Respiratory medicine

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Edited by: Fareed Halteh

Respiratory system anatomy

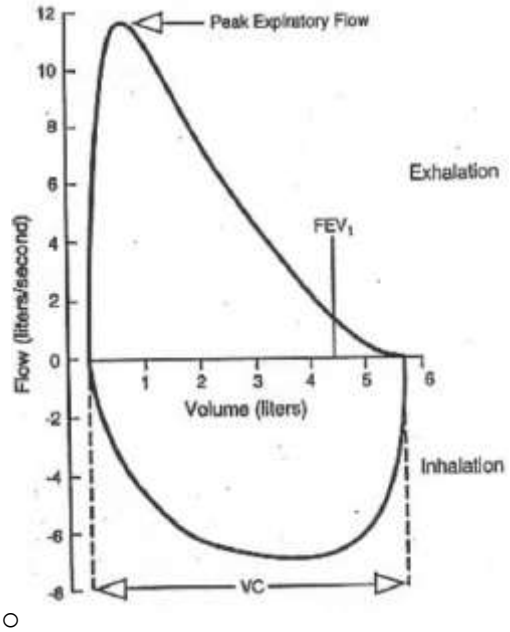
- Anatomically, the respiratory system is divided into the upper and lower respiratory tracts. They are demarcated by the vocal cords or the laryngeal inlet.
- The upper respiratory system consists of: mouth, nose, pharynx, larynx, sinuses, and vocal cords
- The lower respiratory tract begins at the trachea and ends with the alveoli.
- Trachea:
    - 10-12 cm long tube
    - Located slightly right to the midline. Part of it starts in the neck at the level of the cricoid cartilage. The thoracic part ends at the level of the sternal angle.
    - At the level of the sternal angle, the trachea divides into the right and left main bronchi; the site of the division is called the carina.
    - The right bronchus is wider, shorter and more vertical than the left one. This is why inspired objects are most likely to enter the right lung.
    - Trachea is surrounded by a C=shaped cartilage. This will protect it from the esophagus that lies behind it.
    - Divisions of the trachea:
        - Lobar bronchi:
            - Main right bronchus:
                - Upper lobe
                - Middle lobe
                - Lower lobe
            - Main left bronchus
                - Upper lobe
                - Lower lobe
        - Segmental bronchi:
            - Right lung:
                - Superior lobe: apical, posterior and anterior.
                - Middle lobe: lateral and medial
                - Inferior lobe: apical, medial basal, anterior basal, lateral basal, and posterior basal.
            - Left lung:
                - Superior lobe: apico-posterior, anterior, upper lingular, and lower lingular. The upper and lower lingular lobes correspond to the right lung's middle lobe.
                - Inferior lobe: apical, medial basal, anterior basal, lateral basal, and posterior basal.
- Functions of the respiratory system:
    - Functionally the respiratory system is divided into:

        - Conducting airways: extend from the nose to the terminal bronchioles. They include generations 0-16 with the trachea being generation 0. There is no respiratory function because there are no alveoli. Air here is called the anatomical dead space.
        - Transitional airways: reparatory bronchioles; generations 17-18. There are some alveoli here; however, they have no respiratory function. This is a transitional area.
        - Respiratory airways: consist of the alveolar ducts, alveolar sacs, and alveoli. These correspond to generations 20-23. Exchange of gases happens in this area.
- Cartilage:
    - C-shaped cartilage in the trachea
    - Chips of cartilage in the bronchi
    - Absent from bronchioles downwards.
- The respiratory tract is lined by pseudostratisfied columnar epithelium with scattered goblet cells. Each cell is lined by around 200 cilia and numerous alveoli on the apical surgae. The mucus layer is above the epithelium. It is divided into two layers; the lower watery layer called the sol layer, and the upper mucoid layer called the gel later. The hooks of the cilia are attached to the gel layer and form the mucociliary system. Mast cells wander over the mucus layer spraying mediators to keep the normal consistency of the layer.
- Alveoli:
    - There are around 300 million alveoli per lung. Each alveolus is surrounded by an extensive capillary network.
    - The epithelial layer of the alveoli and the endothelial layer of the capillaries with the endothelium lying in between them is called the alveolar-capillary membrane. Gas exchange occurs over this layer.
    - CO_2 crosses the membrane 20 times easier than O_2 does. This is why hypoxemia occurs more readily than hypercapnia.
    - Alveoli communicate between each other via pores of Kohn. These are found in the alveolar walls they help in equalizing the lung's pressure.

Physiology of the respiratory system

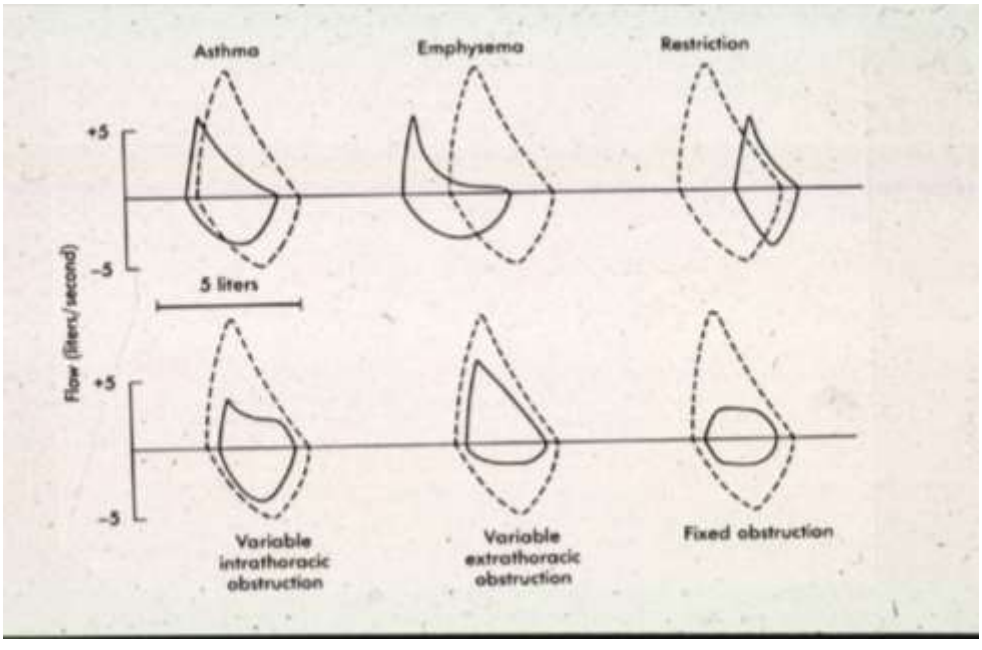
- The main function of the respiratory system is ventilation. This means the continuous renewal of air in the gas exchange area of the lung. Here, air is in proximity to pulmonary blood
- The process of air exchange can be studied by measuring a group of air volume. These volume vary between people according to age, sex, height, and weight in the case of children.
- Pulmonary volumes:
    - Tidal volume (TV): it is the volume of air inspired or expired with each normal breath (at rest without an effort). It ranges between 350-500 mL
    - Inspiratory reserve volume (IRV): it the maximum extra volume of air that can be inspired over the normal tidal volume
    - Expiratory reserve volume (ERV): it is the maximmu extra volume of air that can be expired by forceful expiration after the end of tidal volume
    - Reserve volume or residual volume (RV): it is the volume of air remaining in the lung after the most forceful expiratory.
- If there is no RV, the lung will collapse with every respiratory cyycle.
- Compliance of the lung is the tendency to expand upon increase of the transpulmonary pressure (the pressure between alveoli and the pleura). This is opposed by the tendency of the lung to collapse. The balance between the two makes this residual volume
- Pulmonary capacities:
    - Vital capacity: it is the maximum volume that can be expired forcefully after a forceful inspiration: VC = TV + IRV + ERV
    - Functional residual capacity (FRC): it is the amount of air that remiains in the lung at the end of normal expiration: FRV = RV + ERV
    - Inspiratory capacity (IC): it is the volume of air that can be inspired forcefully after normal expiration. IC = TV + IRV
    - Total lung capacity (TLC): it is the lung's maximum volume. TLC = RV + ERV + TV + IRV
- Measurement of pulmonary function:
    - These measurements need a good technician and a cooperative patient. The device that measures the volume in clinical volume is called a spirometer.
    - Types of spirometers:
        - Wright peak flow spirometer:
            - Advantages: small, moveable, relatively cheap, and doesn't require and electrical source.
            - Disadvantages: has no written record and only records a moment in expiration. This moment is the maximum flow.
            - These have different shapes and sizes

        - Has a chart that contains the normal value of flow rates of normal people depending on age, height, etc…
        - Pulmonary function is the worst at early morning due to changes in hormones.
    - Vitallograph:
        - Similar to peak flow spirometer; however, this device records the whole flow during expiration.
        - Advantages: gives a written record
        - Disadvantages: not portable and needs electricity.
        - Here, after the patient inspires and expires forcefully, the device gives a diagram. The reading represents the vital capacity.
        - Using this device, we cam measure the flow by measuring the velocity.
        - Through this device, we can measure the ratio of $FEV_{1.0}$ (forced expiratory volume in the first second) to FVC. This ratio is rqual to 80% in the normal healthy person. This means that 80% of the lung's vital capacity is expired in the first second of expiration. If the value was less than 80%, this means that the patient has air flow obstruction. If this percentage improves after the administration of bronchodilators, it means that the obstruction is reversible.
        - This type of measurment only measures the volume in the middle airway (trachea, major bronchioles, and small airways are not measured).
        - The 1^{st} pathological changes in the lung usually occur in the small airways.
        - To measure the vlume of small airways, we can measure the MEF (mid expiratory flow). This is done by ignoring the first and last 25% of epiration and measuring the mid 50%
- Uses of spirometers:
    - For identification and qualification of the obstruction.
    - Detection of high risk smokers:
        - After the age of 18, $FEV_{1.0}$ starts to decline in the healthy non-soker individual by 20-30 mL/year
        - In smokers, the $FEV_{1.0}$ declines by 40-90 mL/year.
        - 10-25% of smokers develop chronic obstruction of the airways.
    - Assessment of response to treatment
- Disease of the respiratory system:
    - Obstructive airway disease:
        - In this type FEV_1/FVC ratio is reduced to less than 80%.

        - Caused bronchial asthma, bronchitis, emphysema, bronchiactasis, and cystic fibrosis
    - Restrictive lung disease:
        - In this type, FEV/FVC is normal because FEV_1 and FVC are reduced in equal amounts.
        - Caused by any problem that prevents inflation of the lung:
            - Interstitaial lung diseases like pneumonia
            - Pleural diseases like pneumothorax
            - Chest wall diseaes like muscle paralysis
            - Neuronal causes like respiratory center defect
            - Extrathoracic conditions like ascites, obesity, and pregnancy
            - Space occupying lesion like tumors.
- Resistance in the large airways is more than resistance in small airways. This is due to the larger additive diameter of the small airways.
- The flow volume loop:
    - It shows flow rates during both inspiratory and expiratory phases of the respiratory cycle. It demonstrates air flow is small and large airways
    - During respiration, intrathoracic and intrabronchial pressures change. They increase during expiration and decrease (become negative) during inspiration. Atmospheric pressure remains constant.
    - During inspiration, the intra-tracheal pressure is less than the atmospheric pressure. This leads to the constriction of the extrathoracic trachea.
    - During expiration, the intratracheal pressure is more than the atmospheric pressure. This leads to the dilation of the extrathoracic trachea.
    - 

Normal flow volume loop showing the inspiratory and expiratory phases of the respiratory cycle.

- Extra-thoracic obstruction:
  - Paralyzed vocal cords or nodules in the extra-thoracic trachea.
  - During inspiration: the nodule will add to the narrowing caused by the atmospheric pressure on the extrathoracic trachea. This will increase the resistance decreasing the flow rate. It will show as an amputated inspiratory curve.
  - During expiration: the increase in te intratracheal pressure will dilate the trachea (against atmospheric pressure). This will lead to a normal expiratory curve
- Intrathoracic obstruction:
  - During inspiration, the decrease in intrathoracic pressure will lead to inflation of the lung. This will lead to dilation of the airways, which will omit the effect of the obstruction. This will result in a normal inspiratory curve.
  - During expiration, the increase in the intra-thoracic pressure will compress the lungs. This will decrease the flow rate leading to a lowered peak flow rate (amputated expiratory curve.
- Fixed obstruction:
  - Tumor or corrosion occupying the whole tracheal circumference.
  - The whole wall is rigid, so it will not dilate during any of the phases of the respiratory cycle.
  - The flow volume loop is called a box flow volume loop (amputated expiratory and inspiratory phases)
- Small airway disease:
  - Emphysema or bronchial asthma
  - During inspiration: normal
  - During expiration: the peak is near normal; however, the curve will descend in a concave pattern. The more the concavity, the more severe the disease is.



- Diffusion capacity of carbon monoxide (DLCO)
    - Defined as the ability of a gas to diffuse across a capillary membranes. It is ordinarily assessed by the diffusion capacity of carbon monoxide. This diffusion capacity reflects O_2 diffusion capacity.
    - This test is very sensitive for changes in the parenchyma of the lung.
    - Procedure:
        - Inhalation of small concentration of carbon monoxide. This is done in one breath that is held for 10 seconds.
        - Carbon monoxide is diluted by the gas already present in the alveoli. Moreover, CO is taken up by erythrocytes as they pass through the pulmonary circulation.
        - The concentration of carbon monoxide in the exhaled gas is measured/ DLCO is calculated as the quantity of CO absorbed per minute per mmHg pressure gradient between the alveoli and pulmonary capillaries.
    - The value of DLCO depends on:
        - The alveolar capillary surface area (SA) available for gas exchange.
        - The pulmonary capillary blood volume (BV)
        - Thickness of the alveolar capillary membrane
        - Degree of V/Q mismatch
        - The patient's hemoglobin levels.
    - Causes of decreased DLCO (decreased surface area, decreased blood volume, increased thickness, decreased hemoglobin count)
        - Emphysema
        - Lung-lobe resection
        - Bronchial obstruction
        - Multiple pulmonary emboli
        - Anemia
        - IPF, sarcoidosis, asbestosis, alveolar proteinosis
        - Congestive heart failure (before the development of alveolar and interstitaial edema)
        - Collagen vascular disease
    - Causes of increased DLCO:
        - Supine position
        - Exercise, asthma, obesity
        - Polycythemia
        - Intra-alveolar hemorrhage
        - Left to right intracardiac shunt
        - High carbon monoxide back pressure from smoking
        - Pregnancy
        - V/Q mismatch

Basics of reading a chest X-ray

- While performing an X-ray, the patient stands between the X-ray beam and a film.
- Types of Chest X-ray (according to the direction of the beam)
    - Anteroposterior: the beam source is anterior to the patient while the film is posterior. This is done in bedridden patients
    - Postero-anterior: the beam source is posterior to the patient while the film is anterior to him. This one is more common.
    - Decubitus: taken while the patient is lying down, typically on his side. Useful for differentiating pleural effusions from consolidation (e.g. pneumonia) and loculated effusions from free fluid in the pleural space. In effusions, the fluid layers out (by comparison to an up-right view, when it often accumulates in the costophrenic angles)
    - Lordotic view - used to visualize the apex of the lung, to pick up abnormalities such as a Pancoast tumour.
    - Expiratory view - helpful for the diagnosis of pneumothorax.
    - Oblique view - useful for the visualization of the ribs and sternum. Although it's necessary to do the appropriate adaptations to the x-ray dosage to be used.
- When reading the X-ray, you have to know the patient's gender. This is easy to differentiate based on the presence of absence of a breast shadow. If you know that the patient is a female, and the breast shadow is absent, she might have underwent mastectomy.
- To have a good X-ray, the patient must take a deep breath. This is done to let the diaphragm descend as much as possible. To ensure a good view, count the ribs. You should be able to see 6 anterior ribs and 8 posterior ribs.
- Make sure that the patient stands centrally. To ensure this, notice the distance between the right clavicle and manubrium sterni; then, compare this distance to the left side. These distances should be equal
- Make sure that the clavicles are retracted away from the lung fields.
- You should see the vertebrae and interveretbral discs until T4. Below this level, you should see the shadows of the other vertebrae. If you see below T4, the image is overpenetrated. If you cannot see T4, the image is underpenetrated.
- Look at the trachea; it is a black column of air. It should be central. If the trachea was shifted, it indicates lung collapse; however, the absence of a shifted trachea doesn't exclude lung collapse.
- It is important to look at the ribs in order to rule out any fractures. Fractures might lead to pleural effusion, pneumothorax, or pleurisy.
- Look at the heart and notice its size, shape and position. This is important in the diagnosis of cardiomegaly. To diagnose cardiomegaly, the heart's horizontal diameter should exceed 50% of the horizontal diameter of the chest. If cardiomegaly is present, you

should compare the current X-ray to an older one. Then, you should investigate the causes of cardiomegaly.

- To differentiate between lesions that lie anterior or posterior to the heart, look at the heart's borders. If the borders are not clear, the lesion is anterior. If the borders are clear, the lesion is posterior.
- Always compare between the left and right lung fields. Moreover, define the site, shape, and homogenousity of the lesion. If the borders of the lesion are clear, it is not a lymph node.
- Any straight line on the X-ray is a fissure.
- The usual sites of lung pathology:
    - Apex
    - Hilum and hilar lymph nodes
    - The area behind the heart
    - Costophrenic angle.
- Small circular lesions, referred to as "coin lesions", are indicative of metastasis.
- If you find a big lesion, look for smaller ones. They might inform you about the cause of the insult.
- Sometimes, you may see the azygous lobe; this is normal. The azygous vein might reach deep into the lung tissue; it appears as a coma-shaped shadow.
- If there is an old lesion that did not change in size, it can be ignored.
- One of the differential diagnoses of a hilar lesion is a lesion in the apical segment of the upper lobe.
- Silhouette sign: right lower lobe consolidation. The border of the heart remains visible.
- If the left lower lobe is collapsed, the lesion will be located behind the heart.

