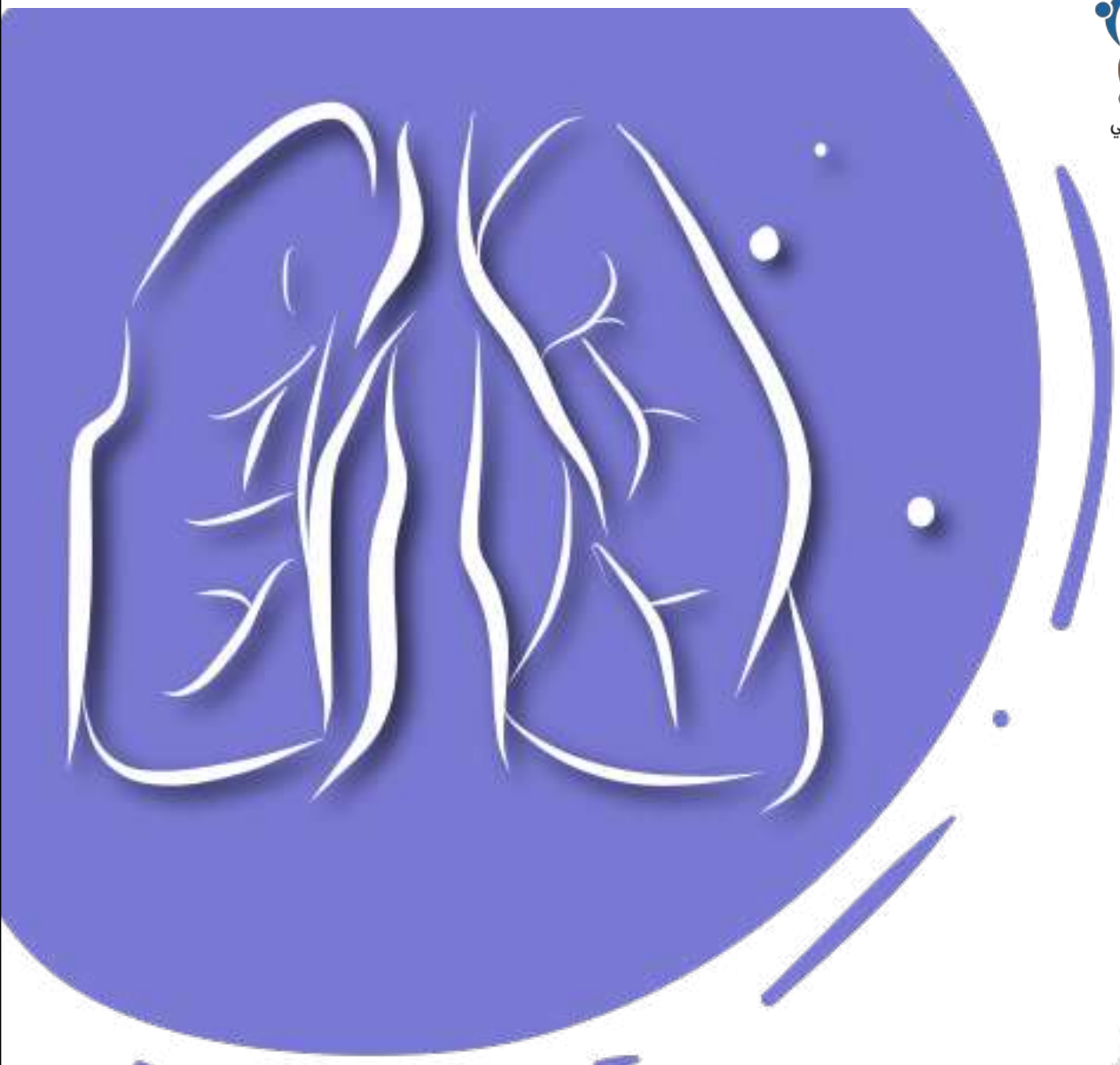
المجلس الطلابي



Respiratory CHAPTER

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SECTION 1 :

OVERVIEW

Respiratory System - Overview by Armando Hasudungan

Objective

1. Describe the structures and functions of the conductive and respiratory zones of airways.
2. Understand the difference between internal and external respiration.
3. Understand the functions of the respiratory system, including non-respiratory functions, like clearance mechanism by mucus and cilia, production of surfactant and its physiological significance

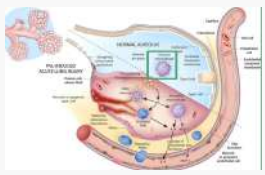
Note:
(1) **Immunoglobulin A (IgA)**
It is a type of antibody that protects against infections of mucous membranes lining the mouth, airway and digestive tract. It is the most common antibody as primary deficiencies, it is predominant Ig isotype in mucosal tissue and is believed to be involved in defense against viral and bacterial infections at these sites.

(1) **Trypsin** is a proteolytic enzyme that digest proteins. Bacteria produce this enzyme, so the muco-ciliary barrier produces antitrypsin to protect the body proteins from bacteria.

Note:
(2) Angiotensin is a peptide hormone that causes vasoconstriction and an increase in blood pressure (regulation of B.P), Produced by kidney

Note:
(3) Surfactant: also called surface-active agent, when added to a liquid, reduces its surface tension, thereby increasing its spreading and wetting properties.

Note:
In addition, the pulmonary macrophages in the alveoli: engulf smaller foreign particles which pass through the muco-ciliary barrier filter

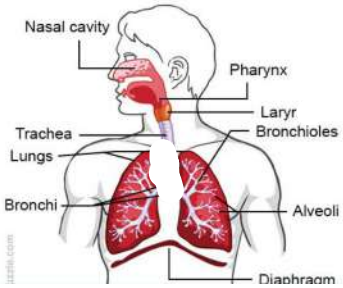


Main goals of respiration:

- **To provide oxygen to tissues.**
- **To remove CO2 from the body**.

The body needs to get rid of CO2 (Acid) because it will participate in production of H+ which will decrease the PH which is dangerous, so our body will try to maintain alkalosis state

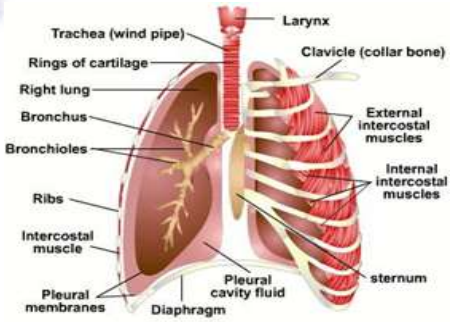
Respiratory passages (airways)



Respiratory system consists of:

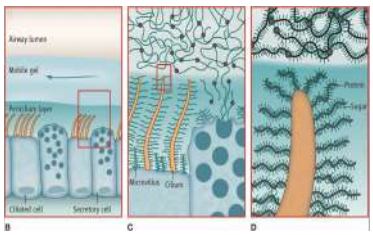
- **Passages (airways)**
- **Muscles**
- **Centers:**

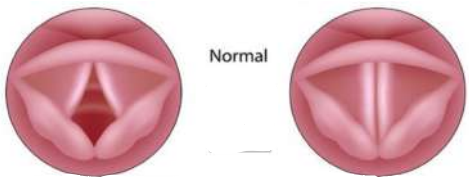
located underneath the medulla. Its main function is to regulate control the rate or speed of involuntary respiration



Functions of the respiratory system include:

- Gas exchange (respiratory function).
- Pulmonary defense: the respiratory mucous membrane has muco-ciliary barrier filter and it produces Immunoglobulin A (IgA) and Alpha-1 antitrypsin. [1]
- Phonation: is the production of sounds by the movement of air through the vocal cords.
- Converting of Angiotensin I in the blood to Angiotensin II by Angiotensin Converting Enzyme (ACE). The enzyme is formed by the lungs. [2]
- Regulating the acid- base status of the body by washing out extra carbon dioxide from the blood.
- Secretion of important substances like surfactant. [3]

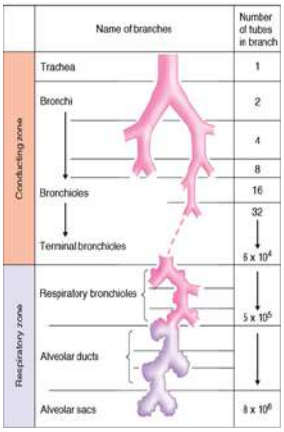




Respiratory passages airways can be divided into:

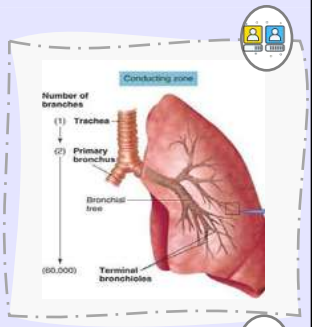
Conductive Zone

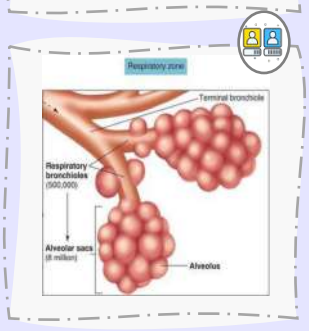
- Starts from nose to the end of terminal bronchioles.
- Help warming, humidification and filtration of inspired air.
- Contains the olfactory receptors for smell sensation.
- Conducts the sound during speech.
- Protective function by cough and sneezing reflexes.



Respiratory Zone (unite):

- Respiratory bronchioles, alveolar. ducts, alveolar sacs and alveoli.
- Function in gas exchange.





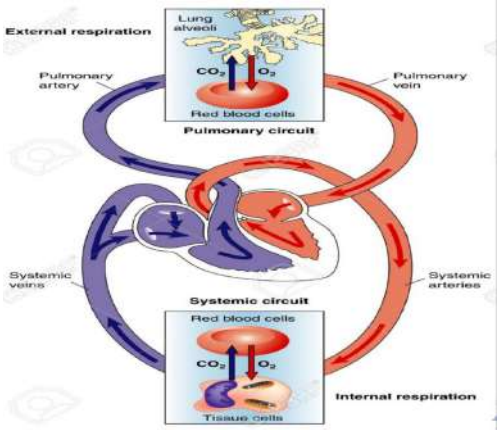
External and Internal respiration

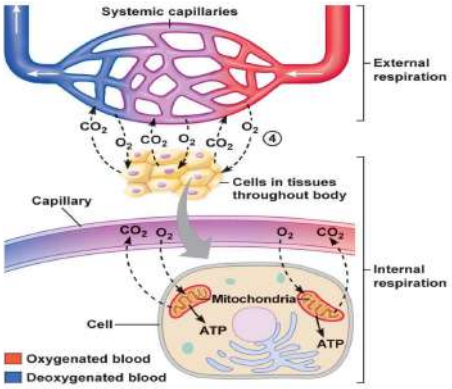
External respiration:

is the process of gas exchange between the alveolar air and the pulmonary capillary blood.

Internal respiration:

is the process of gas exchange between the blood in the systemic capillaries and the tissues.

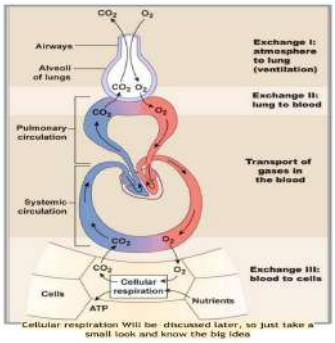




The Respiratory System by Bozeman Science

Three major functional events occurs during External respiration:

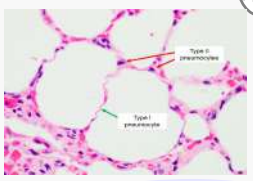
- Pulmonary ventilation inward and outward movement of air between lung and atmosphere.
- Diffusion of oxygen and CO2 between the alveoli and the pulmonary capillary blood.
- Transport of O2 & CO2 in the blood and body fluids to and from the cells.



Note:
(4) During forced respiration we use more muscles than normal respiration.

Respiration could be either:

- Resting (minimal): normal breathing during resting conditions.
- Forced (maximal): normally during exercise and in patients with bronchial asthma, allergy, other pulmonary diseases. [4]



Lining cells of the alveoli:

Type I pneumocytes:

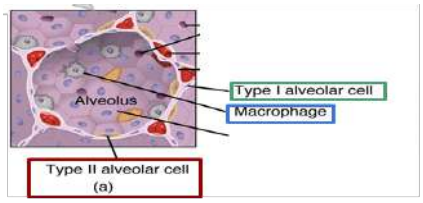
- Type I alveolar epithelial cells which participate in the respiratory membrane , across which gas exchange takes place.

Type II pneumocytes:

- Type II alveolar epithelial cells (10% of the surface area of alveoli)
- Secrete surfactant.

Alveolar macrophages

- Engulf the foreign bodies that reach the alveoli.



From Guyton:

Principle of Surface Tension. let us see what happens on the inner surfaces of the alveoli. Here, the water surface is attempting to contract. This results in an attempt to force the air out of the alveoli through the bronchi and, in doing so, causes the alveoli to try to collapse.

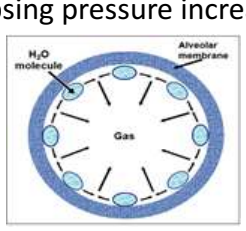
The net effect is to cause an elastic contractile force of the entire lungs, which is called the surface tension

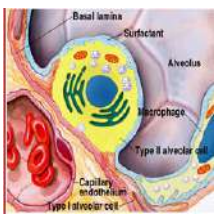
Surface Tension:

- Surface tension tends to oppose alveoli expansion.
- Pulmonary surfactant reduces the surface tension of the fluid lining the alveoli.
- Collapsing Pressure is Caused by Surface Tension and is indirectly related to the size of alveoli (law of LaPlace)
- As the surface tension increases, the collapsing pressure increases.

$$\text{Pressure} = \frac{2 \times \text{Surface tension}}{\text{Radius of alveolus}}$$

this pressure is pushing inward that causes lung recoil





Note :

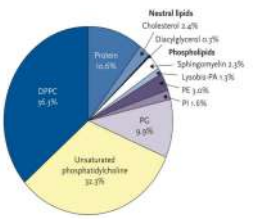
Surface Tension:

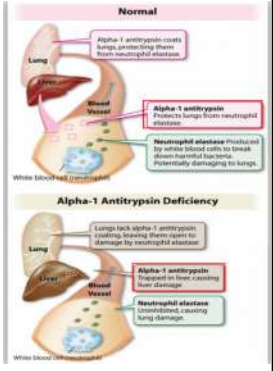
When H2O molecules at the surface of alveoli are attracted to each other by attractive forces that resist distension

The Respiratory System: Surface Tension in the Lungs - Law of Laplace by 5MinuteSchool

Surfactant:

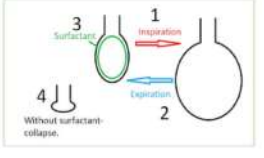
It is a complex compound containing phospholipids especially dipalmitoyl-phosphatidyl choline and other Apoproteins.
The earliest detection of surfactant from fetal alveoli begins between 6-7th month but this could be delayed in others to week 35 of intrauterine life.

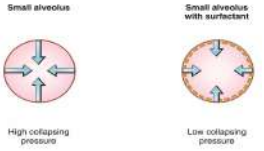




Function of surfactant:

- Reduces surface tension throughout the lung.[5]
- Reducing the effort required by the respiratory muscles to expand the lungs.
- Decreases airway resistance.
- Decreases work of breathing.
- Keep the alveoli dry (deficiency in surfactant increases recoil, the body accommodates by decreasing IP pressure (Intrapleural pressure) . This decrease in pressure will promote capillary filtration, leading to pulmonary edema).
- Prevents alveolar collapse, Surfactant help us to prevent that and collapsing of alveoli will need a lot of energy to return to its normal state .





Note :

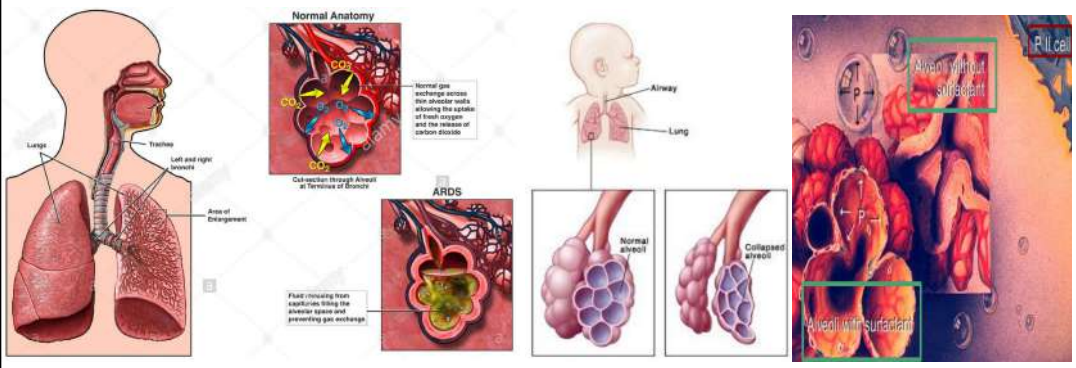
(5) Between the H2O molecules there are hydrogen bonds which make the surface tension Surface tension is pulling the alveoli in that cause lung recoil, sometimes surface tension become very high which lead to alveoli collapsing (that's why we have type II pneumocytes that produce surfactant).

Surfactant deficiency:

Deficiency in premature babies causes respiratory distress syndrome of the newborn (RDS).

Neonatal Respiratory Distress Syndrome:

- Infants born before week 24 will never have surfactant.
- Without surfactant, small alveoli will increase surface tension and that will increase pressures, eventually alveoli will collapse (atelectasis).
- Collapsed alveoli are not ventilated, therefore cannot participate in gas exchange



Prevention:

- Corticosteroid injection to mothers expected to deliver prematurely. This will enhance surfactant maturation.
- After delivery they are given inhaled surfactant.
- Smoking in adults, hypoxia or hypoxemia, decrease the secretion of surfactant and cause adult respiratory distress syndrome.

Note :

Respiratory Distress Syndrome

- Also Known as Hyaline Membrane Disease.
- RDS occurs primarily in premature infants, and its incidence is inversely related to gestational age and birthweight.

Gestational Age	Percentages
Less than 28 wks.	60-80%
32-36 wks.	60-80%
37-39 wks.	60-80%
Term	Rare

Acute Respiratory Distress Syndrome (ARDS) by USMLEFastTrack

General notes about lungs and bronchi:

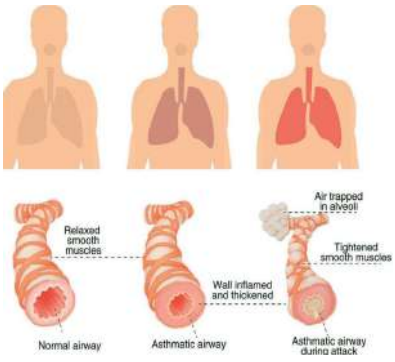
Innervation of Lung and bronchi:

- It is by autonomic nerves, that's why breathing is not under our control.
- Sympathetic stimulation→ releases epinephrine → dilatation of the bronchi.
- Parasympathetic stimulation → releases acetylcholine → constriction of the bronchi.

Locally secreted factors:

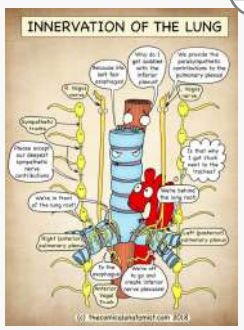
- **Histamine**

Slow reacting substances of anaphylaxis (SRSA) secreted by the mast cells due to allergy as in patients with asthma, and it often causes bronchiolar constriction and increased airway resistance leading to forced breathing. IgA will stick on the surface of mast cells and then will produce antibodies after they get attached again, they will explode histamine + SRSA which are inside the mast cell, and the releasing of that will lead to allergy and other respiratory diseases.



Note :

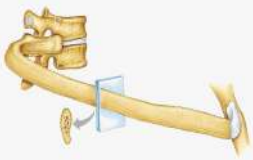
(6) to allow more air into the lungs, which will increase oxygenation of the blood and keep up with the increased flow of blood through the lungs due to the increased heart rate.



Objective

1. Describe the components of the thoracic cage and their articulations.
2. Describe in brief the respiratory movements.
3. List the muscles involved in inspiration and in expiration.
4. Describe the attachments of each muscle to the thoracic cage and its nerve supply.
5. Describe the origin, insertion, nerve supply of diaphragm.

Extra Picture :



Note: the lower border of the rib is sharp.

Thoracic cage

It is Conical in shape and has 2 Apertures or opening , it is formed by bones and their articulations.

Formed by:

1. **Sternum & costal cartilages: anteriorly**
2. **Twelve pairs of ribs: laterally**
3. **Twelve thoracic vertebrae: posteriorly**

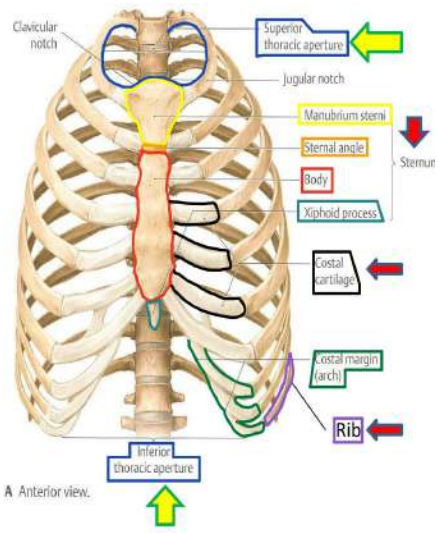
Has 2 Apertures (Opening):

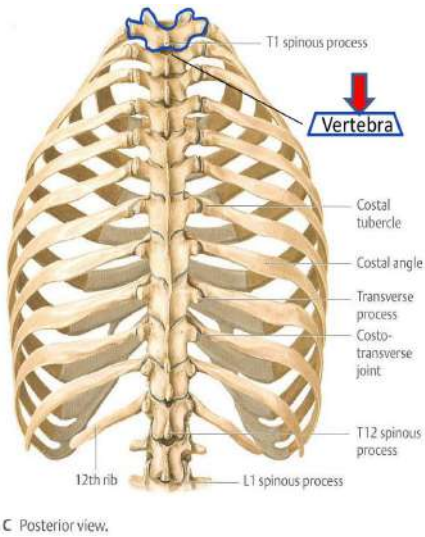
1.Superior (thoracic outlet): narrow, open, continuous with neck obliquely placed facing upward and forward Bounded by:

- Superior border of the manubrium anteriorly
- Medial borders of first rib laterally
- First thoracic vertebrae posteriorly

2.Inferior: wide, closed by diaphragm Bounded by:

- Xiphisternal joint: anteriorly
- Curving costal margin laterally
- Twelve thoracic vertebrae: posteriorly





Articulations:

Primary cartilaginous :

- Costochondral joints= Between ribs and their costal cartilages.
- Interchondral joints*= Between costal cartilages of 6th -10th ribs
- Sternocostal joints= Between costal cartilages and sternum

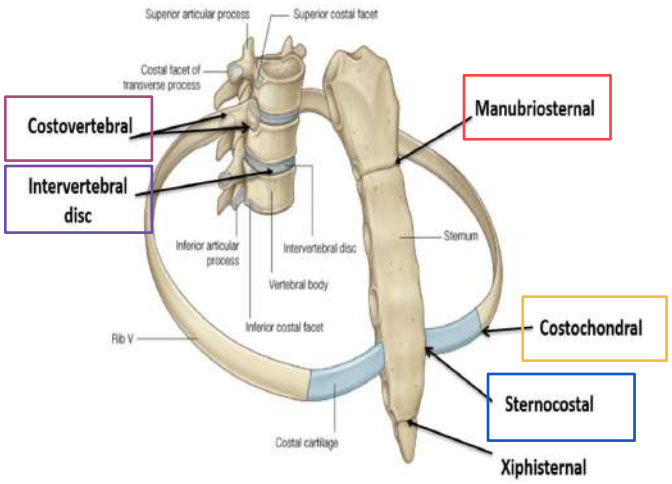
→ 1st costal cartilage.

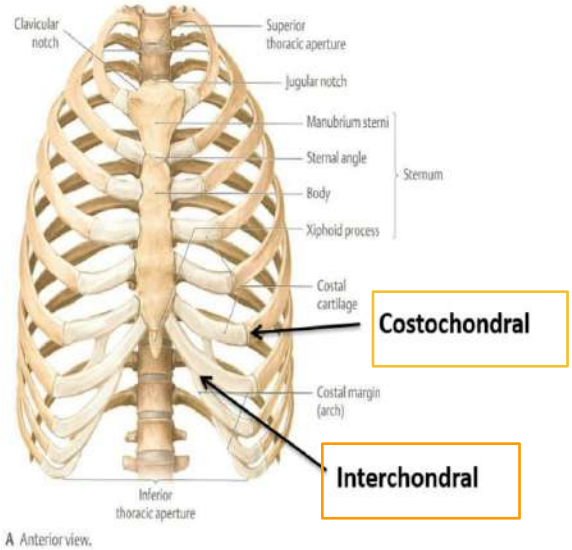
Secondary cartilaginous:

- Intervertebral discs*= Between two vertebrae
- Manubriosternal joint*= Between manubrium and body of sternum
- Xiphisternal joint*= Between body of the sternum and xiphoid process

Plane synovial :

- Costovertebral joints= Between ribs and thoracic vertebrae → Note : each Rib articulates with two vertebrae.
- Sternocostal joints= Between costal cartilages and sternum
  → From 2nd to 7th (Plane synovial)



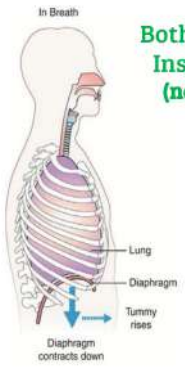


A Anterior view.

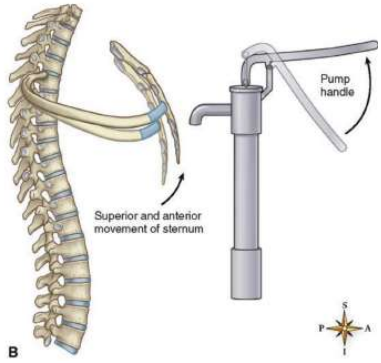
Respiratory Movements:

Movements of DIAPHRAGM and RIBS , can be summarized as following :

DIAPHRAGM		RIBS	
Inspiration (in breath)	**Expiration (out breath)**	**Pump handle movement**	**Bucket handle movement**
Contraction, descent (down) Of diaphragm Increase of vertical diameter of thoracic cavity	Relaxation, **ascent** (up) **Decrease** of vertical diameter of thoracic cavity	Elevation of ribs Increase in **antero-posterior** diameter of thoracic cavity	Elevation of ribs Increase in **lateral** diameter of thoracic cavity

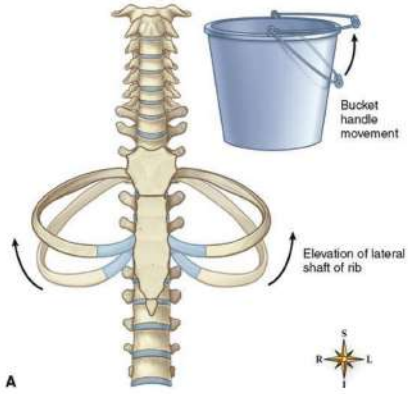


Both Normal and forced Inspiration are active **(needs muscles action)**



Normal Expiration is **Passive**
1. Elastic recoil of lung
2. Relaxation of diaphragm & external intercostal
(No muscles action)

Forced Expiration is **active** **(needs muscles action)**



Inspiratory Muscles

- Active in both normal and forced inspiration = Diaphragm and External intercostal muscles
- Active Only in forced inspiration (Accessory muscles) such as : Scalene muscles and Pectoralis major.

Diaphragm

Origin :

1. Costal: Lower 6 ribs and their costal cartilages
2. Vertebral: upper 3 lumbar vertebrae by
   - Right crus (attached to the upper three lumbar vertebrae)
   - left crus (attached to the upper two lumbar vertebrae)
   - And 5 ligaments :
     - 2x Medial arcuate: connects each crus to 1st lumbar vertebra
     - 2x Lateral arcuate:connects 1st lumbar vertebra to last rib
     - Median arcuate: connects right & left crus
3. Sternal: Posterior surface of xiphoid process

3D view of diaphragm by sohambliss

Note:
Right crus is stronger and bigger because liver is immediately below it

Insertion :

Fibers converge to join the **central tendon** (lies at the level of xiphisternal joint, at 9th thoracic Vertebra).

Nerve supply :

Phrenic nerve (C3,4,5), penetrates diaphragm & innervates it from abdominal surface

Note:
Why the cervical spines? Because first it forms near the neck then it goes down as the embryo develops (folding of embryo)

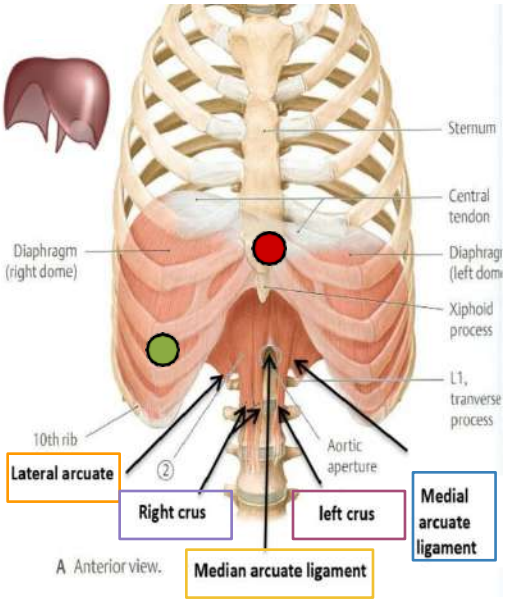
Action:

contraction of the diaphragm
Lead to increase of vertical diameter of thoracic cavity. This action is essential for normal breathing

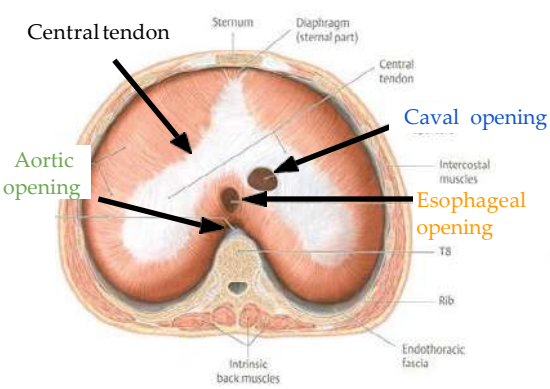
Diaphragm - Definition, Function, Muscle & Anatomy | Kenhub by Kenhub - Learn Human Ana...

Openings of diaphragm (apertures)

- Caval apertures , at level of T8
- Esophageal apertures , at level of T10
- Aortic apertures , at level of T12



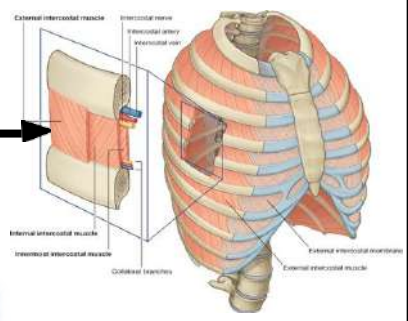
*Superior view



External intercostal muscles (Rib elevators)

- Attachments: from lower border of rib above to upper border of rib below
- Direction of fibers: **downward & medially(forward)**
- Action: rib elevators
- Nerve supply: intercostal nerves

EXTERNAL INTERCOSTAL



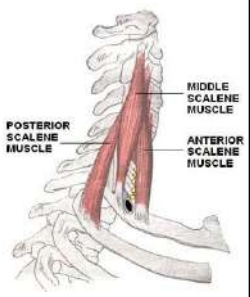
Picture of Pectoralis major:

Muscles of the Thoracic Wall - 3D Anatomy Tutorial by AnatomyZone

Anatomy Thorax Clinical (+ Nerve Block) by Armando Hasudungan

Accessory muscles of Inspiration

Muscle	Scalene muscles	Pectoralis major
Origin	Cervical vertebrae	clavicle + sternum + costal cartilages
Insertion	1st rib (scalenus anterior and Medius) 2nd rib (scalenus posterior)	Bicipital groove of humerus
Action	Elevate 1st & 2nd ribs	**Increases antero-posterior diameter** of thoracic cavity, when arm is fixed

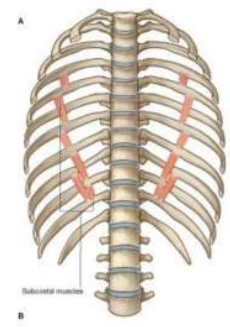


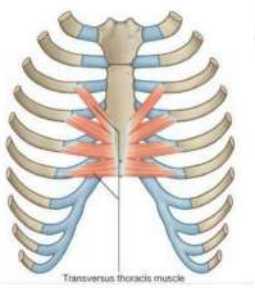
Expiratory muscles

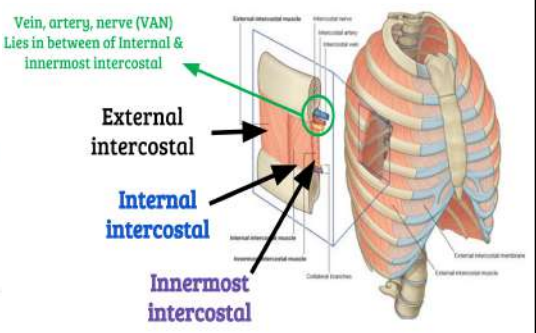
- Two groups: A- Ribs depressors B- Anterior abdominal wall muscles.
- All expiratory muscles act only during forced expiration

A- Ribs depressors

Muscle	subcostal	Transversus thoracic	Internal intercostal	Innermost intercostal
Direction			Backward and Laterally	
Nerve	Intercostal nerve ventral rami from T1 to T11			
Action	Depression of the Ribs			





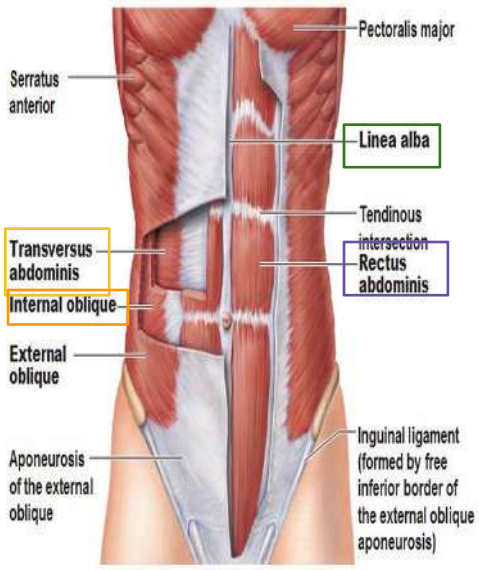


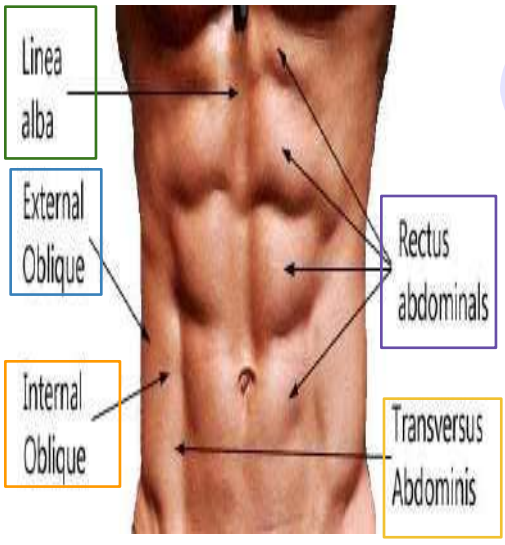
B- Anterior abdominal wall muscles.

Second : Anterior abdominal wall muscles

- It Is formed of 3 layers of muscles of fibers running in different directions (to increase strength of anterior abdominal wall)
- The 3 muscles form a sheath in which a fourth muscles lies (rectus abdominis)
- Muscles are attached to: sternum, costal cartilages and ribs + hip bones
- The aponeurosis of the 3 muscles on both sides fuse in the midline to form linea alba (it is meeting of 3 aponeurosis in both sides, extending from the xiphoid process to symphysis pips)

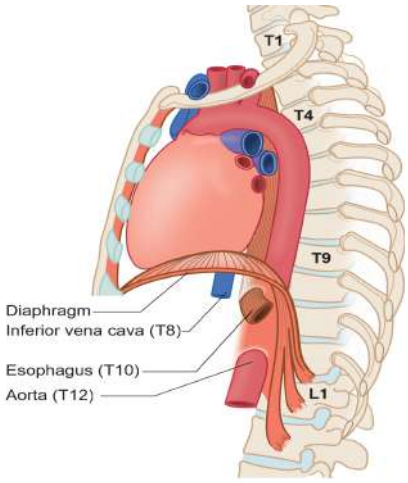
Muscle	External oblique	Internal oblique	Rectus abdominis	Transversus abdominis
Direction	Downward & medially	Upward &medially	Vertical	Transverse
Nerve	lower 5 intercostal nerves (T7-T11), subcostal nerve (T12) and first lumbar nerve.			
Action	(during forced expiration): Compression of abdominal viscera to help in ascent of diaphragm			





Muscles Involved in Respiratory

1. Diaphragm



- The diaphragm is composed of a muscular portion and a central tendon. It is dome-shaped, and descends upon contraction of its muscular portion. It is innervated by the **phrenic nerves** that arise from spinal cord segments **C3 through C5**.
- The diaphragm is formed by the fusion of tissue from 4 sources:
    - The septum transversum gives rise to the central tendon of the diaphragm.
    - The pleuroperitoneal membranes give rise to parts of the tendinous portion of the diaphragm.
    - The dorsal mesentery of the esophagus gives rise to the crura of the diaphragm.
    - The body wall contributes muscle to the periphery of the diaphragm.
- The major muscle of inspiration is the diaphragm. Contraction of the diaphragm enlarges the vertical dimensions of the chest. Also utilized are the external intercostal muscles of the chest wall. Contraction of these muscles causes the ribs to rise and thus increases the anterior-posterior dimensions of the chest.

Apertures in the Diaphragm

- **Caval hiatus** is located to the right of the midline at the level of T8, within the central tendon. It transmits the inferior vena cava and some branches of the right phrenic nerve.
- **Esophageal hiatus** is located to the left of the midline at the level of T10, within the muscle of the right crus. It transmits the esophagus and the anterior and posterior vagus trunks.
- **Aortic hiatus** is located in the midline at the level of T12, behind the 2 crura. It transmits the aorta and thoracic duct.

Clinical Correlate

- Pain Referral: Because the innervation to the diaphragm (motor and sensory) is primarily from C3 through C5 spinal nerves, pain arising from the diaphragm (e.g., subphrenic access) is referred to these dermatomes in the shoulder region.
- A congenital diaphragmatic hernia is a herniation of abdominal contents into the pleural cavity due to the failure of the pleuroperitoneal membranes to develop properly. The hernia is most commonly found on the left posterolateral side and causes pulmonary hypoplasia.
- An esophageal hiatal hernia is a herniation of the stomach into the pleural cavity due to an abnormally large esophageal hiatus to the diaphragm. This condition renders the esophagogastric sphincter incompetent so that contents reflux into the esophagus.

2. Expiratory muscles

- Under resting conditions, expiration is normally a passive process, i.e., it is due to the relaxation of the muscles of inspiration and the elastic recoil of the lungs . For a forced expiration, the muscles of the abdominal wall and the internal intercostal contract. This compresses the chest wall down and forces the diaphragm up into the chest . Included would be external oblique, rectus abdominal, internal oblique, and transverse abdominal muscles.

KAPLAN CORNER

062 Pressure Changes during Breathing by Interactive Biology

The Respiratory System: Lung Compliance - Transpulmonary Pressure - Explained in 2 Minutes! by 5MinuteSchool

Popular Classic (Sp13)- Pressure changes in lungs by Wendy Riggs

Transpulmonary Pressure and Intrapulmonary Pressure – Respiratory by emerson24

Objective

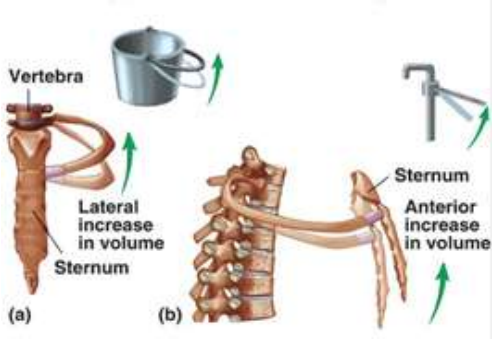
1. List the muscles of respiration and describe their roles during inspiration & expiration.
2. Identify the importance of the following pressures in respiration: atmospheric, intra-alveolar, intrapleural, and transpulmonary.
3. Explain why intrapleural pressure is always subatmospheric under normal conditions, and the significance of the thin layer of the intrapleural fluid surrounding the lung.
4. Define lung compliance and list the determinants of compliance

Introduction :

Lungs can be expanded and contracted By :

- Downward and upward movement of the diaphragm to lengthen or shorten the chest cavity.

- Elevation and depression of the ribs to increase and decrease the anteroposterior diameter of the chest cavity



Respiratory muscles:

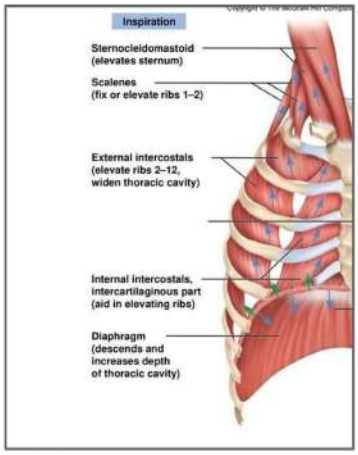
Inspiratory muscles :

○ During Resting Inspiration :

The muscles are

1- diaphragm.

2- external intercostals.



○ During Forced inspiration :

The Accessory muscles of inspiration participate to increase size of the thoracic cavity.

1- Sternocleidomastoid to elevate sternum .

2- Scalene to elevate first two ribs.

3- Pectoralis minor and anterior serratus contract to elevate 3rd–5th ribs.

Expiratory muscles:

○ During Resting Expiration :

It is a **passive process** that depends on the recoil tendency of the lung and needs no muscle contraction

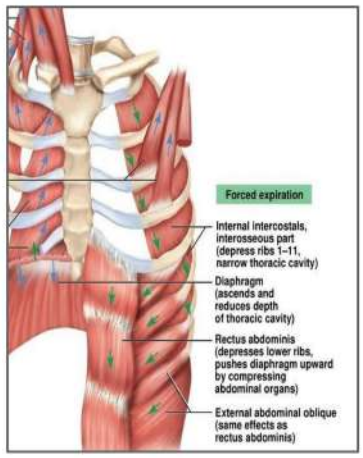
○ During Forced Expiration :

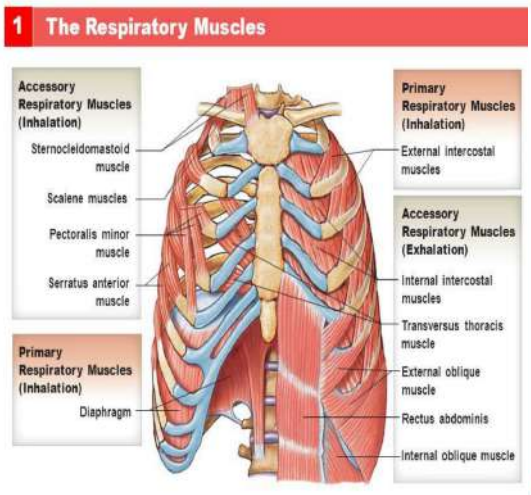
It is active and need contraction of :

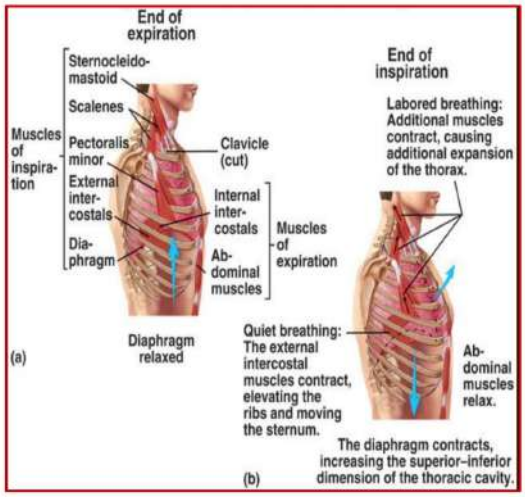
1- The Abdominal muscles .

2- The internal intercostal muscles.

Muscles of exhalation increase the pressure in abdomen and thorax.





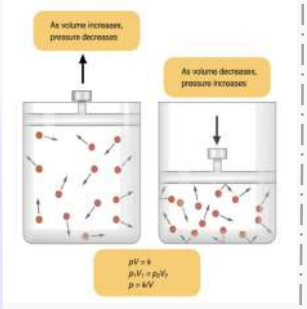


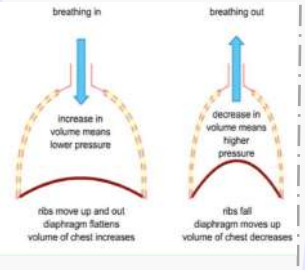
Extra Explanation:

- Remember Boyle's law?

Increased volume causes a decrease in pressure in the alveoli

The pressure changes from 0 to -1. Air flows from the atmosphere (greater pressure) to alveoli (Less pressure). This is when we have the greatest amount of flow into the lungs.





From Linda:

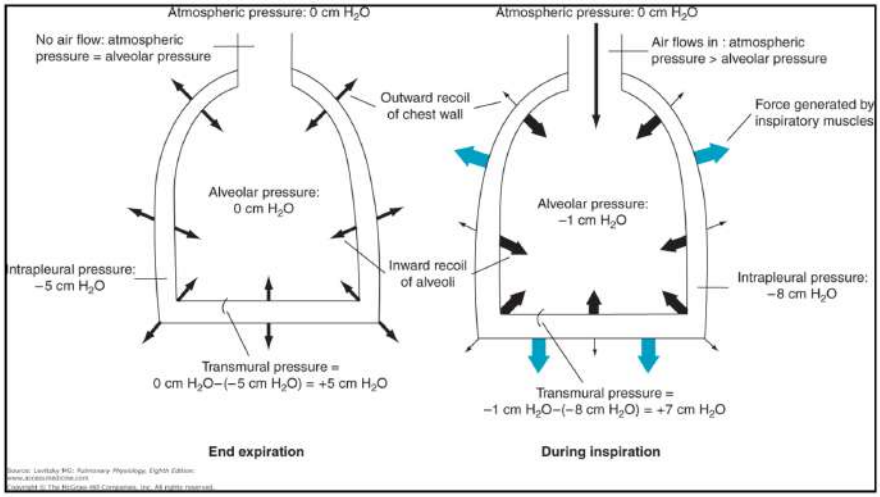
The volume of air inspired in one breath is the tidal volume (TV), which is approximately 0.5 L.
Thus, the volume present in the lungs at the end of normal inspiration is the functional residual capacity plus one tidal volume.

Pressure changes in the lungs during breathing:

- Air will flow from a region of high pressure to the one of low pressure.
- the bigger the difference, the faster the flow.
- If diaphragm and external intercostal muscle contract they will produce space for air and increase the volume as a result the pressure will decrease by 1 mmHg , so (-1 mmHg = 759 mmHg).

- For inspiration, and because of the difference of the pressure between the intra-alveolar and atmospheric pressure the air will enter the lungs.

- The opposite thing is correct for expiration except that the intra-alveolar pressure will increases by 1 mmHg , so (+1 mmHg= 761 mmHg) which makes the air move out of the lungs.



1- Intra-alveolar Pressure :

- During inspiration:

Air flows from outside to inside the lungs, which is known as tidal volume, and the pressure = (-1 mmHg).

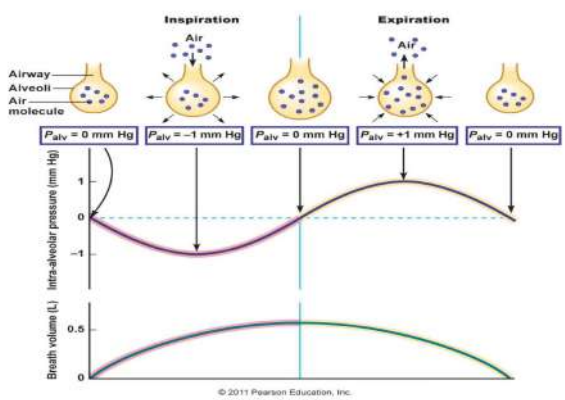
- At the End of inspiration and between breathes:

Air flow stops, and the pressure = (0 mmHg).

- During inspiration:

Air flows out of the Lungs , and the pressure = (+1 mmHg).

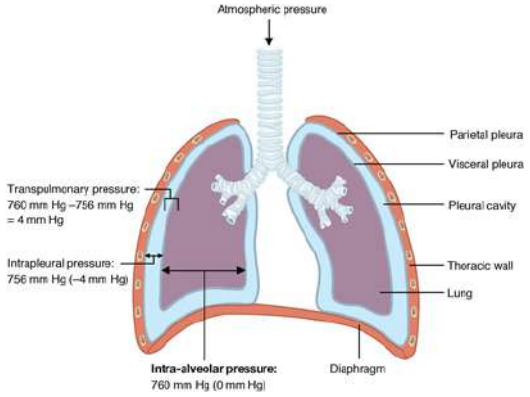
Relation between Intra-alveolar pressure and lung volume

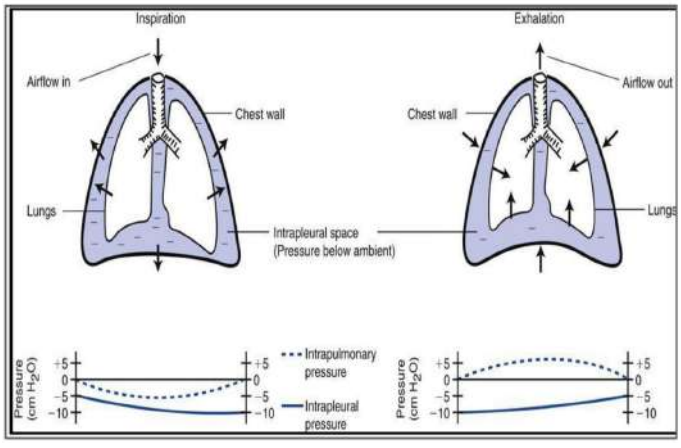


Pressure changes in the lungs during breathing:

2- Intrapleural pressure (IPP)

- At the end of normal expiration and during resting position between breathes it,. The Pressure in the pleural space is negative with respect to atmospheric pressure and it is = (-5) cm H2O.
- During resting inspiration it becomes more negative and be =(-7.5) cm H2O.
- During Forced Inspiration, it is = -20 to - 40 cm H2O while in forced Expiration , it is .: + 30 cm H2O.



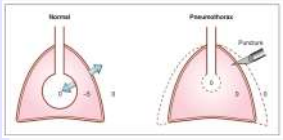


Why is it negative?

- The lung's elastic tissue causes it to recoil, while that of the chest wall causes it to expand. Because of these two opposing forces the pressure in the pleural cavity becomes negative.
- The pleural space is a potential space,(empty) due to continuous suction of fluids by lymphatic vessels.
- Gravity: because the gravity try to pull pleural downward.

From Linda:

Intrapleural pressure in a normal person and in a person with a pneumothorax.



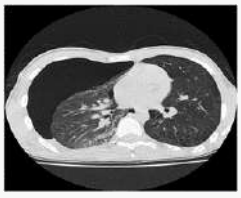
The numbers are pressures in cm H20. Pressures are referred to atmospheric pressure; thus, zero pressure means equal to atmospheric pressure. The arrows show expanding or collapsing elastic forces.

Normally, at rest, intrapleural pressure is-5 cm H20 because of equal and opposite forces trying to collapse the lungs and expand the chest wall.

With a pneumothorax the intrapleural pressure becomes equal to atmospheric pressure, causing the lungs to collapse and the chest wall to expand.

Clinical Correlate :

Pneumothorax, If someone got stabbed in the pleural space the lung will collapse because of the pressure differences between intrapleural pressure and atmospheric pressure and the air will move into pleural space causing problems..



CT scan for pneumothorax (collapsing lung)

Extra Explanation:

- **At rest:**

While you're not breathing, yet. The lung's recoil (elasticity) is forcing the alveoli to shrink (collapse).

The intrapleural pressure (about -5 cmH2O) will apply a force in the opposite direction in order to reach equilibrium.

The alveoli is connected to the atmosphere, so its pressure is equal to the atmospheric pressure. (We don't like big numbers, so we say that Patm is equal to 0)

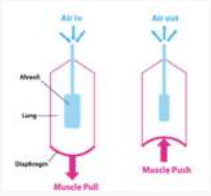
- **Inspiration**:

The diaphragm contracts. The intrapleural pressure decreases to -8 — -7.5. The alveoli expand because the force acting outward (pressure) is greater than the force acting inward (recoil).

- **At the END of INSPIRATION (not expiration),** Air stops flowing. That's because pressure in the alveoli is equal to atmospheric pressure. The pressure is back to 0.
- **Expiration**:

The diaphragm relaxes. The intrapleural pressure rises back to -5 cmH2O. The Alveoli shrinks (Again, Boyle's law) the pressure in the alveoli increases to +1 because of the lungs recoil (elasticity). Air flows out to the atmosphere.

Remember: Elasticity & Alveolar pressure at each step.



From Guyton

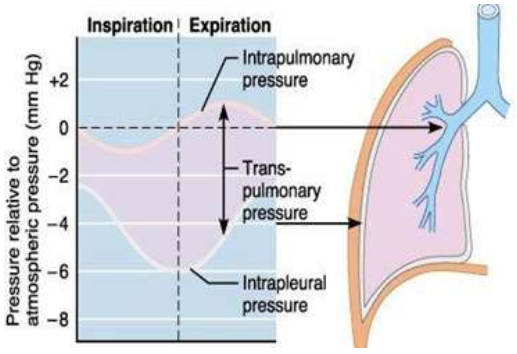
The lung is an elastic structure that collapses like a balloon and expels all its air through the trachea whenever there is no force to keep it inflated. Also, there are no attachments between the lung and the walls of the chest cage, except where it is suspended at its hilum from the mediastinum, the middle section of the chest cavity. Instead, the lung "floats" in the thoracic cavity, surrounded by a thin layer of pleural fluid that lubricates movement of the lungs within the cavity.

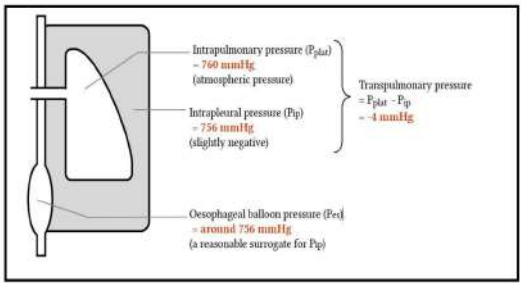
3- Transpulmonary pressure (TPp) (Extending Pressure)

- The difference between the alveolar pressure (Palv) and the pleural pressure(Ppl). (TPp= Palv-Ppl) .
- It is a measure of the elastic forces in the lungs that tend to collapse the lungs (the recoil pressure).
- During rest (end expiration)

Palv=0 and ppl= -5 , so TPp= 0- (-5)= +5 mmHg During inspiration Palv=-1 and ppl= -7.5 , so TPp= -1 - (-7.5)= +6.5 mmHg So, we conclude that As lung volume increases, the transpulmonary pressure increases too.

- The bigger the volume of the lung the higher will be its tendency to recoil.





In Summary

The atmospheric pressure is 760 mmHg

Pressure	During rest	During inspiration	During expiration
Intra-alveolar pressure	(0 mmHg) 760 mmHg	(-1 mmHg) 759 mmHg	(+1 mmHg) 761 mmHg
Intrapleural pressure	(-5 mmHg) 755 mmHg	(-7.5 mmHg) 752.5 mmHg	(just for your information) -6.5 mmHg according to Linda
Transpulmonary pressure TPp = Palv-Ppl	TPp= 0- (-5)= +5 mmHg	TPp= -1 - (-7.5)= +6.5 mmHg	(just for your information) TPp= +1 -(-6.5)= +7.5 mmHg

Compliance of the lung (CL)

Compliance and elastance | Circulatory system physiology | NCLEX-RN | Khan Academy by khanacademymedicine

- The extent to which the lungs will expand for each unit increase in the transpulmonary pressure is called the lung compliance.
- So, the ratio of the change in the lung volume produced per unit change in the distending pressure. It is directly proportional to the volume, and inversely proportional to the pressure. (CL= Δ V / Δ P)
- For both lungs in adult alone without chest and ribs = 200 ml of air/cm H20. While for lungs and thorax together = 110 ml/cm H20.
- Simply, It is the response of the lung to the pressure applied on it.

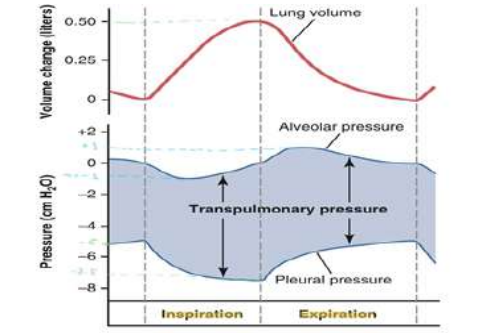


Figure 38-2. Changes in lung volume, alveolar pressure, pleural pressure, and transpulmonary pressure during normal breathing.

- The characteristics of the compliance diagram are determined by the elastic forces of the lungs. These can be divided into:
  - 1/3 is due to elastic forces of the lung tissue itself via elastin (collagen): is a highly elastic protein in connective tissue and allows many tissues in the body to resume their shape after stretching or contracting.
  - 2/3 of the elastic forces caused by surface tension of the fluid that lines the inside walls of the alveoli and other lung air spaces. (because of this we said surfactant is important)

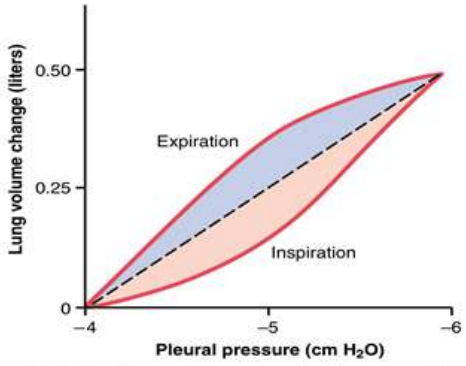


Figure 37-3 Compliance diagram in a healthy person. This diagram shows compliance of the lungs alone.

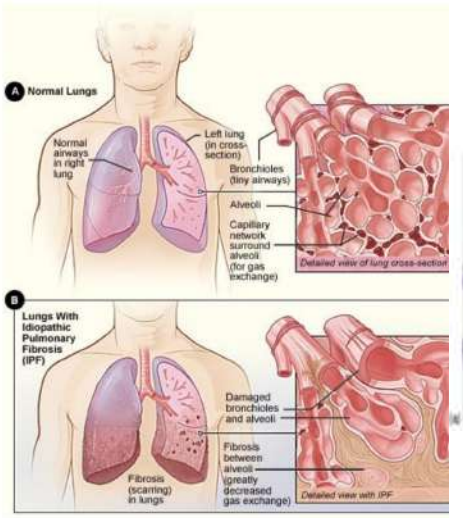
- Think about them like two rubber bands, thin and thick. The thin rubber band easily stretched and is very distensible and compliant. The thick rubber band difficult to stretch and is less distensible and compliant.

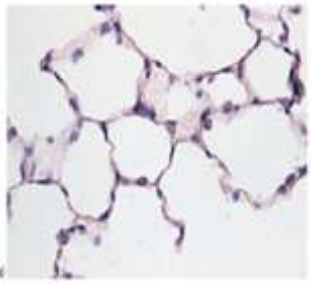
Note:
Fibrosis is not as flexible as elastin, so the compliance will decrease.

Diseases that affect compliance of lung:

Lung compliance is reduced

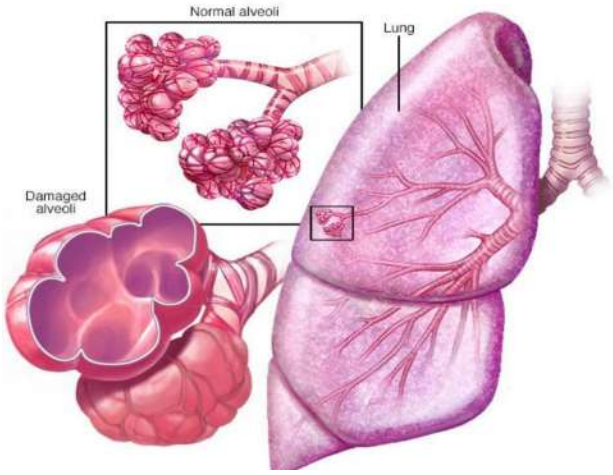
- Pulmonary fibrosis
- Pulmonary edema
- Diseases of the chest wall (i.e.kyphosis, scoliosis, paralysis of the muscles)
- Destruction of elastic fibers with replacement of fibrous tissue (fibrosis)

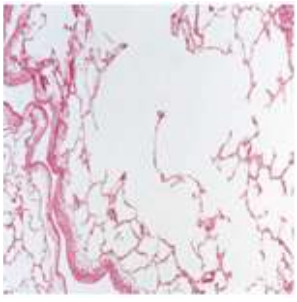




Lung compliance is increased

- Emphysema
- Cause: it destroys the alveolar septal tissue rich with elastic fibers that normally opposes lung expansion.
- In these diseases, the destruction of elastic fibers without replacement.
- Usually infect chronic smokers





Forces Acting on The Lung System

In respiratory physiology, units of pressure are usually given as cm H_2O.1 cm H_2O = 0.74 mm Hg (1 mm Hg = 1.36 cm H_2O)

1. Lung recoil and intra pleural press

- Understanding lung mechanics involves understanding the main forces acting on the respiratory system.
- **Lung recoil** represents the inward force created by the elastic recoil proper ties of alveoli.
    - As the lung expands, recoil increases; as the lung gets smaller, recoil decreases.
    - Recoil, as a force, always acts to collapse the lung.
- **Chest wall recoil** represents the outward force of the chest wall.
    - FRC represents the point where this outward recoil of the chest wall is counter balanced by the inward recoil of the lung.
- **Intra pleural pressure** (IPP) represents the pressure inside the thin film of fluid between the visceral pleura, which is attached to the lung, and the parietal pleura, which is attached to the chest wall.
    - The outward recoil of the chest and inward recoil of the lung create a negative (sub atmospheric) IPP.
    - IPP is the outside pressure for all structures inside the chest wall.

2. Transmural pressure gradient

- **Transmural pressure gradient** (PTM) represents the pressure gradient across any tube or sphere.
    - Calculated as inside pressure minus outside pressure
    - If positive (inside greater than outside), it is a net force pushing out against the walls of the structure
    - If negative (outside greater than inside), it is a net force pushing in against the walls of the structure; depending upon the structural components, the tube/sphere can collapse if PTM is negative or zero
    - At FRC, IPP is negative, and thus PTM is positive. This positive out-ward force prevents alveolar collapse (atelectasis).
    - For the entire lung, PTM is called the trans pulmonary pressure (TPP).

Before Inspiration

- The glottis is open, and all respiratory muscles are relaxed (FRC). This is the neutral or equilibrium point of the respiratory system. Intra pleural pressure is negative at FRC because the inward elastic recoil of the lungs is opposed by the outward-directed recoil of the chest wall. Because no air is flowing through the open glottis, alveolar pressure must be zero. By convention, the atmospheric pressure is set to equal zero.

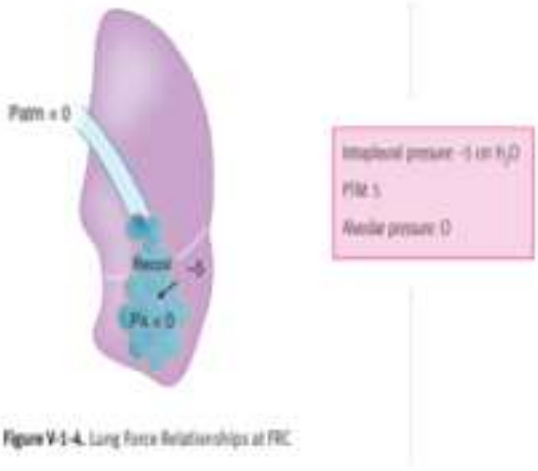


Figure V-1-4. Lung Force Relationships at FRC

KAPLAN CORNER

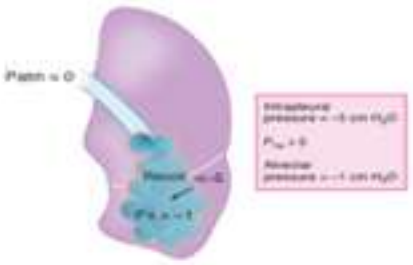
Forces Acting on The Lung System

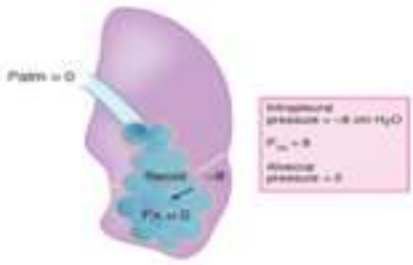
During Inspiration

- Inspiration is induced by the contraction of the diaphragm and external inter-costal muscles that expand the chest wall. The net result is to make intra pleural pressure more negative.
    - The more negative IPP causes PTM (TPP) to increase, which in turn causes expansion of the lungs. The greater the contraction, the greater the change in intra pleural pressure and the larger the PTM (TPP)expanding the lung.
    - The expansion of the lung increases alveolar volume. Based upon Boyle's law, the rise in volume causes pressure to decrease, resulting in a negative (sub atmospheric) alveolar pressure.
    - Because alveolar pressure is now less than atmospheric, air rushes into the lungs.

End of Inspiration

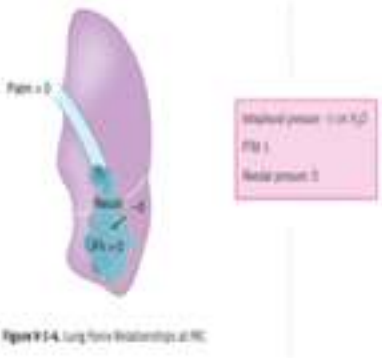
- The lung expands until alveolar pressure equilibrates with atmospheric pressure. The lungs are at their new, larger volume. Under resting conditions, about500 mL of air flows into the lung system in order to return alveolar pressure back to zero.





Expiration

- Expiration under resting conditions is produced simply by the relaxation of the muscles of inspiration.
    - Relaxation of the muscles of inspiration causes intra pleural pressure to return to -5 cm H_2O
    - This decreases IPP back to its original level of -5 cm H_2O, resulting in a decreased PTM. The drop in PTM reduces alveolar volume, which increases alveolar pressure (Boyle's law).
    - The elevated alveolar pressure causes air to flow out of the lungs.
    - The outflowing air returns alveolar pressure toward zero, and when it reaches zero, airflow stops. The lung system returns to FRC.



KAPLAN CORNER

Forces Acting on The Lung System

- The **intra pleural pressure** during a normal respiratory cycle is illustrated. Under resting conditions, it is always a sub atmosphere pressure.
- The **intra alveolar pressure** during a normal respiratory cycle is also illustrated. It is slightly negative during inspiration and slightly positive during expiration.
    - No matter how large a breath is taken, intra alveolar pressure always returns to 0 at the end of inspiration and expiration.
    - By convention, total atmospheric pressure = 0.

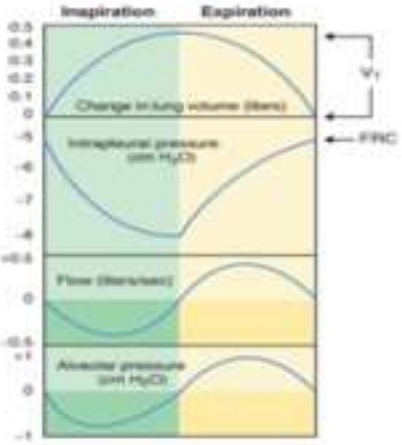


Figure V-1-7. Essentials of Pulmonary Events during a Breath

Lung Compliance

- A static isolated lung inflation curve is illustrated.
- Lung compliance is the change in lung volume (tidal volume) divided by the change in surrounding pressure.
- This is stated in the following formula: Compliance = ΔV/ΔP

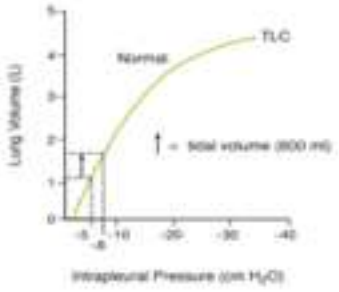


Figure V-1-8. Lung Inflation Curve

Problem

- ❖ Tidal volume = 0.6 liters
- ❖ Intrapleural pressure before inspiration = -5 cm H_2O
- ❖ Intrapleural pressure after inspiration = -8 cm H_2O
- ❖ Lung compliance 0.6 liters/3 cm H_2O =0.200 liters/cm H_2O

- The preceding calculation simply means that for every 1 cm H2O surrounding pressure changes, 200 mL of air flows in or out of the respiratory system. It flows into the system if surrounding pressure becomes more negative (e.g., -5to -6 cm H2O) or out of the system if surrounding pressure becomes more positive (e.g., -5 to -4 cm H2O).
    - Increased compliance means more air will flow for a given change in pressure.
    - Reduced compliance means less air will flow for a given change in pressure.
    - In the preceding curve, although the slope is changing during inflation, Its value at any point is the lung's compliance. It is the relation ship between the change in lung volume (tidal volume) and the change in intra pleural or surrounding pressure.
    - The steeper the line, the more compliant the lungs. Restful breathing works on the steepest, most compliant part of the curve.
    - With a deep inspiration, the lung moves toward the flatter part of the curve, and thus it has reduced compliance. Lung compliance is less at TLC compared to FRC. The figure below shows pathologic states in which lung compliance changes.

KAPLAN CORNER

Respiration-Ventilation 3D Medical Animation By AshlawnPE

Objective

1. Define the various lung volumes and capacities and provide typical values for each.
2. Define ventilation rates, their typical values, and their measurement.
3. Describe FEV1 and its role in differentiating obstructive and restrictive lung diseases.
4. Describe the types of dead space. State a volume for the anatomical dead space.
5. Define the term minute ventilation and state a typical value.
6. Distinguish minute ventilation from alveolar ventilation.

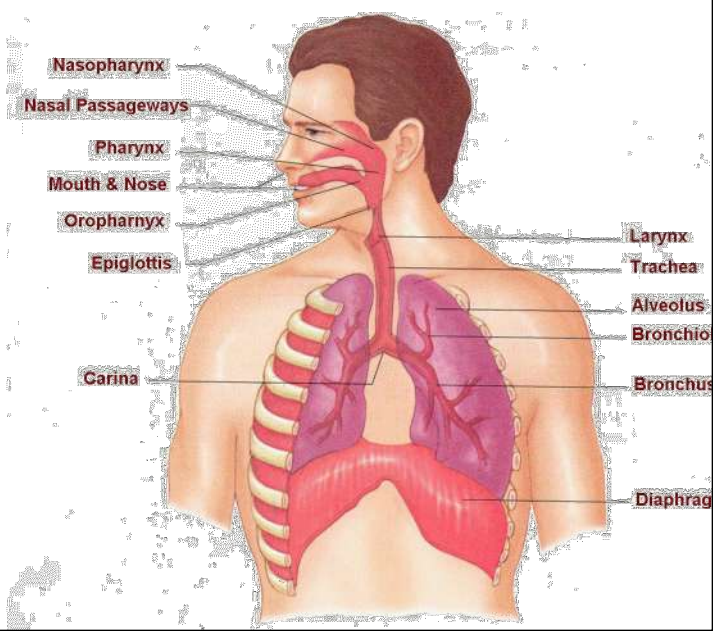
What is COPD ? By HealthSketch

Obstructive vs. Restrictive Lung Disease by USMLEFastTrack

Obstructive Vs Restrictive Lung Diseases by 18Fafo

Respiratory passages (airway):

- Nasal Cavity
- Pharynx
- Larynx
- Trachea
- Thoracic cavity
- Alveoli



External & Internal respiration

External respiration: is the process of gas exchange between the alveolar air and the pulmonary capillary blood.

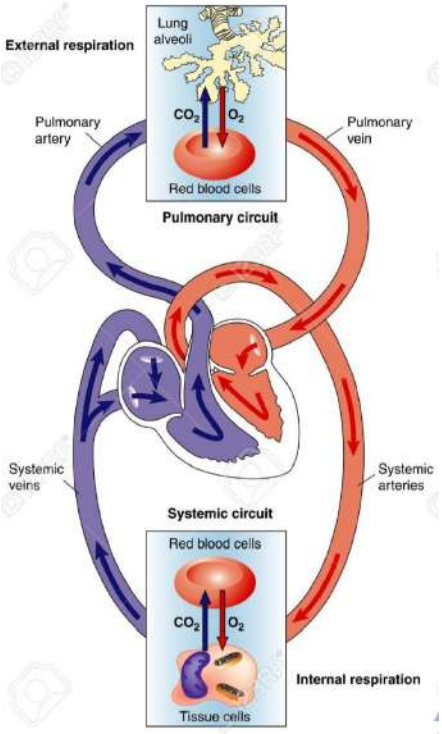
3 major functional events occurs during it:

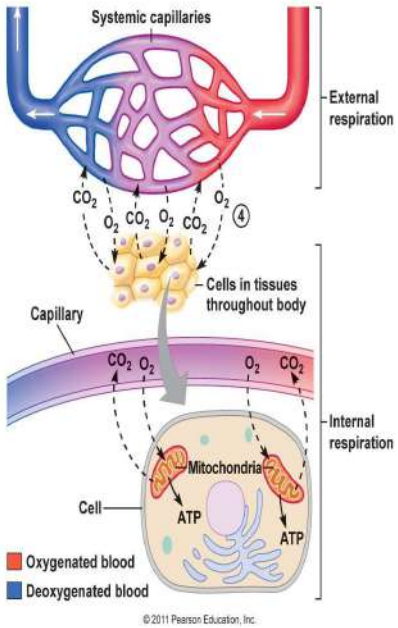
1. Pulmonary ventilation inward and outward movement of air between lung and atmosphere.
2. Diffusion of oxygen and CO2 between the alveoli and the pulmonary capillary blood.
3. Transport of O2 & CO2 in the blood and body fluids to and from the cells.

Internal respiration: is the process of gas exchange between the blood in the systemic capillaries and the tissues.

Respiration could be either:

- **Resting (minimal):** normal breathing during resting conditions.
- **Forced (maximal):** normally during exercise and in patients with bronchial asthma, allergy, other pulmonary diseases.





Note:
During forced respiration we use more muscles than normal respiration

Spirometry

Is a method for measuring the volume and the flow of air that can be inhaled and exhaled. Assess the lung performance, physiological parameters and differentiate between the obstructive and restrictive lung conditions. Spirometry is a widely used, and play a critical role in the diagnosis, differentiation and management of respiratory illness. Effort depended basic lung function test.

Spirogram

Is the drawing of the spirometry for ease in describing the events of pulmonary ventilation, the air in the lungs has been subdivided in this diagram into four volumes and four capacities.

Dead Space and Respiratory Zone in 3 Minutes by Drbeen Medical Lectures

Note:

- **Functional dead space:**

The portion where there is possibility of gas exchange but its not happening due to absent or poor blood flow.

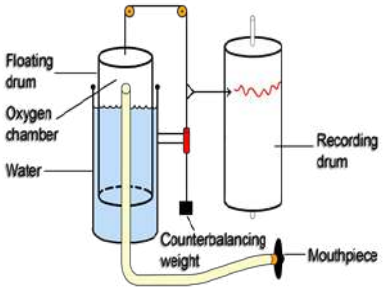
- **Physiological dead space**:

Anatomical and functional dead spaces together defines the physiological dead space.

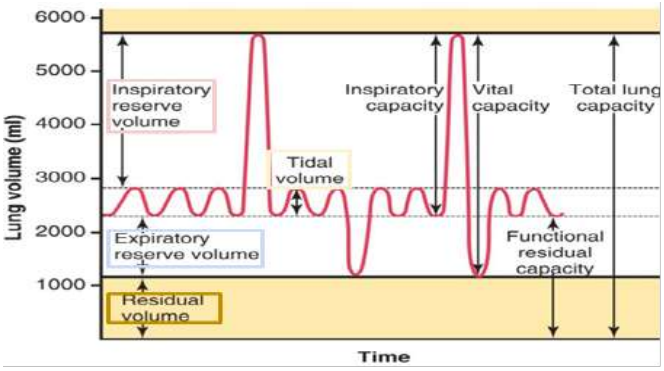
Dead Space : Understading the Physiology Behind it by 100lyric

Spirometry & Spirogram

Spirometry:



Spirogram:



"all values are based on an average 70 kg male"

Dead space

- **Anatomical dead space:**

It is the amount of air that never reach the gas exchange area, but fills respiratory passages where gas exchange does not occur. It occupies t air conducting system down to the terminal bronchioles (conductive zone).

Trachea → Bronchi → Bronchioles → Terminal Bronchioles

It is volume is 2ml/kg or 150 ml. ⅓ of the tidal volume.

Lung volumes & Capacities

The total volume contained in the lung at the end of a maximal inspiration is subdivided into **volumes** and subdivided into **capacities.**

Lung volumes:

By using spirometer, the lungs have 4 main volumes:

1.Tidal volume (TV): is the volume of air inspired or expired with **each** normal breath = 500 ml.

2.Inspiratory reserve volume (IRV): Is the **maximum extra volume** of air that can be inspired over and above the normal tidal volume when the person inspires with full force = 300ml.

3.Expiratory reserve volume (ERV): Is the **maximum extra volume** of air that can be expired by forceful expiration after the end of a normal tidal expiration =1100ml.

4.Residual volume (RV): is the volume of air that still **remain in the lungs** after the most forceful expiration = 1200ml. It is not measured by spirometer.

Lung Volumes and Capacities EXPLAINED UNDER 5 MINUTES !!! by Dr. Arzoo Sadiqi

Note:
Functional residual capacity
it's called functional because it has a main function, it's maintain gas exchange in between breaths even we don't take a new breath

Lung capacities:

Volume is a single value while lung capacities are a sum of two or more volumes.

1.Inspiratory capacity (IC): Is the amount of air a person can breath in, beginning at the normal expiratory level and distending the lungs to the maximum amount.

Equation: IC= TV+IRV → 500+3000 =3500 ml.

2.Functional residual capacity (FRC): is the volume of air remaining in the lungs after normal expiration. It acts as a buffer against extreme changes in alveolar gas levels with each breath. FRC in normal expiration and RV in powerful expiration.

Equation: FRC= RV+ERV → 1100+1200= 2300 ml.

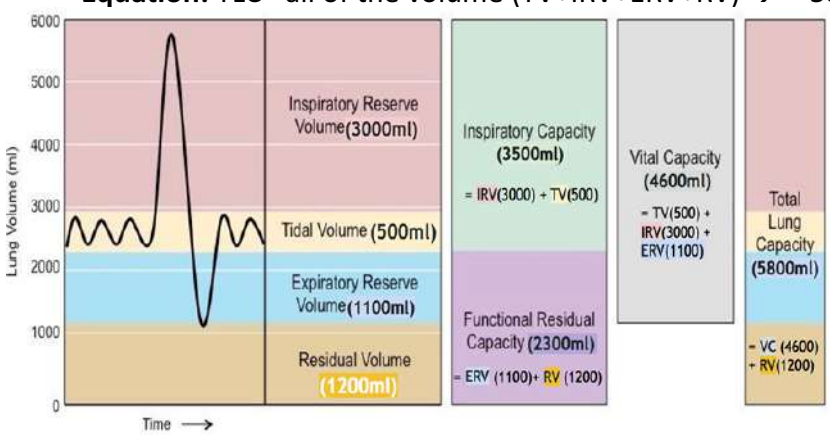
3.Vital Capacity (VC): is the volume of air expired by a maximal expiratory effort after filling the lung to maximal inspiration then expiring to maximum extent.

