease

- **Nutritional interventions**
 - ⇒ **High calorie** diet, including **high fat** intake
 - ⇒ CF → Weight loss → ↑ risk of exacerbations & overall mortality. For that it's important to maintain a high calorie diet
 - ⇒ **the best way to manage diabetes in CF is insulin and high calorie diet** to allow them to convert those calories into stored energy.
 - ⇒ Vitamin supplementation
- **For malabsorption**
 - ⇒ First test for exocrine pancreatic insufficiency → **stool elastase** (if abnormal) → pancreatic enzyme replacement.
 - ⇒ If symptoms persist → acid suppression agent (H₂ receptor antagonist or a proton pump inhibitor)
- **For distal intestinal obstruction syndrome**
 - ⇒ **1st line:** diatrizoate meglumine and diatrizoate sodium solution (**Gastrograffin**) (orally or via an enteral tube)

- ⇒ **2nd line:** iso-osmotic polyethylene glycol and electrolyte (PEG) solution (macrogols) (orally or via an enteral tube)
- ⇒ **3rd line:** surgery
- ⇒ Prevention by : encourage drink plenty of fluids & pancreatic enzyme replacement therapy & regular stool-softening agent such as lactulose.
- **Liver disease**
 - ⇒ If liver function tests are abnormal → ursodeoxycholic acid

Chest infections in cystic fibrosis

- **Organisms**
 - ⇒ Infants and young children become colonised by *Staphylococcus aureus* and then *Haemophilus influenzae*.
 - ⇒ **Pseudomonas aeruginosa is the commonest colonising organism in patients with cystic fibrosis** after the age of 10 years.(40 – 80%)
 - ⇒ ***Aspergillus* colonisation is also common** 19%.
 - ⇒ **Burkholderia cepacia**
 - Gram-negative, aerobic, rod bacteria.
 - Occurs in 5–10% of patients.
 - Often multi drug resistant.
 - **Associated with the worst prognosis**
 - Infection is a relative contraindication to undergoing lung transplant due to its association with poor outcomes.

In cystic fibrosis, *Staphylococcus aureus* infections are more common in childhood while *Pseudomonas* infections become more common in late adolescence and adulthood.

- **Antibiotics**
 - ⇒ **Acute exacerbations**
 - **Combination** of piperacillin-tazobactam, ceftazidime, meropenem **plus** one of the following: a fluoroquinolone, tobramycin, amikacin, or colistin.
 - ⇒ **Chronic *Pseudomonas aeruginosa* infection**
 - **the commonest colonising organism in patients with CF** after the age of 10 years.
 - Azithromycin at the time of the first positive culture
 - test for nontuberculous mycobacteria before initiating azithromycin. Azithromycin should not be given to patients infected with nontuberculous mycobacteria, because it may induce antibiotic resistance.
 - chronic azithromycin may reduce the efficacy of inhaled or intravenous tobramycin.
 - 1st line → nebulised colistimethate sodium
 - 2nd line → nebulised aztreonam, or nebulised **tobramycin**

Tobramycin

- Aminoglycoside antibiotic
- Works by binding to a site on the bacterial 30S and 50S ribosome, preventing formation of the 70S complex. As a result, mRNA cannot be translated into protein → cell death
- Side effects:
 - ⇒ Nephrotoxicity
 - ⇒ ototoxicity (generally irreversible).

Prognosis

- The median survival is now predicted to be at least 40 years for children born in the 1990s.

Occupational lung diseases

- Occupational asthma
- Extrinsic allergic alveolitis (EAA)
- Pneumoconiosis
- Asbestos and the lung
- Pleural mesothelioma
- Silicosis
- Berylliosis
- Coal workers' pneumoconiosis (CWP)

Occupational asthma

Isocyanates are the most common cause of occupational asthma

Serial peak flow measurements at work and at home are used to detect occupational asthma

Overview

- Occupational asthma is a variable airflow obstruction attributable to a particular occupational exposure and not due to stimuli outside the workplace.
- Should be suspected and evaluated in every patient with adult-onset asthma. 5 to 25 % of all adult-onset asthma cases are occupationally related.
- **Occurs more frequently in atopic persons** and smokers.

Causes

- Exposure to the following chemicals are associated with occupational asthma:
 - ⇒ **Isocyanates - the most common cause.** (e.g. occupations include spray painting and foam moulding)
 - ⇒ Metals (**Platinum salts**, Aluminium, Chrome, Manganese, Nickel, Zinc)
 - ⇒ Disinfectant and preservatives (glutaraldehyde, chlorhexidine , formaldehyde)
 - ⇒ Flour
 - ⇒ Proteolytic enzymes

Diagnosis

- Confirmation of asthma
 - ⇒ Spirometry before and after bronchodilator → reversibility of airflow limitation.
- Determine occupational relationship
 - ⇒ Symptoms **become better at weekends / when away from work.**
 - ⇒ **Serial PEFR measurement at work and at home is a useful diagnostic test to assess a workplace contribution**
 - ⇒ Skin test reactivity or immunoassay for specific immunoglobulin E (IgE) can identify sensitization to known occupational sensitizers.

Management

- Reduction of further exposure to the allergen.
 - ⇒ Change the Job if possible
 - ⇒ **Changing the pattern of the particular duties.**
 - ⇒ An alternative is to use **industrial respirators**, which filter out 98-99% of respirable dust from the ambient air.
- Corticosteroid

Occupational asthma should be suspected in all adult patients with asthma.

Hypersensitivity pneumonitis (HP) (also called extrinsic allergic alveolitis)

Saccharopolyspora rectivirgula causes farmer's lung, a type of EAA

Aspergillus clavatus causes malt workers' lung, a type of EAA

Definition

- an immunologic reaction occurring within the pulmonary parenchyma caused by hypersensitivity to an inhaled agent, such as microbial, avian, animal antigens and, less commonly, organic compounds.

Pathophysiology

- Acute HP** is predominantly mediated by antigen-antibody complex formation (**type III hypersensitivity**)
- Subacute and chronic HP** result from an interplay of T helper (Th 1), T17, and T regulatory lymphocytes leading to **lymphocyte infiltration and granuloma formation (delayed hypersensitivity) (type IV)**.
- Despite its name, EAA is not allergic and therefore features associated with allergy and type I reactions do not tend to occur in EAA (ie wheeze, immediate symptoms, raised IgE, positive skin-prick test, eosinophilia of blood or sputum).
- characterised **histologically** by:
 - ⇒ **Alveolar destruction and interstitial inflammation.**
 - ⇒ **Non-caseating granulomas**
 - ⇒ **Asteroid bodies** may be found in or adjacent to the granulomas.

Examples

- Farmer's lung:**
 - ⇒ Caused by spores of *Saccharopolyspora rectivirgula* (formerly *Micropolyspora faeni*)
 - ⇒ **The commonest occupational hypersensitivity pneumonitis**
 - ⇒ **Contaminated hay is the most common source of *Saccharopolyspora rectivirgula***
 - ⇒ **Serum precipitating antibodies to *Saccharopolyspora rectivirgula* is the most useful diagnostic test** (found in 75-100% of cases during an acute episode).

Disease	Antigen Source
Farmer's lung (The commonest occupational hypersensitivity pneumonitis)	spores of <i>Saccharopolyspora rectivirgula</i> (commonly from Contaminated hay)
Bird fanciers' lung	avian proteins
Malt workers' lung	<i>Aspergillus clavatus</i>
Mushroom workers' lung	thermophilic actinomycetes
Maple bark stripper's lung	<i>Cryptostroma corticale</i>
Cheese washer's lung	<i>Penicillium casei</i>

Features

- **Acute:** occur 4-8 hrs after exposure, SOB, dry cough, fever. Symptoms subside after 12 hours to several days (in the absence of additional exposure)
- **Chronic** (months after continuous exposure) : exertional shortness of breath and pulmonary fibrosis (**typically upper-lobe**).

A recurrent common cold with an irritating cough and fever may indicate hypersensitivity pneumonitis.

Investigation

- Chest x-ray
 - ⇒ Upper/mid-zone fibrosis.
 - ⇒ Nodular shadowing or ground glass appearances.
 - ⇒ Classically show diffuse air-space consolidation
- Pulmonary function test: restrictive pattern
- Bronchoalveolar lavage (BAL) → lymphocytic predominance
- **Blood cell count** → **NO eosinophilia**
- **Serology** → **Circulating IgG precipitins**
 - ⇒ Demonstration of precipitating antibodies (precipitins) in the patient's serum to the causal antigen.
 - ⇒ Have a high false negative rate (positive results can be seen in exposed, but asymptomatic individuals). Positive serum avian precipitins are not diagnostic of HP, and only suggest the patient has had exposure to birds.
- Histopathology: Noncaseating granulomas with lymphocytes and polynuclear giant cells

Treatment

- Removal of exposure to the antigen (change of job plan)
 - ⇒ The optimal management
 - ⇒ Symptoms may settle within 12 hours of removal of the antigen.
- Prednisolone

MRCPI-part-1-january-2016: A 65-year-old **farmer** presents with **SOB** and **wheeze** progressively worsening over the past 6 months. He is a **smoker**, and **has two daughters with asthma**. There was obvious wheeze and coarse end-inspiratory crackles on examination of the chest. A chest X-ray shows diffuse non-specific changes consistent with lung disease.

Which would be the next most appropriate investigation?

- ⇒ **Spirometry and reversibility**
- This man either has asthma, chronic obstructive pulmonary disease or farmer's lung
 - Spirometry and reversibility would be the investigation of choice.
 - ❖ A **restrictive defect** would support a diagnosis of **farmer's lung**;
 - ❖ an **obstructive defect with reversibility** would support a diagnosis of **asthma**,
 - ❖ **respiratory obstruction without reversibility** would support a diagnosis of **COPD**.

Pneumoconiosis

Definition

- A group of chronic lung diseases caused by exposure to a mineral dust or a metal.

Types

- Asbestosis
- Silicosis
- Coal workers' pneumoconiosis (black lung disease), and
- chronic beryllium disease.

Risk factor

- In **silicosis** and **coal workers'** pneumoconiosis, exposure should be (at least 10 and usually 20 or more years prior to radiographic changes) (the **cumulative dose** inhaled).
- **Beryllium** is immunologically mediated with a **strong genetic component**, so that the typical dose response demonstrated with the other pneumoconioses is not seen (NO need for cumulative dose)

Features

- Asymptomatic in early stages
- Dyspnoea on exertional dyspnoea , dry cough

Diagnosis

- Chest x-ray
 - ⇒ The presence of non-calcified, multiple (in the hundreds), **rounded opacities** in the **upper zones** is highly suggestive of **silicosis** or **coal workers'** pneumoconiosis.
 - ⇒ **Asbestosis** typically causes **lower lobe fibrosis**.
- **High-resolution CT (HRCT) scan chest**
 - ⇒ more sensitive than CXR in identifying interstitial fibrosis.
- Individuals with silicosis should be tested for TB.

Treatment

- Smoking cessation + removal of occupational exposure
- Patients with respiratory failure → referral for lung transplant
 - ⇒ Absolute contraindications include:
 - Associated other incurable advanced disease
 - Addictions including tobacco,
 - Lack of social support
 - Documented non-adherence to medical therapy.

Exposure to isocyanates most likely associated with squamous-cell carcinoma of the bronchus.

Hard metal lung disease (Cobalt exposure)

- A worker in the hard metal industry, comes with progressive dyspnea. Chest X-ray shows diffuse interstitial fibrosis bilaterally. **what is the typical cellular component found in a bronchoalveolar lavage (BAL) of this patient?**
 - ⇒ **Giant cells**
 - ⇒ Persons working in the **hard metal industry** are prone to develop a condition called hard metal lung disease.
 - ⇒ The pathological diagnosis is giant cell interstitial pneumonia (GIP).

Asbestos and the lung

The most common malignancy associated with asbestosis is bronchogenic carcinoma, not mesothelioma

Risk of asbestos exposure

- Ship building,
- car manufacture,
- boiler making and
- plumbing industries

Asbestos can cause a variety of lung disease from benign pleural plaques to mesothelioma.

Pleural plaques

- The most common form of asbestos related lung disease
- occur after a latent period of 20-40 years.
- rarely cause symptoms
- benign and do not undergo malignant change.
- CXR may shows calcification on both hemidiaphragms which are most likely to be pleural plaques from previous asbestos exposure.
- Do not require long term follow up

Asbestosis (asbestos-related pulmonary fibrosis)

- Diffuse interstitial fibrosis secondary to asbestos inhalation
- Slowly progressive, the latent period is typically 15-30 years.
- The severity of asbestosis is related to the length of exposure. This is in contrast to mesothelioma where even very limited exposure can cause disease.
- Typically causes lower lobe fibrosis.
- Pleural effusions and supradiaphragmatic pleural plaques are common findings on x-ray in patients with asbestosis.
- Biopsy is not mandatory as the diagnosis can be made on clinical and radiological grounds.
- On microscopic examination, asbestosis is marked by interstitial fibrosis with the presence of characteristic asbestos bodies and ferruginous bodies.
- Resistant to treatment with immunosuppressive therapy.
- The risk of lung cancer is raised more than 50-fold in smokers with asbestos.

Pleural mesothelioma

Definition

- Malignant tumor of mesothelial cells of pleura

Epidemiology

- More common in male than female (3:1)

Risk factors

- Asbestos (20- to 40-year after exposure)
- Smoking, alcohol, and diet do not increase the risk.

- Loss of material from chromosome 22 is commonly seen in mesothelioma cell lines

Features

- History of asbestos exposure in 85-90%, latent period of 20-40 years
- Dyspnoea, weight loss, chest wall pain
- pleural effusion

Diagnosis

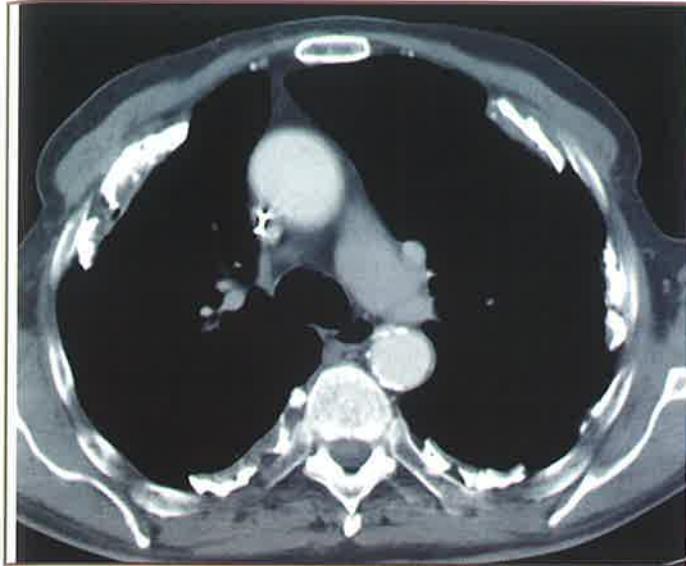
- Chest x-ray showing either a pleural effusion or pleural thickening
- CT chest with contrast → the best next step after chest x-ray
 - ⇒ Multiple nodular pleural lesions (pleural thickening)
- Pleurocentesis (If a pleural effusion is present) for biochemistry and cytology
 - ⇒ exudative and hemorrhagic pleural fluid.
 - ⇒ cytology is only helpful in 20-30% of cases
 - ⇒ don't rely on cytology alone to confirm the diagnosis
- Thoracoscopy biopsy
 - ⇒ the most important investigation to confirm the diagnosis.
 - ⇒ used to investigate cytology negative exudative effusions as it has a high diagnostic yield (around 95%).
 - ⇒ Psammoma bodies are seen on histology
- Positron emission tomography (PET) with CT (PET-CT) as the initial staging after histopathological confirmation of the diagnosis.