Acute respiratory failure

- Respiratory failure is defined as failure to maintain adequate arterial blood gas tensions. By definition, O_2 must be less than 60 mmHg or CO_2 >50 mmHg. One of them is enough to diagnose respiratory failure.
- Types of respiratory failure:
    - Type I: hypoxemic respiratory failure. When O_2 is <60
    - Type II: hypercapnic respiratory failure. When O_2 <60 and CO_2 > 50.
- How to take an ABG (arterial blood gases sample):
    - The patient is breathing room air and not taking O_2 supplements
    - Not on a high altitude. FiO_2 should be normal
    - No intra-cardiac shunt
    - The patient does not have primary metabolic acidosis.
    - The patient is awake, at rest, and not doing any sort of exercise. Physical activity will increase gas exchange.
- Other blood gas measurements:
    - ABG: arterial blood gases. It became available in the 1950's. it is the only reliable diagnostic test for respiratory failure.
    - Indirect measurements of gas tension:
        - Oximetry:
            - not superior to ABG.
            - It measures saturation, not partial pressure. Therefore, it is only beneficial with Hb saturation around 90%. It loses its sensitivity when saturation rises above 95% or falls below 80%.
            - Used in sleep studies, ICU monitoring, operating theaters, and emergency rooms
        - Trancutaneous measurement of PCO_2 and PO_2: not beneficial, used only in ICU and sleep study labs.
- Classifications of respiratory failure:
    - Lung failure:
        - Usually hypoxemic due to a pathology inside the lung. It affects gas transfer and V/Q ratios.
        - in lung failure, there is an initial V/Q mismatch. However, later on, refractory arterial hypoxemia occurs. In this case, the mechanism of hypoxemia is a shunt mechanism due to extreme V/Q mismatch. In this case, despite normal perfusion, ventilation is reduced drastically (zero). This will lead to the delivery of deoxygenated blood to the left side of the heart.
    - Respiratory pump failure:

        - The lung is normal, but the problem is in the pump system. The pump system is made of the diaphgram and other respiratory muscles.
        - If the muscles are weakened, this system will not be able to pump enough air from the atmosphere into the lungs. This is called pump failure.
        - Sometimes, pump failure might result from the presence of an upper airway obstruction:
            - Laryngeal edema
            - Foreign body aspiration
            - Tumors
            - Obstructive sleep apnea.
        - Respiratory pump failure is usually hypercapnic.
    - Defects of respiratory control:
        - Abnormal stimulation of the respiratory centers. Most commonly cause by overdose of narcotics.
        - CVA and intracranial pathologies are less common causes of this type of failure.
        - It is usually hypercapnic.
- Diagnosis of ARF:
    - Clinical suspicion; this is mainly achieved through a thorough history and physical examination. These usually reveal:
        - Pre-existing chronic respiratory diseases
        - Acute illness with high incidence of ARF
        - Symptoms and signs of ARF:
            - Cyanosis: when deoxyganted Hb is > 5
            - Tachypnea: can also be seen in patient with normal PO_2 in cases of execise, hyperventilation syndrome, and Kussmal breathing
            - Dyspnea: dyspnea and respiratory failure are not synonymous.
            - Use of accessory muscles
    - Confirmation by ABG analysis: in acute asthmatic attacks, we initially have low levels of CO_2 because the patient is hyperventilating. However, once we find normal CO_2 levels, this indicates that the patient is unable to hyperventilate due to muscle fatigue. This situation requires aggressive management.
    - Diagnostic steps to identify the specific etiology:
        - A patient presenting with fever and unilateral crackles: severe pneumonia
        - A patient is febrile, orthopnic, with bilateral crackles: pulmonary edema
        - A patient with a barrel chest and silent or poor airy entry: COPD
    - Tests to confirm the suspicion:
        - Chest X-ray: if it is normal, we can exclude pulmonary edema, pneumonia, and fibrosis.
        - Spiral angiogram: not a route diagnostic technique

        - V/Q scan: more available than a spiral angiogram
- Consequences of hypoxemia:
    - Decreased O_2 delivery to vital organs.
    - When PaO_2 falls below 50, saturation levels drop dramatically. This phenomenon is based on the shape of the O_2 dissociation curve.
    - Signs of hypoxemia and acidosis:
        - CNS: restlessness, anxiety, confusion, seizures, coma, and cerebral edema.
        - CVS: tachycardia and arrhythmias.
- Consequences of hypercapnia:
    - An acute increase in CO_2 will lead to respiratory acidosis. This can be life threatening because it can affect the heart's stability. This is why it is important to know the patient's pH rather than his $PaCO_2$.
    - Signs of hypercapnia:
        - Asterexis: flapping tremor
        - Tachycardia
        - Distention of the veins of the forearms (hot arms)
        - Clouding/altered level of consciousness (drowsiness, sleepiness, confusion, and coma)
        - Papilledema: rare sign of severe hypercapnia.
- Mechanisms of acute hypoxemic respiratory failure:
    - Alveolar hypoventilation
        - Caused by:
            - Neuromuscular disease
            - Diseases of the respiratory control center
            - Drugs overdose
            - Apnea
            - Neurological diseases
        - In alveolar hypoventilation, there is an increase in $PaCO_2$ levels. This means that these patients will develop respiratory acidosis.
        - There is an inverse relationship between alveolar ventilation and arterial CO_2. When alveolar ventilation increases, $PaCO_2$ will decrease. This happens in hyperventilation syndrome and on high altitudes.
        - If the decrease in PaO_2 is solely due to hypoventilation, then the alveolar-arterial gradient (A-a gradient) will be normal. Both P_AO_2 and P_aO_2 will be low; however, the difference will be less than 12.
        - Hypoxemia due to hypoventilation is the only mechanism in which the A-a gradient remains normal.
    - V/Q mismatch
        - It is the most common cause of wide A-a gradient.
    - Shunt

    - Diffusion limitation:
        - Diffusion problems cause an increase in A-a gradient; however, this is only appreciable after exercise. Therefore, diffusion limitation is not important cause of increased A-a gradient.
    - Low FiO_2 in cases of high altitudes.
- How can you differentiate between V/Q mismatch and a shunt?
    - If the patient is given 100% O_2, and the PaO_2 was corrected, this indicates a V/Q mismatch. However, if it was not corrected, this is a shunt.
- Calculating the A-a gradient:
    - A-a gradient = $P_AO_2 – P_aO_2$
    - $P_AO_2 = P_iO_2 – 1.25xP_aCO_2$
    - $P_iO_2 = F_iO_2(P_{atm}V_p)$
    - $P_AO_2=F_iO_2(P_{atm}-V_p) – (1.25xP_aCO_2)$
    - The normal value for the A-a gradient is about 10
- At saturation levels above 90%, most of the hemoglobin moelecules are saturated. Thus, increased the P_AO_2 will not increase oxygen content of the blood
- In hypoventilation, hypoxemia is usually corrected with a small increase in the fraction inspired of oxygen.
- V/Q mismatch:
    - It is a major mehanism by which ung diseases cause hypoxemia.
    - Arterial CO_2 content might be normal or elevated.
    - The most common diseases that cause a V/Q mismatch:
        - Chronic airway limitation
        - Interstitial lung disease
        - PE
    - Measure of V/Q mismatch:
        - High A-a gradient
        - It can be measured directly using the “multiple inert gases elimination” technique. However, this technique is not practicl
        - Decreased ventilation relative to perfusion
        - In the affected area, there will be a decrease in P_AO_2 and an increase in P_ACO_2
    - How can we have a normal P_aCO_2 value in V/Q mismatch?
        - Due to the increase in P_ACO_2 in the abnormal areas is compensated for by other normal lung regions. CO_2 extraction is directly proportional to ventilation
        - This means that in cases of V/Q mismatch, the disesase is not homogenous.
- Shunt:

- It is an extreme of V/Q mismatch. In a shunt, there is noo ventilation; however, the blood flow continues. Venous blood reaches the arterial circulation without being oxygenated.
- The shunt causes an increase in the A-a gradient. CO_2 removal is achieved by hyperventilation of the well perfused areas. Therefore, CO_2 concentrations fall within the normal range.
- Small increases in fraction inspired of oxygen have little or no effect. In many cases, you need 100% oxygen to reach an acceptable P_aCO_2 level. Therefore, it is critical to treat this refractory hypoxemia
- Shunts are usually associated with:
  - Cardiac causes or VSD
  - Lung problems (collapsed or fluid-filled alveoli) in cases of pulmonary edema and pneumonia
  - Chest X-ray shows pulmonary infiltrates. Other mechanisms of hypoxemia are associated with a normal chest X-ray
- PEEP migh improve P_aO_2 in cases of refracctory hypoxemia due to a shunt. PEEP will cause:
  - Lung expansion and this will open the collapsed alveoli
  - It keeps lung units at a higher volume; this allows for some ventilation.

- Principles of management:
  - Maintain adequate airway
  - Correct inadequate oxygenation
  - Correct respiratory acidosis
  - Maintain cardiac output and tissue oxygen delivery.
  - Treat the underlying process by its definitive management.
  - Avoid preventable complications: patients usually die of underlying lung diseases or complications like sepsis and respiratory infections.
- Goal of oxygen therapy: Increasing P_aO_2 while avoiding O_2 toxicity:
  - In COPD patients, we only aim for P_aO_2 55-60. The main stimulus of the respiratory center in those patients is oxygen rather than CO_2. If P_aO_2 rises above 60, the respiratory centers will be inhibited causing respiratory acidosis and coma
  - If a pateints is in trauma, we aim for P_aO_2 of about 80
  - In ARDS, we have refractory hypoxia. We aim at P_aO_2 of about 80.
- Mechanisms of O_2 toxicity:
  - Toxicity in COPD patients: excessive O_2 therapy might lead to hypercapnia; however, if it was treated carefully, we can avoid this unfortunate fate.

    - Parenchymal lung injury: thi sis related to both dose and duration. The safest fraction of inspired oxygen is 60%. If you want to administer 70 or 90% oxygen, make sure that this will be for a short duration. An increase in the amount of inspired oxygen will cause free radical toxicity.
- Supplemental O_2 delivery methods:
    - If you require a slight increase in P_aO_2, nasal prongs or a Venturi mask would be sufficient. ABG's need to be taken every half an hour.
    - For higher increases in O_2 levels, a standard face mask or a non-rebreathing mask might be adequate. If they did not suffice, consider endotracheal intubation and oxygen delivery via a closed system
    - PEEP/CPAP: helps patients with reduced FRC due to a lung disease. These help increase FRC by opening areas of microatelectasis. This improve P_aO_2 and convers shunt units to low or normal V/Q units. Here, we have to be careful as these measure might impair oxygenation.
- Measures to correct respiratory acidosis:
    - Goal:
        - Avert life-threatening acidosis without necessarily correcting P_aCO_2.
        - Partial correction is usually sufficient; this is referred to as permissive hypercapnea. We can adapt to permissive hypercapnia.
        - With acute hypercapnia, acidosis will follow because the body does not have time to compensate
    - Management:
        - Pharmacological therapy: bicarbonate admission. It is rarely used and only reserved for severe abnormalities. It might lead to metabolic alkalosis.
        - Mechanical ventilation: radily corrects acidosis. Can be done through intubation or nasal ventilation (BiPAP).
        - Treatment of the underlying disease
        - Treat chronic airflow obstruction using bronchodilators like theophylline and steroids.
- ARF in COPD patients:
    - The mechanism of respiratory failure is a V/Q mismatch with or without hypoventilation. This, these patients improve with slight increases in fraction inspired oxygen.
    - Monitoring hypoxemia and correction of acidosis with ABGs is very important. Do not correct oxygen at the expense of worsening acidosis. However, you need to know that hypoxemia is more dangerous than acidosis.
    - Management of respiratory acidosis by bronchodilators, removal of secretions, and corticosteroids admission
    - Mechanical ventilation must be avoided because it might lead to complications. Less than 10% of the patients require mechanical ventilation.

    - ABG's do not help; there is no absolute ABG to initiate ventilation. The decision depends on the patient's clinical picture. We use mechanical ventilation if:
        - The patient has rapid shallow breathing
        - Has paradoxical abdominal movement
        - The patient has respiratory alternans
- Discussion of arterial blood gas abnormalities using the two-lung unit model: this part contains a lot of repetition. It is intended for those who did not understand the previous discussion.
    - Arterial hypoxemia is defined as an arterial PO_2 less than 80 mmHg in an adult breathing room air at sea level.
    - Hypoxia occurs when there is insufficient Oxygen to carry out normal metabolic functions; hypoxia often occurs when arterial PO_2 fall below 60 mmHg.
    - Hypercapnia is defined as an increase in arterial PCO_2 above the normal range (40±2)
    - Hypocapnia is an abnormally low arterial $PCO_2 < 35$ mmHg
    - To examine the relationship between ventilation and perfusion, we are going to use the two-lung unit model.
        - Two alveoli are ventilated; each of which is supplied by blood from the heart.
        - When ventilation is uniform, half of the inspired gas goes to each alveolus.
        - In this normal unit, the V/Q ratio is 1.
        - The alveoli are perfused with mixed venous blood. This blood contains high levels of CO_2.
        - Alveolar O_2 is higher than mixed venous O_2. This provides a gradient for the movement of O_2 into the blood.
    - Arterial hypoxemia happens through 5 different mechanisms an anatomic shunt, a physiological shunt, V/Q mismatch, diffusion abnormality, and hypoventilation. There are two mechanisms for hypercapnia increased dead space and hypoventilation. A change in cardiac output is the only non-respiratory factor that affects gas exchange.
    - Anatomical shunt:
        - An anatomical shunt occurs when mixed venous blood bypasses the gas exchange unit and goes directly to the arterial blood.
        - Alveolar ventilation, the distribution of alveolar gas, and the composition of alveolar gas are normal; however, the distribution of the cardiac output is changed.
        - Some of the cardiac output passes through the pulmonary capillary bed that supplies the gas exchange unit. However, the rest bypasses the gas exchange units and goes directly into arterial blood. The blood that bypasses the gas exchange unit is called "shunted blood".

        - Because this blood is deoxygenated, this is called a right-to-left shunt.
        - Most anatomical shunts occur within the heart' they occur when deoxygenated blood from the right atrium or ventricle crosses the septa and mixes with blood from the left atrium or ventricle.
        - The effect of this shunt is mixing of deoxygenated and oxygenated blood. This results in varying degrees of hypoxemia.
        - The response to administration of 100% oxygen is blunted. The blood that bypasses the gas exchange units is never exposed to the increased oxygen. Therefore, it continues to be deoxygenated.
        - The degree of persistent hypoxemia in response to 100% oxygen therapy varies with the amount of shunted blood. Normally, the hemoglobin in the blood that perfuses the ventilated alveoli is fully saturated. Therefore, most of the added O_2 will be in the form of dissolved oxygen.
        - The arterial PCO_2 in an anatomical shunt is not increased. The reason behind this is that the central chemoreceptors respond to the elevation in CO_2 by increasing ventilation. If the hypoxemia is severe, the increased respiratory drive, secondary to the hypoxemia, increases the ventilation and can decrease arterial PCO_2 to below the normal range.
    - Physiological shunt:
        - A physiological shunt develops when there is enough perfusion without any ventilation. This is called venous admixture.
        - Using the two-lung unit model, we can say that all of the ventilation goes to the other lung unit. However, perfusion is equally distributed between both units.
        - The unit in which there is no ventilation has a V/Q ratio of zero. The blood perfusing that unit is mixed with venous blood.
        - Due to the lack of ventilation, there will be no gas exchange in that unit. The blood leaving this unit continues to be mixed venous blood.
        - The effect of a physiological shunt on oxygenation is similar to that of an anatomical shunt.
        - Clinically, atelectasis is an example of a lung region of a V/Q ratio of zero. Causes of atelectasis include mucous plugs, airway edema, foreign bodies, and tumors in the airway.
    - Ventilation perfusion mismatch (low V/Q):
        - It is the most common cause of arterial hypoxemia in patients with respiratory disorders.
        - In the most common example. The composition of mixed venous blood, total blood flow, and the distribution of blood flow are normal.

        - However, when alveolar ventilation is distributed unevenly between the two gas exchange units, the unit with decreased ventilation has a V/Q ratio less than 1.
        - The unit with increase ventilation has a V/Q ratio more than 1. This causes the alveolar end-capillary gas composition to vary.
        - Blood coming from the under-ventilated unit will have abnormal O_2 and CO_2 concentrations. However, blood coming for the hyperventilated unit, will have higher O_2 and lower CO_2 content.
        - The A-a gradient will increase because the relative hyperventilation of one unit will not compensate for the underventilation of the other unit. Most of the added oxygen will be in form of dissolved oxygen.
    - Alveolar hypoventilation:
        - Alveolar O_2 is determined by a balance between the rate of oxygen uptake and oxygen replenishment by ventilation.
        - Oxygen uptake depends on blood flow through the lung and the metabolic demands of the tissues.
        - If ventilation decreases, alveolar PO_2 will decrease and arterial PO_2 will, subsequently, decrease. Moreover, alveolar ventilation and alveolar CO_2 are directly related.
        - When ventilation is halved, the alveolar CO_2 content, and thus arterial CO_2 content, doubles.
        - Ventilation insufficient to maintain normal levels of CO_2 is referred to as hyperventilation. Hypoventilation always decreases P_aO_2 and increases P_aCO_2.
        - One of the hallmarks of hypoventilation is a normal A-a gradient. Hypovntilation reduces alveolar O_2 which, in turn, results in a decrease in arterial O_2. Because gas exchange is normal, the difference between alveolar and arterial O_2 remains normal.
        - Hypoventilation is seen in individuals with diseases associated with muscle weakness and in association with drugs that reduce the respiratory drive.
        - In the presence of hypoventilation, areas of atelectasis develop rapidly. Atelectasis increases regions with V/Q rations of 0. When this happens, the A-a gradient rises.
    - Diffusion abnormalities:
        - Abnormalities in O_2 diffusion across the alveolar-capillary barrier can potentially result in arterial hypoxia.
        - Equilibrium m between alveolar and capillary O_2 and CO_2 content occurs rapidly. In fact it happens in a fraction of the time that it takes for red blood cells to transit across the pulmonary capillary network.

- Therefore, diffusion equilibrium almost always occurs in normal subjects, even during exercise.
- An alveolar-arterial PO_2 difference is attributablee to incomplete diffusion (diffusion disequiblibrium) has been observed in normal individuals only during exercise at high altitudes.
- Even in individuals with abnormal diffusion capacity, diffusion at rest is normal.
- Alveolar capillary block or thickening of the ari-blood barrier is an uncommon cause of hypoxemia. Even with a thickened alveolar wall, there is sufficient time for gas diffusion.

- Mechanisms of hypercapnia:
  - Twp major mechanisms account for the development of hypercapnia: hypoventilation and wasted ventilation.
  - As noted previously, alveolar ventilation and alveolar CO_2 are inversely related. When ventilation is halved, alveolar CO_2 and arterial CO_2 are doubled.
  - Hypoventilation decreases PO_2 and increase PCO_2; therefore, it results in a hypoxemia that responds to an enriched source of oxygen.
  - Wasted or dead space ventilation occurs when pulmonary blood flow is interrupted in the presence of normal ventilation. This occurs due a pulmonary embolus that obstructs blood flow
  - The embolus stops the blood flow to pulmonary areas with normal ventilation. This results in an undefined V/Q ratio; here Q is zero.
  - In this situation, the ventilation is wasted because it fails to oxygenate any of the mixed venous blood. The ventilation to the perused regions of the lung is less than idea. This means that there is relative hypoventilation to this area.
  - If compensation does not occur, PCO_2 would increase and PO_2 would decrease. However, compensation starts immediately. Local bronchocontriction shifts the distribution of ventilation to the areas being perfused. As a result, changes in arterial CO_2 and O_2 content are minimal.

Cause	Arterial PO_2	A-a gradient	Response to 100% O_2
Anatomic shunt	decrease	Increase	No change
Decrease F_iO_2	decrease	normal	increased
Physiologic shunt	decrease	increase	decreased
Low V/Q ratio	decrease	increase	increased
Diffusion abnormality	decrease	increase	increased
Hypoventilation	decrease	normal	increased

Acid base disturbances

- Note: For a detailed discussion about acid base calculations, refer to Med Study Book 2: Nephrology. This lecture contains some theoretical information along with some examples. It has nothing on the methodology of calculating acid-base disturbances. In fact, acid-base balance is not an important part of "respiratory medicine". It is more pertinent to nephrology.