Equation: VC= IRV+TV+ERV → 500+3000+1100 = 4600 ml.

4.Total lung capacity (TLC): The volume of air contained in the lungs at the end of a maximal inspiration. It is the sum of all pulmonary volumes.

Equation: TLC= all of the volume (TV+IRV+ERV+RV) → = 5800 ml

Pulmonary Volumes & Capacities By Andrew Wolf



Note:
All lung volumes and capacities are 20-25% less in women than men, they are greater in large athletic people than in small athletic people.

Note:

Why do we choose He?

Because Hi is from the inner gases, when it's enter our body it doesn't diffusion, that means we don't use it! It's only a gas that takes place without any function.

Note:

Example

C1= 10%, V1= 2L(2000ml), C2 = 5%, V2 = ?, RV = ?

Solution:

V2 = FRC = (C1 / C2 -1) x V1 (10 / 5 -1) x 2000 = 2000ml. So when the Hi concentration reduced to the half that means V1 = V2 (5% in V1 .. 5% in V2).

RV = (FRC – EXV) = 2000 – 1100 = 900ml.

Explanation:

The functional residual capacity (FRC), which is the volume of air that remains in the lungs at the end of each normal expiration, is important to lung function. Because its value changes markedly in some types of pulmonary disease, it is often desirable to measure this capacity. The spirometer cannot be used in a direct way to measure the functional residual capacity because the air in the residual volume of the lungs cannot be expired into the spirometer, and this volume constitutes about one half of the functional residual capacity. To measure functional residual capacity, the spirometer must be used in an indirect manner, usually by means of a helium dilution method, as follows. A spirometer of known volume is filled with air mixed with helium at a known concentration. Before breathing from the spirometer, the person expires normally. At the end of this expiration, the remaining volume in the lungs is equal to the functional residual capacity. At this point, the subject immediately begins to breathe from the spirometer, and the gases of the spirometer mix with the gases of the lungs. As a result, the helium becomes diluted by the functional residual capacity gases . Once the FRC has been determined, the residual volume (RV) can be determined by subtracting expiratory reserve volume (ERV), as measured by normal spirometry, from the FRC. Also, the total lung capacity (TLC) can be determined by adding the inspiratory capacity (IC) to the FRC.

Determination of the FRC, RV and TLC

We use Closed Circuit Helium Dilution to Determine FRC , RV and TLC. Why spirometer can't measure them? Because spirometer can only feel the air that have been inspired or expired, and as we mentioned before the residual volume stay in the lung, so the spirometer can't feel it and the FRC + TLC depend on it.

How to use the results?

- Residual volume = FRC – ERV
- Total lung capacity = FRC + IC

$C_1xV_1 = C_2xV_2$

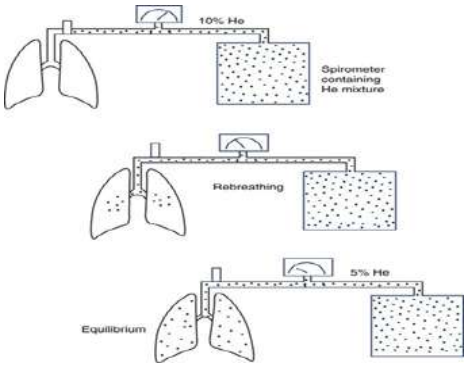
C_1: concentration of H_i in spirometry.

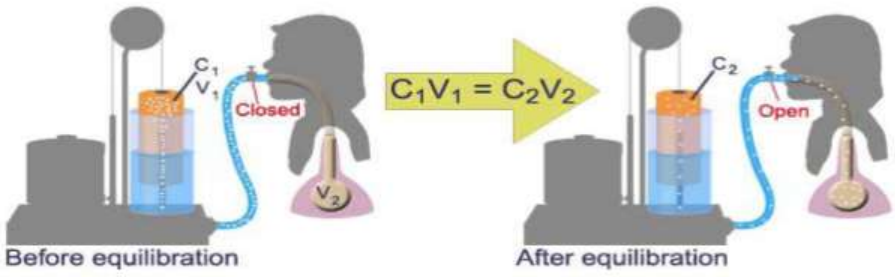
V_1: volume of air in the spirometry.

C_2: Final concentration of helium.

V_2 :Volume of spirometry + FRC.

$$FRC = \left[\frac{C_i HE\ (c_1)}{C_f HE\ (c_2)} - 1 \right] V_i\ (v_1)$$





FEV1/FVC ratio:

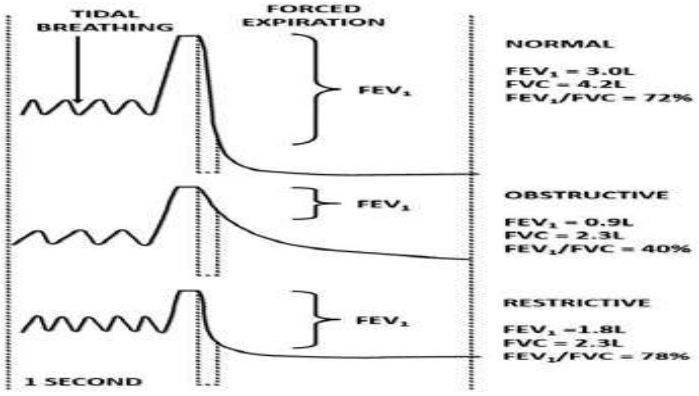
- **Forced Expiratory Volume in One Second (FEV1):** The volume of air expelled during the first second of a forced expulsion after a maximum inspiration.
- **Forced Vital Capacity (FVC):** The volume that after a full inspiration then expire with the most force and speed.
- **Timed vital capacity (TVC):** The person is asked to inspire as deeply as possible and then to breath out as hard and as fast as he can. The expiration is continued until he expired all the air out and thus forced vital capacity Is obtained.

FEV1/FVC ratio normally it is about 80% = 3680ml. It is very useful for diagnosis of obstructive lung diseases , such as emphysema and asthma in which FEV1 is significantly reduced. It is 80-90% of the vital capacity. This ratio differentiates between obstructive and restrictive lung diseases.

It is obtained by: the person is asked to inspire as deeply as possible and then to breath out as hard and as fast as he can. The expiration is continued until he expired all the air out and thus forced vital capacity is obtained. During this process the volume of air expired in the first second is collected and is known as FEV1.

	Restrictive lung diseases	Obstructive lung diseases
Ratio	Normal – increased	Decreased
FEV1	Decreased – normal	Decreased a lot
FVC	Decreased a lot	Decreased – normal
TLC	Decreased	Increased
RV	Decreased	Increased
Examples	Interstitial pulmonary fibrosis	Bronchial asthma, emphysema

Note:
The normal person and the restrictive person all have normal ratio. How do we differentiate between them? By the total lung volume. It's decreased in restrictive person.



Note:
Functionally, the respiratory system is separated into a conducting zone and respiratory zone.

- **Conducting zone:**

Consists of the nose, pharynx, larynx, trachea, bronchi, and bronchioles. These structures form a continuous passageway for air to move in and out of the lungs.

Major Zones

Respiratory zone:

Volume is a single value while lung capacities are a sum of two or more volumes.

- **Definition:** It is the area where gas exchange occur , where air is in proximity to the pulmonary blood.
- **Parts included:** Occupies the space distal to the terminal bronchioles start from the respiratory bronchioles down to the alveolar sacs.

Respiratory Bronchioles → Alveolar Ducts → Alveolar Sacs.

- **Gas exchange:** Gas exchange takes place**.**
- **Volume**: 350 ml/min ⅔ of the tidal volume.

Conducting zone:

Note:

- **Functional dead space:**

The portion where there is possibility of gas exchange but its not happening due to absent or poor blood flow.

- **Physiological dead space**:

Anatomical and functional dead spaces together defines the physiological dead space.

Note:

Some of the air a person breathes never reaches the gas exchange areas but simply fills respiratory passages where gas exchange does not occur, such as the nose, pharynx, and trachea. This air is called dead space air because it is not useful for gas exchange. On expiration, the air in the dead space is expired first, before any of the air from the alveoli reaches the atmosphere. Therefore, the removing the expiratory gases from the lungs..

Note:

Alveolar ventilation is one of the major factors determining the concentrations of oxygen and carbon dioxide in the alveoli.

Note:

The ultimate importance of pulmonary ventilation is to continually renew the air in the gas exchange areas of the lungs, where air is in proximity to the pulmonary blood. These areas include the alveoli, alveolar sacs, alveolar ducts, and respiratory bronchioles. The rate at which new air reaches these areas is called alveolar ventilation

Minute ventilation rate & volume:

Minute respiratory volume (MRV):

Total amount of air moved into and out of respiratory system per minute.

Equation:

respiratory rate x tidal volume → 12 X 500ml = 6000 ml/min.

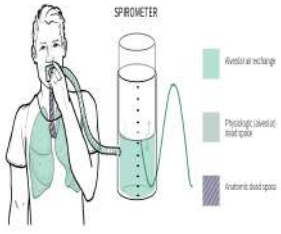
Respiratory rate (RR): Number of breaths taken per minute. Approximately 12-18/ min. MRV could rise to 200 L/min or more than 30 times normal if RR = 40 TV = 4600 ml in young adults man. All lung volume and capacity are about 20 to 25% less in women than in men and are greater in athletic people than in small and asthenic people. Properties that affect volumes and capacities: Age, Gender, Weight, High, Race.

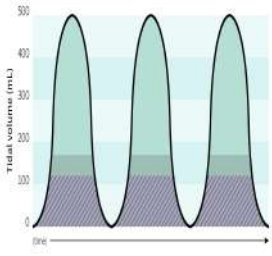
Alveolar ventilation per minute:

Is the total volume of new air entering the alveoli and other adjacent gas exchange areas each minute.

Equation: (TV - Dead Space Volume) X RR → (500 – 150) X 12 = 350 X 12 = 4200 ml/min.

The differences between the (MRV) & alveolar ventilation:





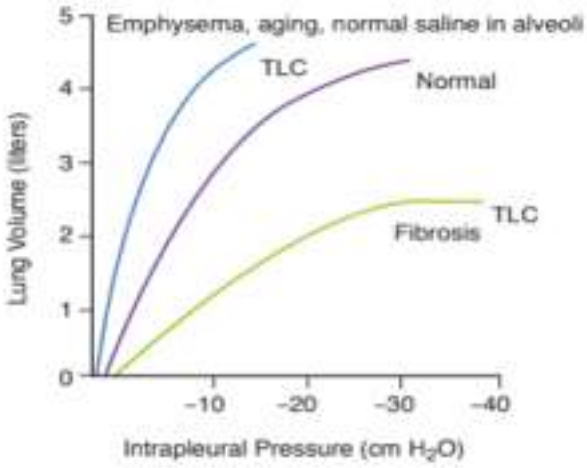
Minute Respiratory Volume	Alveolar Ventilation
Per Minute	
New air moves into the respiratory passages	New air into the alveoli and adjacent gas exchange
MRV= TV X RR	AV= (TV – dead space volume) x RR
It is equal to the tidal volume times the respiratory rate/min.	It is equal to the respiratory rate times the amount of new air that enters these areas with/breath.

Pollution and diseases pattern

Dust particles with an aerodynamic diameter of:

- 10 µm removed by nose and pharynx.
- 2-10µm removed by tracheo-bronchial tree.
- 0.1-2µm removed by within the alveoli.
- Terminal bronchioles and even the alveoli are also sensitive to chemicals such as sulfur dioxide or chlorine gas.
- Cough Reflex: Air is expelled at velocities ranging from 75 to 100 miles/h.

Lung Compliance



- Increased lung ed lung.
- Compliance is an index of the effort required to expand the lungs (to overcome recoil). It does not relate to airway resistance
- Compliance decreases as the lungs are inflated because the curve is nota straight line.
- For any given fall in Intrapleural pressure, large alveoli expand less than small alveoli.
- Very compliant lungs (easy to inflate) have low recoil. Stiff lungs(difficult to inflate) have a large recoil force.

Lung Recoil

Components of Lung Recoil

1. The tissue itself; more specifically, the collagen and elastin fibers of the lung– The larger the lung, the greater the stretch of the tissue and the greater the recoil force.
2. The surface tension forces in the fluid lining the alveoli. Surface tension forces are created whenever there is a liquid–air interface.– Surface tension forces tend to reduce the area of the surface and generate a pressure. In the alveoli, they act to collapse the alveoli; therefore, these forces contribute to lung recoil.
    - Surface tension forces are the greatest component of lung recoil. The relation ship between the surface tension and the pressure inside a bubble is given by the Law of La Place.
    - Pressure ∝ tension /radius

Figure V-1-11. Surface Tension

KAPLAN CORNER

Lung Recoil

- If wall tension is the same in 2 bubbles, the smaller bubble will have the greater pressure. Although the situation is more complex in the lung, it follows that small alveoli tend to be unstable. They have a great tendency to empty into larger alveoli and collapse (creating regions of atelectasis). Collapsed alveoli are difficult to re inflate.
- If the alveoli were lined with a simple electrolyte solution, lung recoil would be so great that lungs theoretically should not be able to inflate. This is prevented by a chemical (produced by alveolar type II cells), surfactant, in the fluid lining a normal lung. Surfactant has 2 main functions:
    1. It lowers surface tension forces in the alveoli; in other words, it lower slung recoil and increases compliance.
    2. It lowers surface tension forces more in small alveoli than in large alveoli. This promotes stability among alveoli of different sizes by decreasing the tendency of small alveoli to collapse (decreases the tendency to develop atelectasis).

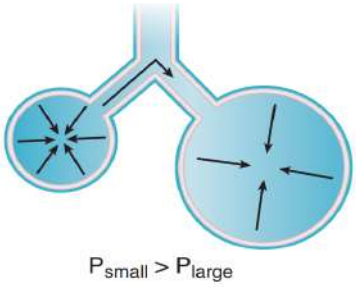


Figure V-1-12. Atelectasis

Pathology in the lung recoil

Pneumothorax

The following changes occur with the development of a simple pneumothorax. The pneumothorax may be traumatic (perforation of chest wall) or spontaneous(rupture of an alveolus):

- Intrapleural pressure increases from a mean at -5 cm H2O to equal atmospheric pressure.
- Lung recoil decreases to zero as the lung collapses.
- Lung recoil decreases to zero as the lung collapses.
- Chest wall expands. At FRC, the chest wall is under a slight tension directed outward. It is this tendency for the chest wall to spring out and the opposed force of recoil that creates the intrapleural pressure of -5 cm H_2O.
- Trans pulmonary pressure is negative. In some cases, the opening of the lung to the pleural space may function as a valve allowing the air to enter the pleural space but not to leave. This creates a tension pneumothorax.
- Strong inspiratory efforts promote the entry of air into the pleural space, but during expiration, the valve closes and positive pressures are created in the chest cavity. Ventilation decreases but the positive pressures also decrease venous return and cardiac output.
- Tension pneumothorax most commonly develops in patients on a positive-pressure ventilator.

Common clinical signs of a tension pneumothorax include:

1. Respiratory distress
2. Asymmetry of breath sounds
3. Deviation of trachea to the side opposite the tension pneumothorax
4. Markedly depressed cardiac output

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Pathology in the lung recoil

Respiratory Distress Syndrome (RDS)

Infant RDS (hyaline membrane disease) is a deficiency of surfactant.

Adult respiratory distress syndrome (ARDS)

is an acute lung injury via the following:

- Bloodstream (sepsis): develops from injury to the pulmonary capillary endothelium, leading to interstitial edema and increased lymph flow
    - Leads to injury and increased permeability of the alveolar epithe-lium and alveolar edema
    - The protein seepage into the alveoli reduces the effectiveness of surfactant.
    - Neutrophils have been implicated in the progressive lung injury from sepsis.
- Airway (gastric aspirations): direct acute injury to the lung epithelium increases permeability of the epithelium followed by edema
- In the figure below, curve A represents respiratory distress syndrome. The curve is shifted to the right, and it is a flatter curve (lung stiffer).
    1. A greater change in intrapleural pressure is required to inflate the lungs.
    2. The tendency for collapse is increased, thus PEEP is sometimes provided.
- Curve B represents atelectasis.
    1. Once alveoli collapse, it is difficult to reinflate them.
    2. Note the high TPP required to open atelectic alveoli (green line, B, in figure below).

Mechanism of breathing

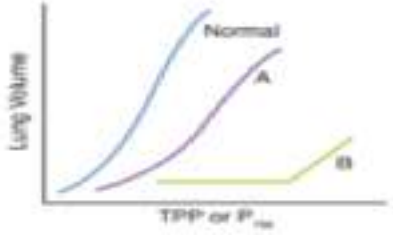

Figure V-1-13. Deficiency of Surfactant

Airway Resistance

Radius of an Airway

In the branching airway system of the lungs, it is the first and second bronchi that represent most of the airway resistance.

- Parasympathetic nerve stimulation produces bronchoconstriction.
- This is mediated by M3 receptors. In addition, M3 activation increases airway secretions.
- Circulating catechol amines produce bronchodilation. Epinephrine is the endogenous agent and it broncho dilates via b2 receptors.
- Resistance = $\frac{1}{radius^4}$

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Airway Resistance

Mechanical Effect of Lung Volume

The figure illustrates that, as lung volume increases, airway resistance decreases.
The mechanisms for this are:

- **PTM:** To get to high lung volumes, IPP becomes more and more negative. This increases the PTM across small airways, causing them to expand. The result is decreased resistance.
- **Radial traction**: The walls of alveoli are physically connected to small airways. Thus, as alveoli expand, they pull open small airways. The result is decreased resistance.

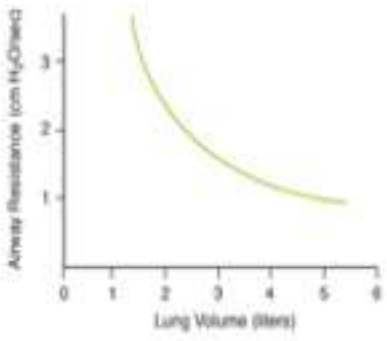

Figure V-1-14. Airway Resistance

Ventilation

Total Ventilation

- Total ventilation is also referred to as minute volume or minute ventilation. It isthe total volume of air moved in or out (usually the volume expired) of the lungs per minute.
- Ve = VT × f (Ve: total ventilation. VT: tidal volume f: respiratory rate)
- Normal resting values would be: VT = 500 mL
- f = 15
- 500 mL × 15/min = 7,500 mL/min

Dead Space

Regions of the respiratory system that contain air but are not exchanging O_2 and CO_2 with blood are considered dead space.

Anatomic Dead Space

Airway regions that, because of inherent structure, are not capable of O_2 and CO_2 exchange with the blood. Anatomic dead space (anatVd) includes the con-ducting zone, which ends at the level of the terminal bronchioles. Significant gas exchange (O_2 uptake and CO_2 removal) with the blood occurs only in the alveoli. The size of the anatVd in mL is approximately equal to a person's weight in pounds. Thus a 150-lb individual has an anatomic dead space of 150 ml.

Composition of the anatomic dead space and the respiratory zone

The respiratory zone is a very constant environment. Under resting conditions, rhythmic ventilation introduces a small volume into a much larger respiratory zone. Thus, the partial pressure of gases in the alveolar compartment changes very little during normal rhythmic ventilation.

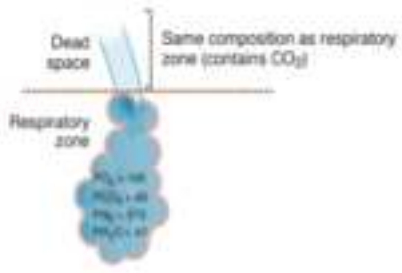

Figure V-1-2. End of Expiration

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Ventilation

Composition at the End of Expiration (Before Inspiration)

- At the end of an expiration, the anatVd is filled with air that originated in the alveoli or respiratory zone.
- Thus, the composition of the air in the entire respiratory system is the same at this static point in the respiratory cycle.
- This also means that a sample of expired gas taken near the end of expiration (end tidal air) is representative of the respiratory zone.

Composition at the End of Inspiration (Before Expiration)

- The first 150 mL of air to reach the alveoli comes from the anatVd.
- It is air that remained in the dead space at the end of the previous expiration and has the same composition as alveolar gas.
- After the first 150 mL enters the alveoli, room air is added to the respiratory zone.
- At the end of inspiration the anatVd is filled with room air.
- The presence of the anatVd implies the following: in order to get fresh air into the alveoli, one must always take a tidal volume larger than the volume of the anatVd.

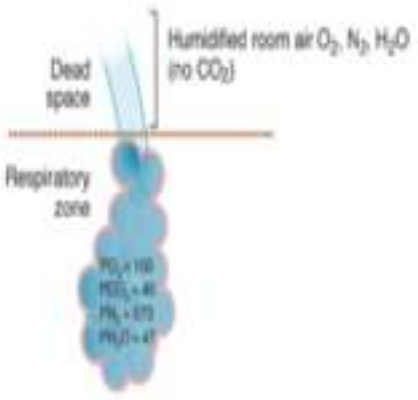


Figure V-1-3. End of Inspiration

Alveolar dead space

Alveolar dead space (alvVd) refers to alveoli containing air but without blood flow in the surrounding capillaries. An example is a pulmonary embolus.

Physiologic Dead Space

Physiologic dead space (physioIVd) refers to the total dead space in the lung system (anatVd + alvVd). When the physiolVd is greater than the anatVd, it implies the presence of alvVd, i.e., somewhere in the lung, alveoli are being ventilated but not perfused.

Total ventilation

V = VT
(f)= 500 (15)
= 7,500 mL/minMinute
ventilation (V•) is the total volume of air entering the lungs per minute.

KAPLAN CORNER

Ventilation

Alveolar Ventilation

Alveolar ventilation V•A represents the room air delivered to the respiratory zone per breath.

- The first 150 mL of each inspiration comes from the anatomic dead space and does not contribute to alveolar ventilation.
- However, every additional mL beyond 150 does contribute to alveolar ventilation .
- V•A = (VT - VD) f= (500 mL - 150 mL) 15 = 5250 mL/min (V•A: alveolar ventilation. VT: tidal volume. VD: dead space. f: respiratory rate)
- The alveolar ventilation per inspiration is 350 mL. This equation implies that the volume of fresh air that enters the respiratory zone per minute depends on the pattern of breathing (how large a VT and the rate of breathing).

Increases in the Depth of Breathing

- There are equal increases in total and alveolar ventilation per breath, since deadspace volume is constant.
- If the depth of breathing increases from a depth of 500 mL to a depth of 700 mL,the increase in total and alveolar ventilation is 200 mL per breath.

Increases in the Rate of Breathing

- There is a greater increase in total ventilation per minute than in alveolar ventilation per minute, because the increased rate causes increased ventilation of dead space and alveoli.
- For every additional inspiration with a tidal volume of 500 mL, total ventilation increases 500 mL, but alveolar ventilation only increases by 350 mL (assuming dead space is 150 mL).

For example, given the following, which person has the greater alveolar ventilation?

	Tidal volume	rate
Person A	600 ML	10/MIN
Person B	300 ML	20/MIN

Answer: Pe t of dead-space ventilation (first 150 mL of each inspiration).Even though total ventilation may be normal, alveolar ventilation is decreased. Therefore, the individual is hypo ventilating. In rapid, shallow breathing, total ventilation may be above normal, but alveolar ventilation may be below normal.

KAPLAN CORNER

Ventilation

Cardiovascular Changes With Ventilation

Inspiration

With inspiration, **intra pleural pressure becomes more negative (decreases).**This increases the PTM across the vasculature, causing the great veins and right atrium to expand. This expansion decreases intravascular pressure, there by increasing the pressure gradient driving VR to the right heart.

- Systemic venous return and right ventricular output are increased.
- An increase in the output of the right ventricle delays closing of the pulmonic valves and typically results in a splitting of the second heart sound.
- Pulmonary vessels expand, and the volume of blood in the pulmonary circuit increases. In addition, because pulmonary vascular resistance(PVR) is lowest at FRC, it increases.
- In turn, venous return to the left heart, and the output of the left ventricle is decreased, causing decreased systemic arterial pressure(drop in systolic most prominent).
- In turn, venous return to the left heart, and the output of the left ventricle is decreased, causing decreased systemic arterial pressure(drop in systolic most prominent).
- This inspiration reduces vagal outflow to the heart (mechanism debatable) resulting in a slight rise in heart rate (respiratory sinus arrhythmia). This is why patients are asked to hold their breath, if clinically possible, when an EKG is ta

Expiration

Expiration is the reverse of the processes above**. Intrapleural pressure becomes more positive (increases)**, i.e., returns to original negative value. PTM returns to its original level, thereby decreasing the pressure gradient for VR.

- Systemic venous return and output of the right ventricle are decreased.
- Pulmonary vessels are compressed, and the volume of blood in the pulmonary circuit decreases.
- The return of blood and output of the left ventricle increases, causing systemic arterial pressure to rise (primarily systolic).
- Vagal outflow increases (mechanism debated), reducing HR (respiratory sinus arrhythmia).
- A Valsalva maneuver is a forced expiration against a closed glottis. This forced expiration creates a positive IPP (see later in this chapter),which compresses the great veins in the chest. This in turn reduces VR.

Positive-pressure Ventilation

Assisted Control Mode Ventilation (ACMV)

In ACMV, the inspiratory cycle is initiated by patient or automatically if no signal is detected within a specified time window. Expiration is not assisted. Expiration is accomplished in the normal manner (passive recoil of the lungs).

Positive End-Expiratory Pressure (PEEP)

In PEEP, positive pressure is applied at the end of the expiratory cycle to de-crease alveolar collapse. It is useful in treating the hypoxemia of acute respira-tory distress syndrome (ARDS) (see Hypoxemia section.)

- Small alveoli have a strong tendency to collapse, creating regions of atelectasis.
- The larger alveoli are also better ventilated, and supplementary oxygen is more effective at maintaining a normal arterial PO_2.
- One downside to positive pressure ventilation and accentuated by PEEP is a decrease in venous return and cardiac output.

Figure V-1-8a. Positive-Pressure Ventilation

Continuous Positive Airway Pressure (CPAP)

- In CPAP, continuous positive pressure is applied to the airways. It is useful intreating obstructive sleep apnea (OSA) since the lung and upper airways (nasopharynx) remain at a larger volume throughout the respiratory cycle.
- CPAP is administered by mask (patient not intubated). The patient breathes spontaneously.

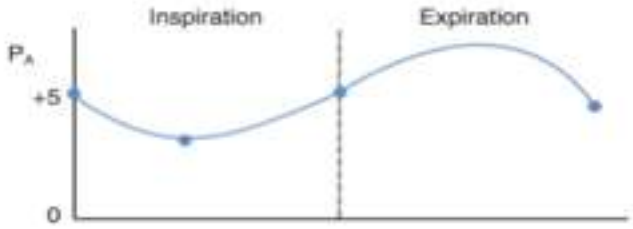


Figure V-1-8b. CPAP

Note:

Introduction

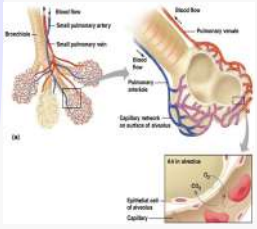
After ventilation of the alveoli with fresh air the next step is the process called diffusion of oxygen(O2) from the alveoli into the pulmonary blood and diffusion of carbon dioxide (CO2) in opposite direction.

Partial pressure of the gas is The rate of diffusion of each of these gases is directly proportional to the pressure caused this gas alone.

Pressure is caused by the constant impact of kinetically moving molecules against a surface.

How does gas has pressure? Gases in form of molecules ,these molecules have kinetic movement, so they're in constant motion. This motion cause Impact of gas molecules, the force of this collisions collected together then will called pressure.

No differences in pressures ⍰ No gases movement ⍰ No gas exchange.



Gas Exchange Physiology Animation - MADE EASY by Medical Institution

Objective 1 2 3 4 5 6 7

- Define partial pressure of a gas
- Understand that the pressure exerted by each gas in a mixture of gases is independent of the pressure exerted by the other gases (Dalton's Law)
- Understand that gases in a liquid diffuse from higher partial pressure to lower partial pressure (Henry's Law)
- Describe the factors that determine the concentration of a gas in a liquid.
- Describe the components of the alveolar-capillary membrane (i.e., what does a molecule of gas pass through).
- Knew the various factors determining gas transfer: -
- Surface area, thickness, partial pressure difference, and diffusion coefficient of gas
- State the partial pressures of oxygen and carbon dioxide in the atmosphere, alveolar gas, at the end of the pulmonary capillary, in systemic capillaries, and at the beginning of a pulmonary capillary.

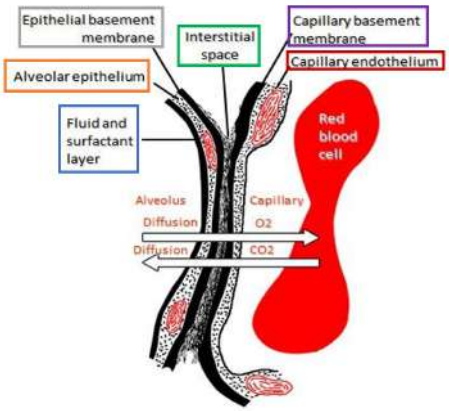
Gas exchange

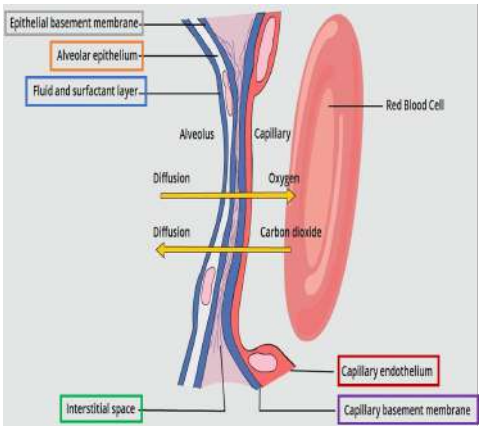
Composition of alveolar air and its relation to atmospheric air:

- The dry atmospheric air enters the respiratory passage is humidified before it reaches the alveoli.
- Alveolar air is partially replaced by atmospheric air with each breath.
- O2 is constantly absorbed from the alveolar air.
- CO_2 constantly diffuses from the pulmonary blood into the alveoli.

Layers of Respiratory Membrane:

- Fluid surfactant layer
- Alveolar epithelium
- Epithelial basement membrane
- Interstitial space
- Capillary basement membrane
- Capillary endothelium





Respiratory Unit

A unit consisting of a respiratory bronchiole, alveolar ducts, atria, and alveoli. The total number of alveoli in the human body is around 300 million, with each having an average diameter of **0.2mm.** The extremely thin walls of these alveoli form part of the **respiratory membrane**, **whose thickness inversely affects the rate of gas diffusion.**

Gas Exchange During Respiration by lovexconquersx

Oxygen movement from alveoli to capillaries | NCLEX-RN | Khan Academy by khanacademymedicin

Factors that affect the rate of gas diffusion through the respiratory membrane:

$$D \alpha \frac{\Delta P \times A \times S}{d \times \sqrt{MW}}$$

D: diffusion rate
P: Partial pressure differences
A: Surface area for gas exchange
S: Solubility of gas
d: Diffusion distance
MW: Molecular weight

1. The diffusion rate of the specific gas:

Diffusion coefficient for the transfer of each gas through the respiratory membrane depends on:

- Directly on its solubility (S) through the membrane.
- Inversely on the square root of its molecular weight (MW).
- The Diffusion Coefficient = **S/√MW** directly proportional.
- **Inversely proportional to The thickness of the respiratory membrane.**

So → **CO_2 diffuses 20 times as rapidly as O_2.**

If we have respiratory failure which gas will be affected first? **O_2**

2. Partial pressure differences(ΔP):

The pressure difference between the two sides of the membrane **(between the alveoli and the blood)**.

- When the pressure of the gas in the alveoli is **greater than** the pressure of the gas in the blood as for O_2
  → net diffusion from the alveoli into the blood occurs.
- When the pressure of the gas in the blood is **greater than** the pressure in the alveoli as for **CO_2**
  → net diffusion from the blood into the alveoli occurs.

Note:
Solubility :
Increase the solubility of gas → increase the diffusion of it.
CO2 is 20 times soluble than O2
CO2 more diffusible than O2

3. Surface area of the membrane(A):

- Removal of an **entire lung** decreases the surface area to **half** normal. Range = 50-100 m2
- In **emphysema** with dissolution of the alveolar wall decreases Surface area to **5-folds** because of loss of the alveolar walls.
- **Increase surface area → Increase Diffusion**. So how the surface area will Decrease ?

In alveoli:

1. By Trypsin.
2. By Obstruction of some bronchioles or bronchi by mucous or tumor.

In pulmonary capillaries:

1. By thrombus or blood clot
2. Loss of perfusion
3. Loss of ventilation

4. Solubility (S):

5. Diffusion distance(d):

The thickness of the respiratory membrane.

- Increasing in the thickness of the respiratory membrane e.g. edema → decreases the rate of diffusion.
- Thickness will decrease during exercise, therefore the rate of diffusion increases.

Note:

- Why N2 inhaled and exhaled in same concentration? Because it's from inner gases that's only take place in our body with any function. There's no diffusion of N2 in our bodies.
- From where the 4% of CO2 came? And why the O2 concentration Reduced to 16%? Because of aerobic metabolism. HOW? We know that: Food stuff + O2 (4%) → ATP +H2O +Urea + CO2(4%).The main goal of this process is producing energy for the muscles but, while I producing ATP there's another product which is CO2. This CO2 is exhaled in the same concentration of the used O2 concentration in this metabolic process. And the O2 will reduced to 16% from 20%, so the O2 is helping in producing CO2.

Partial pressure of gases (in a mixture)

Composition of respiratory air:

Component	Inhaled air	Exhaled air
Nitrogen	79%	79%
Oxygen	20%	16%
Carbon dioxide	Trace	4%

Partial pressure of gases (in a mixture):

- In respiratory physiology, there is a mixture of gases mainly of O_2, N_2, and CO_2.
- The pressure of gas is caused by the constant kinetic movement of gas molecules against the surface.
- The rate of diffusion of each of these gases is directly proportional with the partial pressure of the gas.

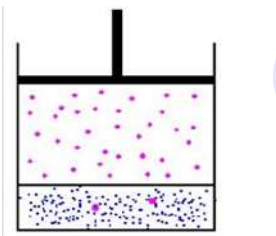
$$\text{Pressure} = \frac{\text{Force}}{\text{Area}}$$

The concept of partial pressure can be explained as follows:
Consider air, which has an approximate composition of 79% nitrogen and 21% oxygen. The total pressure of this mixture at sea level averages 760 mmHg. It is clear from the preceding description of the molecular basis of pressure that each gas contributes to the total pressure in direct proportion to its concentration. Therefore, 79% of the 760 mmHg is caused by nitrogen (600 mmHg) and 21% by O2 (160 mm Hg). Thus, the partial pressure of nitrogen in the mixture is 600 mmHg, and the partial pressureof O2 is 160 mmHg; the total pressure is 760 mm Hg, the sum of the individual partial pressures.
The partial pressures of individual in a mixture are designated by the PO2, PCO2, PN2, and so on.

Dalton's Law of Partial Pressures:

It states that the total pressure exerted by a mixture of gases is the sum of partial pressure of each individual gas present.

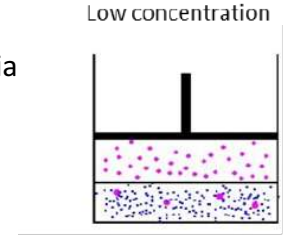
P total = P1 + P2 + P3 + . .



Low pressure equilibrium
Low concentration

Henry's Law:

Gas solubility is proportional to the gas partia pressure.If the temperature stays constant increasing the pressure will increase the amount of dissolved gas. Gases diffuse from high pressure to low pressure.



Double the pressure equilibrium
Double the concentration

- Partial pressure = Concentration of dissolved gas / Solubility coefficient

- Pressure of gases dissolved in water and tissue:

The pressure of gases dissolved in fluid is similar to their pressure in the gaseous phase and they exert their own individual partial pressure.

Note:

Pressure is caused by multiple impacts of moving molecules against a surface. Therefore, the pressure of a gas acting on the surfaces of the respiratory passages and alveoli is proportional to the summated force of impact of all the molecules of that gas striking the surface at any given instant is helping in producing CO2.

Note:

- **Diffusion of Gases Between the Gas Phase in Alveoli and Blood:**

The partial pressure of each gas in the alveolar respiratory gas mixture tends to force molecules of that gas into solution in the blood of the alveolar capillaries. Conversely, the molecules of the same gas that are already dissolved in the blood are bouncing randomly in the fluid of the blood, and some of these bouncing molecules escape back into the alveoli. The rate at which they escape is directly proportional to their partial pressure in the blood.

- **But in which direction will net diffusion of the gas occur?**

The answer is that net diffusion is determined by the difference between the two partial pressures. If the partial pressure is greater in the gas phase in the alveoli, as is normally true for oxygen, then more molecules will diffuse into the blood than in the other direction. Alternatively, if the partial pressure of the gas is greater in the dissolved state in the blood, which is normally true for CO2, then net diffusion will occur toward the gas phase in the alveoli.

When partial pressure is expressed in atmospheres (1 atmosphere pressure equals 760 mm Hg) and concentration is expressed in volume of gas dissolved in each volume of water, the solubility coefficients for important respiratory gases at body temperature are the following:

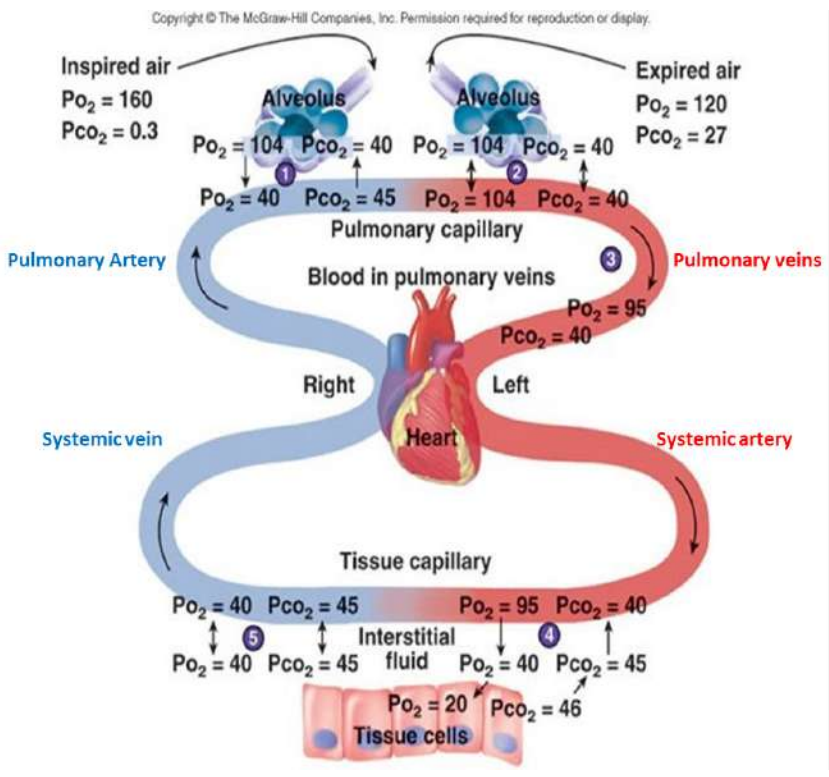
Oxygen	0.024
Carbon dioxide	0.57
Carbon monoxide	0.018
Nitrogen	0.012
Helium	0.008

From this table, one can see that CO_2 is more than 20 times as soluble as O_2. Therefore, the partial pressure of CO_2 (for a given concentration) is less than one twentieth that exerted by O_2.

Partial pressures of respiratory gases as they enter and leave the lungs (at sea level):

	Atmospheric Air* (mm Hg)		Humidified Air (mm Hg)	in dead space	Alveolar Air (mm Hg)		Expired Air (mm Hg)	
N_2	597.0	(78.62%)	563.4	(74.09%)	569.0	(74.9%)	566.0	(74.5%)
O_2	159.0	(20.84%)	149.3	(19.67%)	104.0	(13.6%)	120.0	(15.7%)
CO_2	0.3	(0.04%)	0.3	(0.04%)	40.0	(5.3%)	27.0	(3.6%)
H_2O	3.7	(0.50%)	47.0	(6.20%)	47.0	(6.2%)	47.0	(6.2%)

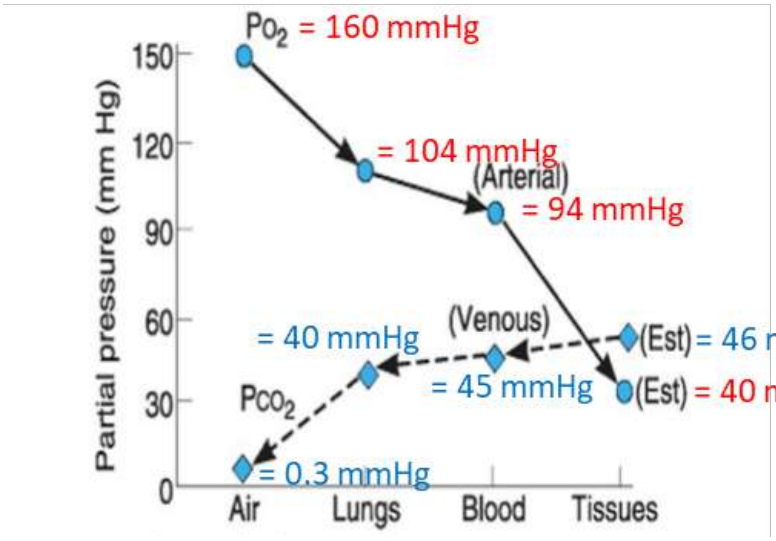
- **Oxygen** concentration in the atmosphere is **21%**
  - So **partial O_2 pressure (PO_2) in atmosphere** =760 mmHg (1 ATM) x **21%** =**160 mmHg**.
  - This mixes with old air already present in alveolus to arrive at PO_2 of **104 mmHg in alveoli**.
- **Carbon dioxide** concentration in the atmosphere is **0.04%**
  - So **PCO_2** in atmosphere =760 mmHg x **0.04% = 0.3 mmHg**
  - This **mixes with** high **CO_2 levels from residual volume** in the alveoli to arrive at PCO_2 of **40 mmHg in the alveoli.**



Explanation the figure:

1. 104 – 40 = 64 Oxygen-diffusing capacity during exercise.
2. Complete Gas exchange. Here the diffusion stops.
3. Why PO2 reduced from 104 to 95? Because of the Physiological shunt: It's the mixing of oxygenated & deoxygenated blood.
4. There're differences in partial pressure so, the O2 & CO2 will move from High to Low.
5. Complete Gas exchange. Here the diffusion stops.

PO2 and PCO2 in air, lungs and tissue :

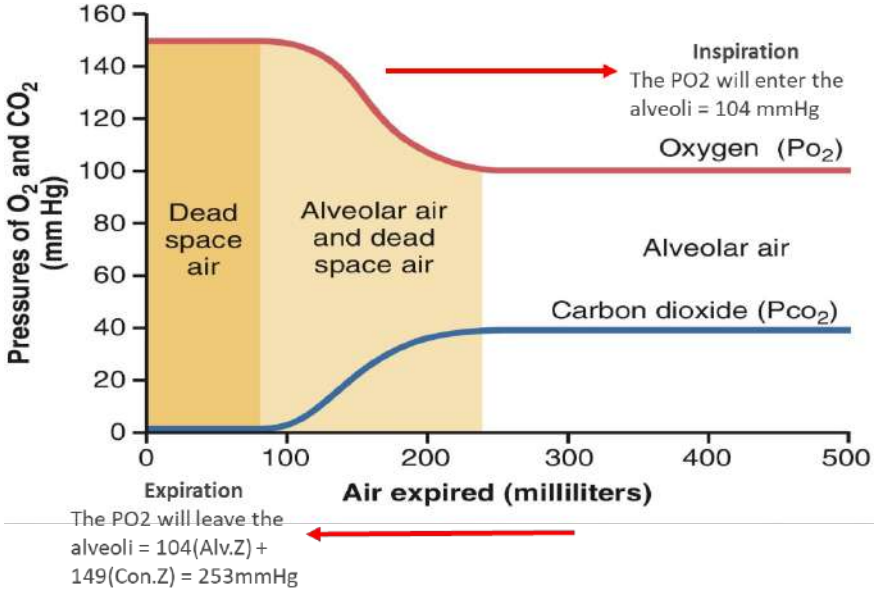


Note:
The change in partial pressure between tissue and pulmonary capillaries is caused by accumulation of gas as the blood circulates the body.

PO2 and PCO2 in air, lungs and tissue :

Cells use oxygen in metabolic activities all the time, which means that the PO_2 inside cells and its surrounding interstitial fluid would decrease. This causes a **partial pressure difference** with the blood in surrounding tissue capillaries, leading to **net diffusion** of O_2 into the interstitial fluid. This deoxygenated blood circulates back into the heart and into the lungs, where the PO_2 of alveolar air causes O_2 to diffuse into the pulmonary capillaries.

The same mechanism happens with CO_2 but in the opposite direction, because cells produce CO_2 instead of consuming it like it does with O_2



- **To summaries:**

	PO2	PCO2
Alveoli	104 mmHg	40 mmHg
Pulmonary capillaries	40 mmHg	45 mmHg
Tissue capillaries	95 mmHg	40 mmHg
Interstitial fluid	40 mmHg	45 mmHg
Calls	23 mmHg	46 mmHg

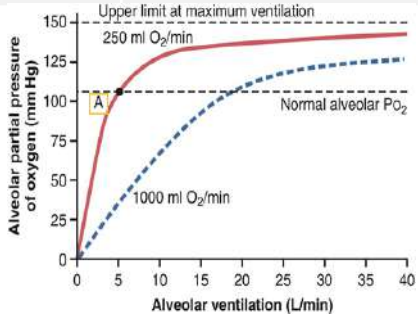
Note:
All lung volumes and capacities are 20-25% less in women than men, they are greater in large athletic people than in small athletic people.

Gas concentrations in the alveoli:

- **Oxygen**

	At resting condition	During exercise
Ventilator rate	4.2 L/min	Must increase 4 times to maintain the alveolar PO2 at the normal value of 104 mmHg (see A)
Volume enter the pulmonary capillaries	250 ml/min	1000 ml/min (x4 normal volume)

Explanation the figure:
This graph shows the ventilation, absorption through the alveoli, and Oxygen alveolar pressure.
if the absorption increases from 250 to 1000 ml O2/min , the alveolar pressure would drop. so the body accommodates by increasing the ventilation.



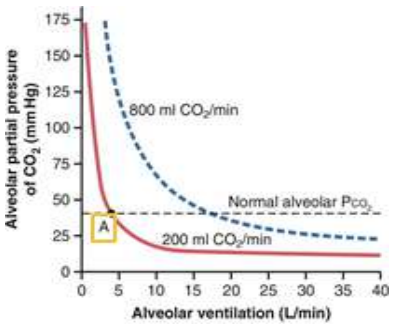
- **Carbon dioxide:**

- Normal rate of excretion from the blood = 200ml/min
- Normal ventilation = 4.2 L/min
- Normal alveolar PCO2 operating point (see A) = 40mmHg.

- **Relations**

- Alveolar PCO2 is directly in proportion to the rate of CO2 excretion. Increases as represented by the dotted curve for 800ml CO2 excretion/min.
- Alveolar PCO2 is inversely proportional to alveolar ventilation

Explanation the figure:
This graph demonstrates excretion, ventilation, and CO2 pressure in the alveoli.
the more excretion, the higher the CO2 pressure will be in the alveoli. so the body accommodates by increasing ventilation to get rid of the excess CO2.



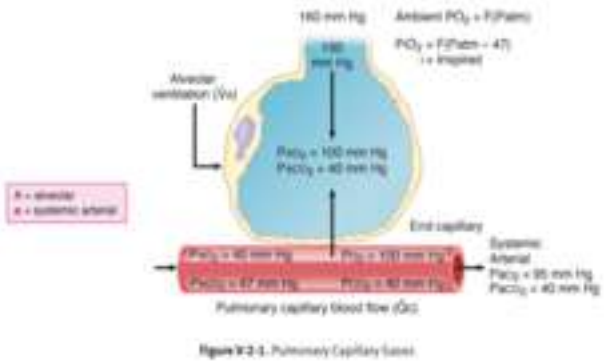
The normal lung

Partial Pressure of a Gas in Ambient Air

- Pgas = Fgas × Patm (Patm: atmospheric pressure. Pgas: partial pressure of a gas. Fgas: concentration of a gas)
- By convention, the partial pressure of the gas is expressed in terms of its dry gas concentration. For example, the PO2 in ambient air is :$PO_2 = 0.21 \times 760 = 160$ mm Hg

Partial Pressure of a Gas in Inspired Air

- Inspired air is defined as air that has been inhaled, warmed to 37°C, and completely humidified, but has not yet engaged in gas exchange. It is the fresh air in the anatVD that is about to enter the respiratory zone.
- The partial pressure of H_2O (PH_2O) is dependent only on temperature and at 37°C is47 mm Hg. Humidifying the air reduces the partial pressure of the other gases present.
- For example, the PO_2 of inspired air is: $PIO_2 = 0.21 (760 - 47) = 150$ mm Hg The figure below shows the pressures of oxygen and carbon dioxide in the alveolar, pulmonary end capillary, and systemic arterial blood.



Note

Dalton's law of partial pressures states that the total pressure exerted by a mixture of gases is the sum of the pressures exerted independently by each gas in the mixture. Also, the pressure exerted by each gas(its partial pressure) is directly proportional to its percentage in the total gas mixture.

- l veolar compartment and pulmonary end capillary blood are the same(perfusion-limited).
- There is a slight change ($PO_2 \downarrow$) between the end capillary compartment and systemic arterial blood because of a small but normal shunt through the lungs.
- Alveolar–systemic arterial PO_2 differences = A - a O_2 gradient.
- This difference (5-10 mm Hg) often provides information about the cause of a hypoxemia.

Factors Affecting Alveolar PCO_2

- Only 2 factors affect alveolar PCO_2: metabolic rate and alveolar ventilation.
- **PACO ∝metabolic CO_2 production/alveolar ventilation**
- At rest, unless there is fever or hypothermia, CO_2 production is relatively constant; so you can use changes of $PACO_2$ to evaluate alveolar ventilation.

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Gas Exchange and Gas Transfer

Alveolar Ventilation

There is an inverse relationship between $PACO_2$ and alveolar ventilation. This is the main factor affecting alveolar PCO_2. Therefore, if ventilation increases,$PACO_2$ decreases; if ventilation decreases, $PACO_2$ increases.

❖ **Hyperventilation**

During hyperventilation, there is an inappropriately elevated level of alveolar ventilation, and $PACO_2$ is depressed.

If V•A is doubled, then $PACO_2$ is decreased by half.

For example, $PACO_2$ = 40 mm Hg

2 × V•A; $PACO_2$ = 20 mm Hg

❖ **Hypoventilation**

During hypoventilation, there is an inappropriately depressed level of alveolar ventilation, and PACO2 is elevated.

If V•A is halved, then $PACO_2$ is doubled.

For example, $PACO_2$ = 40 mm Hg

1/2 V•A; $PACO_2$ = 80 mm Hg

❖ **Metabolic Rate**

There is a direct relationship between alveolar PCO_2 and body metabolism. For $PaCO_2$ to remain constant, changes in body metabolism must be matched with equivalent changes in alveolar ventilation.

- If V•A matches metabolism, then $PACO_2$ remains constant.
- For example, during exercise, if body metabolism doubles, then V•A must double if $PaCO_2$ is to remain constant.
- If body temperature decreases and there is no change in ventilation,$PaCO_2$ decreases, and the individual can be considered to be hyperventilating.

Factors Affecting Alveolar PO_2

The alveolar air equation includes all the factors that can affect alveolar PO_2.

PAO_2 = (patm - 47) FiO_2 - $PACO_2$ / RQ

Practical application of the equation includes differential diagnosis of hypoxemia by evaluating the alveolar arterial (A–a) gradient of oxygen.

There are 3 factors that can affect PAO_2:

1. **Patm** = atmospheric pressure, at sea level 760 mm Hg
   An increase in atmospheric pressure (hyperbaric chamber) increases alveolar PO_2, and a decrease (high altitude) decreases alveolar PO_2.
2. **FiO_2** = fractional concentration of oxygen, room air 0.21
   An increase in inspired oxygen concentration increases alveolar PO_2.
3. **$PaCO_2$** = alveolar pressure of carbon dioxide, normally 40 mm Hg
   An increase in alveolar PCO_2 decreases alveolar PO_2, and a decrease in alveolar PCO_2 increases alveolar PO_2. For most purposes, you can use arterial carbon dioxide ($PaCO_2$) in the calculation.
4. The fourth variable is **RQ**.

   RQ respiratory exchange ratio = $\frac{CO_2 \text{ produced ml/min}}{O_2 \text{ consumed ml/min}}$ = normally 0.8

For example, a person breathing room air at sea level would have

PAO_2 = (760 - 47) 0.21 - 40/0.8 = 100 mm Hg.

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Effect of $PACO_2$ on PAO_2

PIO_2 = P inspired O_2, i.e., the PO_2 in the conducting airways during inspiration.
Because $PaCO_2$ affects alveolar PO_2, hyperventilation and hypoventilation also affect PaO_2.

❖ **Hyperventilation (e.g., $PaCO_2$ = 20 mm Hg)**
$PaO_2 = PiO_2 - PaCO_2$ (assume R = 1)
normal = 150 - 40 = 110 mm Hg
hyperventilation = 150 - 20 = 130 mm Hg

❖ **Hypoventilation (e.g., $PaCO_2$ = 80 mm Hg)**
normal = 150 - 40 = 110 mm Hg
hypoventilation = 150 - 80 = 70 mm Hg

Alveolar–blood Gas Transfer: Fick Law of Diffusion

Simple diffusion is the process of gas exchange between the alveolar compartment and pulmonary capillary blood. Thus, those factors that affect the rate of diffusion also affect the rate of exchange of O_2 and CO_2 across alveolar membranes. (An additional point to remember is that each gas diffuses independently.)
$V\bullet gas = A/T \times D \times (P1-P2)$ (V•gas = rate of gas diffusion)

Structural Features That Affect the Rate of Diffusion

There are 2 structural factors and 2 gas factors affect the rate of diffusion.

1. A = surface area for exchange, ↓ in emphysema, ↑ in exercise
2. T = thickness of the membranes between alveolar gas and capillary blood, ↑ in fibrosis and many other restrictive diseases

A structural problem in the lungs is any situation in which there is a loss of sur-face area and/or an increase in the thickness of the membrane system between the alveolar air and the pulmonary capillary blood. In all cases, the rate of oxy-gen and carbon dioxide diffusion decreases. The greater the structural problem, the greater the effect on diffusion rate.

Factors Specific to Each Gas Present

❖ **D (diffusion constant) = main factor is solubility**

The only clinically significant feature of D is solubility. The more soluble the gas, the faster it diffuses across the membranes. CO_2 is the most soluble gas with which we will be dealing. The great solubility CO_2 is the main reason why it diffuses faster across the alveolar membranes than O_2.

Gas Exchange and Gas Transfer

❖ Gradient across the membrane

- **(P1 - P2):** This is the gas partial pressure difference across the alveolar membrane. The greater the partial pressure difference, the greater the rate of diffusion. Under resting conditions, when blood first enters the pulmonary capillary, the gradient for O_2 is: 100 - 40 = 60 mm Hg
- An increase in the PO_2 gradient across the lung membranes helps compensate fora structural problem. If supplemental O_2 is administered, alveolar PO2 increases, because of the elevated gradient. However, supplemental O_2 does not improve the ability of the lungs to remove CO_2 from blood. This increased gradient helps re-turn the rate of O_2 diffusion toward normal. The greater the structural problem, the greater the gradient necessary for a normal rate of O_2 diffusion.
- The gradient for CO_2 is 47 - 40 = 7 mm Hg.
- Even though the gradient for CO_2 is less than for O2, CO2 still diffuses faster because of its greater solubility.

Recall Question: Which of the following factors increases alveolar PCO_2, assuming no compensation?

A. Decrease in atmospheric pressure (Patm)
B. Increase in fractional concentration of oxygen (FiO_2)
C. Decrease in compliance of alveoli
D. Increase in thickness of the membranes between alveolar gas and capillary blood
E. Increase in body temperature

Answer: E

Diffusing Capacity of The Lung

There are 2 terms that describe the dynamics of the transfer of individual sub-stances between the interstitium and the capillary:

1. If the substance equilibrates between the capillary and interstitium, itis said to be in a **perfusion-limited situation.**
2. If the substance does not equilibrate between the capillary and interstitium, it is said to be in a **diffusion-limited situation.**

- Carbon monoxide is a unique gas in that it typically doesn't equilibrate between the alveolar air and the capillary blood. Thus, it is a diffusion-limited gas. This is taken advantage of clinically, and the measurement of the uptake of CO in mL/min/mm Hg is referred to as the diffusing capacity of the lung (DLCO).
- DLCO is an index of the lung's structural features.

Carbon Monoxide: A Gas That Is Always Diffusion Limited

Carbon monoxide has an extremely high affinity for hemoglobin. When it is present in the blood, it rapidly combines with hemoglobin, and the amount dis-solved in the plasma is close to zero (therefore, partial pressure in the plasma is considered zero). Thus, the alveolar partial pressure gradient (P1 – P2) is simplyP1 (alveolar partial pressure), since P2 is considered to be zero.

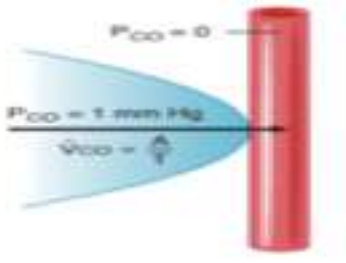

Figure V-2-2. Carbon Monoxide

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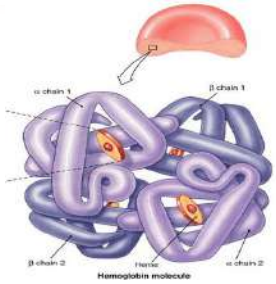
Gaseous Exchange by OSFCPhysE

Biology Carbon Dioxide Transport by rochi916

Objective

1. Understand the forms of oxygen transport in the blood, and the importance of each.
2. differentiate between O2 capacity, O2 content and O2 saturation.
3. Describe the oxygen-hemoglobin dissociation curve.
4. define the P50 and its significance
5. how DPG, temperature, H+ ions and PCO2 affect affinity of O2 for hemoglobin and the physiological importance of these effects.
6. describe the three forms of carbon dioxide that are transported in the blood, and the chloride shift.

Hemoglobin



- oxygen molecules bind loosely and reversibly with Heme portion of Hemoglobin (Heme + Globin)
- The heme portion contains 4 iron atoms, which are capable of carrying 4 O2 molecules (8 atoms)
- Oxygen-carrying capacity of blood determined by its [hemoglobin].
  - Anemia: [Hemoglobin] below normal.
  - Polycythemia: [Hemoglobin] above normal.
- Hemoglobin production controlled by erythropoietin. Production is stimulated by PCO2 delivery to kidneys.
- Loading/unloading depends:
  - PO2 of environment.
  - Affinity between hemoglobin and O2.

Forms of hemoglobin

Oxyhemoglobin	Deoxyhemoglobin	Methemoglobin	Carboxyhemoglobin
Normal heme contains iron in the reduced form (Fe2+). Fe2+ shares electrons and bonds with oxygen.	When oxyhemoglobin dissociates to release oxygen, the heme iron is still in the reduced form.	Has iron in the oxidized form (Fe3+). Lacks electrons and cannot bind with 02. Blood normally contains a small amount.	Reduced heme is combined with carbon monoxide, The bond with carbon monoxide is 210 times stronger than the bond with oxygen, which impairs O2 transport.

Transport of O_2

- PO2 and the concentration gradient plays important factor which determines how much oxygen combines with Hb when the haemoglobin (deoxygenated Hb) is converted to HbO2,
- Main function of blood: Transport of respiratory gases between the lungs and body tissues.
  - If PO2 is high As in pulmonary capillaries O2 binds to hemoglobin and vice versa result in greater Hb saturation.
  - If PO2 is low As in the tissue capillaries Hb releases O2 result in lower Hb saturation

Explanation the figure:
This graph demonstrates excretion, ventilation, and CO2 pressure in the alveoli.
the more excretion, the higher the CO2 pressure will be in the alveoli. so the body accommodates by increasing ventilation to get rid of the excess CO2.

- Forms of Oxygen in blood
  - 97% from the lungs to the tissues is carried in chemical combination and get rapidly diffused and binds to hemoglobin.
  - 3% is physically being dissolved in plasma

$$Hb + 4O2 \rightarrow Hb(O2)4$$

Transport of O_2 by hemoglobin:

- Hb combines with oxygen the compound formed is called oxyhemoglobin, and it depends on the amount of Hb present in the blood.
- Oxygen can combine loosely and reversibly with hemoglobin. Hb+O2 HbO2
- The normal amount of Hb in young adults is about 16 gm/dl of the blood. Each gram of Hb can bind with 1.34 ml of O2 . Thus, 16 x 1.34 = 21.44 ml of O2 /dl.

Partial Pressure Difference:

1. High Partial Pressure of O_2 (Po_2)in Alveoli
2. Low Po_2 in Capillary

- Transport O_2:

Diffusion Difference-Very Short → O2 Diffusion-Very Rapid → O2 Diffuses from Alveoli Into RBC → (Attaches to Heme Molecule) → Carried To Tissues

- Concentration Gradient

- High Concentration of O_2 in Alveoli
- Low Concentration of O_2 in Capillary O_2

Transport of oxygen in arterial blood:

	When blood is 100% saturated with O_2	When blood is 97% saturated	In venous blood	During strenuous exercise
Notes	each gram of Hb carry 1.34 ml O_2	97% of 100% saturation	Amount of oxygen released from the hemoglobin to the tissues is 5ml O2 per each 100ml blood.	During strenuous exercise the oxygen uptake by the tissue increases 3 folds 5ml x 3 folds = 15 ml O_2 is given /100 mlblood
Calculations	Hb x O_2 15g x 1.34	0.97 x 20	O_2 content in 97% saturation — oxygen released to tissue = 19.4 — 5	O_2 content in 97% saturation — oxygen released to tissue during strenuous exercise = 19.4 — 15
O2 content	20 ml.	19.4 ml.	14.4 ml.	4.4 ml.

O_2 capacity, content and saturation:

O_2 content	O_2-binding capacity	Percent saturation	Dissolved O_2
Amount of O_2 in blood (ml O_2/100 ml blood)	Maximum amount of O_2 bound to hemoglobin (ml O_2/100 ml blood) measured at 100% saturation	100 % of heme groups bound to O_2 % saturation of Hb = Oxygen content X100 / Oxygen capacity	Unbound O_2 in blood (ml O_2 /100 mlblood)

Transport of oxygen in the dissolved state:

1. At normal arterial PO_2= 95 mmHg.
   - 95 x 0.003 (The solubility of O_2 in blood is 0.003 mL O_2/100 mL/mm Hg (SOLUBILITY factor)).
   - 0.29 ml of oxygen is dissolved in each 100ml of blood.
2. When the PO2 of the blood falls to 40 mmHg in tissue capillaries.
   - 40 x 0.003.
   - 0.12 of oxygen remains dissolved.

➔ Calculation: from henry's law

$$\text{Partial pressure} = \frac{\text{Concentration of dissolved gas}}{\text{Solubility coefficient}}$$

► concentration of dissolved gas = partial pressure × solubility factor

- 0.17 ml of oxygen is normally transported in the dissolved state to the tissues per each 100 ml of blood.

CO_2 transport

- Large amount of CO2 is continuously produced in the body.
- In the resting state, 4 ml CO2is carried to the lung per 100 ml of blood.
- CO2 is carried in the blood in 3 different forms:

1. 70% of CO2 is transported in Bicarbonate form.
2. 7% directly dissolved in plasma
3. 23% of CO2 binds with deoxyhemoglobin in the RBC (globing part) to form carbamino hemoglobin. Once the blood reaches the pulmonary capillaries, the CO2 detaches from the hemoglobin and diffuses into the alveoli.

Factors affecting CO_2 diffusion:

1. Partial Pressure of CO2 (Pco2)-Higher In Tissues Than In Capillary
2. Concentration Gradient-CO2 Higher In Tissues Than In Capillary
3. Distance-Very Short

Bicarbonate form:

1. CO2 is diffused from the tissue to the RBC.
2. CO2 reacts with H_2O in the presence of carbonic anhydrase (speeds up the process) to form carbonic acid.
3. Carbonic acid is then dissociated into hydrogen ions (bond with Hb to formHHb) and bicarbonate ions.
4. Bicarbonate ions goes into the plasma, and chloride (Cl) ions take its place within the cell to maintain negativity. (chloride shift)
5. Blood is transported to the pulmonary capillaries. Then the bicarbonate ions switch places with the chloride ions present within the RBC.
6. The bicarbonate ions react with the H^+ ions to form CO_2 and H_2O within the RBC.

$$\underset{\text{Carbon dioxide}}{CO_2} + \overset{\text{Water}}{H_2O} \rightleftharpoons \underset{\text{Carbonic acid}}{H_2CO_3} \rightleftharpoons \overset{\text{Hydrogen ion}}{H^+} + \underset{\text{Bicarbonate ion}}{HCO_3}$$

Transport of CO_2 dissolved in plasma:

1. Little carbon dioxide is transported in the dissolved state to the lungs.
2. PCO2 of venous blood is 45 mm Hg and the PCO2 of arterial blood is 40 mmHg.
3. The amount of CO2 dissolved in the blood at 45 mmHg is 2.7 ml/dl (2.7%).
4. The amount of CO2 dissolved at 40 mmHg is about 2.4 ml
5. The difference between 2.7 and 2.4 is only 0.3 ml.
6. About 0.3 ml CO2 is transported in the form of dissolved CO2 by each 100 ml of blood.
7. It is about 7 % of all CO2 is transported in this form.

Transport of CO_2

$H_2O + CO_2$ H_2CO_3 $H^+ + HCO_3^-$

- At the tissues, CO_2 diffuses into the RBC; shifts the reaction to the right.
- Increased [HCO_3^-] produced in RBC → HCO_3^- diffuses into the blood.
- RBC becomes more + → Cl^- attracted in (Cl^- shift).
- H^+ released buffered by combining with deoxyhemoglobin.
- $HbCO_2$ formed → Unloading of O_2.

Remember:
At rest, tissues consume 250 ml O2 /min and produce 200ml CO2.

At pulmonary capillaries

$H_2O + CO_2$ H_2CO_3 $H^+ + HCO_3^-$

- At the alveoli, CO_2 diffuses into the alveoli; reaction shifts to the left.
- Decreased [HCO_3^-] in RBC → HCO_3^- diffuses into the RBC.
- RBC becomes more - → Cl^- diffuses out (reverse Cl^- shift).
- Deoxyhemoglobin converted to oxyhemoglobin
- Has weak affinity for H^+ → Gives off $HbCO_2$.

The oxygen-hemoglobin dissociation curve

It's a S-shape or sigmoid (not linear) curve shows:

1. the progressive increase in the percentage saturation of the Hb (Y-axis)
2. with the increase in the PO_2 in the blood (X-axis).

- PO_2 = 95mmhg due to 97% saturation→ in arterial blood
- PO_2 = 40mmhg due to 75% saturation→ in venous blood

Oxygen Hemoglobin Dissociation Curve (with a mnemonic) by Medicosis Perfectionalis

Oxygen Hemoglobin Dissociation Curve Explained Clearly (Oxyhemoglobin Curve by MedCram - Medical Lectures Explained CLEARLY

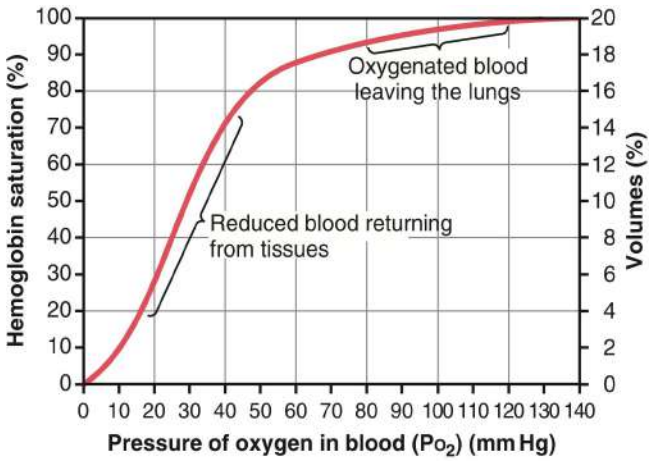
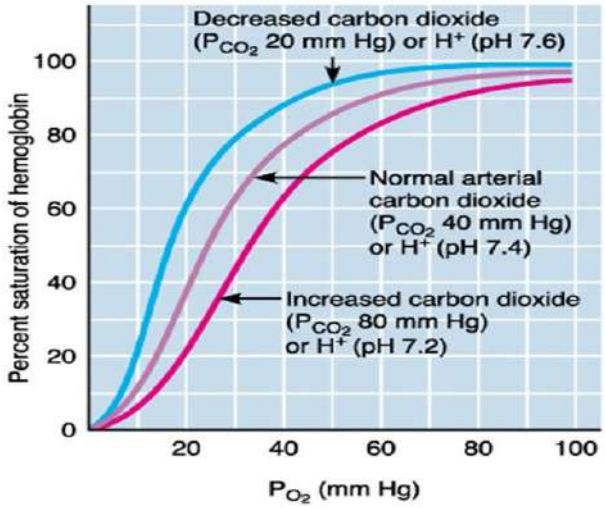


Figure 41-8. Oxygen-hemoglobin dissociation curve.

Factors affecting oxygen-haemoglobin dissociation curve:

	Right shift	left shift
Meaning	the oxygen is unloaded to the tissues from Hb	loading or attachment of oxygen to Hb. hemoglobin affinity for oxygen is increased
pH (H^+ conc)	↓ pH ↑(H+ conc)	↑pH ↓(H^+ conc)
Temperature	↑	↓
(2,3-DPG)	↑	↓
PCO2	↑(Bohr effect)	↓
P50	↑(lower affinity for O_2)	↓(higher affinity for O_2)
Fetal haemoglobin	———	✓

Note:
P50:
the partial pressure of O2 at which 50% of Hb is saturated with O2.
- Fetal Hb: has a P50 of 20 mmHg in comparison to 27 mmHg of adult Hb. "it has more affinity for oxygen " why? so the transport of O2 from mother to the fetus will be easier.



Note:
Hemoglobin in adults is consist of 2a+2B. Unlike in children, it consists of 2a + 2λ.
2,3DPG Binds to Beta chain of Hb & cross link this chain making Hb pocket smaller which leads to the release of O2.
DPG merges the 2 chains of Beta which decrease the area of hemoglobin. So, O2 needs to get out.
Because children do not have beta chain, The effect of DPG is less on them and this explain that:

More PO2 → More Hemoglobin Saturation → More Affinity → Less O2 release → Left shift

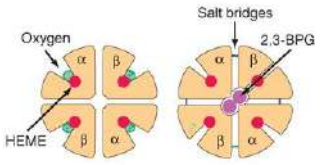
2,3-diphosphoglycerate (2,3-DPG)

- Synthesis: in RBCs from the glycolytic pathway
- Function: it binds tightly to reduced Hb.

➔ facilitate the oxygen release and shifts the dissociation curve to the right.

- Importance: increases in the RBCs in anemia and hypoxemia,

➔ serves as an important adaptive response in maintaining tissue oxygenation.



Bohr effect

At lung:

- Movement of CO_2 from blood to alveoli.
- Decrease blood CO_2 & H^+.
- Increase O_2 affinity of Hb.
- More O_2 transport to tissue.

Note :
That's why when someone inhales smoke (Carbon monoxide) he won't be able to breathe.

Bohr effect vs. Haldane effect | Human anatomy and physiology | Health & Medicine | Khan Academy by khanacademymedicine

At tissue:

- Movement of CO_2 from tissues to blood.
- Increase CO_2 & H^+ in blood.
- Decrease O_2 affinity of Hb.
- More O_2 transport to tissue.

Combination of Hb with CO "displacement of oxygen":

- CO combines with Hb at the same point on the Hb molecule as does oxygen.
- It binds with Hb about 250 times as much as O_2 (affinity of Hb to CO is very high that to O_2).

➔It causes Left shift of the O_2-Hb curve.

Respiratory | Oxygen-Hemoglobin Dissociation Curve by Ninja Nerd Science

Utilization Coefficient

The percentage of the blood that gives up its oxygen as it passes through the tissues capillaries is called utilization coefficient.

$$\text{Utilization Coefficient} = \frac{O_2 \text{ delivered to the tissues}}{O_2 \text{ content of arterial blood}}$$

- Normally at rest : 5 ml/20 ml= 25% ,
- During exercise; 15 ml/20 ml = 75 % - 85%

Diffusing Capacity of The Lung

- At a constant and known alveolar partial pressure, the uptake of carbon monoxide depends only on the structural features of the lung.

  $V \bullet gas = A/T \times D \times (P1\text{-}P2)$

  $V \bullet CO = A/T \times D \times PaCO$
- This measured uptake of carbon monoxide is called the diffusing capacity of the lung (DL; mL/min/mm Hg). It is an index of overall surface area and membrane thickness.
  - With a structural problem, it correlates with the extent of lung damage and is particularly useful when measured serially over time.
  - DL (rate of CO diffusion) decreases in emphysema and fibrosis but increases during exercise.

Oxygen and Carbon Dioxide Transport

Transport of oxygen

Units of Oxygen Content

Oxygen content = concentration of oxygen in the blood, e.g., arterial blood
= 20 volumes %
= 20 volumes of oxygen per 100 volumes of blood
= 20 mL of oxygen per 100 mL of blood
= 0.2 mL of oxygen per mL of blood

Dissolved Oxygen

- Oxygen dissolves in blood and this dissolved oxygen exerts a pressure. Thus, PO2 of the blood represents the pressure exerted by the dissolved gas, and this PO2 is directly related to the amount dissolved.
- The amount dissolved (PO2) is the primary determinant for the amount of oxy-gen bound to hemoglobin (Hb).
- There is a direct linear relationship between PO2 and dissolved oxygen.
  - When PO2 is 100 mm Hg, 0.3 mL O2 is dissolved in each 100 mL of blood (0.3 vol%).
  - Maximal hyperventilation can increase the PO2 in blood to 130 mmHg (0.4 vol%).

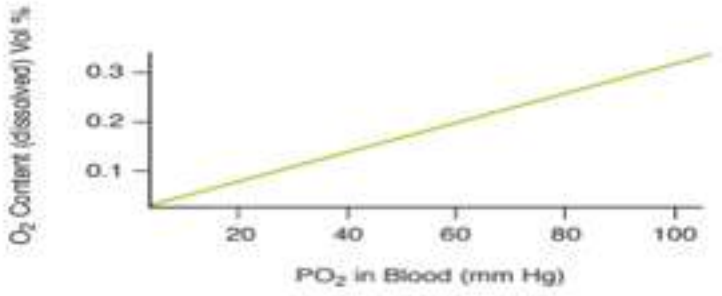


Figure V-3-1. Dissolved Oxygen in Plasma

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Oxygen and Carbon Dioxide Transport

Oxyhemoglobin

- Each Hb molecule can attach and carry up to four oxygen molecules. Binding sites on Hb have different affinities for oxygen. Also, the affinity of a site can and does change as oxygen is loaded or unloaded from the Hb molecule and as the chemical composition of the plasma changes.

Site 4 - O_2 attached when the minimal $PO_2 \cong 100$ mm Hg	systemic arterial blood = 97% saturated
Site 3 - O_2 attached when the minimal $PO_2 \cong 40$ mm Hg	systemic venous blood = 75% saturated(resting state)
Site 2 - O_2 attached when the minimal $PO_2 \cong 26$ mm Hg	P50 for arterial blood. P50 is the PO_2 required for 50% saturation
Site 1 - O_2 usually remains attached under physiologic conditions.	Under physiologic conditions, only sites 2,3, and 4 need to be considered.

- M
- The only significant form in which oxygen is delivered to systemic capillaries is oxygen bound to Hb.

Hemoglobin O_2 Content

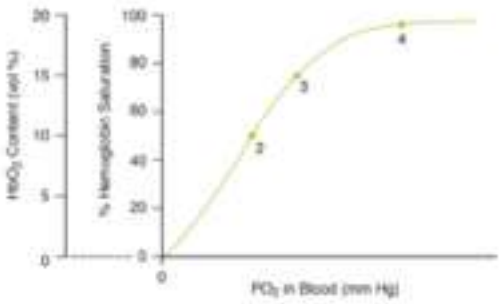
- The number of mL of oxygen carried in each 100 mL of blood in combination with Hb depends on the concentration [Hb]. Each gram of Hb can combine with 1.34 mL of O_2.
- If the [Hb] is 15 g/100 mL (15 g%), then the maximal amount of O_2 per 100 mL(100% saturation) in combination with Hb is:
  - $1.34\ ([Hb]) = 1.34(15) = 20$ mL O2/100 mL blood = 20 vol%
  - This volume represents the "carrying capacity" of the blood.
- The Hb in systemic arterial blood is about 97% saturated with oxygen, which means slightly less than 20 vol% is carried by Hb.
- When blood passes through a systemic capillary, it is the dissolved oxygen that diffuses to the tissues. However, if dissolved oxygen decreases, PO_2 also decreases, and there is less force to keep oxygen attached to Hb. Oxygen comes off Hb and dissolves in the plasma to maintain the flow of oxygen to the tissues.
- Hyperventilation or supplementing the inspired air with additional oxygen in abnormal individual can significantly increase the PaO_2 but has little effect on total oxygen content. For example:

Oxygen and Carbon Dioxide Transport

- Hyperventilation or supplementing the inspired air with additional oxygen in abnormal individual can significantly increase the PaO_2 but has little effect on total oxygen content. For example:

	Dissolved O_2	HbO_2	Total O_2 Content
If PaO_2 = 100 mm Hg	0.3	≅ 19.4	≅ 19.7 vol%
If PaO_2 = 130 mm Hg(hyperventilation)	0.4	≅ 19.4	≅ 19.8 vol%

Oxygen–Hb Dissociation Curves



The figure represents 3 major points on the oxygen–hemoglobin dissociation curve. The numbered sites refer to the hemoglobin site numbers dis-cussed just previously.

❖ The following factors shift the curve to the right:

1. Increased CO2 (Bohr effect)
2. Increased hydrogen ion (decrease pH)
3. Increased temperature
4. Increased 2,3- bisphosphoglycerate (2,3-BPG)

- In each case, the result can be explained as a reduced affinity. However, carrying capacity is not changed, and systemic arterial blood at a PO_2 of 100 mm Hg is still close to 100% saturation.
- The opposite chemical changes **shift the curve to the left**.