Management

- Radiation, with or without chemotherapy
- Surgery (pleurectomy or pneumonectomy) in severe cases if operable

Prognosis

- Poor. The median survival after diagnosis is 1- 2 years
- Bronchogenic carcinoma is the most common malignant pulmonary tumor in patients with asbestos
 - ⇒ Bronchogenic carcinoma is more common than mesothelioma
 - ⇒ The lack of smoking history along with previous asbestos exposure and signs of a pleural effusion make malignant mesothelioma more likely than bronchial carcinoma.



This patient has mesothelioma. The calcification of the pleura is a hallmark of asbestos exposure.



CT scan showing mesothelioma

- There is a large rind of soft tissue related to the left chest wall.
- This is a malignant process as there is destruction of the associated rib.

Silicosis

Overview

- a pneumoconiosis that results from the inhalation of silica dust.
- **Affects upper lobes**
- Increases susceptibility to tuberculosis.
- **Risky jobs**
 - ⇒ Silicosis can affect anyone involved in quarrying (المحاجر), carving, mining, tunneling (حفر الانفاق), grinding (طحن) or sand-blasting (نسف), if the dust generated contains quartz.
 - ⇒ manufacture of toilet bowls, sinks (مغاسل), and ceramics;
 - ⇒ hydraulic fracking while drilling for gas and oil.

Pathophysiology

- Macrophages activated by silica (quartz) → release fibrogenic cytokines → causes inflammation and scarring in the form of nodular lesions in the upper lobes of the lungs.

Classifications

- **Acute silicosis**
 - ⇒ **The most severe form**
 - ⇒ develops a few weeks to 5 years after exposure due to very heavy exposure.
 - ⇒ Chest X-ray shows appearances resembling pulmonary oedema.
 - ⇒ Treatment 1st line → **whole lung lavage**.
- **Accelerated silicosis**
 - ⇒ Develops 5–10 years after first exposure due to less heavy exposure
- **Simple nodular silicosis**
 - ⇒ **the most common type**
 - ⇒ resulting from long-term exposure (10 -30 years) to relatively low concentrations of silica dust
 - ⇒ radiographic nodular changes similar to coal-worker's pneumoconiosis ,

Differential diagnosis

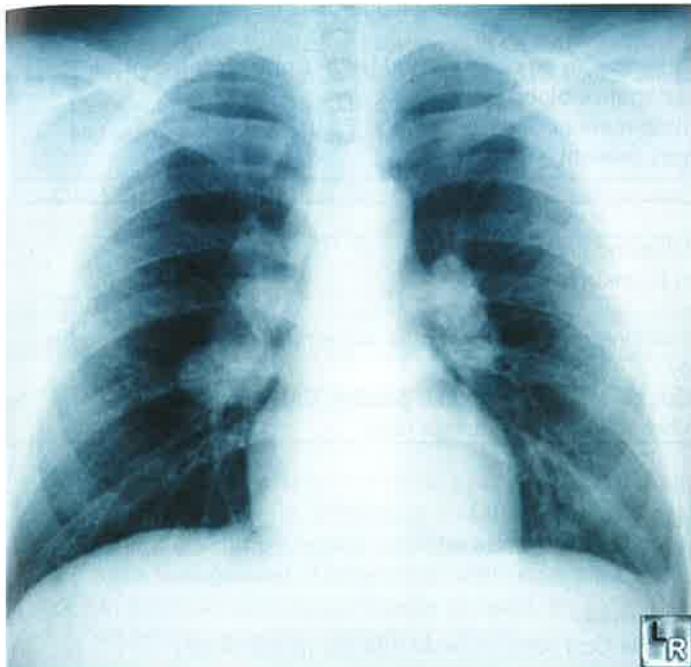
- **Simple nodular silicosis differs from coal-worker's pneumoconiosis in that :**
 - ⇒ the lesions tend to be larger (3-5 mm)
 - ⇒ and it is progressive even after dust exposure ceases

Diagnosis

- **'Egg-shell' calcification of the hilar lymph nodes is pathognomonic for silicosis;**
- Pulmonary function test → usually reveal mixed obstructive / restrictive picture
- biopsy shows silica particles (birefringent) surrounded by collagen

Complications

- ↑ **susceptibility to TB (silica is toxic to macrophages)**
- ↑ incidence of primary **lung cancer**
- ↑ risk of connective-tissue disease, vasculitides, (COPD), and chronic renal failure.



The chest radiograph shows "**eggshell**" **calcification** of the hilar lymph nodes, as seen with **silicosis**.

Berylliosis

Overview

- Jobs at risk: aerospace or nuclear industry workers, manufacture of electronics, manufacture of heat-resistant ceramics, dental prostheses, and metal products
- **Characterized by the presence of noncaseating granulomas in the lungs**, nodular infiltrates, and enlarged lymph nodes (resembles sarcoidosis)
- The presence of glutamic acid at position 69 of the HLA-DP1 beta chain is strongly associated with chronic beryllium disease.

Diagnosis

- **Chest radiograph** shows hilar adenopathy or reticular and nodular lung opacities.
 - ⇒ Chest x-ray → **linear opacities**.
 - ⇒ silicosis and coal workers' → rounded opacities
- **Blood beryllium lymphocyte proliferation test (BeLPT)**
 - ⇒ **the initial diagnostic test of choice** for patients with clinical or radiographic evidence of lung disease
- **Beryllium lymphocyte proliferation test (BeLPT)**
 - ⇒ Sensitive test that identifies individuals sensitised to beryllium.
 - ⇒ Bronchoscopic lavage fluid may be positive when the blood test is negative.
 - ⇒ The occurrence of a **positive BeLPT without granulomas on histology** is an indication of **sensitisation to beryllium and absence of chronic beryllium disease**.

- **Fiberoptic bronchoscopy** with bronchoalveolar lavage (BAL), endobronchial biopsy, and transbronchial biopsy.
 - ⇒ **the next test** for patients with a positive blood BeLPT or a strong clinical suspicion despite a negative blood BeLPT
 - ⇒ To obtain an adequate number of cells for BeLPT
 - ⇒ biopsy → granulomas present

Diagnosis of berylliosis

- requires all three of the following findings:
 - 1) history of beryllium exposure,
 - 2) positive BeLPT,
 - 3) presence of noncaseating granulomas and/or mononuclear cell infiltrates on lung histopathology.
- A clinical diagnosis can also be made based on a positive BAL BeLPT and **lymphocytosis (>20 %)** in bronchoalveolar lavage fluid.

Complications

- ↑ risk for primary lung cancer

Treatment

- cessation of exposure to beryllium
- Acute and chronic berylliosis → Oral corticosteroid therapy (prednisone)

Coal workers' pneumoconiosis (CWP)

Pathology

- CWP results from inhalation and deposition of coal dust particles.
- prolonged exposure to coal leads to pulmonary macrophages becoming filled with carbon, known as carbon-laden macrophages ("dust cells")
- Affects **upper lobes** (high ventilation)

Types

- **Simple CWP**
 - ⇒ like smoking, can produce centrilobular emphysema
 - ⇒ Fine nodular opacifications (< 1 cm) in upper lung zone
 - ⇒ often asymptomatic and the diagnosis is an incidental finding on CXR.
- **Complicated CWP (Progressive massive fibrosis)**
 - ⇒ **Exposure to dust of high silicon content**
 - ⇒ Fine nodular opacifications 1-2 cm with progressive massive fibrosis
 - ⇒ **Chest x ray:** round masses, several centimetres in diameter (> 1 cm), sometimes up to 10 cm. may have necrotic centres.
 - ⇒ Chest CT: Mass-like areas of lung opacification associated with radiating strands are seen; the "sausage-shaped" mass is characteristic.
 - ⇒ Mixed obstructive and restrictive lung

Diagnosis

- Chest x-ray → small interstitial nodules in the upper and mid zones of the lung.

The presence of carbon-laden macrophages is the histologic hallmark of coal workers' pneumoconiosis.

Complications

- ↑ risk of connective-tissue disease and COPD
- ↑ Risk of Caplan syndrome (coal worker's pneumoconiosis that occurs with joint manifestations of rheumatoid arthritis.)
- NO association with lung cancer or TB

Coughing up of black sputum (melanoptysis) is pathognomonic of coal workers pneumoconiosis.

Although coal is mined from under the earth, the upper lobes of the lungs are primarily affected.

Caplan's syndrome

- Coal workers pneumoconiosis associated with rheumatoid arthritis
- Typically bilateral, peripheral nodules 5 mm to 5 cm in size
- peripheral lung nodules with the histopathology of rheumatoid nodules develop on a background of pneumoconiotic opacities.
- In contrast to pneumoconiotic masses, they can develop rapidly, over a period of weeks, and may cavitate or calcify.

Primary ciliary dyskinesia (PCD)

Definition

- A rare **autosomal recessive** disorder characterized by absent or dysmotile cilia caused by a defect in the **dynein** arm of microtubules resulting in abnormal ciliary motion and impaired mucociliary clearance throughout the body.

Features

- Recurrent or persistent respiratory infections (which may lead to bronchiectasis)
- Recurrent Sinusitis, and Otitis media
- Conductive hearing loss
- Male infertility (due to decreased sperm motility as a result of defective flagella)
- Reduced fertility in women and ↑ risk of ectopic pregnancy due to defective movement of the cilia in the fallopian tube
- In 50% of the patients, PCD is associated with situs inversus (**Kartagener's syndrome**): triad of situs inversus, recurrent sinusitis, and bronchiectasis

Differential diagnoses

- **cystic fibrosis**
 - ⇒ The diagnosis of CF is based on typical pulmonary and/or gastrointestinal tract manifestations and positive results on sweat test (pilocarpine iontophoresis).
 - ⇒ A negative sweat test is sufficient evidence to exclude CF.

Diagnosis

- Nasal nitric oxide (NNO) levels
 - ⇒ **the most sensitive and specific screening test for PCD**
 - ⇒ Sensitivity of 97% and specificity of 90% for PCD.
 - ⇒ A low NNO (<100 parts per billion) should be followed up with confirmatory testing (**nasal or bronchial brush biopsy** for ciliary examination) because other conditions such as cystic fibrosis may present with low NNO.
 - ⇒ A high NNO virtually excludes PCD
- **Definitive diagnosis** is usually based on identification of **ciliary abnormalities** on **high speed videomicroscopy analysis (HSVA)** or transmission electron microscopy (TEM). These tests require **nasal or bronchial biopsy**
- Genetic test for dynein arm mutations is difficult due to multiple phenotypes

Treatment

- **Reducing respiratory infections**
 - ⇒ regular use of nebulized (hypertonic) saline, twice daily before airway clearance techniques; inhaled bronchodilator is administered prior to nebulized saline.
 - ⇒ Azithromycin maintenance therapy (250 mg for <40 kg or 500 mg for ≥40 kg, three times a week)

Kartagener's syndrome

primary ciliary dyskinesia (PCD) + situs inversus → Kartagener's syndrome

Definition

- Kartagener syndrome is a subtype of primary ciliary dyskinesia characterized by the triad of situs inversus, chronic sinusitis, and bronchiectasis.
- most frequently occurs in examinations due to its association with dextrocardia (e.g. 'quiet heart sounds', 'small volume complexes in lateral leads')

Pathogenesis

- autosomal recessive mutation.
- **dynein** arm defect results in **immotile cilia**
 - ⇒ **dynein** is a protein found in Cilia and flagella of microtubule

Features

- Dextrocardia or complete situs inversus
 - ⇒ Situs inversus occurs in about half of people with Kartagener syndrome
- Bronchiectasis
- Recurrent sinusitis
- Male infertility and female subfertility (secondary to diminished sperm motility and defective ciliary action in the fallopian tubes)
- Deafness
- Hydrocephalus.

H/O recurrent chest infections , situs inversus, and sperm sample shows nonmotile spermatozoa. The cause of this condition is most likely a mutation in the genes for which protein? → Dynein

You can memorize the cause of Kartagener syndrome by thinking of Kartagener's restaurant that only has 'take-out' service because there is no dine-in (dynein).

Kartagener syndrome: triad of:

1. situs inversus,
2. chronic sinusitis, and
3. bronchiectasis.

Lung cancer: General overview

Epidemiology

- Second most common cancer (after breast cancer in women and prostate cancer in men).
- More common in males except for adenocarcinoma, which is more common in women

Risk factors

- **Smoking**
 - ⇒ increases risk of lung ca by a factor of 10
 - ⇒ **Smoking and asbestos are synergistic**, i.e. a smoker with asbestos exposure has a $10 \times 5 = 50$ times increased risk
 - ⇒ Up to 15% of lung cancers in patients who do not smoke are thought to be caused by **passive smoking**
- **Occupational exposure**
 - ⇒ Asbestos - increases risk of lung cancer by a factor of 5
 - ⇒ **Isocyanates** occurs in chemical workers in the rubber industry → **non-small-cell lung cancer , squamous-cell carcinoma**
 - ⇒ Arsenic, radon, nickel
- Preexisting chronic obstructive pulmonary disease (COPD), tuberculosis, and idiopathic pulmonary fibrosis (IPF).

Coal dust is not a risk factor of lung cancer

Types of lung cancer

- **Non-small cell lung cancer (NSCLC)**
 - ⇒ 85% of all lung cancers
 - ⇒ Most, but not all patients will have a smoking history
 - ⇒ Less malignant than small cell lung cancer, less responsive to chemotherapy.
 - ⇒ The overall 5-year survival rate is about 15%
 - ⇒ **Has main 3 subtypes:**
 - **Adenocarcinoma** ≈ 40% of NSCLC cases
 - ❖ The most common form of lung cancer in non-smokers, women, and young adults
 - ❖ Typically located on the lung periphery → normal bronchoscopy.
 - ❖ May associate with Gynaecomastia.
 - ❖ Histology will show: glandular mucin-producing cells

- **Squamous** ≈ 30% of NSCLC cases
 - ❖ Typically, central (Squamous = Sentral)
 - ❖ Associated with ↑parathyroid hormone-related protein (PTHRP) secretion → hypercalcaemia
 - ❖ Cavitate (In 10% of cases)
 - ❖ Histology will show: Pleomorphic cells in cluster with keratin pearls and intercellular bridges
- **Large cell carcinoma** (10%-15%).
 - ❖ A diagnosis of exclusion. The cells belonging to this cancer will not have mucous, squamous differentiation, neuroendocrine properties, or small cell characteristics. Cells will be large with abundant amounts of cytoplasm, large nuclei, and prominent nucleoli.
 - ❖ Originates from an epithelial cell.
 - ❖ Most commonly grow in the periphery.
 - ❖ Highly anaplastic and poorly differentiated.
 - ❖ Associated ↑beta-hCG
 - ❖ Poorly responsive to chemotherapy and often require surgical excision.
 - ❖ Prognosis is generally poor.
- **Small cell lung cancer (SCLC)**
 - ⇒ Also known as "oat-cell carcinoma"
 - ⇒ 15% of all lung cancers
 - ⇒ Strongly associated with smoking
 - ⇒ Usually centrally located
 - ⇒ Most aggressive cancer which typically presents with a short history and 80–90% will have metastases at the time of presentation.
 - ⇒ Very poor prognosis. median survival is 6–12 months.

Squamous cell cancer

Squamous cell and Small cell lung cancer are both Sentrally (Centrally) located.