- Although acidemia is bad, it may prevent ischemia, infarction, and reduce hypoperfusion injury:
    - It increases cardiac output and splanchinc blood flow
    - It activates many inflammatory pathways
    - It may emit intracellular calcium overload
    - It down-regulates cellular metabolism
    - It shifts the oxygen dissociation curve to the right; this allows for easier O_2 dissociation.
- Effects of alkalemia:
    - Arrhythmias
    - Increased coronary blood flow
    - Increased cerebral blood flow
    - Seizures
    - V/Q mismatch
    - Lung injury
    - Decreased levels of calcium, potassium, magnesium, and phosphorus.
- How to investigate acid-base disorders?
    - Look at the pH: normal, acidemia, alkalemia
    - Know the cause: respiratory, metabolic
    - Calculate the anion gap and calculate Δ anion gap
- What do we need to calculate a patient's acid-base balance? ABG's and electrolytes.
- In acid-base disorders, a pH of 7.4 is only reached in cases of chronic respiratory alkalosis. Otherwise, if we see a pH of 7.4, it indicates the presence of a complex disorder.
- Types of acid-base disturbances:
    - Simple acid base disorders: respiratory acidosis, respiratory alkalosis, metabolic acidosis, or metabolic alkalosis
    - Mixed acid-base disorders: mostly seen in the ICU.
- Metabolic acidosis and metabolic alkalosis can coexist, but how? (Ex. DKA or hypoperfusion)
    - These patients have acidemia

    - They start vomiting. When they vomit, they lose H^+.
    - Here, acidosis and alkalosis develop together. The pH might be normal, but there will be an increase in the anionic gap.
- The Handerson-Hasselbach equation describes the derivation of pH as a measure of acidity. The equation is useful for the estimation of the pH of a buffer solution and for finding equilibrium in an acid-base reaction.
    - The equation: $pH = 6.1 + \log(\frac{[HCO^{3-}]}{[PaCO_2 \times 0.03]}]$
    - Modified equation: $[H^+] = \frac{24 \times PaCO_2}{[HCO^{3-}]}$
    - Cases:
        - Case 1: pH 7.32, $PaCO_2$ 48, PaO_2 15, HCO^{3-} 24; applying the Handerson-Hasselbach equation, are these values correct?
            - pH is acidic; the underlying cause is respiratory; yes, the data is consistent with the Handerson-Hasselbach equation.
        - Case 2: pH 7.5, $PaCO_2$ 30, PO_2 104, HCO^{3-} 15
            - pH alkelemia; when we plug the numbers into the equation, the values don't match. Therefore, the data is inaccurate.
- Anion gap:
    - AG = Na^+ - (Cl^- + HCO^{3-}); the normal value is about 12. It represents the unmeasured anions in the serum. These include phosphate, citrate, sulphate, and negatively charged proteins)
    - Anionic gap categories:
        - High anionic gap metabolic acidosis
        - Normal anionin gap metabolic acidosis (hyperchloremic metabolic acidosis)
    - The nature of the acid determines the anionic gap:
        - If it was HCl: for each mole of HCO^{3-}, 1 mole of Cl^- will be retained. This will lead to a normal anionic gap metabolic acidosis (NAGMA)
        - If it was lactate or acetolactate, HCO^{3-} will be consumed to form sodium salts. This will increase the anionic gap because there is no change in the plasma's chloride. High anionic gap metabolic acidosis (HAGMA)
    - Causes of HAGMA:
        - Lactic acidosis due to anaerobic metabolism. This can be caused by some drugs like metformin, NRTI's, lorazepam, and propofol.
        - Hypoperfusion
        - Decrease oxygen
        - Sepsis due to shunting
        - Ketoacidosis
        - Renal failure
        - Toxins ingestion

    - Causes of NAGMA:
        - GI losses; diarrhea
        - Renal losses: RTA or renal injury
        - Hypoaldosteronism
        - Excess NH_4Cl administration
        - Sigmoidoscopy
        - Acetolzamide administration
    - Causes of a negative anionic gap:
        - Hypoproteinemia
        - Hypoalbuminemia
        - Lithium toxicity
        - Increased K^+, Mg^{2+}, Ca^{2+}, or GI poisoning
- ΔAG:
    - Deviation of the calculated anionic gap from the normal anionic gap.
    - This value is added to the measured HCO^{3-}:
        - If it was more than normal: metabolic alkalosis
        - If it was less than normal: NAGMA
- Causes of metabolic alkalosis:
    - Diuretics
    - Corticosteroids
    - Nasogastric suctioning
    - Vomiting of gastric content
    - Severe dehydration (contraction alkalosis)
- Causes of respiratory acidosis:
    - CNS depression
    - Neurological disorders
    - Increased CO_2 production
    - Airways disaease
    - Inappropriate ventilator settings
- Causes of respiratory alkalosis:
    - Voluntary hyperventilation
    - Anxiety
    - Hypoxemia
    - Liver failure
    - Pneumonia
    - Pulmonary embolism
    - High altitudes
- Clues to complex acid base disturbances:
    - Normal pH

    - PCO_2 and HCO_3^- should deviate in the same direction. In the case of respiratory acidosis, CO_2 is high; the compensatory mechanism is increasing HCO_3^-. However, if HCO_3^- is decreased, it indicates a complex disorder.
    - A change of the pH in a direction opposite to that of the primary disorder. If the patient has a severe lung disease with respiratory acidosis, and the pH was found to be increased, it indicates a complex disorder.
- Clues to diagnosing respiratory alkalosis with metabolic acidosis:
    - In sepsis:
        - Stimulation of the respiratory centers produces respiratory alkalosis
        - Microcirculatory shunting causes metabolic acidosis
    - Salicylate intoxication:
        - Acidosis in the blood
        - Stimulates respiratory centers causing respiratory alkalosis
    - Renal insufficiency + heart failure
    - Liver disease:
        - The increase in progesterone synthesis stimulates the respiratory centers leading to respiratory alkalosis
        - Lactic acidosis due to hypoperfusion
    - Diabetic ketoacidosis + pulmonary embolism
- Causes of respiratory and metabolic acidosis together
    - Cardiopulmnary arrest
    - Alcohol intoxication
    - COPD + DKA
    - Renal failure
    - Severe pulmonary edema
- Cases:
    - ABG: pH 7.23, PCO_2 27, PO_2 100, HCO_3^- 11. Electrolytes: Na^+ 136, Cl^- 100, K^+ 4
        - Anionic gap= 24
        - Delta AG: 12
        - This is a case of HAGMA.
    - pH 7.3, PCO_2 31, PO_2 96, HCO_3 15, Na 136, Cl 108
        - acedmia
        - anionic gap: 12
        - delta AG: 0
        - this is a case of NAGMA
    - pH 7.18, PCO_2 25, PO_2 104, HCO_3 9, Na 138, Cl 109, K 4
        - acidemia
        - anionic gap: 19
        - delta AG: 7

        - this is a case of HAGMA + NAGMA
    - pH 7.47, PCO_2 45, PO_2 86, HCO_3 32, Na 140, Cl 94, K 3
        - alkelemia
        - anionic gap 13 (normal)
        - delta AG: 1
        - simple metabolic alkalosis + respiratory acidosis
    - pH 7.44, PCO_2 30, PO_2 86, HCO_3 32, Na 136, Cl 103, K 4
        - normal pH
        - anionic gap: 13
        - delta gap: 1
        - this is a case of respiratory alkalosis with metabolic compensation
    - pH 7.32, PCO_2 60, PO_2 60, HCO_3 30, AG 12
        - acidemia
        - normal AG
        - respiratory acidosis
    - pH 7.1, PCO_2 50, PO_2 70, HCO_3 15, Na 141, Cl 109, K 4
        - AG: 20
        - Delta AG: 8
        - HAGMA + respiratory acidosis
    - pH 7.4, PCO_2 15, PO_2 110, HCO_3 9, Na 136, Cl 100, K 4
        - AG: 26
        - Delta AG: 14
        - HAGMA + respiratory alkalosis
    - pH 7.41, PCO_2 52, PO_2 76, HCO_3 32, Na 140, Cl 95
        - metabolic alkalosis + respiratory acidosis
    - pH 7.59, PCO_2 35, HCO_3 32, Na 140, Cl 95
        - metabolic + respiratory alkalosis
    - pH 7.39, PCO_2 43, PO_2 98, HCO_3 25, Na 140, Cl 90
        - normal pH
        - AG: 24
        - Delta AG: 12
        - HAGMA + hidden metabolic alkalosis
    - pH 7.14, PCO_2 60, HCO_3 20, Na 136, Cl 86
        - AG: 30
        - Delta AG: 18
        - HAGMA, metabolic alkalosis, and respiratory acidosis
    - pH 7.42, PCO_2 16, HCO_3 10, Na 140, Cl 112
        - AG: 18
        - Delta AG: 6
        - HAGMA + NAGMA

- pH 7.4, PCO_2 40, HCO_3 24, AG=0
  - hypoalbuminemia or paraproteinemia (multiple myeloma)
- What is your diagnosis: pH 7.6, PCO_2 30, PO_2 90, HCO_3 27, Na 134, K 4, Cl 88
  - COPD + sepsis
  - **Pregnancy + hyperemesis**
  - Liver disease + renal failure
  - COPD + diuretics
- What is the best interpretation: pH 7.32, PCO_2 24, PO_2 95, HCO_3 20, Na 135, Cl 101, K 4.5
  - Metabolic acidosis
  - Metabolic acidosis + metabolic alkalosis
  - Metabolic acidosis + respiratory acidosis
  - **Data is inaccurate**

Pleural effusion

- The lung is surrounded by visceral and parietal pleura; in between them lies a potential space called the pleural cavity. The pleural cavity contains minimal amounts of pleural fluid. The parietal pleura is thicker, lines the chest wall and the diaphragm, and it is supplied by the systemic circulation. The visceral pleura covers the lungs and it is supplied by the pulmonary circulation. It is larger in surface area because it covers the whole lungs including the fissures.
- Characteristics of pleural fluid:
    - Volume: 5-20 mL
    - pH: alkaline; 7.6
    - white cell count 1500-1700cell/mm^2:
        - macrophages: 75%
        - monocytes: 24%
        - mesothelial cells: 1%
- Dynamics of pleural fluid:
    - Fluids are kept in blood vessels by two forces the hydrostatic pressure and the oncotic pressure.
    - Both of these pressures are present in the pulmonary and systemic circulations.
    - The oncotic pressure is the same, but the difference is in the hydrostatic pressure.
    - There is a balance between the oncotic and hydrostatic pressures on both sides of the pleural fluid.
    - This maintains the pleural fluid at a constant amount in the pleural space.
    - Any problem with this balance will cause the amount of pleural fluid to increase.
- How does the pleural fluid circulate?
    - The fluid is formed by the parietal pleura and is absorbed by the visceral pleura.
    - An increase in the secretion or a decrease in absorption will lead to accumulation of the pleural fluid.
- Causes of pleural effusion:
    - Increased capillary hydrostatic pressure: heart failure and SVC obstruction
    - Decreased pleural space hydrostatic pressure: rare and it is seen in cases of re-expansion of a pneumothorax. When the lung has collapsed in a case of massive pneumothorax, and suction was performed, the rapid expansion of the lung will cause a decrease in the pleural space hydrostatic pressure
    - Decreased capillary oncotic pressure in cases of cirrhosis, nephritic syndrome, acute glomerulonephritis, and hypoproteinemia.
    - Increased pleural space oncotic pressure caused by an increase in the permeability of the pleura.
- Pleural fluid in a pleural effusion is classified into two types:
    - Exudate: usually rich in proteins. Caused by an increase in the permeability. Can be diagnosed if one of the following criteria was present: (Light's criteria)

        - Rich in proteins compared to serum (>50%)
        - High LDH compared to serum (>60%)
        - LDH of pleural fluid more than 2/3 the upper limit of serum LDH
    - Transudate: usually low protein and LDH content. Caused by an increased in the hydrostatic pressure.
- Cause depending on the nature of the fluid:
    - Transudative:
        - Congestive heart failure
        - Nephrotic syndrome
        - Liver cirrhosis
    - Exudative:
        - Paraneumonic
        - TB
        - Malignant
        - Pulmonary embolism
        - Connective tissue disease
        - Uremia
        - Postcardiac injury syndrome
        - Post CABG
        - Pancreatitis
        - Familial Mediterranean fever (FMF)
        - Myxedema
        - Meig's syndrome: ovarian fibroma, ascites, right pleural effusion
- How to differentiate between types of fluid?
    - Look:
        - Serous: transudative
        - Serosanguinous: serous with a little blood from mthe needle
        - frank blood: hemorrhage
        - Bloody: malignant or pulmonary embolism
        - Purulent: complicated parapneumonic
        - Milky: chylous (lymph)
    - Light's criteria
    - RBC count:
        - <5000: serous
        - 5000-10,000: serosangionous; can still be transudative
        - >10,000 bloody
        - >100,000 hematocrit effusion
    - WBC count:
        - Neutrophil predominance: >50%; parapneumonic effusion or PE
        - Lymphocyte predominance >50%: malignant or TB

    - Eosenophilic: >10%. PE, may indicate fungal or parasitic infection. If it was after the second tap, it is most probably iatrogenic.
    - pH:
        - if it below 7.2, and the patient has pneumonia, think of complicated parapneumonic effusion.
        - Other conditions with acidic effusions:
            - Rheumoatoid arthritis
            - Malignant ; effusion
            - Esophageal rupture
    - Glucose
    - Microbiology: gram stain and culture for all bacterial and fungal infections. If the patient has pneumonia, and the effusion is positive for culture, this is a complicated parapneumonic effusion. This is an indication for drainage; antibiotics will not help in this case.
    - Triglycerides and chylomicrons in the case of chylothorax. The patient has chylothorax if the triglycerides are more than 110.
        - Associated with lymphangioleimyomatosis, trauma, malignany or any conditions that blocks the lymphatics
    - Cytology: for malignant. The sensitivity of the first tap is 60%. Repeated taps increase sensitivity up to 90% with the third tap.
    - Amylase: there are two isoforms of amylase, salivary and pancreatic amylase. In esophageal rupture, salivary amylase is elevated. In cases of pancreatitis, pancreatic amylase is elevated.
    - Creatinine: for urothorax. It is defined as the presence of urine in the pleural space due to a trauma or obstruction that lead to urinary leak into the retroperitoneal space. The kidney and ureters are retroperitoneal structures; therefore, the urothorax will develop ipsiliateral to the affected side. Pleural/serum creatinine ratio of more than 1 is diagnostic of urothorax.
- Clinical picture: physical signs are apparent when the pleural fluid exceed 300 mL.
    - Symptoms of the underlying disease
    - Symptoms due to the presence of an effusion. This depends on the amount and rate of accumulation. These signs include:
        - Dull percussion
        - Decreased TVF
        - Decreased or absent breath sounds
        - Bronchial breathing with collapsed lung
        - Friction rub with inflammation
        - Crepitations
    - With a massive pleural effusion (>1L), you may observe shifting of the mediastinum. This is documented by shifting of the trachea and the apex beat.

- Investigations:
    - Chest X-ray:
        - Fluid in the pleural space can accumulate in many places. The most common form of accumulation is free fluid accumulation. This obliterates the costophrenic angle. Then, it ascens towards the axilla. This is called the meniscus sign
        - If the patient is supine, the fluid will go posterioly; thus, we will not be able to see it.
        - Encysted fluid does not move upon changing the patient's position. Sometime, the fluid can go to the oblique fissure or transverse fissure.
        - Phantom pleural effusion: a pleural effusion that disappears on its own. It may happen in cases of tuberculosis and sarcoidosis.
        - Sometimes, the fluid accumulates below the lung and above the diaphragm. The diaphragm appears elevated. We ask the patient to lie on his/her side to the fluid slope. This procedure is called a decubitus X-ray.
    - CT scan: can be helpful in diagnosis, especially if there is a mass or collapse in the lung
    - Pleural fluid aspiration: (thoracocentesis)
        - It is important as a diagnostic and a therapeutic procedure
        - Aspiration is needed for:
            - Determine the nature of the fluid
            - Protein concentration
            - LDH
            - Sugar, pH, and amylase
            - Cytology
            - Bacteriology
            - Immunology (compliment, ANA, RF)
        - If the underlying disease is heart failure, there is no need for aspiration. The patient is started on medications. If the patient does not respond to medications, aspiration is necessary.
        - Complications:
            - Infection
            - Bleeding
            - Pneumothorax
            - Spleen or liver injuries
    - Pleural biopsy:
        - Blind biopsy: we use a needle to take a biopsy from the visceral and parietal pleura. The needle is called an Abraham needle.
        - Pleuroscopy: bipsy from the site of the lesion
- Treatment:

    - Treat the underlying cause
    - Drain fluid by aspiration; the best is to remove the fluid slowly (less than 2L/day)
    - In patients with incurable causes of effusion, pleurodesis is performed. The two layers of pleura are stuck together to prevent further fluid accumulation.
    - Intrapleural streptokinase: to break down pleural adhesions in cases of encysted effusions.
    - Surgery: for persistent collections caused by increased pleural thickening. Sometimes, a shunt is created to relieve the effusion.
- Summary of causes of pleural effusion:
    - Parapneumonic effusion:
        - Exudative
        - Glucose >60; might be normal if there infection in the fluid
        - A parapneumonic effusion is associated with empyema
        - pH <7.2
        - gram stain or culture positive
        - neutrophilic predominance
    - pulmonary embolism:
        - Generally exudative, but can be transudative.
        - Elevated EBC count with neutrophilic or eosenophilic predominance
    - TB:
        - Exudative pleural effusion
        - Elevated WBC with lymphocyte predominance
        - Staining can miss 90% of the cases. Culture detects up to 40% of cases.
        - PCR increases sensitivity to 80%
    - Malignant effusions:
        - Exudative
        - Bloody
        - Lymphocyte predominance
        - Positive cytology for malignant cells
    - Hepatic hydrothorax:
        - Happens in cases of cirrhosis with significant ascites.
        - This increases the intra-abdominal pressure causing leakage of the fluid to the pleural space.
        - Transudative; serous
        - No further investigations needed
    - Decompensated CHF:
        - Transudative, but can be exudative if patients are on diuretics
        - Bilateral in 70% of the cases
        - Unilateral in 30% of cases (right > left)

- Hemothorax: Hematocrit ratio > 0.5
- Empyema: purulent effusion. You can see it and smell it. pH <7.2
- Urothorax: creatinine ratio >1
- Chylothorax:
  - Triglycerides > 110
  - Presence of chylomicros
- Cardiac causes include CHF, Dressler's syndrome, or pericarditis
- Renal causes:
  - Nephrotic syndrome
  - Urothorax
- GI causes:
  - Liver disease with hypoalbuminemia
  - Hepatic hydrothorax
  - Liver abscess
  - Pancreatic disease
  - Esophageal rupture

ARDS

- Acute respiratory distress syndrome, previously known as adult respiratory distress syndrome, is a condition characterized by acute hypoxemic respiratory failure. ARDS is a typical example of hypoxemic respiratory failure due to pulmonary edema caused by an increase in the permeability of the alveolar capillary barrier
- Pathogenesis: leaking from pulmonary capillaries due to inflammation
- Acute lung injury: it is a clinical stage that precedes the real ARDS. It is a complication of a more widespread systemic response to acute inflammation or injury. It is a characterized by severe hypoxemia of an acute onset with bilateral diffuse opacities on chest X-ray without left atrial or pulmonary hypertension. These patients have a normal left atrium and normal pulmonary pressure. To diagnose ALI PO_2/FiO_2 needs to be in the range of 200-300.
- In a normal individual, PO_2/FiO_2 is 300 or higher. In patients with ARDS, this ratio decreases below 200.
- Conditions leading to ARDS:
    - Direct injury:
        - Pneumonia: common
        - Aspiration with or without pneumonia
        - Inhalation of toxins
        - Near drowning
        - Airway contusion
        - Injuries outside the lung (multiple fractures)
    - Indirect injury:
        - Sepsis
        - Severe trauma
        - Hypertranfusion
        - Cardiopulmonary bypass.
- Sepsis is the most common cause of ARDS.
- ARDS usually causes non-cardiogenic pulmonary edema
- Pathophysiology:
    - The systemic inflammatory response to infection, injury or toxins includes three phases:
        - Initiation: the trigger event that activates the cellular cascade
        - Amplification: recruitment of effector cells
        - Injury: production of cytokines, chemotaxins, and adhesion.
- The aforementioned process will result in:
    - Increased vascular permeability to proteins. This causes interstitial or alveolar edema
    - Increased alveolar closing pressure, which exceeds local trans-pulmonary pressure. This causes early closure of alveoli, which leads to collapse.