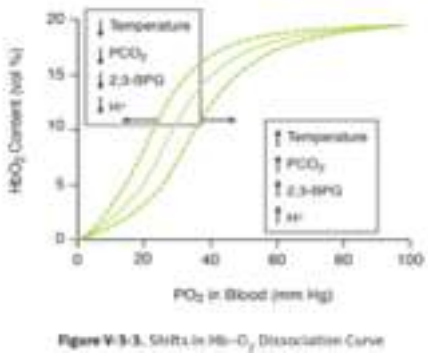


Figure V-3-3. Shifts in $Hb-O_2$ Dissociation Curve

Shift to the Right	Shift to the Left
Easier for tissues to extract oxygen	More difficult for tissues to extract oxygen
Steep part of curve, O_2 content decreased	Steep part of curve, O_2 content increased
P50 increased	P50 decreased

Note that only points on the steep part of the curve are affected.

- Stored blood loses 2,3-bisphosphoglycerate, causing a left shift in the curve, while hypoxia stimulates the production of 2,3-bisphosphoglycerate, there by causing a right shift.

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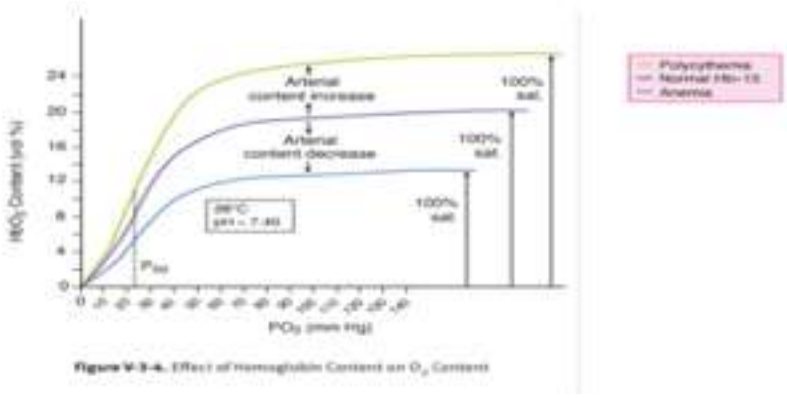
Oxygen and Carbon Dioxide Transport

Hb Concentration Effects

- **Anemia** is characterized by a reduced concentration of Hb in the blood .
- **Polycythemia** is characterized by a higher than normal concentration of Hb in the blood.
- **P50:** In simple anemia and polycythemia, the P50 does not change without tissue hypoxia; e.g., PO2 of 26 mm Hg produces 50% saturation of arterial hemoglobin. The figure below illustrates the effects of an increase and a decrease in hemoglobin concentration. The main change is the plateau or carrying capacity of the blood.
    - Note that the point halfway up each curve, the P50, is still close to 26 mm Hg.



Effects of Carbon Monoxide

Carbon monoxide (CO) has a greater affinity for Hb than does oxygen (240xgreater). The figure below shows that with CO, the O_2-Hb dissociation curve is shifted to the left (CO increases the affinity of Hb for O_2) and HbO2 content is reduced.

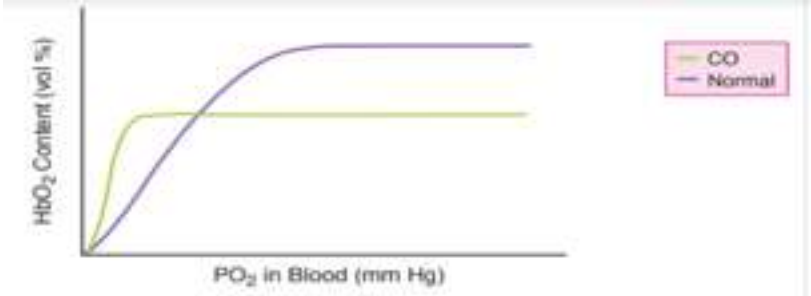


Figure V-3-5. Carbon Monoxide Poisoning

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Oxygen and Carbon Dioxide Transport

The effects of anemia, polycythemia, and carbon monoxide poisoning are summarized below.

	PO_2	Hb Concentration	O_2 per g Hb	O_2 Content
Anemia	Normal	↓	Normal	↓
Polycythemia	Normal	↑	Normal	↑
CO poisoning (acute)	Normal	Normal	↓	↓

O_2 per g Hb + % saturation

- **In anemia**, hemoglobin is saturated but arterial oxygen content is depressed because of the reduced concentration of hemoglobin.
- **In polycythemia**, arterial oxygen content is above normal because of an increased hemoglobin concentration.
- **In CO poisoning**, arterial PO_2 is normal, but oxygen saturation of hemoglobin is depressed.

Transport Of Carbon Dioxide

Dissolved Carbon Dioxide

Carbon dioxide is 24x more soluble in blood than oxygen is. Even though the blood has a PCO_2 of only 47 mm Hg, about 5% of the total CO_2 is carried in the dissolved form.

40–

Carbamino Compounds

Carbon dioxide reacts with terminal amine groups of proteins to form carbamino compounds. The protein involved appears to be almost exclusively hemoglobin. About 5% of the total CO_2 is carried as carbamino compounds. The attachment sites that bind CO_2 are different from the sites that bind O_2.

Bicarbonate

About 90% of the CO_2 is carried as plasma bicarbonate. In order to convert CO_2 into bicarbonate or the reverse, carbonic anhydrase (CA) must be present.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

The steps in the conversion of CO_2 into bicarbonate in a systemic capillary are seen below.

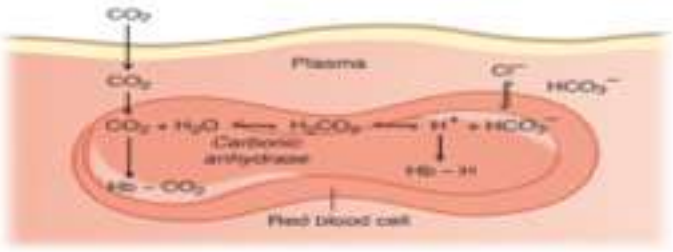

Figure V-3-6. Formation of Bicarbonate Ion

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Oxygen and Carbon Dioxide Transport

- Plasma contains no carbonic anhydrase; therefore, there can be no significant conversion of CO_2 to HCO_3^- in this compartment.
- Because deoxygenated Hb is a better buffer, removing oxygen from hemoglobin shifts the reaction to the right and thus facilitates the formation of bicarbonate in the red blood cells (Haldane effect)
- To maintain electrical neutrality as HCO_3^- moves into the plasma, Cl^- moves into the red blood cell (chloride shift).

In summary:

- Bicarbonate is formed in the red blood cell but it is carried in the plasma compartment.
- The PCO_2 determines the volume of CO_2 carried in each of the forms listed above. The relationship between the PCO_2 and the total CO_2 content is direct and nearly linear.
- Thus, hyperventilation not only lowers the PCO_2 (mm Hg), it also lowers the CO_2 content (vol%).

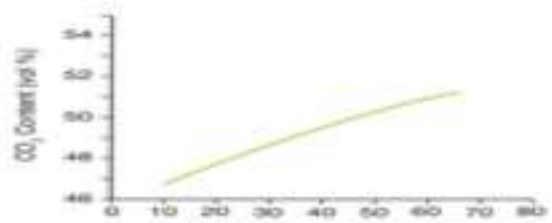

Figure V-3-7. CO_2 Content in Blood

Hypoxia and cyanosis

Ventilation/Perfusion Differences In The Lung

Regional Differences in Intrapleural Pressure (IPP)

- At FRC, the mean value for Intrapleural pressure is –5 cm H2O. However, there are regional differences, and the reason for these differences is gravity.
  - Recall that the pleura is a fluid-filled space.
  - Similar to the cardiovascular system, it is subject to gravitational influences

Regional Difference in Ventilation

- Because IPP is higher (less negative) at the base, the PTM is less, resulting in less distension of alveoli, i.e., there is less volume.
- In contrast, IPP is more negative at the apex, thus the PTM is higher, resulting in a greater volume in alveoli near the apex.
- As described in chapter 1, alveolar compliance decreases as lung volume increases. Thus, alveoli near the base are more compliant than alveoli near the apex. Stated another way, alveoli near the base are on a much steeper portion of the pressure-volume curve than alveoli near the apex (Figure V-4-2).
- Because alveoli near the base are more compliant, there is more ventilation in this region compared to the apex.– (P = height × gravity × density)
- Thus, IPP is higher (less negative) at the base (bottom) of the lung compared to the apex (top).

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Oxygen and Carbon Dioxide Transport

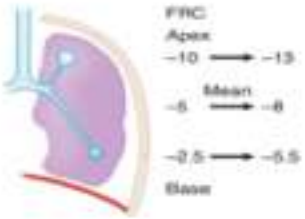

Figure V-4-1. Upright Posture

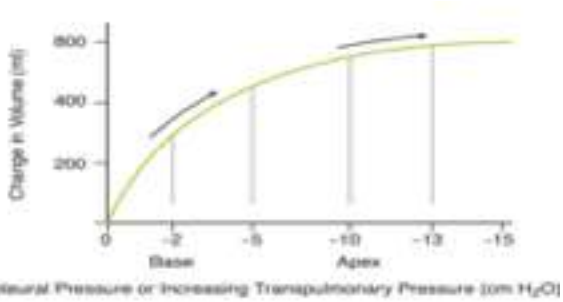

Figure V-4-2. Regional Ventilation

Clini ed to as "west zones" of the lung. The point is that the ventilation perfusion ratio is higher in the apex of the lung (zone 1) in an upright individual than it is in the base of the lung (zone 3).

Regional Differences in Blood Flow

Even in a normal individual, there are regional differences in blood flow through the pulmonary circuit. These differences, for the most part, can be attributed to the effect of gravity.

- Moving toward the base (with gravity), pressure in the pulmonary arteries is higher compared to pressure in the pulmonary arteries of the apex (against gravity).
- Since the intravascular pressure in arteries is higher, there is more blood flow to the base of the lung compared to the apex.

Ventilation–Perfusion Relationships

- The partial pressures of O_2 and CO_2 in alveoli are determined by the combination of ventilation (adding O_2, removing CO_2) and perfusion (removing O_2 and adding CO_2). However, it is not the absolute amount of either that determines the composition of alveolar gases. Instead, it is the relative relationship between ventilation and perfusion that ultimately determines the alveolar gases. This is **ventilation-perfusion matching**.
- In the normal situation, it would be "ideal" if ventilation and perfusion (blood flow) matched, i.e., the ventilation-perfusion ratio is one (Figure V-4-3). If this were the case, then:
    - PaO2 = 100 mm Hg
    - PaCO2 = 40 mm Hg
    - The blood draining the alveolus would have a pH = 7.40 (normal blood pH)
- Although the above is "ideal," it is not often encountered. The figure below illustrates ventilation, blood flow (Q) or perfusion, and the relative ventilation-perfusion relationship for an **upright individual.** Toward the base of the lung:
    - Alveolar ventilation is high relative to the apex (described above).
    - Q is high relative to the apex (described above). However, relative to one another, Q is higher than alveolar ventilation, thus the ventilation-perfusion relationship is <1.0.
    - In short, the alveoli are under-ventilated relative to the perfusion. If alveolar ventilation is inadequate, then it follows that PO_2 falls, PCO_2 rises, and blood pH falls (remember that CO_2 generates H^+).
    - Thus, PaO_2 at the base is <100 mm Hg and $PaCO_2$ is >40 mm Hg.

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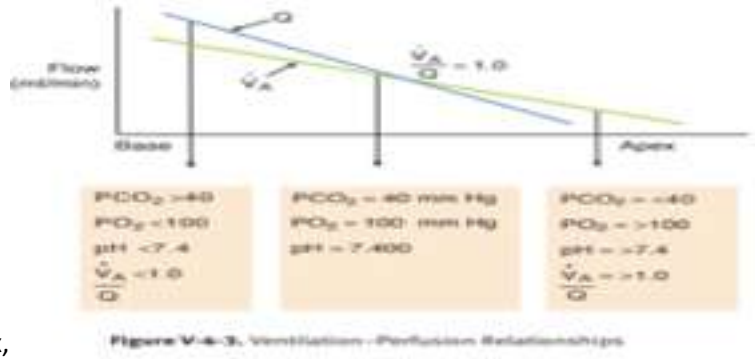


Figure V-A-3. Ventilation-Perfusion Relationships

Moving toward the apex,

- Alveolar ventilation is less relative to the base (described above).
- Q is less relative to the base (described above).
- However, relative to one another, Q is less than alveolar ventilation, thus the ventilation-perfusion relationship is >1.0.
- In short, the alveoli are over-ventilated relative to the perfusion. If alveolar ventilation is excessive, then it follows that PO2 rises, PCO2falls, and blood pH increases (remember that CO2 generates H+).
- Thus, PAO2 at the apex is >100 mm Hg and PACO2 is <40 mm Hg.

❖ The effect of the ventilation-perfusion relationship is a continuum.

- As **V•A/Q falls,** PO2 falls and PCO2 rises.
- As **V•A/Q rises,** PO2 rises and PCO2 falls.

Extremes of V•A/Q Mismatch

Shunt

- If ventilation is zero but there is blood flow, then V•A/Q = 0.
- This is a right-to-left shunt, and the blood gases leaving the alveoli are the same as venous blood (low PO_2, and high PCO_2; Y-axis intercept in figure below). This causes arterial hypoxemia, which is discussed later in this chapter.

Alveolar dead space

If blood flow is zero but there is ventilation, then V•A /Q = ∞.
This is alveolar dead space, and alveolar gases become the same as inspired
(high PaO_2 and $PaCO_2$ = 0; X-axis intercept in figure below).

To summarize:

- As V•A/Q falls, PO2 falls and PCO_2 rises. The extreme is a shunt.
    - Remember, however, that the lower the V•A/Q, the more it "behaves" as a shunt, i.e., the alveolar and blood gases get closer and closer to venous gases. Similar to a shunt, this can lead to arterial hypoxemia, both of which are discussed later in this chapter.
- As V•A/Q rises, PO_2 rises and PCO_2 falls. The extreme is alveolar dead space.– Similar to above, the higher the V•A/Q, the more the situation looks like alveolar dead space.

KAPLAN CORNER

Oxygen and Carbon Dioxide Transport

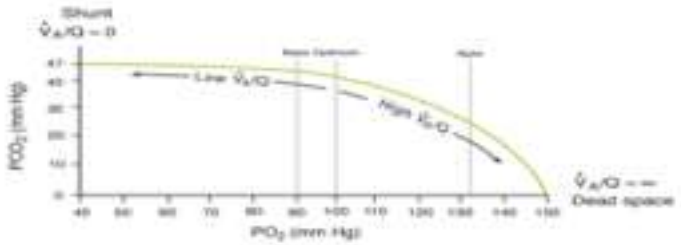


Figure V-4-4. Shunt and Dead Space

Problem

The following ratios rep[illegible]
V•A/Q
A = 0.62
B = 0.73

Both lung units A and B are under ventilated, but of the two, B is better ventilated. Which lung unit had the greatest:

$PACO_2$, end capillary PCO_2? (Answer: A)
PAO_2, end capillary PO_2? (Answer: B)
end capillary pH? (Answer: B)

Hypoxic Vasoconstriction

This is a clinically important phenomenon that is unique to the pulmonary circulation. Whenever there is a decrease in alveolar PO_2, a local vasoconstriction of pulmonary blood vessels is produced. The result is a lowering of blood flow through that lung unit and a redistribution of blood to better-ventilated units.

Problem

If a person inhales a peanut that lodges in a peripheral airway, what changes would you expect for the following variables in the peanut-occluded unit?

$PACO_2$ (increase)
PAO_2 (decrease)
pulmonary end capillary pH (decrease)
blood flow in that lung unit (decrease)

All answers here are based on the fact that blocking the airway produces a shunt. The blood flow decreases because of hypoxic vasoconstriction. Low V•A /Q ratios are associated with hypoxic vasoconstriction. If the pulmonary disease is severe and widespread, the alveolar hypoxia and subsequent arteriolar vasoconstriction increases pulmonary arterial pressure.

Problem

If a small thrombus lodges in a pulmonary artery, what changes would you expect for the following variables in the thrombus-occluded unit?

$PACO_2$ (decrease)
PAO_2 (increase)
pulmonary end capillary pH (increase)

All answers here are based on the fact that the thrombus increases the V•A/Qratio. This produces lung units that act as dead space.

KAPLAN CORNER

Exercise

In exercise, there is increased ventilation and pulmonary blood flow. However, during exercise, ventilation increases more than cardiac output and V•A/Q goes well above 1.0 as one approaches maximal oxygen consumption. Also, the base–apex flows are more uniform.

Review of the normal lung

Before discussing the causes of hypoxemia let's review the normal state using standard values:

- The blood entering the alveolar-capillary unit is mixed venous blood.
- PO_2 = 40 and PCO_2 = 45 mm Hg
- PaO_2 = 100 mm Hg and $PaCO_2$ = 40 mm Hg
- Both gases are perfusion-limited and thus their partial pressures at the end of the capillary are the same as alveolar.
- Arterial blood gas (ABG) sample shows PaO_2 = 95 mm Hg, and $PaCO_2$ = 40 mm Hg.
- The A–a gradient is 5 mm Hg (ranges 5-10 mm Hg but is influenced by age) and is primarily the result of anatomic shunts.

Clinical Correlate

As one ages, the A–a gradient increases because ventilation-perfusion matching becomes less and less "ideal."
One formula for taking this into account is:(age + 4)/4

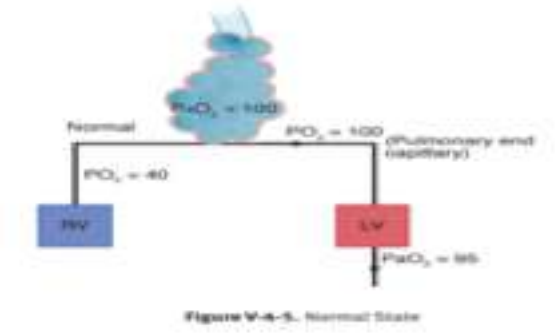


Figure V-4-5. Normal State

Causes of hypoxemia

1. Hypoventilation

- Hypoventilation of the entire lung elevates alveolar PCO_2, and the increase in PCO_2 decreases PO_2. For example, if alveolar ventilation decreases by 50%, alveolar PCO_2 becomes 80 mm Hg (an increase of 40 mm Hg).Assuming a respiratory ratio close to 1.0, alveolar PO_2 decreases by about 40–60mm Hg. If no other problem exists, pulmonary end capillary and systemic arterial PO_2 also decrease by 40 mm Hg.
- Hypoventilation is characterized as an equal decrease in PO_2 in all 3 compartments.
- As a result, A–a is normal and end-tidal PO_2 is still a good index of systemic arterial PO_2 (provided A–a gradient is taken into consideration).The hypoxemia can be relieved by increasing the inspired oxygen, however CO_2 remains elevated because ventilation is unchanged.

In summary:

- There is no increase in the A–a oxygen gradient
- Supplemental oxygen can relieve the hypoxemia.
- End-tidal air still reflects the systemic arterial compartment.
- The problem is not within the lung itself.

KAPLAN CORNER

Clinical Correlate

High altitude is sometimes categorized as a fifth cause of hypoxemia. High altitude causes low PAO_2, similar to hypoventilation. All the observations described here apply, except for PCO_2. At high altitude, a subject hyperventilates, and thus $PACO_2$ and $PACO_2$ are reduced.

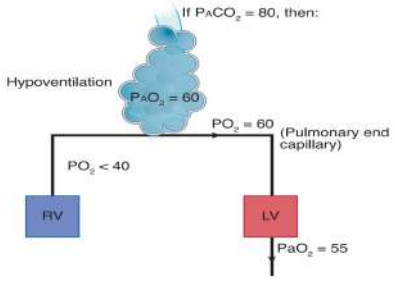


Figure V-4-6. Hypoventilation

2. Diffusion Impairment

- Diffusion impairment means a structural problem in the lung. As can be produced by a decreased surface area and/or increased thick
- In marked diffusion impairment, pulmonary end capillary PO_2 is less than alveolar PO_2. End-tidal PO_2 is not a good index of systemic arterial PO_2.In diffusion impairment, supplemental oxygen corrects the hypoxemia. Note that although the arterial PO_2 may be restored to normal, or even be above nor-mal by supplemental oxygen, there is still an abnormally large A–a gradient.
- In summary:
  - There is an increase in A–a oxygen gradient.
  - Supplemental oxygen can relieve the hypoxemia.
  - End-tidal air does not reflect the arterial values.
  - It is characterized by a decrease in DLCO.

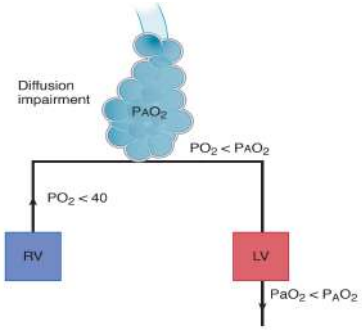


Figure V-4-7. Diffusion Impairment

Bridge to Pathology

- Acutely, hypoventilation can be caused by narcotics and general anesthetics. More chronic conditions include COPD, kyphoscoliosis, and neuromuscular disorders such as Guillain-
- Diffusion problems are commonly seen in pulmonary diseases, s asbestosis, and sarcoidosis. In addition, pulmonary edema can cause a diffusion impairment.

3. Ventilation-Perfusion Mismatch: Low V•A/Q Units

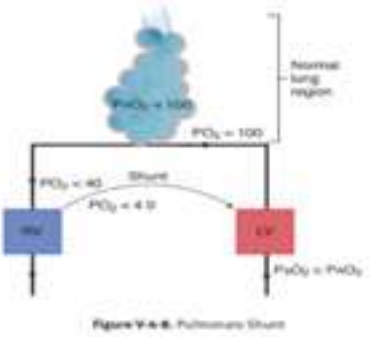
If ventilation to a significant portion of the lungs is markedly compromised, then V•A/Q is << 1.0. As described earlier, low V•A/Q creates alveolar and end-pulmonary capillary blood gases that are approaching venous gases (low PO_2,and high CO_2). The blood from these low V•A/Q units mixes in with blood draining normal alveolar-capillary units, resulting in systemic hypoxemia. Because PAO_2 is normal in areas that don't have low V•A/Q, the A–a gradient is elevated. Supplemental oxygen corrects the hypoxemia because the problem regions still have some ventilation—it is just much lower than normal. Similar to diffusion impairment described above, the increased A–a gradient means end-tidal PO_2 is not reflective of PAO_2.

In summary:

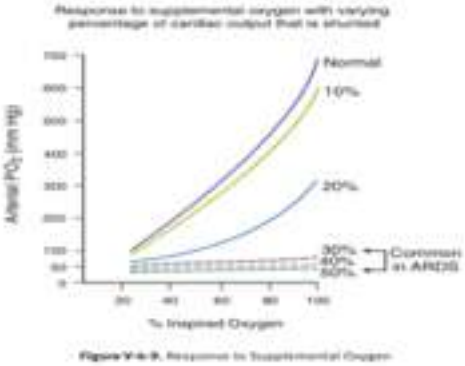
- There is an increased A–a oxygen gradient.
- Supplemental oxygen corrects the hypoxemia.
- End-tidal air does not reflect the arterial values.

KAPLAN CORNER

4 Intrapulmonary Shunt

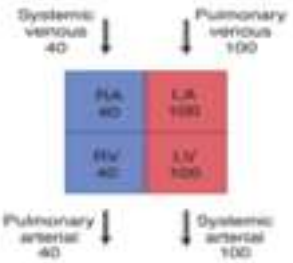


- By definition, systemic venous blood is delivered to the left side of the heart without exchanging oxygen and carbon dioxide with the alveoli. A right-to-left shunt leads to hypoxemia. The figure below illustrates the consequences of an intrapulmonary shunt. The solid-line regions represent the normal areas of the lung. The dashed line represents the shunted blood, which is passing from the right heart to the left heart without a change in chemical composition.
- With an intrapulmonary shunt, systemic arterial PO_2 is less than alv gradient. End-tidal PO_2 does not reflect systemic arterial PO_2.
- When a significant intrapulmonary shunt exists, breathing pure O_2 elevates systemic arterial PO_2 a small amount, but it often doesn't correct the hypoxemia. See Figure V-4-9 for response of PAO_2 with shunt.
- **The failure to obtain a significant increase in arterial PO_2 following the ad-ministration of supplemental oxygen in hypoxemia is strong evidence of the presence of a shunt.**
- **Bridge to Pathology:** Intrapulmonary shunts are caused by atelectatic lung regions (pneumothorax, ARDS), complete occlusion of an airway (mucus plug, foreign body), and the right-to-left shunts created by heart defects, tetralogy of Fallot, for example.
- **In summary:**
  - Increase in A–a oxygen gradient
  - Supplemental oxygen ineffective at returning arterial PO_2 to normal
  - End-tidal air does not reflect the arterial values



5. LEFT-TO-RIGHT SHUNTS

- Pressures are usually higher on the left side of the heart (atria and ventricles),and thus flow is normally left to right. A major characteristic is that hypoxemia never develops in left-to-right shunt. The principal example is an atrial or ventricular septal defect. The normal PO2 values in the left below. Note from the descriptions that follow where the first increase in PO2 develops on the right side.
- Diagnosed clinically with echocardiogram with bubble study
- Most intracardiac shunts are left-to-right shunts. However, long standing uncorrected shunts result in a reversal of the shunt.



KAPLAN CORNER

Oxygen and Carbon Dioxide Transport

Table V-4-1. Consequences of 3 Left-to-Right Shunts

	Atrial Septal Defect	Ventricular Septal Defect	Patent Ductus(newborn)
Systemic arterial PO2	No change	No change	No change
Right atrial PO2	↑	No change	No change
Right atrial PO2	↑	↑	No change
Pulmonary arterial PO2	↑	↑	↑
Pulmonary arterial PO2	↑	↑	↑
Pulmonary arterial PO2	↑	↑	↑

- Atrial septal defect: PO2 increase first appears in right atrium
- Ventricular septal defect: PO2 increase first appears in right ventricle
- Patent ductus: PO2 increase appears in pulmonary artery

Recall Question

In which of the following ways does myasthenia gravis cause hypoxemia?

A. Neuromuscular junction pathology causes hypoventilation, leading to chronic hypoxemia
B. Increases the A-a oxygen gradient
C. Fibrosis and sclerosis of the alveoli cause diffusion impairment
D. Ventilation-perfusion mismatch caused by a fibrotic scar form in the apex of the lung
E. Complete occlusion of an airway caused by a sclerotic foreign body

Answer: A

Control of breathing

Neural regulation of alveolar ventilation

The level of alveolar ventilation is driven mainly from the input of specific chemoreceptors to the central nervous system. The stronger the stimulation of these receptors, the greater the level of alveolar ventilation. Chemoreceptors monitor the chemical composition of body fluids. In this system, there are receptors that respond to pH, PCO2, and PO2.There are 2 groups of receptors, and they are classified by their location.

KAPLAN CORNER

From Guyton + Linda:

You should understand some concepts before you study the lecture:

- Pulmonary blood flow is the cardiac output of the right heart, which is equal to the cardiac output of the left heart. The difference is a result of a small amount of coronary venous blood that drains directly into the left ventricle through the thebesian vein (rather than going to the lungs via the pulmonary artery). Pulmonary blood flow is directly proportional to the pressure gradient between the pulmonary artery and the left atrium and is inversely.

- proportional to the resistance of the pulmonary vasculature (Q= delta P/R). When compared with the systemic circulation. However, the pulmonary circulation is characterized by much lower pressures and resistances, although blood flow is the same. The reason that pulmonary blood flow can be equal to systemic blood flow is that pulmonary pressures and resistances are proportionately lower than systemic pressures and resistances.

- Diffusion-limited gas exchange: the total amount of gas transported across the alveolar/capillary barrier is limited by the diffusion process. In these cases, as long as the partial pressure gradient for the gas is maintained, diffusion will continue along the length of the capillary. Perfusion-limited gas exchange: the total amount of gas transported across the alveolar/capillary barrier is limited by blood flow (i.e., perfusion) through the pulmonary capillaries. In perfusion-limited exchange, the partial pressure gradient is not maintained, and in this case, the only way to increase the amount of gas transported is by increasing blood flow.

Objective

1. Define hypoxia and list its various physiological and pathological causes
2. Define hypo and hyper-ventilation in terms of arterial PCO2 and PO2.
3. Define cyanosis and its clinical presentation
4. Define ventilation/perfusion (V̩/Q) ratio and its normal values.

Ventilation – perfusion ratio (V/Q)

It is the ratio of alveolar ventilation to pulmonary blood flow per minute.
The main function of this ratio is to determine the state of oxygenation in the body.

- The alveolar ventilation at rest: 4.2 L/min
- The pulmonary blood flow is **equal to right ventricular** output per minute: 5L/min
- V/Q ratio (Normal value):**4.2/5 = 0.84**

❖Average V/Q ratio across the lung is 0.8

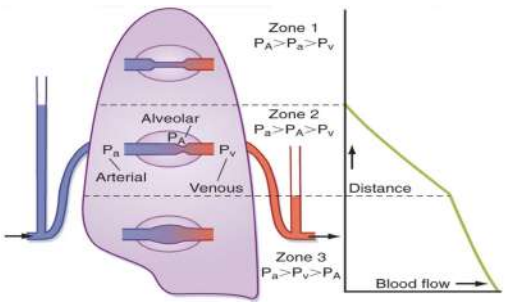
- At the apex V/Q ratio = 3 (moderate degree of physiologic dead space)
- At the base V/Q ratio= 0.6 (represent a physiologic shunt)
- So the **apex is more ventilated <u>than</u> perfused** and the **base is more perfused <u>than</u> ventilated** due to gravity force.
- During exercise the V/Q ratio becomes more homogenous among different parts of the lung.

Increased V/Q Ratio	Decreased V/Q Ratio
Hyperventilation	Hypoventilation
Increased PO2	Decreased PO2
Decreased PCO2	Increased PCO2
PCO2 < 40	PCO2 > 40

Regional Blood Flow and Distribution

Zone 1: Apex	Ventilation is higher than Perfusion. There is more Alveolar Oxygen. because Alveolar pressure is higher than arterial pressure so it compresses the vessels.	Ventilation is higher than Perfusion. There is more Alveolar Oxygen. because Alveolar pressure is higher than arterial pressure so it compresses the vessels.
Zone 2	Ventilation and Perfusion are similar	Ventilation and Perfusion are similar
Zone 3: Base	Ventilation is lower than Perfusion. There is less Alveolar Oxygen. Because Alveolar pressure is less than arterial pressure, so it can't collapse the vessels	Ventilation is lower than Perfusion. There is less Alveolar Oxygen. Because Alveolar pressure is less than arterial pressure, so it can't collapse the vessels

Prone or supine Posture (lying down): In the prone posture, all lung regions are near heart level, so the effect of gravity is much less, and the pulmonary flow is more uniform



Ventilation/perfusion abnormalities

- **Less than normal (physiologic shunt**)
- a certain fraction of the venous blood is passing through the pulmonary capillaries without being oxygenated. i.e shunted blood
- **More than normal (Physiologic dead space)**
- when the ventilation of some of the alveoli is great but the alveolar blood flow is low, ventilation of these alveoli is wasted
- Any mismatch in the ratio can result in **hypoxia.**

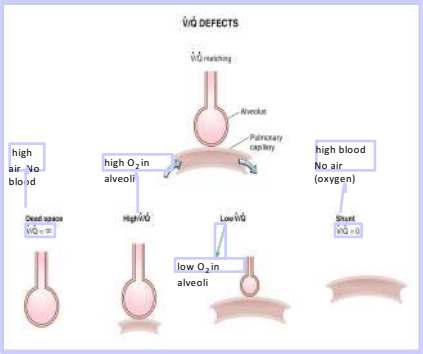
Ventilation/ Perfusion Ratio (V/Q) and V/Q Mismatch by Medicosis Perfectionalis

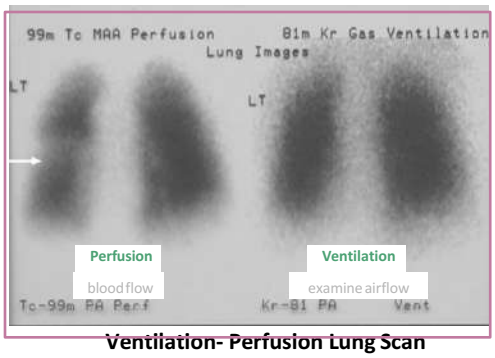
Respiratory System Physiology - Ventilation and Perfusion (V:Q Ratio) Physiology by Armando Hasudungan

V Q mismatch & A-a gradient.mp4 by Michael Thomashow

❖Causes of V/Q Mismatching

- **Causes of non violence uniform ventilation:**
  - Uneven resistance to airflow
  - Collapsed airways (Emphysema)
  - Bronchoconstriction (Asthma)
  - Inflammation (Bronchitis)
- **Non-uniform compliance throughout the lung:**
  - Fibrosis
  - Pulmonary vascular congestion
  - Atelectasis





Ventilation- Perfusion Lung Scan

A ventilation–perfusion (VQ) scan is a nuclear medicine scan that uses radioactive material (radiopharmaceutical)

Dead space:

No gas exchange is possible in dead space, because there is **no blood flow** to receive O_2 from alveolar gas or add CO_2 to alveolar gas.

High V/Q:

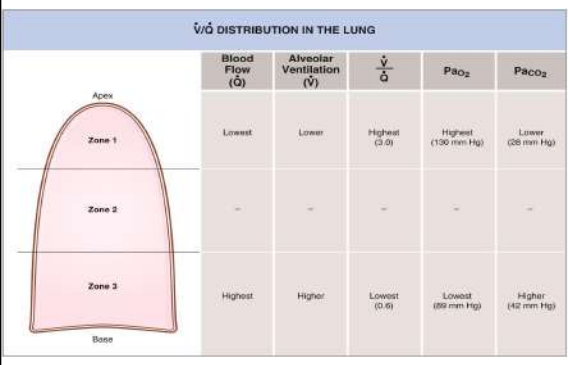
Usually because **blood flow is decreased**. high V/Q regions have some blood flow. Because ventilation is high relative to perfusion, pulmonary capillary blood from these regions has a high PO_2 and a low PCO_2.

Shunt:

Right-to-left shunt is perfusion of lung regions that are **not ventilated**. No gas exchange is possible in regions of shunt, because there is no ventilation to deliver O_2 to the blood or carry away CO_2 from the blood.

Low V/Q:

Usually because **ventilation is decreased**. which has no ventilation, low V/Q regions have some ventilation. Because ventilation is low relative to perfusion, pulmonary capillary blood from these regions has a low PO_2 and high PCO_2.



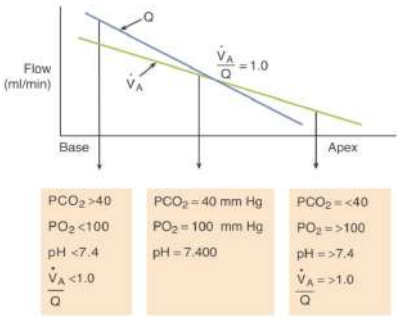


Figure V-4-3. Ventilation–Perfusion Relationships

Types of Hypoxia:

Hypoxia: Is defined as deficiency of oxygen in the tissue cells.

Hypoxic or arterial hypoxia:

Reduced **arterial PO2.**

Causes:

- Alveolar hypoventilation due to central , muscular or neuromuscular causes
- High altitude, reduced compliance, airway resistance, paralysis of respiratory muscles, depressed respiratory center
- Diffusion abnormalities ex: pneumonia ,edema and inflammation
- Seen in conditions like alveolar-capillary block
- Right to left shunt[1]
- Ventilation-perfusion imbalance
- Pulmonary Edema
- Emphysema
- Obstruction

Anemic hypoxia:

Reduction in the oxygen **carrying capacity** of the blood, due to **decreased amount of Hb** or **abnormal type of Hb which is unable to carry oxygen.**
less Hb→ less O2

- The PO2 and % Hb-O2 is normal.

Causes:

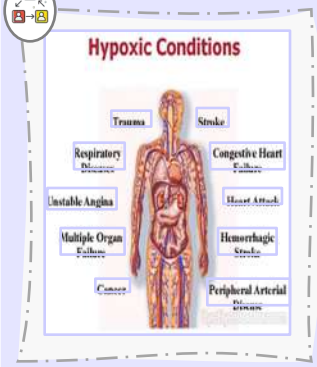
- Anemia
- Abnormal Hb e.g methemoglobin, carboxyhemoglobin, sulfhemoglobin

Note:
Methemoglobin:
If the iron component of the heme moieties is in the ferric, or Fe3+, state (rather than the normal Fe2þ state), it is called methemoglobin. Methemoglobin does not bind to O2.

Note:

right to left shunt:

Shunting of blood from the right heart to the left heart can occur if there is a defect in the wall between the right and left ventricles. In a right-to-left shunt, hypoxemia always occurs because a significant fraction of the cardiac output is not delivered to the lungs for oxygenation and sometimes hypoxia.



Stagnant (hypokinetic/ischemic) hypoxia:

reduced **blood flow** through the tissues, so more and more oxygen is extracted from the blood, and due to slow circulation less oxygen is carried by the blood at the lung , leading to hypoxia.

❖ **Causes:**

- General slowing of the circulation, as in heart failure, shock
- Local slowing e.g vasoconstriction, cold, arterial wall spasm.

Histotoxic hypoxia:

- This is **inability of the tissues to use oxygen** due to inhibition of the oxidative enzyme activity
- This is caused by **inhibition of respiration electron transport chain** in the tissue.
- e.g cyanide poisoning causing blockage of the cytochrome oxidase activity

Effect of Hypoxia:

According to the degree of hypoxia: **(how fast and how severely partial pressure of O2 is decreased)**

1- Fulminant: occurs very rapidly, within seconds.

- Unconsciousness (15-20 seconds)
- Brain tissue death (4-5 minutes)
- Impairment of judgement

2- Acute:

- Slowed body reflexes
- Slurred Speech
- Coma and death may occur
- Inability to perform complex calculations

3- Chronic:

- Fatigue
- Dyspnea
- Cyanosis
- Tachypnea
- Tachycardia
- Headache, nausea, irritability

Treatment:

Is by giving **oxygen therapy** in a tent or high oxygen tension mask. (Only in hypoxia due to the lack of O_2)

This is useful in **hypoxic** hypoxia, but of less value in other types of hypoxia. Histotoxic hypoxia will **not** benefit from O_2 therapy.

Hypercapnia:

Excess of CO_2 in body fluids, it usually occurs with hypoxia, PCO_2 increases above **52 mmHg**, it decreases the PH

→ recall from the 1st lecture: CO_2 always make the medium acidic

Features of hypercapnia

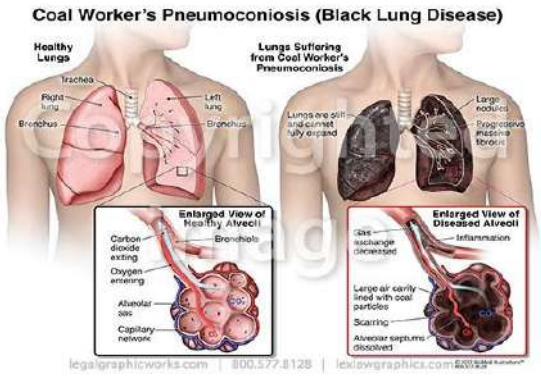
- Peripheral vasodilatation
- Sweating
- Warm extremities and bounding pulse
- Muscle twitching
- Headache, drowsiness and coma
- Papilledema (swelling of optic disc)

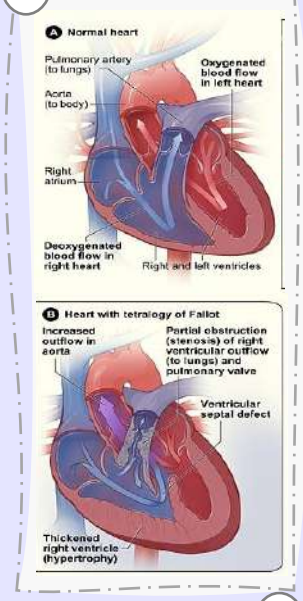
Cyanosis:

- Blue discoloration of the skin and mucous membrane due **to more than 5 g/dl** of reduced (deoxygenated) hemoglobin in blood.
- A person with anemia almost **never** develop cyanosis due to low amount of Hb for 5 grams to be deoxygenated /100ml blood. but can develop it in **polycythemia.**

Causes:

1. Inadequate oxygenation of blood in the lungs
   - High altitude
   - Obstruction of respiratory passages
   - Pneumoconiosis
   - Emphysema
   - CO poisoning
2. Presence of aerated shunt between vessels
   - Coarctation of aorta (aorta is narrow)
   - Fallot's tetralogy (abnormalities in heart)
3. Other
   - Moderate cold
   - Diminished blood flow to tissues





Note:

Raynaud's disease

It is a rare disorder of the blood vessels, usually in the fingers and toes. It causes the blood vessels to narrow when you are cold or feeling stressed. When this happens, blood can't get to the surface of the skin and the affected areas turn white and blue. It may require cervicodorsal preganglionic sympathectomy

Polycythemia vera:

It is a stem cell disorder characterized as a pan hyperplastic, malignant, and neoplastic marrow disorder.

Central cyanosis :

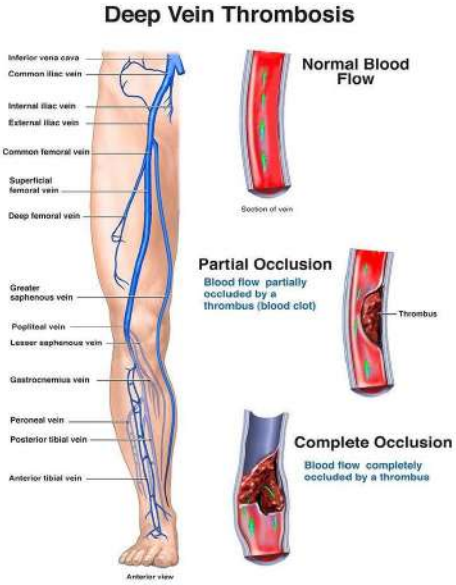
Generalized impairment of circulation. can occur in hypoxic hypoxia.

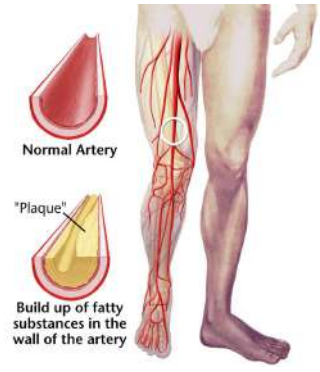
- Cyanotic congenital heart-disease
- Fallot tetralogy[1]
- Tricuspid atresia
- Pulmonary arteriovenous fistula
- Pulmonary diseases
- Acute pulmonary embolism
- Pneumonia
- Chronic Obstructive airway disease
- Restrictive lung disease
- Hemoglobin abnormality

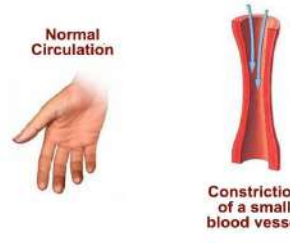
Peripheral cyanosis:

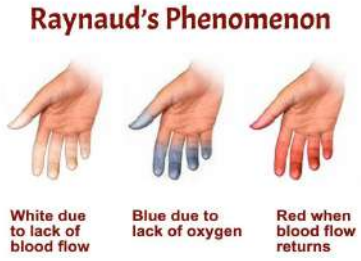
Decreased blood flow through a part of the body

- Reduced cardiac output, as in congestive heart failure
- Mitral stenosis
- Exposure to cold
- Arterial obstruction
- Venous obstruction
- Raynaud's disease
- Polycythemia vera









Chronic Obstructive Lung disease COPD:

- Because of bronchial obstruction in some areas and destruction of the alveolar septa in other areas with patent alveoli those people have some areas of the lung exhibiting serious physiologic shunt and other areas serious physiologic dead space. .(mixed)

- COPD is the most prevalent cause of pulmonary disability today, lung effectiveness as a gas exchange organ may decrease to 10% as in smokers or workers in pollution areas.

Summary

Table 5-6 Causes of Hypoxia

Cause	Mechanism	Pa_{O_2}
↓ Cardiac output	↓ Blood flow	—
Hypoxemia	↓ Pa_{O_2} ↓ O_2 saturation of hemoglobin ↓ O_2 content of blood	↓
Anemia	↓ Hemoglobin concentration ↓ O_2 content of blood	—
Carbon monoxide poisoning	↓ O_2 content of blood Left shift of O_2-hemoglobin curve	—
Cyanide poisoning	↓ O_2 utilization by tissues	—

Control Of Respiration (regulation of breathing) by Armando Hasudungan

The respiratory center | Respiratory system physiology | NCLEX-RN | Khan Academy by khanacademymedicine

Control of Ventilation by Calit2ube

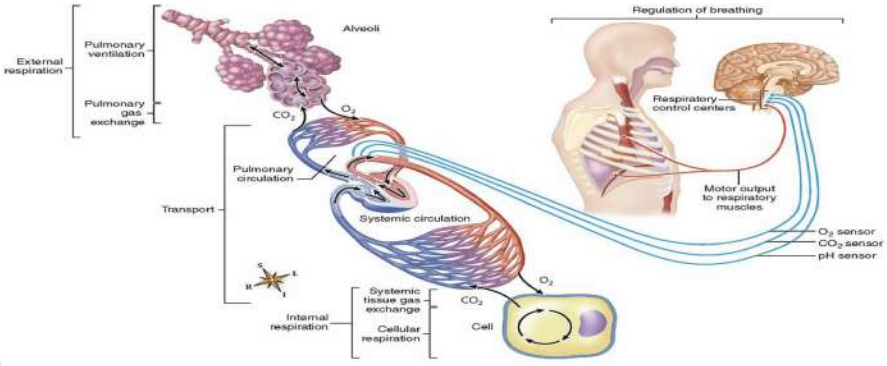
Central chemoreceptors | Respiratory system physiology | NCLEX-RN | Khan Academy by khanacademymedicine

Peripheral chemoreceptors | Respiratory system physiology | NCLEX-RN | Khan Academys by khanacademymedicine

Objective

1. Understand the role of the medulla oblongata in determining the basic pattern of respiratory activity.
2. List some factors that can modify the basic breathing pattern like e.g. a- The Hering-Breuer reflexes, b- The proprioceptor reflexes, c- The protective reflexes, like the irritant, and the J-receptors.
3. Understand the respiratory consequences of changing PO2, PCO2, and PH.
4. Describe the locations and roles of the peripheral and central chemoreceptors.
5. Compare and contrast metabolic and respiratory acidosis and metabolic and respiratory alkalosis.

The overall processes of External Respiration:



All this process is regulated by the respiratory center

Controls of rate and depth of respiration:

Arterial PO2:

When PO2 is VERY low (Hypoxia), ventilation increases.(it will stimulate respiration, but it's not a major player)

"Less sensitive, only major changes in PO2 will cause increase ventilation"

Arterial PCO2:

The most important regulator of ventilation is PCO (very strong stimulus), Small increases in PCO2, greatly increases ventilation.(even a slight increase in co2 means that there's a problem)

➔ Recall CO_2 20 time more soluble than O_2.

Arterial pH:

As hydrogen ions increase (acidosis), alveolar ventilation increases.

- Concentration of H+↑> (acidosis)
- Concentration of H+↓> (alkalosis)
- CO2 + H2O ⇌ H2CO3 ⇌ H+ + HCO3-

Acid/base metabolism in the body is regulated by this chemical equation.

Respiratory centers:

Medullary Respiratory centers

1. Inspiratory area (Dorsal Respiratory Group) DRG:
   - Determines basic rhythm of breathing.
   - Causes contraction of diaphragm and external intercostals.
2. Expiratory area (Ventral Respiratory Group) VRG:
   - Although it contains both inspiratory and expiratory neurons. It is inactive during normal quiet breathing.
   - Activated by inspiratory area **during forceful breathing.**
   - Causes contraction of the internal intercostals and abdominal muscles.

The medullary respiratory center stimulates basic inspiration for about 2 seconds and then basic expiration for about 3 seconds (5 sec/ breath = 12 breaths/min).

Pontine (bridge) Respiratory centers

Transition between inhalation and exhalation is controlled by:

1. Pneumotaxic area:
   - Inhibits inspiratory area of medulla to stop inhalation.
   - Therefore, breathing is more rapid when pneumotaxic area is active. limits the period of inspiration.
2. Apneustic area:
   - Stimulates inspiratory area of medulla to prolong inhalation.
   - Therefore slow respiration and prolonged respiratory cycles will result if it is stimulated.

- If the pneumotaxic became active it will lead to 1-1.5 sec of inspiration (normal=2) and the rate of expiration will increase (faster).
- While Apneustic tries to prolong the inspiration more than normal 2.5-3 sec thus the rate of expiration will be reduced.

Hering-Breuer inflation reflex:

- When the lung becomes overstretched (tidal volume is about 1-1.5L), stretch receptors located in the wall of bronchi and bronchioles transmit signals through vagus nerve to DRG producing effect similar to pneumotaxic center stimulation (because they are overstimulated),
- Switches off inspiratory signals and thus stops further inspiration .
- This reflex also increases the rate of respiration as does the pneumotaxic center.
- This reflex appears to be mainly a protective mechanism for preventing excess lung inflation.

From Guyton:

The respiratory center is composed of several groups of neurons located bilaterally in the medulla oblongata and pons of the brain stem. It is divided into three major collections of neurons:

- A dorsal respiratory group, located in the dorsal portion of the medulla, which mainly causes inspiration.
- A ventral respiratory group, located in the ventrolateral part of the medulla, which mainly causes expiration.
- The pneumotaxic center, located dorsally in the superior portion of the pons, which mainly controls rate and depth of breathing.

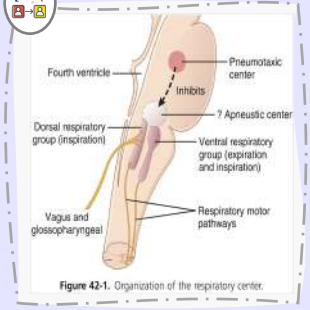
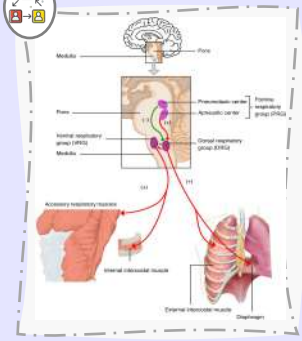


Figure 42-1. Organization of the respiratory center.



Note:

Pneumotaxic center :

The Most important center controlling respiration, because it is the origin of the basic rhythm of inspiration, it is the area that initiate inspiration

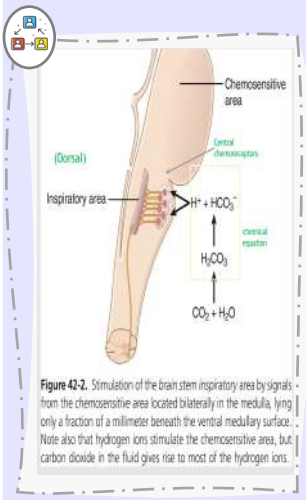


Figure 42-2. Stimulation of the brain stem inspiratory area by signals from the chemosensitive area located bilaterally in the medulla, lying only a fraction of a millimeter beneath the ventral medullary surface. Note also that hydrogen ions stimulate the chemosensitive area, but carbon dioxide in the fluid gives rise to most of the hydrogen ions.

Chemical Control of Respiration

Peripheral and central chemoreceptors

- Peripheral > faster because they are in the blood,but less powerful.
- Central > slower but more powerful.

- Peripheral chemoreceptors could be stimulated by:
  - Decrease PO_2
  - Increase PCO_2
  - Change in H^+ (acidosis)

- O_2 and CO_2 can crosse the BBB and but H^+ cannot.

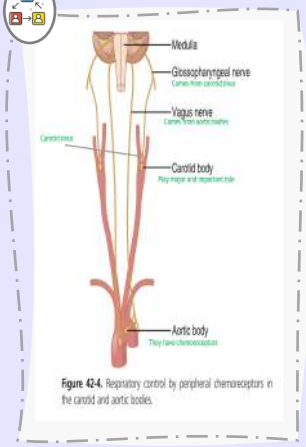


Figure 42-4. Respiratory control by peripheral chemoreceptors in the carotid and aortic bodies.

Why only the peripheral chemoreceptors are detecting hypoxia?

- Due to the position of the peripheral chemoreceptors which are located inside the big blood vessels and their blood supply is 20 times greater than its volume. And It means that the saturation of oxygen inside it is like the arterial blood (PO_2=95 mmHg). Which enables them to detect any decrease in oxygen saturation in arterial blood.
- On the other hand, the central chemoreceptors are surrounded by the interstitial fluid of the brain . And Like any other interstitial fluid in the body, the PO_2 in it is only 40 mmHg. So for this reason, it is unable to detect the changes in the arterial blood PO_2.

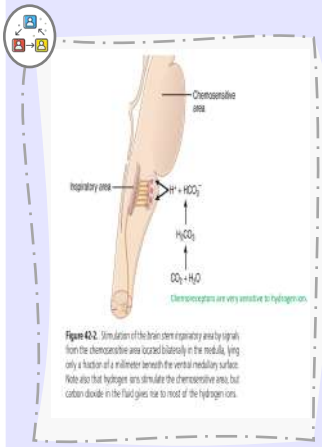
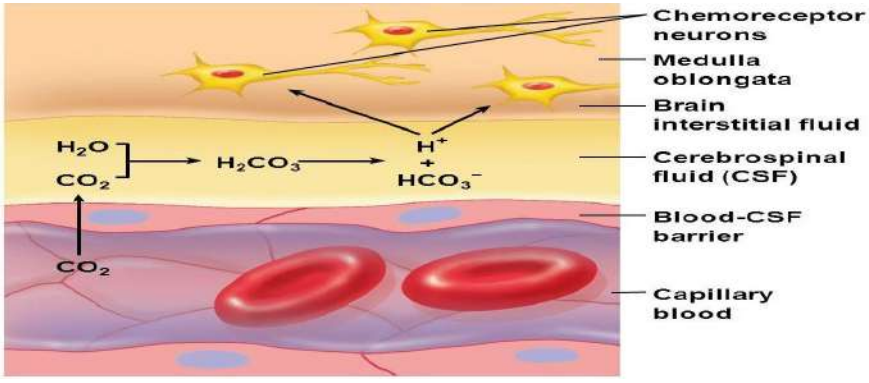


Figure 42-2. Stimulation of the brain stem inspiratory area by signals from the chemosensitive area located bilaterally in the medulla, lying only a fraction of a millimeter beneath the ventral medullary surface. Note also that hydrogen ions stimulate the chemosensitive area, but carbon dioxide in the fluid gives rise to most of the hydrogen ions.

Effect of blood CO2 level on central chemoreceptors:

- Although **carbon dioxide** (can cross BBB) has little direct effect in stimulating the neurons in the chemosensitive area, **it does have a potent indirect effect**. It does this by reacting with the water of the tissues to form carbonic acid, which dissociates into hydrogen and bicarbonate ions; **the hydrogen ions then have a potent direct stimulatory effect on respiration.**



Why does blood carbon dioxide have a more potent effect in stimulating the chemo-sensitive neurons than do blood hydrogen ions?

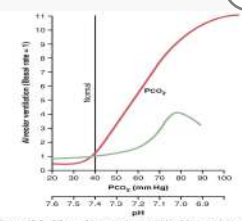
1. The blood - brain barrier is nearly **impermeable** to H^+ ions
2. When the blood PCO_2 **increases**, so does the PCO2 of both the *interstitial fluid of the medulla and the CSF*. (CO_2 passes this barrier very easily) In these fluids, the CO_2 reacts with the water to form new H^+ ions.

Thus, **more H^+ ions are released** into the respiratory chemosensitive sensory area of the medulla when the blood CO_2 concentration increases than when the blood H^+ ion increases. For this reason, respiratory center activity is increased very strongly by changes in blood CO_2, a fact that we subsequently discuss quantitatively.

- Comparing between ↑CO_2 and↑ hydrogen, who's affecting more? **The CO_2**
- why? ↑CO2 in the blood will cause more↑ventilation than increase in blood H+ and that's will NOT affect the CNS (medullary response center) since it does not cross the BBB. On the other hand, CO2 can cross the BBB and it indirectly gives off H+ there from its reaction with H2O (acid/base equation). So, the Cerebrospinal fluid and the interstitial fluid of the medulla the hydrogen ion will stimulate the chemoreceptors directly.
- A change in blood CO_2 concentration has a potent acute effect on controlling respiratory drive but only a weak chronic effect after a few days' adaptation.[3]
- Excitation of the respiratory center by CO_2 is great after the blood CO_2 first increases, but it gradually declines over the next 1 to 2 days.

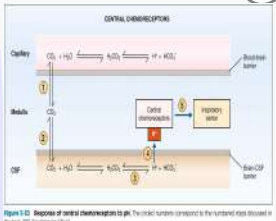
1. Part of this decline results from **renal readjustment** of the H+ ion concentration in the circulating blood back toward normal after the CO_2 first increase.
2. The kidneys increasing the blood HCO_3 , which binds with H^+ ions in the blood and CSF to reduce their concentrations.
3. The HCO_3 ions slowly diffuse through the BBB– CSF barriers and combine directly with the H^+ ions adjacent to the respiratory neurons as well, thus reducing the H^+ ions back to near normal.

From Guyton :



The figure shows quantitatively the approximate effects of blood PCO2 and blood pH (which is an inverse logarithmic measure of hydrogen ion concentration) on alveolar ventilation. Note especially the marked increase in ventilation caused by an increase in PCO2 in the normal range between 35 and 75 mm Hg, which demonstrates the tremendous effect that CO2 changes have in controlling respiration. By contrast, the change in respiration in the normal blood pH range, which is between 7.3 and 7.5, is less than one tenth as great

From Linda :



Commands from the cerebral cortex can temporarily override the automatic brain stem centers. For example, a person can voluntarily hyperventilate (i.e., increase breathing frequency and volume). The consequence of hyperventilation is a decrease in PaCO2, which causes arterial pH to increase. Hyperventilation is self-limiting, however, because the decrease in PaCO2 will produce unconsciousness and the person will revert to a normal breathing pattern. Although more difficult, a person may voluntarily hypoventilate (i.e., breath-holding). Hypoventilation causes a decrease in PaO2 and an increase in PaCO2, both of which are strong drives for ventilation. A period of prior hyperventilation can prolong the duration of breath-holding.

Central and Peripheral Chemoreceptors (CO_2 Detection by Pete Meighan

Peripheral Chemoreceptor System Activity—Role of Oxygen in Respiratory Control

Most of the chemoreceptors are in the **carotid bodies. However, a few are also in the aortic bodies.**

- When the oxygen concentration in the arterial blood falls below normal, the chemoreceptors become strongly stimulated.
- The impulse rate is particularly sensitive to changes in arterial PO2 in the range of 60 down to 30 mm Hg.
- Under these conditions, low arterial PO2 obviously drives the ventilatory process quite strongly.

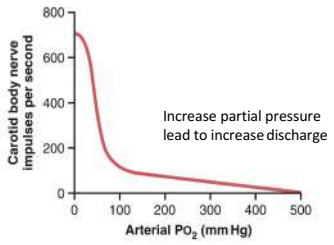


Figure 42-5. Effect of arterial PO_2 on impulse rate from the carotid body.

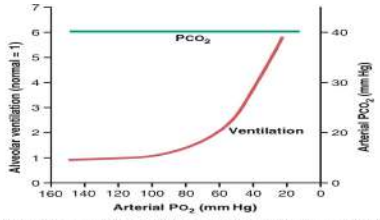
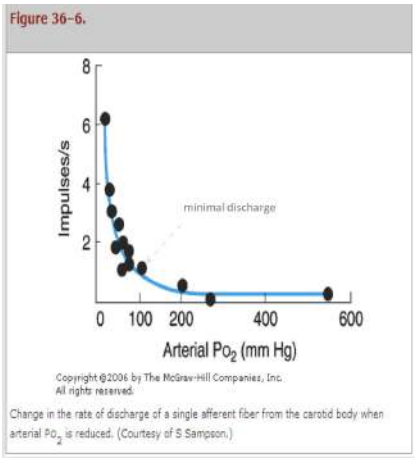


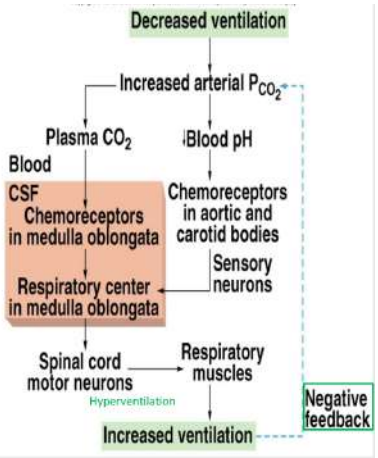
Figure 42-7. The lower curve demonstrates the effect of different levels of arterial PO_2 on alveolar ventilation, showing a sixfold increase in ventilation as the PO_2 decreases from the normal level of 100 mm Hg to 20 mm Hg. The upper line shows that the arterial PCO_2 was kept at a constant level during the measurements of this study; pH also was kept constant.

Effect of Carbon Dioxide and Hydrogen Ion Concentration on Chemoreceptor Activity.

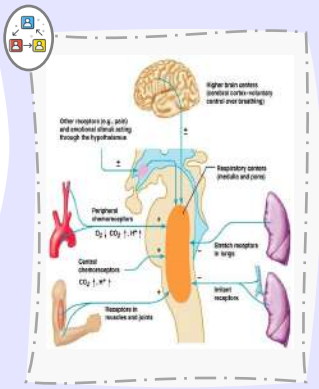
- An increase in either carbon dioxide concentration or hydrogen ion concentration also excites the chemoreceptors and, in this way, indirectly increases respiratory activity.
- There is one difference between the peripheral and central effects of carbon dioxide: the stimulation by way of the peripheral chemoreceptors occurs as much as five times as rapidly as central stimulation, so that the peripheral chemoreceptors might be especially important in increasing the rapidity of response to carbon dioxide at the onset of exercise.

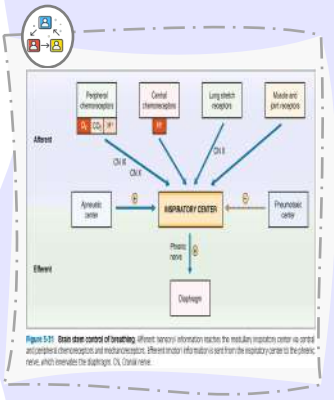
Summary of Chemoreceptor Control of Breathing





Other Factors Influencing Respiration:





Effect of irritant receptors in the airways:

The epithelium of trachea, bronchi and bronchioles is supplied by irritant receptors that are stimulated by irritants that enter the respiratory airways causing coughing, sneezing and bronchoconstriction in bronchial asthma and emphysema.

Function of lung J receptors:

Few receptors in the wall of the alveoli in **juxtaposition** to the pulmonary capillaries. They are stimulated especially when pulmonary capillaries become engorged by blood or when pulmonary edema occur e.g in CHF, their excitation cause the person a feeling of dyspnea.

Respiratory Acidosis	**Respiratory Alkalosis**
Hypoventilation	Hyperventilation
Accumulation of CO2 in the tissues.	Excessive loss of CO_2.
↑ PCO_2	↓PCO_2 (35 mmHg).
↓ pH (Normal= 7.3)	↑ pH
Metabolic Acidosis	**Metabolic Alkalosis**
Ingestion, infusion or Production of a fixed acid.	excessive loss of fixed acids from the body.
↓renal excretion of hydrogen ion.	Ingestion, infusion or excessive renal reabsorption of bases such as HCO_3.
Loss of HCO_3 or other bases from the EC compartment.	↑ pH
Metabolic disorder as diabetic ketoacidosis.	
Utilize more fat —> the byproduct is acid.	

Difference between respiratory acidosis VS metabolic acidosis:

- **Respiratory Acidosis:** occurs when the lungs fail to remove excess carbon dioxide from the bloodstream during the process of respiration.
- **Metabolic Acidosis:** occurs when the digestive and urinary systems fail to breakdown and maintain the proper level of acids in the blood.

The respiratory system can compensate for metabolic acidosis or alkalosis by altering alveolar ventilation.

Control of breathing

Central Chemoreceptors

- Central receptors are located in the central nervous system—more specifically, close to the surface of the medulla. Stimulation of central chemoreceptors increases ventilation.
- The receptors directly monitor and are stimulated by cerebrospinal fluid [H^+] and CO_2. The stimulatory effect of increased CO_2 may be due to the local production of H^+ from CO_2.
- Because the blood–brain barrier is freely permeable to CO2, the activity of these receptors changes with increased or decreased systemic arterial PCO_2.
- H+ does not easily penetrate the blood-brain barrier. Thus, an acute rise in arterial H^+, not of CO_2 origin, does not stimulate central chemoreceptors.
- These receptors are very sensitive and represent the main drive for ventilation under normal resting conditions at sea level.
- Therefore, the main drive for ventilation is CO_2 (H^+) on the central chemoreceptors.

The relationship between the central chemoreceptors and systemic arterial blood can be seen below.

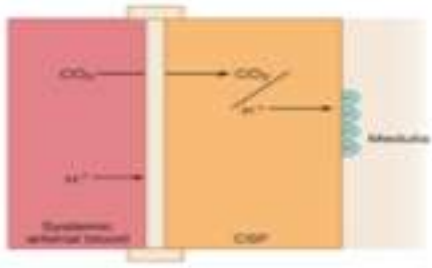


Figure V-3-E. Central Chemoreceptors

- The system does adapt, usually v[illegible]laptation may be the normalization of CSF H^+ by the pumping of HCO_3^- into or out of the CSF.
- There are no central PO_2 receptors.

Peripheral Chemoreceptors

Peripheral receptors are found within small bodies at 2 locations:

1. **Carotid bodies**: near carotid sinus, afferents to CNS in glossopharyngeal nerve IX
2. **Aortic bodies:** near aortic arch, afferents to CNS in vagus nerve X

The peripheral chemoreceptors are bathed in arterial blood, which they monitor directly. These bodies have 2 different receptors:

1. **H+/CO2 receptors**
    - These receptors are less sensitive than the central chemoreceptors ,but they still contribute the normal drive for ventilation.
    - Therefore, under normal resting conditions at sea level, for all practical purposes, the total drive for ventilation is CO_2, mainly via the central chemoreceptors but with a small contribution via the peripheral chemoreceptors.
2. **PO2 receptors**
    - The factor monitored by these receptors is PO_2, not oxygen content.
    - Because they respond to PO_2, they are actually monitoring dissolved oxygen and not oxygen on Hb.
    - When systemic arterial PO_2 is close to normal (≅100 mm Hg) or above normal, there is little any stimulation of these receptors.

KAPLAN CORNER

- They are strongly stimulated only by a dramatic decrease in systemic arterial PO_2.
- Sensitivity to hypoxia increases with CO_2 retention.
- These receptors do not adapt.

Bridge to Pathology/ Pharmacology
The normal CO_2 drive to breathe is suppressed in COPD patients, and by narcotics and general anesthetics.

Clinical Correlate
Although oxygen content is reduced in anemia, the PaO_2 is normal; thus, anemia does not directly stimulate ventilation. However, the reduced oxygen delivery can cause excess lactic acid production, which would in turn stimulate peripheral chemoreceptors.

Central Respiratory Centers

Medullary centers

- Site of the inherent rhythm for respiration.
- Inspiratory center
- Expiratory center
- For spontaneous breathing, an intact medulla must be connected to the diaphragm (via the phrenic nerve). Thus a complete C1 or C2 lesion will prevent diaphragmatic breathing but not a complete C6 or lower lesion.
- The main features involved in the central control of ventilation are seen below.

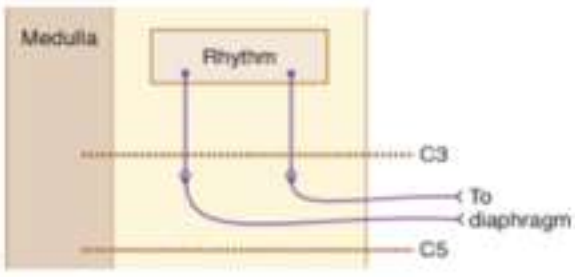


Figure V-3-9. CNS Respiratory Centers

Abnormal Breathing Patterns

- **Apneustic breathing** is prolonged inspirations alternating with a short period of expiration. This pattern is attributed to the loss of the normal balance be-tween vagal input and the pons-medullary interactions. Lesions in these patients are usually found in the caudal pons.
- **Cheyne-Stokes** breathing is periodic type of breathing which has cycles of gradually increasing depth and frequency followed by a gradual decrease in depth and frequency between periods of apnea. It may result from midbrain lesions or congestive heart failure.

KAPLAN CORNER

Objective

1. Describe the globular proteins using common examples ➔Hemoglobin & myoglobin.
2. Study the structure and functions of globular proteins:
   - Hemoglobin (a major globular protein)
   - Myoglobin
   - γ-globulins (immunoglobulins)
3. Know the different types of hemoglobin and difference between normal and abnormal hemoglobin
4. Understand the diseases associated with globular proteins

Types of proteins

Note:
Globin: proteins with functions related to oxygen (transport/storage..etc..)
Globulin: proteins with functions not related to oxygen.

Soluble (globular):

Solubility is due to :

- type of folding that resembles sphere shape
- Polar groups on the protein's surface
- Hydrophobic groups in the interior.

Non soluble (fibrous)

Hemoglobin and Hemoglobinopathies) by Daf189

Oxygen Transport by sheekshampoo

USMLE DIFFERENT TYPES OF HEMOGLOBIN by 100lyric

Type of Globular proteins

Types	Function
Hemoglobin	O_2 transport All over the body
Myoglobin	O_2 storage/supply only in heart and muscle
α1, α2, β-globulins	various functions
γ-globulins (immunoglobulins)	immune function
Enzymes	catalysis of biochemical reactions

Hemoglobin

Functions:

1- Carries O2 from lungs to tissues. 2- Carries CO2 from tissues to lungs.

Normal level (g/dL):

- Males:14-16, while in Females:13-15.

Abnormal Form of hemoglobin :

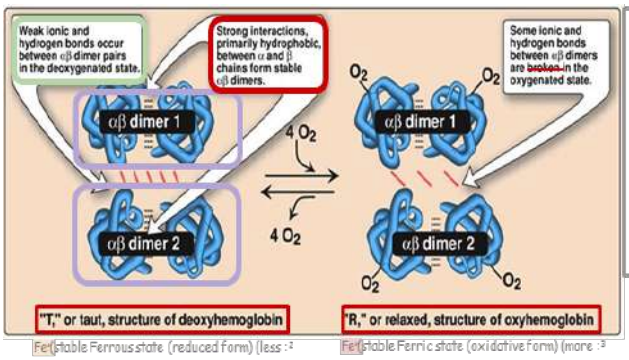
- Carboxy Hb (bound to CO)
- Met Hb
- Sulfa Hb

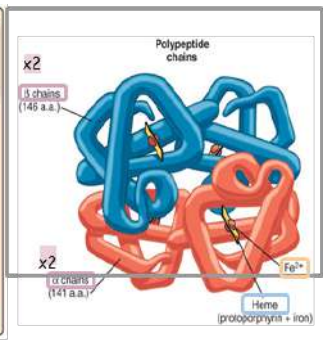
Normal Form of hemoglobin

- HbA (97%) "most abundant
- HbA2 (2%)
- HbF (1%)
- HbA1c

Hemoglobin (HbA)structure

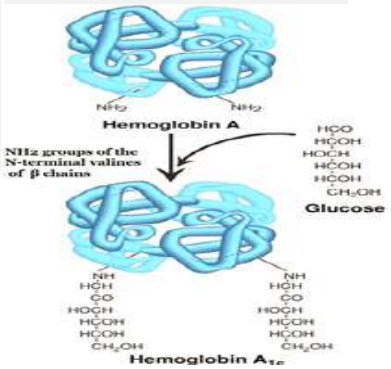
- 4 polypeptide chains
- 2 dimers of ab subunits
- Held together by non-covalent interactions
- Contains 4 heme groups and carries 4 molecules of O2
- 4x2 = 8 Oxygen atoms





Hemoglobin | Human anatomy and physiology | Health & Medicine | Khan Academy by Khan Academy

Types of Hemoglobin

	(HbF) Fetal Hemoglobin	HbA_2	HbA_{1C}
characteristics	Major hemoglobin found in the **fetus** and newborn.	Appears shortly before birth (~8th month)	HbA undergoes non enzymatic **glycosylation**.
Importance	Transfers O_2 from maternal to fetal circulation across placenta. * Due to: Higher affinity for O2 than HbA	Constitutes ~2% of total Hb.	HbA_{1C} levels are high in patients with diabetes Mellitus * Due to: Glycosylation (depends on plasma glucose levels)
Structure	●2 α chains ●2 γ chains.	●2 α chains ●2 δ chains.	

Abnormal Hemoglobins:

When Hemoglobin is Unable to transport O2 due to abnormal structure.

Carboxy-Hb:

CO replaces O2 and binds 200X tighter than O2 (in smokers & heat devices)

Note:
- **Hemoglobin bound to CO2 is called carbaminohemoglobin.**
- **Hemoglobin bound to CO is called** carboxyhemoglobin oxygen

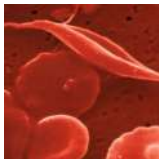
Met-Hb:

Contains oxidized Fe3+ (~2%) that cannot carry O2. The Ferroxidases is the enzyme responsible for oxidation of Fe2+.

Sulfa-HB:

Forms due to high sulfur levels in blood (irreversible reaction), and Can't be reversed by increasing O2 levels

Hemoglobinopathies:



They are disorders of hemoglobin caused by:
- Synthesis of structurally abnormal Hb
- Synthesis of insufficient quantities of normal Hb
- Combination of both

Synthesis of structurally abnormal hemoglobin :

- The best example for that is hemolytic anemia such as sickle cell disease (SCD) is caused by a single base mutation in β-globin gene, producing a single amino acid substitution at position 6 of the β chain of Hb, which will lead to change from **glutamic acid** to **valine** thus forming HbS rather than the normal HbA. The shape of RBCs become sickled.
- HbC is a mild form and Caused by single mutation in β-globin gene. which will lead to change from glutamic to lysine at position 6 of the β chain of Hb

Note:
- α chains are coded by 2 genes absence mild anemia β chains are coded by 1 gene

Synthesis of insufficient quantities of normal hemoglobin

- α-Thalassemia (Mild): Caused by gene mutation Decreased synthesis of α chains
- β-Thalassemia (Severe):Caused by gene mutation Decreased synthesis of β chains Needs regular blood transfusion.

Extra Explanation:
- Methemoglobinemia (MetHb) is a blood disorder in which an abnormal amount of methemoglobin is produced. Methemoglobin is a form of hemoglobin.
- With methemoglobinemia, the hemoglobin can carry oxygen, but is not able to release it effectively to body tissues.

Methemoglobinemia;

- Caused by oxidation of Hb from Fe+2 to ferric (Fe3+) state
- Methemoglobin cannot bind O2
- Patient may present with Chocolate cyanosis which is brownish-blue color of the skin and blood.
- Caused by:

Note:
- An enzyme convert ferric (Fe+3) to ferrous (Fe+2)

- NADH-cytochrome b5 reductase deficiency
- Certain drugs
- Reactive oxygen species

Myoglobin

A globular hemeprotein in heart and skeletal muscle

Structure:

Contains a single polypeptide chain forming a single subunit with eight a-helix structures. it is composed of :

- Charged amino acids -> on the surface of the subunit.
- Nonpolar amino acids -> The interior of the subunit

Function:

- Store and supply oxygen (especially during aerobic exercise.)
- Gives red color to skeletal muscles.

Myoglobin - Structure and Function by 5MinuteSchool

Myoglobin in disease

Myoglobinuria:

- Myoglobin is excreted in urine due to muscle damage (rhabdomyolysis).
- May cause acute renal failure.
- Specific marker for muscle injury
- Less specific marker for heart attack

Note:

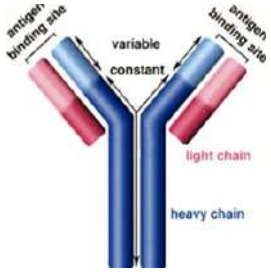
- **Antigens are small "can't be detected by macrophages" -> immunoglobulins neutralize them**
- **-> can be detected by macrophages**

Immunoglobulins

- Defensive proteins produced by the B-cells of the immune system

Function: Neutralize bacteria and viruses

Structure: Y-shaped structure with:2 heavy and 2 light polypeptide chains

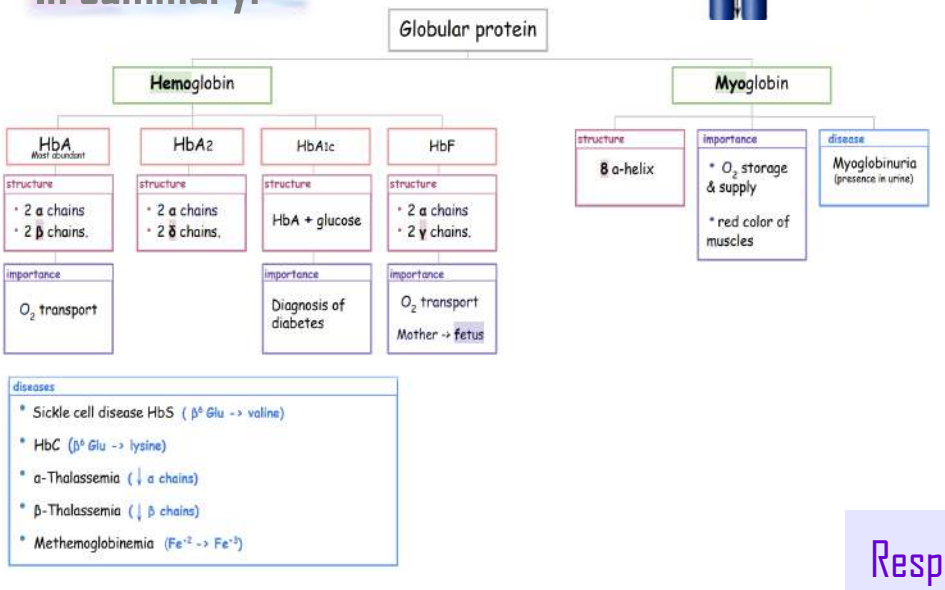


Types:

- IgM
- IgA
- IgG
- IgE
- IgD

Video 15 Ig Antibodies and Immunoglobulin Function by John Thomasl

In summary:



Take home massage

- Amino acid chains fold into shapes that resemble spheres are called globular proteins.
- Fibrous proteins are mainly insoluble, while globular proteins are soluble structural proteins. Hb, Myoglobin, globulines and enzymes are examples of globular proteins.
- Functionally, Hb is for O2 and CO2 transport.
- HbA, HbA2 and HbF are examples of normal Hb, in which the tetrameric structure is composed of 2α constant subunits with 2 changeable β subunits according to Hb type.
- HbA1C is a HbA which undergoes non-enzymatic glycosylation, depending on plasma glucose levels.
- Carboxy-Hb, Met-Hb and Sulf-Hb are examples of abnormal Hb, in which O2 molecules are not transported due to abnormal Hb structure.
- Disorders of Hb caused by synthesis of structurally abnormal Hb and/or insufficient quantities of normal Hb.
- Sickle cell (HbS) and HbC diseases are caused by a single mutation in β-globin gene.
- Glu6 in HbS is replaced by Val, while it is replaced by Lys in HbC.
- Methemoglobinemia is caused by oxidation of Hb, inhibiting O2 binding leading to chocolate cyanosis.
- Thalassemia is caused by a defect in synthesis of either α- or β-globulin chain, as a result of gene mutation.
- α-Thalassemia causes less severe anemia than β-Thalassemia.
- Myoglobin is a globular heme protein, which stores and supplies O2 to the heart and muscle only
- Hb is composed of 4 chains (subunits), while Myoglobin is composed of a single chain.
- Myoglobinuria is a specific marker for muscle injury and may cause acute renal failure.
- Immunoglobulins are defensive proteins produced by the B-cells.
- Immunoglobulins consist of 5 types: IgA, IgD, IgE, IgG and IgM

SECTION 2 :

UPPER RESPIRATORY TRACT

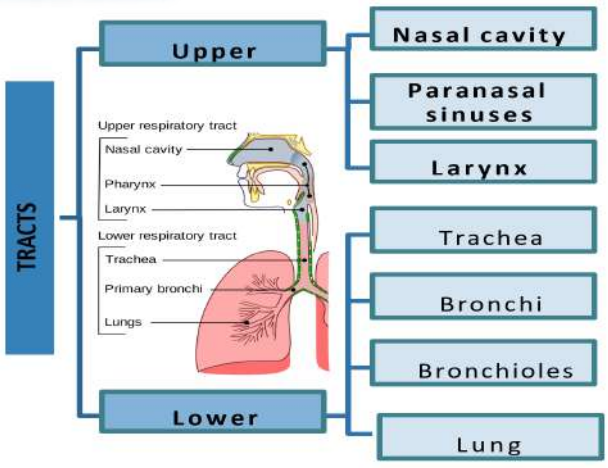
Objective 1

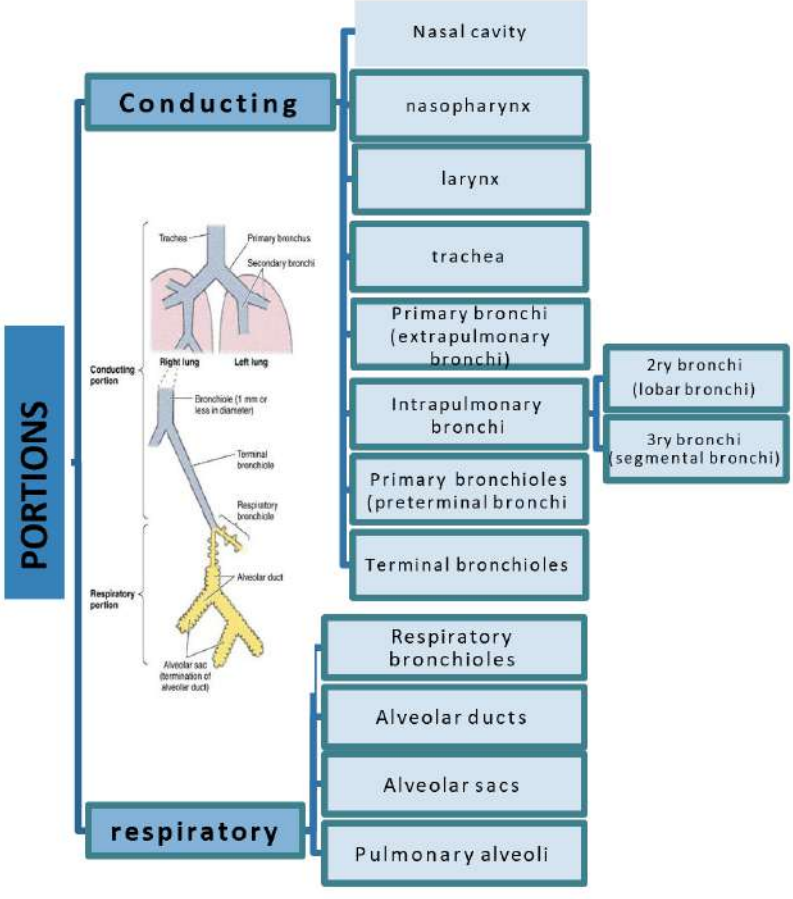
- Describe The microscopic structures of:
  - Vestibule of the nasal cavity.
  - Respiratory mucosa of the nasal cavity.
  - Nasal septum.
  - Olfactory mucosa of the nasal cavity.
  - Mucosa of the paranasal sinuses.
  - Pharynx: with special emphasis on Nasopharynx.
  - Larynx.