Lung adenocarcinoma

- most common type in non-smokers
- peripheral lesion

Non-small cell lung cancer (NSCLC): adenocarcinoma VS squamous cell carcinoma

	Lung adenocarcinoma (AC)	Lung squamous cell carcinoma (SCC)
Location	Peripheral	Central
Characteristics	<ul style="list-style-type: none"> ❑ Most common type of lung cancer worldwide ❑ More common in women and nonsmokers 	<ul style="list-style-type: none"> ❑ Strong association with smoking ❑ Cavitary lesions arising from a hilar bronchus

	Prognosis is usually better than in other types of lung cancer	
Paraneoplastic features	Adenocarcinoma: HPOA → Clubbing	PTHrp → Hypercalcemia
Histology	Glandular tumor Mucin-producing cells (positive mucin staining)	Solid, epithelial tumor Intercellular bridges (desmosomes) Keratin pearls

Bronchioloalveolar carcinoma (BAC) is a pathological subtype of non-small cell lung cancer (NSCLC)

- Adenocarcinoma
- usually demonstrating a peripheral lesion.
- grow along the alveolar walls without actually destroying them.
- alveoli are often filled with mucin.
- **The classic massive clear frothy sputum (bronchorrhoea) can be up to one litre a day.**
- not resectable, poor prognosis.

Features

- Small tumours are often asymptomatic, so the majority of patients have either locally advanced or metastatic disease at diagnosis.
- Most common presenting symptoms are cough, chest pain, haemoptysis, dyspnoea, and weight loss.
- Regional adenopathy and compression of nearby structures may result in superior vena cava syndrome, hoarseness, and dysphagia.
- Obstruction of a central bronchus may result in postobstructive pneumonia

Referral

- Consider **immediate referral for patients with:**
 - ⇒ signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure)
 - ⇒ stridor
- Refer **urgently for chest x-ray for patients with** any of the following:
 - ⇒ haemoptysis
 - ⇒ unexplained or persistent (**longer than 3 weeks**): chest and/or shoulder pain, dyspnoea, weight loss, chest signs, **hoarseness**, finger clubbing, cervical or supraclavicular lymphadenopathy, cough, features suggestive of metastasis from a lung cancer (for example, secondaries in the brain, bone, liver, skin)
 - ⇒ underlying chronic respiratory problems with unexplained changes in existing symptoms
- Refer **urgently (for an appointment within 2 weeks) patients with:**
 - ⇒ persistent haemoptysis (in smokers or ex-smokers aged 40 years and older)

- ⇒ a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)
- ⇒ a normal chest X-ray where there is a high suspicion of lung cancer
- ⇒ a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms where a chest x-ray indicates pleural effusion, pleural mass or any suspicious lung pathology

MRCPUK-part-1-january-2017: H/O Rapid progression (cough, lung mass and weight loss within 2 months) + paraneoplastic peripheral neuropathy. What is the most likely diagnosis?

- ⇒ **Small-cell carcinoma.** (Squamous cell carcinoma and adenocarcinoma are usually very slow growing).

Lung cancer: paraneoplastic features

Paraneoplastic features of lung cancer

- **Squamous cell:** PTHrp → **Hypercalcemia**
- **Adenocarcinoma:** HPOA → Clubbing
- **Small cell:**
 - ⇒ ↑ADH → **SIADH**
 - ⇒ ↑ACTH → **Cushing syndrome**
 - ⇒ **Lambert-Eaton syndrome**

Overview

- Paraneoplastic syndromes are a result of antibody generation from or against malignant cells attacking normal tissue.
- Paraneoplastic syndromes occur in 10% of patients with lung cancer
- Both non-small cell and small cell lung cancers are associated with Paraneoplastic syndromes, although they are **more common with the small cell** due to its neuroendocrine cell origin.

Paraneoplastic features associated with non-small cell lung cancer

- **Hypercalcemia**
 - ⇒ **Squamous cell carcinoma** is the most common type of cancer related to hypercalcemia.
 - ⇒ Parathyroid hormone-related protein (**PTH-rp**) secretion causing hypercalcaemia
 - occurs in about 15%
 - best treated with intravenous fluids and bisphosphonates
- **Hypertrophic pulmonary osteoarthropathy (HPOA)**
 - ⇒ **More common with adenocarcinomas** than squamous cell carcinomas
 - ⇒ Characterized by abnormal proliferation of the cutaneous and osseous tissues at the distal regions of the extremities.
 - ⇒ a triad of **clubbed fingers**, symmetric polyarthritis, and periostitis of the long tubular bones
 - ⇒ It is often painful.

Paraneoplastic features associated with small cell lung cancers

- ↑ ADH → **Syndrome of inappropriate antidiuretic hormone secretion (SIADH)**
 - ⇒ SIADH manifests as euvolemic hypo-osmolar hyponatremia characterized by low serum osmolality and inappropriately high urine osmolality in the absence of diuretic treatment, adrenal insufficiency, heart failure, cirrhosis, or hypothyroidism
- ↑ ACTH → **Hypercortisolism → Cushing syndrome**
 - ⇒ not typical presentation
 - ⇒ hypertension, hyperglycaemia, hypokalaemia, alkalosis and muscle weakness are more common than buffalo hump etc.
 - ⇒ May manifest by Cushingoid facies and hyperpigmentation of the skin
- **Lambert-Eaton syndrome**
 - ⇒ 70% occur in small cell carcinoma
 - ⇒ is a pre-synaptic disorder of auto-antibody IgG directed against the pre-synaptic voltage gated calcium channel (VGCC) leading to impaired acetylcholine release.
 - ⇒ characterised by:
 - Proximal muscle weakness (the cranial nerves and respiratory muscles are usually spared)
 - Depressed or absent tendon reflexes and
 - Autonomic features (for example, dry mouth, impotence, etc).
 - ⇒ Weakness and fatigability can be improved with guanidine hydrochloride
 - ⇒ Unlike myasthenia gravis exercise is associated with increasing muscle strength and there is a negative response to Tensilon.

The presence of hyponatraemia strongly points towards a diagnosis of small cell lung cancer.

Lung cancer: stepwise investigations

- **Chest x-ray**
 - ⇒ The best choice for an initial study.
 - ⇒ No initial examination is complete without a **lateral film**.
 - ⇒ **Normal X-ray of the chest does not exclude bronchial carcinoma**
 - ⇒ **The common appearance** of a tumour arising from the main central airways (70% of all cases) is **enlargement of one or other hilum**.
 - ⇒ An endobronchial lesion commonly leads to partial or complete **atelectasis** and this is **the commonest sign of bronchogenic carcinoma**.
 - ⇒ Consolidation and collapse distal to the tumour might have occurred
 - ⇒ Collapse of the left lower lobe is often hard to identify, as is a tumour situated behind the heart.
 - ⇒ Apically located masses or superior sulcus tumours (Pancoast tumours) can be misdiagnosed as pleural caps, and patients often have a long history of pain in the distribution of the brachial nerve roots.
 - ⇒ The mediastinum might be widened by enlarged nodes.
- **Contrast-enhanced CT of the lower neck, chest, and upper abdomen**
 - ⇒ Perform contrast-enhanced CT of the chest, liver adrenals and lower neck before any biopsy procedure.

- ⇒ Shows size, location and extent of primary tumour; evaluates for hilar and/or mediastinal lymphadenopathy and distant metastases
- **Biopsy**
 - ⇒ If the CT demonstrates a peripheral lung lesion, CT or ultrasound-guided transthoracic needle biopsy should be offered.
 - ⇒ Endobronchial ultrasound (EBUS) guided biopsy is recommended for paratracheal and peri-bronchial intra-parenchymal lung lesions.
 - ⇒ Wherever possible minimally invasive procedures should be undertaken first for mediastinal node sampling (e.g., EBUS) before embarking into more invasive procedures like VATS.
- **Positron-emission tomography (PET)**
 - ⇒ The preferred first test after CT for intrathoracic lymph node assessment
 - ⇒ PET would determine whether there are distant metastases and is performed after the CT.
 - ⇒ For example in a patient with operable non-small-cell lung cancer, if CT has shown enlarged mediastinal nodes , he needs further assessment of his mediastinal nodes prior to surgery, because CT is not particularly good for assessing whether enlarged nodes are inflammatory or malignant. and this can be done with mediastinoscopy or a positron-emission tomography (PET) scan.
 - ⇒ Fluorodeoxyglucose is the usual tracer used for PET imaging in lung cancer
 - ⇒ PET is considered a standard staging study for patients with NSCLC; however, pathological confirmation of abnormal findings is often necessary due to false positives.
 - ⇒ For patients with known metastatic disease, PET is unnecessary.



Atelectasis of a person's right lung

Performance status for patient of lung cancer and COPD

- Assessing a patient's performance status is important when evaluating the most appropriate treatment options.
- It is commonly used by cancer MDTs, but has a role in assessing patients with chronic illnesses including COPD.

WHO (Zubrod) Scale	Description
0	Asymptomatic
1	Symptomatic but ambulatory (can carry out light work)
2	In bed less than 50% of the day. Unable to work but can live at home with some assistance
3	In bed more than 50% of the day (unable to care for self)
4	Bedridden

Staging lung carcinoma

Criteria for staging

- TNM staging takes into account:
 - ⇒ The size and position of the tumour (**T**)
 - ⇒ Whether the cancer cells have spread into the lymph nodes (**N**)
 - ⇒ Whether the tumour has spread anywhere else in the body - secondary cancer or metastases (**M**)
- CT scan is recommended as a staging procedure.
- Where available, PET scanning may be superior.

Chest CT is the best method for staging squamous-cell carcinoma of the lung.

The Tumor, Node, Metastasis (TNM) staging system

- The International Association for the Study of Lung Cancer (IASLC) developed a **eighth edition of the TNM system** in 2018 replaced earlier editions: as fellow

T, N, and M descriptors for the eighth edition of TNM classification for lung cancer

- T: Primary tumor**
 - ⇒ **T_x** → Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
 - ⇒ **T₀** → No evidence of primary tumor
 - ⇒ **T_{is}** → Carcinoma in situ

- ⇒ **T1** → Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
 - T1a(mi) → Minimally invasive adenocarcinoma
 - T1a → Tumor ≤1 cm in greatest dimension
 - T1b → Tumor >1 cm but ≤2 cm in greatest dimension
 - T1c → Tumor >2 cm but ≤3 cm in greatest dimension
- ⇒ **T2** → Tumor >3 cm but ≤5 cm or tumor with any of the following features:
 - 1) Involves main bronchus regardless of distance from the carina but without involvement of the carina
 - 2) Invades visceral pleura
 - 3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
 - **T2a** → Tumor >3 cm but ≤4 cm in greatest dimension
 - **T2b** → Tumor >4 cm but ≤5 cm in greatest dimension
- ⇒ **T3** → Tumor >5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
- ⇒ **T4** → Tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina

- **N: Regional lymph node involvement**
 - ⇒ Nx → Regional lymph nodes cannot be assessed
 - ⇒ N0 → No regional lymph node metastasis
 - ⇒ N1 → Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
 - ⇒ N2 → Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
 - ⇒ N3 → Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
- **M: Distant metastasis**
 - ⇒ M0 → No distant metastasis
 - ⇒ M1 → Distant metastasis present
 - M1a → Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion◊
 - M1b → Single extrathoracic metastasis§
 - M1c → Multiple extrathoracic metastases in one or more organs

Treatment of lung cancer (NICE guidelines 2019)

Non-small-cell lung cancer (NSCLC)

- **Surgery**

- ⇒ for early-stage NSCLC I-IIA (T1a–T2b, N0, M0) → **lobectomy**
- ⇒ Advise to stop smoking, offer nicotine replacement therapy, but do not postpone surgery for that.
- ⇒ Assessment before surgery for NSCLC
 - assess perioperative mortality by using risk scores such as thoracoscore.
 - Avoid surgery within 30 days of myocardial infarction.
 - Consider revascularisation (percutaneous intervention or coronary artery bypass grafting) before surgery for people with chronic stable angina
 - Perform spirometry and transfer factor (TLCO)

- **Radical radiotherapy**

- ⇒ For people with stage I-IIA (T1a–T2b, N0, M0) NSCLC **who decline surgery** or in whom any surgery is contraindicated, offer **radical radiotherapy** with stereotactic ablative radiotherapy (SABR). If SABR is contraindicated, offer either conventional or hyperfractionated radiotherapy.
- ⇒ For eligible people with stage IIIA - IIIB NSCLC who cannot tolerate or who decline chemoradiotherapy, consider **radical radiotherapy** (either conventional or hyperfractionated).

- **Combination treatment (chemoradiotherapy)**

- ⇒ For people with stage II or III NSCLC that are not suitable for or decline surgery.
- ⇒ For people with operable stage IIIA–N2 NSCLC: consider **chemoradiotherapy with surgery**.

- **Systemic anti-cancer therapy (SACT) for advanced NSCLC**

- ⇒ For non-squamous non-small-cell lung cancer, stages IIIB and IV
 - If the tumour tests positive for the epidermal growth factor receptor tyrosine kinase (**EGFR-TK**) mutation → Afatinib
 - If the tumour tests positive for anaplastic lymphoma kinase (**ALK**) gene → Crizotinib or Alectinib
 - If the tumour tests positive for **PD-L1 above 50%** → Pembrolizumab

- If the tumour tests positive for **PD-L1 below 50%** → gemcitabine or vinorelbine and cisplatin or carboplatin
- If the tumour tests positive for **ROS1** → Crizotinib

Contraindications to lung cancer surgery include SVC obstruction, FEV < 1.5, MALIGNANT pleural effusion, and vocal cord paralysis

Treatment of non-small cell lung cancer (NSCLC)

NSCLC stage	Treatment
Stage I (cT1N0 and cT2N0) (primary tumour <5 cm) and stage II (primary tumour >5 cm, or smaller primary tumour with metastasis to a nearby lymph node) (cT1N1, cT2N1 and cT3N0)	Surgery (FEV-1 should be >1.5 litres & no mets)
stage III (ipsilateral lung metastases or multiple metastases to nearby lymph nodes):	Sequential chemo-radiotherapy
Stage IV (metastatic)	chemotherapy alone

- **Absolute contraindications for surgery include:**
 - ⇒ **FEV1 < 1.5 litres** is considered a general cut-off point
 - If the tumour necessitates a pneumonectomy, the post-bronchodilator FEV should be more than 2 litres.
 - ⇒ **Reduction in the gas transfer test of more than 50%** is a contraindication to surgery.
 - ⇒ Metastases.
 - stage IIIb or IV (i.e. metastases present)
 - Tumour near hilum
 - Vocal cord paralysis (implies extracapsular spread to mediastinal L.N)
 - SVC obstruction
 - **Malignant pleural effusion (not just 'pleural effusion' (which may be reactive))**. Most pleural effusions associated with lung carcinoma are due to the tumour (and results in classification as a T4 tumour).
 - **Spread to involve the C8, T1 and T2 nerve roots** occurs by rib erosion by tumour to involve the lower roots of the brachial plexus and is known as a **Pancoast tumour**.