    - Decreased surfactant synthesis to due to injury of type 2 pneumocytes. Although this has a role in the pathogenesis of ARDs, it was found out that ARDS patients have normal surfactant levels. This means that what is affected is the function rather than the amount of surfactant
    - Several clinical trials have been carried out to assess the efficacy of surfactant treatment. The results were not promising; this indicates that surfactant does not play a major role in the pathogenesis of ARDS.
    - The atelactatic regions contribute to a reduction in compliance of the lung as whole.
    - Due to decreased compliance, a large inspiratory pressure must be generated. This means that there will increase work of breathing. The patients starts to breath rapidly.
    - Role of certain mediators:
        - thromboxanaA2: a potent vasoconstrictor. It is active in patients with pulmonary hypertension.
        - Leukotrienes: induce vasoconstriction in airways and lung vessels. Moreover, the increase permeability.
- Diagnostic criteria:
    - Acute onset
    - Refractory hypoxia
    - Diffuse bilateral infiltrates
    - Shunt hypoxemia mechanism
- Investigations:
    - Blood tests: CBC, electrolytes, clotting (PT, PTT), amylase, CRP and blood culture
    - ABG
    - Chest X-ray
    - Pulmonary artery catheterization
- Clinical manifestations:
    - Symptoms and signs of the underlying disease
    - Initial injury:
        - tachypnea, dyspnea, hypoxia, a decrease in CO_2 due to hyperventilation., and increased A-a gradient.
        - Crackles on chest examination
        - Chest X-ray shows normal or minimal interstitial infiltrate
    - ARDS stage:
        - Prominent symptoms
        - Chest X-ray shows diffuse extensive bilateral and alveolar infiltrates.
        - PO_2/FiO_2 <200

        - Severe refractory hypoxia. These patients require non-invasive ventilation, intubation, or mechanical ventilation. Hypoxia cannot be corrected due to the presence of a right-to-left shunt.
- Clinical phases of ARDS:
    - Exudative phase (cellular phase)
        - A lot of cells
        - Alveolar space damage
        - Capillary injury
        - Chest X-ray findings:
            - Bilateral infiltrations
            - Cant' be differentiated from cardiogenic pulmonary edema
    - Proliferative phase: fibrosing alveolitis
        - Improper healing process leads to fibrosis
        - Significant pulmonary hypertension
        - Chest X-ray findings: not as prominent as the exudative phase
        - Here, you cannot do anything
    - Recovery phase:
        - Gradual resolution of hypoxemia
        - Chest X-ray is normal
        - Functionally, the lung is back to normal
        - Alveolar septa are back to normal
- Management:
    - The patient is transferred to the ICU and given sedation with analgesia. Sometimes, the patient might need to be paralyzed using muscle relaxants. This is done to decreased O_2 consumption:
        - Benzodiazepenes: diazepam, medozolam; both cause hypotension
        - Narcotics: morphine, mepridine, fentanyl (widely used nowadays. It is an analgesic that does not cause nausea vomiting, or hypotension)
        - Neuromuscular paralyzing drugs to decrease O_2 consumption. They are used when the patient needs synchronized intermittent mechanical ventilation (SIMV). Muscle relaxants help suppress spontaneous breathing. Side effects of muscle relaxants include prolonged muscles weakness and skin ulcers due to immotility.
    - Fluid administration: needed to keep normal hemodynamics. This means normal blood pressure, no depletion in vascular volume, and PCWP >12 (monitored through a Swan-Ganz catheter)
    - Nutrition: these patients have high metabolic rates. Therefore, high amounts of food are needed to help the patients fight the inflammation. Most of the time, we have to use parenteral nutrition. These patients need a lot of trace elements and vitamins.
    - Ventilation to treat hypoxia:

        - No ideal mode for ARDS ventilation; however, SIMV is the most commonly used mode.
        - Lowerst FiO_2 for adequate oxygenation
        - Use small tidal volume (6 mL/kg) to prevent alveolar collapse. Using high volume ventilation leads to barotrauma
        - PEEP: 5-15 cm H_2O to improve compliance.
    - Pharmacological treatment:
        - No specific treatment
        - Antioxidants: N-acetylcysteine; not much benefit
        - Steroids: no definite role, but one study showed benefits in advanced stages of the disease. Steroids can prevent the fibro-ploriferative phase.
    - We start the treatment with 100% FiO_2. Then, we decrease it gradually using PEEP. The goal is to reach PO_2 of 60 mmHg.
    - Sometimes, it is advised to put the patient in a prone position. However, this comes with disadvantages. Such patients need more nursing care. Moreover, they are prone to dislodgement of canulas and tubes.
- Prognosis:
    - The mortality rate has dropped from 60% to 30%.
    - Poor prognosis is associated with:
        - Chronic liver disease
        - Non-pulmonary organ dysfunction
        - Sepsis (especially in the end stages)
        - Old age.

Sarcoidosis:

- A systemic granumulatous disease that is variable in its clinical presentation and its prognosis. It is a disease of an known etiology; it is classified under autoimmune disorders.
- Epidemiology:
    - varies from country to country and from one region to another within the same country:
        - 1:64,000 Germany
        - 10-20:100,000 USA
    - 80% of the cases are younger than 20 years of age
    - 8 times more common in black patients
    - HLA B8 is associated with more acute cases
    - HLA 13 is associated with more chronic cases
- Immunological phenomena:
    - Increased cellular immune response at the site of the disease activity
    - Increased CD4 lymphocytes. CD4 lymphocytes are responsible for the induction and evolution of the granulomatous inflammatory lesions
    - Increased CD4:CD8 ration at the site of disease activity
    - Decreased CD4:CD8 ratio in the peripheral blood
- Clinical presentation:
    - 30-60% of the cases are asymptomatic: they are diagnosed as an incidental chest X-ray finding
    - Abnormal Chest X-ray in 90% of the cases. This means that a sarcoidosis patient can have a normal chest X-ray
    - Cough, dyspnea, and bronchial hyperreactivity usually indicate endobroncheal involvement.
    - This disease rarely involves the airways
- Course of the disease: this disease is variable in its course
    - Spontaneous remission in 60^ of the cases
    - Progressive chronic disease: rare
    - Fatal disease with cardiac involvement (causes heart failure and cardiomyopathy): rare
- Signs of good and bad prognosis:
    - Good prognosis:
        - Acute onset
        - Erythema nodosum: raised superficial nodules on the anterior aspect of the tibia. They can be seen on other sites; however, the most common site is the tibia.
        - Asymptomatic bilateral hilar lymphadenopathy
        - Age < 40

        - Fever
        - Polyarthritis
    - Bad prognosis:
        - Insidious onset
        - Multiple extrathoracic lesions
        - Black race
        - Lupus pernio
        - Chrnoic hypercalcemia
        - Bone involvement
        - Chronic pulmonary involvement
- Investigations and imaging:
    - Chest X-rays:
        - Manifestations:
            - Normal in 10%
            - Bihilar adenopathy in 50-85% of the cases
            - Increased paratracheal lymph nodes; especially on the right side
            - Parenchymal infiltratess in 35-40% of the cases. These infiltrates can be reticulonodular, interstitial, or alveolar opacities.
            - Upper lobes are affected more than middle lobes. Disease in the lower lobes is rare.
        - Rare manifestations:
            - Unilateral hilar adenopathy is seen in <5% of cases.
            - Miliary pattern
            - Cavitations
            - Multiple nodes
            - Pleural effusions are seen in 4% of the cases
        - Staging:
            - Stage 0 = normal X-ray
            - Stage 1: bilateral hilar lymphadenopathy (BHL)
            - Stage 2: BHL + parenchymal infiltrates
            - Stage 3: parenchymal infiltrates without BHL
            - Stage 4: extensive fibrosis and distortion of the alveolar architecture. This is an irreversible stage of the disease.
    - CT scan: high resolution CT scans; thin cuts
        - Increased lymph nodes: conventional CT is better at detecting lymph nodes
        - Alveolar opacities
        - Ground glass opacities: indicate interstitial changes
        - Honeycomb cyst: fibrosis; stage 4 disease
    - Pulmonary function test:

        - Abnormal lung function test in 40-70% of the cases.
        - Decreased vital capacity and decreased $FEV_{1.0}$. it is a restrictive disease
        - Obstructive defect in 30% of the cases
        - Hypoxia: rare
        - Low DLCO
    - Labs:
        - Hypercalcemia in 2-5% of the cases
        - Hypercalciurea in 15-40% of the cases. Calcium in the urine is more sensitive than calcium in the blood
        - Increase aminotransferases in 10-205 of the cases.
        - Increased liver enzymes
        - Anemia in 2-5% of the cases.
        - Increased ACE activity. This is an indicator of the activity of the disease.
    - Biopsy:
        - The hallmark of the disease is a non-caseating granuloma. The granuloma contains a central core of histocytes, epitheloid cells and multinucleated giant cells. The periphery of the granuloma contains plasma cells, fibroblasts, and collagen.
    - Bronchoscopy + broncheo-alveolar lavage (BAL):
        - BAL: increased lymphocytes and increased CD4:CD8 ratio
        - Transbroncheal biopsy: shows typical non-caseating granuloma
        - Mediastinoscopy for mediastinal lymph node biopsy.
- Miliary presentation refers to the clinical picture of the disease. A miliary presentation means the presence of multiple small nodes.
- Differentiation between sarcoidosis and TB is difficult. In sarcoidosis, you see non-caseating granulomas; however, in TB you see caseating granulomas. Although this is true most of the time, you cannot be 100% sure of your diagnosis. If you misdiagnose the patient as a case of TB, and administer TB treatment, the patient might improve. This is because sarcoidosis tends to remit spontaneously. However, if you misdiagnose a case of TB as sarcoidosis, and treat the patient accordingly, you might worsen the case.
- Treatment:
    - Steroids:
        - Indicated for patient with a granulomatous infection and organ dysfunction.
        - A good response to steroids has been noticed in patients with progressive and active disease.
        - Indications for steroid use:
            - Heart, CNS, or eye involvement
            - Persistent hyprecalcemia
            - Progressive or severe pulmonary involvement

- Immune-suppressive agents:
  - Steroid sparing drugs
  - Methtroxate (10-20 mg/week) for 4-6 months
  - Azathioprine: 100-200 mg/day
  - Cyclophosphamide: toxic and not superior to methtroxate. It is not recommended.
- lung transplant: in refractory cases

DVT and PE

- thromboembolism reflects the relationship between blood clotting and embolization. DVT and acute PE are two manifestations of the same disorder, venous thromboembolism. This concept is supported by the fact that over 90% of PE cases are due to emboli emanating from the proximal veins of the lower extremities. Moreover, anticoagulation is a highly effective therapy for both conditions.
- The Virchow's triad (describes the three contributing factors to the pathogenesis of DVT):
    - Stasis of blood flow
    - Endothelial injury
    - Hypercoagulability of blood due to deficiency of antithrombin II, protein C, and protein S
- DVT:
    - It can subdivided into DVT of a calf vein or thigh vein origin.
    - Thigh vein thrombosis is more important than calf vein thrombosis; it is associated with more complications.
    - Thigh venous thrombosis can be indentified in 20-50% of PE patients.
    - Epidemiology:
        - 27.8% of patients who have underwent a general surgical procedure
        - 54% in patients with a fractured head of femur
        - 66.5% in patients who had a pelvic surgery
    - Risk factors:
        - History of DVT (the most important risk factor)
        - Bed rest (venous stasis)
        - Recent surgery
        - Age >40
        - Malignancy
        - Heart disease
        - Stroke
        - Obesity
        - Pregnancy
        - Oral contraceptive therapy
        - Polycythemia
        - Pulmonary disease
        - Varicose veins
        - Nephrotic syndrome
        - Paroxysmal hemoglobinuria
        - Antithrombin III deficiency
    - Risk categories for prophylactic DVT measures:
        - Group I:

        - The risk of developing DVT is 6%; low risk
        - Patietns are of age 40 or below and admitted for minor surgeries
        - Prophylaxis: early ambulation
    - Group II:
        - Risk: 6-40%
        - Age: > 40
        - Major surgery in the abdomen, pelvis or thorax
        - Prophylaxis: low dose heparin, oral anticoagulants, and early ambulation if possible
    - Group III:
        - Risk: high
        - Age >40
        - Extensive general surgery: malignancy, hip fracture or replacement
        - Prophylaxis: low dose heparin + oral anticoagulant
- Differential diagnosis:
    - Muscle strain, tear, or twisting injury to the leg
    - Leg swelling in a paralyzed limb
    - Lymphangitis or lymph obstruction
    - Venous insufficiency
    - Baker's cyst
    - Cellulitis
    - Knee abnormality
- Clinical manifestations of DVT:
    - Swelling, redness, warmness, and pain
    - Physical examination may reveal a palpable cord (reflecting a thrombosed vein), ipsilateral edema, warmth, and superficial venous dilation.
    - The clinical diagnosis of DVT is not sufficient; these symptoms are not specidic enough.
    - The severity of the symptoms does not correlate with the degree of thrombosis
    - The classical picture of DVt is only present in 50% of the patients; the rest are asymptomatic.
- Investigations:
    - Doppler ultrasound: defines blood flow in veins.
    - Venogram: injection of a contrast material into the veins. It is invasive and expensive; however, it is the best diagnostic test. It has long been considered the "gold standard" for the diagnosis of DVT. However, it is not recommended as an initial screening test.
    - MRI
    - Venous plethysmography

        - Labeled iodine: I^{125} is a radioisotope to tag fibrenogen. The radioisotope accumulates on platelet aggregates. It is a sensitive test.
        - D-dimer: D-dimer is the degradation product of cross-linked fibrin. They are detectable at levels greater than 500ng/mL of fibrenogen. D-dimer is not sensitive for the detection of a DVT. However, it is a specific. The absence of D-dimers can exclude DVT.
    - Complications:
        - Postphlebetic syndrome and permanent swelling. The damage is mainly to the valves; as a result, the lower limb will be congested with blood. This blood will leak out to the surrounding tissues. There, hemoglobin will change to bilirubin salts. These salts are irritants that cause local inflammation and severe itching.
        - Pulmonary embolism: a massive pulmonary embolism kills within an hour of its development. A massive PE represents about 10% of all PE cases. The other 90% reach the hospital. Only 30% of the 90% are properly diagnosed. Of the 30% diagnosed, 8% die and 92% recover the crisis. On the the other hand, 70% of those who were not diagnosed die and 30% survive. All in all, 30% of all PE patients die.
- Pulmonary embolism (PE)
    - Clinical manifestations:
        - Massive pulmonary embolism: the patient dies within one hour, and may never reach the hospital.
        - PE with infraction: medium sized emboli
        - PE without infarction
        - Chronic microembolizations: there are thousands of very small microscopic embolizations that do not give symptoms unless large numbers of capillaries have been closed. The end stage of this condition is pulmonary hypertension and right sided heart failure.
    - Healthy individuals do not die of their first PE unless it was massive.
    - Respiratory consequences of PE:
        - Alveolar dead space or wasted ventilation: if perfusion to a non-ventilated area persists, there will be no benefit of perfusion
        - Pneumoconstriction of smooth muscle of the bronchioles supplying that area in an attempt to correct the V/Q mismatch
        - Congestive atelectasis: collapse of the alveoli that are neither perfused nor ventilated.
        - Infarction: that means death of that segment of the lung. It is rare, and it is usually associated with a preexisting lung disease.
    - Why doesn’t every pulmonary embolus cause infarction?
        - Oxygen and nutrient needs of the lungs come from three sources:

        - Airways and alveoli (PO_2=110)
        - Bronchial arteries (PO_2 =100)
        - Pulmonary arteries (PO_2 = 40)
    - Most patients with a PE do not end up with pulmonary hypertension due to certain characteristics of the pulmonary circulation:
        - The walls of the vessels of the pulmonary circulation are thinner and more compliant than systemic circulation
        - The pressure in the pulmonary circulation is less than in the pressure in systemic circulation
        - There is a large reserve of blood vessels in the pulmonary circulation. These vessels will open to increase the volume of pulmonary circulation. This will be of benefit in cases of shunting of the blood from the systemic to the pulmonary circulation (in cases of PDA)
    - Due to the aforementioned reasons, you have to increase the load in the pulmonary circulation by 5 times in order for pulmonary hypertension to develop.
    - For pulmonary hypertension to occurs, 20% of the pulmonary circulation needs to be occluded.
- Diagnosis of venous thromboembolism (VTE)
    - Diagnosis of VTW is still a challenge in the current medical practice. The chance for a correct DVT diagnosis is 50% even with the most experienced physicians.
    - In cases of PE clinical judgment is better than in cases of DVT; PE manifestations are more obvious than DVT manifestations.
    - Signs and symptoms:
        - Acute shortness of breath due to hyperventilation that is due to hypoxia
        - Anxiousness and sweating.
        - Tachucardia
        - The patient may be cyanosed; cyanosis does not correlate to the size of the obstruction.
        - In the case of an infarction, the patient will have cough, hemoptysis, chest pain, and signs of consolidation.
    - Suggestive methods:
        - Clinical picture of the patient
        - Chest X-ray: in most of the caes it is normal. However, if abnormal, you can notice the following changes:
            - Hyperlucency in the areas ssupplied by the affected vessels

        - Linear atelectasis: small areas of atelectasis not involving the whole lobe
        - Small areas of pleural effusions in the case of infarction
        - Areas of opacity can be seen in cases of infarction.
    - ECG: may be normal, but in most cases you can find:
        - Sinus tachycardia (most common)
        - RBBB
        - Signs of increased pressure in the right ventricle/ inverted T-waves in leads V1-V4
        - $S_1Q_{III}T_{III}$ pattern: rare
    - ABG's: hypocapnia and hypoxia with an increased A-a gradient.
- Diagnostic tests:
    - Spiral CT scan: with IV contrast
    - Pulmonary angiogram: it is the best method; however, it is neither widely used nor widely available.
    - D-dimer: a negative D-dimer can surely exclude PE; however, a positive one does not prove it.
    - Perfusion lung scan: a radioisotope (Technitium) is given IV to detect any abnormality in the pulmonary circulation
    - Ventilation lung scan: the patient inhales Xenon to detect any abnormality in ventilation.
- In cases of PE, a ventilation lung scan is normal; however, a perfusion scan is not. This is the ideal finding.
- To diagnose a PE, you should look for a normal-looking X-ray with an abnormal perfusion scan. Here, the probability of a correct diagnosis increases when the abnormality is seen around a segment occupying a large area. If the corresponding area on a chest X-ray is abnormal, it is not diagnostic. Lung tissue is rarely involved in the case of a PE