Introduction:

nose and larynx
by Brendan Wilkins

Shotgun Histology Nasal Cavit
by WashingtonDeceit





Nasal cavity

- Anterior portion of N.C. : Vestibule.
- Posterior portion of N.C. : Respiratory region & Olfactory region.

The nasal septum divides the nasal cavity into two halves (right and left).

Vestibule

- Lining:
  - is lined with thin skin.
    - Epidermis: (Keratinized stratified Squamous epithelium).
    - Dermis
- Contents:
  - Vibrissae: stiff hairs
  - Sebaceous glands
  - Sweat glands
- Wall:
  - Hyaline cartilage
  - Cancellous (spongy) bone

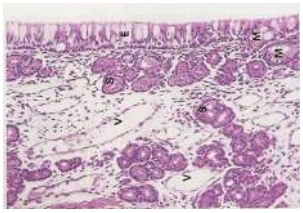
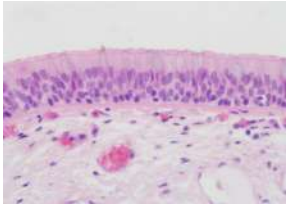
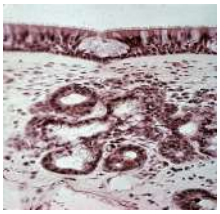
Note:
Sebaceous glands
secrete an oily or waxy matter called sebum

Respiratory region (area) of nasal cavity

- mucosa (mucous membrane):
  - Respiratory Epithelium: Pseudostratified ciliated columnar epithelium with goblet cells.
- Main Types of cells (all touch the basement membrane):
  - 1- Ciliated columnar cells.
  - 2- Goblet cells.
  - 3- Basal cells: are stem cells.
  - 4- DNES cells secret hormones e.g. serotonin.

Note:
DNES =
diffuse neuroendocrine system.

- Lamina propria (Sub-epithelial C.T.):
  - 1- Large arterial plexuses & venous sinuses (Highly vascularized C.T.)
  - 2- Many seromucous glands (acini).
  - 3- Abundant lymphoid elements: Including occasional lymphoid nodules, plasma cells & mast cells.

olfactory region (area) of nasal cavity:

olfactory mucosa :

- **site:**

1-roof of nasal cavity.

2-upper part of nasal septum.

3-over superior concha.

clinical Correlate :
sinusitis is an inflammation swelling of the tissue lining the sinuses. healthy sinuses are filled with air. but when they become blocked and filled with fluid, germs can grow and cause an infection.

Olfactory epithelium:

pseudo-stratified columnar epithelium (without goblet cell)

1- olfactory cells (olfactory nerve cells):

- bipolar neurons
- Dendrite has olfactory vesicle that has nonmotile cilia
- Axons are unmyelinated with Schwann-like cells
- Axons will collect in the lamina propria to form bundles of nerve fibers
- Bundles will collect to form the olfactory nerve

2- sustentacular (supporting) cells: are columnar cells

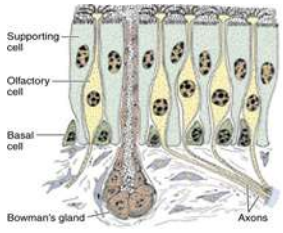
- Function: Physical support and nourishment for olfactory cells

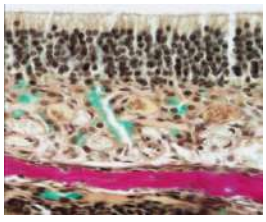
3- basal cells: pyramidal in shape, basal in position and act as stem cells

Lamina propria: Highly (richly) vascularized loose C.T.

Contents:

- Bowman's glands (olfactory glands): are serous acini
- Bundles of unmyelinated nerve fibers: are axons of olfactory nerve cells + Schwann-like cells (glial cells)
- Rich vascular plexus
- Numerous lymphoid elements





paranasal sinuses

lining (mucosa):

- **1- Respiratory epithelium** (Pseudo-stratified ciliated columnar epithelium with goblet cells.)
- **2- Lamina propria.**

Larynx

Mucosa (Mucous membrane):

- Epithelium:

1- Respiratory epithelium: Pseudostratified ciliated columnar epithelium with goblet cells.

2-Non keratinized stratified squamous epithelium

In:

Vocal folds.

- Superior surface of epiglottis
- Lamina propria:

There are 2 pairs of shelf-like mucosal folds:

- 1-Vestibular folds: Are immovable.

L/M: a- Respiratory epithelium.

b- Lamina propria: Loose C.T. with seromucous glands lymphoid elements & adipose cells.

- 2-Vocal folds (cords): have:

Epithelium: non keratinized stratified squamous.

Lamina propria :C.T. containing bundles of elastic fibers and skeletal muscle .

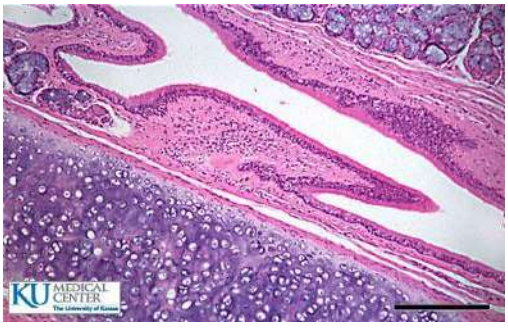
No lymphoid nodules, No seromucous glands.

- Cartilages[1]:

1- Hyaline cartilages: e.g. Thyroid cartilage.

2- Elastic cartilages: e.g. Epiglottis.

- Extrinsic and intrinsic muscles: all are skeletal.
- Ligaments.



Note:
All the cartilages are hyaline expect epiglottis is elastic

Objective

1. Describe the boundaries of the nasal cavity.
2. Describe the nasal conchae and meati.
3. Demonstrate the openings in each meatus.
4. Describe the paranasal sinuses and their functions.
5. Describe the pharynx and its parts.

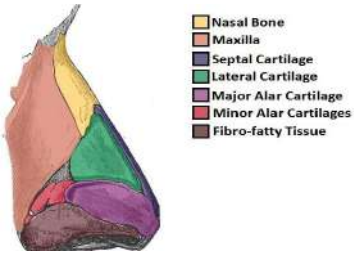
Respiratory System Introduction - Part 1 (Nose to Bronchi) - 3D Anatomy Tutorial by AnatomyZone

Half-Head Model - Nasal Cavity by drbobrd

Nasal Cavity

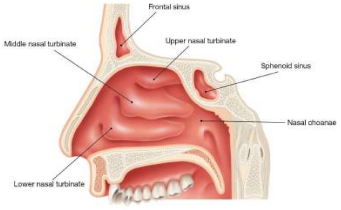
The nose : external (anterior) nares or nostrils, lead to the nasal cavity which formed

- Above by : Bony skeleton.
- Below by: plates of hyaline cartilage.



- **Nasal cavity :**

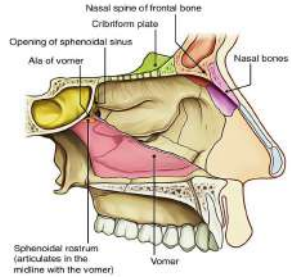
Extends from the external (anterior) nares to the posterior nares (choanae). And can be divided into right & left halves by the nasal septum.



The ROOF of Nasal Cavity:

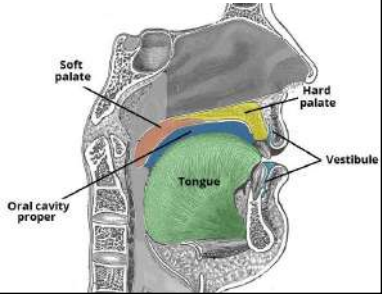
Narrow & formed (from behind forward) by the:

- Body of sphenoid.
- Cribriform plate of ethmoid bone.
- Frontal bone.
- Nasal bone & cartilage.



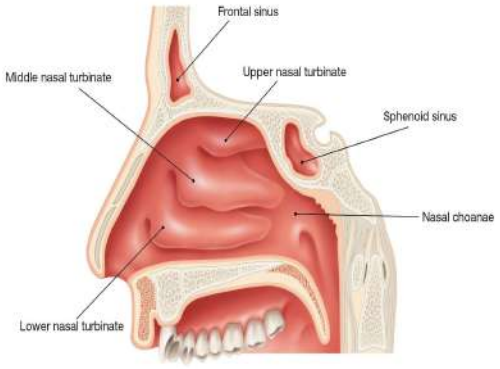
The FLOOR of Nasal Cavity:

Separates it from the oral cavity and formed by the hard (bony) palate.



The LATERAL of Nasal Cavity:

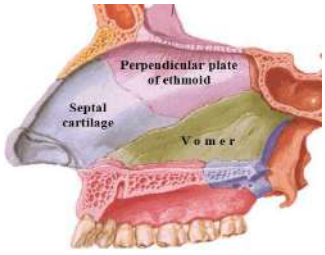
- Shows three horizontal bony projections, the superior, middle & inferior conchae.
- The cavity below each concha is called a meatus and its named corresponding to the conchae.
- The small space above the superior concha is the sphenoethmoidal recess.
- The conchae increase the surface area of the nasal cavity.
- The recess & meati receive the openings of the: Paranasal sinuses & Nasolacrimal duct.



The MEDIAL of Nasal cavity (Nasal Septum):

Osteo-cartilaginous partition Formed by:

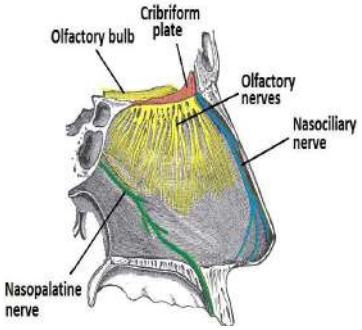
- Perpendicular plate of ethmoid bone.
- Vomer.
- Septal cartilage.

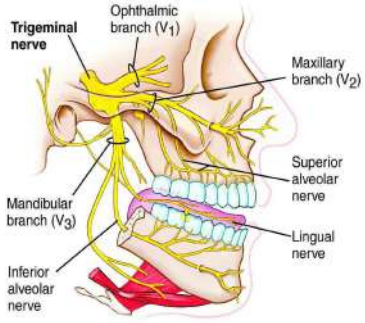


Nerve supply:

- Olfactory mucosa is supplied by olfactory nerves.
- Nerves of general sensation are derived from:

- Ophthalmic nerves
- Maxillary nerves
- Autonomic fibers



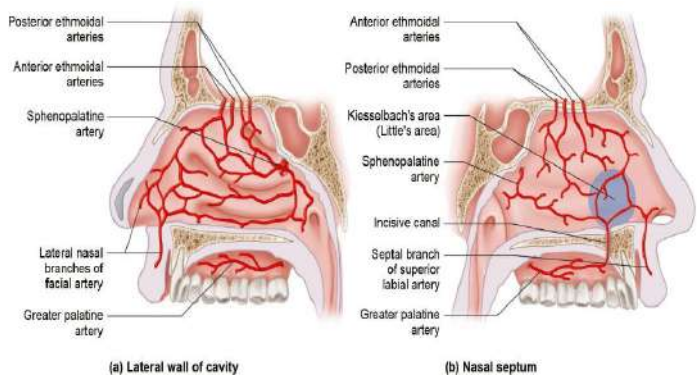


Arterial Supply:

- Branches of the: **maxillary**, **facial** & **ophthalmic** arteries.
- The arteries make a rich anastomosis in the region of the vestibule & the anterior portion of the septum.

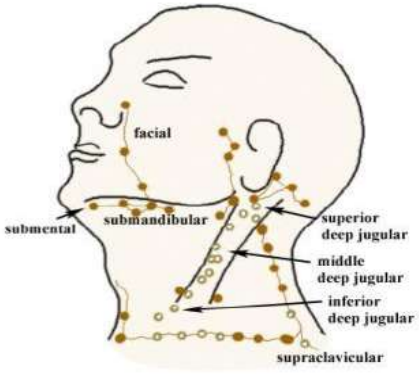
Venous Drainage:

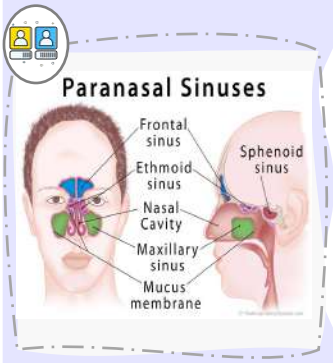
- Drain into the: **facial**, **ophthalmic**, and **spheno-palatine** veins.



Lymphatic Drainage :

- The lymphatics from the vestibule drain into: the submandibular lymph nodes.
- The rest of the cavity drains into the upper deep cervical lymph nodes.





Paranasal Sinuses

What are they ?

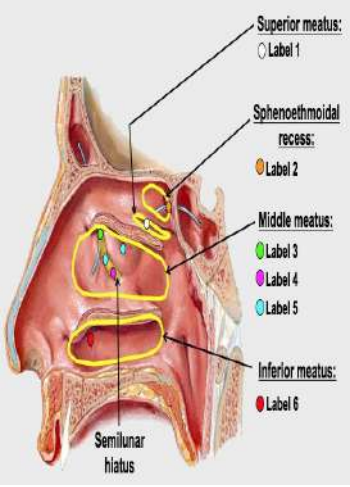
- They are air filled cavities located in the bones around the nasal cavity.
- There are four paired sinuses, named according to the bone in which they are located; Ethmoid, Sphenoid, Frontal and Maxillae.
- They are lined by respiratory mucosa which is continuous with the mucosa of the nasal cavity, and it drains into the nasal cavity.

Functions:

- Lighten the skull
- Act as resonance chambers for speech.
- Air conditioning: The respiratory mucosal lining helps in warming, cleaning and moistening the incoming air.

The drainage :

Drainage in Nasal Cavity	Sinuses and Duct
Sphenoethmoidal recess	sphenoidal sinus
Superior meatus	posterior ethmoidal sinus
Middle meatus	The Maxillary sinuses The Frontal sinuses The anterior ethmoidal sinuses The middle ethmoidal sinuses
Inferior meatus	nasolacrimal duct



Note :
In Summery all sinuses drain into middle meatus EXCEPT :

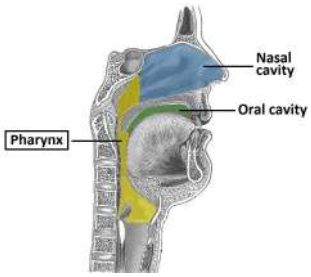
- sphenoidal sinus into Sphenoethmoidal recess
- posterior ethmoidal sinus Into Superior meatus

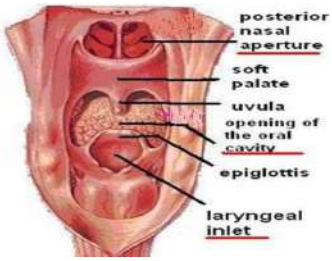
Pharynx

Introduction:

- Muscular tube lying behind the nose, oral cavity and larynx.
- Extends from the base of the skull to level of the 6th cervical vertebra, where it is continuous with the esophagus.
- The deficient of the anterior wall shows the following (from above downward):

1- Posterior nasal apertures.
2- Opening of the oral cavity.
3- Laryngeal inlet.



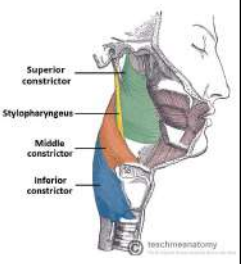


Half-Head Model – Pharynx by drbobrd

Muscles arrangement of the pharynx :

A- Circular muscles :

- Muscles: The three muscles overlap each other



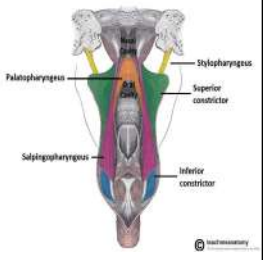
1- Superior constrictor
2- Middle constrictor
3- Inferior constrictor

- Function:

- Propel the bolus of food down into the esophagus. (swallow)
- Lower fibers of the inferior constrictor (Cricopharyngeal) act as a sphincter, preventing the entry of air into the esophagus between the acts of swallowing.

B- Longitudinal muscles:

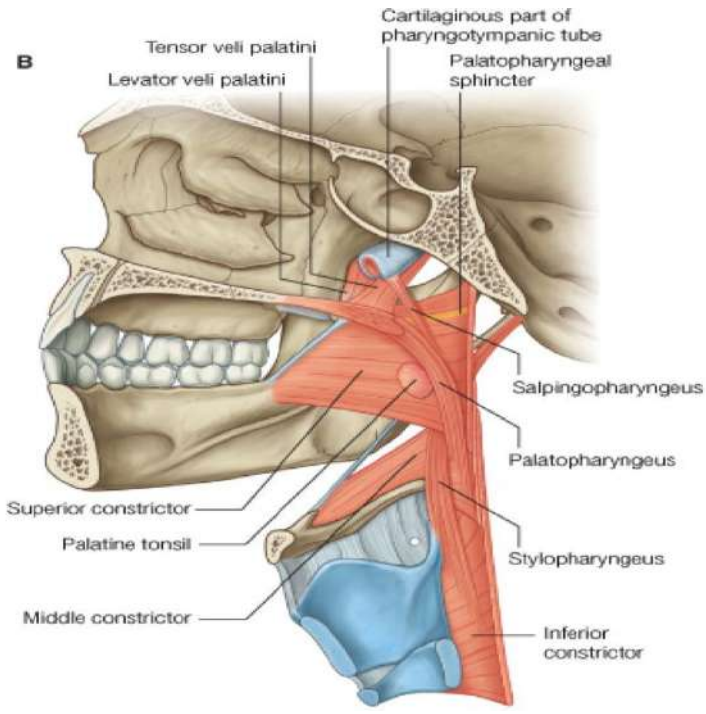
- Muscles:



1- Stylopharyngeus
2- Salpingopharyngeus

- Function:

- Elevate the larynx and pharynx during swallowing.



Nasopharynx:

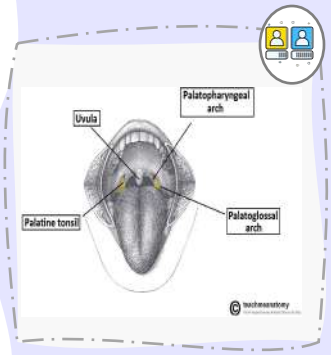
- Extends from the base of the skull to the soft palate.
- Communicates with the nasal cavity through posterior nasal apertures.
- Pharyngeal tonsils (Adenoides) present in the submucosa covering the Roof.
- Lateral wall:

1- Opening of auditory tube with middle ear .
2- Tubal elevation (produced by posterior margins of the auditory tube).
3- Tubal tonsil.
4- Pharyngeal recess.
5- Salpingopharyngeal fold (raised by salpingo-pharyngeus muscle).

Oropharynx:

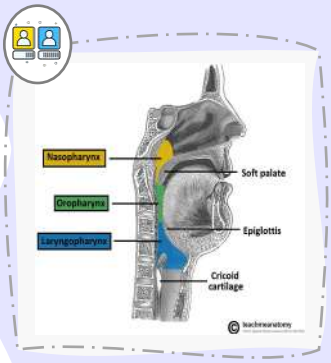
- Extends from soft palate to upper border of epiglottis.
- It lies behind the mouth (tongue).
- Communicates with the oral cavity through the oropharyngeal isthmus.
- Lateral wall:

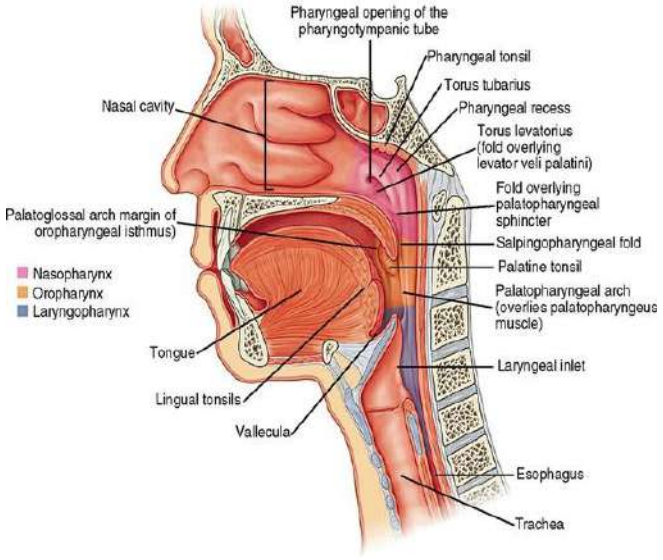
1- Palatopharyngeal fold. (Posterior)
2- Palatoglossal fold. (Anterior)
3- Palatine tonsil. Located between them in a depression is the tonsillar fossa.



Laryngopharynx :

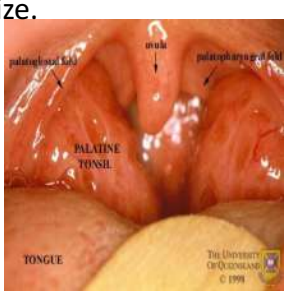
- Extends from upper border of epiglottis to lower border of cricoid cartilage
- It lies behind the laryngeal inlet and the posterior surface of larynx.
- Communicates with larynx through the laryngeal inlet.
- A small depression situated on either side of the laryngeal inlet is called Piriform Fossa.
- It is a common site for the lodging of foreign bodies.
- Branches of internal laryngeal and recurrent laryngeal nerves lie deep to the mucous membrane of the fossa and are vulnerable to injury during removal of a foreign body.





Palatine tonsil

It is Two masses of lymphoid tissue located in the lateral wall of the oropharynx in the tonsillar fossa. Each one is covered by mucous membrane and laterally by fibrous tissue (capsule). It reaches a maximum size during childhood, after puberty it diminishes in size.



- Color: black text1
- Size: 14
- Type : Calibri (Body)

Nerve supply:

- **Sensory**:

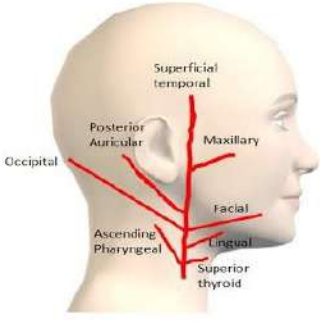
1- Nasopharynx: Maxillary nerve.
2- Oropharynx: Glossopharyngeal nerve.
3- Laryngopharynx: Vagus nerve.

- **Motor**:

All the muscles of pharynx are supplied by the pharyngeal plexus. Except for: the Stylopharyngeus which is supplied by the glossopharyngeal nerve.

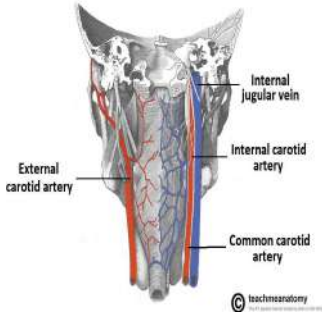
Arterial Supply:

1- Ascending pharyngeal.
2- Ascending palatine.
3- Facial.
4- Maxillary.
5- Lingual.



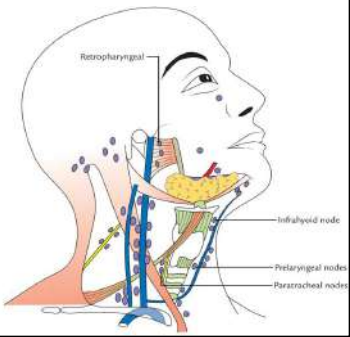
Venous supply:

- Pharyngeal venous plexus, which drains into the internal jugular vein.



Lymphatic Drainage:

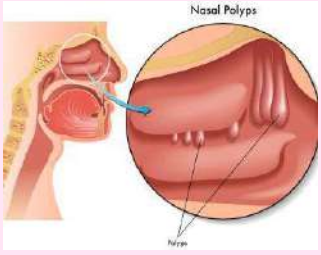
- Deep Cervical lymph nodes (either directly or indirectly) via the retropharyngeal or Paratracheal lymph nodes.



Differentiate angiofibroma and nasopharyngeal carcinoma.

	Angiofibroma	Nasopharyngeal carcinoma
Defnition	Benign tumor of nasal mucosa made up of large blood vessels and fibrous tissue	Malignant tumor of nasopharyngeal epithelium
Demographics	Classically seen in adolescent male very rare in females	Classically seen in Chinese young adults and african kids
Presentation	Presents with profuse epistaxis (nose bleed) (HY)	• Associated with EBV • Often involves cervical lymph nodes
Biopsy		

Differentiate Rhinitis and Nasal polyp.

	Rhinitis	Nasal polyp
Cause	Rhinovirus no 1 cause	• Secondary to repeated rhinitis (HY) • CF (if you see child with nasal polyp, suspect CF) - HY • Asprin intolerant asthma (HY)
		
Presentation	Runny nose, sneezing, congestion	Protrusion of edematous, inflamed nasal mucosa

What is allergic rhinitis? What's it's associated with?

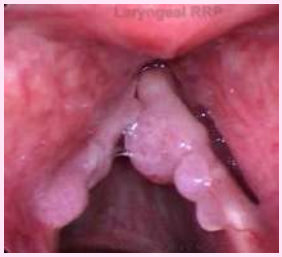
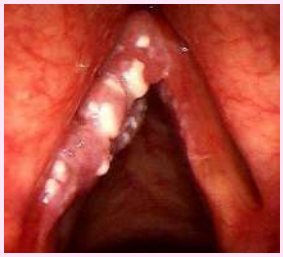
- A type of rhinitis caused due to type 1 hypersensitivity reaction (ex - pollen)
- **Association:**
  - Asthma
  - Eczema
- **Presentation:**
  - Eosinophilic infiltrate

What is aspirin intolerant asthma?

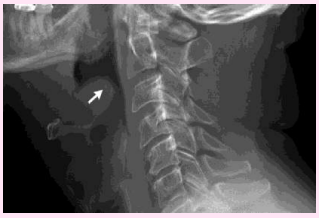
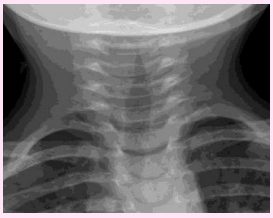
- Presents as triad of asthma, aspirin induced bronchospasm and nasal polyps.
- Seen in 10% of asthma patients

Larynx

Differentiate laryngeal papilloma and laryngeal carcinoma

	Laryngeal papilloma	Laryngeal carcinoma
Defnition	Benign papillary tumor of vocal cord	SCC of epithelial lining of vocal cord
Cause	HPV 6 and 11;	EtOH and smoking (papilloma rarely progress to carcinoma)
Presentation	• Hoarseness of voice • Usually single in adults and multiple in children (HY)	• Hoarseness of voice • Cough and stridor
		

Differentiate acute epiglottitis and laryngotracheobronchitis (croup).

	Acute epiglottitis	laryngotracheobronchitis (croup)
Cause	H. Influenzae type b most common cause (in immunized or non-immunized kids.	Parainfluenza virus most common cause
Presentation	Too much drooling, dysphagia, sore throat, fever, muffled voice, inspiratory stridor	Barking cough and inspiratory stridor
	Risk of actue airway obstruction (medical emergency)	
X-ray	Thumb sign on X-ray 	Steeple sign on X-ray 

What is vocal cord nodule (singer's nodule)? What's its cause?

- Nodule on true vocal cord
- Caused due to excessive use of vocal cord; usually bilateral (wear and tear issue)
- Composed on degenerative myxoid connective tissue
- Treat with rest

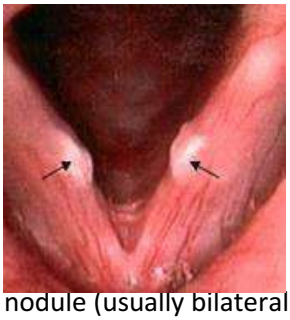


Fig: vocal cord nodule (usually bilateral and seen on true vocal cord)

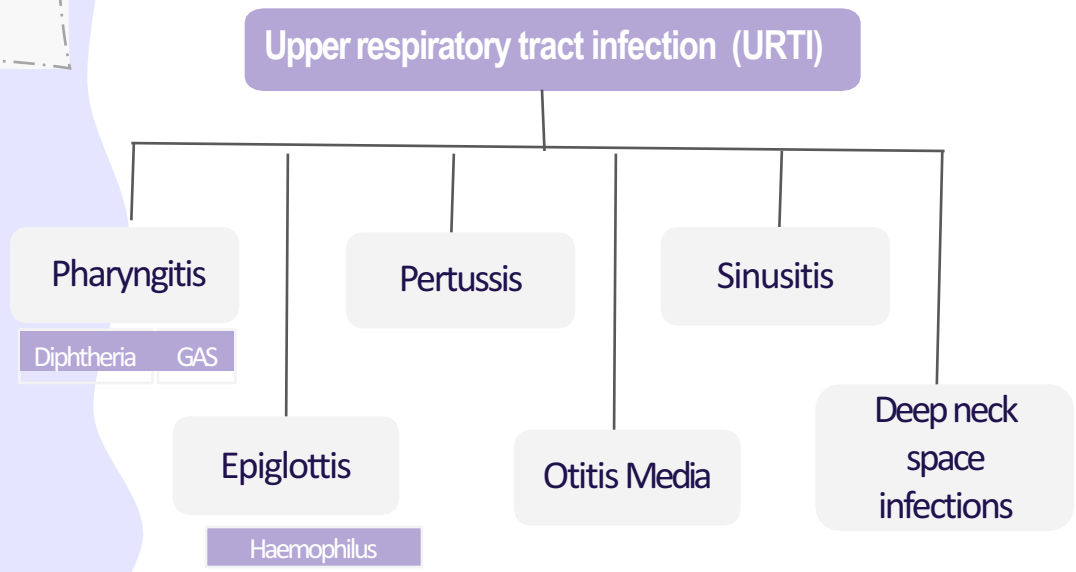
Arabic translation:

- Pharyngitis : التهاب البلعوم
- Diphtheria : مرض الخناق
- Pertussis : السعال الديكي
- Otitis Media : التهاب الأذن الوسطى
- Sinusitis: التهاب الجيوب الأنفية
- Epiglottitis: التهاب لسان المزمار

Objective

1. Discuss the epidemiology and various clinical presentations of URTIs
2. Identify the most important etiological agents causing different URTIs, and discuss their virulence factors, laboratory diagnosis and potential preventative strategies
3. Determine the antibiotic of choice for the different URTIs
4. Discuss complications of GAS and C. diphtheriae infections

Introduction



Note :

Virulence factors:

- Capsule : work as Antiphagocytic for the bacteria.
- M protein in cell wall: work as Antiphagocytic for the bacteria.
- Streptolysin O: toxin that capable of lysing erythrocytes, leukocytes, and platelets.
- Streptolysin S : toxin that capable of lysing erythrocytes, leukocytes, and platelets.
- Streptococcal pyrogenic exotoxins: Superantigen toxin.

GAS (Group A Streptococcus)

It is a Gram-positive cocci in chains , Facultative anaerobic, Catalase negative, and Beta hemolytic (Streptococcus pyogenes).

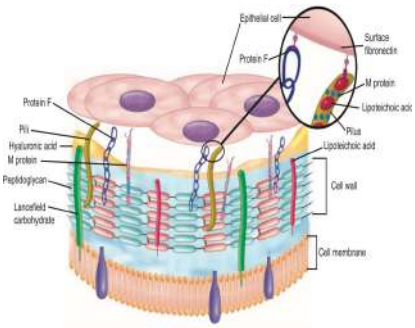
Causes:

Respiratory infections:

- Pharyngitis.
- Otitis
- Sinusitis.

Other infections:

Skin and soft tissue.

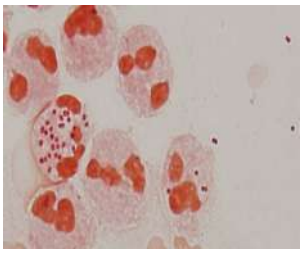


Virulence factors:

- Capsule.
- M protein in cell wall.
- Streptolysin O.
- Streptolysin S.
- Streptococcal pyrogenic exotoxins (SPE).

Moraxella catarrhalis

Gram negative diplococci, Catalase positive, and Oxidase positive.



Causes:

- Otitis.
- Sinusitis.
- Pneumonia.

Treatment:

- Amoxicillin-Clavulanic acid

Hemophilus influenzae

Gram negative pleomorphic, coccoid to rod-shaped cells which known as coccobacilli. It is oxidase and catalase positive. It is facultatively anaerobic and requires specific media contains both X (heme) and V (NAD) factors for growth like chocolate agar which is heated blood and contains the nutrients needed for its growth, and it can be used to confirm the diagnosis.

Clinical correlate : Influenzae Type B is encapsulated so it can invade the blood. We also used the capsule to develop the vaccine against this bacteria.

Types:

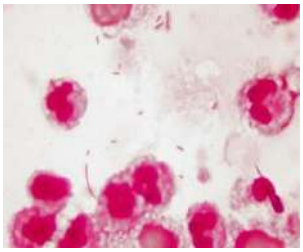
1-Encapsulated (typable) strains:

- Encapsulated (main virulence factor)
- A to F (A,B,C,D,E,F)
- Most important is type b (has a special capsule)
- Prevention through vaccination
- Causes invasive disease (e.g. epiglottis, meningitis), More severe.

2- Non-Encapsulated:

- Causes local infections:

- Sinusitis,
- Otitis
- Pneumonia in elderly.



Treatment:

- Amoxicillin-Clavulanic acid.
- 2nd or 3rd generation cephalosporin

Pharyngitis

Epidemiology:

- Mainly affects children from 5 to 15 years old.
- Very common in Late fall, winter, early spring.

Signs and Symptoms:

- The 4 E's: more related to bacterial
  1- Exudate of tonsils.
  2- Enlarged, tender of lymph nodes >1 cm.
  3- Edema (Pharyngeal)
  4- Erythema (Pharyngeal)
- Fever 38.4 to 39.4º C.
- Sore throat, Pharyngeal erythema, edema , & Fever

Note :

The 3 C's, more related to viral

- **Coryza:**

Inflammation of the mucous membranes lining the nasal cavity, usually causing a running nose, nasal congestion and loss of smell.

- **Cough**
- **Conjunctivitis**

Etiology:

VIRUSES:

- The most common represent around 70%.
- Respiratory viruses such as Enterovirus, HSV, EBV and HIV.

BACTERIAL:

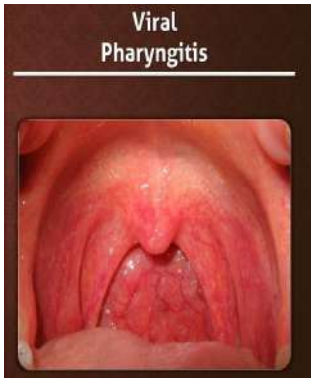
- Group A streptococcus (streptococcus pyogenes), the most common
- Corynebacterium diphtheriae
- Neisseria gonorrhoeae
- Fusobacterium necrophorum (Anaerobic bacteria, cause of Lemierre's syndrome)

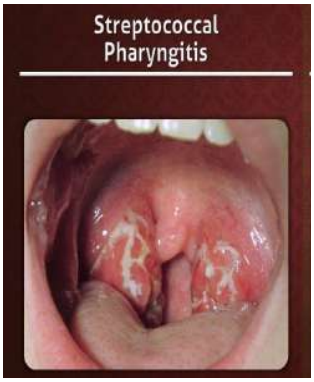
Lemierre's Syndrome:

- It is a complication of a peritonsillar abscess or a post dental infection.
- Clinical Presentation:

- Sore Throat
- Fever
- Shock

- The presenting symptoms are due to IJV thrombophlebitis which leads to multiple septic emboli in the lung.
- It is caused by Fusobacterium Necrophorum
- Treatment is the same as Deep Neck Space infection Meropenem or Piperacillin or Clindamycin for 2 weeks
- If the patient does not respond to the treatment, venotomy must be done.
- We also give a thrombolytic to dissolve the thrombus





GAS Pharyngitis (Group A Streptococcus)

Diagnosis:

Throat swab:

- Rapid Bacterial antigen detection. Imp in ER.
- Culture on blood agar.

Antistreptolysin O.

Treatment :

- Drug of choice: Penicillin for 10 days. In case of Allergy to penicillin, we use: Clindamycin or macrolide (e.g. Clarithromycin).
- Clarithromycin is a new type which has fewer side effects, better penetration, & longer half-life.

Complications :

SUPPURATIVE:

There is formation of pus and it occurs right away after the infection.
e.g. peritonsillar abscess and parapharyngeal space abscess.

NON-SUPPURATIVE:

It occurs 1-6 weeks after acute S. pyogenes infection.

- **Rheumatic fever:**

- When it happens?
after respiratory tract infection.
- What does it do to the body?
mainly cause inflammation of heart (pancarditis), and inflammation of joints, blood vessels, and subcutaneous tissue.
- How it happens?
results from cross reactivity of anti-M protein Ab and the human heart tissue.

- **Acute Glomerulonephritis:**

- When it happens?
after infection of the skin or respiratory tract.
- What are the Symptoms?
Edema, hypertension, hematuria, and proteinuria.
- Why it happens?
Initiated by Ag-Ab complexes on the glomerular basement membrane.

Diphtheria

Note :
Diphtheria is present as normal flora in our bodies, but it is non-toxigenic. When it gets infected with a bacteriophage (which is a virus), it transmits a toxin and becomes toxigenic.
Superantigen toxin.

Epidemiology:

- One of the most common causes of death in unvaccinated children 1-5 years.
- Found most in Non-developing countries.
- Toxin mediated disease

Pathogenesis:

- Rapid progression, tightly adhering gray membrane in the throat.

- **Note**:
- The patient will present with a sore throat, difficulty in breathing and swallowing and drooling of the saliva.
- The membrane can get bigger and bigger until it obstructs the airway and will cause suffocation and death which is why they call this disease.

Etiology:

- Pharyngitis caused by Corynebacterium diphtheriae (a gram-positive bacilli, Aerobic, non-spore forming).
- Virulence:

Diphtheria toxin : It's a toxin produced by C. diphtheriae, which inhibit the protein synthesis of the cell and cause cell death, targets: heart/ nerves/epithelium.

Signs and Symptoms:

- Mainly presents as URTI., one of its characteristic is formation of pseudomembranes in the throat.

- **Note**:

ELEK'S Test :

- A test strip of filter paper containing diphtheria antitoxin is placed in the center of the agar plate. Strains to be tested (patient's isolate), known positive and negative toxigenic strains are also streaked on the agar's surface in a line across the plate and at a right angle to the antitoxin paper strip.

Diagnosis:

- Throat swab.
- Culture on special media containing tellurite (e.g. Tinsdale media).
- ELEK's Test for confirmation of toxin production.

Complications:

- Myocarditis also known as inflammatory cardiomyopathy, is inflammation of the heart muscle.
- Neuritis it is inflammation of a nerve or the general inflammation of the peripheral nervous system. Symptoms depend on the nerves involved.

Treatment:

- We give both Antitoxin and antibiotic. Penicillin can be given or erythromycin if the child is allergic to penicillin.

Prevention:

- Vaccination with diphtheria toxoid.

Epiglottitis

Gram negative diplococci, Catalase positive, and Oxidase positive.

Epidemiology :

- Usually young unimmunized children.

Signs and Symptoms:

- life threatening condition as it affects breathing)

- Clinical presentation with The 3 D's:

- Dysphagia, which is difficulty or discomfort in swallowing
- Drooling saliva uncontrollably from the mouth
- Respiratory Distress.

Etiology:

- H. influenzae Type b.
- S. pneumoniae.
- S. aureus.
- Beta hemolytic streptococci.

Diagnosis:

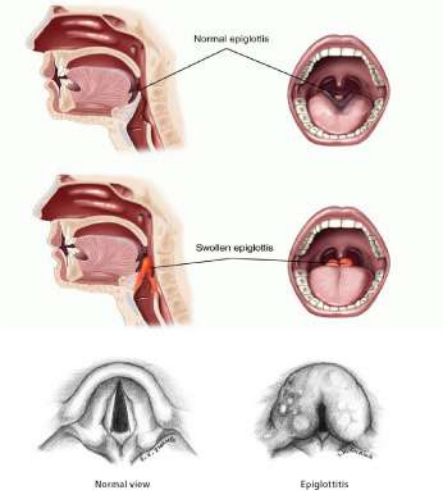
- Blood cultures
- Culture of epiglottic surface under controlled setting, and you can't take swab, because the patient can't breathe.

Treatment:

- Maintenance of airway.
- Empiric treatment: Ceftriaxone + Vancomycin

Prevention:

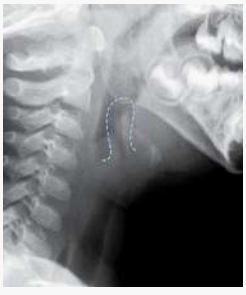
- HiB vaccination



Note:
In case epiglottitis is suspected, the doctor should not try to examine the airway by opening the mouth because it will cause suffocation and the patient might die.
Instead we use the X-ray to diagnose epiglottitis.

It is very rare nowadays because of the development of the vaccine against Hemophilus Influenzae Type B.

Note:



The X-ray may reveal what looks like a thumbprint in the neck, an indication of an enlarged epiglottis.

Pertussis (Whooping cough):

Epidemiology :

- Mainly in infants and children (most severe & deadly).
- Adults can get infected also.

Note:

- Pertussis in infants less than 6 months will present with cyanosis because theses toxins will produce a thick mucus that will block their tiny trachea and prevent air from flowing in.
- In older children the disease will present with whooping cough. In adults, the patients will have a chronic cough.

Etiology:

- Bordetella pertussis (GNB).

The course of the disease :

- Incubation period :

From 1 to 3 weeks, with No symptoms.

- Catarrhal Stage :

From 1 to 2 weeks, with mild occasional cough and runny nose.

- Paroxysmal Stage :

From 2 to 4 weeks , with severe & rapid cough , vomiting and it is dangerous.

- Convalescent Stage :

From 1 to 2 weeks, with Gradual recovery, The cough being to calm .

Extra Explanation :

Pathogenesis:

- The bacteria attach to the cilia of the respiratory epithelial cells.
- It produce toxins (Pertussis toxin) that paralyze the cilia which cause inflammation of the respiratory tract and interferes with the clearing of the pulmonary secretions.
- It also produce Filamentous hemagglutinin (FHA)and Pertactin (PRN), these products are responsible for the clinical features .
- Causes Leukocytosis and Lymphocytosis, and It is the only bacterial infection that causes lymphocytosis.

Virulence:

- Pertussis toxin
- Filamentous hemagglutinin
- Pertactin

Diagnosis:

- Nasopharyngeal swabs, which usually are used for the diagnosis of viral infections
- Special media needed:
  - Charcoal blood (Regan-Lowe)
  - Bordetella selective media (BordetGengou)

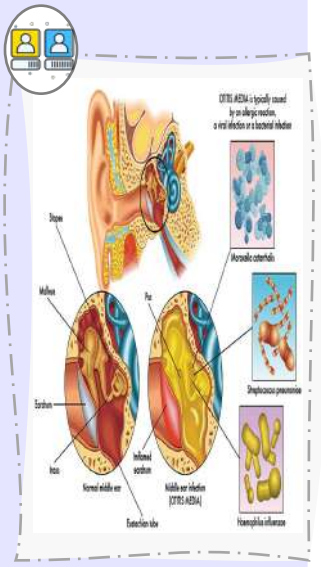
Note:

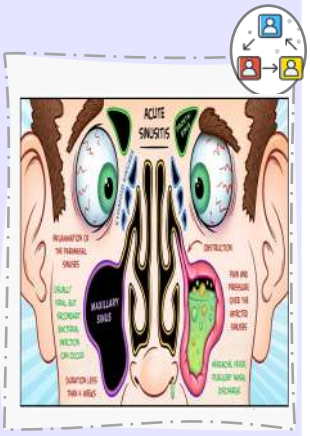
- Erythromycin is also given as a prophylactic treatment to the people who were in contact with an infected individual until the antibodies against the bacteria are produced as a response to the vaccine to prevent further spread of the infection.

Treatment:

- Prevented by vaccination.
- Erythromycin.

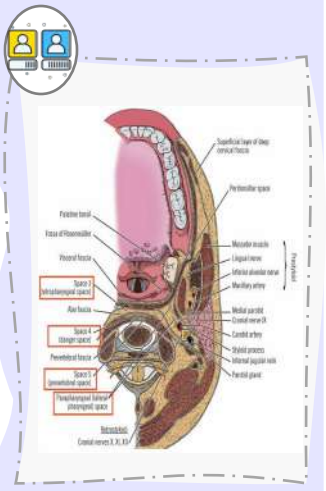
	Acute Otitis Media	Acute Bacterial Sinusitis
Epidemiology	More common in children.	
Etiology	○ **BACTERIAL:** - Streptococcus pneumoniae - H. influenzae - Moraxella catarrhalis - Group A streptococcus, Staph aureus, and Anaerobic bacteria also can cause both of otitis & sinusitis. ○ **VIRAL:** Can be alone or with bacteria. E.g. RVS, Rhinovirus.	
Clinical features	○ Fever ○ tympanic membrane will look erythematous	○ Occurs with viral URTI. ○ nasal discharge ○ sinus pain & low-grade fever.
Diagnosis	○Mainly clinical diagnosis. ○Tympanocentesis: Sometimes is needed and Middle ear fluid can be sent for culture.	○ Mainly clinical diagnosis. ○ Imaging (CT/MRI) when there is suspension of complications.
Treatment	Amoxicillin or Amoxicillin with Clavulanic acid	Amoxicillin with Clavulanic acid for 1 to 2 weeks
General Note	○ There is Fluid and inflammation of the mucosal lining of the middle ear.	○ Can be acute or chronic ○ complication: - Periorbital cellulitis. - Brain abscess & meningitis





Deep neck space infections

- The space includes lateral pharyngeal, retropharyngeal or prevertebral space.
- Patients are very sick and toxic
- Neck stiffness can occur with retropharyngeal space infection/abscess
- Retropharyngeal (danger space) infection may extend to mediastinum and present as mediastinitis



Etiology:

- Usually polymicrobial
- Mainly streptococci and oral anaerobes.

Management :

- Surgery
- Antibiotics: for 2-3 weeks

Meropenem, Piperacillin and Clindamycin.

In Summary

Infection	GAS Pharyngitis	Diphtheria	Epiglottitis
Etiology	Group A streptococcus (streptococcus pyogenes)	Corynebacterium diphtheriae	H. influenzae Type b (mainly)
Diagnosis	○ Throat swab ○ Rapid Bacterial antigen detection ○ Culture on blood agar ○ Antistreptolysin O	○ ELEK's Test ○ Culture on special media containing tellurite (e.g. Tinsdale media)	○ Blood cultures ○ Culture of epiglottic surface (under controlled setting)
clinical features	○ Exudate of tonsils ○ Enlarged, tender of lymph nodes ○ Edema & Erythema ○ Fever 38.4 to 39.4º C	○ Formation of pseudomembranous ○ Diphtheria toxin ○ undeveloped countries	○ dysphagia . ○ drooling. ○ respiratory distress.
management	**Penicillin** x 10 days **Allergy= Clindamycin** or **macrolide**	**Antitoxin + antibiotic (Penicillin or erythromycin)** Vaccination with diphtheria toxoid containing vaccine.	Ceftriaxone & Vancomycin Prevention: HiB vaccination

Infection	Pertussis	AcuteOtitis Media	AcuteBacterial Sinusitis
Etiology	Bordetella pertussis (GNB).	○ S. pneumoniae ○ H. influenzae (non-typable) ○ Viral	-S. pneumoniae -H. influenzae (non-typable) -M. catarrhalis -Anaerobes -Viral
Diagnosis	○ Nasopharyngeal (NP) swabs ○ Charcoal blood or Bordet-Gengou media	○ Mainly clinical diagnosis ○ Tympanocentesis sometimes needed	○ Mainly clinical diagnosis. ○ Imaging (CT/MRI) when there is suspension of complications
clinical features	○ severe coughing ○ vomiting ○ divided into phases	○ Fever ○ tympanic membrane (TM) will look erythematous(red	○ nasal discharge ○ sinus pain ○ Patient have viral URTI.
management	**Macrolide (erythromycin) preventio n :** Acellular pertussis-containing vaccine	Amoxicillin or Amoxicillin Clavulanic acid	Amoxicillin Clavulanic acid for 1 to 2 weeks

Ear, Nose, Throat, Upper Respiratory System Infections

Type infection	Cause vignette/key clues	Common causal agents
Acute otitis media	Red, bulging tympanic membrane, fever 102 – 13, pain goes away if drum ruptures or if ear tube are patent. 5 CA	*Streptococcus pneumoniae* *H.Influenzae* Moraxella catarrhalis RSV Rhinovirus
Otitis externa	Ear pain-list of organism	Normal flora often involve Often mixed infection: *Staph aureus* (from NF)* *Candida albicans* (from NF)* *Proteus* (water organism) *Pseudomonas* (water)
Malignant otitis externa	Sever ear pain in diabetic; life thretening	*Pseudomonas aeruginosa*
Sinusitis	Sinus pain; low-grade fever	As for acute otitis media
Oral cavity disease	Painful mouth-overgrowth of spirochetes and fusiform bacteria	Fusobacterium and treponemes (normal oral spirochetes)
	Some mouth with thick white coating (painful red base under); increased risk: premature infants, AIDS, IC pts, pts on antibiotics, vitamin C deficiency	*Candida*
Sore throat	Inflamed tonsils/pharynx, which may be purulent and may develop abscesses; cervical lymphadenopathy, fever stomach upset; sandpaper rash	*Streptococcus pyogenes* (group A strep) Rash indicates present of erythrogenic exotoxin A
	White papules with red base on posterior plate and pharynx, fever	Coxsackie A
	Throat looking like strep with sever fatigue, lymphadenopathy, fever, rash; heterophile (+); Downey type II cell	Epstein-Barr virus

*NF = normal flora

Ear, Nose, Throat, Upper Respiratory System Infections

Type infection	Cause vignette/key clues	Common causal agents
	Low grade fever with a 1-2 day gradual onset of membranous nasopharyngitis and/or obstructive laryngotracheitis; bull neck from lymphadenopathy; elevated BUN; abnormal ECG; little change in WBC (toxin). Exudate bleeds profusely when dislodged	*Corynebacterium diphtheriae* (diphtheria)
Common cold	Rhinitis, sneezing, coughing; list CA with seasonal peaks	Rhinoviruses (summer-fall) Coronavirus (winter-spring) Human metapneumovirus Adenovirus, many other

Genus: streptococcus

Genus Features

- Gram-positive cocci in chains
- Catalase negative
- Serogrouped using known antibodies to the cell wall carbohydrates
- (Lancefield groups A–O): S. pneumoniae serotyped via capsule; S. pyo- genes serotyped via M protein

Species of Medical Importance

- S. pyogenes
- S. agalactiae (group B streptococci; GBS)
- S. pneumoniae
- Viridans streptococci: S. mutans; S. sanguinis; S. gallolyticus (bovis)

Streptococcus pyogenes

(Group Enterococcus Streptococcus; GAS)

Distinguishing Features

- β hemolytic
- Bacitracin sensitive
- Pyrrolidonyl arylamidase (PYR) positive

Reservoir: human throat; skin

Transmission: direct contact; respiratory droplets

Pathogenesis

- Hyaluronic acid: is non-immunogenic
- M-protein: antiphagocytic, associated with acute glomerulonephritis, rheumatic fever
- Streptolysin O: immunogenic, hemolysin/cytolysin
- Streptolysin S: not immunogenic, hemolysin/cytolysin

Some Bacteria causing upper respiratory tract infection

Spreading Factors

- Streptokinase: breaks down fibrin clot
- Streptococcal DNAse: liquefies pus, extension of lesion
- Hyaluronidase: hydrolyzes the ground substances of the connective tissues
- Exotoxins A–C (pyrogenic or erythrogenic exotoxins)
    - Phage-coded (i.e., the cells are lysogenized by a phage)
    - Cause fever and rash of scarlet fever: superantigens

Diseases: look at tables

Acute suppurative group A streptococcal infection*

Disease	Symptoms
pharyngitis	Abrupt onset of sore throat, fever, malaise, and headache; tonsillar abscesses and tender anterior cervical lymph nodes
Scarlet fever	Above followed by a blanching **"sandpaper" rash** (palms and soles are usually spared), circumoral pallor, **strawberry tongue**, and nausea/vomiting
Pyoderma/impetigo	Pyogenic skin infection (honey-crusted lesions)

also, cellulitis, necrotizing fasciitis, puerperal fever, lymphangitis, erysipelas

Nonsuppurative sequelae to group A streptococcal infections

Disease	Sequelae of	Mechanism/symptoms
Rheumatic fever	Pharyngitis with group A sterp	Antibodies to heart tissue/ 2weeks post pharyngitis, fever, joint inflammation, carditis, erythema marginatum (chorea later) type II hypersensitivity
Acute glomerulonephritis (AGN)	Pharyngitis or skin infection	Immune complexs bound to glomeruli/pulmonary edema and hypertension, "smoky" urine (type III hypersinsitivity)

- Rapid strep test (ELISA-based) misses approximately 25% of infections.
- Culture all negatives.
- Antibodies to streptolysin O (ASO) titer of >200 is significant for rheumatic fever.
- Anti-DNAse B and antihyaluronidase titers for AGN

Treatment: beta lactam drugs, macrolides in the case of penicillin allergy

Prevention: possible prophylactic antibiotics for at least 5 years post-acute rheumatic fever; beta lactams and macrolides

Some Bacteria causing upper respiratory tract infection

Genus: corynebacterium

Corynebacterium diphtheriae

Distinguishing Features

- Gray-to-black colonies of club-shaped gram-positive rods arranged in V or L shapes on Gram stain
- Granules (volutin) produced on Loeff ler coagulated serum medium stain metachromatically
- Toxin-producing strains have β-prophage carrying genes for the toxin (lysogeny, β-corynephage).
- The phage from one person with diphtheria can infect the normal nontoxigenic diphtheroid of another, and thus cause diphtheria.

Reservoir: throat and nasopharynx

Transmission: bacterium or phage via respiratory droplets

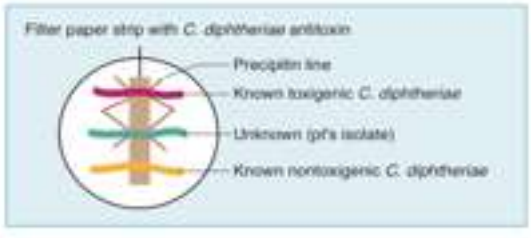
Pathogenesis

- Organism not invasive; colonizes epithelium of oropharynx or skin in cutaneous diphtheria
- Diphtheria toxin (A-B component)—inhibits protein synthesis by adding ADP-ribose to eEF-2
- Effect on oropharynx: Dirty gray pseudomembrane (made up of dead cells and fibrin exudate, bacterial pigment)
- Extension into larynx/trachea → obstruction
- Effect of systemic circulation → heart and nerve damage

Disease: diphtheria (sore throat with pseudomembrane, bull neck, potential respiratory obstruction, myocarditis, cardiac dysfunction, recurrent laryngeal nerve palsy, and lower limb polyneuritis), renal failure

Diagnosis

Elek test to document toxin production (ELISA for toxin is now gold standard)
Toxin produced by Elek test toxin-producing strains diffuses away from growth
Antitoxin diffuses away from strip of filter paper
Precipitin lines form at zone of equivalence



Elek Test

Treatment

- Erythromycin and antitoxin
- For endocarditis, intravenous penicillin and aminoglycosides for 4–6 week

Prevention: toxoid vaccine (formaldehyde-modiied toxin is still immunogenic but with reduced toxicity), part of DTaP, DTP, or Td, boosters 10-year intervals

KAPLAN CORNER

Some Bacteria causing upper respiratory tract infection

Genus: haemophilus

Haemophilus influenzae

Distinguishing Features

- Encapsulated, gram-negative rod; 95% of invasive disease caused by capsular type b
- Requires growth factors X (hemin) and V (NAD) for growth on nutrient or blood agar (BA)
- Grows near S. aureus on BA = "satellite" phenomenon
- Chocolate agar provides both X and V factors

Reservoir: human nasopharynx Transmission: respiratory droplets, shared toys

Pathogenesis

- Polysaccharide capsule (type b capsule is polyribitol phosphate) most important virulence factor
- Capsule important in diagnosis; antigen screen on CSF (e.g., latex particle agglutination); serotype all isolates by quellung.
- IgA protease is a mucosal colonizing factor.

Diseases

- Meningitis
    - Epidemic in unvaccinated children ages 3 months to 2 years – After maternal antibody has waned and before immune response of child is adequate – Up to 1990, H. inf luenzae was most common cause of meningitis age 1–5 (mainly <2); is still a problem if child age <2 and not vaccinated
- Otitis media: usually nontypeable strains
- Bronchitis: exacerbations of acute bronchitis in smokers with COPD
- Pneumonia: 1–24 months; rare in vaccinated children; smokers
- Epiglottitis: rare in vaccinated children; seen in unvaccinated toddlers; H. inf luenzae was major causal agent

Diagnosis: blood or CSF culture on chocolate agar; PCR; antigen detection of capsule (latex particle agglutination)

Treatment: cefotaxime or cetriaxone for empirical therapy of meningitis; check nasal carriage before releasing; use rifampin if still colonized

Prevention

- Conjugate capsular polysaccharide-protein vaccine
- Vaccination effective to prevent type b disease
    - Polyribitol capsule conjugated to protein: (diphtheria toxoid or N. meningitidis outer membrane proteins), making it a T-cell dependent vaccine – Vaccine: 2, 4, 6 months; booster 15 months; 95% effective
- Rifampin reduces oropharynx colonization and prevents meningitis in unvaccinated, close contacts age <2 years

Some Bacteria causing upper respiratory tract infection

Moraxella catarrhalis

Distinguishing Features
- Gram-negative diplococcus
- Close relative of Neisseria Reservoir: normal upper respiratory tract lora

Transmission: respiratory droplets Pathogenesis: endotoxin may play role in disease

Disease(s): otitis media; sinusitis; bronchitis and bronchopneumonia in elderly patients with COPD

Treatment: amoxicillin and clavulanate, second- or third-generation cepha- losporin or TMP-SMX; drug resistance is a problem (most strains produce a β-lactamase)

Genus: bordetella

Genus Features
- Gram-negative small rods
- Strict aerobes

Species of Medical Importance: Bordetella pertussis

Bordetella pertussis

Distinguishing Features: small gram-negative, aerobic rods; encapsulated organism

Reservoir: human (vaccinated)

Transmission: respiratory droplets

Pathogenesis
- B. pertussis is mucosal surface pathogen
- Attachment to nasopharyngeal ciliated epithelial cells is via filamentous hemagglutinin; pertussis toxin (on outer membrane) aids in attachment
- Toxins damage respiratory epithelium.
    - Adenylate cyclase toxin: impairs leukocyte chemotaxis → inhibits phagocytosis and causes local edema
    - Tracheal cytotoxin: interferes with ciliary action; kills ciliated cells
    - Endotoxin
    - Pertussis toxin (A and B component, OM protein toxin): ADP ribosylation of Gi (inhibiting negative regulator of adenylate c yc la s e) interferes with transfer of signals from cell surface to intracellular mediator system: lymphocytosis; islet-activation leading to hypoglycemia; blocking of immune effector cells (decreased chemotaxis); increased histamine sensitivity

Some Bacteria causing upper respiratory tract infection

Stage of whooping cough (pertusis) vs. results of bacterial culture

	Incubation	Catarrhal	Paroxysmal	Convalescent
Duration	7-10 days	1-2 days	2-4 weeks	3-4 weeks (or longer)
symptoms	None	Rhinorrhea, malaise, sneezing, anorexia	Repetitive cough with whoops, vomiting, leukocytosis	Diminished paroxysmal cough, development of secondary complications (pneumonia, seizures, encephalopathy
Bacterial culture				

Diagnosis

- Fastidious/delicate: Regan-Lowe or Bordet-Gengou media; either direct cough plates or nasopharyngeal cultures
- Difficult to culture from middle of paroxysmal stage on
- Direct immun of luorescence (DFA) on nasopharyngeal smear
- PCR and serologic tests available

Treatment: supportive care, i.e., hospitalization if age <6 months; erythromycin for 14 days including all household contacts

Prevention: vaccine DTaP (acellular pertussis: ilamentous hemagglutinin plus pertussis toxoid); immunity wanes 5–7 years; babies are born with little or no immunity (IgA) from mother

Streptococcus pneumoniae

Distinguishing Features

- α hemolytic
- Optochin sensitive
- Lancet-shaped diplococci
- Lysed by bile (bile soluble)

Reservoir: human upper respiratory tract pneumoniae

Transmission: respiratory droplets (not considered highly communicable; oten colonize the nasopharynx without causing disease)

Predisposing Factors

- Antecedent inf luenza or measles infection
- Chronic obstructive pulmonary disease (COPD)
- Congestive heart failure (CHF)
- Alcoholism
- Asplenia predisposes to septicemia

Some Bacteria causing upper respiratory tract infection

Pathogenesis

- Polysaccharide capsule is the major virulence factor
- IgA protease
- Teichoic acid
- Teichoic acid
- Pneumolysin O: hemolysin/cytolysin: damages respiratory epithelium; inhibits leukocyte respiratory burst and inhibits classical complement fixation

Diseases

- Typical pneumonia: most common cause (especially in decade 6 of life); shaking chills, high fever, lobar consolidation, blood-tinged, “rusty” sputum
- Adult meningitis: most common cause; peptidoglycan and teichoic acids are highly inf lammatory in CNS; CSF reveals high WBCs (neu- trophils) and low glucose, high protein
- Otitis media and sinusitis in children most common cause

Laboratory Diagnosis

- Gram stain and culture of CSF or sputum
- Quellung reaction: positive (swelling of the capsule with the addition of type-specific antiserum, no longer used but still tested!)
- Latex particle agglutination: test for capsular antigen in CSF
- Urinary antigen test

Treatment: beta lactams for bacterial pneumonia; cetriaxone or cefotaxime for adult meningitis (add vancomycin if penicillin-resistant S. pneumoniae has been reported in community); amoxicillin for otitis media and sinusitis in children (erythromycin in cases of allergy)

Prevention

- Antibody to capsule (>80 capsular serotypes) provides type-specific immunity
- Vaccine
    - Pediatric (PCV, pneumococcal conjugate vaccine): 13 of most common serotypes; conjugated to diphtheria toxoid; prevents invasive disease
    - Adult (PPV, pneumococcal polysaccharide vaccine): 23 of most common capsular serotypes; recommended for all adults age ≥65 plus at-risk individuals

Group A Strep (Strep pyogenes) – The Pie Genies' Bakery

1. Pie in glass Capsule – Group A Strep is encapsulated
2. Hot Apple – Capsule made out of Hyaluronic Acid
3. Heating Lamp w/ "B" Light – Beta Hemolytic
4. 1st Baker
    a. Baker Holding Honey Crusted Pie – Impetigo
    b. Red Handkerchief – Strep throat, red inflamed throat
    c. Red Mittens on Baker - Erysipelas, red lesion with well demarcated borders, S Pyogenes is the most common cause.

2nd Baker w/ Cape – represents Strep Toxins 3 issues

5. Scarlett Fever –
    a. Strawberry Tongue
    b. Red Handkerchief - Pharyngitis,
    c. Red Gingerbread Man - widespread rash that spares the face.
6. Cape w/Bolt - Toxic Shock Like Syndrome mediated by a super antigen – SpeA, SpeC
7. Burnt Gingerbread man - Necrotizing Fasciitis -SpeB

Master Chef – M Protein in GAS well main virulence factor for Rheumatic Fever, will interfere with opsonization, antiphagocytic, M Protein will mimic antibodies in heart and cause issues with Mitral Valve in heart

8. Chef Swatting away other chef – Antiphagocytic action
9. Miter hat - Very antigenic and elicits a humoral response, creating an antibodies to myosin in cardiac muscle (Molecular mimicry), damages mitral valves
10. Red Handkerchief – Pharyngitis precipitates RF, NOT IMPETIGO
11. Cupcakes w/ JONES on them
    a. J = Joints
    b. "Heart" = Heart Problems
    c. Nodules on exterior surfaces
    d. Erythema marginatum
    e. Sydenham's Chorea
12. Phone cord that looks like a glomerulus - Post Strep Glomerulonephritis, type III hypersensitivity reaction (deposition *of* antibodies in glomerulus)
    a. Puffy Cheeks – Puffy Cheeks w/ nephritis
    b. Bottle of Cola – Cola Colored Urine
    c. Calendar – Occurs 2 weeks after strep infection
    d. Can occur after pharyngitis and impetigo
    e. Pencil – TXT is penicillin
13. Baker on bottom Right 3 more virulence Factors
    a. O Shaped Donuts – Streptolysin O, allows Strep to be Beta Hemolytic, we generate ASO antibodies to this
    b. Phosphate Cupcakes – Streptokinase, converts plasminogen to plasmin.
    c. Twists – DNA'ases, depolymerize DNA
14. Basset hound – Bacitracin sensitive
15. Lady checking a box of donuts – Tongs are antibodies, check ASO titers to see if there was a Group A Strep Infection.

SKETCHY CORNER

Corynebacterium Diphtheria - Corazon de la Corrida

1. Purple Hues - Gram Pos, non-spore forming
2. Guy playing Morocco's that are blue and red – Bacteria is club shaped and y or v shaped, Metachromatic granules that stain with aniline dyes, Metachromatic granules will stain red and the rest of the cell will stain blue.
3. Zig Zag shape in the morocco - V or y shape the bacteria will form
4. 2 subunits A and B, A is active and B is binding
    1. Man playing an accordion wearing a bow tie - Toxin causes Ribosylation of elongation factor 2, this will inhibit ribosome function inhibiting protein synthesis leading to cell death
    2. Kids in the stand eating grey cotton candy wrapped with a plastic wrap - This will lead to pseudomembranous exudate that will be found in the oral pharynx
5. Bull extending its neck with droplets coming out of the mouth and nose - Found in throat and tonsils because the infection is transmitted by respiratory droplets, Can cause airway obstruction and lymphopathy, this will cause bulls neck (thickening of the neck)
6. Cape in the shape of a heart - Can lead to myocarditis like arrhythmias and heart block. Lethal effect of diphtheria
7. Man eating the sausage links - Will damage the myelin of nerve fibers, the sausage man eating the myelin having a neuropathy.
8. Television and kid laughing - Lab diagnosis -plate on Tellurite and Loeflers media (tele like television and loughlers will be the kid laughing like enjoying a show)
9. Bulls tongue sticking out and licking the matador - Eleks test – in-vitro assay that has antitoxin on it.
10. Why it's in another language - Immigrants most likely to get this
11. Syringes in the bull - DTaP vaccine is used, given with tetanus and pertussis. Toxoid Vaccine

SKETCHY CORNER

Haemophilus Influenza - "Phyllis's Chocolate Covered Cherries"

1. Red Hues - Gram Neg
2. Shape of the candy machine and candy on top of the machine - Coccobacillary Shape
3. Chocolate sign – Grown in chocolate agar
4. 10 cent sign – Needs Factor 10 "Hemodin"
5. 5 cent sign - Grown on chocolate agar needs factor 5 (NAD, nicotinamide) and factor 10 (Hemodin) "hemoTEN"
6. Child Coughing and aerosol spray - Infection primarily moved by aerosol transmission leading to droplets going to respiratory track calling pneumonia
7. Child sticking out the red tongue screaming - Disease Epiglottitis - symptoms Drooling, inflamed epiglottis, strider, drooling
8. Cherries - "cherry red epiglottis"
9. Child plugging his ears - Otitis Media
10. Meningitis helmet and Bee flying around - Meningitides - only caused by type B capsular form.
11. Sickles attached to belts - Sepsis and Septic arthritis in patients without a spleen, hemophilic infections, especially sickle cell disease
12. Syringe and Capsule with the Bee flying around it - Vaccine for only the type B capsule is conjugated with diphtheria toxoid and haemophilus type B capsule
13. **Dip**ped for 2.18 - Vaccinate between 6 weeks - 18 months (bound to diphtheria) Dip=Diphtheria
14. Three Axes -Treatment Ceftriaxone
15. Rifle - Treatment for close contacts is rifampin

SKETCHY CORNER

Bordetella Pertussis – Board and Care

1. Streamers to represent pili - Respiratory droplets are very infective using Pilus called filamentous hemagglutinin
2. Bow tie - Pertussis Toxin - Ribosylates Gi disabling it
3. GI uniform - Toxic inhibits GI, Disabled Gi (G inhibitor Protein)
4. Military Camp - Leads to a rise in cAMP
5. Popcorn, overabundance of white kernels - ADP Disables Chemokine receptors for lymphocytes leading to an overabundance of white blood cells in the blood stream, lymphocytosis
6. EF Shield - Adenylate cyclase toxin acts like the anthracis toxin edema factor, increases cAMP, Edema Factor, Most Virulent
7. Tractor on the middle road cutting the grass- Tracheal toxin damages ciliated cells in the epithelium, tractor cuts long cilia grass
8. Vet coughing vigorously - Catarrhal phase, limited symptoms nonspecific, most bugs, most contagious. 1-2 weeks
9. Whooping Horn - Paroxysmal - characteristic cough "Whoop"
10. 100 days war banner - Convalescence stage - final stage lasting 3 months with a cough, 100 day cough, most susceptible to secondary infections
11. Crow - Treatment Macrolides
12. Syringe with cell phone - DTaP - **acellular** vaccine using purified antigens
13. Red Hues - Gram Neg
14. Aerobic
15. Non motile

SKETCHY CORNER

Strep Pneumonia "the alpha knight tournament"

1. Purple Background - G+
2. α knight tournament – α hemolytic, partial hemolysis where the surrounding zone is a green hue
3. **Strep Pneumonia Knight**
4. Armor – Polysaccharide Capsule is major virulence factor
5. Chin is exposed – Optochin sensitive, optochin inhibits the growth of strep pneumo
6. Double Lance – Lancet shaped diplococci
7. Mud on horses legs - Bile soluble, meaning it does not grow in Bile
8. Rust Colored single lobe on chest – Rust colored sputum and lobar pneumonia
9. Squire mopping up muddy mess MOPS - Meningitides, Otitis Media, Pneumonia, Sinusitis
10. Number 1 sign – number one cause of all these diseases.
11. Cracked Shield with the symbol of IgA dimer molecule - Protease that cleaves IgA that allows invasion of mucosa reducing host defenses
12. Sickle - Removal of spleen leads to susceptibility of infection by encapsulated organisms like in sickle cell anemia.
13. Crows – azithromycin Macrolides
14. 3 Axes - Ceftriaxone
15. **Adults** in the **M**ezzanine, **Children** on the **G**round - 2 pneumococcal vaccines, adult is a 23 valiant polysaccharide vaccine, children is 7 valent but conjugated to a protein. Adults will have a T-Cell independent response creating IgM that does not last long. Adding the protein adds a more robust antigen response leading to a production of IgG in children.

Strep Viridians

1. No Armor – Not encapsulated
2. Jesters mask protects face including the chin – optochin resistant
3. Donkey with bile resistant boots – Bile resistant
4. Foul Yellow teeth on donkey – associated with dental carries
5. Deck of cards with plate shield - Synthesizes Dextran's from glucose which allows strep viridians to adhere to any fibrin from platelets that has been damaged in the heart.
6. Strep Sanguineous adheres to fibrin platelet aggregates in damaged heart valves, most commonly occurs in mitral valve.

SKETCHY CORNER

Extra Explanation :

RNA sense in viruses

- Positive sense (+ve strand): (5' to 3') viral RNA signifies that a particular viral RNA sequence may be directly translated into the desired viral proteins.
- Negative sense (-ve strand): This RNA (3' to 5') cannot be translated into protein directly. Instead, it must first be transcribed into a positive sense RNA that acts as an mRNA. Some viruses (Influenza, for example) have negative sense genomes and so must carry an RNA polymerase inside the virion.

Objective

1. Acquire the basic knowledge about structure and classification of these viruses infecting the respiratory system.
   Including (**Influenza** viruses, **Parainfluenza** viruses, Respiratory syncytial virus (**RSV**) and human metapneumovirus (HMPV), **Measles** virus, and **Mumps**)
2. Describe their epidemiology and pathogenesis
3. Identify the respiratory infections and the clinical features of URTI and LRTI.
4. Describe their epidemiology and pathogenesis
5. Know the laboratory diagnosis, and treatment of these infections.
6. Recognize the methods for prevention.

Respiratory Tract Infections:

Introduction:

- They are the commonest of human infections and cause a large amount of morbidity and loss of time at work (sick leave). They are common in both children and adults.
- Mostly caused by viruses. Mostly are self-limiting disease, which mean the disease tends to go away on its own, without treatment.
- Mostly are mild and confined to the upper respiratory tract (URT). [1]
- URT-infection may spread to other organs causing more severe infection and death .

Note:
(1) If it gets to the lower respiratory tract it become severe.

Arabic Translation:
Croup = مرض الخناق

Note:
(2) Lower respiratory tract infections

Clinical Manifestations (symptoms) :

- Common cold (rhinitis).
- Pharyngitis.
- Tonsillitis.
- Sinusitis & otitis media.
- Croup (acute laryngotracheobronchitis).
- Acute bronchitis, Acute bronchiolitis and Viral pneumonia. [2]

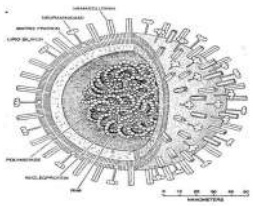
Common respiratory viruses::

Name of the virus	Family	Disease
1) Influenza virus	Orthomyxoviridae	URTI and LRTI
2) Parainfluenza virus	Paramyxoviridae	LRTI
3) Respiratory syncytial virus		
4 Rhinovirus	Picornaviridae	URTI
5 Coronavirus	Coronaviridae	URTI and LRTI
6 Adenovirus	Adenoviridae	URTI and eye infections
7 Human metapneumovirus	Paramyxoviridae	LRTI

Orthomyxoviridae Family

- Influenza virus, Avian flu and Swine flu -

1: Influenza virus :



Structural features:

- 8 helical Segmented genome (Negative polarity **ssRNA**)
- Enveloped virus with 2 projecting glycoprotein spikes -:
  - Haemagglutinin (H)
  - Neuraminidase (N)

Influenza viral proteins :

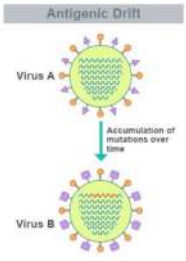
Haemagglutinin (H) [3]	Neuraminidase (N) [4]
Attachment to the host cell surface receptors. No Attachment = No infection	Responsible for release of the progeny viral particles from the infected cell.
Antibodies to the HA is responsible for immunity. our immune system use it as an antigen .	___
16 haemagglutinin antigenic type, (H1 – H16).	9 neuraminidase antigenic type, (N1 – N9).
Human associated H antigenic type are H1, H2, H3 Other H for animals, though it can infect human (*).	Human associated N antigenic type are N1, N2. Other N for animals, though it can infect human 1

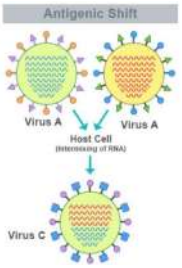
Epidemiology:

- Seasonal, spreads mostly in winter.
- Highly susceptible to mutations and rearrangeable within the infected host.
- Past antigenic shifts:
  - 1918 → H1N1 "Spanish Influenza" → 2040 million deaths.
  - 1957 → H2N2 "Asian Flu" → 12 million deaths.
  - 1968 → H3N2 "Hong Kong Flu" → 700,000 deaths.
  - 1977 → H1N1 Reemergence → not pandemic .

Types of influenza virus:

Influenza Virus Types	Type A	Type B	Type C
Infect	Human and Animal.	Human only.	Human only.
Cause	Human: Epidemic & Pandemic. Animal: Epizootic.	Outbreak.	Mild illness.
Antigenic changes	- Antigenic drift - Antigenic shift = Reassortment = rearrangement	Antigenic drift only.	———





- Antigenic **drift** → **Minor change** in genetic material.
- Antigenic **shift** → **Major change** in genetic material.