Small-cell lung cancer (SCLC)

- **Early-stage SCLC** (T1–2a, N0, M0): Consider surgery
- **Limited-stage disease SCLC** (T1–4, N0–3, M0) → 4 to 6 cycles of **cisplatin-based combination chemotherapy + thoracic radiotherapy + prophylactic cranial irradiation**
- **Extensive-stage disease SCLC** (broadly corresponding to T1–4, N0–3, M1a/b – including cerebral metastases) → **platinum-based** combination chemotherapy up to a maximum of 6 cycles + thoracic radiotherapy with prophylactic cranial irradiation

Treatment of small cell lung cancer (SCLC)

Stage of SCLC	Treatment
Early stage (T1-2a,N0,M0)	Surgery
Early stage (T1-2a,N0,M0)- Limited disease (T1-4,N0-3,M0)	4-6 cycles cisplatin-based chemotherapy, carboplatin if poor renal function/poor performance status +/- radiotherapy
Extensive disease (T1-4, N0-3, M1a/b)	6 cycles platinum-based combination chemotherapy + thoracic radiotherapy if good response

The most appropriate next step in management for patients with SCLC who have a response to initial chemotherapy → Prophylactic cranial irradiation should be considered

Palliative care

- Impending endobronchial obstruction → external beam radiotherapy and/or endobronchial debulking or stenting
- pleural effusion → pleural aspiration, talc pleurodesis for longer-term benefit.
- to reduce cough → opioids, such as codeine or morphine
- superior vena cava obstruction → chemotherapy and radiotherapy
- for the **immediate relief** of severe symptoms of superior vena caval obstruction → stent insertion
- for symptomatic brain metastases → dexamethasone
- for bone metastasis who need palliation and for whom standard analgesic treatments are inadequate → single-fraction radiotherapy

Lung cancer induced superior vena cava obstruction (SVCO)

Overview

- SVCO an oncological emergency caused by compression of the SVC.
- 60 % of patients present with SVC syndrome without a preexisting diagnosis of cancer.
- Most commonly associated with lung cancer.
 - ⇒ Up to 4% of patients with lung cancer will develop SVCO at some point during their disease.
 - ⇒ SVCO is much **more likely to be associated with right sided lung lesion** 4 times than with left sided lesions

Causes

- **Lung cancer**
 - ⇒ **Non-small cell lung cancer (the most common cause ≈ 50%)**
 - ⇒ Small cell lung cancer (25%)
- Non-Hodgkin lymphoma (NHL) (10%)
- Other malignancies (15%)
 - ⇒ metastatic seminoma, Kaposi's sarcoma, breast cancer
- Aortic aneurysm
- Mediastinal fibrosis
- Mediastinal goitre
- SVC thrombosis

Features

- **Dyspnoea is the most common symptom**
- Swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- Headache
- Visual disturbance
- Pulseless jugular venous distension
- CXR is abnormal in around 85% of cases, mediastinal widening is common.

Association

- **Recurrent laryngeal nerve palsy (voice hoarseness):** usually occurs with malignant tumour but can occur with aneurysm of aortic arch.
- Horner's syndrome due to involvement of sympathetic chain.
- elevated non-pulsatile jugular venous pressure (JVP)
- Compression of vital structures can result in stridor and dysphagia.

Diagnosis

- **Duplex ultrasound**
 - ⇒ The initial imaging study for patients with mild symptoms
- **Contrast-enhanced CT**
 - ⇒ The initial study for patients with clinical features suggestive of moderate SVC syndrome
- **Venography**
 - ⇒ The first line in severe or life-threatening symptoms
 - ⇒ Catheter-based (standard) venography is preferred over CT venography because it also provide immediate treatment by thrombolysis (pharmacologic or mechanical) and SVC stenting

Management

- **Dexamethasone**
 - ⇒ Corticosteroids are most useful where the cause of compression is an underlying haematological malignancy.
 - ⇒ **SVCO: immediate management → Dexamethasone IV + LMWH.**
- **Stenting**
 - ⇒ **Relieves symptoms quicker than chemotherapy or radiotherapy.**
- **Radiotherapy**
 - ⇒ may be an option later. If radiotherapy is used initially then stenting becomes significantly more difficult due to local fibrosis.
 - ⇒ Mediastinal radiotherapy leads to symptomatic relief in 80% of patients

Pancoast tumor

- An apical lung carcinoma
- Located in the superior sulcus of the lung (superior sulcus tumor)
- Predominantly non-small cell lung cancer (NSCLC)
- May lead to the development of Pancoast syndrome: a group of symptoms secondary to the mass effect of the tumor on surrounding structures
 - ⇒ Cervical sympathetic ganglion (stellate ganglion): → Horner syndrome (ipsilateral miosis, ptosis, and anhidrosis)

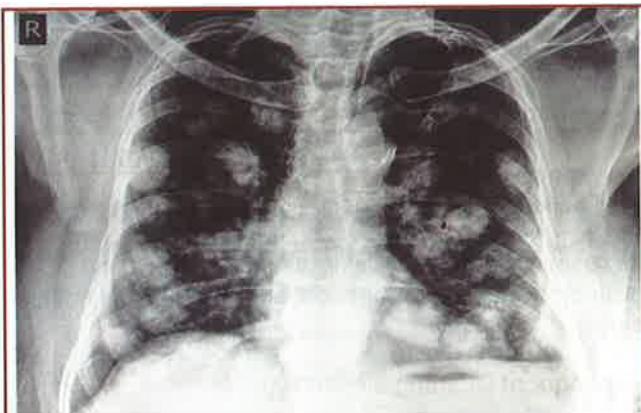
- ⇒ Recurrent laryngeal nerve: → hoarseness
- ⇒ Phrenic nerve: → paralysis of the hemidiaphragm (visible as elevated hemidiaphragm on chest x-ray)
- ⇒ **Brachial plexus:** → shoulder pain, sensorimotor deficits (eg, atrophy of intrinsic muscles of the hand)
- ⇒ Brachiocephalic vein: → unilateral edema of the arm and facial swelling
- **The investigation of choice → CT of chest**
- Treatment: usually inoperable on presentation → radiation and chemotherapy

Lung metastases

Metastatic carcinoma is the most common malignant tumour found in the lung

- **Metastatic carcinoma is the most common malignant tumour found in the lung**
- Malignant metastases to the lung can present as a solitary enlarging nodule, as multiple nodules or with diffuse lymphatic involvement.
- The most common causes of malignant nodules are primary lung cancer, lung metastases, and carcinoid tumors.
- Breast, **Colorectal**, renal and lung primaries are the commonest underlying tumours.
- An incidental pulmonary nodule that has clearly grown on serial imaging or is 18-fluorodeoxyglucose (FDG)-avid on positron emission tomography (PET)/CT is likely to be malignant and should be evaluated with biopsy.
- A diagnosis can usually be secured by percutaneous computed tomography- (CT-) guided biopsy.

Lung cancer with multiple brain metastases →Hospice care is appropriate.



Metastatic carcinoma

Chest X-ray shows secondary tumors as **multiple, well-circumscribed, noncalcified nodules**.

The most common cancer to present with metastases to the hand is lung cancer.

Carcinoid lung tumour

Carcinoid tumour as general (see gastroenterology section)

- neuroendocrine tumours of predominantly enterochromaffin cell origin.
- can occur in the small intestine, bronchi, rectum appendix or stomach.

Overview

- The vast majority of bronchial adenomas are carcinoid tumours, arising from the amine precursor uptake and decarboxylation (APUD) system, like small cell tumours.
- Carcinoid tumours (so called argentafinomas as they take up silver) are neuroendocrine cells
- **originate from Kulchitsky (K) cells in the lung**
- Most often located in the main bronchi, and occur most frequently in the right middle lobe.
- **slow growing**
- smoking is **NOT** a risk factor

Epidemiology

- 1% of lung tumours
- 10% of carcinoid tumours.
- typical age = 40-50 years
- The incidence is equal between men and women.

Feature

Recurrent haemoptysis with segmental collapse on x-ray is a typical presentation of bronchial carcinoid.

- Often asymptomatic
- long history of cough, recurrent haemoptysis
- Recurrent infections: carcinoid tumours → (80-90%) develops in a bronchus → bronchial obstruction → lower respiratory tract infection.
- Carcinoid syndrome (rare)
 - ⇒ depends on associated liver metastases
 - ⇒ occurs in less than 10% of patients with carcinoid tumours, but occurs most commonly in GIT tumours.
 - ⇒ can secrete a number of vasoactive compounds (including serotonin and bradykinin), which result in bronchospasm, diarrhoea, skin flushing and right-sided valvular heart lesions.
- ⇒ **Paraneoplastic syndromes**
 - **ACTH secretion and subsequent Cushing's syndrome.**
 - Ectopic growth hormone-releasing hormone [GHRH] and subsequent acromegaly
 - Multiple endocrine neoplasia (MEN) type 1 where pancreatic neuroendocrine tumours predominate.

Investigations

The 'cherry-red' lesion is a typical finding of lung carcinoid.

- **Chest-X ray**
 - ⇒ often centrally located and not seen on CXR.
 - ⇒ A carcinoid tumour in the left lower lobe bronchus could cause distal collapse of the left lower lobe.
- **Bronchoscopy:**
 - ⇒ **Identifies up to 80% of carcinoid tumours in the main bronchi.**
 - ⇒ seen as a highly vascular 'cherry-like' tumour ('cherry red ball')
 - ⇒ Biopsy is usually followed with brisk bleeding and should be done via **rigid bronchoscopy**.
 - ⇒ The histological picture of **granular eosinophilic staining of the cytoplasm**, is highly suggestive of a carcinoid tumour.
 - ⇒ Histologically, these tumors consist of compact nests of epithelial cells surrounded by neat, delicate connective tissue capsules.
 - ⇒ **histology might not be necessary prior to surgery if the clinical picture is typical.**
- **Plasma chromogranin A** is an effective **screening test** for carcinoid as it is **very sensitive**, but it is not specific.
- **24-hour urinary excretion of 5-hydroxyindoleacetic acid** is **more specific** for the **diagnosis**, but false positives and negatives are present.

Management

- Surgical resection
 - ⇒ **A person with an isolated pulmonary carcinoid should be referred for tumour resection,**
 - ⇒ **histology might not be necessary prior to surgery if the clinical picture is typical.**

Prognosis

- if no metastases then 90% survival at 5 years

Lung fibrosis: Causes

Acronym for causes of upper zone fibrosis: CHARTS

- **C - Coal worker's pneumoconiosis**
- **H - Histiocytosis/ hypersensitivity pneumonitis**
- **A - Ankylosing spondylitis**
- **R - Radiation**
- **T - Tuberculosis**
- **S - Silicosis/sarcoidosis**

Fibrosis predominately affecting the upper zones

- Extrinsic allergic alveolitis
- Coal worker's pneumoconiosis/progressive massive fibrosis
- Silicosis (Silica is found in coal dust)
- **Sarcoidosis**
- Ankylosing spondylitis (rare)
- Histiocytosis: Pentalaminar X bodies (Birbeck granules) found on bronchoalveolar lavage (BAL) are diagnostic.
- Tuberculosis
- Allergic bronchopulmonary aspergillosis and farmers lung
- Radiation

Fibrosis predominately affecting the lower zones

- Idiopathic pulmonary fibrosis (IPF) (previously known as Cryptogenic fibrosing alveolitis (the more common cause))
- Most connective tissue disorders (except ankylosing spondylitis)
- Asbestosis
- **Drug-induced**
 - ⇒ Cardiac drugs: **amiodarone**, hydralazine
 - ⇒ Cytotoxic agents: busulphan, **bleomycin**, cyclophosphamide, leflunomide
 - ⇒ Anti-rheumatoid drugs: methotrexate, sulfasalazine, gold
 - ⇒ Antibiotics: **nitrofurantoin**
 - ⇒ Ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide).
 - ⇒ Opiates: e.g. heroin abuse

Baseline pulmonary function testing is important in patients receiving bleomycin

Pulmonary fibrosis can occur following pneumonia

Idiopathic pulmonary fibrosis (IPF)**Definition**

- Progressive fibrosis of the interstitium of the lungs when **no underlying cause exists**.

Epidemiology

- Most common type of interstitial lung disease (ILD)
- Typically seen in patients aged 50-70 years
- Men are affected more than women

Pathophysiology

- Recurrent microinjuries to the alveolar wall → ↑growth factors secreted by the injured epithelial cells (most commonly: **Transforming growth factor-beta (TGF-beta)**) → recruit **fibroblasts** → differentiate into myofibroblasts → secrete interstitial collagen, which accumulates due to imbalance between interstitial collagenases and their tissue inhibitors.

Risk factors

- Genetic predisposition,
- Cigarette smoking, environmental pollutants
- Chronic microaspiration.

Features

- Gradual onset (over several months) of exertional dyspnoea and dry cough
- **Bibasal** crackles on auscultation
- Clubbing occurs in two-thirds of cases.

Diagnosis

- **Chest X-ray:** Bilateral **lower-zone** reticulonodular shadows
- **High resolution computed tomography (HRCT)**
 - ⇒ **The investigation of choice**
 - ⇒ **Showa** radiographic pattern of **usual interstitial pneumonia (UIP)**:
 1. Peripheral (subpleural), bibasilar reticular opacities
 2. Architectural distortion, including **honeycomb changes** and traction bronchiectasis or bronchiolectasis
- Spirometry → restrictive picture (FEV1 normal/decreased, FVC decreased, FEV1/FVC increased)
- Transfer factor (TLCO) reduced, **most useful in determining prognosis.**
- **Lung biopsy by video-assisted thoracoscopy (VATS)**
 - ⇒ If HRCT is not diagnostic
 - ⇒ Finding → Honeycombing and collagen deposition with fibroblast foci
- **Exclusion of other known causes of interstitial lung disease**

Usual interstitial pneumonia (UIP): is a radiologic and pathologic description and can be seen in conditions other than IPF, especially connective tissue diseases, rheumatoid arthritis. Once these other conditions are reasonably excluded, a clinical diagnosis of IPF can be made. Hence UIP does not always mean IPF. But in IPF, the radiologic and pathologic pattern is UIP.

Management

- Supportive care (eg, supplemental oxygen, pulmonary rehabilitation, seasonal influenza and pneumococcal vaccination)
- **Antifibrotic agents** → **pirfenidone or nintedanib**
 - ⇒ Action → suppresses fibroblast proliferation
 - ⇒ Indication → mild-moderate disease IPF (FVC 50-80 % predicted).
 - ⇒ Benefit → reduces disease progression by 30 %
 - ⇒ Side effects → drug-induced liver injury
- Immunosuppressant therapies such as azathioprine, prednisolone and mycophenolate mofetil **should not be used** in IPF.
- **Lung transplant**

Prognosis

- poor, average life expectancy is around 3-4 years
- increased risk of developing lung cancer (by 7- to 14-fold).



Chest X-ray shows sub-pleural reticular opacities that increase from the apex to the bases of the lungs



CT scan showing advanced pulmonary fibrosis including 'honeycombing'

Bronchiolitis obliterans (BO)

Definition

- 'Bronchiolitis obliterans' is the term used to describe **fibrous scarring** of the small airways, characterized by **fixed airway obstruction**.

Mechanism

- submucosal and peribronchiolar inflammation and fibrosis **without any intraluminal granulation tissue**
- BO should not be confused with bronchiolitis obliterans organising pneumonia (BOOP), a completely different disease.

Causes

- Inhalation of toxic fumes
- Exposure to mineral dust
- Respiratory infections: Viral, Mycoplasma, Legionella
- post-transplantation: Bone marrow, heart-lung or lung transplantation
- Connective tissue disorder: **Rheumatoid arthritis** or **SLE**
- **Penicillamine treatment**
- inflammatory bowel disease

Feature

- dry cough and dyspnoea.
- wheeze might be audible.

Diagnosis

- Should be considered in a nonsmoker when airflow limitation is irreversible or associated with a gas transfer abnormality.
- Should be considered in association with recent toxic fume exposure, symptoms of viral infection, history of organ transplantation, or concomitant rheumatic disease.
- **HRCT:** shows expiratory air trapping (mosaic or diffuse), bronchial wall thickening, and centrilobular nodules
- **Spirometry** → mixed obstructive/restrictive picture
- **Transfer factor may be low but the transfer coefficient (K_{CO}) is often normal.**
- **Lung biopsy**
 - ⇒ An open or thoracoscopic lung biopsy is required to make a definitive diagnosis
 - ⇒ will show → a mural concentric narrowing of the lumina of the bronchioles.
 - ⇒ Transbronchial lung biopsy is often **Inadequate** for diagnosis because the disease is patchy.

Differential Diagnosis

- Bronchiolitis obliterans is often misdiagnosed as asthma, chronic bronchitis, emphysema or pneumonia.
 - ⇒ Asthma → reversible airflow limitation on spirometry (unlike BO)
 - ⇒ COPD → significant cigarette smoking history and no exposure to the etiologic agents for BO.
 - ⇒ Cryptogenic organising pneumonia (COP) : differ from BO in:
 - **'cryptogenic** means **unknown cause**'.
 - granulation tissue in the alveoli and bronchioles on histopathology
 - Spirometry → restrictive pattern
 - Responds very well to steroids

Treatment

- No optimal treatment. Patients rarely respond to steroids and the prognosis is poor.
- This disease is irreversible and severe cases often require a lung transplant

a history of inhalational exposure or hematopoietic cell or lung transplantation, the combination of airflow limitation on spirometry and HRCT showing expiratory air trapping (mosaic or diffuse), bronchial wall thickening, and centrilobular nodules are sufficient to make a diagnosis of bronchiolitis obliterans.