- PE prevention:
    - Identify high risk patients. These are patients with DVT risk factors; give them prophylaxis
    - Prompt diagnosis and treatment of DVT
    - Recognize early PE's. The patient is unlikely to die from the first PE.
- Treatment:
    - Treat DVT or PE with therapeutic levels of unfractionated IV heparin, adjusted subcutaneous heparin, or low molecular weight heparin for at least 5 days. Overlap this treatment with oral anticoagulants for 4-5 days. Consider a longer course of heparin for massive PTE or severe iliofemoral DVT

        - For most patients, heparin and oral anticoagulants can be started together. Heparin is discontinued on day 5-6 if the INR has been in the therapeutic range for 2 consecutive days.
        - Continue oral anticoagulant therapy for at least 3 months with a target INR of 2.5 (range 2-3)
        - Patients with reversible or time limited risk factors can be treated for 3-6 months. Patients with a first episode of idiopathic DVT should be treated for at least 6 months. Patients with recurrent venous thrombosis or patients with a continuous risk factor such as cancer inhibitor deficiency states or with antiphospholipid antibody syndrome should be treated indefinitely
        - The use of thrombolytic agents continues to be highly individualized, and clinicians should have some latitude in using these agents. Patients with hemodynamically unstable PTE or massive iliofemoral thrombosis are the best candidates.
        - Inferior vena caval filter placement is recommended when there is a contraindication to or failure of anticoagulation, for chronic recurrent embolism with pulmonary hypertension, and with concurrent performance of surgical pulmonary embolectiomy or pulmonary endartectomy.
- Anticoagulation, a detailed discussion:
    - Types:
        - Heparin
        - Warfarin
        - Fondaparinux
    - Heparin: low molecular weight heparin or unfractionated heparin
        - Mechanism of action: unfractionated heparin (UFH) binds to antithrombin t omake it 1000-4000 times more effective. It inactivates thrombin and factor Xa. Low molecular weight heparin (LMWH) works on factor Xa only.
        - LMWH is the drug of choice for DVT; however, it can be used in cases of PE

	UFH	LMWH
Mechanism of action	Antithromin activation	Works on factor Xa
route	IV, SC	SQ
T 1/2	2 hours	4 hours
Anticoagulant response	Unpredictable	predictable
Monitoring	Needs monitoring by PTT	No need for monitoring
Major side effects	More	less
Antidote	More effective	Less effective

        - Side effects:
            - HIT

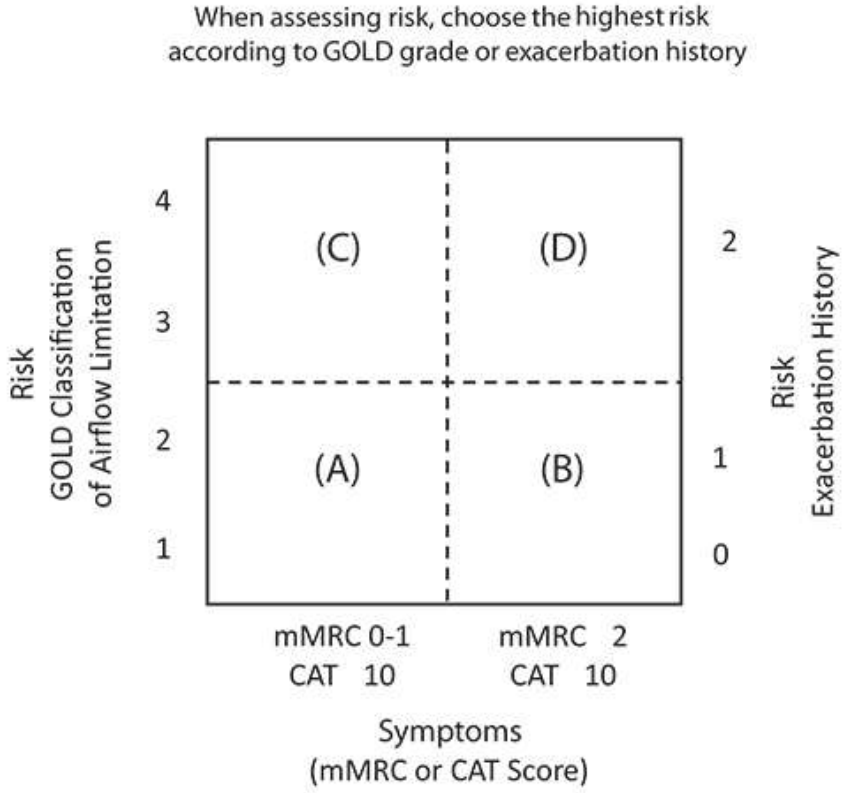
        - Bleeding
        - Hypersensitivity
        - Osteoporosis (long term use)
        - Alopecia
- Contraindications:
    - Severe thrombocytopenia
    - Uncontrolled/active bleeding
    - Bleeding disorders
    - Hypersensititivity
    - Alcoholics
    - Severe hypertension
- The antidote is protamine
- LMWH is preferred in:
    - Pregnancy
    - CA patients
    - Treatment for extended periods of time; the risk of osteoporosis is less
- UFH is preferred in:
    - Patients with high risk for bleeding; the antidote works better against UFH.
    - Unstable patients: we can't use LMWH, because SC administration requires good blood pressures
- Heparin induced thrombocytopenia (HIT)
    - Types:
        - Type I: within 1-2 days of treatment, common and not serious
        - Type II: starts 4-10 days after treatment, immune response where antibodies develop against the complex of heparin and platelet factor 4 (Anti-H-PF4), more common in patients treated with UFH.
    - Always monitor platelets count in patients on heparin. If it drops >50% or/and thromboembolic symptoms develop, manage:
        - Stop using heparin and all heparin products
        - Treat HIT-II:
            - Anticoagulants with a direct thrombin inhibitor effect: Lepirudin or Argatrotan. Lepirugen shouldn't be used with chronic kidney disease patients.
            - Start warfarin when platelet count >100,000 and continue thrombin inhibitors.

- Fondaparinux:
  - Factor Xa inhibitor
  - Route: SC
  - Indications:
    - DV prophylaxis
    - Treatment DVT and PE
  - Alternative to UFH and LMWH
  - Treatment does not cause HIT, so it is useful in patients with a history of HIT
  - Risk of bleeding is similar to heparin
  - No antidote
  - Cannot be monitored
  - Contraindications: Creatinine clearance <30, creatinine clearance between 30-80 is a relative contraindication
- Warfarin:
  - Vitamin K antagonist
  - Mechanism of action: decreased activation of factors 10, 9, 7 and 2. These factors are vitamin K dependent
  - Monitored using INR (PT)
  - Onset of action: 3-5 days
  - Many drug-drug interactions
  - Side effects:
    - Intraocular hemorrhage: most common
    - Warfarin necrosis: idiosyncratic: full thickness skin necrosis requiring skin graft
  - Warfarin guidelines and target INR levels:
    - Normal INR: 0.9-1.2
    - PE and DVT: 2-3; if recurrent: 3.5
    - Atrial fibrillation: 2-3; alternative: aspirin if risk of bleeding is high
    - Prosthetic metallic heart valves: 3-4

COPD

- COPD is a group of disorders that present with narrowing of airways or limitation of expiration. Obstruction, in this case, is extrathoracic. These disorders include emphysema, chronic bronchitis, and other obstructive diseases.
- Chronic bronchitis: symptoms of productive cough for most of the days of three months of two consecutive years after ruling out other causes.
- Emphysema: pathological definition; it is defined as destruction and dilation of the area distal to the terminal bronchioles. A biopsy is not usually needed.
- Asthma: chronic narrowing of the lower airways characterized by reversible changeable generalized narrowing of the airways with or without treatment, inflammation of the airway, wheezes, and cough.
- There is no chronic bronchitis alone or emphysema alone. It is usually a mix of these diseases.
- Asthma is a reversible disease; however, it might become irreversible
- Cough and sputum are more common in CB than in asthma and emphysema. Emphysema is an irreversible process
- COPD does not cause clubbing; if you see clubbing, suspect lung fibrosis or lung CA.
- Since asthma is an inflammatory process, steroids are a large part of the treatment
- Risk factors for COPD:
    - Smoking
    - Air pollution
    - Occupational inhalants
    - Respiratory infection:
        - Recurrent childhood infections: chest infections, tonsillitis, and otitis media.
        - Adult recurrent infections
    - Genetic factors: alpha-1-antitrypsin deficiency and cystic fibrosis
    - Congenital factors: immotile cilia syndrome
    - Gastroesophageal reflux
    - Miscellaneous factors: alcohol abuse, Behget's disease, and rheumatoid arthritis
- Effects of smoking on airways and lungs:
    - The risk of death in COPD needs 15 years to normalize
    - At the beginning, smokers start to complain of sputum and cough early in the morning. With days, they complain of increased amounts of sputum, increased frequency of cough, and deterioration of lung function and blood gases.
    - Decrease in FEV_1: normally, FEV decreases with age; however, with smokers, this decrease is more prominent. It might reach zero at the age of 70.
    - With smoking, all airways are affected; however, the earliest changes occur in the small airways

    - It affects the lung parenchyma by increasing the amount of elastases; this destroys the protective enzymes. These patients become more exposed to destructive materials.
- GOLD classification:
    - I → FEV > 80% : mild
    - II → FEV 50-80%: moderate
    - III → FEV 30-50%: severe
    - IV → FEV <30%: very severe.
- Modified GOLD classification:
    - Criteria used for:
        - Treatment options
        - Predicting prognosis
        - Predicting number of exacerbations



Patient Category	Characteristics	Spirometric Classification	Exacerbations Per Year	mMRC	CAT
A	Low Risk, Less Symptoms	GOLD 1-2	1	0-1	<10
B	Low Risk, More Symptoms	GOLD 1-2	1	2	10
C	High Risk, Less Symptoms	GOLD 3-4	2	0-1	<10
D	High Risk, More Symptoms	GOLD 3-4	2	2	10

- Chronic bronchitis:

    - 90% of cases of chronic bronchitis are associated with smoking
    - In smokers, the likelihood of COPD development is related to the amount of smoking. 50% of patients with >40 pack years will have chronic bronchitis.
    - Pathogenesis:
        - Smoking causes irritation of the respiratory tract's mucus membranes. This will cause an increase in mucus production, an increase in the number of mucus secreting cells, and weakness of ciliary system. As a protective mechanism, the patients will cough to excrete the sputum.
        - Narrowing of the lumen due to the thickening of the mucus membrane.
    - Pathophysiology:
        - In a normal person, the minute ventilation is 5 liters for the lung and 5 liters for the airway. However, in cases of chronic bronchitis, due to the narrowing of the lumen, the amount of inspired air less than what is required to saturate the blood Hb. In this case, there is a hypoventilated area with normal perfusion. This will create a shunt causing hypoxia. Hyperventilation in the adjacent areas will not compensate for hypoxia because the blood leaving the hyperventilated area will be fully saturated, and will not be able to carry excess oxygen.
        - In chronic bronchitis, unlike emphysema, there will be CO_2 retention.
        - Hypoxia will cause narrowing of the pulmonary blood vessels. This process is reversible at the beginning; however, as the disease progresses, it will become permanent, which will cause pulmonary hypertension. Acidosis potentiates the effect of hypoxia on pulmonary hypertension.
        - Hypoxia causes polycythemia
        - This will ultimately lead to right sided heart failure
    - Clinical picture:
        - The picture of the patient is called the blue bloater
        - The patient looks hypoventilated with cough and sputum. Patients present with a puffy face, plethora, cyanosis, and neck veins distention.
        - Despite of this picture, if you ask the patient to walk, the patient will be able to walk without any difficulties.
        - Chest X-ray is not informative. Looks normal
- Emphysema:
    - Temporary dilation of the airway should be excluded. This includes pneumonia patients.
    - Types of emphysema:
        - Cento-acinar (centro-lobular): the most common type; caused by smoking. This type involves the upper lobes.
        - Pan-acinar (pan-lobular): this type involves the lower lobes; it is seen in patients with alpha-1-antitrypsin deficiency.

    - Pathophysiology:
        - Dilation of the area distal to the terminal bronchioles
        - This dilation will cause compression of the capillaries mesh network around the alveoli.
        - In this case, there will be normal or excessive ventilation to an area with a compromised blood supply. This is called waste ventilation.
        - Waste ventilation will cause hypoxemia.
        - The body will make an effort to increase the amount of inspired air; this is followed by fatigue and hypoventilation. This is opposite to what happens in the case of chronic bronchitis (shunt)
    - Clinical picture:
        - The picture of the patient is called a pink puffer
        - If the patient can still hyperventilate, there will be no cyanosis
        - Dilation of the alveolar spaces will push the chest anteriorly. This makes the pateints appear in full inspiration the whole time. In normal individuals, the ratio of the transverse diameter to the AP diameter is 2:3; however, in cases of emphysema, this ratio decreases.
        - Severe wasting of fat; slim appearance.
        - Leaning forward due to hyperinflation. The patients try to lift the diaphragm upwards.
        - Purse lip expiration.
    - Chest X-ray:
        - Hyperinflation; seen as hyperlucency
        - Low and flat diaphragm
        - Long slender heart
        - Central congested hila and peripheral ischemia
        - Horizontal ribs and intercostal spaces. In the lateral view, the sternum is pushed anteriorly. The space behind the sternum is enlarged.
- The major difference between emphysema and chronic bronchitis is DLCO. In emphysema, there is a vascular defect, which causes a decrease in DLCO. In chronic bronchitis, the DLCO is normal.
- Mechanism of purse lip expiration:
    - Simply speaking, the patient tries to the shift the equal point pressure (EPP) more proximally to prevent collapse.
    - In normal individuals, lung inflation and deflation depends on three pressures; the pleural pressure, the elastic recoil pressure, and the alveolar pressure. During expiration, the elastic recoil will build up the alveolar pressure. While air is leaving, the pressure inside the airway is equalized until the pleural pressure equals the alveolar pressure. This point is called EPP. It is normally located in

the upper airway. Distal to this point, the airway is supposed to collapse. However, due to the presence of cartilage, it doesn't.
    - In emphysema, during expiration, there is low alveolar pressure. This shifts the EPP distally; this will cause air trapping and lung hyperinflation.
    - With purse lip expiration, the decrease in alveolar pressure will decrease. This will cause the EPP to shift to a more proximal area.
- General guidelines for management of stable COPD:
    - Smoking cessation
    - Bronchodilators:
        - Methylxanthine: only available in oral and injection forms. It has a narrow therapeutic range
        - Anticholenergics: only available in inhalational form
        - Beta agonists: in advanced cases, we can use short and long acting preparations together. Short acting like salbutamol (ventolin) and long acting like salmetrol and formetrol.
    - Antiinflammatory agents: NSAID's and steroids
    - Mucolytic agents
    - Antibiotics: if associated with an infection
    - Immunization: pneumococcus and influenza
    - Oxygen therapy
- COPD exacerbation (definition)
    - Increased severity of shortness of breath
    - Increased amount of sputum
    - Change in the color of sputum
    - Fever: not necessary
    - Exacerbation could be due to other disease or complications such as pneumothorax, MI, and IHD
- Why do we give bronchodilators?
    - Some patients show reversibility due to an overlap with asthma
    - According to Bau's law: the increase in flow is proportional to the fourth degree of radius. An increase of diameter from 1 cm to 2 cm will increase the flow by 16 times.
- Treatment based on modified GOLD criteria:
    - General guidelines:
        - SABA are needed in all patients
        - LABA are indicated in moderate to severe cases
        - ICS indicated in GOLD 3-4 or groups C/D. however, these patients have higher risk for pneumonia. And this treatment is not used as a long term treatment

        - Don’t use mast cell stabilizers or leukotriene modulators because they are not effective
        - Monitor blood gases when FEV falls below 50%; this is when oxygen levels start to fall
        - Oxygen is the most important parameter for monitoring:
        - Criteria for continuous oxygen:
            - PO_2 <55%
            - O_2 saturation <88%
            - PO_2 55-60 or O_2 sat 88% with pulmonary hypertension, edema or congestive heart failure
        - None of the COPD medications decrease the deterioration in FEV
        - Best management is with:
            - O_2 therapy
            - Smoking cessation
            - Lung volume reduction
            - Lung transplant
    - Treatment of stable COPD (According to modified GOLD)
        - Group A: single SABA or short acting anticholinergic
        - Group B: LABA or long acting anticholinergic
        - Group C: combination therapy of ICS + LABA. Alternatives include 2 LABA’s, SABA + theophylline, or Roflumlast
        - Group D: ICS + LABA
        - Symptoms of exacerbation:
            - Increased severity of shortness of breath
            - Increased sputum
            - Change in color of sputum
            - Fever
        - Investigations: chest X-ray, ECG, O_2 saturation
        - SABA + anticholinergic
        - Systemic steroids
        - Moderate to severe: give empirical antibiotics
        - Non-invasive PPV
    - Why do do we give steroids?
        - Shortens recovery time
        - Decreased risk of relapse
        - Decreased hospital stay
        - The dose is 40 mg of prednisolone for 10-14 days.
    - Common pathogens in COPD: Maroxela, Pneumococcus, and H. influenza

- Alpha-1-antitrypsin deficiency:
    - It is a deficiency in the glycoprotein alpha antitrypsin. This protein belongs to the family of serine protease inhibitors.
    - Think of this condition in a young (<45 years) smoker with COPD. Family history of both liver and lung disease and/or increased LFT.
    - It is more common in caucasians
    - Patients with alpha-1-antitrypsin deficiency can also develop progressive liver fibrosis and cirrhosis. They have increased risk for hepatomas.
    - Alleles:
        - P_iM: moderately fast: most common
        - P_iF: fast
        - P_iZ: slow
    - Patients with alpha-1-antitrypsin deficiency have:
        - P_iZ or P_iZZ (most affected
        - P_iMA: 60% of those are normal
        - Patients with P_iZ do not develop COPD; however, they are mostly affected with liver cirrhosis and fibrosis
    - Diagnosis:
        - Serum alpha-1-antitrypsin levels
        - Genetic testing for P_i locus
        - Liver biopsy
    - Treatment:
        - Alpha-1-antiprotease:
            - Pooled human alpha-1-antitrypsin (expensive
            - IV
            - Given to:
                - P_iZ
                - Serum antitrypsin <11 mmol/L
                - Abnormal chest CT and spirometry
            - The patient must be a non-smoker or an ex-smoker
        - Patients with COPD:
            - Bronchodilators
            - Antibiotics, as needed
            - Yearly vaccines
            - Smoking cessation
    - If empyema is severe, the only treatment is lung transplantation
    - IV infusion has no oeffect oon liver disease. The only treatment for liver cirrhosis is liver transplant

Bronchial asthma

- A chronic inflammatory disease of the airways. Many cells play a role in this inflammation. These include mast cells, eosinophils, and T-lymphocytes. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough. These exacerbations most commonly happen at night or early in the morning. These symptoms are associated with airflow limitation. This limitation is partially reversible with or without treatment.
- Pathophysiology:
    - Complex interaction of cell, mediators, and cytokines. It results in:
        - Inflammation
        - Bronchial hyperreactivity
        - Airflow limitation
        - Cariability
        - Reversibility
    - Inflammation (in details):
        - Constitutive cells such as epithelial cells, mucus glands, endothelial cells, and myofibroblasts.
        - Resident cells such as bone marrow-derived mast cells and macrophages.
        - Infiltrating cells such as eosinophils, CD4, neutrophils, basophils, and platelets.
        - These aforementioned cells will lead to the generation of mediators that can induce bronchocontriction. The mediators include histamine, platelet activating factor, and some derivatives of the arachedonic acid cascade (PGD2, PGC4, PGE4, LTC4, LTD4, and LE4).
        - Infiltration of airways by mast cells, eosinophils, activated T-lymphocytes, and neutophils.
        - Mast cells degranulate as a result of IgE mediated stimulation.
        - Cytokine production
        - Edema of the airway mucosa due to inflammation and increase capillary permeability.
        - Death from severe asthma usually occurs due to blockage of the airways via a mucus plug. The presence of a mucus plug is associated with hyperplasia and metaplasia of goblet cells.
    - Airway hyperreactivity (in details)
        - Neuroloical influences regulate many aspects of airway function. These include scular permeability, and the release of inflammatory cells.
        - Airway hyperrreactivity is an exaggerated bronchoconstrictive reponse by the airways due to a verity of stimuli. These include histamine, methacholine, cold air, and environmental irritants.