Note:
This virus is highly susceptible to mutations and rearrangements within the infected host. That's why it's hard to make a specific drug for it.

Note:
- (3) Glycoprotein found on the surface of influenza viruses. (More)
- (4) Enzymes that hydrolyze glycoside bonds, leading to the degradation neuraminic acids.

Note:
If there is only one of the human associated antigenic in a virus, either H or N, this virus can infect a human.

Extra Explanation :

Antigenic drift (minor change)
- A mechanism for variation in viruses that involves the accumulation of mutations within the genes that code for antibodybinding sites. This results in a new strain of virus particles. which cannot be inhibited as effectively by the original antibodies.

Antigenic shift (major change)
- The process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype having a mixture of the surface antigens of the two or more original strains.

Pathogenesis:

Infects the epithelial cells of the nose, throat, bronchi and occasionally the lungs. According to the host's immunity, it can either be localized as URTI or spread to the LRT and Viremia and fever usually occur.

Transmission: Inhalation of infectious aerosol droplets

Incubation period: 1-4 days

Symptoms : Fever, malaise, headache, cough, chills, sore throat, generalized pain.

Prognosis: Usually self-limiting disease.

Complications:

- Primary influenza pneumonia. [5]
- Secondary bacterial pneumonia. [6]
- Reye's syndrome. [7]

Note:

- **aerosol droplets:**

Accumulation of solid particles or liquid droplets in air or another gas.

Lab diagnosis:

Direct detection of influenza A or B virus from : -
Nasopharyngeal Aspirate (NPA) , Sputum , respiratory secretion, & Nasopharyngeal swab.

- **Routine testing** by direct detection of Influenza A or B virus from:
  - Sputum.
  - Nasopharyngeal swab aspirate (NPA).
  - Respiratory secretion **by direct immunofluorescent assay (IFA).**
- Other detection methods:
  - Tissue culture.
  - PCR . [8]

Note:

- (5) If virus enters the lung directly without infect URT first.
- (6) Bacteria enters the lungs in response to viral infection
- (7) fatty degeneration of CNS and Liver ,If you give Aspirin to child with viral infection.
- (8) Polymerase chain reaction: a rapid technique for in vitro amplification of specific DNA or RNA sequences, allowing small quantities of short sequences to be analyzed without cloning. We will do this when the IFA shows (apple green fluorescence) which means type A so we want to determine which strain of influenza

Treatment:

- **Amantadine**: for Influenza A virus only.
- **Rimantadine**, Oseltamivir (Tamiflu) or Zanamivir (Relenza) :

For both Influenza A & B viruses & Can be used as treatment of prophylaxis.

Prevention:

1- The flu shot vaccine, which is Inactivated "Killed vaccine. It is Given to people older than 6-months, either healthy or those with chronic medical conditions.

2- The nasal spray flu vaccine "Flu mist" which is Live attenuated.it is Approved for healthy people between 5-49 years.

Both contain two strains of current circulation of Influenza A&B viruses. (affect both A&B). The vaccine should be given in Oct & Nov before the influenza season begins.

Note:

- **Killed vaccine :**

Grown in culture then killed by Heat or formaldehyde.

- **Live attenuated :**

Contains living organisms

2 : Avian flu (H5N1 or H3N8):

Other than common Influenza virus, the Orthomyxoviridae divided into subtypes based on the haemagglutinin and neuraminidase proteins.

- There are two serious Flu (Typical of Orthomyxovirus family) :

1-Swine flu (H1N1)

2- Avian Influenza type A virus (H5N1)

Arabic Translation:
Swine Flu = انفلونزا الخنازير

Arabic Translation:
Avian Flu = انفلونزا الطيور

Epidemiology :

Wild birds are the natural reservoir for the virus, They shed the virus in saliva, nasal secretion and faces. All domestic poultry are susceptible to infection. become infected, when they eat food contaminated with secretion or excretion from infected bird. Avian influenza virus do not usually infect human. Poultry farmers and who are in close contact with poultry have high risk to get infected.

Symptoms in human :

Ranges from typical flu to severe such as acute respiratory disease, Diarrhea, abdominal pain and bleeding from the nose.

Lab diagnosis : PCR, Throat swab, to detect the viral RNA.

Treatment: Oseltamivir & Zanamivir. should be initiated within 48 hours.

Extra Explanation:

What is antigenic changes ?

- Influenza virus is highly susceptible to mutations and rearrangements within the infected host, which can lead to formation of new set of antigens expressed in the virus.
- Thus, formation of new set of antigens will create a difficulty to control the infection of the virus, which can lead to epidemic disease.
- Ex: if (Human H2) and (Avian H3 Human can't accept it) (viruses where H represent type of Hemagglutinin) unite to produce a new virus (Human H3 humans and avian can accept it and it is more aggressive)

So how can they unite ?

- By a creature which can accept both type of hemagglutinin which is usually "pigs"

Paramyxoviridae Family

- ParaInfluenza virus, RSV & Human metapneumovirus, Measles virus, and Mumps virus -

1: Parainfluenza Virus:

Enveloped virus with -ve polarity ssRNA genome with 5 se

Transmission: Inhalation of infectious aerosol droplets mainly in winter

Lab diagnosis: routine testing : direct Immunoflourecent assay (IFA), by Nasopharyngeal swab, Sputum and , Nasopharyngeal Aspirate (NPA) . Other detection : tissue culture and PCR.

Clinical syndromes:

Syndrome	Syndrome Croup or acute laryngotracheobronchitis	Bronchiolitis and Pneumonia
Infecting type	PIV Type-I, II	PIV Type-III
Host	infants and young children.	young children
symptoms	Fever, harsh cough, difficult inspiration can lead to airway obstruction which may require hospitalization and tracheostomy	_____

Treatment and prevention:

Supportive treatment, No specific treatment or vaccine available

2- Respiratory Syncytial Virus (RSV) and Human metapneumovirusI

Structural features :

Enveloped virus with (-ve polarity ssRNA).

Transmission:

- Inhalation of infectious aerosol droplets mainly in winter.
- RSV virus is very contagious with 36 days as Incubation periods
- The importance of RSV lies in its tendency to invade the LRT of infant

Clinical syndromes: :

- 1) **Bronchiolitis**:

Life-threatening disease in infants especially under 6 month of life. With respiratory distress and cyanosis, it can lead to a chronic lung disease later in life or be fatal.

- 2) **Pneumonia**: Can also be fatal in infants.

Lab diagnosis: :

- **Direct detection of the virus:**

From sputum, nasopharyngeal swab, aspirate (NPA) or respiratory secretion by direct immunofluorescent assay (IFA) and ELISA.

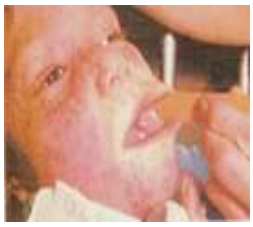
- **Other detection methods:**

Isolated of virus by cell culture from (NPA) with multinucleated giant cell or syncytia as cytopathic effect (C.P.E)or PCR.

Treatment and prevention:

- **Ribavirin** administered by inhalation for infants with severe condition.
- Infants will be hypoxic and need hospitalization for oxygen inhalation and should be isolated than other infants.
- **No vaccine** available, but passive immunization immunoglobulin can be given for infected premature infants.

3- Measles Virus



Arabic Translation:
Measles = الحصبة

Measles - causes, symptoms, diagnosis, treatment, pathology by Osmosis

Structural features :

Enveloped virus with -ve polarity ssRNA genome

Transmission:

- Inhalation of infectious aerosol droplets.
- Measles virus infects human only. Most cases in preschool children, very infectious, infection occurs mainly in winter and spring.

Clinical syndromes: :

- **Incubation period**: 7-10 days.
- **Prodromal symptoms:** High Fever, cough, conjunctive & running nose.
- **Koplik's spot** [9]: small red papules with white central dots appear mostly in buccal mucosa.
- **Rash**: Maculopapular rash first on face, trunk, extremities. it is red, & become confluent, last for 4 - 5 days, then disappears the skin become brownish, and desquamation. recovery complete in normal children with lifelong immunity & complication can occurs.

Note:
(9) little spots inside the mouth that are highly characteristic of the early phase of measles (rubeola)

Pathogenesis:

The virus infects first epithetical cells of upper respiratory tract then the virus spread to the blood causing viremia infect the endothelial cells of blood vessels, The virus reaches the lymphoid tissue where it replicates further and disseminates to the skin causing maculopapular rash

Complication:

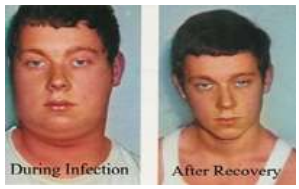
1-Encephalitis: Acute or subacute sclerosing panencephalitis (SSPE).
2-Giant cell pneumonia: in immunocompromised children is rare due to direct invasion of measles virus to lung tissue.

Lab diagnosis:

Serology by detection of IgM Ab using ELISA. in case of SSPE, detection of measles Abs in CSF or detection or viral NA using PCR.

Treatment & Prevention:

No specific treatment. prevention by giving the live attenuated vaccine (MMR) for Measles, Mumps, & Rubella (to all children 15 months age and booster dose at school entry), it give excellent long last protection.



4- Mumps Virus:

Arabic Translation:
Mumps = النكاف

Note:
(10) Complications are more common in adults

Note:
Orchitis:
inflammation of one or both testicles. usually unilateral, rarely leads to sterility.
Oophoritis:
inflammation of ovaries

It is Causing an **acute benign viral parotitis** which is painful inflammation and swelling of salivary gland and mainly parotid glands. it is a disease of children (5-15 years), but also can be seen in young adult with more complicated feature.

Structural features :

Enveloped virus with -ve polarity ssRNA genome, The viral envelope is covered by two glycoprotein spikes, hemagglutinin and neuraminidase.

Transmission:

- Inhalation of infectious aerosol droplets during sneezing and coughing, direct contact with saliva.
- Mumps virus infects human only, Highly infectious and peak in winter
- Long incubation period 18-21 days.

Pathogenesis:

Infection started in the epithelial cells of upper respiratory tract, then virus
spread by viremia to parotid gland mainly and to other organs as: testes,
ovaries, pancreas and CNS.

Lab diagnosis:

Serology by detection of IgM Ab using ELISA, cell culture and isolation of the virus from saliva, detection of viral NA using PCR.

Clinical syndromes:

starts with moderate fever, malaise, pain on chewing or swallowing, particularly acidic liquids.
Sudden onset of fever and painful swelling of parotid gland.
Self-limiting disease resolve within one week.
Solid and long-life immunity developed.

Complications: [10]

Aseptic meningitis, Encephalitis, Pancreatitis, Thyroiditis, Orchitis and Oophoritis. inflammation of one or both testicles.

Treatment& & Prevention:

No specific antiviral treatment but there is the Vaccine which is MMR Live attenuated vaccine for Measles, Mumps and Rubella given to all children in their 15 month and the booster dose at school entry. It Gives excellent long last protection

Objective

1. Acquire the basic knowledge about structure and classification of these viruses infecting the respiratory system.
Including (Coronavirus (**SARS** & Middle East Respiratory Syndrome - Coronavirus COV (**MERSCoV**), **Rhinovirus**, **Enteroviruses**, **Adenovirus**, and **EBV**)
2. Describe their epidemiology and pathogenesis
3. Identify the Target group and modes of transmission and Clinical manifestations.
.
4. Describe their epidemiology and pathogenesis
5. Know the laboratory diagnosis, and treatment of these infections.
6. Recognize the methods for prevention.

Coronaviridae Family

- SARS CoV and MERS CoV -

Structural features:

Enveloped virus with +ve polarity ss-RNA genome.

Transmission:

Inhalation of infectious aerosol droplets.

Clinical features:

It is the second cause of common cold [1.] It Cause zoonotic diseases and can
infects humans and animals

Treatment:

No specific antiviral treatment. For severe cases, current treatment includes
care to support vital organ functions.

Severe forms of Corona virus:

- 1) Severe Acute Respiratory Syndrome (SARS)
- 2) Middle East Respiratory Syndrome (MERS)

1- Severe Acute Respiratory Syndrome (SARS):

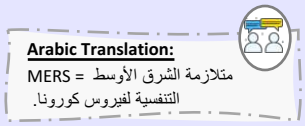
In winter of 2002, a new respiratory disease known as (SARS) emerged in China after a new mutation of coronavirus. The animal reservoir may be cats or bats. Then the disease spread worldwide due to travelling. It is Associated with high mortality due to respiratory failure.

Symptoms:

SARS starts with high fever followed by cough with difficulty in breathing (atypical pneumonia).

2- Middle East Respiratory Syndrome (MERS):

In September 2012, a case of novel (New) coronavirus infection was reported involving a man in Saudi Arabia who was admitted to a hospital with pneumonia and acute kidney failure. This virus has been named as Middle East Respiratory Syndrome- CoronaVirus (MERS-CoV) ,virus closely related to several bat coronaviruses.



Epidemiology:

MERS-CoV infected several human cells , including lower but not upper respiratory, kidney ,intestinal, and liver cells. So far, all the cases have been linked to countries in and near the Arabian Peninsula. Highly infectious, Peak in winter, with incubation period
(2-14 days).

Transmission:

close contact with ill people, it's not epidemic or pandemic., close contact with infected animals

Prevention:

People should protect themselves from respiratory illnesses by taking everyday preventive actions:

- Wash hands often with water and soap or use an alcohol-based hand sanitizer.
- Cover nose and mouth with a tissue when cough or sneeze.
- Avoid touching eyes, nose and mouth with unwashed hands.
- Avoid personal contact with sick people
- Clean and disinfect frequently touched surfaces such as toys and doorknobs.

Risk group:

- Individuals with weakened immune systems
- People with pre-existing medical conditions (or comorbidities) such as diabetes, cancer, and chronic lung, heart, and kidney diseases

Clinical features:

- Some people also had gastrointestinal symptoms including diarrhea and nausea/vomiting. Some infected people had mild symptoms (such as cold like symptoms) or no symptoms at all and they recovered completely.
- Most people with confirmed MERS CoV infection developed severe acute respiratory illness.
- They had fever, cough, and shortness of breath.

Complication:

Severe complications include pneumonia and kidney failure. About 30% of infected people died (specially those who had included in the risk group)

Diagnosis:

- Detection of the viral nucleic acid (NA) by PCR (Polymerase Chain Reaction).
- Other methods : Isolation of the virus from Nasopharyngeal aspiration (NPA) by cell culture.

Picornaviridae Family

- Rhinovirus and Coxsackieviruses -

1- Rhinovirus :

Structural features:

Nonenveloped virus with (+ve polarityssRNA) genome, more than 100 serotypes available.

Transmission:

Inhalation of infectious aerosol droplets.

Clinical features:

- Rhinoviruses are the 1st cause of common cold, responsible of 60% of all cases.
- The main symptoms of common cold are sneezing, clear watery nasal discharge with mild sore throat , and cough.

Lab Diagnosis:

Detection for viral NA by using PCR and direct immunofluorescence assay.

Treatment and prevention:

Usually self-limiting disease, No specific treatment, and No vaccine available.

2- Coxsackieviruses :

Structural features:

Non-enveloped virus with + polarity ssRNA genome Coxsackieviruses group A & B,Echovirus, Enteroviruses.

Transmission:

Inhalation of infectious aerosol droplets.

Clinical features:

- Coxsackieviruses cause herpangina and pharyngitis
- Echovirus & other Enteroviruses cause respiratory symptoms.

Lab Diagnosis:

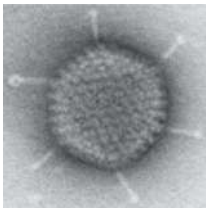
routine testing by detection of the viral NA from NPA using PCR.

Treatment and prevention:

Usually self-limiting disease, no specific treatment, and no vaccine available.

Adenoviridae Family

- Adenovirus -



Structural features:

Non-enveloped virus with ds-DNA genome .

Pathogenesis:

Adenovirus infects epithelial cell lining respiratory tract, conjunctiva, urinary tract,
gastrointestinal tract and genital tract. But it can't affect the brain and cause meningitis or encephalitis.

Lab Diagnosis:

Routine testing by direct detection of the Ag from NPA by direct IFA.
Other detection methods: tissue culture, PCR.

Clinical syndrome:

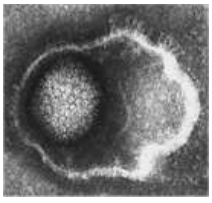
- 1.Phrayngitis and tonsillitis
- 2.Pharyngioconjunctivitis
- 3.Conjunctivitis
- 4.Pneumonia: in preschool children.
- 5.Gastroenteritis
- 6.Acute hemorrhagic cystitis.
- 7.UTI (Cervicitis and urethritis).

Treatment and prevention:

No specific treatment or vaccine.

Herpesviridae Family

- Epstein - Barr Virus (EBV) -



Structural features:

enveloped , icosahedral dsDNA virus.
- It is lymphotropic.
- It has oncogenic properties and can cause :
(Burkitt's lymphoma. Nasopharyngeal carcinoma).

Epidemiology:

- **Distribution:**

worldwide (Mainly in teenagers & young adults)

- **Relation between Age and Socio-economic status:**

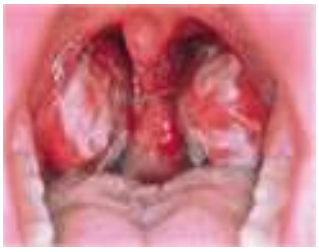
Low Socio-economic class → early childhood. (Mild)
High Socio-economic class → adolescence . (Severe)

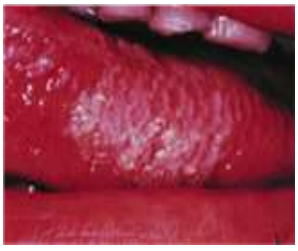
Transmission:

Mainly through Saliva and knowing as [kissing disease], and rarely through Blood.

Clinical features:

Immunocompetent host	Immunocompromised host
○ Asymptomatic (in young children) ○ Infectious mononucleosis (in adolescence) [or glandular fever] ○ Incubation period = 4-7 weeks ○ Can present with Fever, sore throat , tonsillitis, malaise , pharyngitis, hepatitis, hepatosplenomegaly & abnormal LF. ○ Complications : (acute airway obstruction, splenic rupture, CNS inf)	**Can cause :** ○ Lymphoproliferative disease (LD). ○ oral hairy leukoplakia (OHL) ○ Nasopharyngeal carcinoma ○ Burkitt's lymphoma

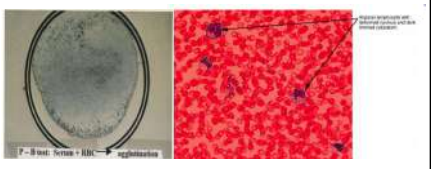




Diagnosis:

○ **Hematology** : WBC .lymphocytosis (Atypical lymphocytes)
○ **Serology tests**:

1. Non-specific AB test ;
- Heterophile Abs +ve.
- Paul-Bunnell or monospot test.



2. EBV-specific AB test :
- Detection of IgM Abs to EBV capsid antigen by ELISA .

Treatment and prevention:

there is no treatment or vaccine for infectious mononucleosis.

Viral infections of the respiratory system

Influenza Virus

Distinguishing Features
- Envelope contains two glycoproteins, H and N
- Used to serotype virus

Reservoir
- Influenza A (birds, pigs, humans)
- Influenza B (humans only)

Transmission
- Direct contact
- Respiratory
- 1997 H5N1 strain jumped directly from birds to humans
- 2009 H1N1 strain—quadruple reassortment virus (North American swine, avian, human; Asian and European swine)

Pathogenesis
- Antigenic drift
    - Influenza A and B – Slight changes in antigenicity due to mutations in H and/or N – Causes epidemics
- Antigenic shift
    - Influenza A only
    - Rare genetic reassortment
    - Coinfection of cells with two different strains of inf luenza A (H5N1 and H3N2); reassortment of segments of genome – Production of a new agent to which population has no immunity – Responsible for pandemics

Disease: influenza
- Headache and malaise
- Fever, chills, myalgias, anorexia
- Bronchiolitis, croup, otitis media, vomiting (younger children)
- Pneumonia/secondary bacterial infections
- Can lead to Reye syndrome or Guillain-Barré syndrome

Diagnosis
- Rapid tests (serology)
- Clinical symptoms plus season

Treatment
- Amantadine/rimantadine (current isolates are commonly resistant):
    - Inhibit viral uncoating
    - Administer orally
- Zanamivir/oseltamivir
    - Neuraminidase inhibitors
    - Zanamivir is inhaled
    - Oseltamivir is given orally

Prevention

- Killed vaccine
  - Two strains of influenza A (H3N2, H1N1, for example) and one strain of influenza B are incorporated into the vaccine
- Live, attenuated vaccine
  - Intranasal administration
  - Similar composition
  - No longer recommended

Adenoviridae

Virus Characteristics

- dsDNA, nonenveloped
- Hexons, pentons, and fibers

Viruses of Medical Importance

- Adenovirus
- Over 50 serotypes
- Subgroups A–F

Adenovirus

Reservoir: ubiquitous in humans and animals

Transmission: respiratory, fecal-oral, direct contact

Pathogenesis

- Penton fibers act as hemagglutinin
- Purified penton fibers are toxic to cells
- Lytic, latent, or transforming: virus is lytic in permissive cells and can be chronic or oncogenic in nonpermissive hosts; the adenoviruses are standard example of permissive host (where virus is produced) and nonpermissive host (where virus is not produced but transformed)

Disease

- Acute respiratory disease (ARD) and pneumonia: spring and winter peak incidence; children, young military recruits, college students serotypes 4 and 7; cough, conjunctivitis, fever, pharyngitis, hoarseness
- Pharyngoconjunctivitis: swimming pool conjunctivitis, pink eye; fever, sore throat, coryza, red eyes; nonpurulent
- Acute hemorrhagic cystitis: mostly boys age 5–15; dysuria, hematuria
- Gastroenteritis: daycare (not as common as rotavirus); serotypes 40 and 41
- Myocarditis
- Transplant patients

Diagnosis: serology; ELISA

Treatment: supportive care for otherwise healthy patients; cidofovir and alpha globulins for immunocompromised or severely diseased

Prevention: live, nonattenuated vaccine

Adenovirus – A den of lions

1. Cold dark shades of blue with some red – DNA Virus (Blue), Adenoids and oropharynx (red)
2. Lions are all yawning exposing tonsils – tonsillitis
3. Naked David – Naked virus
4. Dripping stalactites - Transmission via respiratory droplets
5. Feces – Fecal oral transmission
6. Children in cam, kid swimming in red pool - Most at risk is little children, military recruits, and public pools
7. Blood dripping from David crotch – causes hemorrhagic cystitis
8. 3 major disease processes
   a. Tonsillitis
   b. Hemorrhagic cystitis
   c. Lions w/ red glowing eyes – viral conjunctivitis
9. Tranquilizer gun w/ "live lions" sign - Soldiers will always get a vaccine, a live one, for military recruits

SKETCHY CORNER

Viral infections of the respiratory system

Coronaviridae

Family Characteristics
- Enveloped, helical
- Positive-sense ssRNA
- Hemagglutinin molecules make up peplomers on virus surface, which give shape like sun with corona

Viruses of Medical Importance
- Coronavirus
- Severe acute respiratory syndrome coronavirus (SARS-CoV)

Coronavirus
- Second most common cause of the common cold
- Winter/spring peak incidence

SARS-CoV

Reservoir: birds and small mammals (civet cats)

Transmission: respiratory droplets; virus also found in urine, sweat, and feces; original case is thought to have jumped from animal to human

Disease: severe acute respiratory syndrome (SARS)
- Travel to Far East or Toronto
- Clinical case definition includes fever of >38.0 C (100.4 F), flu-like illness, dry cough, dyspnea, and progressive hypoxia
- Chest x-ray may show patchy distribution of focal interstitial infiltrates

Diagnosis
- Includes clinical presentation and prior history of travel to endemic area or an association with someone who recently traveled to endemic area
- Lab tests: detection of antibodies to SARS-CoV, RT-PCR, and isolation of the virus in culture

Treatment: supportive; ribavirin and interferon are promising

MERS-CoV (Middle Eastern Respiratory Syndrome)

Reservoir: bats and camels

Disease and transmission: similar to SARS

Measles Virus

Distinguishing Characteristics: single serotype; H-glycoprotein and fusion protein; no neuraminidase

Reservoir: human respiratory tract

Transmission: respiratory route

Pathogenesis: ability to cause cell: cell fusion → giant cells; virus can escape immune detection

Viral infections of the respiratory system

Disease

- Measles: presentation generally 3 Cs (cough, coryza, and conjunctivitis) with photophobia; Koplik spots → maculopapular rash from ears down → giant cell pneumonia (Warthin-Finkeldey cells)
- Subacute sclerosing panencephalitis: rare late complication (mean time 7–10 years); mutant measles virus persists in brain, acts as slow virus; chronic CNS degeneration

Diagnosis: serology

Treatment: supportive, ribavirin (experimental)

Prevention: live, attenuated vaccine, MMR and meningoencephalitis Diagnosis: clinical; serology; ELISA, IFA, hemagglutination inhibition

Mumps Virus

Distinguishing Characteristics: negative-sense ssRNA; helical; enveloped; single HN glycoprotein, also F protein; single serotype

Reservoir: human respiratory tract

Transmission: person to person via respiratory droplets

Pathogenesis: lytic infection of epithelial cells of upper respiratory tract and parotid glands → spread throughout body

Disease: mumps

- Asymptomatic to bilateral parotitis with fever, headache, and malaise
- Complications include pancreatitis, orchitis (leads to sterility in males)

Treatment: supportive

Prevention: live, attenuated vaccine, MMR

Epstein-Barr Virus (EBV)

Reservoir: humans EBV

Transmission: saliva, 90% of adult population is seropositive

Pathogenesis

- Virus infects nasopharyngeal epithelial cells, salivary and lymphoid tissues → latent infection of B cells (EBV binds to CD21 and acts as a B-cell mitogen) → results in production of atypical reactive T cells (Downey cells), which may constitute up to 70% of WBC count
- Heterophile antibodies are produced (due to B cell mitogenesis)

Diseases

- Heterophile-positive mononucleosis, “kissing disease”: fatigue, fever, sore throat, lymphadenopathy, splenomegaly; latency in B cells
- Lymphoproliferative disease: occurs in immunocompromised patients; T cells can’t control B-cell growth
- Hairy oral leukoplakia: hyperproliferation of lingual epithelial cells; occurs in AIDS patients

Malignancies

- Burkitt lymphoma: cancer of the maxilla, mandible, abdomen; Africa; malaria cofactor; AIDS patients; translocation juxtaposes c-myc onco- gene to a very active promoter such as immunoglobulin gene promoter
- Nasopharyngeal carcinoma: Asia (most common cancer in southern China); tumor cells of epithelial origin
- Hodgkin and non-Hodgkin lymphoma

Diagnosis: heterophile-antibody positive (IgM antibodies that recognize Paul-Bunnell antigen on sheep and bovine RBCs)

Treatment: symptomatic, for uncomplicated mononucleosis

Picornaviridae

Family Characteristics

- Small, naked, icosahedral
- Positive-sense ssRNA
- Summer/fall peak incidence
- Resistant to alcohol, detergents (naked capsid)
- Divided into genera:
    - Enteroviruses: fecal-oral transmission, do not cause diarrhea, peak age <9 years, stable at pH 3
    - Rhinoviruses: not stable under acidic conditions, growth at 33 C (91.4 F)
    - Heparnavirus

Viruses of Medical Importance

- Enteroviruses (acid-stable): polio virus; coxsackie virus A; coxsackie virus B; D68; echoviruses
- Rhinoviruses (acid labile)
- Heparnaviruses: HAV

Virus	Transmission	Pathogenesis	Diseases	Diagnosis	Treatment/ prevention
Enterroviruses					
Piolo	Fecal-oral	Virus target anterior horn motor neuron	Asymptomatic to fever of unknown origin; aseptic meningitis; paralytic piolo (flaccid asymmetric paralysis, no sensory loss)	Serology (virus absent from CSF)	No specific Antiviral/ live vaccine (Sabin); killed vaccine (Salk)

Viral infections of the respiratory system

Virus	Transmission	Pathogenesis	Diseases	Diagnosis	Treatment/ prevention
Enterroviruses					
		Neural fatigue	Post-piolo syndrome	Patient with piolo decades earlier, progressive muscle atrophy	
Coxasackie A	Fecal oral	Fecal-oral spread with potential for disseminatio n to other organs; often asymmetric with viral sheeding	Hand, foot, and mouth (A16); herpangina; aseptic meningitis; acute lymphoglandular pharyngitis; common cold	Virus isolation from throat, stool, or CSF	No specific treatment/ handwashi ng
Coxasackie B	fecal oral	As above	Bornholm disease (devil's grip); aseptic meningitis; sever systematic disease of newborns; **myocarditis**	As above	No specific/ handwashi ng
D68	Fecal-oral, respiratory	Invade mucosa, lymphatics; potential spread to CNS	Motor-neuron disease, respiratory disease	Serology/RT-PCR	No specific/ IVIG/ handwashi ng
Echoviruses	Fecal-oral	As above	Fever and rash of unknown origin; aseptic meningitis	As above	No specific/ handwashi ng

Viral infections of the respiratory system

Virus	Transmission	Pathogenesis	Diseases	Diagnosis	Treatment/ prevention
Rhinovirus					
Rhinovirus	Respiratory	Acid lablie; grows at 33 C (91.4 F); over 100 serotypes	Common cold; #1 cause, peak summer/fall	Clinical	No specific/ handwashing
Heparnavirus					
HAV	Fecal-oral	Virus targets hepatocytes; liver function is impaired	**Infectious hepatitis**	IgM to HAV serology	No specific/ killed vaccine and hyperimmune serum

Paramyxovirus – Paranormal Mixer

1. Moon w/ orange hues - Single stranded Negative Sense RNA Virus
2. Replicates in the cytoplasm – only exception is orthomyxovirus
3. Ghosts in sheets and envelopes – Enveloped
4. Droplets in sprinkler – respiratory droplets transmission
5. Live Puppet show w/ pregnant women running away– Live MMR vaccine, do not give to pregnant women
6. Ghost weasel on left and ruby dress – **Measles and Rubeola** (same Name)
7. 4 C's on the vest - 4 C's to diagnose measles, Cough, Conjunctivitis, Koplic Signs, Coryza
8. Coughing, drippy nose, red eyes on weasel
9. Bowl of blue marbles - koplic spots (blueish spots on a red background near the molars on the mucosa)
10. Sweat drops on Poppa weasel – fever of 104
11. Rubies falling down the head downwards - Maculopapular rash late, starts on the head and works down
12. Solid dress – confluence rash
13. 2 lungs bow tie – complications, pneumonia
14. Weasel with turban - Subacute sclerosing pan encephalitis – look for anti measles antibodies in the CSF – no treatment
15. Tales of SSPEnce – SSPE
16. Tentacles w/ Berries stuck together - HA (causes RBC's to stick together), and
17. Hand stuck together - fusion proteins causes multinucleated giant cells, found in lymphoid tissue, causes red inclusion bodies.
18. Party hat to weasel friend w/a look - Vitamin A to reduce mortality and complications
19.
20. Mumps mummies w/ big cheeks – **Mumps** replicates in salivary glands, can cause
21. Single orchid - orchitis w/ impaired fertility and testicular atrophy
22. Neck brace - Meningitis can also happen
23. Vaccine puppet show – MMR Vaccine
24. Fusion protein, Neuraminidase (scapel), And HA
25. Tombstone on the right w/ little baby ghosts - Respiratory Syncytial Virus (RSV) –
26. Baby holding Letter G - Attaches to G protein to infect respiratory epithelial cells
27. Ghost baby tree and infiltrates - Bronchiolitis, pneumonia, Most common cause of these in infants
28. Ghost baby w/ sticky hands - Virulence factors – syncium – Fusion protein causing them to stick together
29. Ribs surrounding baby kids - Ribavirion can be used to treat in adults
30. Extra Pale w/ IgG rattle covered in fusion slime - Palivisumab – monoclonal antibody,
31. Seals in the background - Parainfluenza – seal bark cough
32. 3 wolves – all 3 virulence factors, NA, HA, Fusion
33. Church w/ steeple – steeple radiographic sign on xray, Croup – inspiratory strider a howling noise (church door open) - laryngeotracheobronchitis

SKETCHY CORNER

Coronavirus – Kingdom of SARS

1. Bright Pos Sun – RNA Pos SS
2. Crown – Corona
3. King with crown wearing a robe – Encapsulated virus
4. Missing statue of David – not naked
5. Long spiraling road with helical trees – helical virus
6. Sneezing and blowing nose – causes common cold
7. Kings respiratory tract design - SARS and Middle east respiratory syndrome, acute bronchitis
8. Castle with king outside – Castle (nucleus) king outside -Replicates in the cytoplasm

SKETCHY CORNER

Epstein-Barr virus – Ye Olde Epstein Bar

1. Blue hues – Double stranded DNA
2. Causes infectious mononucleosis.
3. People trying to kiss – spread through mouth secretions – Kissing disease
4. **Guy sweating w/ fever – has infectious mono**
5. Knocking over the drink onto the knight, the night is furious and grabs on the back of neck – **tender lymphadenopathy in posterior cervical**
6. **Armor w/ T on it – T cell**
7. **B on shoulder and sword – cytotoxic T cells TH8**
8. Knight is reacting in a violent way – **reactive lymphocytosis, aka downy cells**
9. Stains on coat – look like a downy cell w/ oval or folded in nucleus
10. Random cow behind bar w/ spleen spot - T Cells proliferate **causing splenomegaly**
11. Archer asleep w/bow next to him in white - Targets B lymphocytes (white cells) in a new host, EBV remains Latent in B Cells
12. Must B 21- EBV Envelope (glycoprotein) binds to CD 21, that is a receptor for compliment component CD3, to infect B Cells
13. Man's mouth w/ tonsillar exudates – Pharyngitis
14. Differs from strep pharyngitis (more often seen in children), mono occurs in late teens and adulthood (most likely asymptomatic in children)
15. Red pencil - Develop a maculopapular rash w/ penicillin treatment
16. Amoxicillin and ampicillin – reaction is not an allergic reaction
17. **Crab - Increased risk factor for 3 cancers**
    a. **OWL picture in the background - Weakened immune systems develop B cell lymphoma, Hodgkin's lymphoma mixed cellularity.**
    b. **Kid in Africa clothing w/ mouthful of crab puffing out cheeks - Non Hodgkin's lymphoma, Burkett lymphoma, Most common translocation is t8:14**
    c. **Crab pinching nose - Asian people nasopharangyel carcinoma**
18. **Old guy w/immunocompromised cane and hairy beard - Oral hairy leukoplakia – not a precancerous lesion, in HIV pts**
19. Medieval dart board – Monospot IgG test - Diagnosed during acute infection secretes heterophile sheep antibodies that agglutinate

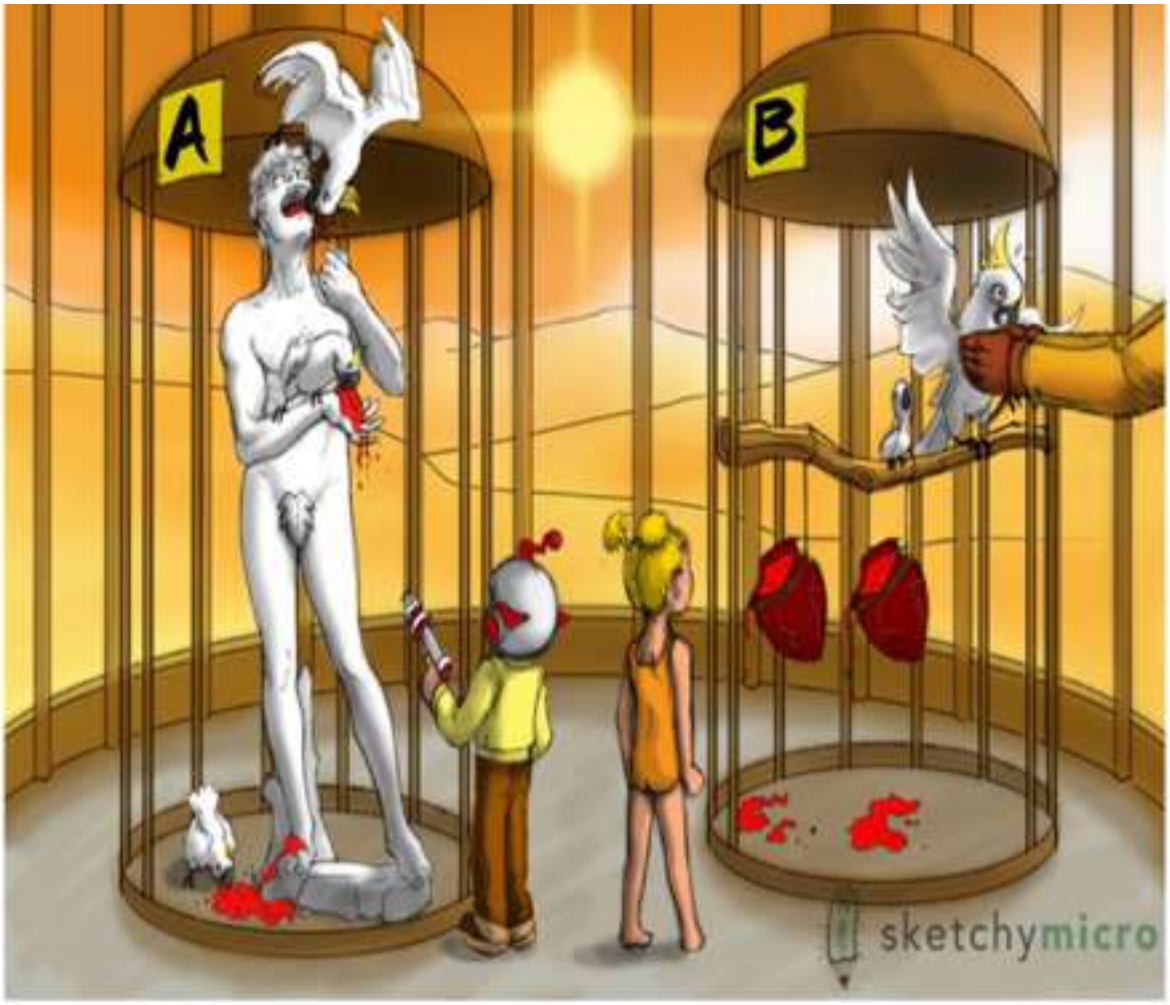
No contact jousting allowed in the bar - Must **avoid contact sports due** to the risk of splenic rupture

SKETCHY CORNER

Rhinovirus – Rhino Petting Zoo

1. Sun w/ pos sign and orange hue – Pos RNA Single Strand
2. Small rhinos – pico virus
3. Statue of David – Naked
4. Camera in David's hand
5. Lemon w/ rhino sneezing - **Transmitted via inhalation** due to it being **acid labile**
6. Please wash hands – transmitted through fomites
7. One camera w/ strap wrapped around horn – Mechanism: attaches to I-CAM1 to enter host cells
8. Hanging out under shade tree with thermometer – needs to keep to cool temp and grows best in 33c of the upper respiratory tract
9. Rhino playing in mud that is dripping down chin onto the chest - Upper respiratory tract
10. Multicolor canopy - Ridiculous number of serotypes, 113 total, so no vaccine

SKETCHY CORNER



Coxsackievirus – Coxsackie Cockatoos

1. Orange Hues with Sun – Pos Sense SS RNA virus
2. Pico- Picornavirus
3. Statue of David – Naked virus
4. A and B cages – 2 flavors of cocksackie virus
5. David red hands, foot, and mouth – hand, foot, and mouth disease
6. Red seeds – red vesicular rash
7. Kid with meningitis helmet – aseptic (no bacteria on gram stain) meningitis
8. Little girl in swimsuit – summertime
9. Cocksackie B
10. Heart seed bags – dilated cardiomyopathy
11. Zoo keeper grabbing cockatoo by chest- devils grip, Bornholm's disease – extreme unilateral sharp pain in chest – pleurodynia
12. Txt is supportive care

SKETCHY CORNER

Picornavirus Family – The Peak-orna Animal Nursery

1. Sun w/ positive sign – Pos sense single strand RNA
2. Peak – Picornavirus
3. Statue of David – Naked Viruses
4. Feces all over - Fecal oral transmission
5. Rhinovirus is respiratory. Don't get confused
6. Coin machine – insert and you get an output, everything is inside the coin machine to make it work - POS Sense RNA Replication uses the host transcription factors, since it is the same sense as host cell, it only needs host RNA polymerase.
7. Tickets start together but break up at the end - Viral RNA is transmitted into long protein product that contains viral proteases to cleave it.
8. only going to illustrate when in nucleus - All RNA positives replicate in the cytoplasm, Host cell RNA polymerase is in the cytoplasm. So this makes sense.
9. Hep A hippos –hippo arm labeled with "A" tag and Liver sign
10. Aviary – enterovirus – polio (flamingo) – Cocksackie And B cockatoos, Mockingbirds (echovirus)
11. Aviary shaped like a head w/ "100% aseptic inside" – Aseptic meningitis
12. Bags of food to represent lab findings
13. No sugar added – glucose levels normal
14. No roganisms – nothing found when plated, aseptic
15. Source of protein – protein is elevated
16. Space helmet - meningitis
17. Rhino – Rhinovirus – common cold – not transmitted fecal oral.
18. Mud on rhino face to symbolize a URI

SKETCHY CORNER

Objective

1. Define rhinitis and cough.
2. Classify drugs used in the treatment of rhinitis.
3. Expand on the pharmacology of different drug groups used in the treatment as; antihistamines, leukotriene antagonists, corticosteroids, decongestants and anticholinergics.
4. Describe the pharmacology of different expectorants and mucolytics used in the treatment of productive cough.
5. Describe the pharmacology of antitussives (cough suppressants)

Rhinitis

Definition :

It is the irritation and/or inflammation of mucous membrane Inside nose.

Types :

- **Acute** : Persist 7-14 days.
- **Chronic** : Persist more than 6 weeks.
- **Allergic** : seasonal; hay fever and perennial (persistent)
- **Infectious** : infection with bacteria, fungi & viruses.

Signs & Symptoms :

Rhinorrhea "Runny nose", Sneezing, Nasal congestion, post nasal drip and Systemic effect such as fever and body aches".

Treatment :

- **Environmental control** (dust control, pets etc.)
- **Allergen immunotherapy** (vaccines etc.) *for modulating the immune response.

Preventive therapy

Pharmacological

- **Anti-Histamine** (H1-receptor antagonist)
- **Anti-Allergics**
  -Cromolyn sodium (masts cell stabilizer)
  -Montelukast (Leukotriene receptor antagonist)
- **Corticosteroids**
- **Decongestants** (alpha-adrenergic agonists)
- **Anti-Cholinergics**
- **Antibiotics** (if there's a bacterial infection)

Histamine

Introduction :

Histamine has no clinical application, but Antihistamines have important therapeutic applications. Histamine is a chemical messenger mostly generated in mast cells that mediates a wide range of cellular responses including :

- H1 action : Allergic and inflammatory responses, Antihistamine can work here
- H2 action : Gastric acid secretion, Antihistamine can work here
- H3 action : Neurotransmission in parts of the brain
- H4 action :Regulating immune responses

Antihistamines (H1 receptor antagonists):

The term antihistamine without modifying objective refers to the classic H1-receptor blockers. These drugs do not interfere with the formation or release of histamine. They block the receptor mediated response of a target tissue.

<table>
<tr><th>1st generation</th><th>2nd generation</th><th>3rd generation</th></tr>
<tr><td>Alkylamine: Chlorpheniramine (Chlorphenamine)
Ethanolamine: Dimenhydrinate
Diphenhydramine
Ethylenediamine: Antazoline</td><td rowspan="2">Cetirizine</td><td>Levocetirizine</td></tr>
<tr><td>Phenothiazine: Promethazine
Piperazine: Cyclizine
Piperidine: Azatidine
Ketotifen
Miscellaneous: Cyproheptadine</td><td>Fexofenadine
(least sedating)</td></tr>
<tr><td></td><td>Loratadine
(has advantage over other 2nd generation drugs that it has less effect on clarity “less sedating effect”)</td><td>Desoloratadine</td></tr>
<tr><td>short duration
-Interactions with enzyme inhibitors (macrolides, antifungal, calcium antagonists)
-Additive pharmacodynamic ADRs</td><td colspan="2">long duration (better control)
-No drug interaction
-Minimal ADRs since they are more specific for H1 receptors</td></tr>
<tr><td>o The older 1st generation drugs are still widely used because they are effective and inexpensive.
o These drugs penetrate the BBB and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects.</td><td colspan="2">o Second generation (non-sedating) agents are specific for H1 receptors and they carry polar groups, they do not penetrate the BBB causing less CNS depression</td></tr>
<tr><td colspan="3"><u>All are used systemically or topically</u></td></tr>
</table>

H1 Blockers Have:

- **Rhinitis**
- **Conjunctivitis**
- **Urticaria**
- **Flu**

Good control of:

Poor control of:

- **Asthma**
- **Otitis**
- **Anaphylaxis**
- **Sinusitis**
- **Atopic dermatitis**

Indication :

Note :
You have to differentiate very well between Alpha-adrenergic and cholinergic. And know that it has therapeutic effects on rhinitis or any H1 receptors, while other blocking effects on muscarinic or adrenergic receptors are considered side effects. So cardiac patients have to be careful when taking these drugs

Indications Linked to H1 Block

-Allergies
-Itching (Even if non allergic)
-Others:
- Insomnia
- Sleep aid
- Vertigo
- Anxiety
- Cough

Antihistamines

Indications not linked to H1 block

Cholinergic	α Adrenergic	Serotonin	Histamine H1	~~Histamine H2~~
⬆Dry mouth ⬆Urinary retention ⬆Sinus tachycardia	⬆Hypotension ⬆Dizziness ⬆Reflex tachycardia	⬆Appetite	⬇Allergic inflammation, itching, sneezing, rhinorrhea ⬇Neurotransmission in CNS ⬆Sedation ⬇Cognitive & psychomotor performance ⬆Appetite	

Side Effects Interactions

Drugs: antihistamine

1- Antihistamine Drugs (FIRST LINE)	
Actions	● The action of all the H1 receptor blocker is qualitatively similar ●They are much **more effective** in **<u>preventing symptoms</u>** than reversing them once they have occurred ●Most of these drugs have additional effects (especially 1st generation) unrelated to their blocking **H1 receptors**, which probably reflect binding of H1 antagonists to: ○ Cholinergic ○ Adrenergic ○ Serotonin receptors
Therapeutic Uses	**1.Allergic rhinitis:** relieves rhinorrhea, sneezing, and itching of eyes and nasal mucosa **2. Motion sickness ,** sleeping & anxiety. **3. Nausea and vomiting**: promethazine **4.Common cold:** dries out the nasal mucosa. Often combined with nasal decongestant and analgesics **5. Allergic dermatoses:** can control itching associated with insect bites.
Pharmacokinetics	● H1 receptor blockers are well absorbed after oral administration ● Maximum serum levels occurring at 1-2 hours ● Average plasma half life is 4 to 6 hours ●have high bioavailability and distributed to all tissues including CNS ● Metabolized by the hepatic cytochrome P450 system ●Excretion occur via kidney except **fexofenadine** excreted in feces unchanged
ADRs	● **Sedation** ● **tinnitus** ● **fatigue** ● **dizziness** ● **blurred vision** ● **dry mouth.** These reactions were more evident in 1st generation.
Drug interaction	● **CNS depressants** ● **cholinesterase inhibitors**
Over-dose	The most **common** and **dangerous** effects of acute poisoning are those **on CNS**; **including hallucinations, excitement, ataxia** and **convulsions**

Note :
Ataxia: abnormal gait

Antihistamines - Learn with Visual Mnemonics! by VL Studios

Antihistamine Pharmacology by NerdyNutter

Drugs: Anti-allergic

2- Anti-allergics		
Type	**Mast cell stabilizers**	**Leukotriene receptor antagonists**
Example	Cromolyn (another name for cromoglycate) and Nedocromyl	Montelukast
M.O.A	Histamine release (mast cell stabilizers by inhibiting Cl channels), i.e. can act only as a prophylactic; it does not antagonize releases histamine.	Block leukotriene action
Uses	○ **Used in children for prophylaxis of perennial allergic rhinitis** should be given on daily basis and never stop abruptly even if the child is showing an improvement	**for prophylaxis of lower respiratory tract allergies** (e.g. perennial allergen, exercise or aspirin induced asthma) **more than on upper respiratory tract allergies** (e.g. chronic rhinosinusitis)
ADRs	Can induce cough, wheezes, headache, rash, …etc.	As in asthma

Note :
We can't use antihistamine in asthma because the chemical mediator is leukotriene not histamine

Drugs: Corticosteroids

3- Corticosteroids (for severe cases of rhinitis and asthma)	
Example	Beclomethasone, budesonide and fluticasone
M.O.A	It has Anti-inflammatory effect by blocking phospholipase A2 and arachidonic acid synthesis which lead to inhibit prostaglandins & leukotrienes synthesis that's why corticosteroids are important in asthma? inhibits the synthesis of leukotrienes.
Uses	○ Administered topically (inhaled) as steroid spray ○ Given if severe intermittent or moderate persistent symptoms Local corticosteroids are preferably used more than systemic ones. ○ Why? To reduce the side effects.
ADRs	Nasal irritation, fungal infection, hoarseness of voice

Note :
Effectiveness of different drug groups in controlling symptoms of Rhinitis :

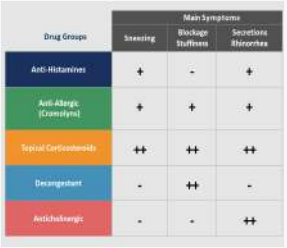
Drug Groups	Main Symptoms		
	Sneezing	Blockage Stuffiness	Secretions Rhinorrhea
Anti-Histamines	+	-	+
Anti-Allergic (Cromolyns)	+	+	+
Topical Corticosteroids	++	++	++
Decongestant	-	++	-
Anticholinergic	-	-	++

Drugs: Decongestants

4- Decongestants		
Type	**Systemic**	**Topical**
Example	Pseudoephedrine	**1-Phenylethylamines**: ○Phenylephrine ○Methoxamine **2-Imidazoline**: ○ Naphazoline ○Oxymetazoline HCL ○Xylometazoline HCL
M.O.A	α-adrenergic agonists. They make vasoconstriction of blood vessels in nasal mucosa & reduce the rhinorrhea.	
Uses	Treatment of nasal stuffiness	
ADRs	nervous , insomnia, tremors,palpitations, and hypertension.	Can cause Rebound nasal stuffiness (repeated administration 10 days -2 weeks)
C.I	hypertension, heart failure, angina pectoris, hyperthyroidism and glaucoma.	

Note :
Pseudoephedrine has many side effects because of the ephedrine which is a sympathomimetic

Note :
Effectiveness of different drug groups in controlling symptoms of Rhinitis :



Drugs: Anticholinergics

5- Anticholinergics	
Example	Ipratropium
Uses	○ Nasal drops to control rhinorrhea (excess nasal secretions & discharge), so very effective in vasomotor rhinitis (watery hyper-secretion). ○ Bronchodilator in asthma.
ADRs	Minimal systemic side effects (wheezing, bladder pain, cough producing mucus).

Cough

How Do We Cough? - The Mechanism of Coughing - Cough Reflex Animation - Learn Human Body by Science Art

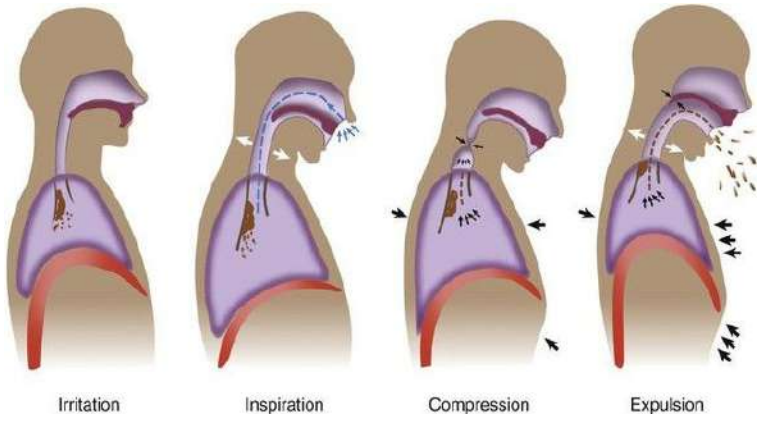
Introduction:

The respiratory tract is protected mainly by:

- Mucociliary Clearance , it ensures optimum tracheobronchial clearance by forming sputum in optimum quantity & viscosity.
- Cough Reflex, it exhales sputum out, if not optimally removed by the mucociliary clearance mechanism and ciliary movements.

What is Coughing ?

- Coughing is sudden expulsion of air from the lungs through the epiglottis at an amazingly fast speed which reach (100 miles/ hrs.) to get rid of unwanted irritants.
- Abdominal & intercostal muscles contract, against the closed epiglottis, so the pressure of air is forcefully expelled to dislodge the triggering irritant.



Types :

- **Productive** or wet which is usually Useful.
- **Dry** or irritant, usually is not useful, and could be secondary to irritant vapors, gases, infections, and cancer.

Treatment :

- For **Productive Cough**:

- Mucolytics
- Expectorants

- For **Non-productive (Dry) Cough**:

- Antitussive Agents (cough suppression)

Drugs: Expectorants

Expectorants: act by removal of mucous through different types of stimulations

	Reflex Stimulation	Direct Stimulation
M.O.A	Irritate GIT ↓ stimulate gastropulmonary vagal reflex ↓ loosening and thinning of secretions	Stimulate secretory glands ↓ Increase respiratory fluids production
Example	Guaifenesin	Iodinated glycerol,Na or K iodide/ acetate , Ammonium chloride, Ipecacuahna.
ADRs	Dry mouth, chapped lips, risk of kidney stones (increases uric acid excretion). *It is useful for patients with gout because it increases uric acid excretion.	Unpleasant metallic taste, hypersensitivity, hypothyroidism, swollen salivary glands (overstimulation of salivary secretion), & flare of old TB.
Uses	○ Common cold ○ Bronchitis ○ Pharyngitis ○ Chronic paranasal sinusitis The ultimate outcome is that cough is indirectly diminished	

3 Mucolytics by Trevor Tessier

Drugs: Mucolytics

Used to dissolve or breakdown mucus in the respiratory tract → mucus is less viscous → coughed up easily.

	N-Acetyl Cysteine	Bromhexine & Ambroxol (Ambroxol is a metabolite of Bromhexine)	Pulmozyme Dornase Alpha or rhDNAase
Overview	A free radical scavenger used in acetaminophen overdose	It helps to: ○ Increase Immune defense. ○ Decrease antibiotics usage. ○ Decrease pain in acute sore throat	A recombinant human-deoxyribonuclease-1 enzyme which is genetically engineered that is nebulized + Full benefit appears within 3-7 days
M.O.A	Increase Breakdown of S-S bonds in glycoprotein in mucous → which lead to less viscid mucous.	○ Increase Synthesize of serous mucus ○ Increase activate ciliary clearance	Cleavage of extracellular bacterial DNA, that contributes to viscosity of sputum **in case of bacterial infection only**
ADRs	Bronchospasm, stomatitis, rhinorrhea, rash, nausea & vomiting	Rhinorrhea, lacrymation, gastric irritations, hypersensitivity	Voice changes, pharyngitis, laryngitis, rhinitis, chest pain, fever, rash
Uses	Most mucolytics are effective as adjuvant therapy in COPD, asthma, bronchitis (when there is excessive, thick mucus). In bronchiectasis, pneumonia &TB they are of partial benefit and hardly any benefit in cystic fibrosis &severe infections → give rhDNAase		

Other Mucolytics :

○ **Hypertonic Saline & NaHCO3 :**

Work by Decreasing Viscoelasticity by Increasing Water Content.

○ **Steam inhalation:**

Work by Decreasing Adhesiveness .

Drugs: Antitussive

Stop or reduce cough by acting either:

Peripherally :

Acts on the receptors of the respiratory center.

1- Inhibitors of airway stretch receptors				
Location	In Pharynx	In Larynx	In Tracheobronchial Airway	During bronchoscopy or bronchography
Uses	Demulcents forms a protective coating (Soothing)	Emollients forms a protective coating.	Aerosols or inhalation of hot steam	local anesthetic aerosols
Drugs	○ Lozenges ○ Gargles	○ Menthol ○ Eucalyptus	○ Tincture benzoin compound. ○ Eucalyptus	○ Lidocaine ○ Benzocaine ○ Tetracaine
2- Inhibitors of pulmonary stretch receptors in alveoli				
Drug	○ Benzonatate			
M.O.A	sensitivity (numbing) of receptors by local anesthetic action.			
ADRs	○ Drowsiness, dizziness, dysphagia, allergic reactions. ○ Overdose → mental confusion, hallucination, restlessness & tremors			

Drugs: Antitussive

Stop or reduce cough by acting either:

Centrally :

It acts on the cough center itself.

	OPIOIDS	NON-OPIODS
Drug	Codeine (very potent) Pholcodine	Antihistamines (>sedating) Dextromethorphan
M.O.A	activating μ opioid receptors	Dextromethorphan increases threshold at cough center. It has benefits over opioids in being: As potent as codeine. Less constipating. No respiratory depression. No inhibition of mucociliary clearance. No addiction.
ADRs		Normal dose: Nausea, vomiting, dizziness, rash & pruritus. High dose: Hallucinations + opiate like side effects on respiration & GIT

Rhinitis & cough drugs + Asthma & COPD treatment

Cromolyn and Nedocromil

Prevent degranulation of pulmonary mast cells and ↓ release of histamine, PAF, and LTC4 from inflammatory cells

Prophylactic use:

- Decreased symptoms and bronchial hyperactivity (BHR), especially responses to allergens
- Minimal systemic toxicity but may cause throat irritation and cough. Relieved by a β2 agonist

Antileukotrienes

- Zafirlukast and montelukast are antagonists at LTD4 receptors with slow onset of activity used prophylactically for many forms of asthma, including antigen, exercise, or drug-induced (e.g., ASA).
- Zileuton is a selective inhibitor of lipoxygenases (LOX), ↓ formation of all LTs. It has a more rapid onset (1-3 hours) and is adjunctive to steroids.

Glucocorticoids

- Block mediator release and ↓ BHR via ↓ PGs, LTs, and inflammatory interleukins (ILs)
- Surface-active drugs (budesonide, flunisolide) used via inhalation for both acute attacks and for prophylaxis
- May cause oropharyngeal candidiasis (prevented with spacers and gargling)
- Low dosage may also prevent the desensitization of β receptors that can occur with overuse of β2 agonist
- Prednisone (oral) and IV steroids generally reserved for severe acute attacks

clinical correlation:

- All asthmatics need a short-acting beta-2 agonist for acute attacks. For prophylaxis, glucocorticoids are most often used.
- For COPD (emphysema, chronic bronchitis), multiple bronchodilators are used including beta-2 agonists and M blockers.

Rhinitis & cough drugs

HISTAMINE

- Histamine is an autacoid present at high levels in the lungs, skin, and gastrointestinal tract. It is released from mast cells and basophils by type I hypersensitivity reactions, drugs, venoms, and trauma.
- Histamine receptors are of the serpentine family, with 7 transmembrane–spanning domains with G-protein–coupled second messenger effectors.

H1 activation:

- ↑ capillary dilation (via NO) → ↓ BP
- ↑ capillary permeability → ↑ edema
- ↑ bronchiolar smooth muscle contraction (via IP3 and DAG release)
- ↑ activation of peripheral nociceptive receptors →↑ pain and pruritus
- ↓ AV nodal conduction

Rhinitis & cough drugs

H2 activation:

- ↑ gastric acid secretion → ↑ gastrointestinal ulcers
- ↑ SA nodal rate, positive inotropism, and automaticity

Mechanism of action:

- H1 antagonists act as competitive antagonists of histamine and therefore may be ineffective at high levels of histamine.
- Vary in terms of both pharmacologic and kinetic properties, but all require hepatic metabolism and most cross the placental barrier.

Uses:

- Allergic reactions: hay fever, rhinitis, urticaria
- Motion sickness, vertigo
- Nausea and vomiting with pregnancy
- Preoperative sedation
- OTC: sleep aids and cold medications
- Acute EPSs

Side effects: extensions of M block and sedation (additive with other CNS depressants)

Drug	M block	Sedation	Animation	Other characteristics
Diphenhydramine	+++	+++	+++	Widely used OTC drug
Promethazine	+++	+++	++	Some α block and local anesthetic action
Cholrpheniramine	++	++	++	Possible CNS stimulation
Meclizine	++	++	++++	Highly effective in motion sickness
Cetirizine	+/-	+	0	
Loratidine	+/-	0	0	No CNS entry
Fexofenadine	+/-	0	0	No CNS entry

Extra Explanation :

RNA sense in viruses

- Positive sense (+ve strand): (5' to 3') viral RNA signifies that a particular viral RNA sequence may be directly translated into the desired viral proteins.
- Negative sense (-ve strand): This RNA (3' to 5') cannot be translated into protein directly. Instead, it must first be transcribed into a positive sense RNA that acts as an mRNA. Some viruses (Influenza, for example) have negative sense genomes and so must carry an RNA polymerase inside the virion.

Objective

1. Acquire the basic knowledge about structure and classification of these viruses infecting the respiratory system.
   Including (**Influenza** viruses, **Parainfluenza** viruses, Respiratory syncytial virus (**RSV**) and human metapneumovirus (HMPV), **Measles** virus, and **Mumps**)
2. Describe their epidemiology and pathogenesis
3. Identify the respiratory infections and the clinical features of URTI and LRTI.
4. Describe their epidemiology and pathogenesis
5. Know the laboratory diagnosis, and treatment of these infections.
6. Recognize the methods for prevention.

Respiratory Tract Infections:

Introduction:

- They are the commonest of human infections and cause a large amount of morbidity and loss of time at work (sick leave). They are common in both children and adults.
- Mostly caused by viruses. Mostly are self-limiting disease, which mean the disease tends to go away on its own, without treatment.
- Mostly are mild and confined to the upper respiratory tract (URT). [1]
- URT-infection may spread to other organs causing more severe infection and death .

Note:
(1) If it gets to the lower respiratory tract it become severe.

Arabic Translation:
Croup = مرض الخناق

Note:
(2) Lower respiratory tract infections

Clinical Manifestations (symptoms) :

- Common cold (rhinitis).
- Pharyngitis.
- Tonsillitis.
- Sinusitis & otitis media.
- Croup (acute laryngotracheobronchitis).
- Acute bronchitis, Acute bronchiolitis and Viral pneumonia. [2]

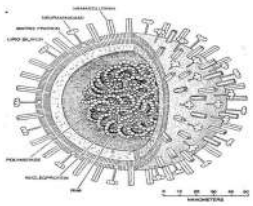
Common respiratory viruses::

Name of the virus	Family	Disease
1) Influenza virus	Orthomyxoviridae	URTI and LRTI
2) Parainfluenza virus	Paramyxoviridae	LRTI
3) Respiratory syncytial virus		
4 Rhinovirus	Picornaviridae	URTI
5 Coronavirus	Coronaviridae	URTI and LRTI
6 Adenovirus	Adenoviridae	URTI and eye infections
7 Human metapneumovirus	Paramyxoviridae	LRTI

Orthomyxoviridae Family

- Influenza virus, Avian flu and Swine flu -

1: Influenza virus :



Structural features:

- 8 helical Segmented genome (Negative polarity **ssRNA**)
- Enveloped virus with 2 projecting glycoprotein spikes -:
  - Haemagglutinin (H)
  - Neuraminidase (N)

Influenza viral proteins :

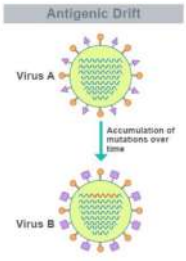
Haemagglutinin (H) [3]	Neuraminidase (N) [4]
Attachment to the host cell surface receptors. No Attachment = No infection	Responsible for release of the progeny viral particles from the infected cell.
Antibodies to the HA is responsible for immunity. our immune system use it as an antigen .	___
16 haemagglutinin antigenic type, (H1 – H16).	9 neuraminidase antigenic type, (N1 – N9).
Human associated H antigenic type are H1, H2, H3 Other H for animals, though it can infect human (*).	Human associated N antigenic type are N1, N2. Other N for animals, though it can infect human 1

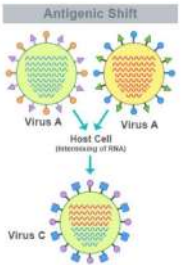
Epidemiology:

- Seasonal, spreads mostly in winter.
- Highly susceptible to mutations and rearrangeable within the infected host.
- Past antigenic shifts:
  - 1918 → H1N1 "Spanish Influenza" → 2040 million deaths.
  - 1957 → H2N2 "Asian Flu" → 12 million deaths.
  - 1968 → H3N2 "Hong Kong Flu" → 700,000 deaths.
  - 1977 → H1N1 Reemergence → not pandemic .

Types of influenza virus:

Influenza Virus Types	Type A	Type B	Type C
Infect	Human and Animal.	Human only.	Human only.
Cause	Human: Epidemic & Pandemic. Animal: Epizootic.	Outbreak.	Mild illness.
Antigenic changes	- Antigenic drift - Antigenic shift = Reassortment = rearrangement	Antigenic drift only.	———





- Antigenic **drift** → **Minor change** in genetic material.
- Antigenic **shift** → **Major change** in genetic material.

Note:
This virus is highly susceptible to mutations and rearrangements within the infected host. That's why it's hard to make a specific drug for it.

Note:
- (3) Glycoprotein found on the surface of influenza viruses. (More)
- (4) Enzymes that hydrolyze glycoside bonds, leading to the degradation neuraminic acids.

Note:
If there is only one of the human associated antigenic in a virus, either H or N, this virus can infect a human.

Extra Explanation :

Antigenic drift (minor change)
- A mechanism for variation in viruses that involves the accumulation of mutations within the genes that code for antibodybinding sites. This results in a new strain of virus particles. which cannot be inhibited as effectively by the original antibodies.

Antigenic shift (major change)
- The process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype having a mixture of the surface antigens of the two or more original strains.

SECTION 3 :

LOWER RESPIRATORY TRACT

SECTION 3 :

LOWER RESPIRATORY TRACT

Objective

1. Identify the development of the laryngotracheal (respiratory) diverticulum.
2. Identify the development of the larynx.
3. Identify the development of the trachea.
4. Identify the development of the bronchi & Lungs.
5. Describe the periods of the maturation of the lung.
6. Identify the most congenital anomaly.

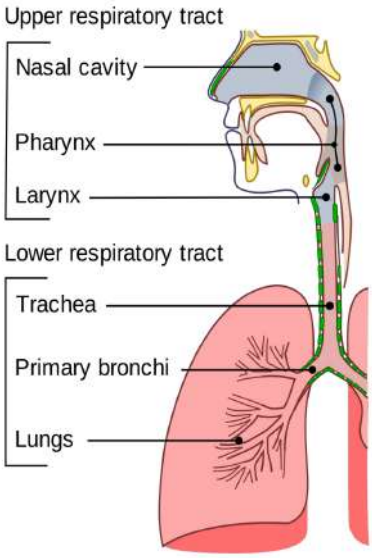
Respiratory system

Upper Respiratory tract

- Nose
- Nasal cavity and paranasal sinuses
- Pharynx (Laryngopharynx)
- Larynx

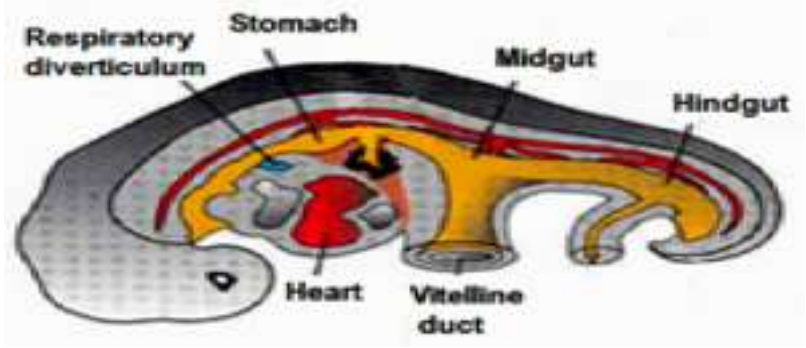
Upper Respiratory tract

- Trachea
- Bronchi
- Lungs



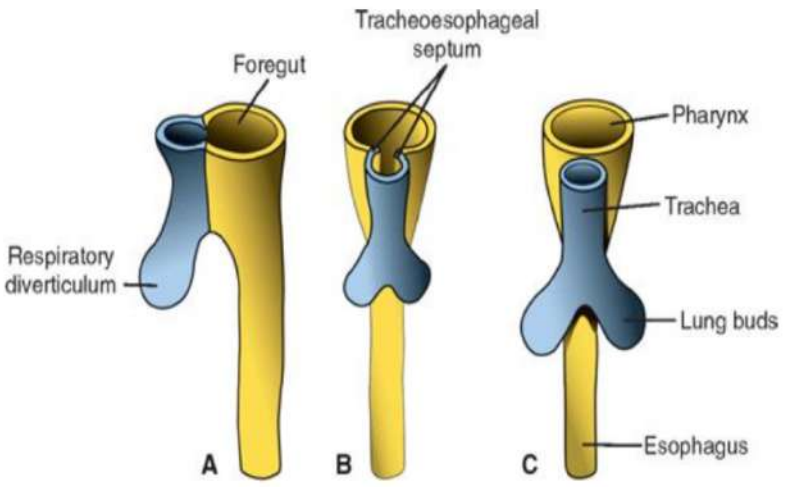
Development of the Lower Respiratory Tract :

- Begins to form during the 4th week of development as a median outgrowth (*laryngotracheal groove*) from the caudal part of the ventral wall of the primitive pharynx (foregut).
- The groove invaginates (fold within itself) and forms *laryngotracheal (respiratory) diverticulum*.



Tracheoesophageal Septum:

- A longitudinal tracheoesophageal septum develops and divides the diverticulum into :
  - Dorsal portion: primordium of the oropharynx and esophagus
  - Ventral portion: primordium of larynx, trachea, bronchi and lungs
- Ventral portion further divides into :
  - The proximal part of the respiratory diverticulum remains tubular and forms larynx & trachea.
  - The distal end of the diverticulum dilates to form lung bud, which divides to give rise to 2 lung buds (primary bronchial buds)



Clinical Correlate :

Pulmonary hypoplasia

occurs when lung development is stunted. This condition has 2 congenital causes:

(1) congenital diaphragmatic hernia (a herniation of abdominal contents into the thorax, which affects the development of the left lung).

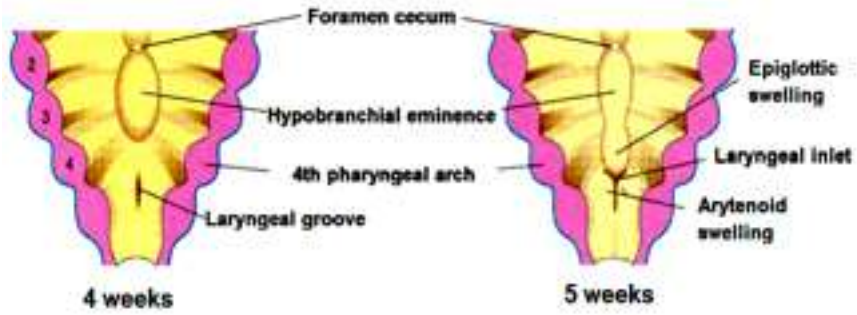
(2) bilateral renal agenesis (this causes oligohydramnios, which increases the pressure on the fetal thorax and Potter's sequence). One of the features of Potter's sequence is bilateral pulmonary hypoplasia.

Laryngotracheal Diverticulum:

- The endoderm lining the laryngotracheal diverticulum gives rise to the: epithelium & glands of the respiratory tract.
- The surrounding splanchnic mesoderm gives rise to the: connective tissue, cartilage & smooth muscles of the respiratory tract.

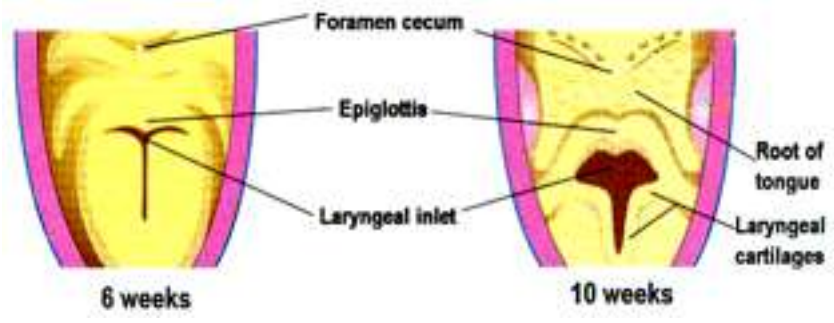
Development of the Larynx:

- The opening of the laryngotracheal diverticulum into the primitive foregut becomes :the laryngeal orifice.
- The epithelium & glands are derived from : endoderm.
- Laryngeal muscles & the cartilages of the larynx (except epiglottis) develop from the: mesoderm of 4th & 6th pairs of pharyngeal arches.



Development of the Epiglottis:

- It develops from : the caudal part of the hypopharyngeal eminence (a swelling formed by the proliferation of mesoderm in the floor of the pharynx).
- Growth of the larynx and epiglottis is rapid during the first three years after birth. By this time the epiglottis has reached its adult form.



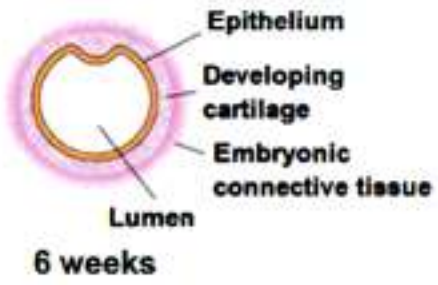
Recanalization of larynx:

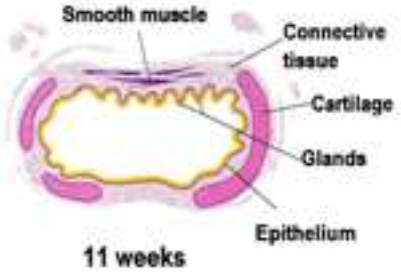
- The laryngeal epithelium proliferates rapidly resulting in: temporary occlusion of the laryngeal lumen.
- Recanalization of larynx normally occurs by : the 10th week.
- Formed during recanalization :

1- Laryngeal ventricles 2-vocal folds 3- vestibular folds

Development of the Trachea:

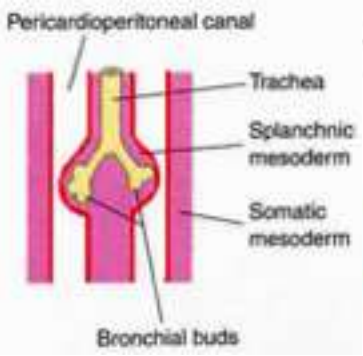
- The endodermal lining of the laryngotracheal tube distal to the larynx differentiates into : the epithelium glands of the trachea and pulmonary epithelium
- The cartilages, connective tissue, and muscles of the trachea are derived from : the mesoderm.

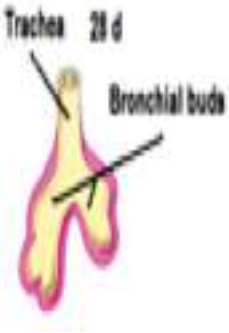


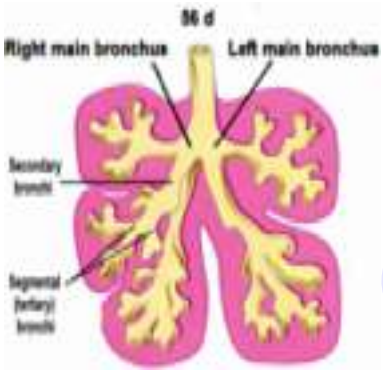


Development of the Bronchi and lung:

- The 2 primary bronchial grow laterally into the pericardio-peritoneal canals (part of intra-embryonic celome) which is the primordia of pleural cavities.
- Bronchial buds divide and re-divide to give the bronchial tree.
- The right main bronchus is slightly larger than (wider) than the left one and is oriented more vertically.
- This embryonic relationship persists in the adult.
- The main bronchi subdivide into secondary & tertiary (segmental) bronchi which give rise to further branches.
- The segmental bronchi 10 in right lung and 8 or 9 in the left lung begin to form by the 7th week
- The surrounding mesenchyme also divides.
- Each segmental bronchus with its surrounding mass of mesenchyme is the primordium of a bronchopulmonary segment.

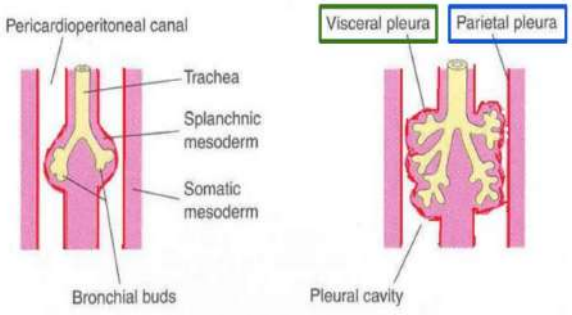


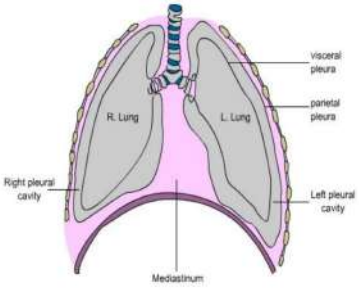




Development of the Pleura:

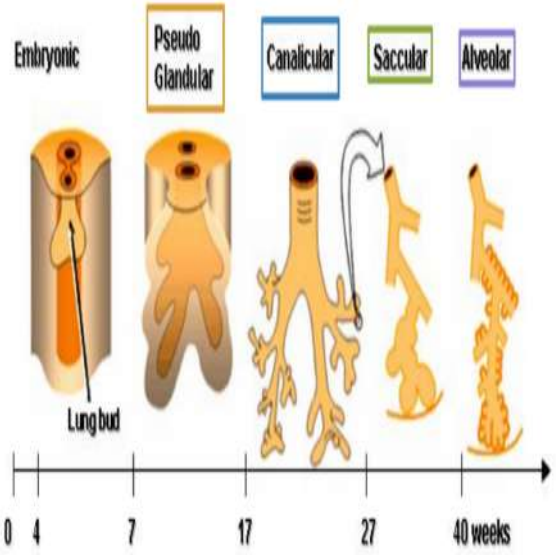
- As the lungs develop they acquire a layer of visceral pleura from splanchnic mesenchyme.
- The thoracic body wall becomes lined by a layer of parietal pleura derived from the somatic mesoderm.