Post-extubation stridor (PES)

Prevalence

- PES is a frequent complication of intubation, occurring in 2-16% of cases.

Pathophysiology

- pressure and ischaemia → damage to the mucosa of the larynx → inflammatory response → laryngeal oedema → acute respiratory compromise necessitating emergency reintubation.

Risk factors for post-extubation stridor from laryngeal edema

- prolonged duration of intubation,
- traumatic intubation, (variably defined as ≥ 36 hours to ≥ 6 days)
- large tube size (>8 mm in men, >7 mm in women)
- Excessive cuff pressure
- Aspiration
- Tracheal infection
- A history of asthma
- Female gender**

Obstructive sleep apnoea (OSA)

Sleep apnoea causes include obesity and macroglossia

Definition

- Cessation of breathing during sleep because of upper airway obstruction leads to apnea (respiratory arrests of ≥ 10 seconds) and hypopnea (reduction of airflow by $\geq 50\%$ for ≥ 10 seconds).

Epidemiology

- More common in men : ♂ > ♀ (2:1)

Causes

- Obesity: the most important risk factor**
- macroglossia: acromegaly, hypothyroidism, amyloidosis
- large tonsils
- Marfan's syndrome
- Small pharyngeal opening
- Coexisting COPD
- Sedatives such as alcohol
- Collar size (Neck size)** greater than (17 inches) 43 cm is strongly associated.

Features

- Excessive daytime somnolence as a result of repeated arousals.
- Repetitive apnoeas (cessation of airflow for more than 10 seconds) and hypopnoeas (50% reduction in airflow for greater than 10 seconds)
- loud snoring, gasping, choking or interruptions in breathing while sleeping
- morning headaches

Complications

- Pulmonary hypertension and cor pulmonale
- Hypoxia-induced cardiac arrhythmia
- increased risk of premature death, **sudden death**
- myocardial infarction, **stroke**,
- motor vehicle accidents due to microsleep
- metabolic syndrome (hypertension, insulin resistance → ↑ risk of type 2 diabetes.)
- neurocognitive dysfunction, vascular dementia
- reduced libido and erectile dysfunction
- CBC may show polycythemia (\uparrow Hct, \uparrow Hb): Hypoxia induces erythropoietin secretion by the kidneys, which stimulates the blood marrow, leading to increased RBC production

Obstructive sleep apnea is one of the most common causes of secondary hypertension.

Diagnosis : Sleep studies

- **Overnight polysomnography:** first-line method
 - ⇒ **The gold standard diagnostic test is.**
 - ⇒ Classic findings
 - ⇒ Diagnose **OSA** if the **Apnoea-Hypopnoea Index (AHI)**:
 - ≥ 15 episodes/hour.
 - ≥ 5 episodes/hour + **additional symptoms** (eg: excessive daytime sleepiness, insomnia, mood disorder, or cognitive dysfunction) or **comorbidities** (eg: HTN, IHD, stroke)
 - ⇒ To assess severity of obstructive sleep apnoea → Apnoea-Hypopnoea Index (AHI):
 - mild → 4-14 episodes
 - moderate → 15-30 episodes
 - severe → >30 episodes

The diagnosis of obstructive sleep apnea requires sleep studies and should not be made based on clinical tools or questionnaires alone such as Epworth Sleepiness Scale (used to diagnose excessive daytime sleepiness) or Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria)

In-laboratory polysomnography is the gold standard for the diagnosis of sleep-related breathing disorders

Following weight loss, CPAP is the first-line treatment for moderate/severe obstructive sleep apnoea

Management

- Weight loss. **the definitive management.** But takes time
- Continuous positive airways pressure ventilation (**CPAP**) : **the treatment of choice**
 - ⇒ **the most appropriate initial and quickest management**
- Intra-oral devices (e.g. **Oral appliance**, mandibular advancement)
 - ⇒ if CPAP is not tolerated or for patients with mild OSA where there is no daytime sleepiness
- Upper airway surgery : if CPAP or an oral appliance are declined or ineffective.
- Pharmacological agents: limited evidence
 - ⇒ **Modafinil** is a drug that is licensed for excessive daytime sleepiness in people with OSA treated with CPAP, as well as for narcolepsy.
- Avoid sedatives drugs/excess alcohol

Obesity hypoventilation syndrome (OHS) (Pickwick syndrome)

Obesity + feature of OSA + diurnal abnormal ABG ($\uparrow \text{PCO}_2$) \rightarrow (OHS)

Definition

- a combination of obesity (body mass index [BMI] $\geq 30 \text{ kg/m}^2$) and daytime hypercapnia ($\text{PaCO}_2 \geq 45 \text{ mm Hg}$ in arterial blood gas analysis) in the absence of other causes for hypoventilation.

Diagnostic criteria

- BMI $\geq 30 \text{ kg/m}^2$. Commonly affects **morbidly obese individuals**. 90% of patients with OHS have coexistent OSA.
- Arterial blood gasses showing **diurnal hypercapnia** ($\text{PaCO}_2 > 45 \text{ mm Hg}$)
 - ⇒ serum bicarbonate $\geq 27 \text{ mEq/L}$
- Polysomnography: hypoventilation during sleep with or without obstructive apnea events
- Exclusion of other possible causes of hypoventilation (eg, neuromuscular disease).

Treatment

- 1st line: noninvasive positive airway pressure (PAP) together with lifestyle modifications for weight loss.

Pneumothorax

Classification

- **primary pneumothorax** : if there is no underlying lung disease.
- **secondary pneumothorax** : if there is underlying lung disease

Features

- Sudden onset of chest pain, sometimes radiating to the shoulder
- Dyspnoea (may not be a dominant feature)
- Dry cough

- **Hamman's sign** (or 'crunch') is a **clicking sound** synchronous with the heart-beat, heard over the sternal edge in mediastinal emphysema or **Left-sided pneumothoraces**.

Risk factors

- Young adult males, **often tall and slim**, are frequently affected by **spontaneous pneumothorax**.
- Patients with **Marfan** syndrome are prone to **recurrent pneumothoraces**.

Investigations

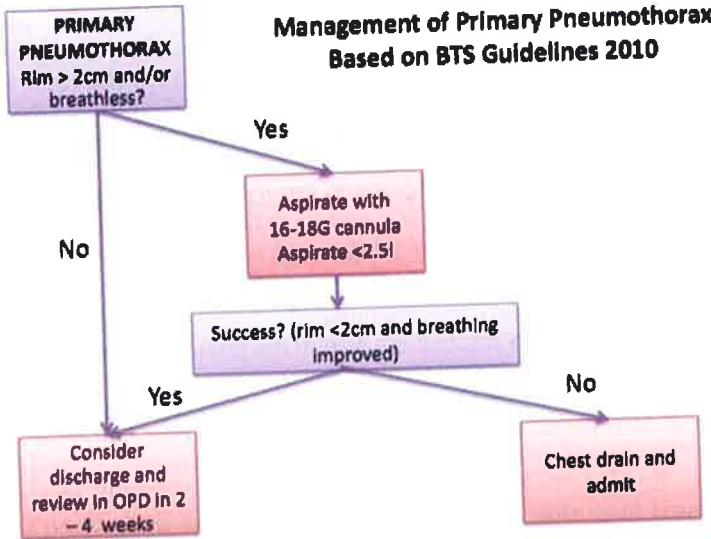
- **Chest x ray** : 1st step to **confirm the diagnosis**
 - ⇒ Questions sometimes discuss the size of the pneumothorax in percentage terms rather than giving the interpleural distance.
 - ⇒ A 30% pneumothorax ≈ 2 cm
 - ⇒ A 50% pneumothorax is likely to have a rim of > 3cm.
- **CT chest**
 - ⇒ The next step after chest x-ray to investigate the underlying cause of recurrent pneumothorax
- **Video assisted thoracoscopy**
 - ⇒ If CT not help in pointing to **underlying cause of recurrent pneumothorax**

Differential diagnosis

- **Large bullae in COPD can mimic a pneumothorax:**
 - the most appropriate management option → **CT chest to confirm**
 - place a needle or chest drain would be **disastrous** → shrinkage of the lung

Management

- **Primary pneumothorax**
 - ⇒ **Definition:** Spontaneous primary pneumothorax is defined as:
 - Age less than 50-years-old
 - No significant smoking history, minimal smoking history would still be considered as primary pneumothorax
 - No evidence of underlying lung disease.
 - ⇒ **Caused by the rupture of apical pleural blebs.**
 - ⇒ **Management**
 - If the rim of air is < 2cm and the patient is not short of breath then **discharge** should be considered
 - If the rim of air is ≥ 2cm or **the patient is breathless** → **Needle aspiration**
 - If **following aspiration** the rim of air is < 2cm and the breathing has improved then discharge should be considered with outpatient review.
 - If needle aspiration fails (defined as > 2 cm or still short of breath) → **chest drain** should be inserted
 - If a patient with a pneumothorax requires oxygen, this should be given at 10 L/min.



- **Secondary pneumothorax**

⇒ **Definition:** the patient is ≥ 50 years old, or has significant smoking history or evidence of underlying lung disease.

⇒ **Management:**

- If the rim of air is $< 2\text{cm}$ → aspiration
- If the rim of air is $\geq 2\text{cm}$ → **chest drain** → **Insert a small-bore chest drain (8-14 FG)** and attach to an underwater seal drain
- If aspiration fails (i.e. pneumothorax is still $>1\text{cm}$) → a chest drain should be inserted.
- **if the patient is very dyspnoeic a drain should be inserted even though the pneumothorax is small ($< 2\text{cm}$).**
- All patients should be admitted for at least 24 hours
- High flow oxygen should be given in all cases of pneumothorax, as it facilitates re-absorption of the pleural air, which is predominantly composed of nitrogen.

Asthmatics should be treated as a secondary pneumothorax

Tension pneumothorax

- should be suspected in people on mechanical ventilators or nasal non-invasive ventilation who suddenly deteriorate, and is frequently missed in the intensive care unit setting.
- Treatment → needle thoracocentesis
 - ⇒ use a 3-6-cm-long cannula to perform needle thoracocentesis.
 - ⇒ the cannula should be left in place until bubbling is confirmed in the underwater-seal system to confirm proper function of the intercostal tube.

If the history and examination are suggestive of a pneumothorax and the patient being relatively stable (**tension pneumothorax are not suggested**), the most appropriate first step would be → **confirmation with chest x ray** rather than place a needle or chest drain.

Chest drains for pneumothorax

- **Point of insertion** → in the 'safe triangle', in the mid-axillary line, **above a rib margin**
- **Chest drain situations**
 - ⇒ When the patient coughs, nothing happens. When he breathes in and out, the fluid in the tube moves up and down that means → Air is no longer draining from the pleural space, but the drain is still working. Air is not bubbling out of the drain when the patient coughs because the air has stopped draining from the pleural space and the lung has re-inflated.
 - ⇒ If a drain does not bubble or swing, then it is blocked or kinked and is not working.
- **Next step after failure of chest drain**
 - ⇒ **Negative suction** is necessary if the drain is still bubbling but the lung has not fully re-inflated on the chest X-ray. After chest drain if pneumothorax fails to re-expand or if there is a persistent air leak (bubbling present) after 48 hours, then you should → refer the patient to a respiratory specialist because negative suction might be required using a high-volume/low-pressure suction system.
 - ⇒ **Cardiothoracic surgical referral** → **Video assisted thoracoscopic surgery**
indications:
 - persistent pneumothorax despite low-pressure, large-volume suction, and the chest drain in position and is bubbling (may be have a **bronchopleural fistula**)
 - Persistent air leak (more than five to seven days of drainage)
 - **Second ipsilateral pneumothorax for bullectomy and pleurectomy.**
 - Bilateral spontaneous pneumothorax
 - Certain occupations, for example, pilots or divers.
 - ⇒ **Chemical pleurodesis** through the chest drain:
 - used in older patients or frail individuals with recurrent pneumothorax, where surgery would be high risk.

Fitness to fly

- Pneumothorax is an absolute contraindication to air travel as trapped air may expand and result in a tension pneumothorax.
- In general, it should be safe to travel approximately 1- 2 weeks after successful drainage of a pneumothorax with full expansion of the lung.

Diving

- The British Thoracic Society (BTS) guidelines state: '*Diving should be permanently avoided unless the patient has undergone bilateral surgical pleurectomy and has normal lung function and chest CT scan postoperatively.*'

Images

Chest x ray reveals a 3.2 cm rim of air around the lung.

Pleural effusion

Classification , pathophysiology and causes

	Exudate (> 30g/L protein)	Transudate (< 30g/L protein)
Pathophysiology	<ul style="list-style-type: none"> ↑ Capillary hydrostatic pressure (increased capillary wedge pressure) ↓ Capillary oncotic pressure 	<ul style="list-style-type: none"> ↑ Capillary permeability (e.g., due to inflammation)
Causes	<ul style="list-style-type: none"> infection: pneumonia, TB, sub-phrenic abscess connective tissue disease: RA, SLE neoplasia: lung cancer, mesothelioma, metastases pancreatitis pulmonary embolism Dressler's syndrome yellow nail syndrome 	<ul style="list-style-type: none"> heart failure hypoalbuminaemia <ul style="list-style-type: none"> ⇒ liver disease, ⇒ nephrotic syndrome, ⇒ malabsorption hypothyroidism Meigs' syndrome

Investigation

- **Chest x-rays** should be performed in all patients
- **Ultrasound thorax:**
 - ⇒ the next most appropriate step after chest x-ray
 - ⇒ Ultrasound is better for pleural imaging than CT.
 - ⇒ it increases the likelihood of successful pleural aspiration and is sensitive for detecting pleural fluid septations
- **Pleural aspiration**
 - ⇒ ultrasound is recommended to reduce the complication rate
 - ⇒ a 21G needle and 50ml syringe should be used
 - ⇒ fluid should be sent for pH, protein, lactate dehydrogenase (LDH), cytology and microbiology
- **Thoracoscopy**
 - ⇒ the investigation of choice in patients with cytology negative exudative effusions.
- Video-assisted thoracoscopic surgery (VATS)
 - ⇒ A minimally invasive procedure, used if the diagnosis remains unclear

Light's criteria

- Developed to distinguish between a transudate and an exudate.
- The BTS recommend using the criteria for borderline cases:
 - ⇒ exudates have a protein level of >30 g/L, transudates have a protein level of <30 g/L
 - ⇒ if the protein level is between 25-35 g/L, Light's criteria should be applied.

	Exudates	Transudate
Pleural fluid protein/serum protein ratio	> 0.5	≤ 0.5
Pleural fluid LDH/serum LDH ratio	> 0.6	≤ 0.6
Pleural fluid LDH	> $\frac{2}{3}$ the upper limit of normal serum LDH	< $\frac{2}{3}$ the upper limit of normal serum LDH

To differentiate exudates from transudates, remember that Exudates have Extra (think protein, LDH).