        - It is not known whether bronchial hyperreatcivity is acquired or present at birth
        - It is though that inflammation is the stimulus from bronchial hyperreactivity
        - The degree of bronchial hyperreactiity usually correlates with the clinical severity of asthma.
    - Airway obstruction:
        - Caused by:
            - Acute bronchoconstriction
            - Mucus plugging
            - Bronchial wall edema
            - Inflammatory cell infiltration
            - Airway wall remodeling
            - Smooth muscle hypertrophy
    - Airflow limitation:
        - Defined as FEV/FVC ratio of less than 75%
        - During remission, this can be normal
- Atopy:
    - Defined as genetic susceptibility for developing immunoglobilin IgE directed at epitopes expressed on common environmental allergens. These include dust mites, animal proteins, pollens, and fungi.
    - Atopic asthma has seasonal variational. Avoidance of the offending agents might result in dramatic improvements
    - Atopy manifests as allergic asthma, allergic rhinitis, allergic sinusitis with eosiphelia, and high serum IgE level.s
- Non-atopic asthma:
    - No positive family history of asthma
    - No positive immediate hypersensititvy reactions to skin-prick tests following exposure to aero-allergens
    - No elevated serum IgE levels.
    - These patients are older than atopic patients.
- Risk factors for asthma:
    - Genetics:
        - There is a major hereditary contribution to the etiology of asthma
        - The inheritence pattern is complex
        - Multiple chromosomal regions may contain genes that contribute to asthma
        - High serum IgE levels are linked to chromosomes 5q, 11q, 12q
        - Strong correlation between bronchial hyperreactivity and high levels of serum IgE

    - Sex and race
        - The overall prevalence is greater in females
        - Black race is associated a high risk of asthma death
    - Environmental factors
        - Allergens and occupational factors are important causes of asthma
        - Air pollution; outdoor and indoor pollutants contribute to worsening of asthma symptoms by triggering bronchocontriction and increasing hyperreactivity.
    - Respiratory infections:
        - Viral respiratory infections are common precipitators of asthma
        - Some theories suggest that atypical bacteria, like chlamydia and mycoplasma, may also be involved.
- Clinical features:
    - Cough
        - Mechanism: stimulation of airway sensory nerves by inflammatory mediators.
        - It is often provoked by respiratory irritants such cigarette smoke and by cold air, laughter, and cough itself
        - Cough induced by deep breath suggests a hyperreactive asthmatic airway.
        - Usually, it is a dry cough. Few days later, it might be associated with sputum
    - Dyspnea:
        - 10% of patients with acute asthma have no symptoms due poor perception of the symptoms. This may lead to death, especially in the elderly.
        - Dyspnea rarely presents as the only symptom
        - Mechanism: increased work of breathing due to high airway resistance.
    - Chest tightness:
        - Substernal pressure
        - Chest pain
        - Nocturnal awakening
        - Differential diagnosis: IHD or GERD
    - Wheezes
- Clinical signs:
    - Signs of bronchospasm are due to:
        - Direct result of diffuse airway narrowing and hypersecretion of mucus
        - The indirect result of reflex influences. This is due to increased work of breathing, increased metabolic demands, and diffuse sympathetic nervous system discharge.
    - Signs include:
        - Tachypnea and tachycardia

        - Diffuse musical wheezes
        - Prolonged expiratory phase
        - Use of accessory muscles
        - Pulsus paradoxus
        - Cyanosis
- Investigations:
    - We use investigations to:
        - Diagnose
        - Evaluate severity
        - Treatment options
    - Pulmonary function test:
        - Spirometry for FEV/FVC ratio:
            - FEV/FVC ratio <75% indicates airflow limitation.
            - Reversibility of airflow limitation in characteristic of asthma. This can be demonstrated by a 15% improvement in FEV 5-10 minutes after treatment with a short acting beta agonist.
        - Peak expiratory flow rate (PEFR)
            - Home monitoring with EPFR can be useful in:
                - Diagnosis
                - Identification of environmental triggers of asthma
                - Detection of early signs of deterioration when symptoms change
            - Long term monitoring is useful for severe brittle asthma and for those with poor perception of asthma symptoms
            - Variability:
                - Diurnal variation of PEFR of 20%
                - This is diagnostic for asthma
                - In general, the degree of proportional to the degree of asthma.
                - A high degree of variability signs unstable asthma that demands increased medications.
    - Arterial blood gas:
        - During severe attacks.
        - The more severe the attack, the lower the arterial oxygen tension.
        - The mechanism of hypoxia in asthma is a V/Q mismatch.
        - Hypocapnia and respiratory alkalosis in 75% patients with acute asthma
        - Normal PCO_2 with FEV values approaching about 15-20% of the predicted value.
    - Challenge test:

        - Indications: when spirometry and EPFR are normal in spite of typical asthma symptoms.
        - Methacoline challenge test: after taking a baseline FEV, a low dose of methacoline is given by inhalation. Te concentration is gradually increased while repeating FEV.
        - If FEV drops by 20% below the baseline, the test is positive.
        - Methacoline test is typical. Its sensitivity is 95%; however, it is not specific
    - Exercise test:
        - It is a form bronchoprovocation test. It is used more in children; it is physiological; however, it can be affected with cardiac function of the patient.
        - Using a standard 6-minute protocol, a 15% fall in FEV or a 20% fall in PEFR is diagnostic.
    - Other tests:
        - Sputum for eosenophilia
        - Chest X-ray
        - Blood eosenophilia
        - Serum IgE levels.
- Differential diagnosis of asthma:
    - Cardiac asthma
    - Vocal cord dysfunction
    - COPD
    - Upper airway obstruction
- Treatment:
    - Factors to consider before treatment:
        - Careful assessment of symptoms, spirometry and PEFR
        - Use of bronchodilators and antiinflammatory medications according to the patient's needs using a staging system.
        - Measures should be taken to avoid irritants.
        - Patient's education is an important factor in asthma control.
    - The most important and effective treatment is smoking cessation and stopping exposure to environmental agents.
    - Treat rhinitis with intranasal steroids.
    - Symptoms-based monitoring is as effective as PEF
    - Short term control:
        - SABA: first choice; sulbutamol and albutamol.
        - Systemic steroids:
            - Indications: peak flow <80% after 3 treatments with SABA
            - Decreased frequency of ER visits.

- Administration:
    - Oral: is as effective as IV
    - IM: given if patient is vomiting
    - IV: used in cases of respirratory failure.
- Anticholinergics: (ipratropium bromide)
    - Mechanism of action: decrease cGMP. This relives contraction of bronchial smooth muscles.
    - Used only for short term treattemnt. In cases of COPD, it is used as a long term treatment
- Oxygen: the goal is to keep PO_2, at least, at 60 mmHg or at O_2 saturation above 90%

- Long term control:
    - Inhaled corticosteroids (ICS):
        - most potent and most effective.
        - Indications preferred for chronic treatment if the disease cannot be controlled with SABA.
        - Budenoside is safe in pregnancy; other drugs are category C
        - Dose response wave-form is flatted in patients with mild persistent asthma; this means that a higher dose has no benefit. In case of severe persistent asthma, the dose response wave form is not flattened; this means a higher dose is better.
        - ICS and safety:
            - Little, if any effect on the pituitary adrenal axis.
            - No increased risk of fractures
            - Cataracts and glaucoma are less common that oral corticosteroids.
            - May cause easy bruising in elderly
            - May cause slowing of forth.
            - Higher doses cause oral thrushes.
    - LABA: (salmoterol and formeterol)
        - Never use because mask the symptoms. Moreover, they increase morbidity and mortality. They should be always used with ICS>
        - Indications: if symptoms are not controlled with SABA and ICS
        - Note recommended in acute or asthma or acute treatment
    - Mast cell stabilizers: (cromolym sodium and Nedocromil)
        - 2^{nd} line of treatment after SABA, ICS, and LABA
        - Mechanism of action: decrease degranulation of mast cells.
    - Leukotriene modifiers (Montoleuast, Zafirulukast, and Zilaton)
        - Leukotriens are potent chemical mediators released from mast cells, basophils, and eosenophils. Their mechanism of action

includes smooth muscle contraction, mucus production, airways edema, vasoconstriction, and increased arachidonic acid release.

- Indications: used in patients with allergy
- Mechanism of actions: leukotrine receptor antagonstis (Monteleukast and Zafirulkast), and 5-lipooxygenase pathway inhibitors (Zilaton)
- Less potent than LABA and ICS
- More often used in children; never preferred in adults.
- Side effects (rare) eosenophilic vasculitis.

- Methylaxanthines (theophylline)
  - Narrow therapeutic index (5-15mcg/mL)
  - Signs of toxicity include:
    - Nausea and vomiting
    - Headache
    - Tremor and palpitations
    - Death is usually due to:
      - Hypotension
      - Seizures
      - Arrhythmias
  - Given as a sustained release preparation
  - Theophylline and ICS are inferior in efficiency to LABA and ICS.
  - Long acting anticholinergeics (trioprem) are not used in asthma treatment.
- Immuno-modulators (Omalizumab);
  - Anti IgE
  - Indications:
    - Allergy
    - Severe uncontrolled persistent asthma on LABA and ICS

Cystic fibrosis

- Autosomal recessive disease due to mutations affecting a gene located on the long arm of chromosome 7. This gene encodes for a protein called CFTR (Cystin Fibrosis Transmembrane Regulator). This protein is essential for salt and water movement across cell membranes.
- In normal epithelium, the transport of chloride ions across the membranes occurs through two types of channels; CFTR dependent channels and calcium dependent channels.
- In cystic fibrosis, the CFTR dependent channels are defective. The impact of this defect is a decrease of chloride entry in sweat glands. This will result in an increase in chloride ion concentration inside the sweat ducts. In the airways, chloride will enter the airway lumen. This will result in increase sodium and water entry to the cells. This results in a thick dehydrated mucus in the airways.
- In the airways, chloride normally leaves the cells through the channel. This channel inhibits the entrance of Na and water to the cells; in the case of cystic fibrosis, we have defective channels. This will prevent chloride from leaving the cell into the lumen. Water and sodium will enter into the cells this well result in thick mucus, which will end with bronchiactasis
- In the sweat glands, choride normally enters the cells. This enhances sodium entrance. In the case of cystic fibrosis, chloride will not the cell. This will result in the accumulation of sodium and chloride ions in the lumen. This results in sweat high in NaCl.
- Systemic effects of cystic fibrosis:
    - Pancreatic insufficiency
    - Steatorrhea
    - Malabsorption meconeum ileus in the newborn. Distal intestinal obstruction is more common in adults; this is called meconeum ileus equivalent syndrome.
    - Billiary cirrhosis
    - Gallbladder stones
    - Absent vas deferns.
    - Male infertility; they have intact spermatogenesis; however, there is a problem in transport.
    - Female infertility due to amenorrhea caused by malnutrition. This might be due to tenacious cervical secretion
    - Cystic fibrosis arthroprathy (not an important manifestation)
    - Patients might develop DM
    - Patients rarely develop amyloidosis
- Diagnosis:
    - DNA analysis: due to the large number of cystic fibrosis mutations, DNA analysis is not used for primary diagnosis. The primary diagnosis of cystic fibrosis relies on a combination of clinical criteria and analysis of sweat chloride values.

    - Sweat chloride test: the values of Na and Cl concentrations vary with age. In adults, concentrations above 60-70 mEq/L discriminate between patients with cystic fibrosis and patients with other lung diseases. 1-2% of patients with clinical syndrome of CF have normal sweat chloride values. Hypoproteinemic edema and steroids cause false negative results.
    - Nasal transepithelial potential is raised in the diagnostic range in patients with cystic fibrosis. Sweat acini do not secrete in response injected beta adrenergic agonist. This procedure is expensive and it is rarely used.
- Treatment:
    - The major objective for cystic fibrosis therapy are to promote clearance of secretions, control lung infections, provide adequate nutrition, and prevent intestinal obstruction.
    - Lung disease treatment: Same as bronchictais + recombinant human DNAse.
    - Gastrointestinal treatment:
        - Maintencnace of adequate nutrition is critical for the heath of patients with cystic fibrosis.
        - Most of the patients with cystic fibrosis benefit from enzymatic replacement.
        - Replacement of fat-soluble vitamins, particularly vitamin E and K

Bronchiectasis

- The name is derived from bronkos (windpipe) and ektais (stretching or extension).
- Bronchiectasis is defined as abnormal permanent dilation of the medium sized bronchi due to destruction of the muscular and elastic components of their walls.
- Typical bronchiechtasis is characterized by:
    - Chronic infections which could be a cause or a consequence
    - Production of large amounts of foul smelling purulent sputum.
- Atypical bronchiechtasis is bronchiectasis with a dry cough.
- Bronchiechtasis is a disease of the lower lobes due to lack of gravitational drainage. However, if the disease was associated with TB, ABPA, cystic fibrosis, the apical and posterior segments of the upper lobes will be affected.
- Reid's classification:
    - Cylindrical or tubular bronchiechtasis: the bronchi appear as uniformly dilated tubes.
    - Varicose bronchiechtasis: the bronchi appear irregular; they resemble varicose veins.
    - Saccular or cystic bronchiechtasis: the affected bronchi have a ballooned peripheral appearance. The bronchi end with blind sacs without any recognizable distal structures.
- Pathogenesis:
    - It occurs in the proximal cartilagenous division of the bronchi
    - Its major cause is inflammation: mediated by elastase and collagenase.
    - The end result of inflammation of the bronchial walls is the destruction of their elastic and muscular components
    - The surrounding undamaged lung tissue exerts contractile forces that expand the damaged bronchi. This creates the characteristic dilation observed on X-rays and CT scans.
    - In longstanding bronchiechtasis, the peribronchial alveolar tissue is damaged by inflammation.
    - The lower lobes are the most commonly involved lobes. The upper lobes are involved in cases of TB, ABPA, and cystic fibrosis.
- Functional changes :
    - Impaired tracheobronchial clearance
    - Airway colonization and infection with pathogenic organisms
    - Obstructive end-arteritis, which cases decreased total pulmonary areterial flow. This leads to pulmonary hypertension.
- Causes:
    - Infectious:

- Direct infection without host defense impairment: it could bacterial, viral, or fungal. This cause is no longer a common cause due to anti-microbial therapy.
- Infection due to ciliary dysfunction:
    - An autosomal recessive disease characterized by chronic cough, chronic rhinitis, and chronic sinusitis due to a defect in the cilia. The cilia are immotile.
    - Because embryonic cilia are defective, body asymmetry is randomized. This means that 50% of these patients have situs inversus. When there is situs inversus, chronic sinusitis, and bronchiechtasis, this condition is called Kartagner's syndrome. It is a subgroup of primary ciliary dyskinesia.
    - There is considerable variation in the clinical presentation of primary ciliary dyskinesia. However, the most commonly observed features are recurrent respiratory infections and recurrent sinusitis.
    - Most men with this syndrome have living immotile spermatozoa. They are infertile. Some of these men have motile spermatozoa, but immotile cilia. Women, likewise, have decreased fertility.
- Cystic fibrosis: the most common organisms are Staph aureus and P. auroginosa.
- Young's syndrome: patients with this disease have inspissated secretions that impair the transport function of the cilia.
- Infections due to GI disorders: patients with hypogammaglobulinemia, especially panhypoglobulinemia, may have bronchiechtasis

- Non-infectious causes:
    - Part or manifestation of a systemic inflammatory disease: these include rheumatoid arthritis, ulcerative cholitis, scleroderma, and Sjogren's syndrome
    - Exposure to toxins: examples include inhalation of a toxic gas or aspiration of acidic gastric contents.
    - Yellow nail syndrome:
        - A triad of yellow nails, lymphedema, and respiratory tract illnesss.
        - Respiratory manifestations include pleural effusions, bronchiectasis, recurrent pneumonia, bronchitis, or sinusitis.
        - More common in females
        - This conditions results from an abnormality of the lymphatic vessels (hypoplastic lymph vessels) with impaired drainage. This leads to subungal edema and lymphedema of the extremities
    - Alpha-1-antitrypsin deficiency: these patients develop panacinar emphysema; however, they may develop bronchiectasis

        - ABPA
        - Obstruction: the lesion here is focal. It might be due to a tumor or a foreign body.
- Clinical manifestations:
    - Chronic productive cough
    - Sputum that is purulent (green), foul smelling, and exceeds 150 mL per day.
    - Hemoptysis: in 50-70%, it is mild. Hemoptysis is due to friable inflamed mucosa. However, it can be massive due to erosions and ulcerations of the hypertrophied bronchial circulation.
    - Dyspnea, fatigue, and fever in severe cases.
- Physical examination:
    - Crepitations (crackles/rales): coarse, large caliber crepitations throughout the whole chest. They are heard during the full length of the inspiratory phase.
    - Finger clubbing: seen in advanced or severe disease.
- Pulmonary function tests:
    - FEV/FVC ratio: slightly decreased or normal
    - DLCO: might be decreased.
    - This disease is an obstructive disease with V/Q mismatch and shunting as mechanisms responsible for hypoxia
    - Cor pulmonale occurs in a minority of patients
- Radiographic findings:
    - Chest X-ray
        - May be normal
        - In cystic bronchiectasis, the bronchi appear as rings or cysts. They are called ring shadows or “bunches of grapes” sign. However, this finding is not specific.
        - Radiologicla findings might imitate those of sarcoidosis or lung fibrosis
        - Tramline or tram-track shadow lines: in cylindirical bronchiectasis. The dilated airways appear crowded and parallel, especially at the periphery.
    - High resolution CT:
        - Gives image of 1 or 1.5 mm thick sections
        - It is the definitive diagnostic modality for bronchiectasis
        - Highly sensitive: 97%
        - Gives you a clue about the cause
    - Bronchoscopy:
        - Invasive and uncomfortable
        - If the disease is focal, we use a fiberoptic bronchoscope.
        - If the disease is diffuse, we use a rigid bronchoscope. The procedure involves coating the airways with a radio-opaque iodinated lipid die.
    - Sputum staining and culture: it is used as a guide for the best antibiotic therapy.