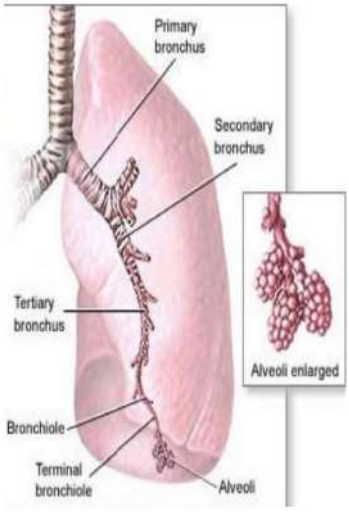




Maturation of the lungs

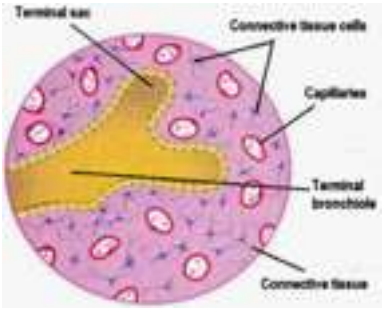
- Maturation of lung is divided into 4 periods:
  1. Pseudoglandular (5 - 16 weeks)
  2. Canalicular (16 - 26 weeks)
  3. Terminal sac (26 weeks - birth)
  4. Alveolar (late fetal period - childhood)
- These periods overlap each other because the cranial segments of the lungs mature faster than the caudal ones

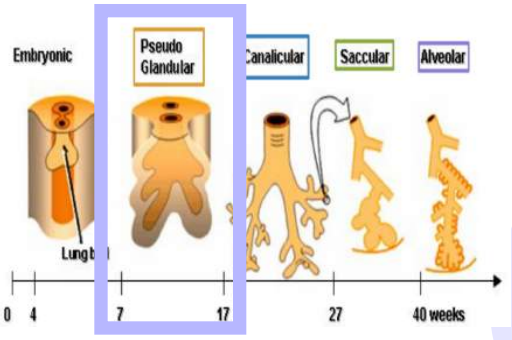




Pseudo glandular (5 - 16 weeks):

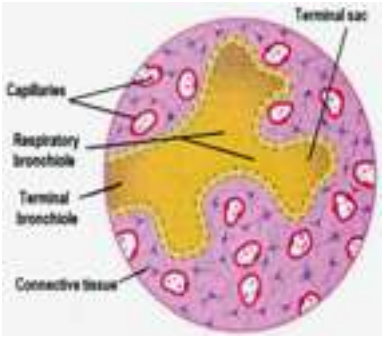
- Developing lungs somewhat resembles an exocrine gland during this period.
- By 16 weeks all major elements of the lung have formed except those involved with gas exchange (alveoli).
- Respiration is NOT possible.
- Fetuses born during this period are unable to survive.

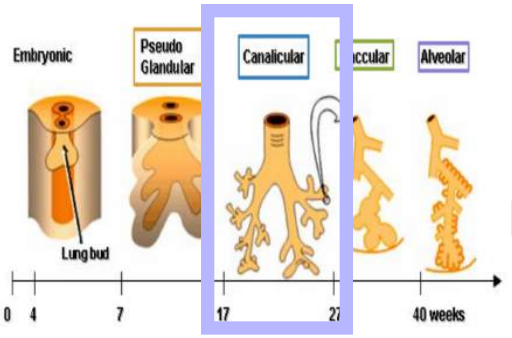




Canalicular (16 - 26 weeks):

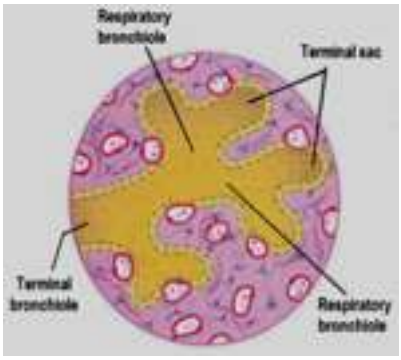
- Lung tissue becomes highly vascular.
- Lumina of bronchi and terminal bronchioles become larger.
- By 24 weeks each terminal bronchiole has given rise to two or more respiratory bronchioles.
- The respiratory bronchioles divide into 3 to 6 tubular passages called alveolar ducts.
- Some thin-walled terminal sacs(primordial alveoli) develop at the end of respiratory bronchioles.
- Respiration is possible at the end of this period.
- Fetus born at the end of this period may survive if given intensive care (but usually die because of the immaturity of respiratory as well as other systems)

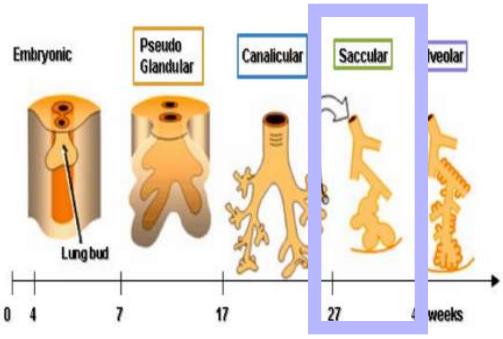




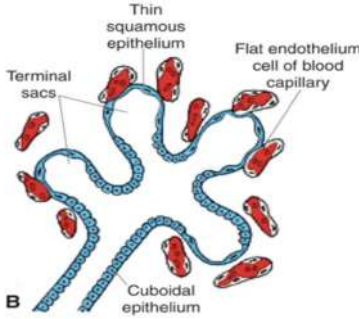
Terminal sac (26 weeks - birth) :

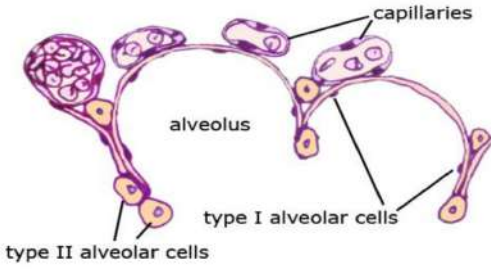
- Many more terminal sacs develop.
- Their epithelium becomes very thin.
- Capillaries begin to bulge into developing alveoli.
- The epithelial cells of the alveoli and the endothelial cells of the capillaries come in intimate contact and establish the blood-air barrier.
- Adequate gas exchange can occur which allows the prematurely born fetus to survive





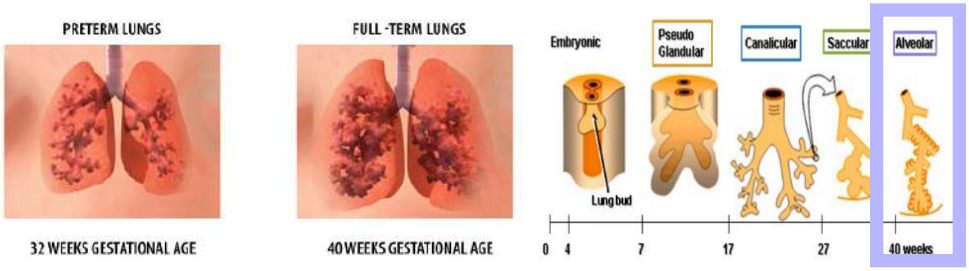
- By 26 weeks the terminal sacs are lined by:
  - Squamous type I pneumocytes
  - Rounded secretory, type II pneumocytes, that secrete a mixture of phospholipids called surfactant.
- Surfactant production begins by 20 weeks and increases during the terminal stages of pregnancy.
- Sufficient terminal sacs, pulmonary vasculature& surfactant are present to permit survival of a prematurely born infants
- Fetuses born prematurely 24-26 weeks may suffer from respiratory distress due to surfactant deficiency but may survive if given intensive care.





Alveolar 32 weeks – 8 years (post natal) :

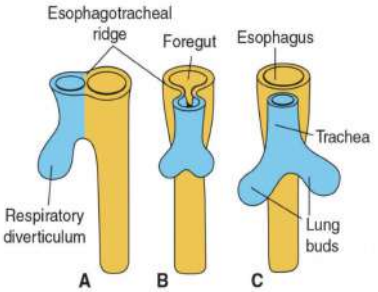
- At the beginning of the alveolar period, each respiratory bronchiole terminates in a cluster of thin-walled terminal saccules separated from one another by loose connective tissue.
- These terminal saccules represent future alveolar sacs.
- Characteristic mature alveoli do not form until after birth; so 95% of alveoli develop postnatally.
- About 50 million alveoli, one sixth of the adult number are present in the lungs of a full-term newborn infant.
- From 3-8 year or so, the number of alveoli continues to increase and forming additional primordial alveoli.
- By about the eighth year, the adult complement of 300 million alveoli is present.

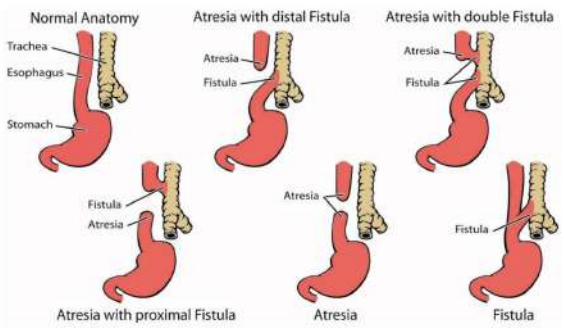


Developmental anomalies

Tracheoesophageal Fistula :

- An abnormal passage between the trachea and esophagus.
- Results from incomplete division of the cranial part of the foregut into respiratory and esophageal parts by the tracheo-esophageal septum.
- Occurs once in 3000 to 4500 live births.
- Most affected infants are males.
- In more than 85% of cases, the fistula is associated with esophageal atresia (esophagus ends in a blind-ended pouch rather than connecting normally to the stomach)





Development of respiratory system

Embryology of lower respiratory system

- During week 4 of development, the lower respiratory system (trachea, bronchi, and lungs) begins to develop as a single **respiratory (laryngotracheal) diverticulum** of endoderm from the ventral wall of the **foregut**. The respiratory epithelium develops from **endoderm** while the muscles, connective tissues, and cartilages develop from mesoderm.
- The respiratory diverticulum enlarges distally to form the **lung bud.**
- The diverticulum and lung bud then bifurcate into the **2 bronchial buds**, which then undergo a series of divisions to form the major part of the bronchial tree (main, secondary, and tertiary bronchi) by month 6.
- The tertiary segmental bronchi are related to the bronchopulmonary segments of the lungs.
- To separate the initial communication with foregut, the **tracheoesophageal septum** forms to separate the esophagus from the trachea.
- A critical time in lung development is the **25–28th** weeks. By this time, the Type I and II pneumocytes are present and gas exchange and surfactant production are possible.
- Premature fetuses born during this time can survive with intensive care. The amount of surfactant production is critical.

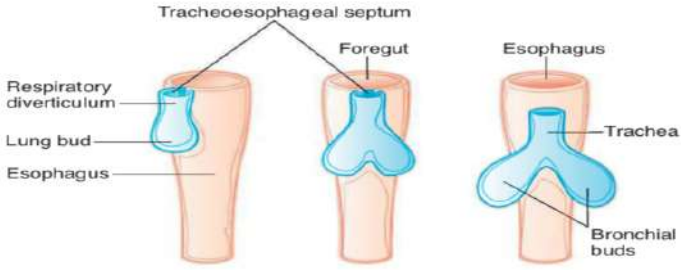


Figure II-2-2. Development of the Lower Respiratory System

Congenital anomalies

1. A **tracheoesophageal fistula** is an abnormal communication between the trachea and esophagus caused by a malformation of the tracheoesophageal septum. It is generally associated with the following:
2. **Esophageal atresia** and **polyhydramnios** (increased volume of amniotic fluid)
    - Regurgitation of milk
    - Gagging and cyanosis after feeding
    - Abdominal distention after crying
    - **Reflux** of gastric contents into lungs causing pneumonitis

The fistula is most commonly (90% of cases) located between the esophagus and **distal third of the trachea**.

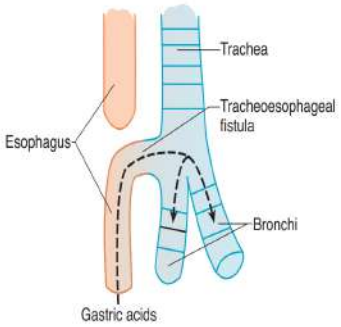


Figure II-2-3. Tracheoesophageal Fistula (Most Common Type)

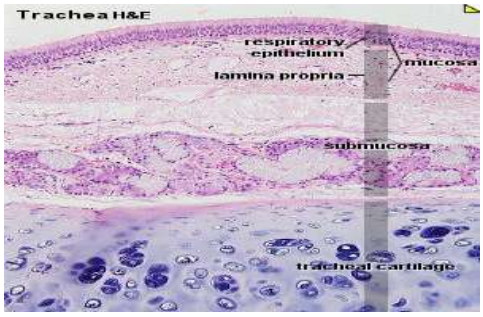
KAPLAN CORNER

Objective 2

- Describe The microscopic structures of the wall of:
  - Trachea.
  - Primary or extrapulmonary bronchi.
  - Intrapulmonary (secondary and tertiary) bronchi.
  - Bronchioles.
- Describe The microscopic structures of :
  - Interalveolar septum.
  - Alveolar phagocytes.
  - Pleura.

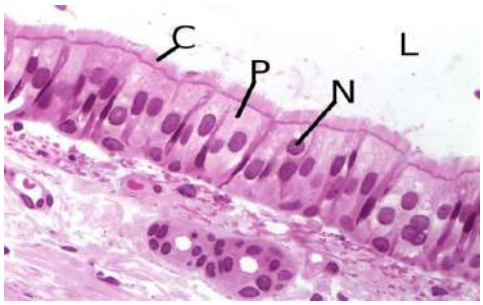
Trachea

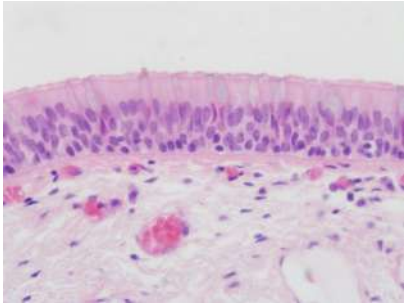
- The wall of trachea is formed of:
  - Mucosa.
  - Submucosa.
  - Adventitia.



Mucosa

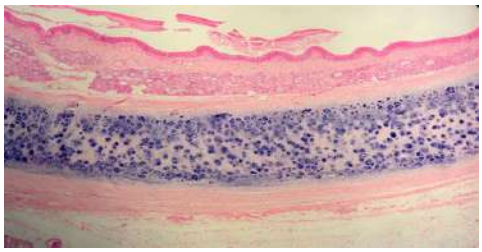
- Epithelium: Respiratory epithelium
- Lamina propria.
- Elastic lamina:
  - It is formed of elastic fibers.
  - It separates lamina propria from submucosa.

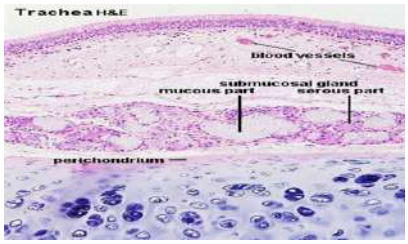




Submucosa

- C.T.
- Numerous mucous & seromucous glands.
- Lymphoid elements





Adventitia

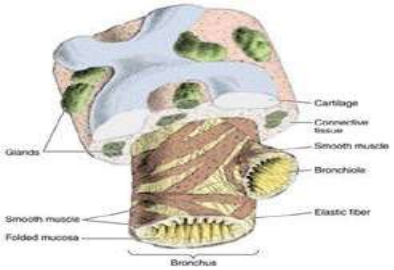
- Fibroelastic C.T.
- C-shaped rings (12-16) of hyaline cartilage.
- Trachealis muscle (bundle of smooth muscle fibers) connects the 2 ends of each C-shaped (incomplete) rings of cartilage.

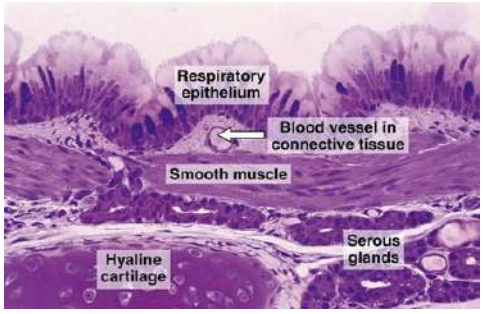
Extrapulmonary Bronchus (1ry Bronchus)

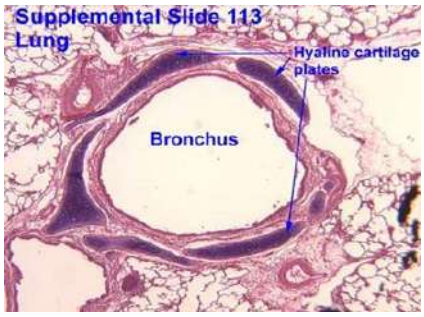
Generally have the same histological appearance as the trachea

Intrapulmonary Bronchus (2ry & 3ry Bronchi)

- Mucosa.
- Muscle coat.
- Submucosa.
- Adventitia.







Mucosa

- Epithelium: Respiratory epith.
- Lamina propria
- No elastic lamina

Muscle coat (complete)

Two distinct layers of smooth muscle fibers spirally arranged in opposite direction.

Submucosa

C.T. contains:

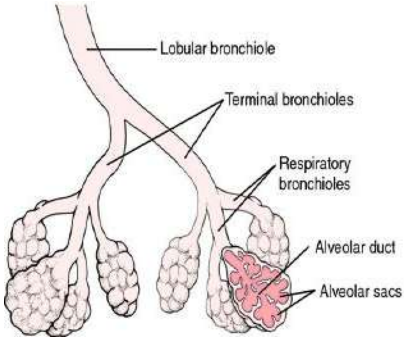
- Seromucous glands.
- Lymphoid elements.

Adventitia

- Loose C.T.
- Irregular plates of hyaline cartilage(complete layer).
- Solitary lymphoid nodules

Bronchioles

- 1- Preterminal (1ry) Bronchioles: Are less than 1mm in diameter.
- 2- Terminal (2ry) Bronchioles: Less than 0.5mm in diameter
- 3- Respiratory (3ry) Bronchioles.



Preterminal Bronchioles

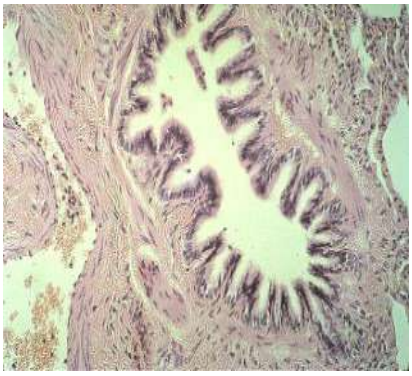
Mucosa

Mucosa has longitudinal folds:

- Epithelium: Simple ciliated columnar epith. with occasional goblet cells.
- Lamina propria: C.T. rich in elastic fibers.

Smooth muscle

2 helically arranged smooth muscle layers



Adventitia

C.T

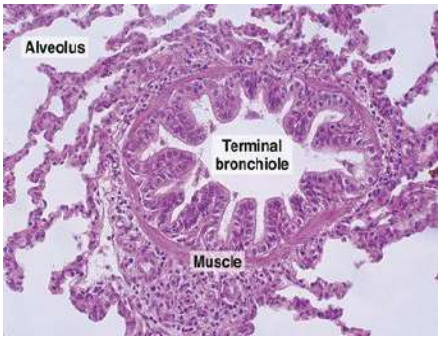
No cartilage, No seromucous glands, No lymph nodules.

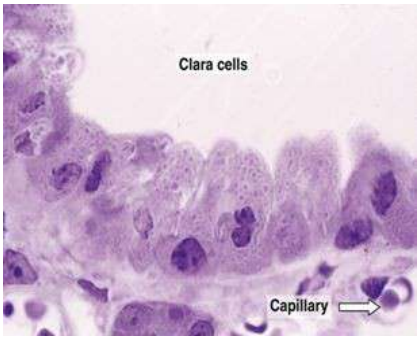
Terminal Bronchioles

Similar structure to preterminal bronchioles, but:
Epithelium: Simple cuboidal partially ciliated epithelium With Clara cells (With NO goblet cells).

Clara cells

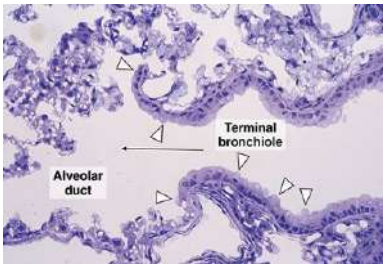
- Structure: columnar cells (non ciliated).
- Functions:
  - Degrade toxins in inhaled air.
  - Divide to regenerate the bronchiolar epith.
  - Produce surfactant-like material.

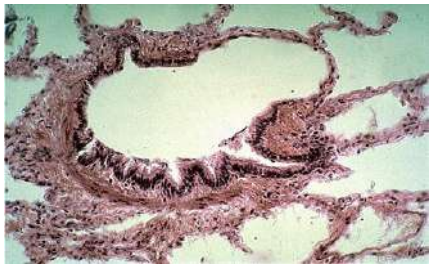




Respiratory Bronchioles

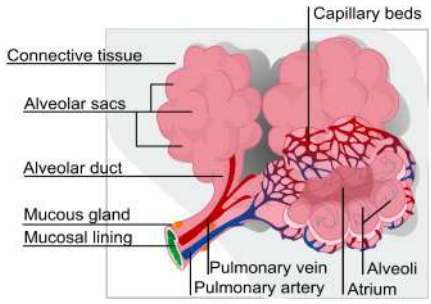
Are similar in structure to terminal bronchioles But: their walls are interrupted by the presence of few pulmonary alveoli.





Alveolar Ducts

- The wall of alveolar ducts consist of pulmonary alveoli.
- Alveolar duct → ends by: atrium → communicates with: 2-3 alveolar sacs.



Pulmonary Alveoli

Definition: They are small out-pouching of respiratory bronchioles, alveolar ducts & alveolar sacs

Topics:

1. Interalveolar septa.
2. Alveolar epithelium.
3. Alveolar phagocytes (Lung macrophages).

Interalveolar septa.

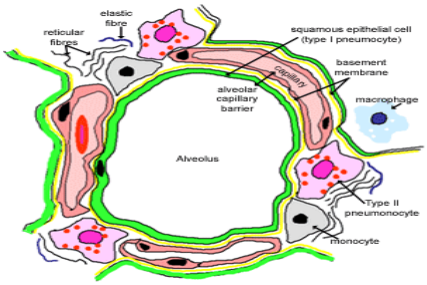
Definition: The region between 2 adjacent alveoli.

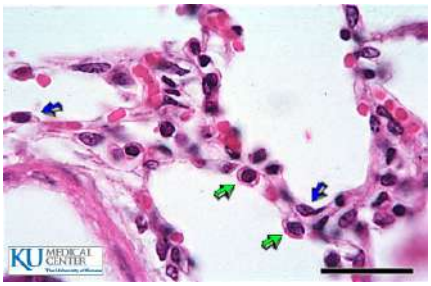
Components:

- Alveolar Epithelium:
  - Lines both sides of interalveolar septum
  - Type I Pneumocytes & ype II Pneumocytes
- Interstitium.

Type I Pneumocytes

- Line 95% of the alveolar surface.
- Less numerous than type II pneumocytes.
- L/M: simple squamous epith.
- Function: Exchange of gases.



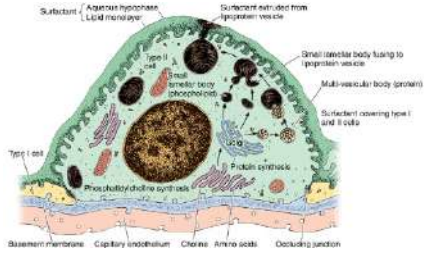


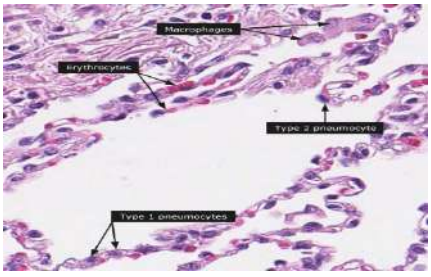
Type II Pneumocytes

- Line 5% of the alveolar surfaces.
- Are more numerous than type I pneumocytes.
- Are cuboidal or rounded cells, With Foamy cytoplasm. With central & rounded Nucleus.
- The cytoplasm contains membrane-bound Lamellar
- bodies (contain pulmonary surfactant).
- Function:

  1- Synthesis & secretion of pulmonary surfactant.

  2- Renewal of alveolar epithelial cells: Type II cells can divide to regenerate both type I & type II pneumocytes.





Interstitium

- Continuous Pulmonary Capillaries.
- Interstitial C.T.:
  - C.T. Fibers: elastic fibers & type III collagen (reticular fibers).
  - C.T. Cells: Fibroblasts, Macrophages, Mast cells, Lymphocytes.

Alveolar phagocytes

"Lung macrophages", "Dust Cells"

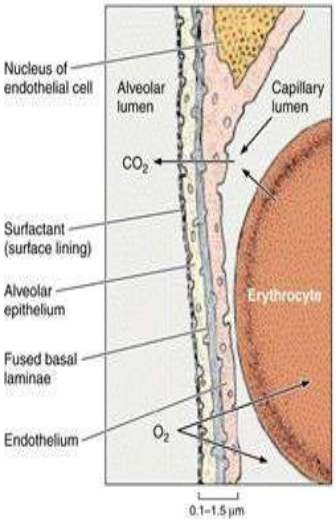
- In the lumen of pulmonary alveoli.
- In the interstitium of interalveolar septa.
- Function: Phagocytose particulate matter (e.g. dust) & bacteria in the lumen of pulmonary alveoli and in the interstitium of interalveolar septa.

Blood-gas Barrier (Blood-air Barrier)

Definition: It is the region of the interalveolar septum that is traversed by O2 & CO2.

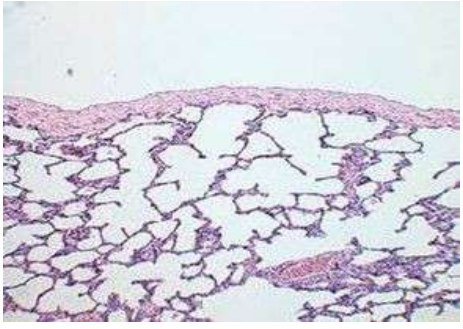
Components:

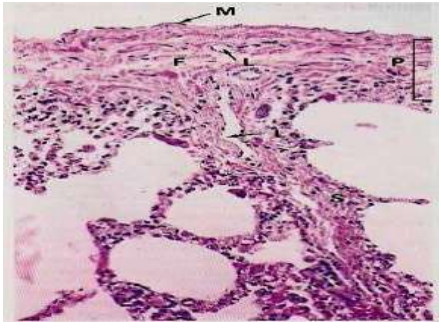
1. Thin layer of surfactant.
2. Type I pneumocyte.
3. Fused basal laminae of type I pneumocytes & endothelial cells of the pulmonary capillary.
4. Endothelial cells of the pulmonary capillary.



Pleura

- Is formed of two layers: Parietal and visceral. It is formed of simple squamous mesothelium.
- The two layers are separated by serous fluid.
- The visceral layer has sub-epithelium loose C.T that extends into the lung tissue.





Histology of the lower respiratory tract

Respiratory histology

- lung is an organ that functions in the intake of oxygen and exhaling of CO2. Approximately 14 times each minute, we take in about 500 mL of air per breath. Inspired air will be spread over 120 square meters of the surface area of the lungs. The air–blood barrier has to be thin enough for air to pass across but tough enough to keep the blood cells inside their capillaries.
- Because lungs are opened to the outside world, they are susceptible to environmental insults in the form of pollution and infectious bacteria.
- The lungs receive the entire cardiac output and are positioned to modify various blood components. The pulmonary endothelium plays an active role in the metabolic transformation of lipoproteins and prostaglandins. **The enzyme that converts angiotensin I to angiotensin II is produced by the lung endothelial cells.**

Clinical Correlate

- Any disease that affects capillaries also affects the extensive capillary bed of the lungs. Bacteria which colonize the lungs may damage the barriers between the alveoli and the capillaries, gaining access to the bloodstream (a common complication of bacterial pneumonia).
    - With allergies, smooth-muscle constriction reduces the diameter of air tubes and results in reduced air intake.
    - Lung cancers commonly develop from bronchi (smoking, asbestos, and excessive radiation are the main causes).
    - Mesothelioma is a malignant tumor of the pleura (causative agent: asbestos dust).

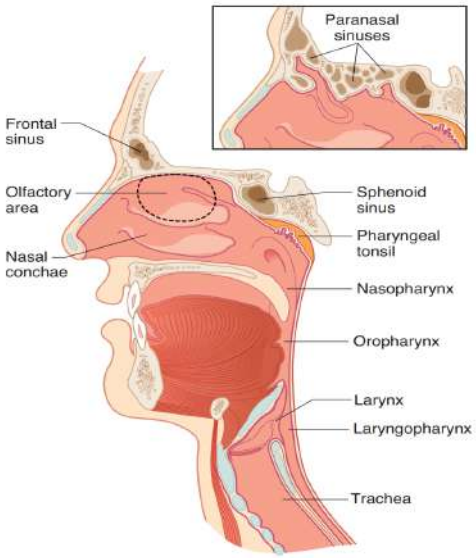


Figure II-2-11. Respiratory Pathways

KAPLAN CORNER

Histology of the lower respiratory tract

	Trachea	Bronchi	Bronchioles
Epithelia	Pseudostratified ciliated columnar (PCC) cells, goblet cells	PCC to simple columnar cells	Ciliated, some goblet cells, Clara cells in terminal bronchioles
Cartilage	16-20 C-shaped cartilaginous rings	Irregular plates	None
Glands	Seromucous glands	Fewer seromucous glands	None
Smooth muscle	Between open ends of C-shaped cartilage	Prominent	Highest proportion of smooth muscle in the bronchial tree
Elastic fibers	Present	Absent	Absent

Tr

- The **trachea** is a hollow tube, about 10 cm in length (and about 2 cm in diameter), extending from the larynx to its bifurcation at the carina to form a primary bronchus for each lung. The most striking structures of the trachea are the C-shaped hyaline cartilage rings. In the human there are 16–20 of them distributed along the length of the trachea. The rings overlap in the anterior part of the trachea. The free posterior ends of the C-shaped cartilages are interconnected by smooth-muscle cells.

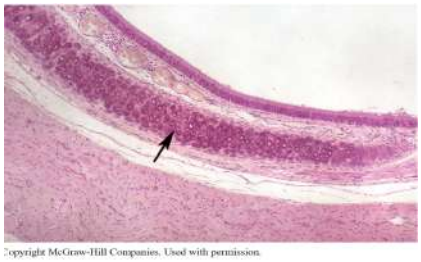


Figure II-2-12. Trachea with a hyaline cartilage ring (arrow) and pseudostratified columnar epithelium

- The trachea is composed of cor ...a, an incomplete muscularis, and an incomplete adventitia.
- The mucosa has 3 components: a pseudostratified epithelium, an underlying vascularized loose connective tissue (lamina propria) that contains immune cells, and a thin layer of smooth-muscle cells (muscularis mucosa).
- The submucosa is a vascular service area containing large blood vessels. Collagen fibers, lymphatic vessels and nerves are also present in this layer.
- The outside covering of the trachea, the adventitia, is composed of several layers of loose connective tissue.
- The epithelial lining of the trachea and bronchi is pseudostratified columnar in which all cells lie on the same basal membrane but only some reach the luminal surface. The only other place in the body with this epithelium is the male reproductive tract.

Histology of the lower respiratory tract

Clinical Correlate

- If mucosal clearance is ineffective, or the mechanism overwhelmed, infection (pathogenic bacteria) or pneumoconiosis (dust-related disease) may follow.
- In cystic fibrosis, the secreted mucous is thick or viscous and the cilia have a difficult time moving it toward the pharynx. Patients with this disease have frequent infections of the respiratory system

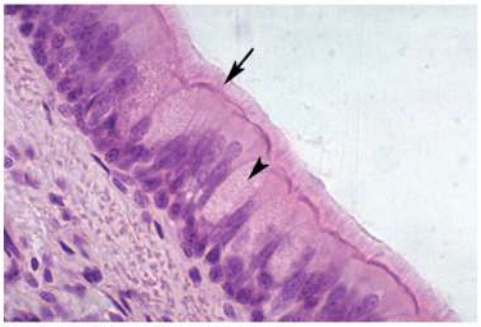


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Figure II-2-13. Pseudostratified Columnar Epithelium with Goblet Cells (arrowhead) Surrounded by Ciliated Cells (arrow)

Tracheal Epithelial Cell Types

- **Columnar cells** extend from the basal membrane to the lumi apical cilia per cell that are intermingled with microvilli. The cilia are motile and beat to help move the secreted mucous layer over the lining of the trachea and out of the respiratory system.
- **Goblet cells** secrete a polysaccharide mucous material into the lumen of trachea. Mucous production is supplemented by secretions of the submucosal mixed glands. The mucous layer of the respiratory system traps particulate substances (dust, bacteria, and viruses) and absorbs noxious water-soluble gases such as ozone and sulfur dioxide. The mucous sticky layer is moved by the beating cilia toward the pharynx where it is swallowed. This movement is known as the mucociliary escalator system. Most material (dust and bacteria) is trapped in the mucous layer, and is removed and digested.
- **Pulmonary neuroendocrine (PNE) cells** are comparable to the endocrine cells in the gut. These epithelial neuroendocrine cells have been given various names
- **APUD** cells (**A**mino-**P**recursor-**U**ptake-**D**ecarboxylase), **DNES cells** (**D**iffuse **N**euro**E**ndocrine **S**ystem) K (Kulchitsky) cells. These cells occur in clusters and are often located at airway branch points.
- **Brush cells** may represent goblet cells that have secreted their products or intermediate stages in the formation of goblet or the tall ciliated cells. They have short microvilli on their apical surfaces. Some of these cells have synapses with intraepithelial nerves, suggesting that these cells may be sensory receptors.
- **Basal cells** are stem cells for the ciliated and goblet cells. The stem cells lie on the basal membrane but do not extend to the lumen of the trachea. These cells, along with the epithelial neuroendocrine cells, are responsible for the pseudostratified appearance of the trachea.

Clinical Correlate

- Patients lacking dynein have immotile cilia or **Kartagener syndrome**. With immotile cilia, patients are subject to many respiratory problems because their cilia cannot move this mucous layer with its trapped bacteria. Males also possess immotile sperm.
- The columnar and goblet cells are sensitive to irritation. The ciliated cells become taller, and there is an increase in the number of goblet cells and submucosal glands. Intensive irritation from smoking leads to a squamous metaplasia where the ciliated epithelium becomes a squamous epithelium. This process is reversible

KAPLAN CORNER

Histology of the lower respiratory tract

Bronchi

- The **bronchial tree** forms a branching airway from the trachea to the bronchioles. When the primary bronchi enter the lung, they give rise to 5 secondary or lobar bronchi—3 for the right lung and 2 for the left. The 5 lobes are further subdivided into 10 tertiary or segmental bronchi in each lung, which form bronchopulmonary segments.
- The epithelial lining of the bronchi is also pseudostratified. It consists of **ciliated columnar cells, basal cells, mucous cells, brush cells and neuroendocrine** (APUD, DNES, or K) **cells**. There are also seromucous glands in the submucosa that empty onto the epithelial surface via ducts. The walls of bronchi contain irregular plates of cartilage and circular smooth-muscle fascicles bound together by elastic fibers. The number of goblet cells and submucosal glands decreases from the trachea to the small bronchi.

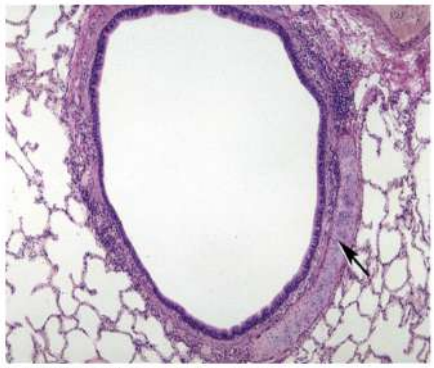


Figure II-2-14. Bronchus with a Plate of Cartilage (arrow)

Clinical Correlate: Bronchial metastatic tumors arise from Kulchitsky cells.

Bronchioles

- The **wall of a bronchiole** does not contain cartilage or glands. The smooth-muscle fascicles are bound together by elastic fibers. The epithelium is still ciliated, but is a simple cuboidal or columnar epithelium rather than pseudostratified. The epithelial lining of the airway is composed of **ciliated cells** (goblet and basal cells are absent in the terminal bronchioles) and an additional type called the **Clara cell.**
- **Clara cells** (also called bronchiolar secretory cells) are nonciliated and **secrete a serous solution similar to surfactant**. They aid in the **detoxification of air- borne toxins,** and serve as **a stem cell for the ciliated cells** and for themselves. The number of Clara cells increases in response to increased levels of pollutants like cigarette smoke. **Clara cells are most abundant in the terminal bronchioles, where they make up about 80% of the epithelial cell lining**; they are also involved with chloride ion transport into the lumens of the terminal bronchioles.

Clinical Correlate

Chronic obstructive pulmonary disease (COPD) affects the bronchioles and includes emphysema and asthma.

- Emphysema is caused by a loss of elastic fibers and results in chronic airflow obstruction.
- Asthma is a chronic process characterized by a reversible narrowing of airways.
- Asthma is reversible; emphysema is not.

KAPLAN CORNER

Histology of the lower respiratory tract

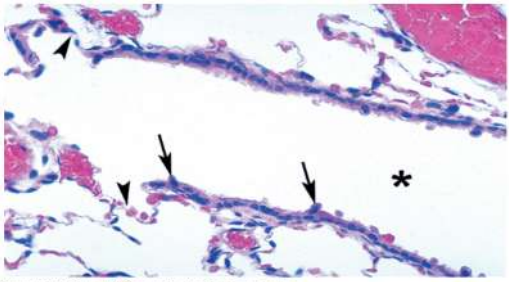


Figure II-2-15. Terminal bronchiole lumen (asterisk) with epithelium containing ciliated cells and Clara cells (arrows)

The **terminal bronchiole** is the last conducting bronchiole. This bronchiole is followed by respiratory bronchioles which are periodically interrupted by alveoli in their walls. The goblet cells are absent from the epithelial lining of the respiratory bronchioles; however, this epithelium is still lined with a sparse ciliated cuboidal epithelium which prevents the movement of mucous into the alveoli. After the last respiratory bronchiole, the wall of the airway disappears and air enters the alveoli.

Alveolar ducts, alveolar sacs, and the alveoli

The alveolar ducts and sacs have little or no walls and consist almost entirely of alveoli. The alveoli constitute 80–85% of the volume of the normal lung. There are 300 million alveoli in the lungs, each ~200 microns in diameter. The cuboidal epithelium of the respiratory bronchioles and the alveolar ducts are continuous with the squamous cells lining the alveoli.

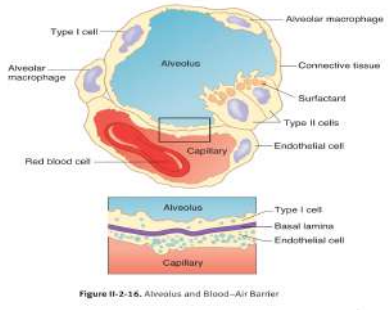


Figure II-2-16. Alveolus and Blood–Air Barrier

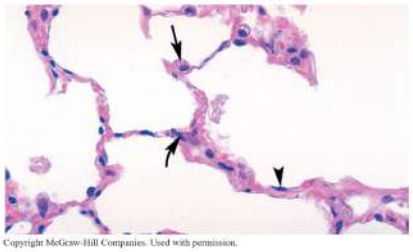


Figure II-2-17. Alveoli with Type I Pneumocytes (arrowhead), Type II Pneumocytes (arrow), and Alveolar Macrophage (curved arrow) in the Alveolar Wall

The type I pneumocyte is the major cell lining cell of the alveolar surfaces (also called small alveolar cell or alveolar type I cell).

- Represent only 40% of the alveolar lining cells, but are spread so thinly they cover 90–95% of the surface
- Primarily involved in gas exchange
- Post-mitotic

The type II pneumocyte is the other major alveolar cell (also called great alveolar cell [because of its size], granular pneumocyte, septal cell, corner cell, niche cell, or alveolar type II).

- Constitute 60% of the cell lining the alveoli, but form only 5–10% of the surface
- Produce and secrete surfactant
- Large, round cells with "myelin figures" in their apical cytoplasm which represent the remnants of surfactant after histological processing
- Serve as stem cells for themselves and the type I cell

KAPLAN CORNER

Histology of the lower respiratory tract

Surfactant

- **Surfactant** is essential to maintain the normal respiratory mechanics of the alveoli. Production of surfactant in the fetus is essential for the survival of the neonate as it takes its first breath. Surfactant is composed of a mixture of phospholipids and surfactant proteins whose function is to aid in the spreading of the surfactant at the alveolar air–water interface. The phospholipids act as a detergent which lowers the surface tension of the alveoli and prevents alveolar collapse during expiration.
- Most surfactant is recycled back to Type II cells for reutilization; some of it undergoes phagocytosis by macrophages.

Clinical Correlate

- Corticosteroids induce the fetal synthesis of surfactant. High insulin levels in diabetic mothers antagonize the effects of corticosteroids.
- Infants of diabetic mothers have a higher incidence of respiratory distress syndrome.

Alveolar Wall

- In the **alveolar wall** under the alveolar epithelium is a rich network of capillaries arising from pulmonary arteries. The alveolar wall contains a variety of cells and extracellular fibers. The cells include fibroblasts, macrophages, myofibroblasts, smooth-muscle cells, and occasional mast cells. Type I and II collagens, as well as elastic fibers, are in the septa. Type I collagen is present primarily in the walls of the bronchi and bronchioles. Twenty percent of the mass of the lung consists of collagen and elastic fibers. Elastic fibers are responsible for the stretching and recoiling activities of the alveoli during respiration. These microscopic elements are responsible for the recoil of the lungs during expiration.
- Gas exchange occurs between capillary blood and alveolar air across the blood– gas barrier. This barrier consists of surfactant, the squamous Type I pneumocytes, a shared basal lamina, and capillary endothelium. The distance between the lumen of the capillary and the lumen of the alveolus can be as thin as 0.1 microns. There are openings in the wall of most alveoli that form the **pores of Kohn**. These pores are thought to be important in collateral ventilation. The diameter of these alveolar pores can be as large as 10 to 15 microns.

Alveolar Macrophages

- The **alveolar macrophages** are derived from monocytes that exit the blood vessels in the lungs. The resident alveolar macrophages can undergo limited mitoses to form additional macrophages. These cells can reside in the interalveolar septa as well as in the alveoli. Alveolar macrophages that patrol the alveolar surfaces may pass through the pores of Kohn.
- There are ~1–3 macrophages per alveolus. Alveolar macrophages vary in size, 15–40 microns in diameter. These macrophages represent the last defense mechanism of the lung. Macrophages can pass out of the alveoli to the bronchioles and enter the lymphatics or become trapped in the moving mucous layer and propelled toward the pharynx to be swallowed and digested.

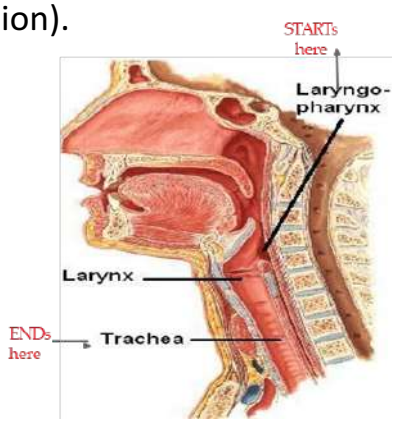
Clinical Correlate: Alveolar macrophages have several other names: dust cells because they have phagocytosed dust or cigarette particles, and heart failure cells because they have phagocytosed blood cells that have escaped into the alveolar space during congestive heart failure.

KAPLAN CORNER

Objective

1. Describe the Extent, structure and functions of the larynx.
2. Describe the Extent, structure and functions of the trachea.
3. Describe the bronchi and branching of the bronchial tree.
4. Describe the functions of bronchi and their divisions.

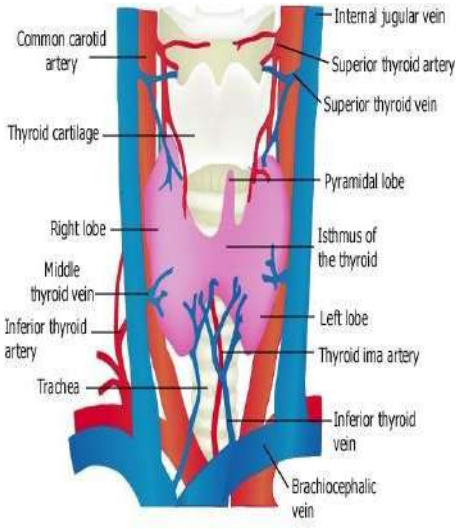
- The larynx is the part of the respiratory tract which contains the vocal cords.
- In adult it is about 2 -inches- long tube.
- The larynx has function in:
  - Respiration (breathing).
  - Phonation (voice production).
  - Deglutition (swallowing).



Relations of the Larynx:

Its related to major critical structures in the neck:

- Arteries:
  - 3 carotid arteries (common, external, and internal)
  - 3 thyroid arteries (superior, inferior thyroid arteries, and thyroidema artery)
- Veins:
  - 2 jugular veins (internal and external)
- Nerves:
  - Laryngeal nerves (superior laryngeal, and recurrent laryngeal)
  - Vagus nerve

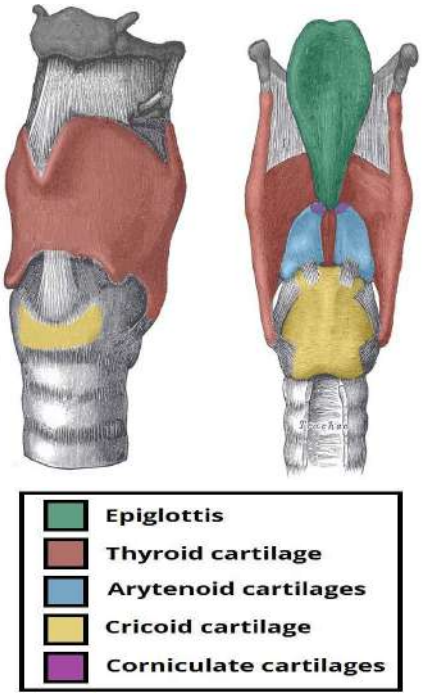


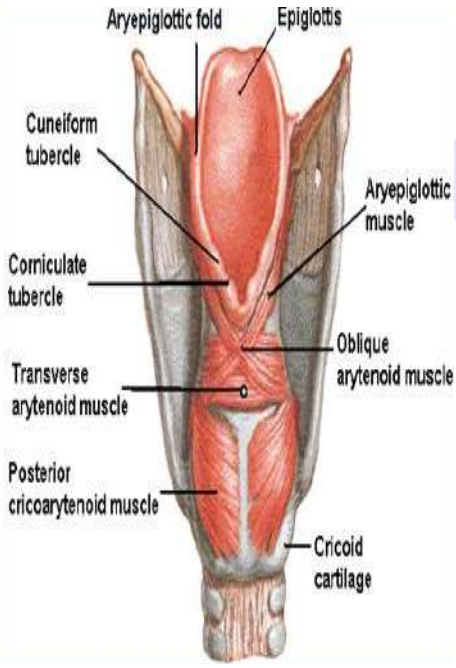
Larynx Components

- The larynx consists of four basic components:
  - Cartilaginous skeleton
  - Membranes and Ligaments
  - Mucosal Lining
  - Muscles (intrinsic & Extrinsic)

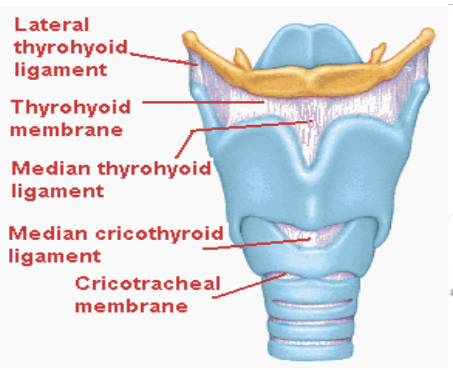
1. Cartilaginous Skeleton:

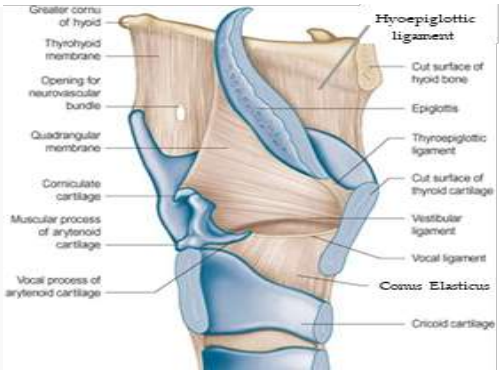
- The Cartilaginous skeleton is made up of 9 cartilages:
- 3 single cartilages:
  1. Epiglottis
  2. Thyroid
  3. Cricoid
- 3 pairs of cartilages:
  1. Arytenoid
  2. Coniculate
  3. Cuneiform
- All the cartilages are hyaline EXCEPT the Epiglottis, it's elastic.
- The cartilages are: Connected by joints, & ligaments. Lined by membranes. Moved by muscles.



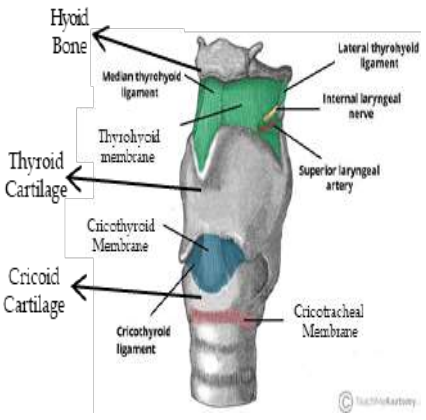


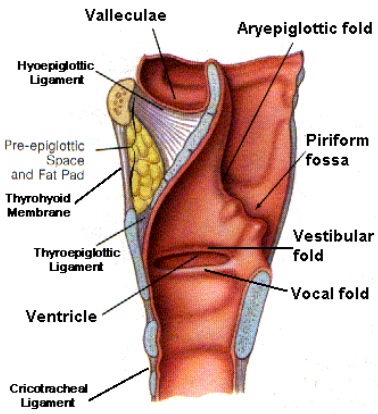
2. Membranes and Ligaments:



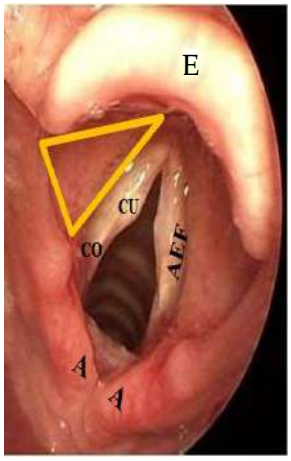


1. Thyrohyoid membrane (between the hyoid bone and the Thyroid Cartilage)
    - It has 2 thickenings: median thyrohyoid ligament and 2 x lateral thyrohyoid ligaments
2. Cricothyroid Membrane “Conus Elasticus” (between the Thyroid Cartilage and the Cricoid Cartilage)
    - It’s upper margin form the vocal ligament which forms the vocal fold or true vocal fold.
    - Its lower margin is attached to the upper border of cricoid cartilage.
3. Cricotracheal Membrane (between the Cricoid Cartilage and Trachea)
4. Hyoepiglottic ligament (between the epiglottis and the hyoid bone)
5. Thyroepiglottic ligament (between the epiglottis and the thyroid)
6. Quadrangular “aryepiglottic” Membrane (In between epiglottis and arytenoid)
    - It’s lower margin form the vestibular ligament which forms the vestibular fold or false vocal fold.

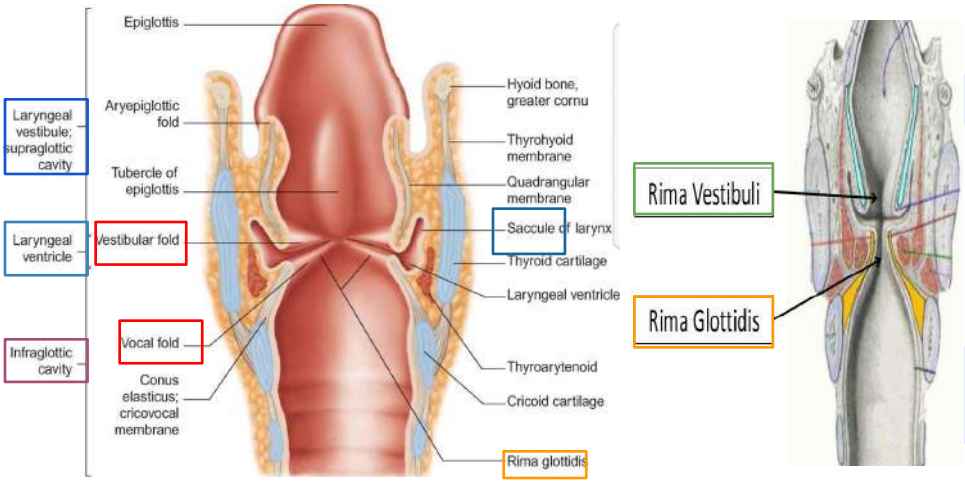




Laryngeal inlet and cavity:



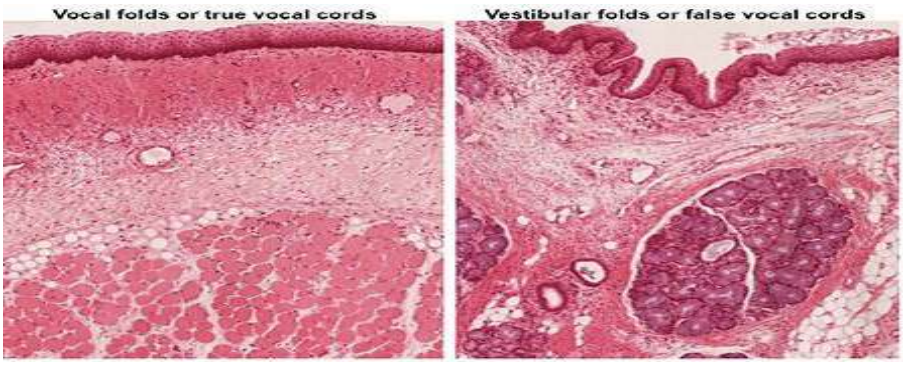
- The upper opening of the larynx into the laryngopharynx.
- It is directed upward and backward
- It opens into the laryngeal part of the pharynx, (laryngopharynx).
- Bounded:
  - Anteriorly: upper border of the epiglottis (E)
  - Posteriorly: Arytenoid (A)
  - Laterally: Aryepiglottic folds (AEF)



- The laryngeal cavity extends from the laryngeal inlet to the lower border of the cricoid cartilage.
- Rima vestibuli is a narrow region between the vestibular folds.
- Rima glottidis is a more narrow region between the vocal folds.
- It's divided into three parts:
  1. supraglottic (vestibule) :the part above the vestibular folds.
  2. ventricle : the part between vestibular & vocal folds
  3. infraglottic : the part below the vocal folds.
- The ventricle has an upward invagination called saccule which is rich in goblet cells

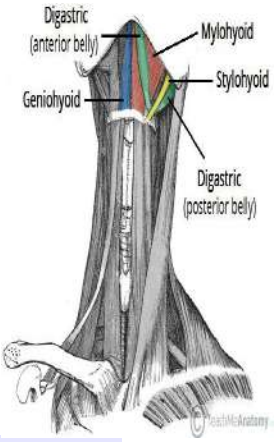
3. Mucosal Lining:

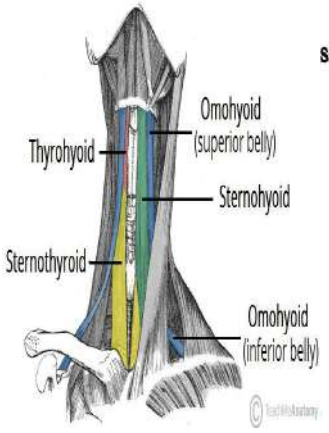
- The laryngeal cavity is lined by: ciliated columnar epithelium
- EXCEPT the surface of the vocal cords it's lined by: Non-keratinized stratified squamous epithelium
- Because they're exposed to trauma during phonation.(voice production)
- The ventricle part has an upward vagination called saccule that contains goblet cells (mucous glands) to lubricate the vocal cords.

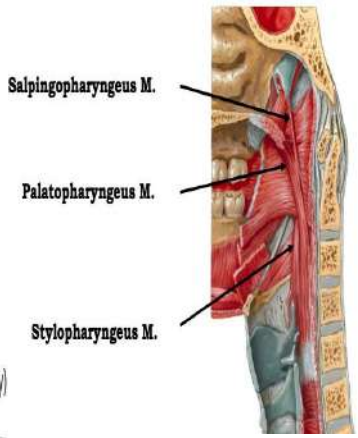


4. Muscles:

- Extrinsic muscles: subdivided into two groups:
  - Elevators of the larynx:
    - Suprahyoids (MSGD): mylohyoid, stylohyoid, geniohyoid, digastric
    - Longitudinal muscles of the pharynx (SSP): stylopharyngeus, salpingopharyngeus, palatopharyngeus.
  - Depressors of the larynx: infrahyoid: sternohyoid, sternothyroid, omohyoid.

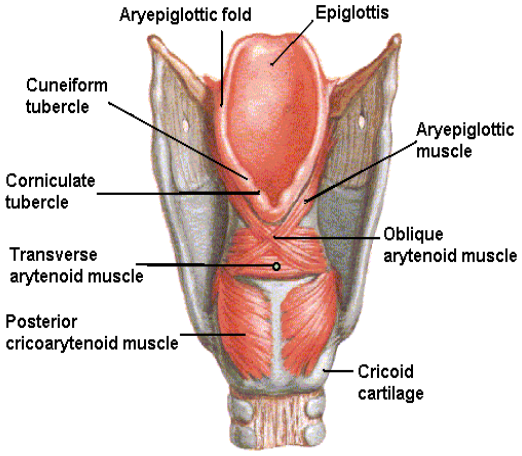


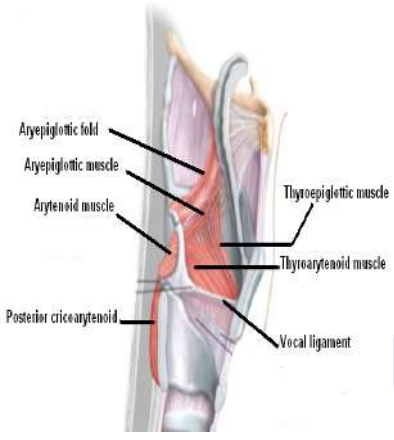




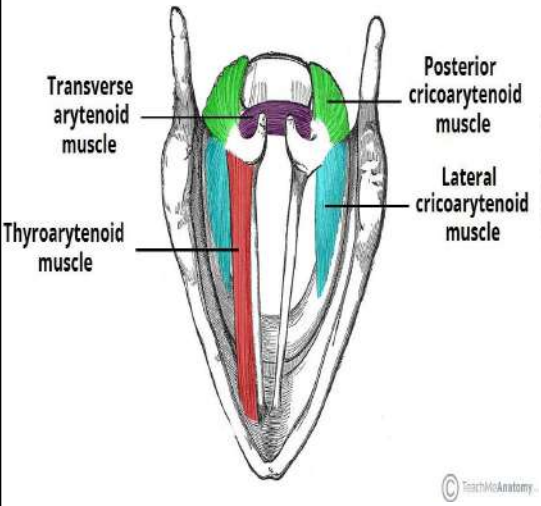
4. Muscles:

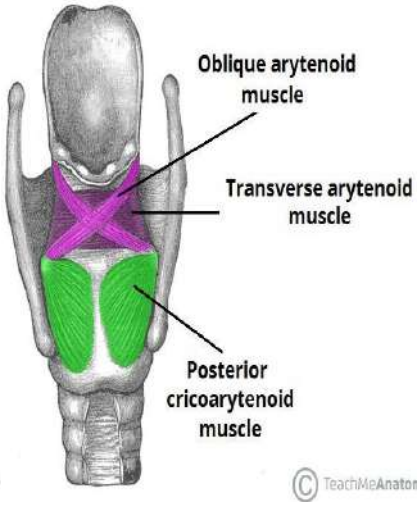
- Intrinsic muscles: subdivided into two groups:
  - Muscles controlling the laryngeal inlet:
    - Oblique Arytenoid muscle
    - Aryepiglottic muscle





  - Muscles controlling Movement of the vocal cord:
    - Decrease Vocal cord length and tension: Thyroarytenoid muscle (Vocalis)
    - Increase vocal cord length and tension: Cricothyroid muscle (Only one can found outside the larynx)
    - Adductors: Lateral Cricoarytenoid, and Transverse Arytenoid
    - Abductors: Posterior Cricoarytenoid





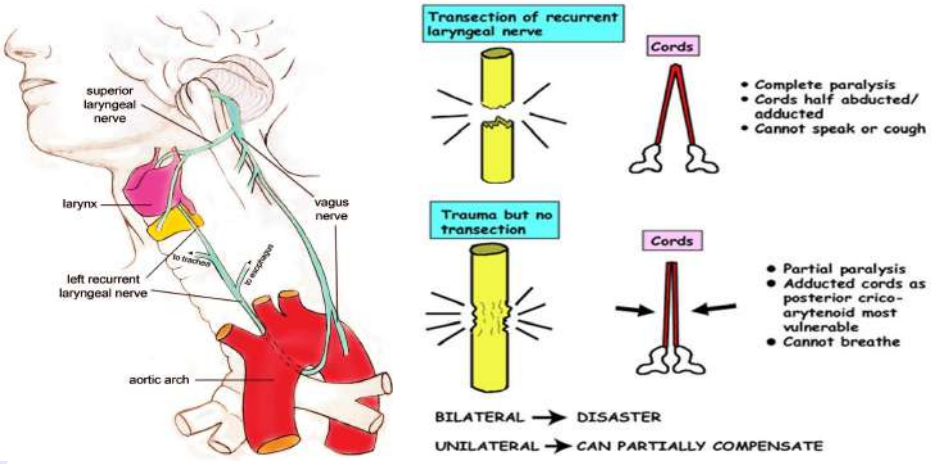
Nerve supply and Semon's Law

Motor:

- All intrinsic muscles are supplied by recurrent laryngeal nerve of vagus nerve EXCEPT cricothyroid, it's supplied by external laryngeal nerve of superior laryngeal of vagus.

Sensory:

- Above the vocal cord = Internal laryngeal nerve of branch superior laryngeal of vagus nerve
- Under the vocal cord = Recurrent laryngeal nerve. Of vagus nerve.

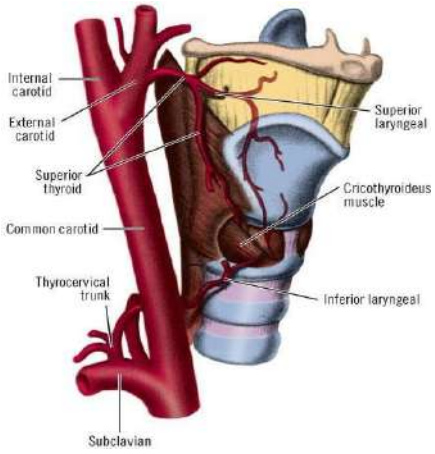


Semon's Law (damage of recurrent laryngeal nerve):

- Semon's Law indicates the different effect between damage (surgical trauma) and transection of the recurrent laryngeal nerve due to surgery in region of the neck (e.g. thyroidectomy or parathyroidectomy):
  - Transected: complete paralysis, cannot speak, cannot cough BUT can breathe.
  - Trauma without transection: partial paralysis, adducted vocal cords, AND cannot breathe.
  - In non-transected nerve damage:
    - Bilateral (both sides) = VERY dangerous
    - Unilateral = can partially compensate

Note :The nerve fibers supplying the abductors lie in the periphery of the recurrent laryngeal nerve and any lesion involves these fibers first before involving the deeper fibers that supply the adductors.

Blood supply



Arteries:

- Upper half : Superior laryngeal artery, branch of superior thyroid artery.
- Lower half: Inferior laryngeal artery, branch of inferior thyroid artery.

Veins:

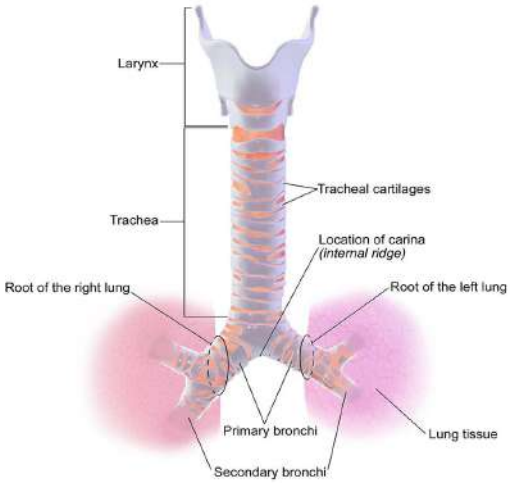
- Accompany the corresponding arteries.

Lymphatics:

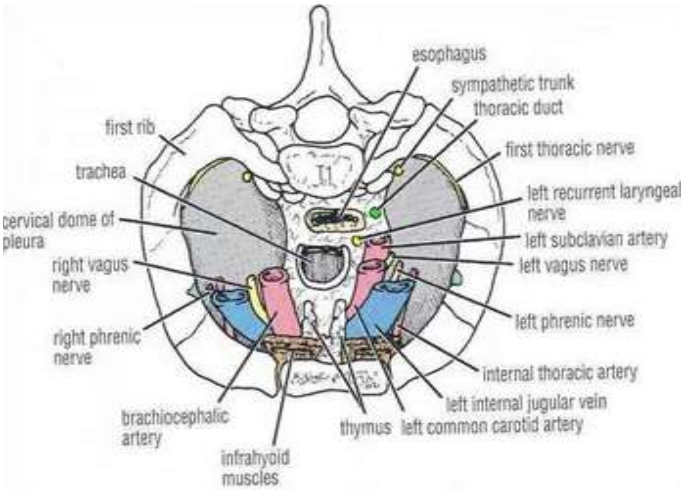
- The lymph vessels drain into the deep cervical lymph nodes.

Trachea

- Mobile, fibrocartilage tube
- In adult it is about 5 inches long tube with 1 inch in diameter
- Begins: Below the cricoid cartilage (at C6)
- Ends: Thorax (behind sternal angle) lower border of T4
- Divides into: right and left primary(main) bronchi
- Its wall supported by 16-20 horseshoe cartilage anteriorly.
- The ridge at the bifurcation from inside is called carina
    - It is the most sensitive part of the respiratory tract
    - It's associated with the cough reflex



Relations



Anterior:

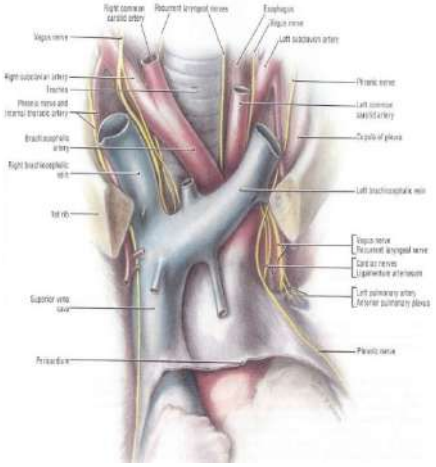
- Sternum
- Thymus
- Left brachiocephalic vein
- Arch of the aorta
- Origin of: brachiocephalic artery left common carotid artery

Posterior:

- Esophagus
- Left recurrent laryngeal n.

Right:

- Azygos vein
- Right vagus nerve
- Right pleura



Left:

- Left vagus nerve
- Left phrenic nerve
- Left pleura
- Arch of the aorta
- Left common carotid artery
- Left subclavian artery

Blood & Nerve supply

Artery Supply:

- Inferior thyroid and bronchial arteries (from descending thoracic aorta)

Venous Supply:

- Drain into inferior thyroid vein.

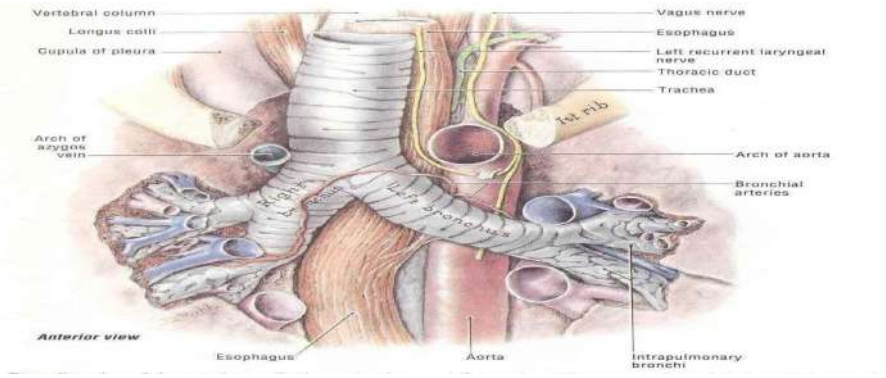
Nerve Supply:

- Branches of the vagus nerve and recurrent laryngeal nerve give sensory fibers to supply the mucous membrane.
- Trachealis is supplied by branches of the sympathetic trunks.

Lymphatics:

- Drain into pre and para tracheal lymph nodes

Bronchi



Right bronchus:

- One inch long., wide,short,more vertical bronchus
- Gives superior lobar before entering the hilum and gives the inferior and middle lobar after.

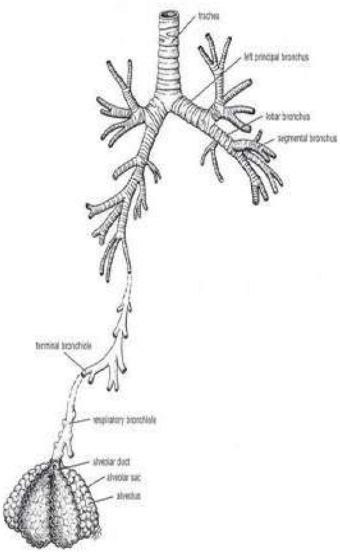
Left bronchus:

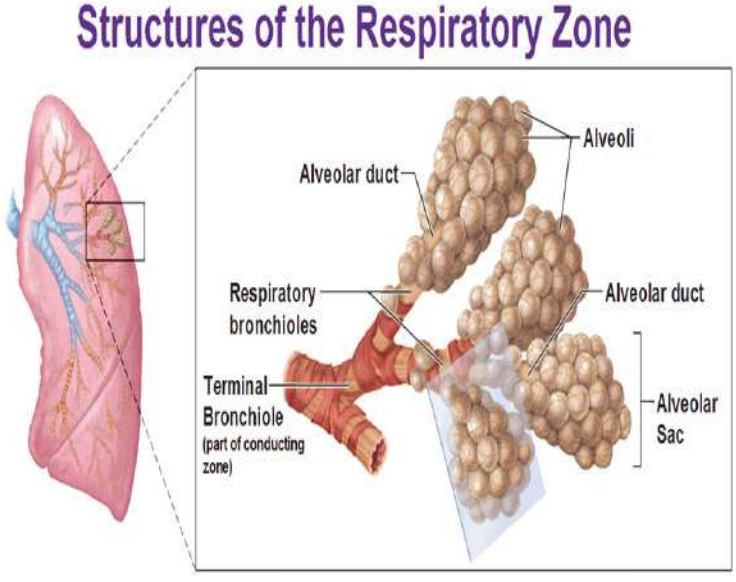
- Two inches long., narrow,long, more horizontal bronchus
- Gives superior and inferior lobar after entering the hilum. (no middle lobar)
- Passes below the aortic arch and in
- front of the esophagus.

Divisions:

- Within the lung each bronchus divides and redivides into number of branches that can be divided into two groups:

1. Conduction zone branches
   - Primary (main) bronchi.
   - Secondary (lobar) bronchi.
   - Tertiary (segmental) bronchi. (supply the bronchopulmonary segment).
   - Smaller bronchi.
   - Bronchioles.
   - Terminal bronchioles.
2. Respiratory zone branches
   - Respiratory bronchioles.
   - Alveolar ducts.
   - Alveolar sacs.
   - Alveoli.





Objective

1. Understand asthma as an episodic, reversible bronchoconstriction caused by increased responsiveness of the tracheobronchial tree to various stimuli.
2. Know that asthma is divided into two basic types: extrinsic or atopic allergic and intrinsic asthma.
3. Understanding the morphological changes (gross and microscopic) seen in the lungs in cases of severe asthma.

Bronchial Asthma

Definition:

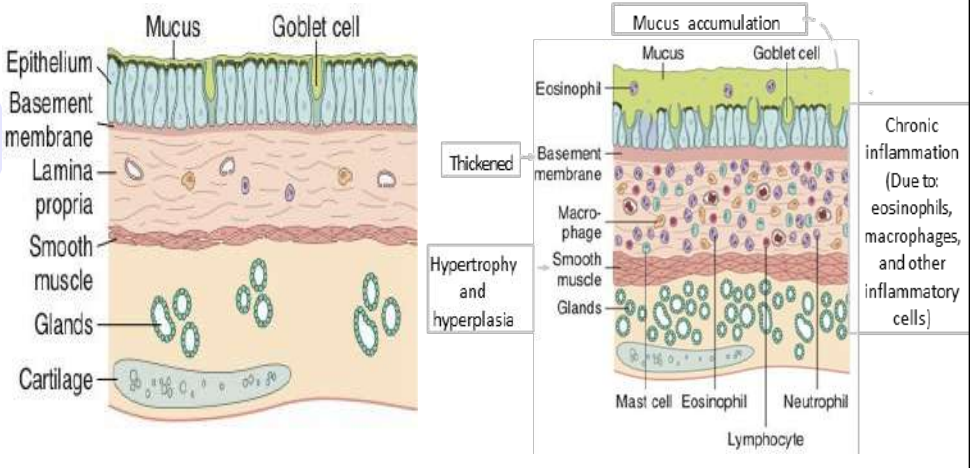
A chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness and cough.

Note:
Wheezing occurs when the small airways of the lungs become narrow or constricted. This makes it difficult to breathe, and can cause a whistling sound when breathing out

Hallmarks of Bronchial Asthma:

- Intermittent and reversible airway obstruction
- Chronic bronchial inflammation with eosinophils
- Bronchial smooth muscle cell hypertrophy and hyper-reactivity.
- Increased mucus secretion

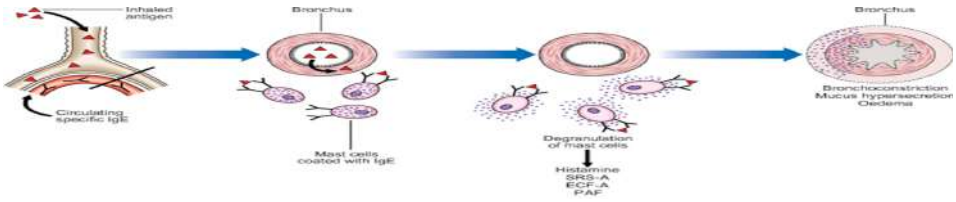
Airway comparison:



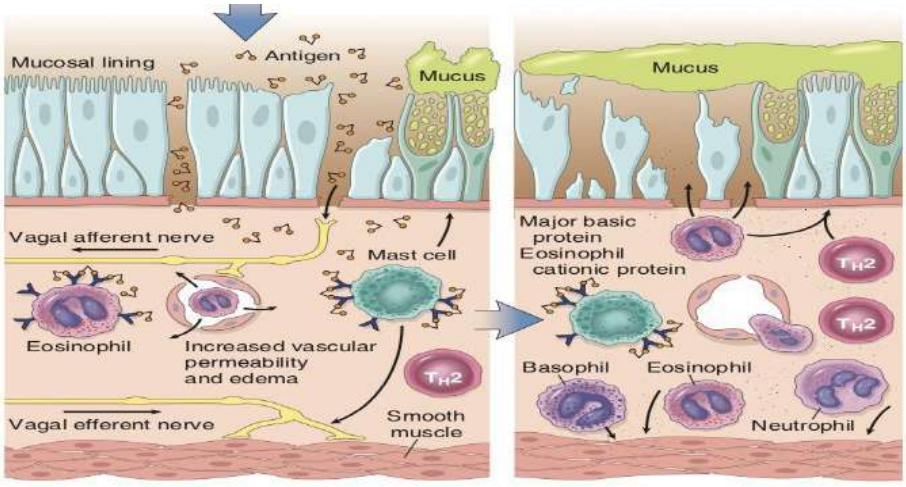
Normal airway

Airway in asthma

Pathogenesis



- **Step 1**: Triggering of asthma
- **Step 2**: Immediate phase (minutes)
- Re-exposure to antigen (Ag)
- Immediate reaction is triggered by: Ag-induced cross-linking of IgE bound to Fc receptors on mast cells.
- Mast cells release preformed mediators that directly and via neuronal reflexes induce:
  - Bronchospasm.
  - Increased vascular permeability.
  - Mucus production.
  - Recruitment of leukocytes.
- **Step 3**: Late phase (hours)
- Leukocytes recruited to the site of reaction: neutrophils, eosinophils, basophils, lymphocytes, monocytes.
- These cells will release additional mediators that initiate the late phase of asthma.
- Several factors released from eosinophils (e.g., major basic protein, eosinophil cationic protein) also cause damage to the epithelium.



Cytokines produced by Type 2 helper T (TH2) cells:

	Function
IL-4	Stimulate IgE production.
IL-5	Activates eosinophils which play a major part in the pathogenesis of asthma. Because they produce basic proteins, which cause asthma, damage bronchial wall, incite inflammation, and induce contraction of bronchial smooth muscles.
IL-9	Damages the bronchial epithelium directly.
IL-13	Stimulates IgE and mucus production.

Repeated bouts of inflammation lead to structural changes in the bronchial wall **(Airway remodeling)**:

- Hypertrophy of bronchial smooth muscle.
- Hypertrophy of mucus glands.
- Increased vascularity and deposition of subepithelial collagen.

Types of Bronchial Asthma

1- Extrinsic asthma (Atopic):

- Bronchospasm is induced by inhaled antigens
- Atopic/allergic Asthma 70%
- Type 1 hypersensitivity reaction* mediated by IgE, induced by exposure to extrinsic antigen/allergens e.g. food, pollen, dust, etc,
- Family history: positive Skin test: positive

2- Intrinsic asthma (Non-Atopic):

- A disease in which the bronchial hyper- reactivity is induced by non-immune mechanisms
- Non-atopic/Not allergic Asthma 30%
- Initiated by diverse, non-immune mechanisms.
- Family history: uncommon Skin test: Negative

3- Drug-induced asthma:

- NSAIDs, and especially aspirin may provoke asthma.

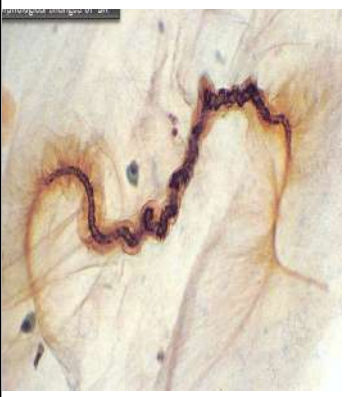
4- Occupational asthma

- Stimulated by fumes, dusts, and other chemicals.

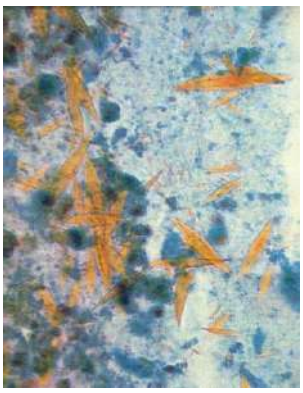
Diagnosis

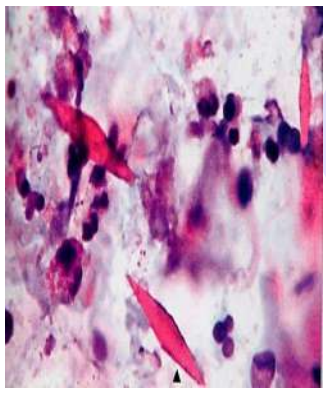
Diagnosis of extrinsic asthma by:

- Skin test using antigen: positive (immediate wheal and flare reaction)
- Radioallergosorbent test (RAST): presence of IgE in the blood.
- Spirometry: pulmonary function test
- Sputum sample → Histological findings of the sputum:
  - Curschmann spirals: collection of mucus with a special shape.
  - Charcot Leyden crystals: looks like crystals, made up of eosinophil proteins.
  - Large numbers of eosinophils (especially in atopic asthma).