Pleural infection

- All patients with a pleural effusion in association with sepsis or a pneumonic illness require **diagnostic pleural fluid sampling**
- **Indications for chest tube insertion in patients with an infected pleural effusion** are:
 - ⇒ Frankly purulent pleural fluid
 - ⇒ **Pleural pH < 7.2** in the setting of an infected pleural effusion
 - ⇒ Presence of organisms on a Gram stain of the pleural fluid
 - ⇒ Loculated pleural effusions
 - ⇒ Poor clinical progress despite antibiotic treatment

- What test can be performed to assess if the effusion is an empyema?
 - ⇒ Centrifugation of the pleural aspirate
 - If the pleural fluid is turbid or milky it should be centrifuged. If the supernatant (liquid which lies above the sediment) is clear, the turbid fluid was due to cell debris and empyema is likely

Characteristic pleural fluid findings

- Low glucose
 - ⇒ Empyema
 - ⇒ Rheumatoid arthritis effusions (\downarrow glucose, \downarrow pH < 7.2 , \uparrow LDH, \uparrow cholesterol, \uparrow RF)
 - ⇒ Tuberculosis
 - ⇒ Malignancy
 - ⇒ Oesophageal rupture
 - ⇒ Lupus
- Raised amylase
 - ⇒ Pancreatitis,
 - ⇒ Oesophageal perforation
- Heavy blood-staining
 - ⇒ Mesothelioma, malignancy.
 - ⇒ Pulmonary embolism
 - ⇒ Tuberculosis

Complications of plural fluid drainage

- Re-expansion pulmonary oedema
 - ⇒ This is a potentially life-threatening condition which can occur when a large volume of fluid or air is rapidly drained,
 - ⇒ It is suggested by sudden onset of shortness of breath, cough and hypoxaemia following chest drain insertion.

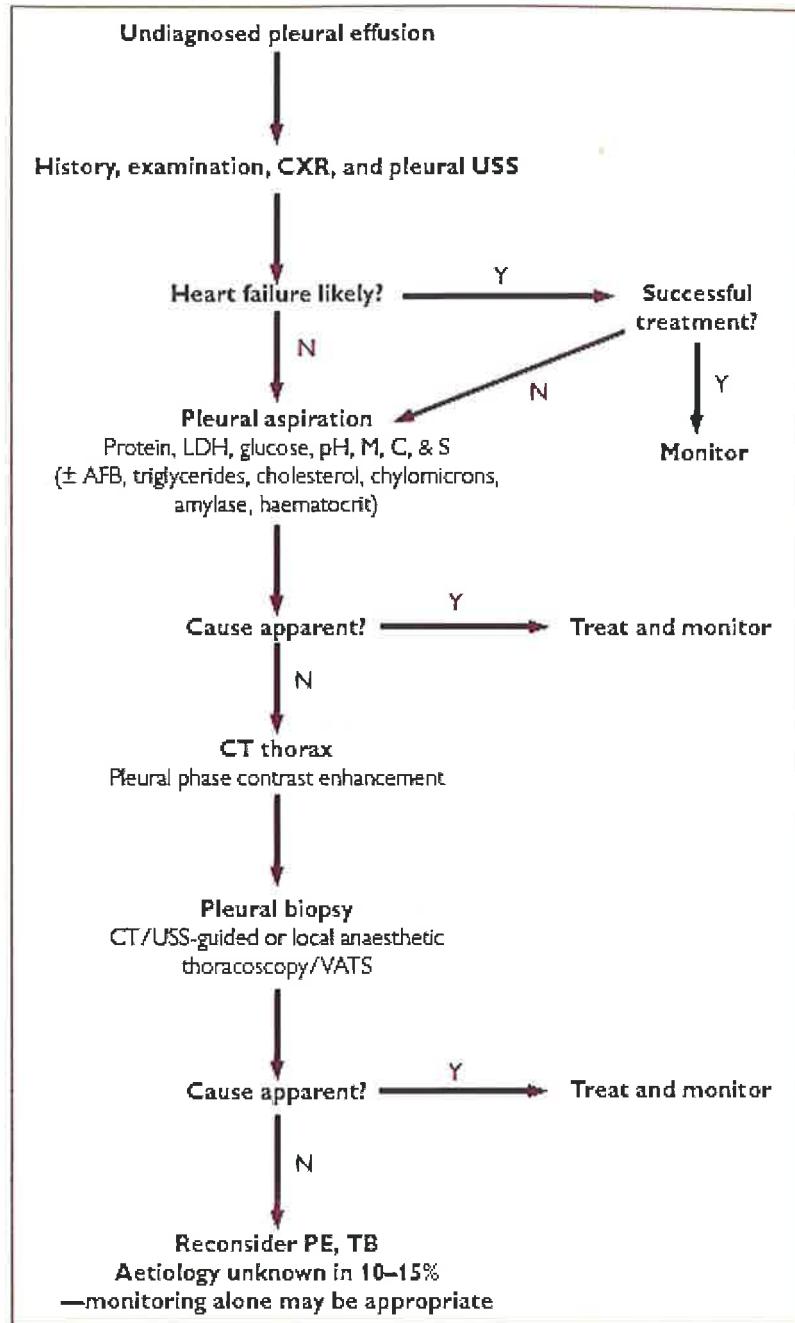
Exudate typically appears cloudy, has an increased cell count, and has high levels of protein, albumin, and LDH.

Transudate is usually clear, has a decreased cell count, and has low levels of protein, albumin, and LDH.

MEAT has low glucose: **M**alignancy, **E**mpyema, **A**rthritis (rheumatoid pleurisy), and **T**uberculosis are causes of pulmonary effusion associated with low glucose levels.

Pleural fluid with a bloody appearance suggests a malignant etiology or haemothorax

Diagnostic algorithm for the patient with a pleural effusion



Oxford handbook of respiratory medicine, 3rd edition

MRCPUK-part-2-march-2018: A patient admitted with severe pneumonia and pleural effusion, despite treatment with Tazocin®. Needle aspiration of 15 ml of pleural fluid reveals it to be pus-coloured, with a pH of 7.1 and a glucose level of 3.1 mmol/l. what is the most important intervention?

- ⇒ Chest drain insertion

Meigs syndrome: A triad of ascites, right pleural effusion, and benign ovarian tumor

Chylothorax

Definition

- Accumulation of chyle (a **fatty** lymphatic fluid with milky appearance) in the pleural space.
- Chyle is a lymphatic fluid with a high content of triglycerides in the form of chylomicrons, which produce the milky appearance.

Causes

- Nontraumatic chylothorax : Malignancy (classically lymphoma) is the leading cause.
- Traumatic chylothorax: surgical injury to the thoracic duct is the most common cause

Features

- Symptoms induced by the mechanical effects of a pleural effusion

Diagnosis

- Pleural fluid
 - ⇒ **for triglyceride and cholesterol levels:**
 - **elevated** triglyceride strongly supports the diagnosis.
 - Low cholesterol will differentiate chylothorax from cholesterol pleural effusion (Pseudochyle → low triglyceride , high cholesterol and empyema)
 - ⇒ **Milky appearance is a classic sign of chylothorax**
 - ⇒ Pleural fluid is classically exudative with a high lymphocyte count (>70 %), a normal glucose level, a low LDH, and a low cholesterol level).
 - ⇒ **Detection of chylomicrons by lipoprotein electrophoresis is the definitive diagnostic test** but not routinely performed

Haemothorax

Definition

- Bleeding into the pleural space

Causes of nontraumatic haemothorax

- Most common: spontaneous pneumothorax
- Less common
 - ⇒ Vascular disease
 - ⇒ Malignancy

- ⇒ Coagulation disorders
- ⇒ Necrotizing pneumonia

Diagnosis

- Pleural fluid analysis
 - ⇒ Bloody appearance
 - ⇒ RBC count > 5,000 cells/ml
 - ⇒ **haematocrit that is more than half that of peripheral blood.** (Haematocrit > 0.5 × peripheral hematocrit). This distinguishes it from a blood-stained effusion.

Management

- The treatment of choice is to **insert a large intercostal drain (28-32 F).** If this reveals continued bleeding, a thoracotomy might be required.

A hemothorax, however small, must always be drained because blood in the pleural cavity will clot if not evacuated, resulting in a trapped lung or an empyema.

Eosinophilic Pulmonary Diseases

Definition

- Eosinophilic pulmonary diseases are a heterogeneous group of disorders characterized by the accumulation of eosinophils in alveolar spaces, the interstitium, or both.

Causes of pulmonary eosinophilia

- **Known etiology**
 - ⇒ Allergic bronchopulmonary aspergillosis (ABPA)
 - ⇒ Helminth infections
 - ⇒ Drug-induced pneumonitis (eg, antibiotics, phenytoin, or L-tryptophan)
 - ⇒ Eosinophilic granulomatosis with polyangiitis (previously referred to as Churg-Strauss syndrome)
 - ⇒ Loffler's syndrome
 - ⇒ Tropical pulmonary eosinophilia
- **Unknown etiology: The two primary eosinophilic pulmonary diseases of unknown etiology are**
 - ⇒ Acute eosinophilic pneumonia
 - ⇒ Chronic eosinophilic pneumonia

Diagnosis based on:

- 1) Demonstration of opacities on chest imaging **and**
- 2) Identification of eosinophilia in peripheral blood, bronchoalveolar lavage fluid, or lung biopsy tissue

Acute eosinophilic pneumonia

Definition

- Chronic eosinophilic pneumonia is an **idiopathic acute** disorder characterized by an abnormal accumulation of eosinophils in the interstitial and alveolar spaces of the lung.

Features

- Acute eosinophilic pneumonia is an acute febrile illness of less than four weeks duration (often less than seven days), a nonproductive cough, and progressively worsening dyspnea.
- malaise, myalgias, night sweats, and pleuritic chest pain.

Association

- new onset or resumption of cigarette smoking.

Diagnosis based on:

- Acute** febrile illness of short duration (**one month or less**),
- hypoxemic respiratory failure,
- diffuse pulmonary opacities on chest radiograph, and
- bronchoalveolar lavage eosinophilia (>25 %), after
- exclusion of infection, vasculitis, or other known precipitants (eg, drugs, irradiation)

Treatment

- In severe hypoxemia or respiratory failure requiring mechanical ventilation → methylprednisolone
- Mild to moderate (eg, spo₂ >92 %) → oral prednisone

The classic presentation of idiopathic acute eosinophilic pneumonia is the rapid onset of acute respiratory failure in a previously healthy patient. diffuse radiographic opacities, and bronchoalveolar lavage with ≥25 % eosinophils, and absence of infection or other known precipitant.

Chronic eosinophilic pneumonia

Definition

- Chronic eosinophilic pneumonia is an **idiopathic chronic** disorder characterized by an abnormal accumulation of eosinophils in the interstitial and alveolar spaces of the lung.

Feature

- dyspnea, cough, fever, and wheezing over **4 weeks to several months**.

Diagnosis

- Chest imaging shows predominantly peripheral or pleural-based opacities described as the "photographic negative" of pulmonary edema, are virtually **pathognomonic**
- Bronchoalveolar lavage (BAL)
 - ⇒ To look for eosinophilia → cell count showing eosinophilia (>25 %).
 - ⇒ To exclude infection.
- Infections and drug-induced pulmonary eosinophilia need to be excluded.

Treatment

- Prednisolone

Tropical pulmonary eosinophilia

Definition

- Tropical pulmonary eosinophilia is an immune hyper-responsiveness to microfilariae that become trapped in the lungs. It is a clinical manifestation of lymphatic filariasis, a parasitic infection caused by nematodes (roundworms) such as *Wuchereria bancrofti*.

Epidemiology

- Seen in endemic areas of lymphatic filariasis (mainly India and South East Asia)
- Occurs more frequently in males than in females

Features

- Dry cough that is frequently paroxysmal and nocturnal.
- Asthma-like attacks → wheezing
- fatigue, malaise, and weight loss,

Diagnosis

- ↑blood eosinophils
- ↑serum immunoglobulin E.
- ↑ filarial antibody titers (**confirmatory test**)

Differential diagnosis

- Tropical pulmonary eosinophilia is distinguished from Loeffler's syndrome by
 - A. the severe and protracted course,
 - B. measurable antibodies against filarial antigens, and
 - C. the therapeutic response to diethylcarbamazine.
- If treated late or left untreated, it can lead to pulmonary fibrosis with chronic respiratory failure.

Treatment

- Diethylcarbamazine for 12 to 21 days.
- Bronchospasm can be managed with bronchodilators and short-term corticosteroids.

The diagnostic criteria for tropical pulmonary eosinophilia include:

- 1) history of residence or travel to a filarial endemic region,
- 2) paroxysmal nocturnal cough with dyspnoea,
- 3) leucocytosis with peripheral blood eosinophilia >3,000/microL,
- 4) elevated serum IgE and an antifilarial antibodies (IgG and IgE) levels,
- 5) pulmonary infiltrations in chest x-ray, and
- 6) clinical improvement with DEC (diethylcarbamazine).

Löffler's syndrome

Definition

- Löffler syndrome is a form of eosinophilic pulmonary disease characterized by absent or mild respiratory symptoms (most often dry cough), transient CXR shadowing and blood eosinophilia, thought to be due to parasites such as *Ascaris lumbricoides* (the most common parasite) causing an alveolar reaction.

Features

- Fever, cough and night sweats which often last for less than 2 weeks.

Diagnosis based on

- Characteristic and often transient respiratory symptoms
- Chest x-ray findings → **fleeting migratory pulmonary opacities**
- **Peripheral blood eosinophilia.**
- Exclusion of other types of eosinophilic lung disease (e.g. acute eosinophilic pneumonia → severe hypoxemia, and typically a lack of increased blood eosinophils at the onset of disease).

Treatment

- Symptomatic and may consist of corticosteroids.
- Generally, a self-limiting disease, usually resolves within 1 month.

Cryptogenic organising pneumonia (COP)

Definition

- A rare type of inflammatory interstitial lung disease, characterised by a buds of **granulation tissue in the alveoli and bronchioles on histopathology**
- other names: Bronchiolitis obliterans organising pneumonia (BOOP)

Causes

- **Idiopathic:** most common 'cryptogenic' means **unknown cause!**.
- Secondary organising pneumonia: connective tissue disease, malignancy, infection, drugs and toxins

Epidemiology

- Typically, age of onset is 50 to 60 years
- Men and women affected equally.

Feature

- Mimic community-acquired pneumonia (eg, cough, dyspnea with exertion, weight loss).

Investigations

- Chest X-ray: bilateral patchy infiltrates
- Chest CT: multiple ground-glass or consolidative opacities that tend to be at the lung periphery

- ⇒ **Reversed halo sign**, better known as an **atoll sign** (a region of ground-glass opacity surrounded by crescentic or annular denser tissue) .
- Pulmonary function tests (PFTs) →restrictive pattern

Diagnosis

- Exclusion of any possible cause (e.g. COVID-19 → do PCR)
- For **definitive diagnosis** → **lung biopsy** → excessive proliferation or "**plugs**" of **granulation tissue within alveolar ducts and alveoli** (Masson bodies). Granulation tissue extends uniformly into the alveolar ducts and **does not distort pulmonary architecture**, unlike **usual interstitial pneumonia**.
 - ⇒ If clinical presentation, radiographic appearance and bronchoscopy with bronchoalveolar lavage is consistent with COP, surgical lung biopsy is not required for diagnosis.

Treatment

- 1st line: Prednisolone (usually effective)
- 2nd line: cyclophosphamide or azathioprine

Prognosis

- Relapse is common

Cryptogenic organizing pneumonia (COP)

- High-resolution CT of the chest → **bilateral ground-glass opacities**
- **Exclude other possible causes**
- **Persistent pulmonary opacities despite antibiotic treatment.**
- Lung biopsy → **granulation tissue plugs in small airways**

Cryptogenic Organizing Pneumonia/<https://ncbi.nlm.nih.gov/>

Pulmonary hypertension (PH)

Definition

- Sustained elevation in mean **pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise**, pulmonary artery wedge pressure ≤15 mmHg and pulmonary vascular resistance > 3 Wood units.