- Treatment:
    - Goals:
        - Elimination of an identifiable underlying problem
        - Improved clearance of trachebronchial secretions
        - Control of infection, particularly during acute exacerbations.
        - Reversal of airflow obstruction
    - Appropriate treatment should be instituted when a treatable cause is found:
        - Chest physiotherapy with vibration, percussion, and postural drainage.
        - Mucolytic agents to thin the secretions and allow for better clearance.
        - Aerosolized recombinanat DNAse, which decreases the viscosity of the sputum by breaking down the DNA released from neutrophis. This was shown to improve pulmonary function in cystic fibrosis; however, similar benefits have not been found with patients suffering from bronchiectasis.
        - Antibiotics:
            - Have an important role in the management of the disease
            - For patients with infrequent exacerbations characterized by an increase in the quantity and purulence of the sputum, antibiotics are used during the acute episode.
            - Although the choice of antibiotics can be guided using Gram stain and culture, empiric treatment should be started immediately.
            - When P. aeruginosa is present, therapy with aminoglycosides or third generation cephalosporines may be appropriate.
        - Bronchodilators:
            - Used to improve obstruction and aid in the clearance of secretions.
            - These are particularly useful in patients with aorwau hyperrreactivity and reversible airflow obstruction.
        - Surgical therapy:
            - It was common in the past; however, antibiotics and supportive therapy have decreased the need for surgical treatment
            - When bronchiectais is localized and the morbidity is substantial despite adequate medical therapy, surgical resection of the involved lung region should be considered.
        - When massive hemoptysis does not resolve with conservative therapy, therapeutic options include resection and bronchial arterial embolization
        - In patients with extensive diseases, chronic hypoxemia and cor pulmonale may indicate the need for long term supplemental oxygen.
        - Lung transplant in selected patients.
- Complications:
    - Pneumonia
    - Empyema

    - Pneumothorax
    - Abscess formation
    - Massive hemoptysis
    - Cor pulmonale
    - Amyloidosis (rare)
- Extra notes:
    - Evidence based medicine on the role of nebulized antipseudomonas: recent strials and studies have shown that using nebulized antipseudomonas decreases the rate of exacerbation and hospitalization; however, it was not proven to decrease mortality.
    - Bronchospcopy can be done with a rigid bronchoscope (this requires general anesthesia) or with a flexible bronchoscope
    - ABPA (allergic bronchopulonary aspergillos): it is a complex hypersensitivity reaction n asthmatic patients. It occurs when the bronchi become colonized by Aspergillus. Repeated episodes of bronchial obstruction, inflammation, and mucoid impaction can lead to brochiectasis, fibrosis and respiratory compromise. The pathogenesis of this disease is not completely understood.

Tuberculosis

- TB is a mycobacterial infection.
- Mycobacteria can be divided into:
    - Tuberculous: cause by mycobacterium tubercolosis and occasionally M. bovis or M. africanum.
    - Non-tuberculous caused by: M avium complex (MAC), M. Kansasii, and M. bovis.
- The non-tuberculous bacteria form the majority of mycobacterium species. These are environmental organisms, and they are rarely pathogenic. Some have been found to cause disease in Man, particularly in those with HIV or longstanding disease.
- Clinical features of non-tuberculous infections are not specific. Most the time they have constitutional symptoms with increased respiratory symptoms.
- Clinical diagnosis to differentiate between tubercculous and non-tuberculous infections:
    - Staining for sputum and broncho-alveolar lavage (BAL). this method is not diagnosis; the stain indicates the presence of acid fast bacilli.
    - Culture: needs 7 weeks; it is diagnostic
    - Polymerase chain reaction (PCR)
- Tuberculosis:
    - Caused mainly by mycobacterium tuberculosis; however, it can be caused by M. bovis and M. africanum.
    - It can affect any age group. The problem with tuberculosis is when it affects children. Here, it is more aggressive. Children may acquire the infection through close contact. When we isolate a tuberculosis infection from an adult, we have to make sure that every child in close contact with the infected adult is not infected.
    - Most of the time, you get the infection without any real symptoms. The symptoms are flu-like and may remit spontaneously.
    - Tuberculosis can be activated many years after the primary infection. This why a positive PPD test can be seen in a previously infected individual. These individuals carry viable mycobacteria in their tissues; a positive test does not necessarily imply an active disease.
    - When a person has a positive PPD test with an abnormal chest X-ray, there is a 5% chance of reactivation within the next 5 years. In these patients, a prophylactic INH treatment is started (6 months)
- Clinical features:
    - Pulmonary and extra-pulmonary manifestations. The latter are more common thn before. This shift in features involves a change in the organism’s nature; this makes treatment more difficult.
    - MDRTB (multi-drug resistant TB): caused by a strain of Mycobacterium tuberculosis that is resist to Rifampicin and INH. MDRTB is very difficult to

treat. It has a high mortality rate despite the best medical care. In Jordan, MDRTB is not common.

- Primary TB:
  - The great majority of the patients are asymptomatic. Occasionally, they might present with vague illness associated with cough and wheezes.
  - Small transient pleural effusions
  - Erythema nodusum
  - Enlargement of the lymph nodes: they might compress the bronchi. This leads to collapse of segments or lobes of the lung. Patients remain remarkably, and the collapse disappears as the primary complex heals.
  - A persistent collapse can give rise to subsequent middle lob bronchiectasis. This is referred to as Brock's syndrome.
- Miliary TB:
  - It is the result of acute diffuse dissemintation of tubercle bacilli via the blood stream. It can occur within a year of the primary Tb episode; however, it can occur later as a manifestation of reactivation. Rarely, it can happen due to reinfection. This entity is difficult to diagnose in the elderly.
  - Miliary TB is universally fatal without treatment
  - The disease is called miliary TB due to the presence of multiple small nodule on chest C-ray. This presentation is not specific for miliary TB; patients with sacroidosis, staphylococcal, or mycoplasmal infection might present with the same radioographic findings.
  - Miliary Tb can present in a non-specific manner. Here, it presents as a gradual onset of ill health, weight loss, and fever.
  - May cause TB meningitis
  - In miliary TB, mycobacterium tuberculosis can be isolated from blood, urine and bone marrow. Aspiration is positive for Mycobacterium TB.
  - In the early stages of the disease, the are no abnormal physical signs; however, during later stages, the liver and spleen may enlarge.
  - Choroidal tubercle in the eyes.
- Adult post-primary TB (secondary TB):
  - Typically, there is a gradual onset of symptoms over weeks or months. These symptoms include tiredness, malaise, anorexia, weight loss,, fever, and cough.
  - Drenching night sweats: there are uncommon; they are usually due to anxiety
  - These symptoms are non-specific. They can be seen in other diseases, especially lymphomas.
  - Hemoptysis: as streaks of blood or massive hemoptysis

        - Secondary TB can present with:
            - Consolidation and pneumonia that affect the upper lobe
            - Lung abscess due to cavitations. This might lead to the formation of open TB, which is Tb that spreads from the lung to airways. It is characterized by infections.
            - Unilateral pleural effusions that are diagnosed with aspiration. Here, the yield is not high. This can also be diagnosed using a biopsy; for the biopsy we use an Abraham needle. The yield here is no more than 75-80%.
            - Pneumonia of the upper lobe is an indication for the investigation of TB.
- Diagnosis:
    - Imaging:
        - Chest X-ray: the X-ray typically shows a patchy or nodular shadow in the upper zones of the lung. This is accompanied with lost volume and fibrosis without or without cavitations. A single X-ray does not give an indication for the severity of the disease.
        - CT scan: here, you can see cavitations, mediastinal lymph nodes, and bone destruction.
    - Staining:
        - The sputum is stained with Ziel-Nilsen stain for acid and alcohol fast bacilli. This test is not specific for TB. It can be positive in non-tuberculous TB.
        - in a staining or culture test, you should take 3 sputum samples. If the samples were negative and you still suspect TB, bronchopy with BAL are indicated.
        - To induce sputum production, you can use hypotonic saline solutions.
    - Culture: on Lowestein-Jensen media for 7-8 weeks. It is difficult to wait for the results; empirical treatment should be started when clinical suspicion has been established.
    - Fibreoptic bronchoscopy: this is done with a wash from the affected lobes. This is useful of no sputum is available. The yield is usually high..
    - Biopsies: for confirmation
    - Adenosine test: here, the benefit is not clear; the culture remains as the gold standard for diagnosis.
    - PCR
    - CBC: the patients are slightly anemic, leucopenic, with a slight increase in the lymphocyte/neutrophil ratio.
- Treatment:
    - Option 1:

        - Six months of with rifampicin (1-3 times per day; 600 mg/day if >55 kg or 450 mg/day if <55 kg), isoniaized (300 mg).
        - This treatment is the standard for patients with pulmonary lymph node disease. These drugs are given as a combination tablet.
        - Pyrazinamid : supplements treatment for the 1st two months (25 mg/kg/day).
        - Ethambutol (15-20 mg/kg/day)
        - Vitamin B12 to prevent neuropathies
    - Option 2 (longer treatment)
        - This is indicated if there are complications such as stenosis of airways, or stridor. Here, treatment is given for 1 year.
        - If there is bone TB, treatment lasts for 9-12 months.
        - TB meningitis: 6 months
    - MDRTBS:
        - Use three drugs to which the organism is sensitive.
        - If the patient is resistant to any of the aforementioned drugs, we can use capreomycin, ciprifloxacin, oflmaxacin. Amikacin, or ethionamide.
    - Side effects of treatment:
        - Rifamapicin:
            - Staining of bodily secretion in pink color. The patient should be warned of a change in urine, tears, or sweat color.
            - Color of contact lenses changes to orange.
            - May cause hepatitis and acute renal failure.
        - INH:
            - allergic reactions; rash and fever.
            - INH induced hepatitis occurs in less than 1% of the patients. This complication might be fatal. The drug should be stopped promptly. Patients at high risk for developing this disorder include patietns with positive HBV test.
        - Ethambutol: eye problems; eyes should be tested routinely.

Pneumonia

- Pneumonia is an infectious inflammation of the alveolar duct, alveoli, an interstitium .it could be viral, bacterial, fungal or parasitic. Pneuomonitis is an infectious or a non-infectious entity of the alveolar duct, alveoli, or interstitium. Non-infectious causes include lupus, allergy, and gastric juices.
- Pathogenesis:
    - After the inhalation of the pathogen, it colonized the oropharynx.
    - Then, it passes via the airways to the alveoli where it causes the infection. Therefore, the infection can be isolated by a throat swab with a few exceptions; viruses and Mycobacterium tuberculosis doo not colonize the oropharynx; hence, they can't be isolated using a throat swab
    - If staphylococcus aureus was isolated, it may be due to a contamination.
    - Anaerobes do not colonize the throat, as well. Therefore, if they were isolated, this indicates contamination.
- Pneumonia syndrome:
    - Typical: (staph pneumonia)
        - Sudden onset
        - High grade fever (>39) and shaking chills
        - Productive cough with green/yellow sputum
        - Toxic looking patient
        - Loss of appetite
    - Atypical (chlamydia or viruses)
        - Gradual onset
        - Low grade fever
        - Dry cough
        - Non-toxic look
        - Good appetite
- Factors affecting mortality:
    - Multilobluar pneumonia
    - Advanced age
    - Serious underlying disease (DM, chronic renal failure)
    - Mechanical ventilation
    - Renal impairment.
- Risk factors:
    - Decreased BMI or recent weight loss: impaired nutrition causes loss of immunity
    - Current smoker: more than 1 pack/day
    - Previous respiratory infections (influenza or other viral infections). Patients with a previous step pneumonia or staph aureus infection have a higher chance for developing pneumonia within two weeks of the original infection

    - Patients with COPD, asthma or bronchiectasis. Whether smokers or not, these patients have higher risks for infection. The most common organisms are strep pneumonia, hemophilus influenza, and Moraxella catarrharalis. Bronchiectasis patients are at a high risk for being infected with Pseudomonas.
    - Malignancy: especially if on chemotherpay with neutropenia.
    - DM: they have a higher mortality rate; therefore, antibiotic therapy must be started as soon as possible.
    - Chronic liver disease due to decreased immunity. These patients might have an altered level of consciousness; they are at a high risk for aspiration pneumonia.
    - Patients with stroke, epilepsy, or undergoing surgery with general anesthesia.
- Diagnosis:
    - History: can't be used alone due to interobserver variability
    - Typical symptoms:
        - Fever (very common), chills, rigors, and sweating. The fever is usually a high grade fever.
        - Toxic appearance
        - Cough: initially dry, then productive
        - Chest pain: unilateral pleuritic pain. It is important to differentiate between pleuritic and muscular chest pain. To do so, ask the patient to move his/her trunk forward and sideways. If they experience pain, this is muscle pain.
    - Pleuritic chest pain alone can be due to many entities including pneumonia, PE, pulmonary infarction, pneumothorax, and pleurisy.
    - Physical examination:
        - Problems with physical:
            - Interobserver variability
            - Diagnosis of community acquired pneumonia is correct in <40% of examinations. Therefore, a chest X-ray must be performed to get the correct diagnosis.
        - Signs:
            - Decreased expansion (due to pleuritic pain)
            - If collapsed, tracheal deviation towards the collapsed lung
            - Increased TVF unless there is parapneumonic effusions.
            - Decreased percussion note due to perfusion or effusion
            - Auscultation: decreased breath sounds, increased vocal resonance, whispering pectoriloquy, and egophony.
    - Investigations:
        - Etiology:
            - The most common cause of community acquired pneumonia is strep pneumonia

        - The most common cause of hospital acquired pneumonia is pseudomonas followed by staph aureus.
- The manifestations of the disease are due to the host's response rather than the organism itself. Therefore, the clinical picture does not give a clue about the organism
- Sputum is rarely rewarding
- Blood culture is not useful in acute cases.
- Serology is not useful for acute cases. Its only benefit is the presence of arising titer. This is good for epidemiological studies. A 4-fold rise in titer over a period of 4 weeks indicates the presence of a recent infection.
- Sputum:
    - Reliable only if there >25 neutrophils/HPF and <10 epithelial cells/HPF.
    - Good for legionella and Hemophilus.
- Investigations for risk:
    - Oxygenation and ABGs: pneumonia with hypoxia is an indication for admission
    - CBC
    - Assessment of severity. High neutrophils indicate septicemia. Hb <10 indicates Mycoplasma infection.
    - Electrolytes: low sodium and potassium with pneumonia indicates Legionella infection
    - BUN and creatinine: uremia, high creatinine and pneumonia indicate a Legionella infection or any other severe infection. These are indications for ICU admission
    - Glucose
    - Liver enzymes: high levels of liver enzymes with pneumonia indicate viral pneumonia or tuberculosis.
    - Chest X-ray:
        - Pneumonia cannot be diagnosed without consolidation or infiltrates on chest X-ray
        - It is used for diagnosis and assessment of severity. Severe cases present with multilobular infections that are associated with parapneumonic effusions.
        - Any pleural effusion >1 cm in thickness must be investigated using a CT scan. The CT scan is used to assess multiloculated effusions.
    - Effusion fluid:
        - Pus
        - LDH >1000

        - Multilocular
        - Positive culture
    - Microbiology
- When to admit the patient: many systems have been devised to assess the severity of pneumonia. These include PSI, CURB-65, CRB-65, and IDSA. Here is the IDSA system it depends on the following points:
    - Age
    - Liver changes
    - Changed level of consciousness
    - Respiratory rate >30
    - Systolic blood pressure <90
    - Comorbidities (CHF or renal disease)
    - Tachycardia
    - Glucose >252
    - HCT <30
    - PaO_2 <60
    - Pleural effusion
- Treatment: depends on the severity of the disease
    - Mild with no comorbidity, age <60; two options:
        - Macrolide + 2nd generation cephalosporine or augmentin
        - Oral fluorquinolone
    - Moderate (floor admission)
        - Ceftriaxone + macrolide
        - IV levofloxacin
    - Severe (ICU): patients might require a ventilator
        - IV macrolide)can cause venous irritation; it is best given using a central line + beta lactamase inhibitors
        - Macrolide + 3rd generation cephalosporine
        - Macrolide + 4th generation cephalosporine
    - Patients should be observed for 48-72 hours. If there is no response to treatment, check the culture. Change the treatment accordingly.

Pulmonary arterial hypertension

- Pulmonary artery systolic pressure >30 with a mean pressure >20
- Diagnosis: echo or right side catheterization
- Classification:
    - Primary pulmonary hypertension
    - Secondary pulmonary hypertension
- Primary pulmonary hypertension:
    - It is a rare disease; the incidence is 1-2/1,000,000.
    - It is a diagnosis of exclusion
    - It is a disease of younger age groups; usually 3rd or 4th decades.
    - Most of the patients are females (3:1)
    - This disease has a poor prognosis due to the lack of treatment. Survival rate used to be 30% for 3 years; however, with new drugs, it increased to 65% in 5 years.
    - 7-15% of the cases are familial. Genetic abnormalities include an abnormality on chromosome 2 at the 2q31-31 loci. These regions code for BMPR2 (bone morphogenic protein receptor II) gene. Therefore, family history is important in these cases.
    - The cause is still unknown. The process of the disease includes an initial endothelial injury. This injury causes inflammation of the area, endothelial thickening, hyperplasia, and hypertrophy. This leads to narrowing of the lumen, increased resistance, then hypertension.
- Secondary hypertension:
    - Causes:
        - Vasoconstriction secondary to hypoxemia:
            - The commonest cause of this type is COPD. Other causes include obstructive sleep apnea, obesity hypoventilation syndrome, neuromuscular disease, chest wall diseases, and living in high altitude.
            - Vasoconstriction happens as a defensive mechanism. The hypoventilated area with constrict to presence its blood supply for other areas that need it.
        - Destruction of the capillary bed that will lead to increase in the resistance, then hypertension (Causes):
            - COPD
            - Chronic pulmonary embolism
            - Interstitial lung disease
            - Vasculitis
            - HIV
            - Toxins

- Drugs: fenfluramine, ammphetamines, tryptophan, and chemotherapy
- Connective tissue disease
- Portal hypertension
- Schistosomiasis

▪ Volume/pressure overload:
- Disorders of left heart disease cause pulmonary hypertension because of pressure or volume overload. If someone has a left-to-right shunt, volume overload will develop in the pulmonary circulation. This will lead to vasoconstriction, increase in the resistance, and, finally, hypertension. Left heart failure will lead to volume overload.
- Valvular diseases can cause this type of heart failure.
- Pericardial diseases like constrictive pericarditis
- Extrinsic pressure on the vasculature than can be caused by sarcoidosis, fibrosing mediastintis (secondary to TB, fungal infections, or drugs) or any other cause of fibrosis.

o Clinical approach:

▪ Important clues on history and physical examination:
- Hear murmurs
- History of DVT or PE
- Raynaud's phenomenon, arthritis, rash
- Heavy alcohol consumption or hepatitis
- Heavy snoring or obesity

▪ Symptoms directly related to PAH are not specific. These include dyspnea on exertion, syncope, cough, hoarseness, fatigue, chest pain, hemoptysis, and right side heart failure symptoms.