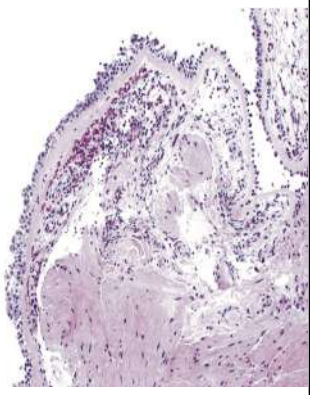
Curschmann's spiral





Charcot–Leyden Crystals

Morphology:



- Thickening of airway wall
- Sub-basement membrane fibrosis
- Increased submucosal vascularity
- An increase in size of the submucosal glands and goblet cell metaplasia of the airway epithelium.
- Hypertrophy and/or hyperplasia of the bronchial muscle

Clinical features:

- Dyspnea
- Increase in residual volume and anteroposterior diameter
- Wheezing
- Cough → nocturnal and/or morning cough
- Tightness of chest
- Subtle deficits can be detected by pulmonary function tests.
- Difficult expiration
- **Status asthmaticus**

Complications

- Airway remodeling
- Superimposed infections
- May develop to other COPD4
- Pneumothorax1 and Pneumomediastinum2
- Status asthmaticus5
- In some cases cor pulmonale3 and heart failure develop

Prognosis of Asthma

- Remission (reduce, decrease):
  - 50% of cases of childhood asthma resolve spontaneously but may recur later in life.
  - Remission in adult-onset asthma is less likely.
- Mortality:
  - Death occurs in ~0.2% of asthmatics.
  - It is usually (but not always) preceded by an acute attack and about 50% are more than 65 years old.

Prevention of Asthma

- Control of factors contributing to asthma severity:
  - Exposure to irritants or allergens has been shown to increase asthma symptoms and cause exacerbations.
- Skin test:
  - Results should be used to assess sensitivity to common indoor Allergens.
  - All patients with asthma should be advised to avoid exposure to allergens to which they are sensitive.

In SUMMARY:

Definition

Inflammatory disorder of the airway, which is characterized by increased responsiveness of the bronchial mucosa and bronchial wall to various stimuli, it's also characterized by episodic attacks and it's reversible, which means that it can be reversed by avoiding the stimuli.

Signs and symptoms

- Dyspnea."Most serious"
- Wheezing.
- Cough."Not a major symptom"

Types:

- Extrinsic (atopic): common in children.
- Intrinsic (non-atopic):
  - Usually happens in adults.
  - These patients don't have history of hypersensitivity.
  - Usually come after exercise(exercise induced intrinsic asthma): Exercise causes dehydration which will increase the osmolality of the sputum which is associated with secretion of certain chemical mediators(especially Leukotrienes C4,D4,E4 which will cause bronchospasm).
  - Aspirin (block PGs—> enhance leukotrienes C4,
  - D4, E4—> bronchoconstriction)

In SUMMARY:

Pathogenesis

1. Entry of antigen, then it is engulfed by APCs and presented to T-lymphocytes, especially CD4.
2. Activates the CD4 T-lymphocytes and transform them into TH2 cells.
3. TH2 cells start secreting these cytokines:
    - IL-4: will stimulate the B-lymphocytes to secrete IgE(has a main role in hypersensitivity type 1), this IgE will bind to certain receptors on mast cells, then the antigen will come and bind to the antibody, then the mast cell will release the granules(which contain histamine, serotonin and other chemical mediators) which will cause vasodilation and edema.
    - IL-5: Can be secreted by T&B lymphocytes, it will facilitate the recruitment of eosinophils, which will also release their granules(has major basic proteins) which will cause damage to the bronchial epithelium, then the damaged epithelium will secrete eotaxin which will recruit more eosinophils.
    - IL-9: Act directly on the bronchial epithelium and will cause damage to it.
    - IL-13: Same action as IL-4.

Pathological changes in asthma:

- Hyperplasia/ Hypertrophy and spasm(due to stimulation and irritation of the nerves endings specially nerves from the vagus nerve)
- Excessive mucus secretion with accumulation of eosinophils.

Asthma

What is asthma?

- Reversible airway bronchoconstriction, most commonly seen due to allergic stimuli (atopic asthma)
- Associated with allergic rhinits, eczema (atopic dermatitis) and family history of atopy (tendency of type I hypersensitivity reactions)
- Commonly seen in kids

What is pathogenesis of asthma? (HY)

- Allergens induce TH2 phenotype in genetically susceptible patient. TH2 secretes:

IL-4	Induces class switching to IgE
IL-5	Attracts eosinophils
IL-10	Stimulates TH2 and inhibits TH1

- IgE coats mast cells and next time same allergen is encountered, massive mast cell degranulation occurs.
    - Histamines (arteriolar vasodilation and increase vascular permeability) and leukotriene (vasoconstriction, increased vascular permeability (by constricting pericytes), and bronchoconstriction) are released by mast cells.

What is late phase reaction in asthma? (HY)

- Eosinophils release MAJOR BASIC PROTEIN that damages cells and induces bronchoconstriction

What are clinical features of asthma?

- Productive cough, dyspnea, wheezing in response to allergen exposure (episodic).

What are biopsy findings in asthma?

- Curschmann spirals (spiral shaped mucus plug)
- Charcot-leyden crystals (HY) (eosinophil derived MAJOR BASIC PROTEIN that indicate eosinophilic inflammation)

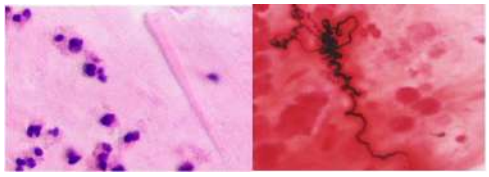


Fig: Carcot leyden crystal on left and curschmann spiral on right

What are nonallergic causes of asthma?

- Exercise
- Viral infection
- Asprin (HY)
- Occupational exposure

What is presentation of asprin intolerant asthma?

- Nasal polyps (nasal polyp in kids highly associated with CF)
- Bronchospasm with aspirin

PATHOMA CORNER

Lung Pathology

1.2 - Asthma & Bronchiectasis

1. **Asthma**
2. **General:**
   a. In asthma, obstruction prevents air from leaving the lungs (trapped in distal airways): (Kid obstructing exit)
   b. Asthma is characterized by a hyperactive airway (HYPERACTIVE TO BEE)
   c. Asthma In comparison to COPD is a transient **reversible process,** caused by hyperactive airways that leads to intermittent airway inflammation and obstructive symptoms (BACKWARDS CAP)
   d. ASHTMA is characterized by **chronic bronchial Inflammation** with **eosinophils** (Flame with a slingshot)
   e. Asthma is characterized by **smooth muscle hypertrophy** and hyperactivity and increase mucus section (MUCUS DRIPPING and GRIP ON LIMB)
   f. Atopic asthma involves a **type I hypersensitive reaction,** with common triggers being animal dander, pollen, dust and other environmental antigens (ANTIGENIC SQUIRREL)
3. **Mechanism of Action:**
   a. The antigen is picked up by an antigen presenting cell and then presented to a TH2 helper T cell where it gets too activated
      i. Interleukins 4, 5, 13 are activated
      ii. Interleukins 4, 13 will activate B cells that **will make a lot of IgE**
      iii. This signals to the B cells to produce IgE (IL4 and IL13) (IgE archer aiming at beehive)
   b. The inflammatory reaction in asthma is a type 1 hypersensitivity reaction (IgE production and mast cell degranulation) (1 finger in the air)
      i. BEE HIVE = Mast cell
   c. When antigen is reintroduced it binds to the IgE on mast cells and crosslinks the IgE which leads to degranulation (SQUIREEL CROSS LINKING BEEHIVE)
      i. This degranulation release leads to release of histamine, acetylcholine, leukotrienes and other pro-inflammatory cells (BEE RELEASE)
4. **Phases of Asthma:**
   a. **Early Phase:**
      i. Pro-inflammatory molecules released by mast cells induce **bronchoconstriction,** mucus production and vasodilation in large airways (GRIPPING DROOLING, DILATED SLEEVES)
   b. **Late Phase:**
      i. Inflammation consisting of eosinophils, neutrophils and T-cells occurs 4-8 hours after the early phase (LATE FLAME CAP)
      ii. **Eosinophils** are a characteristic finding of Asthma
      iii. This is causing damage to the airways (EOSINOPHILS EVERYWHERE)
      iv. A major source of damage form eosinophilic inflammation is release of major basic protein, an anthelmintic toxin that causes epithelial damage, histamine release and further eosinophil chemotaxis (DAMAGED MAJOR BASE SIGN)
      v. Chronic **inflammation** form repeated attacks causes permeant structural changes to bronchial wall (CHRONIC FLAME CAPE)
   1. This includes thickened basement membrane and smooth muscle hypertrophy and hypertrophy of submucosal mucosal glands (THICK CONCRETE BASE AND A BUFF KID AND MUCOUSY EATER BOTTLE)
   c. **Histology:**
      i. **Mucus plugs** in bronchi and bronchioles (Can plugged with mucus)
      ii. **Eosinophilic infiltration of the airways** is one of the hallmarks of atoptic asthma (eosinophils in sputum and eosinophilia)
      iii. Slothing of epithelium can lead to the formation of **Kurshmann spirals,** which are whorled deposits of epithelial cells (Curly string from plugged can)
      iv. **Charco-Layden crystals** are thin, needle like concretions of eosinophilic proteins seen in the sputum of asthmatics (PINK JACKS)

5. **Clinical Presentation:**
   a. **Expiratory wheezing** from bronchoconstriction is common in asthma exacerbation (KID WITH PARY BLOWER)
   b. **Acute dyspnea** is a common symptom of asthma exacerbation (KID PUFFING OUT AIR)
   c. **Chronic cough** especial nocturnal cough, in children it may be the only symptom (kid waking up form cough)
   d. Asthma is highly associated with atopy, so a family history of allergies is common (FAMILY PHOTO)
   e. Severe asthma attacks can lead to pulsus paradoxus, a drop in systolic BP> 10mmHg on inspiration (PULSUS PARADOXUS)
6. **Imaging:**
   a. Air trapping in acute exacerbations can be seen on chest x-ray as a hyper inflated lung (flattened diaphragm, and lengthening of the cardiac silhouette) (KITE with XRAY)
7. **Pulmonary Function Tests:**
   a. Classic spirometry findings in asthma are a FEV1/FVC <.7 and an FEV1 <80% expected (FALLING FEV1/FVC)
   b. In between attacks these attacks are probably normal
8. **Laboratory Tests:**
   a. Patients with acute asthma exacerbations will have an initial respiratory alkalosis form hyperventilation (can progress to acidosis as severity increases) (BLOWING OH bubbles that end up popping)
9. **Non-atopic Asthma:**
   a. **Viral infections** are a common inciting cause of non-atopic asthma exacerbations (VIRAL Lantern)
   b. **Second hand smoke** are another common inciting cause of non-atopic asthma exacerbations (ASHTRAY)
   c. **Aspirin** is a the most common drug induced cause of non-atopic asthma exacerbations (UMPIRE HOLDING LACROSS STICK)
      i. Inhibiting COX-1 shifts AA metabolism to LOX pathway à Leukotrienes à bronchoconstriction
   1. LTC4, LTD4, LTE4
10. **Bronchiectasis**
11. Bronchiectasis is characterized by permanent dilation of the bronchi and bronchioles (due to infections and inflammation that destroys the muscle and elastic tissue supporting the airway) (DILATED POMEGRANATES)
   a. Same area of the lung each time
   b. Recurring bacteria lanterns: bronchiectasis is caused by **chronic recurrent bacterial infections**
   c. **Tumors** causing obstruction can lead to distal infection, thus initiating the cycle of infection/ inflammation à bronchiectasis
   d. **Chronic Fibrosis** is the most common cause of bronchiectasis in the US (thick secretions cause obstruction leading to infection/inflammation) (tree sap)
   e. **Primary cilia dyskinesia** is another possible cause of bronchiectasis (secretions are not cleared due to dysfunctional cilia)
   f. Tuberculosis is the most common cause of bronchiectasis worldwide
12. Bronchiectasis primarily affects the lower lobes (Seen on CXR and CT as CROWDED bronchial markings extending to the edge of the lung periphery (CROWDED LOWER POMEGRANATES)
13. Bronchiectasis is characterized by copius sputum production, often described as "cup fulls"
   a. Can have hemoptysis

Objective

1. Identify differences between extrinsic and intrinsic asthma
2. Identify types of allergens and their role in allergic sensitization
3. Explain the inflammatory processes operating in allergic asthma
4. Explain the airway remodeling

Immunology of asthma

Asthma is a clinical syndrome characterized by:

1. Reversible airway obstruction
2. Increased bronchial reactivity
3. Airway inflammation

Symptoms:

- Breathlessness
- Wheezing
- Persistent cough
- Chest tightness

Classification

	Non-atopic asthma (intrinsic)	Atopic asthma (extrinsic)
Severity	Very severe	Less severe
Prevalence	Older patients (10-33% of asthmatics)	60-90% children 50% of adults
History of allergy	Not needed	Needed
Serum IgE	Normal	High
Skin test	Negative	Positive (in 70-85%)

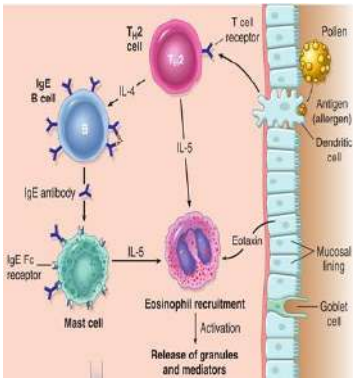
Allergens are linked to the risk of developing asthma.

- Indoor: Dust mites, pets, cockroaches, mold.
- Outdoor: Spores, grass, weed pollens.

APCs and allergic response

There are 2 different types of APCs present in the lung:

1. Myeloid Dendritic cells: they develop asthma symptoms.
2. Plasmacytoid Dendritic cells: They aid in respiratory tolerance to the allergen.



Note:

Atopy: genetic tendency to develop allergy.

Atopic: asthma caused by an external allergen.

Non-atopic: asthma triggered by internal factors.

Allergic response

Sensitization

- The allergen binds to the dendritic cells, pushing it to activate Th2 cells.
- Th2 cells release multiple cytokines, including IL-4-5-9-13.
- Il-4 activates B-cells, Causing a class switch and releasing IgE, which will bind with mast cells.

Response

Early:

- Allergen will bind with mast cells, releasing mediators such as histamine and prostaglandin.
- This causes bronchoconstriction, edema and mucus
- plugging.
- Occurs within seconds or minutes.
- Reversible and responds to bronchodilators

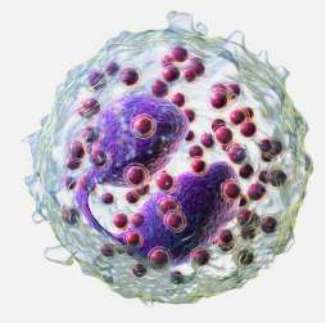
Late:

- Eosinophils released by IL-5 and T-lymphocytes are stimulated, causing inflammation.
- 8-10 hours after early response.
- Responds to steroids

The Role of Cells & Cytokines in Allergic Asthma

Th2 cells during allergic asthma secrete: Interleukin (4,5,9 & 13)
This causes:

- Production of IgE
- Eosinophils attraction
- Airway inflammation
- Increase in bronchial reactivity



The inflammatory cells interact with:

- Nervous system
- Airway epithelium
- Bronchial muscles

Cytokines

IL-4:

- Regulates isotype switching to IgE in B cells.
- Induces MHC II (in antigen presenting cells)
- Induces adhesion molecules.
- Activates mast cells and eosinophils.

IL-5

- Increases eosinophils production.
- Release eosinophils from bone marrow.

IL-13

- Induces inflammation.
- Stimulate mucus hypersecretion .
- Induces subepithelial fibrosis.

Cells

Eosinophils:

- Initiate asthmatic symptoms by causing tissue damage.
- IL-10 can inhibit eosinophils' production

Regulatory T-cells

- Suppress asthmatic symptoms.
- Some asthmatics lack this function.

Airway inflammation and Bronchial Reactivity

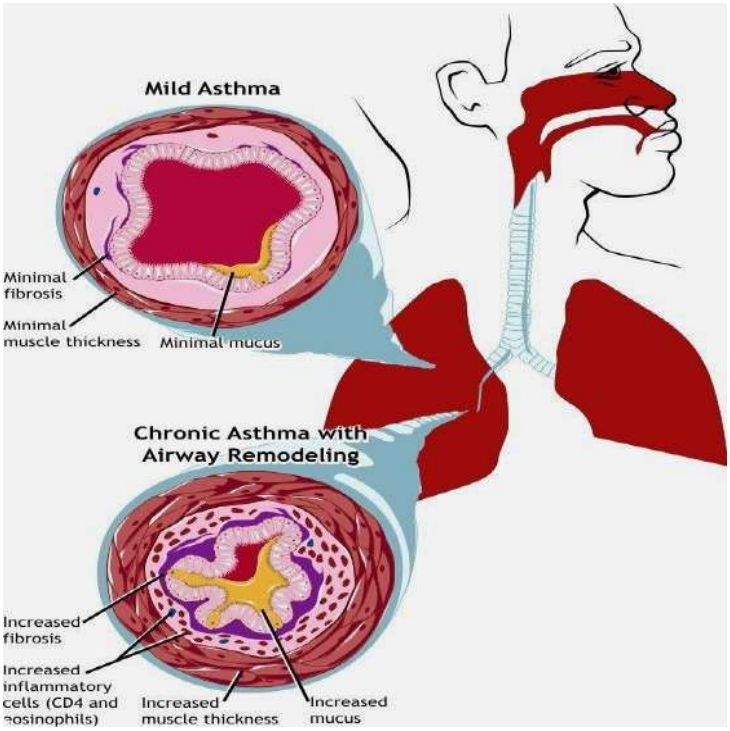
Activation of inflammatory cells (eosinophils and mast cells) and their mediators will act on:

1. Airway and smooth muscles → hyperplasia and hypertrophy
2. Mucous glands → hyperplasia
3. Lung Fibroblasts → activation and collagen deposition (fibrosis)
4. Airway → chronic inflammation

This will cause airway remodeling and bronchial reactivity, which will eventually lead to chronic inflammation.

Outcomes

- Airway remodeling: Leads to fibrosis and irreversible airway obstruction
- Bronchial Reactivity: Bronchus becomes more reactive to some non-specific irritants and cause asthma attack.
    - Non-specific irritants include: Chemicals, smoke, strong perfume, sulphur dioxide, air pollutants and infections



Objective

1. Different types of drugs used for treatment of asthma and COPD.
2. Differentiate between treatment and prophylactic therapy for asthma.
3. Recognize the different types of bronchodilators regarding pharmacokinetics, pharmacodynamics, uses and side effects.
4. Identify the different anti-inflammatory drugs for asthma in respect to kinetics, dynamics, uses and side effects.

Bronchial Asthma

Asthma is a chronic inflammatory disorder (Obstructive diseases) of bronchial airways that result in airway obstruction in response to external stimuli or triggers.

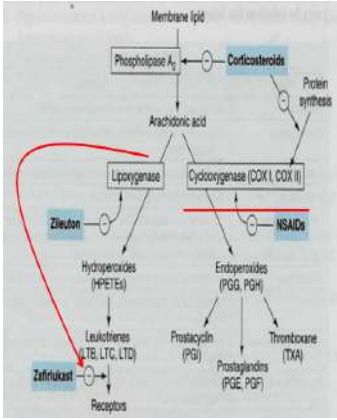
Characters of airways in asthmatic patients :

- Airway hyperreactivity:
  - Is an abnormal sensitivity of the airways to any external stimuli.
  - Results in release of endogenous inflammatory mediators. e.g. histamine, leukotrienes
- Inflammation:
  - ↑ Edema, swelling.
  - ↑ Thick mucus production.
- Bronchospasm:
  - Constriction of the bronchial smooth muscles.

Note:
Aspirin is NSAID which will inhibit the cyclooxygenase enzyme, so most of arachidonic acid will be converted through 5-lipoxygenase to leukotrienes instead which causes bronchoconstrictors, and they are important chemical mediators in the pathogenesis of asthma.

Triggers of asthma:

- Exogenous chemicals or irritants
- Chest infections
- Stress
- Exercise (in cold air)
- Pets
- Seasonal changes
- Emotional conditions
- Some drugs (as aspirin, β-bockers)



Symptoms of asthma

Asthma produces recurrent episodic attack of :

- Acute bronchoconstriction
- Shortness of breath
- Chest tightness
- Wheezing
- Rapid respiration
- Cough

Symptoms can happen each time the airways are irritated by inhaled irritants or allergens.

Anti asthmatic drugs

Bronchodilators	Prophylactic
It is a **quick relief** → Treat acute episodic attack of Asthma. - Antimuscarinics - Short acting ß2-agonists - Xanthine preparations	It is for **control** (Anti-inflammatory) → Reduce the frequency of attacks and nocturnal night awakenings. - Corticosteroids - Mast cell stabilizers - Leukotrienes antagonists - Anti-IgE monoclonal antibody - Long acting ß2-agonist

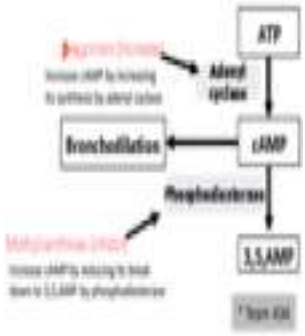
Bronchodilators

Supply

- Parasympathetic supply:
  - M3 receptors in smooth muscles and glands
  - Action: Bronchoconstriction +Increase mucus secretion.
- Sympathetic supply:
  - B2 receptors in smooth muscles and glands.
  - Action :Bronchodilation +Decrease mucus secretion.

β- adrenoceptor agonists (Sympathomimetics)

Mechanism of action



- stimulate β2 Directly → stimulate adenyl cyclase → ↑ cAMP → bronchodilation.
- Increase mucus clearance by increasing ciliary activity.
- Stabilization of mast cell membrane

Classification

- Non selective β-agonist: epinephrine – isoprenaline
- Selective β2-agonist : salbutamol, terbutaline, salmeterol, formeterol.

	A. Non-selective β-agonist
Drugs	Epinephrine (Adrenaline), Isoprenaline
Pharmaco-kinetics	○ Given S.C, I.M (Not effective orally). ○ Rapid onset of action (maximum effect within 15 min). ○ Has short duration of action (60-90 min).
Clinical uses	○ Epinephrine: Non-selective adrenergic agonist (α1, α2, β1, β2). ○ Potent bronchodilator. ○ Adrenaline is the drug of choice for acute anaphylaxis (hypersensitivity reaction).
ADRs	○ Hyperglycemia. ○ Skeletal muscle tremor. ○ CVS side effects (β1 actions): tachycardia, arrhythmia, hypertension.
CI	○ CVS patients :hypertension, heart failure. ○ Diabetic patients. ○ Asthmatic patient with hypertension.

	B. Short acting β2 agonist
Drugs	○ Salbutamol, terbutaline.
Pharmacokinetics	○ Salbutamol (albuterol): mainly given by inhalation, orally, I.V ○ Terbutaline: mainly given by inhalation, orally, s.c. ○ Have rapid onset of action (15- 30 min) ○ Short duration of action (4-6 hr).
Clinical uses	○ Drugs of choice for acute episodic attack of asthma.

	C. Long acting β2 agonist
Drugs	○ Salbutamol
Pharmacokinetics	○ Salmeterol & formoterol are given by inhalation. ○ Long acting bronchodilators (12 hours) due to high lipid solubility (creates depot effect).
Clinical uses	○ Are NOT used to relieve acute episodes of asthma. ○ Used for nocturnal asthma. ○ Combined with inhaled corticosteroids to control asthma (prophylactic medication)

Advantages of selective 2 agonists

- Suitable for asthmatic patients with CV disorders as hypertension or heart failure , due to minimal CVS side effects .

Disadvantages of selective 2 agonists

- Skeletal muscle tremors.
- Nervousness
- Tolerance (β-receptors down regulation).
- Overdose may produce tachycardia due to β1stimulation.

	Muscarinic antagonists
Drugs	○ Ipratropium, Tiotropium
MOA	○ Act by blocking muscarinic receptors (non-selective)
Pharmacodynamics	○ Inhibit bronchoconstriction and mucus secretion with no anti-inflammatory action. ○ Less effective than β2-agonists. ○ Does not diffuse into the blood . ○ Does not enter CNS. ○ Quaternary derivatives of atropine (polar).
Pharmacokinetics	○ Given by aerosol inhalation. ○ Have delayed onset of action (Never used as rescue medications) ○ Ipratropium: has short duration of action (3-5 hrs) ○ Tiotropium: has longer duration of action (24 hrs)
Clinical uses	○ Main choice in chronic obstructive pulmonary diseases (COPD). ○ In asthma combined with β2 agonists & corticosteroids.
ADRs	○ Have minimal systemic side effects.

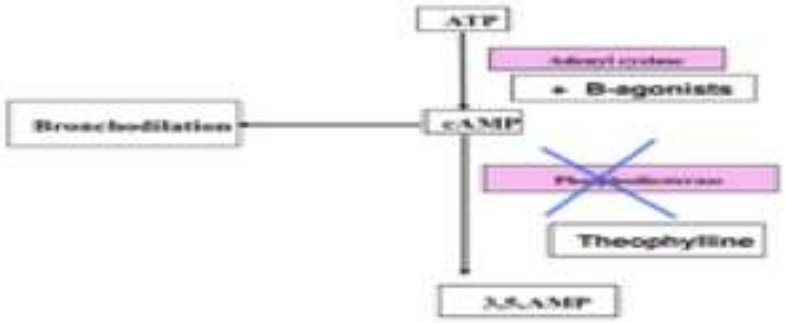
	Methylxanthines (Xanthine preparations)
MOA	○ Are phosphodiestrase inhibitors: ↑ cAMP → bronchodilation ○ Adenosine receptors antagonists. ○ Increase diaphragmatic contraction ○ Stabilization of mast cell membrane
Pharmaco kinetics	○ T ½= 8 hours ○ Metabolized by Cyt P450 enzymes in liver. ○ Theophylline is given orally. ○ Aminophylline is given as slow infusion.

Pharmacological effects	○ Bronchial muscle relaxation.
	○ ↑contraction of diaphragm → improve ventilation.
	○ CVS: ↑ heart rate, ↑ force of contraction
	○ GIT: ↑ gastric acid secretions
	○ Kidney: ↑renal blood flow, weak diuretic action
	○ CNS stimulation:
	  ○ stimulant effect on respiratory center.
	  ○ decrease fatigue & elevate mood.
	  ○ Overdose: tremors, nervousness, insomnia, convulsion.

Clinical uses	○ Theophylline: second line drug in asthma ○ Aminophylline: for status asthmaticus
ADRs	○ Low therapeutic index (narrow safety margin) monitoring of theophylline blood level is necessary. ○ GIT effects: nausea & vomiting ○ CVS effects: hypotension, arrhythmia. ○ CNS side effects: tremors, nervousness, insomnia, convulsion.
Drugs interactions	○ Cyt P450 Enzyme inducers (phenobarbitone & rifampicin): ↑ metabolism of theophylline → ↓ T ½. ○ Cyt P450 Enzyme inhibitors (erythromycin): ↓ metabolism of theophylline → ↑ T ½.

β- adrenoceptor agonists vs Methylxanthine:

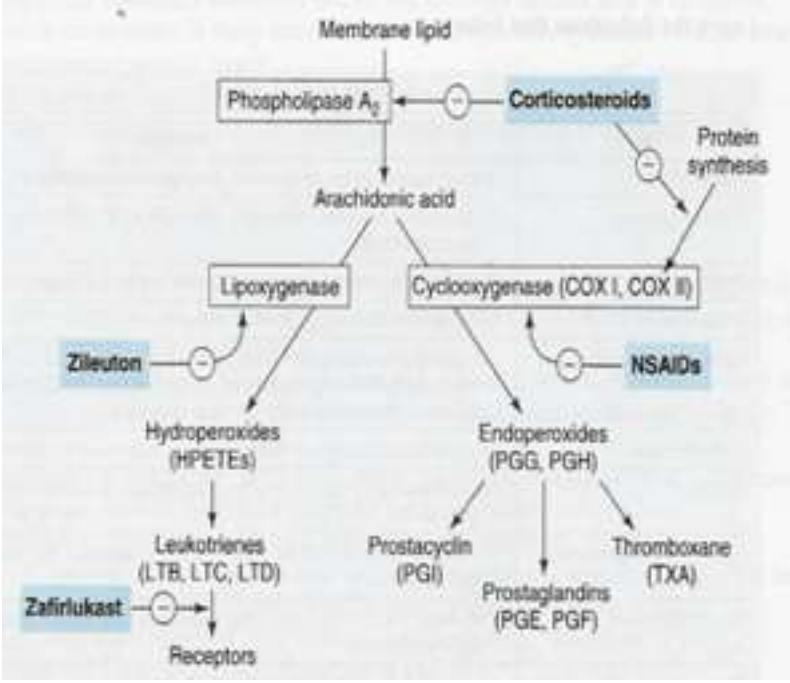
Same action different mechanism .



Anti-inflammatory Agents

They are control medications / prophylactic therapy act by :

- ↓ bronchial hyperreactivity.
- ↓ inflammation of airways
- ↓ the spasm of airways



Glucocorticoids

Mechanism of action

- Anti-inflammatory action due to:
  - Inhibition of phospholipase A2
  - ↓ prostaglandin and leukotrienes .
  - ↓ Number of inflammatory cells in airways.
  - Mast cell stabilization →↓ histamine release.
  - ↓ capillary permeability and mucosal edema.
  - Inhibition of antigen-antibody reaction.
- Upregulate β2 receptors (have additive effect to B2 agonists).

Glucocorticoids in asthma

- Are not bronchodilators .
- Reduce bronchial inflammation
- Reduce bronchial hyperreactivity to stimuli
- Maximum action at 9-12 months.
- Effective in allergic, exercise, antigen and irritant-induced asthma .
- Have delayed onset of action (effect usually attained after 2-4 weeks).
- Given as prophylactic medications, used alone or combined with β2 agonists.

Pharmacological action

- Anti-inflammatory actions
- Immunosuppressant effects
- Metabolic effects : Hyperglycemia + ↑ protein catabolism + ↓ protein anabolism + Stimulation of lipolysis (fat redistribution).
- Mineralocorticoid effects: sodium/fluid retention + ↑ potassium excretion (hypokalemia) + ↑ blood volume (hypertension) + Behavioral changes: depression Bone loss (osteoporosis) due to: Inhibited bone formation + ↓ calcium absorption from GIT.

Administration

- Inhalation: Given by inhalation (metered-dose inhaler). Have first pass metabolism therefore less side effects so it's the best choice in prophylaxis of asthma. e.g. Budesonide & Fluticasone, beclometasone.
- Orally: Prednisone, methyl prednisolone .
- Injection: Hydrocortisone, dexamethasone.

Clinical Uses of glucocorticoids

- Treatment of inflammatory disorders (asthma, rheumatoid arthritis).
- Treatment of autoimmune disorders (ulcerative colitis, psoriasis and after organ or bone marrow transplantation as immunosuppressants.
- Antiemetics in cancer chemotherapy
- Systemic corticosteroids are reserved for: Status asthmaticus (i.v.)

Side effects

- Due to systemic corticosteroids:

1- Fluid Retention, Hypertension, Weight gain, Hyperglycemia
2-Growth retardation in children
3-Adrenal suppression
4-Cataract
5-Osteoporosis
6-Susceptibility to infections
7-Fat distribution
8-Psychosis

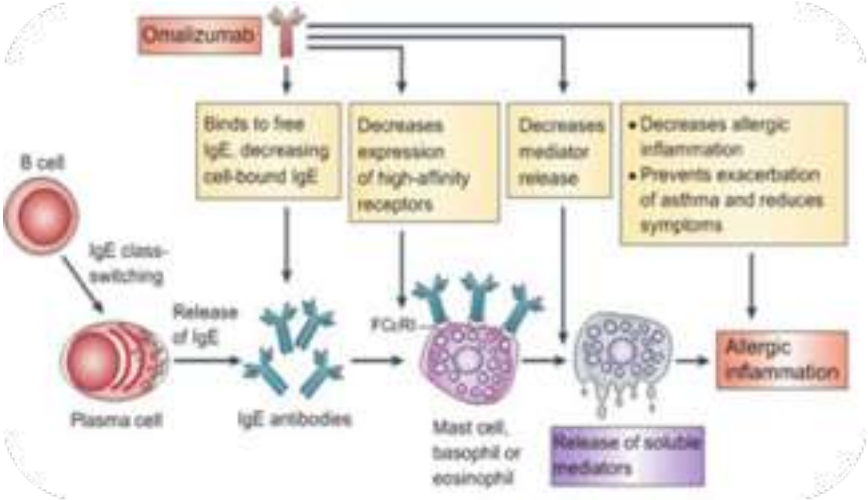
- Inhalation has very few side effects but can cause the following:
  - Oropharyngeal candidiasis (thrush).
  - Dysphonia (voice hoarseness)

Withdrawal of systemic corticosteroids

Abrupt stop of corticosteroids should be avoided and dose should be tapered (adrenal insufficiency syndrome). Administration and withdrawal should be gradual.

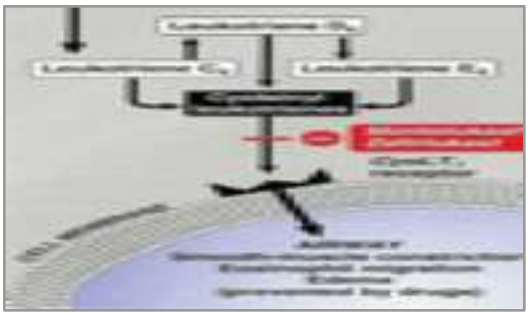
	Anti-IgE monoclonal antibody
Drugs	○ Omalizumab
MOA	○ A monoclonal antibody directed against human IgE . ○ Prevents IgE binding with its receptors on mast cells & basophiles. ○ Decrease the release of allergic mediators.
Pharmacokinetics	○ Given by inhalation (aerosol, nebulizer). ○ Have poor oral absorption (10%).
Clinical uses	○ Prophylactic therapy in asthma especially in children. ○ Allergic rhinitis . ○ Conjunctivitis.
ADRs	○ Bitter taste ○ Minor upper respiratory tract irritation (burning sensation, nasal congestion)

Note:
Disadvantages
Expensive-not first line therapy



	Mast cell stabilizers
Drugs	○ Cromoglycate (also called cromolyn) , Nedocromil
MOA	○ Act by stabilization of mast cell membrane. ○ They are not bronchodilators, so they are not effective in acute attack of asthma . ○ Prophylactic anti-inflammatory drugs . ○ Reduce bronchial hyperreactivity. ○ Effective in exercise, antigen and irritant-induced asthma. ○ Children respond better than adults.
Pharmacokinetics	○ Given by inhalation (aerosol, nebulizer). ○ Have poor oral absorption (10%).
Clinical uses	○ Prophylactic therapy in asthma especially in children. ○ Allergic rhinitis . ○ Conjunctivitis.
ADRs	○ Bitter taste ○ Minor upper respiratory tract irritation (burning sensation, nasal congestion)

	Leukotrienes antagonists
Drugs	○ Zafirlukast , Montelukast and Pranlukast
Target	○ Leukotrienes: inflammatory mediators synthesized by inflammatory cells found in the airways (eosinophils, macrophages, mast cells) , and produced by the action of 5-lipoxygenase on arachidonic acid. ○ Examples of Leukotrienes: • Leukotriene B4: chemotaxis of neutrophils. • Cysteinyl leukotrienes C4, D4 & E4: bronchoconstriction , ↑ bronchial hyperreactivity and ↑ mucosal edema and mucus secretion .
MOA	○ selective, reversible antagonists of cysteinyl leukotriene receptors (CysLT1 receptors). ○ bronchodilators ○ Have anti-inflammatory action ○ Less effective than inhaled corticosteroids. ○ Have glucocorticoids sparing effect.
Pharmaco-kinetics	○ Taken orally.
Clinical uses	○ Prophylaxis of mild to moderate asthma (e.g. aspirin-induced asthma, antigen and exercise-induced asthma) ○ Not effective in acute attack of asthma. ○ Can be combined with glucocorticoids (additive effects, low dose of glucocorticoids can be used).
ADRs	○ Elevation of liver enzymes, headache, dyspepsia



Chronic Obstructive Pulmonary Disease (COPD)

- a chronic irreversible airflow obstruction, lung damage and inflammation of the air sacs (alveoli) .
- characterized by chronic bronchitis and emphysema (destruction of walls of alveoli).
- Smoking is a high risk factor but air pollution and genetic factors can contribute.

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Treatment:

1. Inhaled bronchodilators

- Inhaled antimuscarinics:
  - Ipratropium & tiotropium.
  - Superior to β2 agonists in COPD
- β2 agonists, be used either alone or combined:
  - salbutamol + ipratropium (short acting)
  - salmeterol + Tiotropium (long acting-less dose frequency).

2. Oxygen therapy

3. Lung transplantation

4. Inhaled glucocorticoids

5. Antibiotics specifically macrolides such as azithromycin to reduce the number of exacerbations.

Inhaled bronchodilators in COPD

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  - Superior to β2 agonists in COPD
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	A. Muscarinic antagonists
Drugs	○ Ipratropium, Tiotropium
MOA	○ Act by blocking muscarinic receptors (non-selective)
Pharmacodynamics	○ Inhibit bronchoconstriction and mucus secretion with no anti-inflammatory action. ○ Less effective than β2-agonists. ○ Does not diffuse into the blood . ○ Does not enter CNS. ○ Quaternary derivatives of atropine (polar).
Pharmacokinetics	○ Given by aerosol inhalation. ○ Have delayed onset of action (Never used as rescue medications) ○ Ipratropium: has short duration of action (3-5 hrs) ○ Tiotropium: has longer duration of action (24 hrs)
Clinical uses	○ **Main choice in chronic obstructive pulmonary diseases (COPD).** ○ In asthma combined with β2 agonists & corticosteroids.
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Drugs	○ Salbutamol, terbutaline.
Pharmacokinetics	○ Salbutamol (albuterol): mainly given by inhalation, orally, I.V ○ Terbutaline: mainly given by inhalation, orally, s.c. ○ Have rapid onset of action (15- 30 min) ○ Short duration of action (4-6 hr).
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Pharmacokinetics	○ Salmeterol & formoterol are given by inhalation. ○ Long acting bronchodilators (12 hours) due to high lipid solubility (creates depot effect).
Clinical uses	○ Are NOT used to relieve acute episodes of asthma. ○ Used for nocturnal asthma. ○ Combined with inhaled corticosteroids to control asthma (prophylactic medication)

In SUMMARY:

Bronchodilators (relievers for bronchospasm)

Drugs		
B2 agonists Salbutamol, terbutaline	– Short acting – main choice in acute attack of asthma – Inhalation	↑Adenyl cyclase ↑ cAMP
Salmeterol, formoterol	Long acting, Prophylaxis Nocturnal asthma	
Antimuscarinics Ipratropium (Short) Tiotropium (long)	**Main drugs For COPD** Inhalation Inhalation	Blocks M receprtors
Xanthine derivatives Theophylline Aminophylline	(orally) (parenterally)	Inhibits phosphodi esterase ↑ cAMP

Anti-inflammatory drugs (prophylactic)

Corticosteroids (Inhibits phospholipase A2) Dexamethasone, Fluticasone, budesonide	Inhalation
prednisolone	Orally
Hydrocortisone	parenterally
Mast stabilizers Cromoglycate (Cromolyn), Nedocromil	Inhalation, prophylaxis in children
Cysteinyl antagonists (CyLT1 antagoist) Zafirlukast, montelukast	orally
Omalizumab (Anti IgE antibody)	Injection (SC)

Asthma Treatments

Asthma overview

- Asthma is an inflammatory disease associated with bronchial hyperreactivity (BHR), bronchospasm, increased mucus secretion, edema, and cellular infiltration.
- Early asthmatic responses (EAR) lasting 30–60 minutes are associated with bronchospasm from the actions of released histamine and leukotrienes.
- Late asthmatic responses (LAR) involve infiltration of eosinophils and lymphocytes into airways → bronchoconstriction and inflammation with mucous plugging.
- Management of asthma includes bronchodilators to provide short-term relief and anti inflammatory agents to reduce bronchial hyperactivity and protect against cellular infiltration.

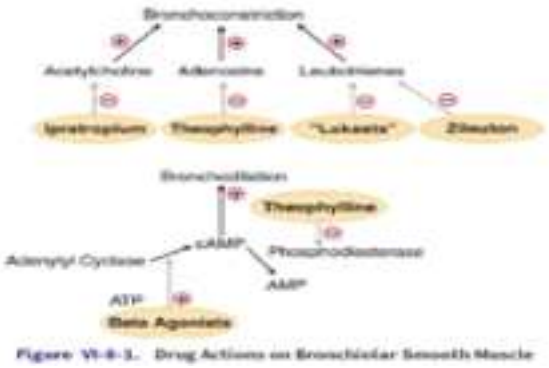


Figure VI-8-1. Drug Actions on Bronchiolar Smooth Muscle

Beta-receptor ag

- Beta-2 selective drugs (albuterol, metaproterenol, terbutaline) are widely used for relief of acute bronchoconstriction and in prophylaxis of exercise-induced asthma (see Figure VI-8-1).
- Longer-acting drugs (e.g., salmeterol) may decrease nighttime attacks (prophylaxis only) and permit dosage reduction of other agents.
- Aerosolic forms have low potential for systemic toxicity but may cause anxiety, muscle tremors, and cardiovascular toxicity with overuse.

Muscarinic-receptor blockers

- Ipratropium and tiotropium used via inhalation cause bronchodilation in acute asthma, especially in COPD patients, and they may be safer than β agonists are in patients with cardiovascular disease.
- They are the drugs of choice in bronchospasm caused by β blockers.
- There are minor atropine-like effects.

Theophylline

- Bronchodilators via inhibition of phosphodiesterase (PDE) → ↑ cAMP; and also by antagonism of adenosine (a bronchodilator)
- Mainly adjunctive; regular use may decrease symptoms, but narrow therapeutic window predisposes to toxicity → nausea, diarrhea, CV (↑ HR, arrhythmias) and CNS excitation
- Many drug interactions; toxicity ↑ by erythromycin, cimetidine, and fluoroquinolones
- Aminophylline IV sometimes used in bronchospasm or status asthmaticus

KAPLAN CORNER

Objective

1. Understand that this group of disorders is characterized by increase to airflow, owing to partial or complete obstruction at any level of the bronchial/bronchiolar.
2. Know that the major obstructive disorders are chronic bronchitis, emphysema, asthma and bronchiectasis.
3. Be aware that the symptom common to all these disorders is "dyspnea" (difficulty in breathing) but each have their own clinical and anatomical characteristic.
4. Know that chronic bronchitis and emphysema almost always coexist.

Introduction

Diffuse pulmonary diseases can be classified into two categories:

1. Obstructive airway diseases
    - Characterized by limited airflow, usually resulting from an increase in resistance caused by partial or complete obstruction at any level.
    - Obstruction → Air trapped in lungs, Airway close prematurely at high volume
2. Restrictive airway diseases
    - Characterized by reduced expansion of lung accompanied by decreased total lung capacity.
    - Restriction is due to stiffness inside lung tissue or chest wall cavity→ inability to Reach full volume

	Obstructive	Restrictive
Forced Vital Capacity(FVC)	Normal or slightly Decreased	Decreased
Forced Expiratory volume in 1 SEC (FEV1)	Decreased	Normal or Decreased
(FEV1/FVC)	Decreased	Normal or Increased

Common symptoms in lung diseases

- Wheezing "Major sign of asthma"
- Cough Productive cough→ COPD Non-productive→ Restrictive
- Dyspnea "Could happen at rest if the disease was severe"

Chronic Bronchitis

Definition

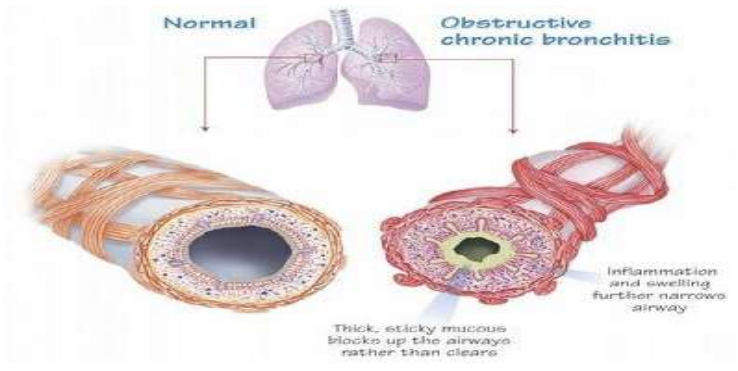
- A chronic obstructive airway disease characterized by the presence of chronic productive cough that Persists for at least 3 consecutive months in at least 2 consecutive years.

Etiology:

- Cigarette smoking and pollutants (sulfur dioxide, nitrogen dioxide).
- Infection (due to mucus and sputum excessive production)
- Genetic factors e.g. cystic fibrosis.

Pathogenesis:

- The distinctive feature of chronic bronchitis is hypersecretion of mucus, beginning in the large airways.
- Cigarette smoking and/or air pollutants → Inflammation → Release of Histamine, bradykinin and prostaglandin → Increased capillary permeability → Cellular exudation → Edema of mucus membrane → Hypersecretion of mucus → Persistent cough.



Note:
Patients suffering of this disease may be called Blue Bloaters! Why?
Blue because of cyanosis. Bloater: the obstruction of his airways by excessive mucus, inflammatory cells and the thickened mucus glands, therefore he will not be able to expire air so the air will be trapped in his lungs ⍰ "bloated"

Note:
How can a lung disease cause heart failure "Cor pulmonale"?
Accumulation of mucus in the lumen of bronchi → Hypoxemia → Increase resistance in pulmonary blood vessels → increase pressure in the pulmonary artery → Pulmonary hypertension (pulmonary pressure is higher than 25 mmHg) → increase pressure inside the right side of the heart → Heart failure "Cor pulmonale".

Clinical presentation

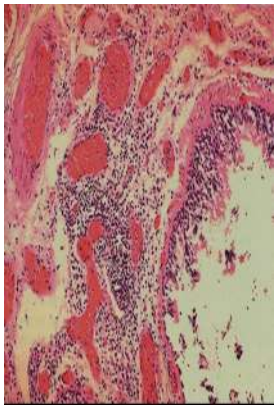
- Persistent productive cough
- Hypercapnia and Hypoxemia
- Dyspnea
- Cyanosis in severe cases

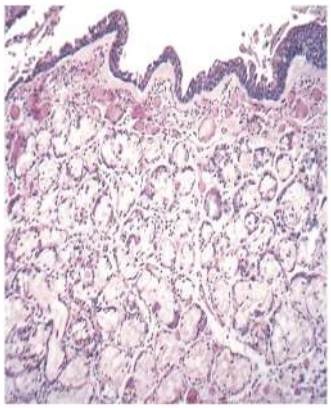
Complications

- Cor pulmonale
- Death due to further impairment of respiratory functions after superimposed acute bacteria infection.
- Emphysema

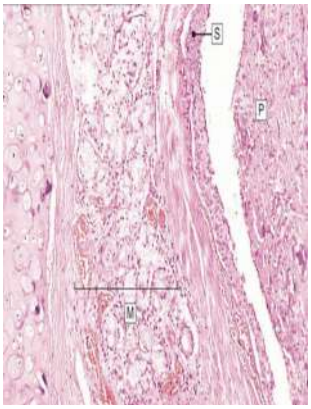
Morphology

- Goblet cell hyperplasia: increase in their number
- Presence of mucus bulges & mucosa contains pus with neutrophils, mucus, and bacteria
- Hypertrophy and Hyperplasia of mucosal and submucosal glands leads to overproduction of mucus.
- Increase in thickness of subepithelial mucus glands. This will lead to an increase in the Reid Index 1
- In contrast with asthma; there is no eosinophils in chronic bronchitis.





Chronic bronchitis. The lumen of the bronchus is above. Note the marked thickening of the mucous gland layer (approximately twice-normal) and squamous metaplasia of lung epithelium.



Abnormal amount of mucus causes plugging of the airway lumen (P)

Emphysema

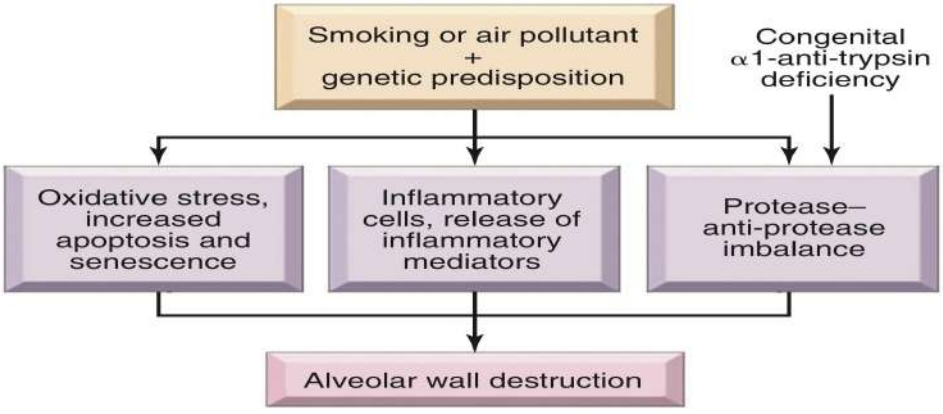
Definition

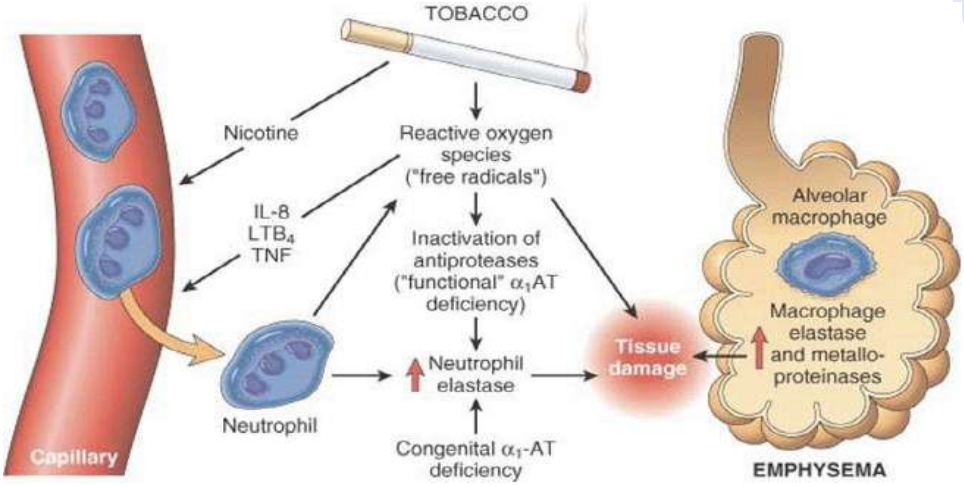
- Permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of their walls, without obvious fibrosis.
- Associated with loss of recoil and support of small airways —> tendency to collapse with obstruction.

Etiology:

- Smoking, (causes chemical inflammation).
- Inhaled pollution.
- Congenital deficiency of the
- anti-protease enzyme (α1-anti-trypsin)

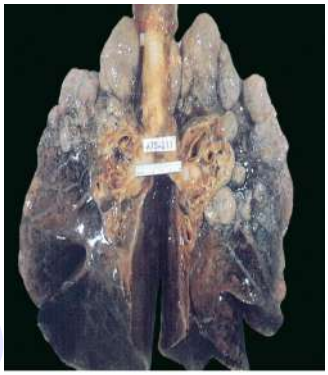
Pathogenesis:



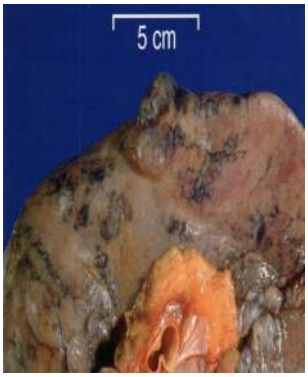


Types of emphysema

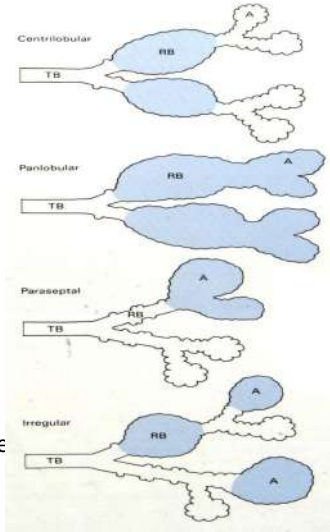
	Centriacinar (centrilobular) "most common"	Panacinar (panlobular)	Distal acinar (paraseptal)	Irregular
Location	Central or Proximal alveoli of the acini.	Uniform injury, total damage of the alveoli.	The distal alveoli of the acinus.	Can affect any part of the respiratory tract.
Cause	Smoking	Genetic condition: Alpha-1 antitrypsin deficiency	Unknown	Invariably associated with scarring such as that resulting from healed inflammatory diseases.
Features	Common in upper Lobes.	Common in lower lobes	Occurs adjacent to areas of fibrosis or atelectasis. More severe in the upper half of the lungs	Asymptomatic



Bullous emphysema with large apical and subpleural bullae.

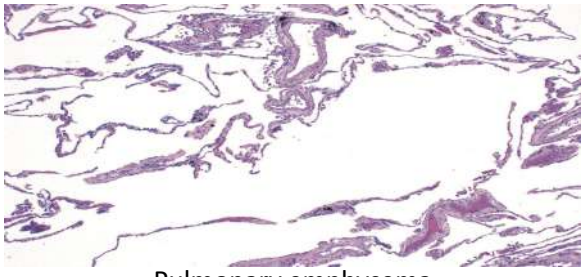


Distal acinar (paraseptal emphysema) forming multiple cyst-like structures with spontaneous pneumothorax.



Morphology

- Histological features:
  - Large airspaces.
  - Reduced radial traction on the small airways.
  - Loss of elastic tissue.
  - Diminished alveolar capillaries.
- Gross features:
  - Voluminous lungs. “In panacinar emphysema only”
  - Pale lungs. “In panacinar emphysema only”



Pulmonary emphysema

There is marked enlargement of the air spaces, with destruction of alveolar septa but without fibrosis. Note the presence of black anthracotic pigment.

Note:

(1)A patient with emphysema who also has pronounced chronic bronchitis and has a history of recurrent infections. Dyspnea will usually be less prominent, and in the absence of increased respiratory drive the patient will retain carbon dioxide(Acidosis), becoming hypoxic and often cyanotic.

Note:

(2) Due to destruction of small capillaries in alveolar wall and hypoxia lead to pulmonary vascular spasm.

Clinical features

- Dyspnea (Fish-mouth breathing)
- Barrel chest. ”Increase in anteroposterior diameter of the chest” due to:

1- air-trapping with inflammation.

2- hypersecretion of viscid contraction in the small airways.”

- Patients are known as “Pink Puffers”.
- Usually coexist with Chronic bronchitis.

Complications

- Pneumothorax.
- Cor pulmonale
- Death may occur either due to pulmonary failure with respiratory acidosis[1] or due pulmonary hypertension[2]

Bronchiectasis

Definition

- Permanent Dilation of the Bronchi and the Bronchioles caused by destruction of the smooth muscle and the supporting Elastic tissue.

Etiology:

- Bronchial obstruction:
  - Localized: Tumors,Foreign bodies or mucous impaction.
  - Systemic: Bronchial Asthma and Chronic bronchitis
- Congenital or Hereditary:
  - Congenital bronchiectasis
  - Cystic Fibrosis
  - Primary Ciliary Dyskinesia
  - Intralobar sequestration of lung
  - Immunodeficiency
- Suppurative Pneumonia
  - Klebsiella spp.
  - Staphylococcus aureus

Pathogenesis:

Two intertwined processes that contribute to Bronchiectasis Obstruction and Chronic Infection:

- Step 1: A foreign Body enters the body leading to obstruction.
- Step 2: Impaired mucociliary clearance, mucus stasis and accumulation which in turn further makes the airways susceptible to microbial colonization.
- Step 3: the persistence of the pathology with superadded infection leads to a “vicious circle” of inflammation and tissue damage.
- Step 4: inflammatory damage to the bronchi which will lead to irreversible dilation and loss of elasticity of the alveolar wall leading to bronchiectasis.

Clinical features

- Severe persistent cough with sputum (Mucopurulent sputum) and sometimes with blood, the sputum has bad smell.
- Clubbing of fingers.
- Fever, hypoxemia, hypercapnia.
- Dyspnea, rhinosinusitis, and hemoptysis.

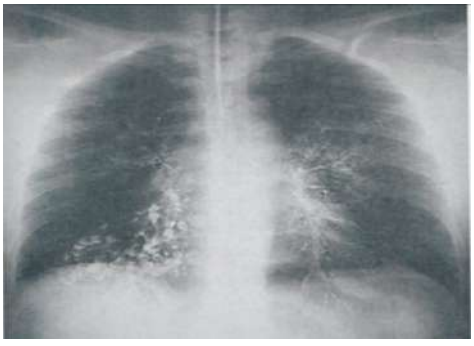
Complications

- If severe, obstructive pulmonary function develop.
- Lung abscess.
- Rare complications: metastatic brain abscess and
- amyloidosis

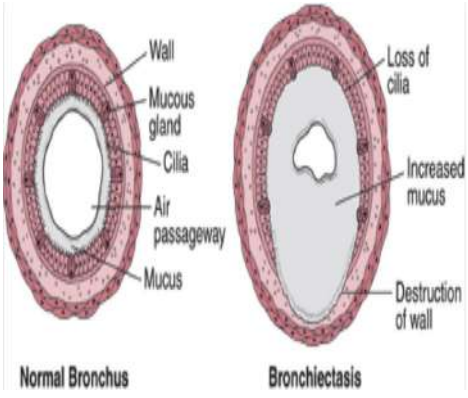
Note:

X- Ray:
Small dense (purulent) nodule-like areas (dilated bronchi) in lower/ middle lobes, also there is increased Broncho vascular shadowing.

Grossly :
Large purulent dilated bronchi.

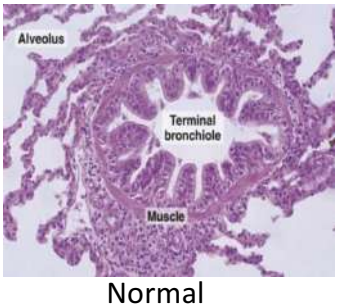


Bronchiectasis, Chest radiograph

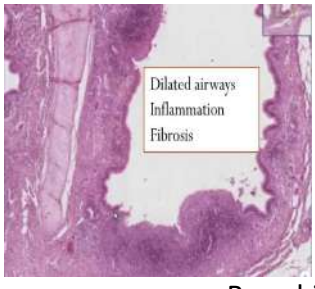


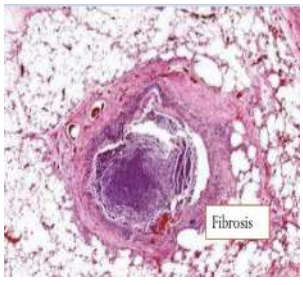
Morphology

- Dilated airways up to four times, reaching the pleura.
- Inflammation
- Fibrosis



Normal





Bronchiectasis

Kartagener Syndrome

(Immotile Cilia syndrome or Ciliary Dyskinesia)

Definition

- Autosomal Recessive disease characterized by the absence of outer and inner Dynein Arms causing immotile cilia.

Characteristics:

It causes a malfunction in the cilia therefore loss of defense in the Upper respiratory trac, staphylococcus aureus

Diagnosis:

- Genetic Study.
- Electron Microscope.

Complication

- Recurrent respiratory tract infections, e.g. Sinusitis
- Infertility in Males.
- Deafness (Can't hear).

Clinical correlate:
Usually theses patients present with:
1-Pancreatitis.
2-Malabsorption.
3-Upper respiratory tract infections.
4-Bronchiectasis

Diagnosis:
By sodium test (Sweat test): usually they have low sodium in sweat.

Cystic Fibrosis

(Mucoviscidosis)

Definition

An inherited Disease causing thicky, sticky mucous secretion to build up in the lung and digestive tract causing Bronchiectasis.

In SUMMARY:

Chronic Bronchitis

- **Definition** (clinical): Persistent chronic productive cough for a period of 3 months over 2 consecutive years.
- **Etiology**: Almost all patients are smokers." Usually coexist with emphysema"
- **Symptoms**: dyspnea, productive cough, wheezing "sometimes not always" due to obstruction of the lumen of the bronchi by excessive mucus production.
- Histological presentations:
  - Mucus secreting bronchial glands become hypertrophic/hyperplastic therefore there thickness will increase and will occupy a lot of space in the bronchial wall.
  - Congested blood vessels."when there is inflammation there is vasodilation → increased vascular permeability"
  - Submucosal edema.

Emphysema

- **Definition** (Pathological): Chronic obstructive airway disease characterized by abnormal dilation and destruction of the airspaces distal to the terminal bronchioles (which includes the Respiratory bronchioles, alveolar duct and alveoli).
- **Etiology**: Smoking. "usually coexist with chronic bronchitis"
- **Symptoms**:
  - Dyspnea
  - Productive cough
  - If advanced the patient will have Honeycomb lung appearance and barrel chest "due to increase in the anteroposterior diameter of the thoracic cavity",
  - "Pink puffer.": Pink because he has no cyanosis and puffer because he blows air out"
- **Types:**

- Centriacinar:
  - Only the respiratory bronchioles are dilated
  - Common in smokers.
- Panacinar:
  - Respiratory bronchioles, alveolar duct and acini are dilated.
  - Common in patients with α1-antitrypsin deficiency.
- Distal acinar:
  - Dilatation of the distal part of the acini.
  - Causes bullae" if the bullae rupture it will cause pneumothorax"
  - Common in non-smokers and young people.
- Irregular
  - Can affect any part.
  - Usually in inflammatory conditions "patients with previous pneumonia, old TB"

Bronchiectasis

- **Definition**:

Chronic obstructive airway disease characterized by abnormal and permanent dilatation of bronchi and bronchioles associated with inflammation and fibrosis and pus formation.

- **Etiology**:

Bronchial obstruction or due to congenital abnormalities.

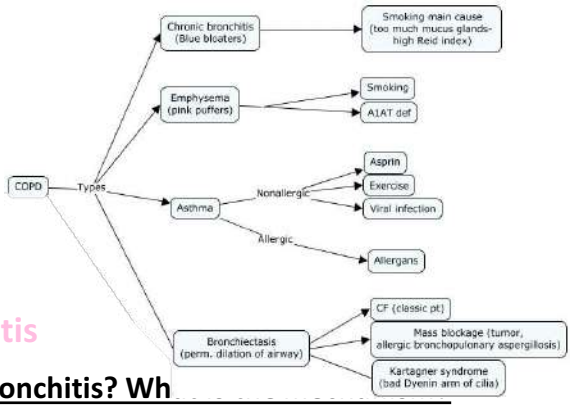
- **Symptoms**:

dyspnea, productive cough (purulent, copious sputum with bad smell due to anaerobes.)

Chronic Obstructive Pulmonary Disease

What is COPD? What are some findings?

- COPD is obstruction to getting air out of lungs.
- **Findings:**
  - Low FEV_1:FVC ratio - Decreased FVC, even more low FEV1
  - Normal FEV_1:FVC is 80%. Normal TLC = 7 L.
  - Increased TLC due to **air trapping**



Chronic bronchitis

What is chronic bronchitis? Wh

- chronic productive cough lasting at least 3 months over a minimum of 2 years
- hypertrophy of bronchial mucinous glands--patients cough up **cups of mucous**

Describe pathophysiology of chronic bronchitis and histology of airway?

- Below lamina propria are serous glands (secrete water to humidify air) and mucous glands (secrete mucus to trap pollutants).
- With chronic smoking, mucus glands undergo hypertrophy and hyperplasia. This causes tons of mucus production, and the mucus can plug airways causing hypoxemia.
- **Other:**
  - Epithelium is pseudostratified columnar
  - Lamina propria has venules that warm the cold air coming from outside

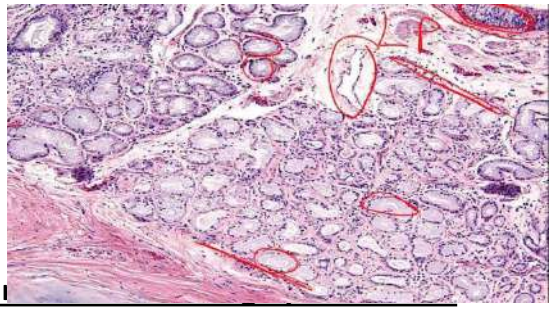


Fig: Cross section of chronic bronchitis. Top right portion has respiratory epithelium, bottom left has cartilage. It's clearly visible that mucus glands make >50% thickness of airway.

With what is chr

- Smoking

PATHOMA CORNER

Chronic Obstructive Pulmonary Disease

What are the clinical features of chronic bronchitis?

- productive cough due to excessive mucous production,
- cyanosis ('blue bloaters') - mucus plugs trap CO_2;
- increased risk of infection (anytime you plug a tube, it increases risk of infection behind the block)
- Reid index Increases to >50 from <40%;
- Cor pulmonale (pulm HTN) - due to globally low PAO_2 in lungs (low PAO_2 induces vasoconstriction)

What is Reid index?

- It's the ratio of thickness of airway mucous gland to total thickness of airways. Normally, it's <40%.

Emphysema

What is emphysema?

- Destruction of alveolar air sac and multiple sacs combine to become one.
- Due to loss of elasticity of air sacs, lung becomes like a shopping bag, not effectively expelling air out.
- Also, elasticity of air sacs attached to bronchioles keep the bronchiole open during expiration. When the sacs are gone, then bronchioles collapse during expiration.

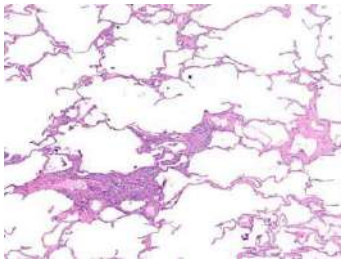


Fig: Histology of emphysema showing multiple air sacs combining to make one.

What is pathophysiology of emphysema?

- Imbalance between protease and antiprotease. Inflammation induces high protease activity. So, smoking leads to inflammation which leads to emphysema.

What is acinus?

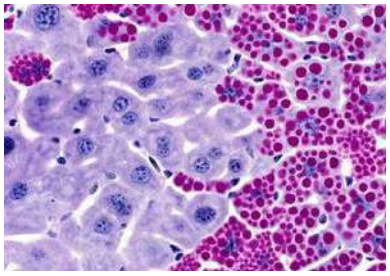
- Functional unit of lung (a terminal broncheole and alveoli associated with it)

Why does A1AT deficiency cause cirrhosis?

- A1AT deficiency is due to misfolding of mutated protein, mutant A1AT accumulates in ER of hepatocytes which results in liver damage.
- A1AT is doesn't go to blood and lung because it's not exported by liver.

What does liver biopsy in A1AT deficiency show? (HY)

Pink-purple, PAS-positive (a stain) globules in hepatocytes. Note - mucin and tropheryma whipplei are also PAS +ve



Chronic Obstructive Pulmonary Disease

Describe the genetics of A1AT transmission.

- PiM - normal allele
- PiZ - mutant allele

PIMM	Norman healthy person
PiMZ	• Haterogytoes; usually asymptomatic (low circulating A1AT) • Significant emphysema risk with smoking
PiZZ	• Homozygous mutant • Significant risk for panacinar emphysema and cirrhosis

Differentiate two classic causes of emphysema (destruction of alveolar air sacs).

Smoking (no. 1 cause of emphysema)	A1AT deficiency (alpha 1 antitrypsin) -
Pollutants cause inflammation that induce protease mediated damage to alveoli	A1AT is an important antiprotease that inhibits protease damage to alveoli
Centriacinar emphysema seen mainly in upper lobes (upper lobes have more air)	Panacinar emphysema seen mainly in lower lobes
	Can cause liver cirrhosis too
Complications: hypoxemia and cor pulmonale (pulm HTN)	Complications: hypoxemia and cor pulmonale (pulm HTN)

What are clinical presentation of emphysema?

- Dyspnea and cough
- **Minimum sputum -** contrast to chronic bronchitis
- Prolonged expiration with pursed lips (pink puffer) - pursed lips create back pressure to prevent airway collapse (pt are not cyanotic because they are oxygenated; in chronic bronchits, broncheoles are plugged up)
- Barrel chest - increased anterior-posterior diameter of lung
- Weight loss - use muscles to breathe
- **Late complication:**
    - Cor pulmonale
    - Hypoxemia in late stage due to loss of capillaries

Chronic Obstructive Pulmonary Disease

Bronchiectasis

What is bronchieatasis?

- Necrotizing damage to airway walls lead to permanent dilation of bronchioles
- Imagine if you blow air into a big tube, the air will just move randomly inside the tube and might not come out

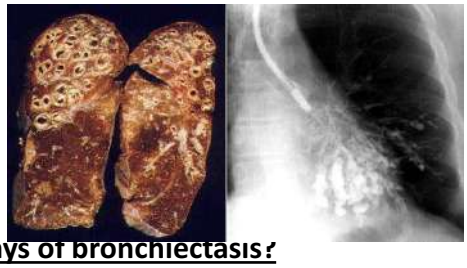


Fig: large dilated structures are airway, not coeleaced alveoli

What is pathophys of bronchiectasis?

- Loss of muco-ciliary clearance system is the main problem. Mucus accumulation followed by bacterial overgrowth leads to pus filled infection and permanent dilation of airways.

What are come cauases of bronchiectasis?

- CF (classic pt)
- Allergic bronchopulmonary aspergillosis - classically seen in asthamits and CF pt.
- Kartagener syndrome (mutation of dyenin arm cilia)
- Tumor or foreign body that blocks airway (infection behind block can cause necrosis).

What is presentation and complication of bronchiectasis?

- Cough, dyspnea and foul smelling sputum
- **Complication:**
    - secondary systemic amyloidosis (HY) - systemic increase in SAA (an acute phase reactant) produced chronically due to chronic inflammation. SAA is converted to AA that's deposited.
    - Hypoxemia and cor pulmonale

What is presentation of Kartagener syndrome?

- Sinusitis (cilia in nasal sinus not working well)
- Infertility
- Inversion of body organs (ex - heart on right)
- Bronchiectasis

Lung Pathology

1.1 - COPD & Emphysema

1. **Obstructive Lung Disease**
2. In COPD, obstruction prevents air from leaving the lungs (trapped in distal airways) (OBSTRUCTING STREET)
3. COPD causes irreversible obstruction (NO U TURN)
a. In comparison to asthma is a transient **reversible process,** caused by hyperactive airways
4. Cigarette smoking is the most important risk factor for COPD (SMOKER)
5. Emphysema occurs distally, while chronic bronchitis involves the airways the more proximal airways
a. Respiratory bronchiole (PROXIMAL STREET)
b. Alveolar duct: (DISTAL CUL-DE-SAC PATH)
c. Alveolar sac: (END OF CUL-DE-SAC PATH)
6. **Emphysema: Pink Puffer**
a. Affects the distal airways in the alveolar walls
b. **Definition**: Permeant Enlargement of the distal airspaces of the corresponding lung hyperinflation and chronic air trapping
    i. **Centriacinar:** affects **respiratory bronchioles** and spares the alveolar ducts and sacs (YELLOW GRASS)
        1. Affects the upper 2 lungs of the lung preferentially (SWEATY UPPER HALF OF JERSEY)
        2. Toxins collect in the respiratory bronchioles and activate an inflammatory response (TOXIC HOCKEY PUCK)
        3. **Neutrophils** recruited to distal airways
        4. Produce **elastase** (FIRST RESPONDER CUTTING THE ELASTASE)
        5. This leads to **raised COMPLIANCE** in the distal airway (Raised compliance book) = floppy
        6. Collapse at the distal terminal bronchioles causes air trapping (Collapsed At The Terminal Street)
    ii. **Panacinar:** Associated with alpha-1 antitrypsin deficiency but can be seen in sever emphysema (N
        1. AAT is the **major serum inhibitor** of neutrophil elastase (AA trimming)
        2. AAT deficiency à uninhibited neutrophil elastase à destruction of distal airways
        3. Occurs throughout the lung (leaves all over the cul-de-sac)
        4. Effects the lower lobes (Bottom of the shirt is torn)
        5. AAT is produced in the liver so this accumulates in the hepatocytes à leads to liver damage and cirrhosis
        6. Non-secreted AAT stains PAS positive (PASS FRISBEE)
        7. Young patients (young trimmer): **Inherited**
        8. Smoking increases emphysema risk in patients with AAT deficiency (Directly inhibits AAT)
            a. Increases neutrophils to the area because of inflammation
            b. Directly oxidizes and activates AAT
        9. Smoking with Early AAT will develop symptoms way earlier
c. **Signs and Symptoms:**
    i. Emphysema presents with **gradually progressive dyspnea** (Huffing and Puffing)
    ii. Bilateral Wheezing (Party Blower)
    iii. Tripod position: armed is propped up (KID SITTING DOWN)
    iv. **Purse lips**: helps maintain pressure to inflate distal airways (purse lips)
    v. May cause weight loss (hockey man lost weight)
        1. Muscles are used for breathing
    vi. Emphysema can cause **pulses paradoxes** (causes a >10mmHg decrease in systolic pressure during inspiration)
    vii. Distant lung and heart sounds (heart and sailboats fall away)

d. **X-ray:**
    i. **Hyper inflated:** Lungs expand and push the chest out
    ii. Chest X-ray: flat diaphragm, 10+ **posterior rib shadows**, increased parenchymal radiolucency, lengthened cardiac silhouette (vertical heart)
    b. **Pulmonary Function Test:**
    i. COPD causes increased total lung capacity (Full "Total Load"
    ii. COPD causes increased functional residual capacity "Full Residual bin" (left over after a normal expiration)
    iii. **FEV1:** 1 second is not enough time for them to breath otherwise the lungs will collapse
        1. (ForeEVer #1" sign)
    iv. **FVC: Forced Vital Capacity:** Exhale all of the air after a full breath: Also decreased because of air trapping just not as much
        1. FEV1/ FVC (FEV1 is really low and FVC is low)
        2. Low ratio (Both signs are dropping)
        3. Less than .7 (The hockey stick)
    v. Emphysema causes a low DLCO (Diffusion capacity of the lung for carbon monoxide (Trash on the street and on the groud)
        1. How well oxygen can go from the alveoli into the lung
        2. Decreased because of damage into the alveoli
        3. Hyperventilation EARLY in the course maintains normal arterial oxygen levels (Normal PaO2) (Pink face)
            a. Hyperventilation early in the course causes **respiratory alkalosis** (Blowing OH bubbles)
        4. In LATE emphysema there is severe air trapping (CO2 retention an **respiratory Acidosis)**
            a. Can't blow off the CO2 anymore so the bubbles start to pop
            b. Severe decrease in DLCO à decreased PaO2 à cyanosis

e. **Bronchitis: (Blue Bloater)**
    c. Occurs in the terminal bronchioles (ROAD TERIMNATES)
    d. Chronic Bronchitis: Defined as a productive cough (hacking up sports drink)
    e. Lasts for at least 3 months (NUMBER 32)
    f. Chronic Bronchitis involves mucus gland hypertrophy and hypersecretion in larger airways (trachea bronchi and bronchioles) (MUCUS ON TRACHEAL STICK)
    g. Mucus hypersecretion **causes mucus plugs** in the bronchioles à distal airway obstruction à distal airway obstruction (In chronic bronchitis)
    h. Chronic bronchiolitis (as part of chronic bronchitis) causes **goblet cell metaplasia and proliferation** (Goblet bottles in terminal street)
    i. **Early in course:** mucus plugs trap air in distal airways à increased PaCO2 and **respiratory ACIDOSIS** (in chronic bronchitis) (CO2 FUMES)

f. **Cyanosis of the skin**
    j. O2 supplementation can decrease RR causing respiratory failure in COPD patients and inhibits the firing of peripheral chemoreceptors (aortic arch and carotid bodies sense decrease in PaO2) (O2 knocking over arch)
    k. **Heart:**
    l. Hypoxic goalie stretching net: Chronic hypoxemia in COPD à hypoxic vasoconstriction à pulmonary arterial hypertension
    m. Corked hear bottle: Pulmonary hypertension due to hypoxic vasoconstriction in COPD can lead to right heart failure (COR PULMMONAE)

SKETCHY CORNER

Objective

1. Understand the structure and constituents of the lung interstitial as well as the restrictive changes which occur in diseases of the interstitial (ILD)
2. Know the symptoms of ILD: progressive breathlessness and cough
3. Know subtypes of ILD: acute and chronic
4. Discuss the causes, morphology and outcome of acute ILD
5. Appreciate the pathogenesis of chronic ILD regardless of their type.
6. Become aware of the classification of interstitial lung diseases.
7. Discuss examples of interstitial lung diseases including:
   - Idiopathic pulmonary fibrosis
   - Pneumoconiosis
   - Hypersensitivity pneumonitis
   - Goodpasture syndrome
   - Sarcoidosis

Restrictive Lung Disease

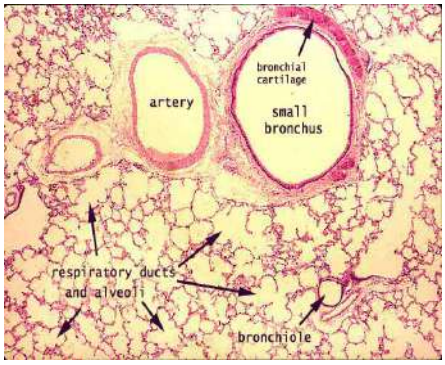
Definition

Group of diseases characterized by reduced expansion of lung parenchyma and decreased total lung capacity.

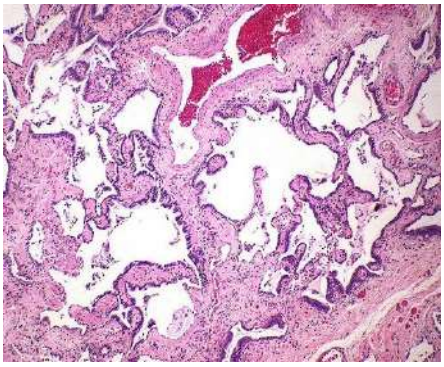
Note:
The final stage of all restrictive lung disease is extensive fibrosis with honeycomb lung.

Intrinsic lung disease

- Also called: disease of the lung parenchyma or primary ILDs (Interstitial Lung Diseases)
- It causes inflammation or scarring of the lung tissue or result in filling of the air spaces with exudate and debris (pneumonitis).
- They are characterized by:
  - Inflammatory infiltrates in the alveolar interstitial space.
  - The interstitium becomes thickened and fibrotic which will lead to “Stiff Lung” and results in decreased oxygen-diffusing capacity.
  - They could be acute or chronic.



Normal lung

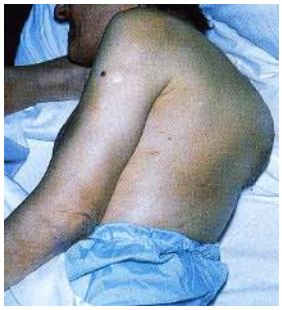


Honeycomb lung

Extrinsic disorders

- Also called: extraparenchymal diseases.
- They are related to components of the respiratory pump: chest wall, pleura, respiratory muscles.
- Abnormalities of chest wall include:
  - Bony abnormalities (kyphosis or kypho-scoliosis)
  - Massive pleural effusion
  - Morbid obesity
  - Neuromuscular disease of respiratory muscles.