Epidemiology

- more commonly affects female

Pathophysiology : Increased pulmonary vascular resistance

- **Occlusive vasculopathy** (e.g., PE, connective tissue diseases)
- **Hypoxic** pulmonary vasoconstriction: chronic hypoxic pulmonary vasoconstriction → airway smooth muscle hypertrophy and pulmonary vascular bed destruction → ↑ pulmonary vascular resistance
- **Inflammation** (e.g., COPD) → ↑ inflammatory cell infiltration of intima → thickened endothelial wall → intimal fibrosis
- ↑ Increased pulmonary vessel pressure: due to left heart dysfunction
- ↑ endothelin and ↓ vasodilators (e.g., NO, prostacyclin) → vasoconstriction

Causes according to WHO Classification

- Group 1: Pulmonary arterial hypertension (PAH), Idiopathic, familial
 - ⇒ collagen vascular disease, HIV, sickle cell disease
 - ⇒ drugs and toxins → e.g. **amphetamines**, cocaine (but not heroin).
- Group 2: Pulmonary hypertension with left heart disease
- Group 3: Pulmonary hypertension secondary to lung disease/hypoxia
 - ⇒ COPD, interstitial lung disease, sleep apnoea, high altitude
- Group 4: Pulmonary hypertension due to thromboembolic disease
- Group 5: Miscellaneous conditions: lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis

Features

- **Exertional dyspnoea is the most frequent symptom**
- **Symptoms of right ventricular (RV) failure** (eg, exertional chest pain or syncope, loud P2, elevated jugular venous pressure, right-sided murmurs, edema, right upper quadrant pain, ascites, and pleural effusion)

Investigations

- **Transthoracic echocardiography is the initial test of choice**
 - ⇒ If left heart disease (LHD) explain the PH → RHC is not indicated.
 - ⇒ If no LHD explain the PH → **investigate for pulmonary causes**
 - Chest CT
 - Pulmonary function testing (PFTs)
 - ventilation-perfusion (V/Q) scanning → chronic thromboembolic disease
 - Obstructive sleep apnoea
 - Autoimmune serologies
 - HIV serology
 - ⇒ If pulmonary dysfunction explain the PH → RHC is not indicated.
 - ⇒ If pulmonary investigations did not explain the PH → Do RHC
- **Right heart catheterization (RHC)** is the **best investigation** for diagnosing pulmonary hypertension
 - ⇒ mostly for patients with no cardiac or respiratory causes explaining the PH → to evaluate for PAH.
 - ⇒ The diagnosis of primary pulmonary hypertension (PAH) requires RHC that demonstrates mean pulmonary artery pressure (mPAP) >20 mmHg at rest, pulmonary vascular resistance (PVR) ≥3 Wood units, and a **mean pulmonary capillary wedge pressure (PCWP) <15 mmHg**.
 - ⇒ a mPAP ≥20 mmHg, **PCWP ≥15 mmHg**, and a normal or reduced cardiac output is consistent with **left heart disease- pulmonary hypertension (LHD-PH)**.
- **Pulmonary angiography is the definitive diagnostic test.**

Management

- First step: Treat any underlying conditions, for example with anticoagulants or oxygen.
- Second step: perform **acute vasodilator testing** to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as intravenous epoprostenol or inhaled nitric oxide
 - ⇒ If there is a positive response to acute vasodilator testing → oral calcium channel blockers (nifedipine or extended-release diltiazem)
 - ⇒ If there is a negative response to acute vasodilator testing:
 - endothelin receptor antagonists: bosentan

- phosphodiesterase inhibitors: sildenafil
- prostacyclin analogues: treprostinil, iloprost

Complication

- Cor pulmonale (right ventricular failure).

Prognosis

- Pregnant with pulmonary hypertension have a high mortality of 30% - 50% - highest immediately after delivery.

Sarcoidosis

Sarcoidosis CXR

- 1 = BHL
- 2 = BHL + infiltrates
- 3 = infiltrates
- 4 = fibrosis

Definition

- Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas.

Epidemiology

- More common in black people (African descent) and subjects of Caribbean origin
 - ⇒ in Europe, sarcoid is commonest amongst Caucasians and has a significantly higher incidence in the Irish.
- More common among females than males ♀ > ♂ (2:1)
- Typically affects young adults.
- More common in non-smokers

Pathology

- Noncaseating granulomas in the organ involved.
 - ⇒ the characteristic pathological feature of sarcoidosis.
 - ⇒ may occur anywhere
 - ⇒ The central area of the granuloma will occasionally contain a Schaumann body, formed of crystallised material (**calcium phosphate**).
 - ⇒ These granulomas have the capacity to produce 1,25 vitamin D explaining the associated hypercalcaemia.

Features

- Often asymptomatic in the early stages (≈ 50%) → **Incidental chest x ray finding.**
- Enlargement of lymph nodes
 - ⇒ **The most common physical exam finding**
- Pulmonary (most common)
 - ⇒ Dry cough
 - ⇒ Dyspnoea (Pulmonary fibrosis)
- Extrapulmonary

- ⇒ **Skin lesions:** seen in 25 %, often an early finding.
 - **Erythema nodosum:** tender erythematous nodules on the lower extremities and is a predictor of a good prognosis.
 - **lupus pernio:** indurated plaques with discoloration of the nose, cheeks, lips, and ears. It is a predictor of a poor prognosis.
- ⇒ **Arthralgia:** typically targets the **ankle joint**.
- ⇒ **Uveitis** (25% of cases): red, painful eyes and blurred vision
- ⇒ Neurologic: (5% of cases) → Cranial nerves (e.g. facial nerve or Bell palsy).
- ⇒ Parotid swelling: (5% of cases)
- ⇒ **Löfgren syndrome** (LS): a combination of erythema nodosum (EN), hilar adenopathy, migratory polyarthralgia, and fever → **has 95 % specificity for sarcoidosis**.
- ⇒ Hypercalcaemia: (10% of cases) → nephrocalcinosis and nephrolithiasis.
- ⇒ Systemic symptoms
 - Fever
 - weight loss

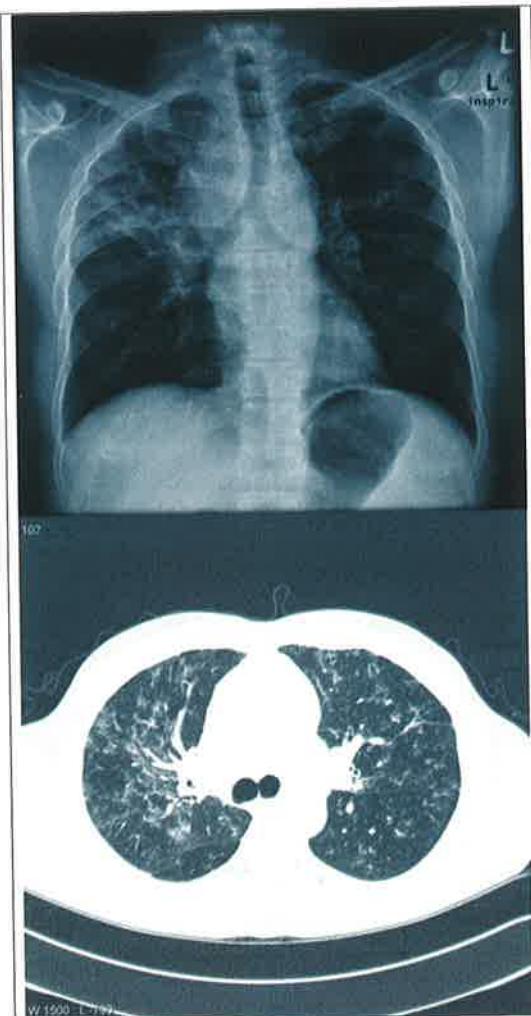
Investigations

Sarcoidosis is a diagnosis of exclusion of granulomatous lung diseases, including tuberculosis and histoplasmosis. Occupational history should be taken to exclude both berylliosis and silicosis which can present in a similar manner to sarcoidosis.

- **Chest x ray**
 - ⇒ **Best initial test**
 - ⇒ abnormal in 85% of lung sarcoid
 - ⇒ may show:
 - * **bilateral hilar lymphadenopathy**.
 - Lung fibrosis typically affects the upper zones
- **CT scan:**
 - ⇒ If they have **typical findings on a radiograph with a typical clinical presentation** (eg, in the context of Lofgren's disease) then a **CT scan may not be necessary**.
 - ⇒ It is the best next step after chest x ray in **atypical presentation**.
 - ⇒ demonstrate the degree of fibrosis, micronodules in a subpleural or bronchoalveolar distribution, fissure nodularity and bronchial distortion.
 - ⇒ Irregular linear opacities and ground-glass shadowing may also be seen.
 - ⇒ If the CT scan is diagnostic, then mediastinoscopy, bronchoscopy or biopsies can often be avoided.
- **Tissue biopsy** → **Non-caseating granulomas**
 - ⇒ **The gold standard test**
 - ⇒ If the history and radiology is typical, the biopsy is not necessary.
 - ⇒ **With less characteristic presentations, positive biopsies are needed.**
 - ⇒ **If you are asked to specify the investigation most likely to confirm the diagnosis, only transbronchial biopsy will determine whether non-caseating granulomas are present or not** → **Transbronchial lung biopsy** is therefore **the diagnostic investigation of choice**.
 - ⇒ **Skin biopsy** for skin lesions
- **Routine blood tests**
 - ⇒ **CBC:** Leukopenia in 5-10% of patients
 - ⇒ **ESR** → Elevated

- ⇒ **Creatinine** → elevated in renal involvement
- ⇒ **Electrolytes** → **Hypercalcaemia** (Seen only in 10% of patients)
 - **produced by macrophages within the granulomas** ↑1-alpha-hydroxylase
→ activates vitamin D → ↑ **Ca**
- ⇒ Hypergammaglobulinaemia (↑ Immunoglobulins) in 30-80%.
- **Exclusion of granulomatous lung diseases**
 - ⇒ **TB should be excluded** by sending sputum or BAL washings for AFB
 - **A positive tuberculin test in a patient with chronic sarcoidosis is suggestive of active tuberculosis**
 - ⇒ Occupational history to exclude both berylliosis and silicosis
- **Lung parenchyma involvement** → **Spirometry**
 - ⇒ **usually shows a restrictive defect (Decreased gas-transfer factor (Tlco) with decreased gas-transfer coefficient (Kco))**
- **Cardiac involvement**
 - ⇒ **ECG**: cardiac sarcoidosis (e.g. heart block → prolonged PR interval)
 - ⇒ Abnormalities in ECG or echocardiogram which suggest cardiac sarcoidosis should be confirmed with **cardiac magnetic resonance imaging (CMR)** or positron emission tomography (PET).
- **CNS involvement** → **CSF**: Intrathecal oligoclonal band production, elevated protein and lymphocytosis
- **Broncho-alveolar lavage**
 - ⇒ typically shows a lymphocytosis
 - ⇒ increased CD4+/CD8+ ratio
- **ACE levels**
 - ⇒ have a sensitivity of 60% and specificity of 70% and are therefore **not reliable in the diagnosis of sarcoidosis although they may have a role in monitoring disease activity.**
- **Kveim test** (where part of the spleen from a patient with known sarcoidosis is injected under the skin) is **no longer performed** due to concerns about cross-infection

The gold standard test → **transbronchial biopsy** → **noncaseating granulomas**



Chest x-ray and CT scan showing stage 2 sarcoidosis with both bilateral hilar lymphadenopathy + interstitial infiltrates.

The reticulonodular opacities are particularly noted in the upper zones.

Remember that pulmonary fibrosis (which this case has not yet progressed to) may be divided into conditions which predominately affect the upper zones and those which predominately affect the lower zones - sarcoidosis is one of the former.

The CT of the chest demonstrates diffuse areas of nodularity predominantly in a peribronchial distribution with patchy areas of consolidation particularly in the upper lobes.

There is some surrounding ground glass opacities. No gross reticular changes to suggest fibrosis.

Staging of chronic sarcoidosis

Stage	Finding	Likelihood of spontaneous resolution
0	Normal chest radiograph	>90%
I	Bilateral hilar lymphadenopathy (BHL)	60-90%
II	BHL plus pulmonary infiltrates	40-60%
III	Pulmonary infiltrates (no BHL)	10-20%
IV	Pulmonary fibrosis (+/- bullae)	<20%

Differential diagnosis of bilateral hilar lymphadenopathy

- Sarcoidosis
- Tuberculosis
- Malignancy including lymphoma
- Cystic fibrosis
- Churg Strauss disease
- HIV
- Extrinsic allergic alveolitis
- Phenytoin
- Pneumoconiosis, especially **berylliosis**. Exposure to beryllium is seen in the nuclear power, telecommunications, semi-conductor and electronics industries.

Management

The majority of patients with sarcoidosis get better without treatment

- Mild disease (Patients with asymptomatic and stable stage 2 or 3 disease who have only **mildly** abnormal lung function) → NO treatment
 - ⇒ Sarcoidosis remits without treatment in approximately two-thirds of people
- Moderate to severe disease
 - ⇒ First-line → **Prednisolone**. Indications for steroids:
 - patients with chest x-ray stage 2 or 3 disease who have **moderate to severe** or progressive symptoms.
 - Systemic involvement: hypercalcaemia, eye, heart or neuro involvement
 - ⇒ Second-line: Methotrexate is the first choice of second-line agent.
 - ⇒ Third-line: Infliximab given in combination with methotrexate or azathioprine
 - ⇒ Lung transplantation should be considered in all patients with advanced pulmonary fibrosis and associated pulmonary hypertension.

Prognosis

Erythema nodosum is associated with a good prognosis in sarcoidosis.

- Factors associated with a good prognosis
 - ⇒ HLA B8
 - ⇒ Lofgren's syndrome (bilateral hilar lymphadenopathy, erythema nodosum, polyarthritis and fever).
- Factors associated with poor prognosis
 - ⇒ insidious onset, symptoms > 6 months (chronic pulmonary involvement)
 - ⇒ absence of erythema nodosum
 - ⇒ extrapulmonary manifestations: e.g.
 - Lupus pernio: a chronic raised indurated (hardened) lesion of the skin, often purplish in colour, and is associated with sarcoid.
 - Splenomegaly
 - Cardiac involvement: Cardiac sarcoidosis is rare but can manifest as a prolonged PR interval.
 - Chronic hypercalcaemia
 - Nasal mucosal involvement
 - Neurosarcoidosis
 - ⇒ CXR: stage III-IV features
 - ⇒ black people (Afro-Caribbean or Afro-American race)
 - ⇒ Age of onset >40 years

Lofgren's syndrome

Lofgren's syndrome: a variant of sarcoidosis with **acute** clinical presentation with **tetrad of:**

1. Migratory polyarthritis (acute arthritis), most commonly involves ankles (>90%).
2. Erythema nodosum.
3. Bilateral hilar lymphadenopathy.
4. Fever.

Overview

- Seen in less than 5 -10 % of sarcoidosis
- Typically, more common in Scandinavian patients and less common in Afro-Caribbean patients
- Typically occurs in young females
- **Carries an excellent prognosis**
- Usually self-limiting

Other sarcoidosis variants

Heerfordt syndrome : a variant of sarcoidosis with **chronic** clinical presentation with **tetrad of:**

1. Parotitis
2. Uveitis
3. Facial palsy
4. Fever

Yellow nail syndrome

Definition

- Yellow nail syndrome is an uncommon disorder characterized by the triad of pulmonary disease, lymphedema, and yellow nails

Features

- Nails are yellow, thickened, curved, with loss of the lunula and cuticle, and may become detached from the nail bed.
- Congenital lymphoedema
- Pulmonary disease (**bronchiectasis**, pleural effusions)
- Chronic sinusitis



Hepatopulmonary syndrome (HPS)

Definition

- oxygenation defect induced by **pulmonary vascular dilatation** in patients with liver cirrhosis or portal hypertension.

Mechanism

- The vascular dilatation is thought to be induced by increased pulmonary levels of nitric oxide.

Prevalence

- It is seen in 15-30% of patients with cirrhosis.