▪ Physical findings (signs of right sided heart failure)
- Right ventricular heave
- Systolic ejection murmur at the left sternal border
- Loud pulmonic component of S2
- Prominent A wave on JVP
- Right sided 4^{th} heart sound
- Tricuspid regurgitation murmur
- Prominent V wave on JVP
- Hepatomegaly
- Pulsatile liver
- Ascites
- Peripheral edema

- Investigations:
  - CBC: polycythemia due to hypoxemia
  - LFT: liver failure cause hepatopulonary syndrome through intrapulmonary shunting
  - PT, PTT, hypercoagulable state: check for liver function and thromboembolism
  - HIV test
  - ECG: right axis deviation in cases of right sided heart failure and P-pulmoonle in left sided heart failure
  - Chest X-ray and CT scan for ILD
  - VQ scan in cases of PE
  - PFT, ABG, spirometry, lung volume, and DLCO: in primary pulmonary hypertension, patients have normal spirometry and lung volumes, low DLCO, normal Hb.
  - Echo: to measure pulmonary arterial pressure, shunting, and left ventricular ejection fraction
  - Right heart catheterization
  - Nocturnal polysomnography: for obstructive sleep apnea
- Management:
  - The higher the pulmonary arterial pressure, the worse the prognosis
  - Treatment of secondary pulmonary arterial hypertension (PAH) depends on treating the underlying disease
  - Medical management:
    - O_2 supplementation to prevent deterioration of hypoxemia
    - NIPPV (non-invasive positive pulmonary ventilation) for obstructive sleep apnea, obesity hypoventilation syndrome, and neuromuscular disease
    - Anticoagulants: in primary PAH and thromboembolic disease
    - Diuresis and digoxin: in right heart failure
    - Vasodilator therapy to pulmonary vasculature:
      - Only when the patient shows response to vasoactive supplements.
      - To assess the effectiveness of vasodilators, you should perform right sided heart catheterization. Inject a vasocative substance, then measure the pulmonary arterial pressure to compare with the one you took before the procedure. If there was a response, you give vasodilators as a treatment. If there was no response, you cannot use vasodilators. Less than

        - Less than 20% of patients with primary PAH and less than 10% of patients with secondary PAH show response to vasodilator therapy.
        - Types of vasodilators:
            - Calcium channel blockers: dihydropiridines
            - Prostaglandin analogues
            - Endothelin receptor antagonists
            - PDE-5 inhibitors
- surgery is the last resort treatment. It is used to treat the underlying cause or the complication soft the disease. It is done when there are anatomical defects like ASD, or VSD.
- If surgery doesn't solve the problem, a lung transplant can be performed

Pneumothorax

- Causes:
    - Spontaneous: due to rupture of a subdural bulla, especially in young thin males
    - Trauma or iatrogenic: central line, biopsy, positive pressure ventilation
    - Asthma/ COPD
    - TB/ pneumonia/ lung abscess// cystic fibrosis / lung CA
    - Connective tissue diseases: Marfan or Ehlers Danlos syndrome
- Symptoms:
    - Asymptomatic: especially if fit, young, or a small pneumothorax
    - If symptomatic: sudden onset of shortness of breath and/or pleuritic chest pain
- Signs:
    - Decreased chest expansion
    - Hyperresonant percussion note
    - Decreased breath sounds
    - Shifted trachea: in tension pneumothorax
- Management:
    - If the lesion is small and the patient is stable, only observe with high flow oxygen
    - If large, pace a small anterior chest tube. A chest tube is mandatory in a pneumothorax patient receiving positive pressure ventilation.

Interstitial lung disease:

- A diverse group of disorders common in:
    - Clinical presentation: shortness of breath
    - Diffuse disease on chest X-ray
    - Restrictive PFT with decreased DLCO and increased A-a gradient
- Classification:
    - Occupational and environmental:
        - Hypersensitivity pneumonitis
        - Organism-dust induces: byssinosis
        - Inorganic dust induced: asbestosis, silicosis, coal worker pneumonitis
    - Idiopathic interstitial fibrosis:
        - Idiopathic pulmonary fibrosis
        - Organizing pneumonia
    - Other causes:
        - Collagen vascular disease
        - Sarcoidosis
        - Eosinoophilic granuloma
        - LAM
        - Vasculitis related
        - Eosenophilic
- Occupational and environmental:
    - Hypersensitivity pneumonitis:
        - Types:
            - Acute
            - Chronic
            - Subacute
        - Immune-mediated granulamatous infection
        - Poorly formed granulomas are typical
        - Causes:
            - Farmer's lung
            - Bird-fancier lung
            - Grain dust
            - Crack cocaine
        - Think of the disease in a patient with recurrent/persistent pneumonia with a history of exposure to one or more of the aforementioned factors.
        - Diagnosis by history
        - BAL: increased lymphocytes; helper: suppressor ratio <1

        - Best treatment: stop the offending agent. If the disease is acute, give steroids
    - Organic dust induced:
        - Byssinosis (Monday chest tightness) due to inhalation of cotton
        - Not immune-mediated: no sensitization needed
        - History:
            - Early stage: chest tightness
            - Late stage: regular chest tightness towards the end of the 1st day of work week
    - Inorganic dust-induced:
        - Asbestosis:
            - You have to differentiate between asbestosis and exposure asbestosis.
            - Asbestosis exposure:
                - Changes involving midthorax sparing both costophrenic angles and apices
                - Pleural thickening and plaques are completely benign. These are not manifestations of asbestosis
                - The most common manifestation of asbestosis exposure is the 1st 10 years is pleural effusion. Caries from serous to blood; 1/3 have eosinophils.
            - Malignant mesothelioma:
                - 80% associates with asbestos exposure (not necessarily asbestosis)
                - Tumor arises from mesthelial cells of the pleura
                - Latency period > 40 years
                - Not associated with smoking
                - Rapidly fatal disease
            - Asbestosis:
                - Parynchemal fibrosis and impairment in th bases of the lung.
                - Cause: prolonged exposure to asbestos
                - Occurs after 10 years of moderate exposure
                - Latency period > 30 years
                - Associated with lung CA (squamous and adenocarcnoma)
                - Treatment: no specific treatment
        - Coal (coal worker pneumoconiosis)
            - Simple and progressive
            - Upper lungs

                - Progression correlates with the amount ingested. Complication of CWP are not associated with the ingested amount
                - No hilar involvement, no association with TB, no specific treatment
                - Caplan syndrome: seropositive RA + massive CWP
            - Beryllium:
                - Cell mediated immune response
                - Causes perihilar lymphadenopathy; similar to sarcoidosis
                - Needs two years of exposure
                - Suspect in patients working in high-tech electronic or in ceramic industry
                - Diagnosis:
                    - History of beryllium exposure
                    - Positive beryllium lymphocyte transfer test (BeLPT)
                    - Lung biopsy: interstitial cell infiltrate (mononuclear cells) and/or non-caseating granuloma
                - This disease can be treated with steroids and methroxate
            - Silicosis:
                - The most prevalent occupational disease in the world
                - Requires years to develop; latency of 20-30 years
                - Involves the upper lobes. The lesion is fibrocalcific with hilar eggshell calcifications.
                - Silicosis increases the risk of TB and CA. treat with anti-TB drugs
                - Silica is considered a human carcinogen e
                - Differential diagnosis:
                    - TB
                    - CWP
                    - Beryllosis
                - Treatment:
                    - No specific treatment, but if symptoms are rapidly worsening consider TB
                    - Steroids are beneficial in acute cases, but not in chronic cases
                    - Consider lung transplant in severe cases
                - Silica is ingested by alveolar macrophages and renders them ineffective.
- Idiopathic diseases:
    - Idiopathic pulmonary fibrosis:
        - Diagnosis of exclusion
        - 50% of ILD

        - Equal incidence in males and females.
        - Average age: 55 years
        - Clubbing is seen in 50-60% of patients
        - Smoking increases the disease
        - 10-30% are ANA positive
        - Symptoms:
            - Dry cough
            - Shortness of breath
            - Malaise
            - Weight loss
            - Arthalgia
        - Signs:
            - Cyanosis
            - Clubbing
            - Fine end inspiratory crepitations
        - Complications:
            - Respiratory failure
            - Increased risk for lung cancer
        - Investigations:
            - ABG: decreased oxygen and increased carbon dioxide
            - Chest X-ray: honeycomb lung in advanced disease
            - Spirometry: restrictive disease with decreased TLC and decreased DLCO
            - BAL: increased lymphocytes, neutrophils, and eosinophils
        - Treatment:
            - Oxygen
            - Vaccinations
            - Consider lung transplant
            - Steroids with or without cyclophosphamide
        - Notes:
            - Indications for a biopsy:
                - To characterize the lung pathology
                - Rule out CA, infection, or vasculitis
            - Contraindications:
                - Negative environmental history
                - Age >60
                - Clunning
                - Coarse crackes and honeycomb lungs
    - Cryptogenic organizing pneumonia:

- Consider in patients with insidious onset (weeks to 102 months) of cough, fever, dyspnea, malaise, and myalgia.
- Patients are irresponsive to antibiotics
- How to differentiate from IPF?
    - COP has a good prognosis and is responsive to steroids
    - IPF has more insidious onset (>6 months)
    - Patients with IPF do not have fever
- Lung biopsy is the definitive diagnostic test
- Treatment of choice: steroids

Obstructive sleep apnea (OSA)

- Definitions:
    - Apnea:
        - Cessation of airflow at the mouth and the nose for >10 seconds during sleep (undefined oxygen desaturation)
        - Cessationo f airflow for <10 seconds with an oxygen desaturation >40%
    - Hypopnea: a reduction in the amplitude of airflow or thoracoabominal movement more than 50% of the baseline measurement for more than 10 seconds with an arousal or oxygen desaturation more than 4%.
    - Central apnea: an apnea accompanied by an absence of diaphragmatic EMG and thoracoabdominal movement
    - Obstructive apnea: apnea with continued or raised EMG diaphragmatic activity and/or thoracoabominal wall movement.
    - Mixed apnea: apnea with both central and obstructive components. The central component should last for, at least, one respiratory cycle length
- Obstructive sleep apnea:
    - Recurrent upper airway obstructions during sleep
    - Spectrum of severity: normal → snoring → obstructive sleep apnea
    - Syndrome:
        - Frequent episodes of apnea and hypopnea
        - Respiratory disturbance index >10 events/hour of sleep
        - Symptoms of functional impairment.
- Sleep:a period of rest for the body and mind, during which volition and consciousness are in partial or complete abeyance and thebodily functions partially suspended. Sleep ha s also been described as a behavioral state marked by characteristicimmobile posture and diminished but readily reversible sensitivity to external stimuli.
- Sleep architecture:
    - Sleep architecture describes the structure of sleeping
    - Sleeping is a complex and active process made of different stages.
    - Sleep is divided into:
        - NREM sleep (non-rapid eye movement)
        - REM sleep (rapid eye movement)
    - NREM sleep is further divided into 4 stages:
        - Stage 1: 1-2.5%
        - Stage 2: 45-55%
        - Stage 3: 3-8%
        - Stage 4: 10-15%
    - REM sleep:
        - Characterized by dreaming
        - Eyes move rapidly under the eyelids

        - Decrease in muscle tone (paralysis)
- Obstructive sleep apnea occurs when the upper airway repeatedly collapses during sleep. This causes cessation of breathing (apnea) or inadequate breathing (hypopnea) and sleep fragmentation.
- Risk factors:
    - Certain jaw or facial structures or attributes such as a recessed chin
    - Being overweight or having a large neck size of approximately 17 inches or larger in males or 16 inches or larger in females
- What causes the airway to collapse during sleep?
    - Extra tissue in the back of the throat such as large tonsils or uvula
    - A decrease in the tone of the muscles holding the airway open
    - Nasal obstruction
- Prevalence:
    - 32.6 million people
    - 4% of men and 2$ of women aged 30-60
    - It is as common as adult asthma
    - Majority of cases remain undiagnosed and untreated
- Identification criteria
    - Excessive daytime sleepiness unexplained by other factors with two or more of the following:
        - Loud disruptive snoring
        - Nocturnal choking/gasping
        - Nocturnal poses in breathing
        - Recurrent nocturnal awakening
        - Unrefreshing sleep
        - Daytime fatigue
        - Impaired concentration
- Symptoms:
    - Daytime sleepiness
    - Snoring
    - Choking witnessed apnea
- OSA has been linked to:
    - Premature death
    - Hypertension
    - Ischemic heart disease
    - Stroke
    - Road traffic accidents
- Acute cardiovascular effects of OSA
    - Normal sleep induces a fall in blood pressure:
        - Reduced heart rate, stroke volume, and cardiac output

        - Reduced peripheral resistance, and sympathetic nervous system activity
    - OSA causes cyclical variations in these variables due to:
        - Exaggerated negative intrathoracic pressure:
            - Inspiratory efforts occur against a closed airway
            - Inreased transmural pressure resulting in increased afterload
            - Increased venous return to the right ventricle with a shift of the interventricular septum causing reduce left ventricular filling
            - Reduced stroke volume and a fall in blood pressure
        - Hypoxia:
            - Gradually increasing hypoxia starts several seods after the apnea begins with further delay in sensing at the peripheral chemoreceptors
            - Hypoxia causes bradychardia in the absence of airflow
            - Increased sympathetic nerve activity which is proportional to the degree of hypoxia
            - Vasoconstriction and increased heart rate starting during but peaking after the apnea
        - Arousal:
            - increasing respiratory efforts cause arousal; the critical mechanism that causes the airway to open and breathing to resume
            - Arousal contributes to the sympatheic drive at the end of the apnea
        - Apnea termination:
            - Sudden changes at apnea termination cause an increase in stroke volume, heart rate, and cardiac output, under hypoxic conditions, into a constricted arterial system
            - Cyclical surges of blood pressure
            - Sleep resumes rapidly and pharyngeal collapse recurs
            - This may be repeated hundreds of times a night turning sleep from a time of cardiovascular rest to a time of cardiovascular stress
    - Reoxygentation phenomenon:
        - Reoxygenation, repeated many time a night, causes changes in reperfusion. This increases free radical production along with oxidative stress
        - This is considered a major contributor to the cardiovascular consequences observes in this group of patients.
    - Other mechanisms for damage:
        - Higher cytokine levels
        - Insulin resistance
        - TNF-alpha and IL-6

- Obstructive sleep apnea is considered as independent risk factor for cardiovascular diseases including hypertension.
- Undiagnosed or untreated OSA may have severe financial consequences on the healthcare system.
- Polysomnography:
    - The simultaneous monitoring of multiple physiological parameters during sleep. It is used to assist in the identification and treatment of sleep disorders.
    - Screening parameters:
        - Flow
        - Microphone
        - Thorax
        - Abdomen
        - ECG
        - Saturation
        - Body position
- Management:
    - Lifestyle modification
    - Medical
    - Surgical
    - Mechanical

Lung cancer

- The number 2 cancer among males after prostate cancer
- The number 2 cancer among females after breast cancer
- Number 1 cause of death among males and females
- Risk factors:
    - Smoking: 85% of lung Ca is linked to smoking. Smoking increases the risk by 10 times
    - Environmental and occupations:
        - Asbestos:
            - Exposure alone: 6 times more risk
            - Snoring alone 10 times more risk
            - Asbestos with smoking 60 times more risk
            - Mostly associated with squamous and adenocarcinoma.
        - Radon, nickel, arsenic, and chromium
    - Idiopathic pulmonary fibrosis: 60-65% risk of developing bronchogenic CA
    - Pulmonary paryhnchemal fibrosis: any ILD or any inflammatory process that causes fibrosis will increase the risk of lung CA. these cause scar carcinoma
    - History of COPD
- Types:
    - Non-small cell CA (NSCLC)
        - Adenocarcinoma: the most common; subtype: bronchoalveolar
        - Squamous cell carcinoma
        - Large cell CA (the least common)
    - Small cell CA (SCLC): subtype oat cell CA
        - The worst prognosis
        - Small cell CA is mostly related to smoking
- NSCLC
    - Adenocarcinoma: most common
        - Peripheral lesions
        - Found incidentally
        - Many arise in old parynchemal scars
        - Bronchoalveolar CA:
            - Cough with large amount of frothy sputum
            - It has the least association with smoking
        - Early metastasis
    - Squamous cell carcinoma:
        - Central
        - Late metastasis
        - Often associated with obstructive symptoms (atelactasis and pneumonitis)

        - It is the most likely to cavitate (thick walled >4 mm)
        - Associated with hypercalcemia as a paraneoplastic syndrome
    - Large cell CA:
        - Peripheral lesion
        - Tends to metastasize
        - Paraneoplastic syndrome: gynecomastia
- SCLC:
    - Central
    - Never cavitates
    - Early metastasis, extremely aggressive. All symptoms evolve within 8 weeks
    - The most common subtype is oat cell CA
    - Paraneoplastic syndrome:
        - SIADH
        - Ectopic ACTH
        - Lambert Eaton syndrome
- Symptoms of lung CA are related to:
    - Local tumor growth:
        - Cough, wheezes, shortness of breath
        - Hemoptysis
        - Recurrent chest infection (post-obstructive pneumonia)
        - In cases of invasion:
            - Esophagus: dysphagia
            - Left recurrent laryngeal: hoarseness of voice
            - T1 and sympathetic chain: Horner's syndrome
            - Lymphatics: massive pleural effusion
            - SVC: SVC syndrome
            - Pericardium: cardiac tamponade
            - Heart: conduction defects
            - Diaphragm: paralysis
    - Distant metastasis
    - Symptoms of paraneoplastic syndrome: a clinical syndrome involving non-metastatic effects associated with cancer:
        - Hypercalcemia: PTH- like hormone production:
            - Associated with squamous cell carcinoma
            - Ca is proportional to the tumor's bulk
            - Less often seen with LCC
        - SIADH, ectopic ACTH, and Eaton-Lambert syndrome:
            - Associated with small cell CA
            - Note: diabetes insipidus is not a paraneoplastic syndrome. If it happens, think of brain metastasis

        - Gynecomastia: associated with large cell CA
        - Hypertonic pulmonary osteoarthropathy (HPO):
            - Associated with adenocarcinoma
            - Patients get clubbing and new bone formation in the long bones
            - Presents with painful ankles with clubbing
        - Other:
            - Dermatomyositis
            - Acanthosis Nigricans
            - Thrombophila migrans
- Diagnosis:
    - History and physical examination
    - Chest X-ray
    - CT abdomen and chest
    - Bronchoscopy and biopsy
    - Percutaneous FNA
    - PET scan: the best staging method, allows for functional analysis, staging, and identification of metastatic lesions
- Staging:
    - NSCLC: TNM staging
        - T:
            - T_{is}: carcinoma in situ
            - T_0: no evidence
            - T1: <3 cm
            - T2: >3cm or any size with pleural invasion or obstructive pneumonitis extending to the hilum but not to the whole lung
            - T3: involves chest wall, diaphragm, mediastial pleura or malignant effusion is present
            - T4: any size involving mediastinum, heart, great vessels, trauma, esophageal CA or malignant effusion is present
        - N:
            - N0: no lymph nodes
            - N1: ipsilateral peribronchial, hilum
            - N2: ipsilateral mediastinum
            - N3: contralateral mediastinum, hilum, scalene, supraclavicular
        - M:
            - M0 : no metastasis
            - M1: distant metastasis
- Treatment:
    - NSCLC:

- Stage 1: Tis, T1, T2 N0 M0
- Stage II: T3 N0 M0, or T1/T2 N1
- Stage IIIa: T3 N1 M0, or T1-3 N2 M0
- Stage IIIb: any T with N3 M0, or T4 N0-2 M0

→ surgery + CTX + RTX

- Stage IV: any T, N with M1 → palliative CTX + RTX

- Other lung tumors:
    - Carcinoid:
        - 2.5% of all lung CA
        - Endobronchial muass
        - Secretes, peptides , hormones, and neuroamines. These include ACTH, ADH, serotonin, and somatostatin
        - Occurs in young patients
        - Often resectable and is curable by surgery
    - Benign lung tumors:
        - Hamartoma:
            - Lung is a common site
            - Peripheral
            - Silent, asymptomatic
            - Popcorn calcifications in 20% of cases
            - Benign, no need for surgical resection
        - Adenomas
        - Leiomyoma
        - Chondroma
        - Teratoma