Features

- Dyspnoea
- **Platypnoea (dyspnoea whilst standing) and Orthodeoxia (hypoxaemia exacerbated by being upright) are characteristic**
 - ⇒ Due to the predominance of vascular dilatation in the lung bases. Blood flow to these areas is increased in the upright position.
 - ⇒ Hepatic disease → intrapulmonary vasodilatation mainly in the lower lobes → right-to-left shunting (similar to pulmonary arteriovenous malformations) → increased blood flow through the lower lobes when the patient moves from the supine to the erect position → blood from the lower lobes, which is more poorly oxygenated, entering the left side of the heart → oxygen desaturation in the erect position.

Investigations

- The diagnosis of HPS can only be made in a patient who has liver disease, impaired oxygenation, and intrapulmonary shunt when other etiologies have been excluded.
- **Contrast-enhanced transthoracic echocardiography is the best test to demonstrate intrapulmonary vascular dilatation. It can also exclude intracardiac shunting which may result in similar signs and symptoms to hepatopulmonary syndrome.**

⇒ Method

- performed by injecting agitated saline intravenously during transthoracic echocardiography.

⇒ Interpretation

- In a **normal** subject microbubbles are visualised in the right ventricle within seconds, which are then absorbed in the alveoli.
- Immediate visualization in the left ventricle (within three cardiac cycles) indicates **intracardiac shunting**.
- Delayed visualisation in the left ventricle (3-6 cardiac cycles) is diagnostic of **intrapulmonary shunting**.

- Impaired oxygenation is confirmed when an arterial blood gas analysis demonstrates an **alveolar-arterial (A-a) oxygen gradient ≥ 15 mmHg** or an arterial oxygen tension (PaO_2) < 80 mmHg (10.7 kPa)
- Chest imaging and pulmonary function testing are often normal

Treatment

- Liver transplantation is the only proven beneficial available treatment, with 85% of patients showing resolution or significant improvement in gas exchange postoperatively.

Prognosis

- It is a poor prognostic indicator.

Pulmonary alveolar microlithiasis (PAM)**Definition**

- Pulmonary alveolar microlithiasis (PAM) is a rare, autosomal recessive disorder, characterized by widespread deposition of calcium phosphate microliths throughout the lungs.

Epidemiology

- PAM has the highest prevalence in Turkey, Japan, and Italy

Pathophysiology

- It occurs in the absence of disorders of calcium metabolism.
- *SLC34A2* gene mutations → ↓ activity of the type IIb sodium-phosphate cotransporter (which located mainly in alveolar type II cells) → **accumulation of phosphate in the alveoli → formation of microliths**
- *SLC34A2* gene is responsible for the uptake of phosphate released from phospholipids in outdated surfactant.

Feature

- **Most patients are asymptomatic despite striking radiological abnormalities.** often found incidentally during imaging studies for another reason.
- Symptoms included dyspnea, nonproductive cough, chest pain

Diagnosis

- **Chest x-ray:** 'sandstorm-appearing' is a typical diagnostic finding (diffuse scattered micronodules, often obscuring the contours of the heart and diaphragm)
- HRCT: micronodular calcifications, diffuse ground glass opacities
- Bronchoalveolar lavage (BAL) and transbronchial biopsy can be useful if the diagnosis is uncertain.
 - ⇒ BAL and **biopsy show the characteristic calciospherocitosis (microliths) in the alveoli** (deposition of calcium and phosphate crystals).

Treatment

- There is no established therapy for PAM.
- Lung transplantation is the only effective therapy.

Pulmonary Alveolar Proteinosis (PAP)

Definition: A rare diffuse lung disease characterized by the progressive accumulation of surfactant protein in the alveoli, that characteristically stain for periodic acid-Schiff (PAS)

Epidemiology: Common in males (M: F = 4:1), the typical age at presentation is 40 to 50 years.

Pathophysiology: ↓ alveolar macrophages → ↓ ability to remove surfactant → ↑surfactant accumulation in the alveoli.

Causes

- **Autoimmune:** due to granulocyte macrophage-colony stimulating factor (GM-CSF) antibodies, **the most common**
- congenital
- Secondary: chronic infections, immunosuppressants, organic dusts, malignancies.

Feature

- progressive dyspnea, cough, sputum production, fatigue, and weight loss

Diagnosis

- Chest x-ray: bilateral symmetric alveolar opacities located centrally in mid and lower lung zones, sometimes resulting in a "bat wing" distribution.
- High resolution computed tomography (HRCT): ground-glass opacification that **typically spares the periphery** and may have a "crazy-paving" appearance due to thickening of the interlobular and intralobular septa.
- Spirometry → shows a restrictive pattern (↓lung capacity, ↓CO diffusion)
- Autoantibodies : ↑ autoantibody against GM-CSF in serum and BAL fluid
- **Flexible bronchoscopy with broncho-alveolar lavage (BAL)**
 - ⇒ **The standard diagnostic test**
 - ⇒ **PAS-positive stains**

Treatment

- **Whole lung lavage:** excess surfactant is removed from the lungs via saline solution; may require repeated application
- Treatment of the underlying condition

Carbon monoxide poisoning

Confusion, pyrexia and pink mucosae are typical features of carbon monoxide poisoning

Carbon monoxide poisoning - most common feature = headache

Epidemiology

- Carbon monoxide is the **commonest** cause of poisoning-associated death in UK

Causes

- House fires
- Wood-burning stoves
- Furnaces in enclosed and poorly ventilated spaces. Often involves multiple individuals (e.g., family) during the winter
- Fumes from cleaning fluids and paint removers that contain methylene chloride (dichloromethane) can also cause carbon monoxide poisoning. When breathed in, methylene chloride is converted into CO gas.

Pathophysiology

- The affinity of hemoglobin for CO is ~ 240 times stronger than for O₂ → formation of COHb (carboxyhemoglobin) → ↓ oxygen-carrying capacity of hemoglobin → tissue hypoxia
- COHb → Shift the O₂ dissociation curve to the left → ↑ affinity for O₂ → ↓ release of O₂ in tissue

Questions may hint at badly maintained housing e.g. student houses

Features of carbon monoxide toxicity

- Nonspecific symptoms
 - ⇒ **Headache: the most common symptom ≈ 90% of cases**
 - ⇒ Dizziness
 - ⇒ Fatigue
 - ⇒ Nausea/vomiting
- Neurotoxicity
 - ⇒ Altered mental status (e.g., agitation, confusion, somnolence, memory loss)
 - ⇒ Seizures
 - ⇒ Loss of consciousness/coma
 - ⇒ **Cerebellar signs are the most reliable indicator of significant neurological toxicity**
- Cardiorespiratory toxicity
 - ⇒ **Inhalation of hot smoke** → upper airways burn → mucosal swelling → **Bronchoscopy is the best tool to establish whether there is significant oedema or mucosal ulceration obstructing the airways.**
 - ⇒ hypertension, tachycardia
 - ⇒ Shock
- **COHb levels have prognostic implications**, which are summarised here:

- ⇒ < 30% cause only headache and dizziness
- ⇒ 40–60% produces syncope, tachypnoea, tachycardia and fits
- ⇒ 60% cause an increasing risk of cardiorespiratory failure and death.

Suspect carbon monoxide poisoning when multiple people from the same confined household complain of the headache and fatigue.

Diagnosis

- **Arterial blood-gas analysis**
 - ⇒ Typical carboxyhaemoglobin (COHb) levels:
 - < 3% non-smokers
 - < 10% smokers
 - 10 - 30% symptomatic: headache, vomiting
 - >30% severe toxicity
 - ⇒ PaO₂: usually appears normal
- **Direct spectrophotometric measurement of Carboxyhaemoglobin (COHb) in a blood-gas analyser is the gold standard.**
 - ⇒ A bedside HbCO oximeter is now available
- ECG and cardiac monitor for all patients for 4 – 6 hours → signs of myocardial ischemia; arrhythmias

Pulse oximeters cannot distinguish between COHb and HbO₂. Pulse oximetry appears normal because carboxyhaemoglobin has similar absorption spectra to oxyhaemoglobin.

Management

- First-line: 100% oxygen → **Give high-flow oxygen (12 l/min) via a tight-fitting mask without a re-breathing circuit**
- Second-line: hyperbaric oxygen
 - ⇒ shorten the washout of COHb, but access and transfer times to a hyperbaric chamber can make this not practical.
 - ⇒ **Indications for hyperbaric oxygen**
 - CO level >25 %
 - Loss of consciousness
 - Severe metabolic acidosis (pH <7.1)
 - Evidence of end-organ ischemia (eg, ECG changes, chest pain, altered mental status)
 - pregnancy
- In severe cases intubation and mechanical ventilation may be required

Carbon monoxide (CO) poisoning	
Pathophysiology → increased affinity of carbon monoxide with haemoglobin results in tissue hypoxia	
The most common symptom is → headache	
Standard pulse oximetry (SpO_2) is unable to distinguish between oxyhemoglobin and COHb.	
Diagnosis: blood gas analysis to confirm the diagnosis based on the carboxyhaemoglobin (COHb) level. <ul style="list-style-type: none"> ▪ < 3% → non-smokers ▪ < 10% → smokers ▪ 10 - 30% → symptomatic: headache, vomiting ▪ > 30% → severe toxicity 	
Treatments: <ul style="list-style-type: none"> ▪ <u>Mild to moderate</u> → 100% high-flow oxygen via a non-rebreather mask ▪ <u>Severe:</u> COHb > 30%, complicated with CNS or cardiac events or pregnancy → hyperbaric oxygen 	
PassOnExam	

Smoking cessation

Action of smoking

- Nicotine is a stimulant and releases dopamine in the brain that leads to addictive effects of smoking.
- Its effects can be replaced in other ways using nicotine replacement therapy and this reduces the addiction to cigarette smoking.

General points of treatment

- Advise all people who smoke to stop
- Offer referral to a local smoking cessation service for behavioural support and drugs (a combination of drug treatment and behavioural support may be the best option)
- Advise to stop abruptly.
- Patients should be offered nicotine replacement therapy (NRT), varenicline or bupropion.
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking on or before a particular date (target stop date)
- If unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months unless special circumstances have intervened
- Do not offer NRT, varenicline or bupropion in any combination
- **Starting date of the treatment**
 - ⇒ Start NRT on the quit date.
 - ⇒ Start varenicline or bupropion 7-14 days before the quit date.
- **Duration of treatment**
 - ⇒ Prescribe NRT for 2 weeks after stop date
 - ⇒ Prescribe varenicline or bupropion FOR 3- 4 weeks after stop date.
- **Varenicline or combination NRT (a patch plus a short-acting preparation) have been shown to be the most effective treatments.**
- Varenicline or bupropion should not be prescribed to pregnant or breastfeeding women or young people aged under 18.
- No one form of NRT is more effective than another.
- Reviewed 2 weeks after stopping smoking, and the CO level measured at 4 weeks.

Nicotine replacement therapy (NRT)

- Available in a choice of formats, including Gum, Inhalator, Sublingual tablet, Nasal and Oral spray, and Transdermal patch
- Nice recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past.
- **Duration**
 - ⇒ The duration of treatment with NRT is 8–12 weeks (depending on which form of NRT is used and which dose is initiated), followed by a gradual reduction in dose.
 - ⇒ For children over the age of 12 years, treatment should be limited to 12 weeks.
 - ⇒ Treatment with NRT can be stopped abruptly or tapered gradually
- **No absolute contraindications**
- **Adverse effects:** Headache, dizziness, Nausea, vomiting, Rash, urticaria.

Varenicline

- **Mode of action:** a partial nicotinic receptor agonist → reduces the rewarding and reinforcing effects of smoking by preventing nicotine binding to the receptors.
- **Duration**
 - ⇒ Advise the person to stop smoking 7–14 days after starting varenicline.
 - ⇒ The recommended course of treatment is 12 weeks.
 - ⇒ Varenicline may be stopped without tapering the dose. However, immediately after stopping treatment with varenicline, up to 3% of people experience an increase in irritability, urge to smoke, depression, or insomnia. Consider tapering the dose in these people.
- **Contraindications**
 - ⇒ Aged under 18 years.
 - ⇒ Pregnancy.
 - ⇒ End-stage renal disease.
- **Common adverse effects**
 - ⇒ **Nervous system:** headache; somnolence, dizziness, dysgeusia.
 - ⇒ **Psychiatric:** abnormal dreams, insomnia
 - ⇒ **GIT** upset and dry mouth

Bupropion

- **Mode of action:** selective dopamine and noradrenaline re-uptake inhibitor
- **Duration**
 - ⇒ Advise the person to stop smoking 7–14 days after starting bupropion.
 - ⇒ If no effect is seen after 7 weeks, discontinue treatment with bupropion.
- **Contraindications**
 - ⇒ Age under 18 years
 - ⇒ Pregnancy
 - ⇒ History of **seizures**.
 - ⇒ CNS tumour.
 - ⇒ History of **bulimia or anorexia nervosa**.
 - ⇒ History of bipolar disorder.
 - ⇒ Severe hepatic cirrhosis.
- **Common adverse effects**
 - ⇒ **Psychiatric** : insomnia, depression, agitation, anxiety
 - ⇒ **Nervous system:** tremor, concentration disturbance, headache, dizziness, taste disorders.
 - ⇒ **GIT** upset and dry mouth

Bupropion: contraindicated in epilepsy

Medications used for Smoking cessation

	NRT	Varenicline	Bupropion
Action	Nicotine replacement therapy	partial nicotinic receptor agonist	Norepinephrine and dopamine reuptake inhibitor
Effectiveness	Effective with combination of two forms of NRT	Effective	Less effective than NRT and Varenicline
Date of starting	on the quit date	7–14 days before quit date.	7–14 days before quit date
Duration	8–12 weeks	12 weeks	7 weeks
Absolute contraindications	NO absolute contraindications	<ul style="list-style-type: none"> ▪ Aged < 18 years ▪ Pregnancy ▪ End-stage renal disease 	<ul style="list-style-type: none"> ▪ Age < 18 years ▪ Pregnancy ▪ History of seizures ▪ CNS tumour ▪ bulimia or anorexia nervosa ▪ bipolar disorder ▪ Severe hepatic cirrhosis
Prescribe with Cation	<ul style="list-style-type: none"> ▪ Chronic diseases (DM, HTN, RF, MI, CVA) ▪ Epilepsy. 	<ul style="list-style-type: none"> ▪ Cardiovascular, renal & psychiatric illness. ▪ Epilepsy 	<ul style="list-style-type: none"> ▪ Conditions lower the seizure threshold (e.g. Alcohol abuse, head trauma, diabetes, antipsychotics). ▪ Hepatic & renal impairment.
Common adverse effects	Headache, dizziness, Nausea	Headache, abnormal dreams, insomnia & GI upset	Headache, insomnia, depression, tremor.

Pregnant women

- **Assessment**

- ⇒ NICE recommended in 2010 that all pregnant women should be tested for smoking using carbon monoxide detectors, partly because '*some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense.*'
- ⇒ All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

- **Adverse effects of smoking in pregnancy**

- ⇒ **Reduces birth weight**
- ⇒ increases risk of miscarriage and still birth.
- ⇒ The infant has a greater risk of sudden infant death syndrome.
- ⇒ affect ovarian function in female children.

- ⇒ **increases lung maturity**, possibly by enhancing the production or secretion of cortisol. This makes neonates less likely to develop respiratory distress syndrome, but as lung maturation is often abnormal babies may have reduced lung function and increased rates of other respiratory illnesses.
- **Interventions in pregnant smoker**
 - ⇒ first-line: cognitive behaviour therapy and support from stop Smoking Services
 - ⇒ second line: NRT
 - NRT should only be used if smoking cessation without NRT fails.
 - Pregnant women should remove the patches before going to bed
 - ⇒ **varenicline and bupropion are contraindicated**