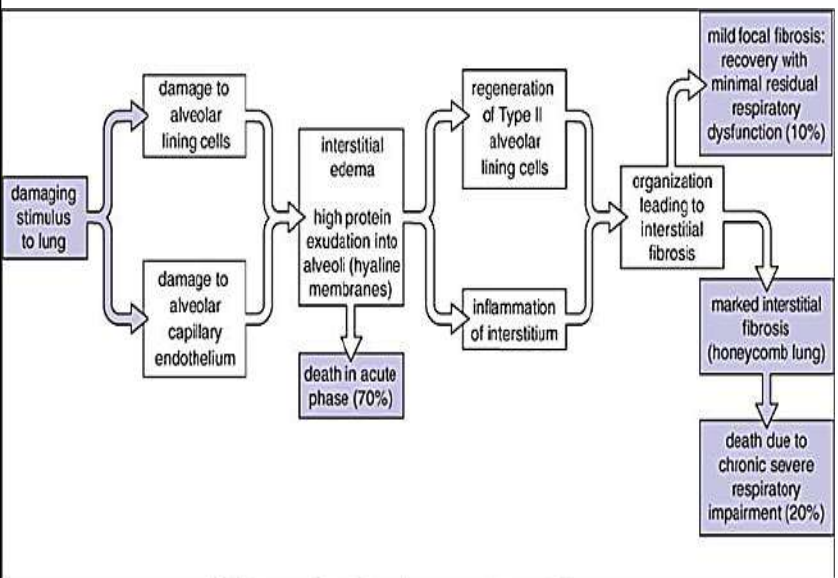
- Flexion (kyphosis) and lateral deviation (scoliosis) of the spine have the combined effect of reducing chest volume.
- This compromises respiratory function and may cause restrictive lung disease.



Acute restrictive lung diseases (INTRINSIC TYPE)

1. Adult respiratory distress syndromes
2. Neonatal respiratory distress syndromes

1- Acute Respiratory Distress Syndrome (ARDS)

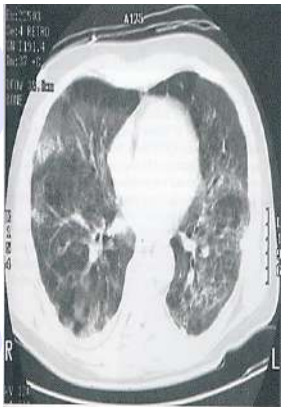


Etiology:

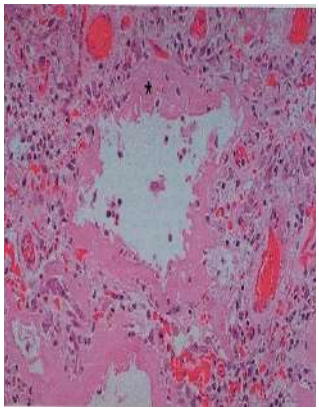
Can be caused by many conditions:

- Direct injury to lung:
  - **Pneumonia**
  - Aspiration of gastric contents
  - Pulmonary trauma, fat embolism
  - Post lung transplant, near drowning
  - Toxic inhalation injury (irritants such as chlorine, O2 toxicity)
  - Severe acute respiratory syndrome: the virus is a coronavirus that destroys type II pneumocytes and causes diffuse alveolar damage.

- Indirect injury to lung:
  - **Sepsis**, shock, transfusion, uremia
  - Severe trauma (e.g. bone fractures, head injury, burns, radiation)
  - Cardiopulmonary bypass, acute pancreatitis
  - Overdose with street drugs such as heroin
  - Therapeutic drugs such as bleomycin
  - Hematologic conditions e.g. multiple transfusion, coagulation disorder.



Fine granularity (ground glass appearance)



Diffuse alveolar damage, microscopic

Diffuse alveolar damage, gross: lung edema

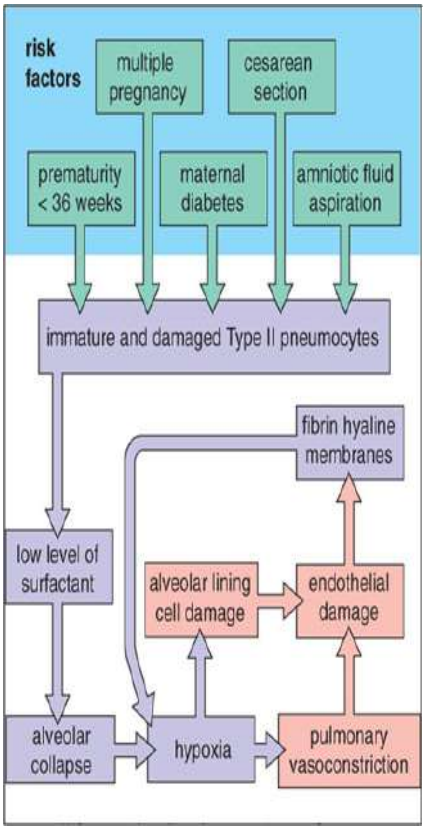
2- Neonatal Respiratory Distress Syndromes (NRDS)

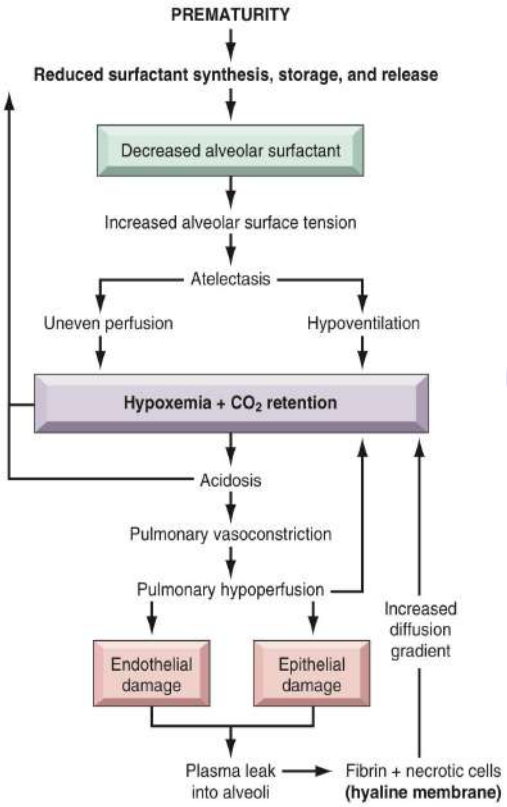
- It is the most common cause of respiratory failure in the new-born and is the most common cause of death in premature infants.

Etiology

- Inability of the immature lung to synthesize sufficient surfactant*
- It is the same as ARDS except that it is
- caused by a deficiency of pulmonary surfactants in new-borns, most often as a results of immaturity.

Pathogenesis





Chronic restrictive Lung disease (INTRINSIC TYPE)

Definition

Heterogenous group of disorders characterized by bilateral often patchy pulmonary fibrosis mainly affecting the walls of alveoli.

Major Categories

They are categorized based on clinicopathologic features and characteristic histology.

Idiopathic fibrosing:

Usual interstitial pneumonia (idiopathic pulmonary fibrosis)

Occupational: Pneumoconiosis

- Anthracosis and coal worker's pneumoconiosis,
- Silicosis
- Berylliosis
- Asbestosis

Immune diseases

- Sarcoidosis
- Goodpasture syndrome
- Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
- Systemic lupus erythematosus
- Systemic sclerosis (scleroderma)
- Wegener granulomatosis

Drug

- Chemotherapy, methotrexate, bleomycin toxicity

Smoking related

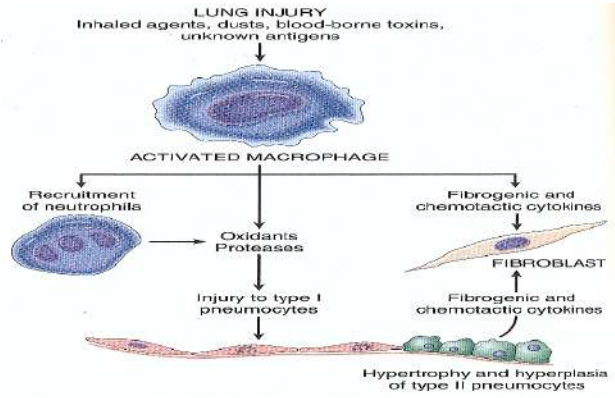
- Eosinophilic granuloma
- Desquamative interstitial pneumonia
- Respiratory bronchiolitis-associated interstitial lung disease

Radiation Reactions

Occur after radiation with diffuse alveolar damage, severe atypia of hyperplastic type II cells and fibroblasts

Pathogenesis

- Lung injury
- Influx of inflammatory cells into the alveoli and alveolar walls
- Release of chemical mediators and promotion of fibrosis
- Distortion of the normal structure of alveoli



Idiopathic pulmonary fibrosis

Definition

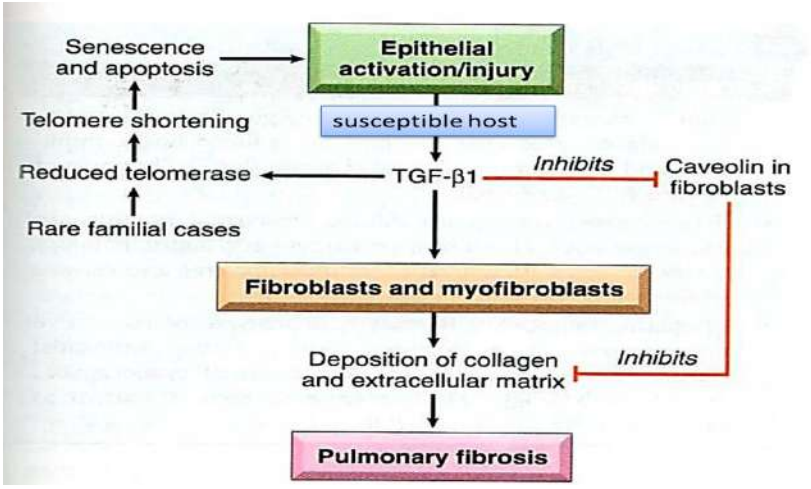
- A restrictive lung diseases characterized by reduced lung compliance. It is characterized by subpleural patchy interstitial fibrosis, fibroblastic foci and formation of cystic spaces (honeycomb lung).
- Also called: Usual interstitial pneumonia

Causes

- Unknown? Genetic
- The resulting injury to alveolar epithelial cells set in motion event that lead to increase local production of fibrogenic cytokines such as TGF-β

Pathogenesis

- The injured epithelial cells are the source of profibrogenic factors such as TGF-βI secondary to down regulation of caveolin I



Clinical features

- Gradually increasing (progressive) dyspnea on exertion and dry cough
- Most patients are 55 to 75 years
- X ray: early: ground glass fine granularity, advanced: honeycomb lung

Morphology

Honeycomb change, gross
Fibrosis in the subpleural region

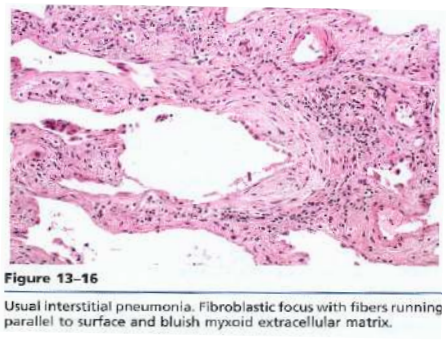


Figure 13–16
Usual interstitial pneumonia. Fibroblastic focus with fibers running parallel to surface and bluish myxoid extracellular matrix.

Complications

- Hypoxemia, cyanosis and clubbing
- Gradual deterioration in pulmonary status despite medical treatment
- Prognosis: poor, the median survival is about 3 years.

Pneumoconiosis

Definition

Lung disorders caused by inhalation of mineral dusts leading to lung damage.

Etiology

- The most common mineral dusts are coal, silica, asbestos, beryllium
- The development of pneumoconiosis depends on:
  - The amount of dust retained in the lung and airways.
    a. Concentration of the dust in the ambient air.
    b. Duration of the exposure.
    c. Effectiveness of the clearance mechanisms.
  - The size (1-5 µm)).
  - Their solubility and physiochemical activity.
  - The possible additional effects of other irritants, tobacco smoking.

Pathogenesis

- The pulmonary alveolar macrophage is a key cellular element in the initiation and perpetuation of inflammation, lung injury and fibrosis.
- Alveolar macrophages engulf the inhaled particles and release cytokines such as IL-1 → recruitment of other inflammatory cells; inflammation → damage of the alveolar epithelium → fibroblast proliferation and collagen deposition (fibrosis)

Mineral Dust–Induced Lung Disease

Agent	Disease	Exposure
Coal dust	Simple coal worker's pneumoconiosis: macules and nodules Complicated coal worker's pneumoconiosis: PMF	Coal mining
Silica	Silicosis	Sandblasting, quarrying, mining, stone cutting, foundry work, ceramics
Asbestos	Asbestosis, pleural effusions, pleural plaques, or diffuse fibrosis; mesothelioma; carcinoma of the lung and larynx	Mining, milling, and fabrication of ores and materials; installation and removal of insulation

PMF, Progressive massive fibrosis.

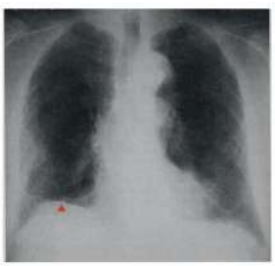
1. Coal worker's pneumoconiosis (CWP)

Definition

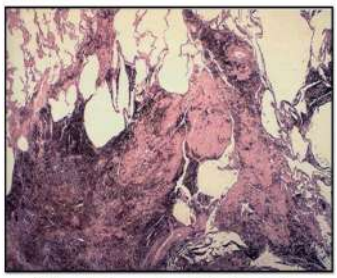
Accumulation of coal dust in the lungs and the tissue's reaction to its presence.

Categories

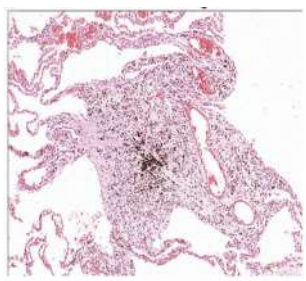
- Anthracosis:
  - Asymptomatic.
  - Commonly seen in urban dwellers and tobacco smokers.
  - Caused by accumulation of carbon in the lungs.
- Simple CWP
  - Black macules 1-5 mm are scattered through the lung.
- Complicated CWP
  - Also called, progressive massive fibrosis (PML).
  - Extensive fibrosis & compromised lung function.
  - Characterized by multiple, dark black scars exceed 2-10 cm.
  - Produces cough, dyspnea, and lung function impairment.
  - Complication: cor pulmonale.



Pneumoconiosis, radiograph



Coal worker's pneumoconiosis, microscopic



2. Silicosis

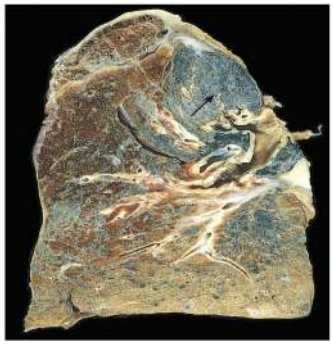
Definition

fibrotic pulmonary nodular disease caused by long term exposure to inhalation of crystalline silica particles (alpha-quartz or silicon dioxide).

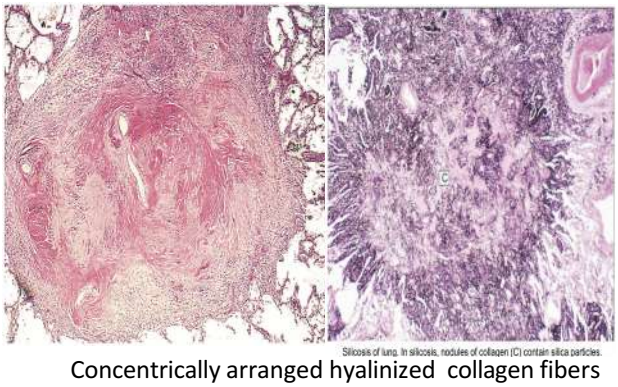
Characteristics

- Industrial exposure: mining of gold, tin, copper and coal, sandblasting, metal grinding, ceramic manufacturing
- stony-hard large fibrous scars
- eggshell calcification
- Fibrous pleural plaques may develop
- Predispose to lung cancer and tuberculosis

Morphology



Scarring has contracted the upper lobe into a small dark mass (arrow). Note the dense pleural thickening



Concentrically arranged hyalinized collagen fibers surrounding an amorphous center. The “whorled" appearance of the collagen fibers is quite distinctive fo silicosis.

3. Asbestosis

Definition

Occupational exposure to asbestos is linked to parenchymal interstitial fibrosis.

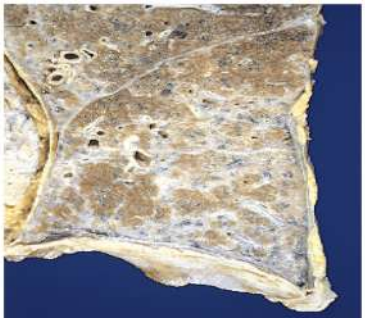
Etiology

Characterized by the presence of asbestos bodies (Ex:ship-building industry), which are seen as golden brown, fusiform or beaded rods with a translucent center. Apparently they are formed when macrophages attempt to phagocytose asbestos fibers; the iron “crust" is derived from phagocyte ferritin,

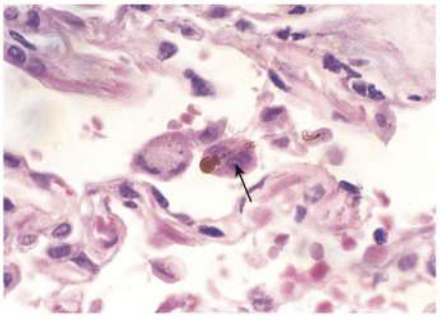
Complications

- Localized fibrous plaques, or, rarely, diffuse fibrosis in the pleura.
- Pleural effusion
- Pleural adhesions
- Lung carcinoma (Bronchogenic carcinoma)
- Malignant pleural and peritoneal mesothelioma
    - The risk for developing lung carcinoma is increased about 5-fold for asbestos workers; the relative risk for mesotheliomas, is more than 1000 times greater. Concomitant cigarette smoking greatly increases the risk for lung carcinoma but not for mesothelioma.

Morphology



severe interstitial fibrosis diffusely affecting the lower lobe of the lung



Asbestos bodies

Granulomatous diseases

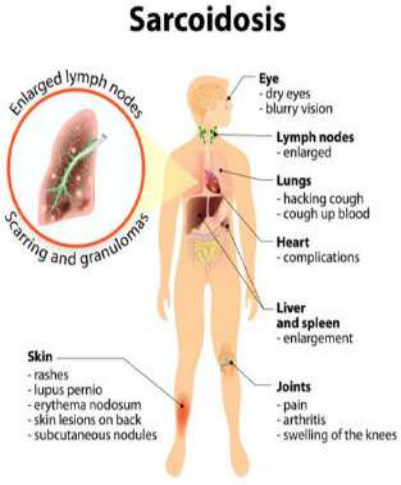
1. Sarcoidosis

Definition

Immunological multisystem disease of unknown aetiology (thought to be autoimmune) characterized by noncaseating granulomatous inflammation in many tissues and organs.

Epidemiology

- Affecting all races &both sex equally

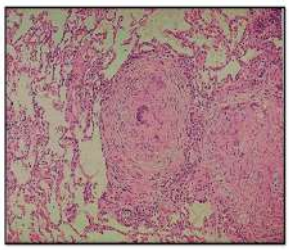


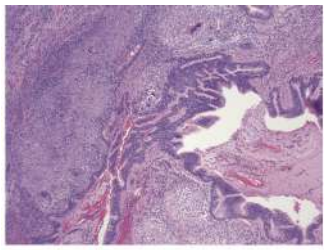
Note:
Sarcoidosis is often confused with TB (the distinction is that there is no caseation)

Sites

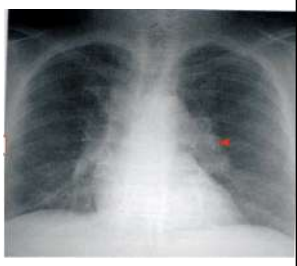
- Lungs (occurs in 90% of cases, with formation of granulomas and interstitial fibrosis)
- Lymph nodes, predominantly, intrathoracic hilar and paratracheal lymph nodes
- Skin (erythema nodosum, painless subcutaneous nodules)
- Eyes (dry eyes, iritis)

Morphology





Non-Necrotizing interstitial granuloma



Bilateral hilar lymphadenopathy

2. Hypersensitivity Pneumonitis

Definition

Immunologically mediated disorder affecting airways (alveoli) and interstitial. Also called extrinsic allergic alveolitis.
Associated with heightened sensitivity to inhaled antigens.

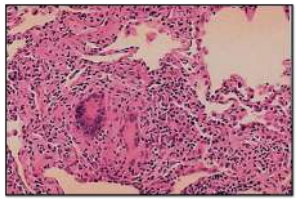
Antigens

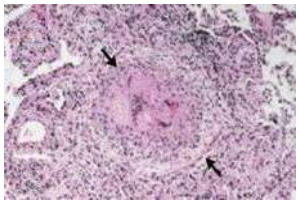
Inhalation of organic dust containing antigens:-

	Antigens
Farmer's lung	• Thermophilic actinomycetes • Micropolyspora faeni in hay
Pigeon breeder's (psittacosis)	• Birds • Pigeons
Air-cooler lung	• Thermophilic bacteria
Bagassosis	• Sugarcane bagasse

Morphology

- Non-caseating granuloma
- Chronic inflammation
- Cells: CD4+, CD8+, plasma cells, macrophages





Clinical features

- Fever
- Cough
- Dyspnea

In SUMMARY

Definition

Group of diseases (of various aetiologies) characterized by decreased lung volume and compliance.
Spirometry: LEV1 and LVC decreased (ratio is normal)

Symptoms

- Chronic dry cough
- Dyspnea (varying in severity)

Complications

- Cor pulmonale (Pulmonary hypertension → 25+ mmHg in the pulmonary artery)

Diagnostics

- Radiology (x-ray, CT)
- Spirometry
- Cytology (sputum, bronchial brushing, washing, bronchoalveolar lavage)
- Biopsy: Endobronchial, transbronchial, open lung biopsy, VAT (video assisted thoracoscopic)

Etiologies

1. Thoracic cage deformity:
   - Decreased lung expansion
   - Fever, kyphoscoliosis
   - Guillain-Barré syndrome; weakens intercostal muscles

2. Idiopathic pulmonary fibrosis:

- Familial.
- Affecting the interstitial of the lung/alveolar wall.
- Do not affect the air spaces themselves, but the tissues around them.
- Honeycombed lung due to entrapped air (anthracosis → low po2 high pco2)
- Affects lower part of the lung
- Bilateral peripheral reticulation → fibrosis shrinks the lung (trapped air → dilated alveoli)
- Temporal heterogeneity fibrotic distribution
- Histological: Blue stain indicating prevalent connective tissue (Masson's trichrome stain)
- Associated with usual interstitial pneumonia
- **Pathogenesis:**
  - Injury affecting macrophages leading to cytokine release.
  - MUCB4 gene mutation (chromosome 9) mutation → higher tendency to develop fibrosis
  - Shorter telomeres (Reduced genes that encode for telomerase) → shorter cell life (type I pneumocytes) → senescence + apoptosis → when they die they secrete:
- TGF-b1 → fibrogenic → stimulating fibroblasts and myofibroblasts → collagen
- Low Caveolin (inhibits TGF-b1 → there will be nothing to counteract it)
  - Treatment:
    - Perfinidone (TGL-b1 antagonists)
    - Nentedanib (tyrosine kinase antagonist)

3. RDS(Adult/Neonatal), DAD(diffuse alveolar damage), HMPD(hyaline membrane pulmonary disease):

- Very severe dyspnoea and hypoxia
- Very severe road traffic accident, major surgery, aspiration of gastric content, C section, severe acute pancreatitis, hypovolemic shock, septicaemia
- 70% die
- Effect:
  - Edema
  - In the lung → atelectasis → collapse
  - The 50% who survive end up with chronic pulmonary fibrosis
  - Morphology: CT scan → White lung syndrome due to fibrin and debris → form a hyaline membrane around the alveoli
- Risk factors of NRDS (surfactant deficiency):
  - Premature neonates (<36 weeks)
  - Multiple pregnancies
  - Maternal diabetes
  - C-section
  - Amniotic fluid aspiration

4. Atypical pneumonia

- Could lead to interstitial pneumonitis
- Usually caused by Influenza virus
- Oedema in the interstitial and chronic inflammatory infiltration
- Inflammatory cells are lymphocytes (viral infection), and not neutrophils

5. Drug addiction

- Heroin
- Amiodarone (antiarrhythmic)

6. Pneumoconiosis

- Caused by inhaling mineral dust 1-5mm in diameter
- Coal → coal worker's pneumoconiosis
- Silica → Silicosis (most common) (silica in sand contains quartz, which is fibrogenic)
- Building industry
- Concentric fibrosis
- Higher risk of TB for unknown reasons
- Asbestos → Asbestosis
- Carcinogenic (mesothelioma)
- Ship-building industry
- Asbestos fibers causes bleeding › forms hemosiderin (prussian blue stain shows ferruginous bodies)

7. Sarcoidosis:

- Idiopathic but now thought to be autoimmune.
- Symptoms include Uveitis, arthritis, dryness of mouth, lack of lacrimation, etc
- Often confused with TB (the distinction is that there is no caseation)

8. Hypersensitivity pneumonitis (extrinsic allergic alveolitis)

- Sensitivity to inhaled organic material
- Ill defined granulomas (poor granulomas)
- Especially in upper lobes
- Causes:
  - Pigeons
  - Desert cooler
  - Incense
  - Birds
  - Farmer's lung → microsporum → extrinsic allergic alveolitis

Restrictive Diseases

What are 4 examples of restrictive lung disease?

- Idiopathic (1^0), 2^0 pulmonary fibrosis
- Pneumoconioses
- Sarcoidosis
- Hypersensitivity pneumonitis (pigeon breeder's lung)

What are etiologies of 1^0 and 2^0 pulmonary fibrosis?

Primary	Increased TGF beta → induce fibrosis
Secondary	Amiodorone, bliomycin, radiation

You need lung transplant for pulmonary fibrosis

What is pneumoconiosis? What's its pathophysiology?

- Interstitial lung disease caused due to chronic occupational exposure with fibrogenic material.
- Pathophys - macrophages ingest fibrogenic material and induce fibrosis

What are some examples of pneumoconiosis?

Example	Risk group	Complication	Presentation
Silicosis	Sand blasters	• High risk of TB (inhibits phagolysosome formation) • High risk for lung carcinoma	• Silicotic nodule (lots of collagen with minimum inflammation)
Berylliosis	Beryllium miners Aerospace workers	High risk for lung cancer	Non caseating granuloma in hylar nodes and other organs
Asbestosis	Construction workers Plumbers Shipyard workers	High risk of lung carcinoma (more) and mesothelioma	• Asbestos body (ferruginous body) in biopsy - ferritin and hemosiderin coat asbestos • Pleural plaques

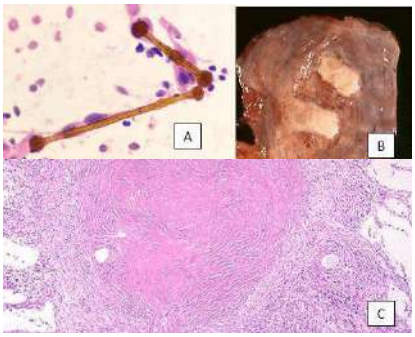


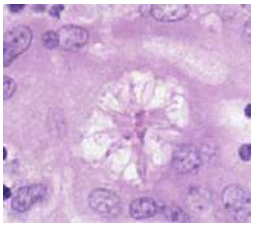
Fig: A: Asbestos body (ferritin and hemosiderin coated asbestos particle); B: pleural plaque on diaphragmatic pleura; C: Silicotic nodule, notice lots of collagen with minimum inflammation

PATHOMA CORNER

Restrictive Diseases

What is presentation of sarcoidosis?

- Sarcoidosis is non-caesating granuloma in multiple organs (most commonly localized in lungs and hyalar lymph nodes)
- Presentation: non specific - fatigue, wt loss, joint pain and arthritis
- Others: uveitis, erythema nodosum, cardiac sarcoidosis, neurosarcoidosis (affects CN often)etc
- **Hypercalcemia** (HY)
    - 1 alpha hydroxylase activity of epithelial histiocytes convert vit D to active form
- **Asteroid bodies** are seen in biopsy (not-specific; can be seen in giant cells of any granulomas)



What is hypersensitivity pneumonitis (aka extrinsic allergic alveolitis)?

- It is granuloma and interstitial inflammation caused due to inhaled organic or non-organic matter (aka **pigeon breeder's lung**).
- **pathologys**:
    - Ab-Ag complex forms in lung that activates neutrophils and eventually lymphocytes. Lymphocytes mediate most damages
- **Cause:**
    - many organic and non-organic matters
- **Presentation:**
    - fever/cough hours after exposure
    - Chronic exposure leads to interstitial lung disease

How is iron stored in body?

Free Fe produces ROS by Fenten reaction so cells store free Fe in ferretin protein or hemosiderin

Ferretin	Hemosiderin
Intracellular protein that acts as buffer against Fe overload or shortage (protein can be secreted too)	Intracellular complex made of Ferretin and other stuff
Fe in Ferretin can be given out when needed	Fe here is poor source to supply to body
Plasma Ferretin correlates well with total Fe in body; so serum ferretin a common test to access anemia.	

Lung Pathology

2.1 - Restrictive Lung Disease (Overview)

1. Torn compliance contract: lung compliance decreased in restrictive lung disease
2. Total "Load" Capacity overturned: total lung capacity (TLC) decreased in restrictive lung disease. Therefore unable to take a very large breath
3. 5 second rule!
4. Elevated FEV1/FVC signs: Forced Expiratory Volume in 1sec / Forced Expiratory Volume (FEV1/FVC) is elevated (>80%) in restrictive lung disease
5. Falling FVC sign: FVC decreases in restrictive lung disease (FEV1/FVC increases)
6. FEV1 banner pulled tight: increased elasticity of pulmonary interstitium (interstitial restrictive lung disease) → airway widening and decreased resistance to expiratory flow → maintains FEV1 (though still decreased)
7. Overturned residual capacity: Functional Residual Capacity (FRC) is decreased in restrictive lung disease.
8. Restrictive corset cough: non-productive cough in interstitial lung disease (INTRINSIC restrictive lung disease)
9. Over-exerted breath: restrictive lung disease starts with dyspnea on exertion and can progress to dyspnea at rest
10. Ripping corset velcro straps: interstitial lung disease (INTRINSIC restrictive lung disease) can cause dry crackles ("velcro rales") usually heard best at the lung bases.
11. X jolly roger: interstitial lung disease (INTRINSIC restrictive lung disease) can be seen on x-ray (diffuse reticulo-nodular opacities)
12. Reticular knotted pattern: interstitial lung disease (INTRINSIC restrictive lung disease) commonly presents with reticulo-nodular, diffuse, and bilateral opacities on x-ray
13. Tight red corset ribbons: chronic interstitial lung disease can cause pulmonary hypertension (destruction of lung parenchyma and reduction in alveolar capillaries → increased pulmonary arterial resistance)
14. Corked bottle with heart ship: Pulmonary hypertension can cause right heart failure (COR PULMONALE)
15. Pleural shirt: Pleural diseases (e.g. mesothelioma) and pleural effusions can cause EXTRINSIC restrictive lung disease
16. Muscles and cut communication wire: neuromuscular diseases (e.g. polio or myasthenia gravis) can cause EXTRINSIC restrictive lung disease when diaphragmatic and intercostal muscles affected
17. Locked chest of drawers: Spine malpositioning (e.g. kyphoscoliosis, ankylosing spondylitis) can restrict chest wall expansion and cause EXTRINSIC restrictive lung disease
18. Obese Governor Pickwick: Obesity can limit chest wall expansion and cause EXTRINSIC restrictive lung disease
19. Shallow breathing into bag: obese patients may take faster smaller breaths due to extrathoracic restriction (retention of carbon dioxide)
20. Low extra reserves: the most common indicator of obesity-related restrictive lung disease is a reduction in Expiratory Reserve Volume (ERV)
21. Hypoxic blue face: obese patients may develop chronic restrictive lung disease → retention of carbon dioxide (Obesity Hypoventilation Syndrome) with high PaCO2 and low PaO2
22. 2.1 - Restrictive Lung Disease (Overview)
23. Tight vascular vest chains: obesity can cause chronic hypoxia → chronic pulmonary vascular constriction → pulmonary hypertension
24. Corked bottle with heart ship: pulmonary hypertension caused by obesity-related restrictive lung disease can lead to right heart failure (COR PULMONALE)
25. fibrotic pulmonary trees: idiopathic pulmonary fibrosis (INTRINSIC restrictive lung disease)
26. Dusty factory: pneumoconioses (INTRINSIC restrictive lung disease)
27. Soccer player: sarcoidosis (INTRINSIC restrictive lung disease)
28. Odorless colorless plastic trash littered on ground: DLCO is LOW in INTRINSIC restrictive lung disease only (e.g. pulmonary fibrosis, pneumoconiosis) because diffusion surface is destroyed
29. Ground glass mirror: reticulo-nodular opacities may be described as "ground glass"

SKETCHY CORNER

Lung Pathology

2.2 - Idiopathic Pulmonary Fibrosis (IPF)

1. Restrictive corset: interstitial lung diseases (e.g. idiopathic pulmonary fibrosis (IPF) produce restrictive lung disease
2. Fibrotic pulmonary tree: pulmonary fibrosis (a component of many of the interstitial lung diseases)
3. "Idiot": Idiopathic pulmonary fibrosis (IPF) is the prototypical fibrosing disorder
4. Repeating red grapes: IPF is associated with repeated cycles of alveolitis (of unknown origin)
5. Cracks in epithelial stones: recurring inflammation damages type 1 and type 2 alveolar cells in the alveolar epithelium
6. Dumping coins: damaged type-1 pneumocytes release cytokines → TGF-beta-1 activates fibroblasts → pulmonary fibrosis
7. Patchy distribution of grapevines: IPF is associated with a patchy fibrosis (due multiple fibroblastic foci) on histology
8. "jUIcy graPe": usual Interstitial pneumonia (UIP) is the patchy fibrotic histology seen in IPF
9. Cobblestone patio: IPF is associated with a cobblestone appearance of the pleural surface (retraction scars along the interlobular septa)
10. Bare lower branches: fibrotic changes in IPF appear as bilateral or diffuse reticular opacities, most prominent in LOWER LOBES (on X-ray or CT)
11. Branches under shirt: the opacities of IPF distribute along SUB-PLURAL regions and interlobular septa
12. Honeycomb treat: alveoli collapse and dilated proximal airways in IPF appear as "honeycombing" on CT and gross pathology
13. CAP gun going "BOOP": cryptogenic organizing pneumonia (COP) also known as bronchiolitis obliterans organizing pneumonia (BOOP) is another cause of pulmonary fibrosis
14. Plug in gun: COP is associated with intraluminal plugs of granulation tissue leading to alveolar collapse and consolidation → alveolar collapse and consolidation
15. Sudden gunfire: COP causes acute onset of cough and dyspnea
16. Fire bandana: COP presents with fever and weight loss
17. Moon face: COP can be treated with oral corticosteroids
18. Mortar and pestle: many drugs (e.g. amiodarone, bleomycin, methotrexate) can cause pulmonary fibrosis
19. Fibrous radiation shield: patients with history of thoracic radiation can develop radiation pneumonitis and pulmonary fibrosis
20. Wet pleural shirt: radiation pneumonitis can present with pleural effusion
21. Moon face: radiation pneumonitis can be treated with oral corticosteroids
22. Lupus wolf: collagen vascular diseases (e.g. lupus) can cause pulmonary fibrosis
23. Scaly dragon: systemic sclerosis can cause pulmonary fibrosis
24. Inflamed joint lanterns: rheumatoid arthritis can cause pulmonary fibrosis

Lung Pathology

2.3 - Pneumoconioses

1. Particulates in air: pneumoconioses are interstitial lung diseases caused by the inhalation of organic and inorganic particulates
2. Restrictive corset: pneumoconioses can present with a restrictive lung disease picture (reduced lung compliance, FEV1, FVC, and TLC)
3. Screw with nuts: in the macrophages, asbestos fibers are coated with an iron containing proteinaceous material → ferruginous bodies (brown "beaded appearance" on H&E)
4. Larger particles on belt: larger particles (10-15 microns) will get trapped in upper airway
5. Sweeping medium particles: particles 5-10 microns in diameter are cleared by mucociliary transport in the trachea and bronchi
6. Small particles trapped at bifurcations: particles 1-5 microns in diameter lodge at the bifurcation of respiratory bronchioles → phagocytosed by macrophages
7. Small particles in cages: particles 1-5 microns in diameter are engulfed by alveolar macrophages → cytokine release
8. Dropping coins: cytokines (PDGF, IGF) released from macrophages are the cause of inflammation and fibrosis in pneumoconioses
9. Shark tattoo: collagen production from the release of growth factors leads to pulmonary fibrosis and restrictive lung disease
10. Cigar: tobacco smoke worsens symptoms and clinical course of all the pneumoconioses
11. Black panther coal: pulmonary anthracosis consists of asymptomatic pigment deposition in interstitial tissue and hilar nodes (contained in macrophage "dust-cells")
12. Streaked black sails: streaks of anthracotic pigment are seen throughout the lungs (lymphatic spread of "dust cells")
13. Hilar coal cages: anthracotic pigment is deposited in the hilar lymph nodes (lymphatic spread of "dust cells")
14. Coal on lung coral: simple CWP is characterized by "coal macules" and focal fibrotic "coal nodules" (predominantly in the upper lobes)
15. X-ray flag: simple CWP shows small, rounded, opacities, in the upper lobes
16. Puffer fish in center: simple CWP produces centriacinar emphysema (mostly in the upper lobes)
17. Bigger chunks on lung coral: Complicated CWP is characterized by massive blackened opacities and fibrosis (predominantly in the upper lobes)
18. Sandblaster: exposure to silica occurs in foundries, mines, sandblasting (quartz is particularly fibrogenic)
19. Sand crystals on lung coral: silicotic nodules are found mostly in the upper lung fields
20. Whorled shell: silicotic nodules contain concentrically arranged collagen
21. Fragrance from whorled shell: silicotic nodule will appear as weakly birefringent particles under polarized light
22. Honeycomb pattern: nodules coalesce to form large scars with areas of honeycombing in between (cystically dilated)
23. Hilar shells: silicosis causes "egg-shell" calcification of the hilar lymph nodes (fibrosed lymph nodes
24. Cowboy breaking cage: silicosis increases risk of TB infection (disrupt phagolysosome and promote apoptosis)
25. Big rust holes: In the setting of a pulmonary TB infection, nodules of silicotuberculosis can form, containing a central zone of cassation
26. Pink insulation: asbestos exposure can cause asbestosis: a pneumoconiosis characterized by slow progressive and diffuse pulmonary fibrosis)
27. Ship builder: asbestos can be found on ship plumbing insulation, ceiling tiles and floor tiles
28. Nails and screws: asbestos fibers may be straight, stiff, and brittle (amphibole) or curly and flexible (serpentine)
29. Straight nail in shirt: amphibole fibers can penetrate the epithelium and enter the interstitium (more pathogenic than "serpentine")
30. Lower barnacles: the fibrosis of asbestosis predominantly affects the subpleural lower lung fields
31. Large buttons: pleural plaque formation is the most common manifestation of asbestos exposure (benign, no asbestos bodies)
32. Honeycomb shape: in asbestosis, fibrosis progresses to Large inelastic fibrous tissue segments with intervening areas of "honeycombing

Lung Pathology

2.4 - Sarcoidosis & Berylliosis

1. Soccer ball: sarcoidosis (a multisystem granulomatous disease with major pulmonary findings)
2. Intact macro-CAGES: sarcoidosis is associated with non-caseating granulomas (a collection of macrophages without an area of central necrosis)
3. Black female soccer captain: sarcoidosis is most common in African Americans (particularly young females between 20-39)
4. No smoking sign: sarcoidosis is more common in non-smokers
5. Helper T squires: CD4+ helper T-cells are activated in Sarcoidosis
6. "BAL" bottle: bronchoalveolar lavage shows an elevated CD4+ to CD8+ ratio (> 2:1) in sarcoidosis
7. No reaction to feather: sarcoidosis can cause anergy to common skin antigens that usually elicit type-IV (delayed) immune reactions (e.g. Candida, PPD test)
8. Antibody keys: sarcoidosis can cause polyclonal hypergammaglobulinemia (due to Helper T cell dysregulation)
9. Multiple purple panels: granulomas may contain multinucleated giant cells (formed by the fusion of activated macrophages)
10. Ball with star panels: giant cells may contain asteroid bodies (stellate inclusions)
11. Show-man with purple cleat: granulomas may contain Schaumann bodies that show up as a purple spot on histology
12. Calcified leather cleat: Schaumann bodies contain laminated calcium and protein
13. Balls in the field: non-caseating granulomas can be found throughout the lung interstitium in sarcoidosis
14. Soccer balls at the midline: non-caseating granulomas can occur in hilar and paratracheal lymph nodes → hilar lymphadenopahty
15. Hilar soccer balls in lung tree: in sarcoidosis, enlarged bilateral hilar and mediastinal lymph nodes can be seen on chest x-ray
16. Fibrotic lung tree: in sarcoidosis, pulmonary granulomas can be replaced by diffuse interstitial fibrosisv
17. Dyspneic player: pulmonary sarcoidosis presents with a gradual onset of dyspnea (on exertion)
18. Coughing player: pulmonary sarcoidosis can present with a dry cough
19. Skinny goalie with flame bandana: sarcoidosis presents with other constitutional symptoms (malaise, fever, anorexia, weight loss)
20. Painful spotted shin guards: sarcoidosis can present with erythema nodosum (raised red painful nodules on anterior legs; no granulomas)
21. Gravel nodules: sarcoidosis can present with subcutaneous nodules (non-painful; contain abundant granulomas)
22. Purple face paint: sarcoidosis can cause lupus pernio (violaceous rash on nose and cheeks)
23. Blurry red rimmed goggles: sarcoidosis can cause anterior uveitis → redness, blurry vision, glaucoma
24. Retina street lights with broken wires: sarcoidosis can present with retinal and optic nerve involvement → vision loss
25. Dry water bottle: sarcoidosis can present with lacrimal and salivary gland involvement → dry eye and dry mouth
26. Liver spot cow: sarcoidosis can involve the liver → granulomatous hepatitis
27. Restrictive net: cardiac sarcoidosis may cause restrictive cardiomyopathy
28. Raised milk glass: Sarcoidosis can cause hypercalcemia (due to hypervitaminosis D)
29. 1-α Box: activated macrophages in granulomas produce 1-α-hydroxylase (converts Vitamin D into its active form, 1-25-dihydroxyvitamin D)
30. Sunny street lights: extra 1-α-hydroxylase produced in the granulomas may lead to hypervitaminosis D → hypercalcemia
31. Stones in leaked milk: sarcoidosis can present with hypercalciuria → calcium kidney stones
32. Raised ACE card: sarcoidosis can present with increased levels of angiotensin converting enzyme (ACE) (produced in the granulomas)
33. Moon face balls: progressive sarcoidosis can be treated with glucocorticoids
34. Building aircraft: beryllium dust is found in nuclear and aerospace industries (exposure can lead to berylliosis)
35. Macro-CAGES with soccer ball: berylliosis presents with non-caseating granulomas (similar to sarcoidosis)
36. Particles falling on top of fibrotic lung tree: interstitial fibrosis in berylliosis may be more prominent in upper lobes

SKETCHY CORNER

Objective

1. Describe the structure of the spirometry.
2. Identify the physiological factors that influence the pulmonary function tests (PFTs).
3. List the different indications of pulmonary function tests (PFTs).
4. Compare between PFTs in obstructive and restrictive pulmonary diseases.
5. Interpret the changes in PFTs in smokers in comparison to non-smokers.

Lung Function Tests

1. Spirometry: It is the measurement of the speed and the amount of air that can be exhaled and inhaled.
2. Body Plethysmography test: The patient is required to sit in an airtight chamber that resembles a small telephone booth. Inside the chamber is an affixed spirometer, which is used to determine the flow properties of the patient.
3. Cardiopulmonary Stress Testing: Used for evaluation of dyspnea that is out of proportion to findings on static pulmonary function tests.
4. Diffusing Capacity of Lung for Carbon Monoxide: To evaluate the presence of possible parenchymal lung disease.
5. Pulse Oximetry: The principle is measurement of O2 saturation by spectrophotometry.

Spirometry

Spirometry is a method to record volume movement of air into and out of the lungs.

Spirometry is a simple most commonly used test to:

- Assess the lung performance.
- Measure the physiological parameters: Lung volumes, Capacities, Flow rate.
- Play a critical role in the diagnosis, differentiation and management of respiratory diseases.
- Differentiate between the obstructive and restrictive lung conditions.

Physiological conditions affecting lung functions:

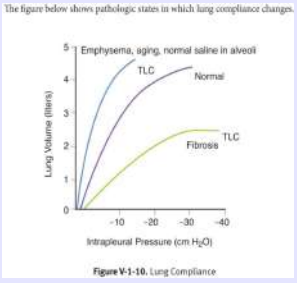
- Age
- Gender
- Height
- Eight
- Ethnic group
- Pregnancy

General Indications of Spirometry :

- Symptoms:
  - Dyspnea
  - Cough
  - Sputum production
  - Chest pain
- Signs:
  - Cyanosis
  - Clubbing
  - Chest deformity
  - Diminished chest expansion
  - Hyperinflation
  - Diminished breath sounds
  - Prolongation of expiratory phase & crackles
- Arterial blood gas analysis shows: Hypoxemia, hypercapnia
- Abnormal chest X Ray.

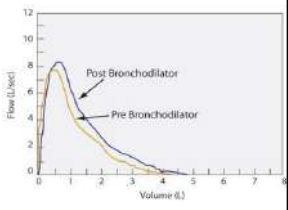
Extra Explanation:
Obstructive disease (Emphysema):
the patient will have difficulty creating a positive alveolar pressure (+1) during expiration. That is caused by the decrease in elasticity (recoil) in the lung, and thus an increase in compliance.

Extra Explanation:
Restrictive disease (Fibrosis):
the patient will have difficulty creating a negative alveolar pressure (-1) during inspiration. That is caused by an increase in elasticity (recoil) in the lung, and thus a decrease in compliance. As you can see in the graph, emphysema has a higher TLC because of the increased compliance, while Fibrosis has a decreased TLC.



Specific Indications of Spirometry :

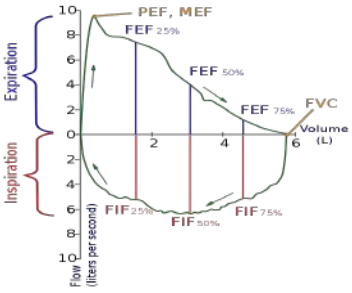
- To detect respiratory disease in patients presenting with symptoms of breathlessness, and to distinguish respiratory from cardiac disease.
- To diagnose or manage asthma.
- To diagnose and differentiate between obstructive and restrictive lung disease.
- Describe the course of diseases affecting PFTs:
  - Neuromuscular diseases: Gillian Barre Syndrome, Myasthenia gravis
  - Pulmonary diseases: Obstructive airway diseases, Interstitial lung diseases
  - Adverse reactions: Drugs with known pulmonary toxicity [Pulmonary fibrosis]
- To measure response to treatment of conditions which spirometry detects.
- To assess the therapeutic interventions:
  - Bronchodilator therapy
  - Steroid treatment for asthma
  - Chronic obstructive lung disease
  - Interstitial lung disease

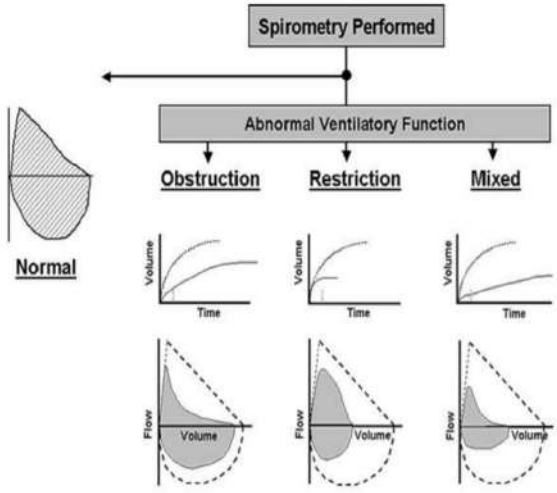


- To conduct pre-operative risk assessment before anesthesia. Pre operative indications:
  - To determine the suitability of patients for anaesthesia.
  - To assess the risk for surgical procedures known to affect lung function.

Results classification

- Normal
- Obstructive
- Restrictive
- Combined





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  - Diminished chest expansion
  - Hyperinflation
  - Diminished breath sounds
  - Prolongation of expiratory phase & crackles
- Arterial blood gas analysis shows: Hypoxemia, hypercapnia
- Abnormal chest X Ray.

Maintaining accuracy

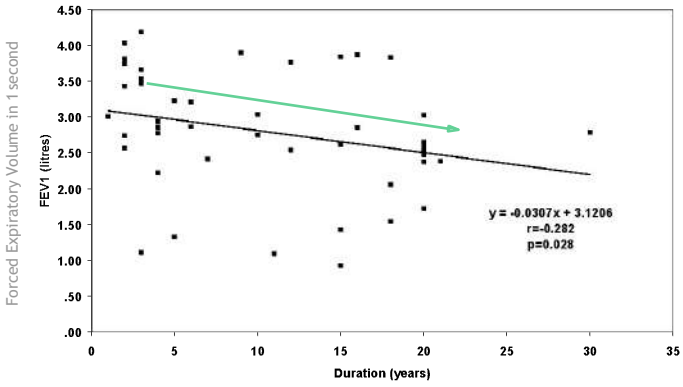
The most common reason for inaccurate results:

- Inadequate or incomplete inhalation.
- Additional breath taken during the test
- Lips not sealed around the mouthpiece.
- Slow start to forced exhalation
- Some exhalation through the nose.
- Coughing.

Smoking and Spirometry

Effect of smoking on lung function:

- Non-Smoker: In normal healthy non smoker subject after the age of 30 the expected decline in Lung function parameter [FEV1] is 25–30 ml/ year.
- Smoker: The average rate of decline of lung function in smokers as measured by Forced Expiratory Volume in 1 sec [FEV1] is 60-70 ml / year.



Impaired lung function in DM (diabetes mellitus)

- Type 1 and type 2 diabetic patients showed a significant reduction in the:
  - Forced Vital Capacity [FVC]
  - Forced Expiratory Volume in one Second [FEV1]

Spirometry & HbA1c

- Increase in mean HbA1c: is associated with decrease in lung function parameters FEV1 and FVC.

Diagnosis of COPD

- Symptoms: cough, sputum, dyspnea
- Exposure to risk factors: tobacco, occupation, indoor/outdoor pollution.

➔ In the present of these , we can use Spirometry to confirm the diagnose

Spirometry and CemENT INDUSTRY :

Lung function parameters:

- FVC
- FEV1
- FEF 25-75%
- PEF were significantly decreased in cement mill workers compared to their matched controls.

Spirometry and WELDING INDUSTRy :

Lung function parameters

- FVC
- FEV1
- PEF were significantly impaired in welding workers compared to their matched controls.

Spirometry and OIL SPILL Y :

Lung function parameters

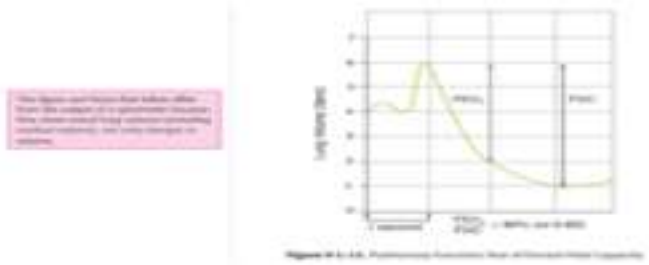
- FVC
- FEV1
- FEF 25-75% were impaired in subjects exposed to crude oil spill in sea water.

Lung Function in Health and Disease

Pulmonary function testing

Vital Capacity

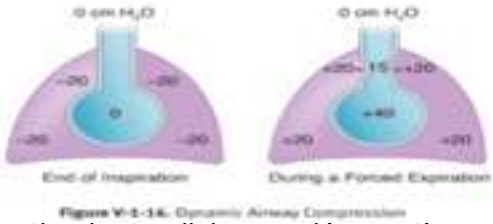
- Vital capacity (VC) is the maximum volume of air that an individual can move in a single breath. The most useful assessment of the VC is to expire as quickly and forcefully as possible, i.e., a "timed" or forced VC (or FVC). During the FVC maneuver, the volume of air exhaled in the first second is called the forced expiratory volume in 1 sec (FEV_1).



- There are 2 key p
    1. **FVC:** this is total volume exhaled
        - Because age, gender, body size, etc., can influence the absolute amount of FVC, it is expressed as a percent of predicted (100% of predicted being the "ideal").
    2. **FEV_1 (forced expiratory volume in 1 second):** although this volume can provide information on its own, it is commonly compared to the FVC such that one determines the FEV_1/FVC ratio.
        - This ratio creates a flow parameter; 0.8 (80%) or greater is considered normal.
- Thus, this PFT provides a volume and a flow.
- **Restrictive** pulmonary disease is characterized by reduced volume (low FVC, but normal flow), while **obstructive** disease is characterized by reduced flow (low FEV_1/FVC).

Physiology of a PFT

In the figure below, the picture on the left shows that at the end of an inspiratory effort to TLC, IPP is very negative. This negative IPP exists throughout the lungs during a passive expiration and thus the PTM is positive for both alveoli and airways.



The picture on the right shows th ion.

- A forced expiration compresses the chest wall down and in, creating a positive IPP. The level of positive IPP generated is dependent upon effort.
- This forced expiration creates a very positive alveolar pressure, in turn creating a large pressure gradient to force air out of the lungs.
- However, this positive IPP creates a negative PTM in the airways. It is more negative in the large airways, e.g., trachea and main stem bronchi. These regions have structural support and thus do not collapse even though PTM is very negative.

KAPLAN CORNER

- Moving down the airways toward alveoli, the negative PTM ultimately compresses airways that lack sufficient structural support. This is dynamic compression of airways.
- This compression of airways creates a tremendous resistance to air flow. In fact, the airway may collapse, producing infinite resistance. Regard-less, this compression creates a level of resistance that overwhelms any and all other resistors that exist in the circuit and is thus the dominant resistor for airflow.
- Once this occurs, elastic recoil of the lung becomes the effective driving force for airflow and airflow becomes independent of the effort. This means airflow is a property of the patient's respiratory system, hence the reason this test is very diagnostic.
- Because this resistance is created in small airways, the entire volume of the lungs cannot be expired, creating residual volume (RV).Because PFTs measure flow (FEV_1/FVC) and volume, they accurately diagnose obstructive (low flow) and restrictive disease (low volume, normal flow).

Obstructive versus Restrictive Patterns

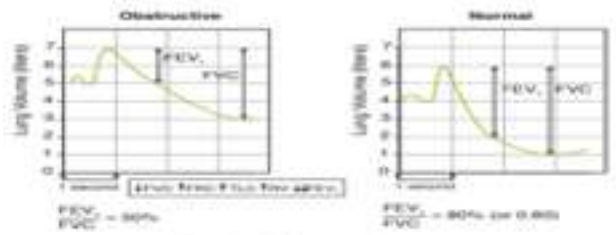
The following figures demonstrate a standard PFT, the measurement of FVC,FEV_1, and FEV_1/FVC.

Obstructive pulmonary disease

Obstructive disease is characterized by an increase in airway resistance that ismeasured as a decrease in expiratory flow. Examples are chronic bronchitis,asthma, and emphysema.

Obstructive pattern

- Total lung capacity (TLC) is normal or larger than normal, but duringa maximal forced expiration from TLC, a smaller than normal volumeis slowly expired.
- Depending upon the severity of the disease, FVC may or may not bereduced. If severe enough, then FVC is diminished.



Bridge to Pharmacology

Treatment of obstructive disease includes b2-agonists (short- and long-acting), M3 blockers such as ipratropium, PDE inhibitors, mast cell stabilizers, leukotriene-receptor blockers, and steroids.

Bridge to Pathology

There are 4 basic pathologic alterations that can occur in obstructive disease:
1-Bronchoconstriction. 2- Hypersecretion. 3- Inflammation. 4- Destruction of lung parenchyma (emphysema)

KAPLAN CORNER

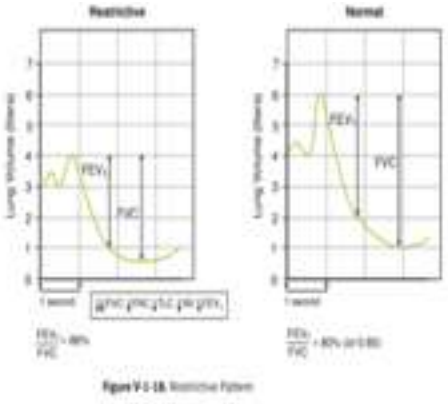
Lung Function in Health and Disease

Restrictive pulmonary disease

Restrictive pulmonary disease is characterized by an increase in elastic recoil—a decrease in lung compliance—which is measured as a decrease in all lung volumes. Reduced vital capacity with low lung volumes are the indicators of restrictive pulmonary diseases. Examples are ARDS and interstitial lung diseases such as sarcoidosis and idiopathic pulmonary fibrosis (IPF).

Restrictive pattern

- TLC is smaller than normal, but during a maximal forced expiration from TLC, the smaller volume is expired quickly and more completely than in a normal pattern.
- Therefore, even though FEV_1 is also reduced, the FEV_1/FVC is often increased.
- However, the critical distinction is low FVC with low FRC and RV.

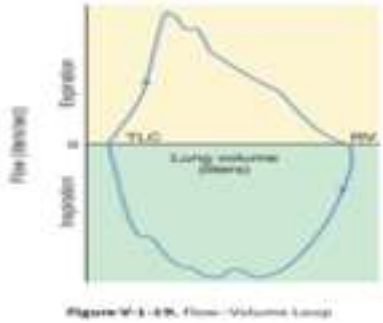


Variable	Obstructive Pattern (e.g., Emphysema)	Restrictive Pattern (e.g., Fibrosis)
TLC	↑	↓ ↓
FEV_1	↓↓	↓
FVC	↓	↓↓
FEV_1/FVC	↓	↑ or normal
Peak flow	↓	↓
FRC	↑	↓
RV	↑	↓

- FVC is always decreased when pulmonary function is significantly compro-mised.A decrease in FEV_1/FVC ratio is evidence of an obstructive pattern. A normalor increased FEV_1/FVC ratio is evidenc of a restrictive pattern, but a low TLCis diagnostic of restrictive lung disease.

Flow–Volume Loops

The instantaneous relationship between flow (liters/sec) and lung volume is useful in determining whether obstructive or restrictive lung disease is present. In the loop shown below, expiration starts at total lung capacity and continues to residual volume. The width of the loop is the FVC.



KAPLAN CORNER

Lung Function in Health and Disease

- Loops found in obstructive and restrictive disease are shown below.
- In obstructive disease, the flow–volume loop begins and ends at abnormally high lung volumes, and the expiratory flow is lower than normal. In addition, the down slope of expiration “scallops” or “bows” inward. This scalloping indicates that at any given lung volume, flow is less. Thus, airway resistance is elevated(obstructive).

- In **restrictive disease**, t ends at unusually low lung volumes. Peak flow is less, because overall volume is less. However, when expiratory flow is compared at specific lung volumes, the flow in restrictive disease is somewhat greater than normal.

Lung and Pleura

Adult thoracic cavity

- The **thoracic cavity** is kidney-shaped on cross section and is bounded anterolaterally by the bony thorax (sternum, ribs, and intercostal spaces) and posteriorly by the thoracic vertebrae. Superiorly, the thoracic cavity communicates through the **thoracic inlet** with the base of the neck. (Note, however, that clinically this region is usually called the **thoracic outlet**.) Inferiorly, the thoracic outlet is closed by the diaphragm which separates the thoracic from the abdominal cavity.
- The thoracic cavity is divided into 2 **lateral compartments**: the lungs and their covering of serous membranes, and a **central compartment** called the **mediastinum** which contains most of the viscera of the thorax.

Intercostal Spaces:

- There are 11 **intercostal spaces** within the thoracic wall .The spaces are filled in by 3 layers of intercostal muscles and their related fasciae and are bounded superiorly and inferiorly by the adjacent ribs.
- The costal groove is located along the inferior border of each rib (upper aspect of the intercostal space) and provides protection for the intercostal nerve, artery, and vein which are located in the groove. The vein is most superior and the nerve is inferior in the groove (VAN).
- The intercostal arteries are contributed to anteriorly from branches of the internal thoracic artery (branch of the subclavian artery) and posteriorly from branches of the thoracic aorta. Thus, the intercostal arteries can provide a potential collateral circulation between the subclavian artery and the thoracic aorta.

KAPLAN CORNER

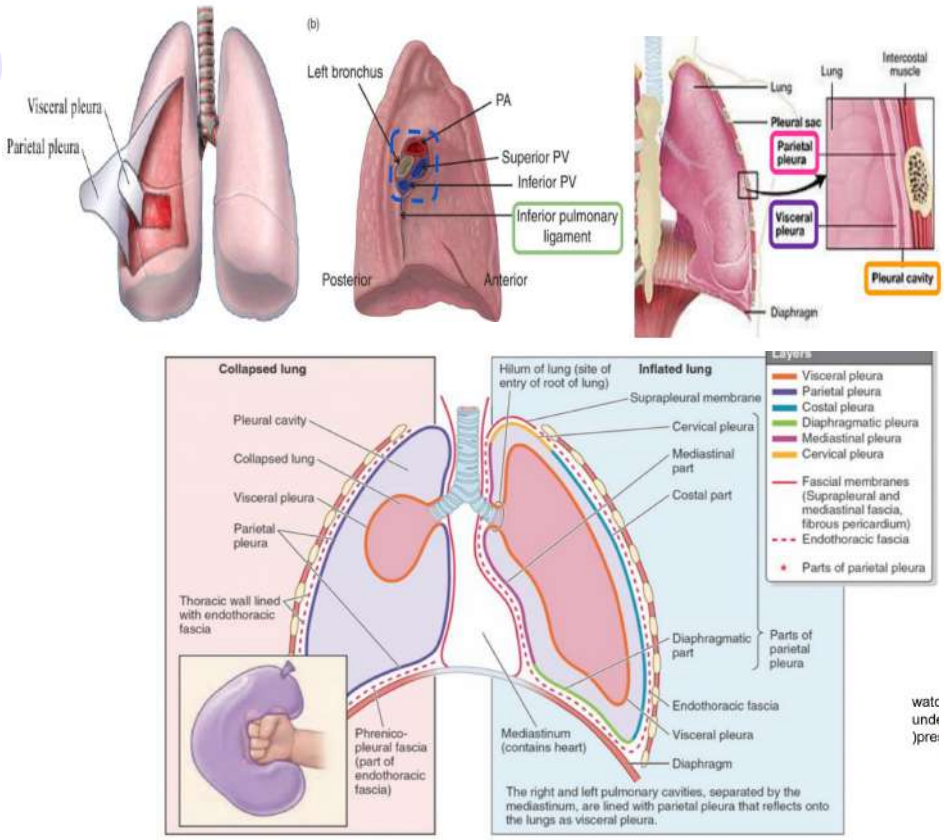
Objective

1. Describe the anatomy of the pleura regarding parietal and visceral pleura.
2. List the parts of parietal pleura and its recesses.
3. Describe the surface anatomy of both pleura and lungs.
4. Describe the anatomy of lungs : shape, relations, nerve supply & blood supply.
5. Describe the difference between right & left lungs.
6. Describe the formation of bronchopulmonary segments and the main characteristics of each segment in the lung.

Anatomy of pleura
by Sam Webster

Pleura

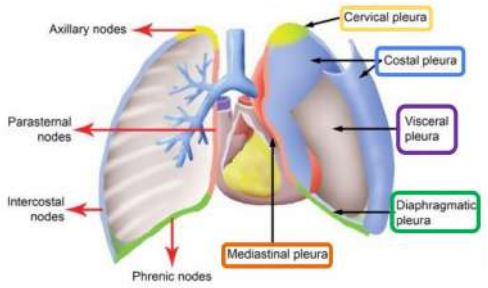
- Double-layered serous membrane enclosing the lung. Has two layers:
  - Parietal layer :which lines the thoracic walls
  - Visceral layer :which covers the surfaces of the lung
- The two layers continue with each other around the root of the lung,where it forms a loose cuff hanging down called the pulmonary ligament.
- The space between the two layers, the pleural cavity, contains a thin film of pleural serous fluid(5-10ml).



Parietal pleura

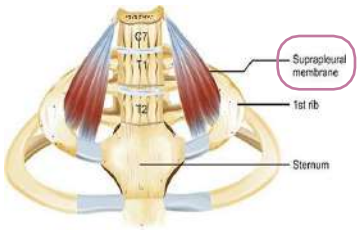
- It is divided according to the region in which it lies and the surfaces it covers, into:

1. Cervical pleura.
2. Costal pleura.
3. Mediastinal pleura.
4. Diaphragmatic pleura.

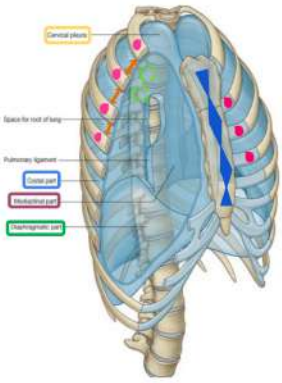


❖ Cervical pleura:

Projects upward into the neck: About one inch above the medial 1/3rd of clavicle. It lines the under surface of the Suprapleural membrane.



❖ Costal pleura:



lines, the back of the:
-Sternum.
-Ribs.
-Costal cartilages.
-Intercostal spaces.
-Sides of vertebral bodies

❖ Mediastinal pleura:

Covers the Mediastinum: At the Hilum, It is reflected on the vessels and bronchi, that enter the hilum of the lung. It is continuous with the visceral pleura.

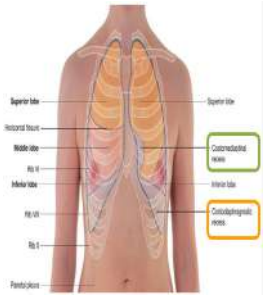
❖ Diaphragmatic pleura.

Covers the: thoracic (Upper) surface of the Diaphragm

Pleural recess

❖ Costodiaphragmatic Recess

- Slit like space between Costal and Diaphragmatic Pleura , along the inferior border of the lung enters through it in deep inspiration.



❖ Costomediastinal Recess

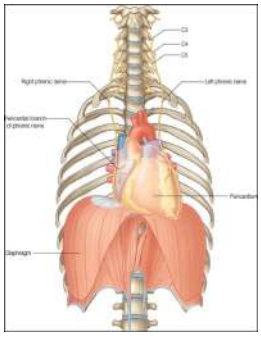
- Slit like space between Costal and Mediastinal Pleura , along the anterior border of the lung enters through it in deep inspiration.

Pleura nerve supply

❖ Parietal

- It is sensitive to (PPTT) pain, pressure, temperature, and touch.
- It is supplied as follows:

- Cervical and Costal pleura is segmentally supplied by the intercostal nerves. - Mediastinal pleura is supplied by phrenic nerves.
- Diaphragmatic pleura is supplied over the domes by phrenic nerves, around the periphery by lower 6 I ntercostal nerves



❖ Visceral

- sensitive to stretch only and is supplied by t he autonomic fibers from the pulmonary plexus.

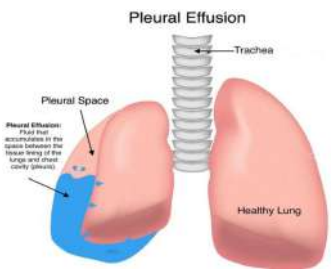
Pleural effusion

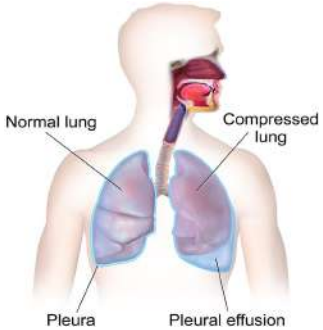
- Double-layered serous membrane enclosing the lung. Has two layers:
- It is an abnormal accumulation of pleural fluid about 300 ml in the Costodiaphragmatic pleural recess (normally 5-10 ml fluid)

Causes :

-Inflammation.
-TB. (most common)
-Congestive heart disease.
-Malignancy.

- The lung is compressed and the bronchi are narrowed.
- Auscultation would reveal only faint & decreased breathing sounds over compressed or collapsed lung lobe.
- Dullness on percussion over the effusion.

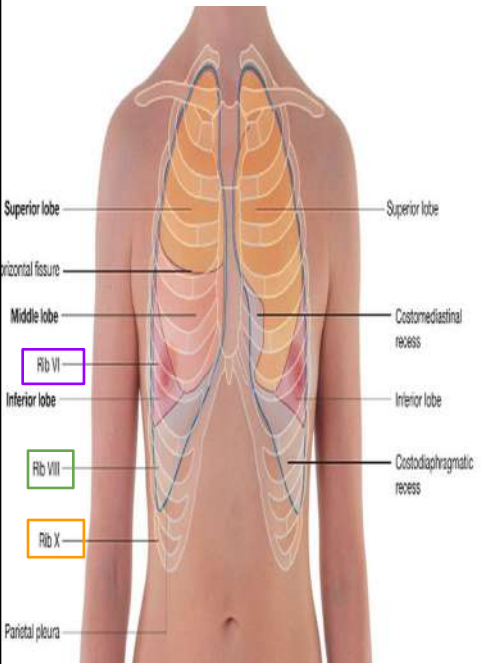


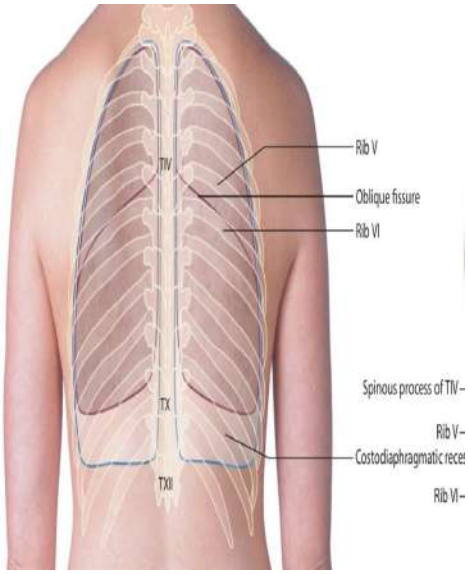


Surface anatomy of pleura

Apex:	Lies one inch above the medial 1/3 of the Clavicle.
Anterior margin:	Right pleura: extends vertically from Sternoclavicular joint to xiphisternal joint (6th costal cartilage). Left pleura: extends from Sternoclavicular joint to the 4th costal cartilage, then deviates laterally and extends to lateral margin of the sternum to form cardiac notch then turns sharply downward to xiphisternal joint (6th costal cartilage).
Inferior margin:	Passes around the chest wall, on the 8th rib in midclavicular line, 10th rib in mid-axillary line and finally reaching to12th rib adjacent to vertebral column posteriorly (T12).
Posterior margin :	Along the vertebral column from the apex (C7) to the inferior margin (T12).

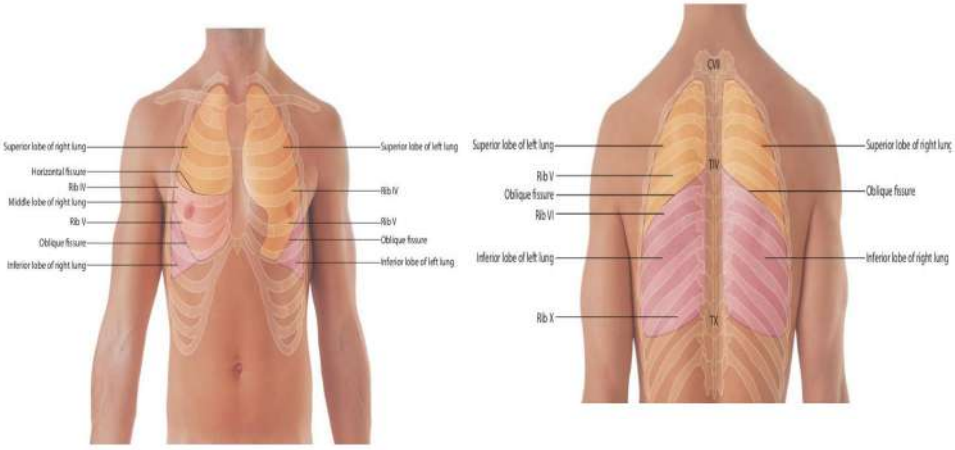
Surface Anatomy - Pleura Lung (3D) by RCSI

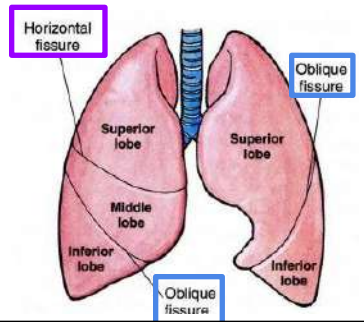




Surface anatomy of Lung

Apex, anterior border	Correspond nearly to the lines of Pleura but are slightly away from the median plane
Inferior margin:	passes around the chest wall , on the 6th rib in midclavicular line , 8th rib in mid-axillary line and finally reaching to 10th rib adjacent to vertebral column posteriorly. - As pleura but more horizontally and finally reaching to the (T10) not (T12)
Posterior margin :	Along the vertebral column from the apex (C7) to the inferior margin (T10)
Oblique fissure:	Represented by a line extending from 3rd or 4th thoracic spine, obliquely ending at 6th costal cartilage.
Transverse fissure: (Only in the right lung)	Represented by a line extending from 4th right costal cartilage to meet the oblique fissure.

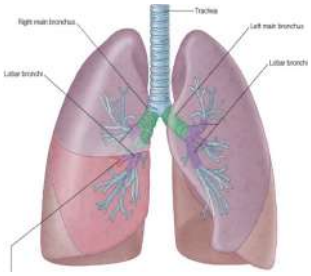




The Lung

Located in:

thoracic cavity, one on each side of the mediastinum



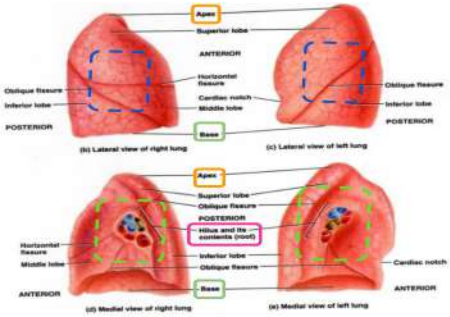
Conical in shape.
Covered by the visceral pleura.
Suspended free in its Own pleural cavity.
Attached to the mediastinum only by its root.

Each lung has:

1. Apex & Base:
Identify the top and bottom of the lung, respectively.

2. Costal surface:
Surrounded by the ribs and intercostal spaces from front, side and back.

3. Medial surface:
Where the bronchi, blood vessels, and lymphatic vessels enter or leave the lung at the Hilum.
It is also related to the structures forming the Mediastinum.

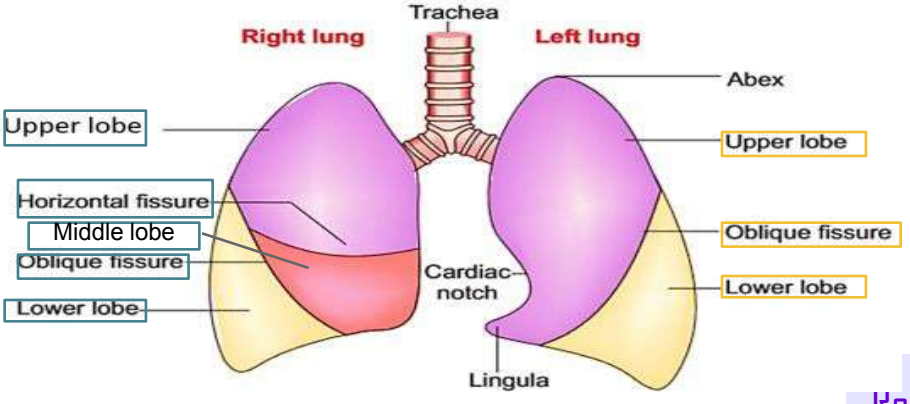


❖ Left Lung :

- Divided by one oblique fissure.
- 2 lobes, Upper and lower.
- There is No horizontal fissure.
- It has a cardiac notch at lower part of its anterior border.

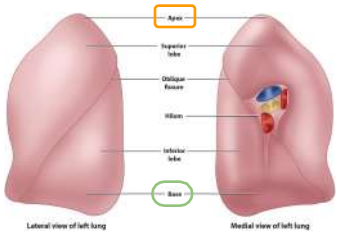
❖ Right lung :

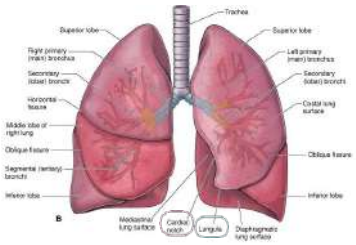
- Divided by 2 fissures (oblique & horizontal)
- 3 lobes (upper, middle and lower lobes).
- Larger & shorter than left lung



Apex and Base

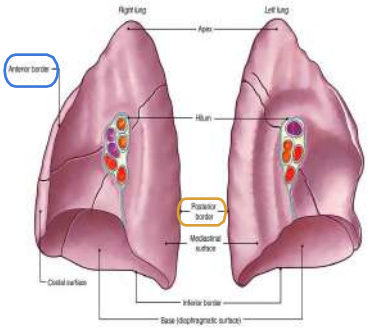
Apex	Projects into the root of the neck (0.5-1 inch above medial 1/3 ofclavicle). It is covered by cervical pleura. It is grooved anteriorly by subclavian artery.
Base	inferior or diaphragmatic surface , is concave and rests on the diaphragm.





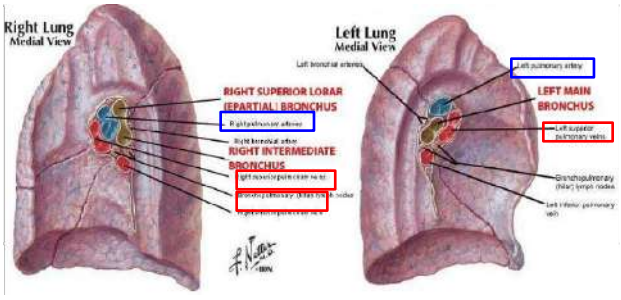
Borders

Anterior border	Is sharp, thin and overlaps theheart. Anterior border of left lung presents a cardiac notch at its lower end, has a thin projection called the lingula below the cardiac notch.
Posterior border	is rounded, thick and lies beside the vertebral column.



Lung Roots:

Bronchi	Right lung root	Left lung root
Bronchi	2 bronchi Lie posterior	One bronchus Lies posterior
Pulmonary artery	Superior	
Pulmonary veins	Are inferior and anterior	



The surfaces of lung

Mediastinal surface:

❖ Mediastinal surface of right lung :

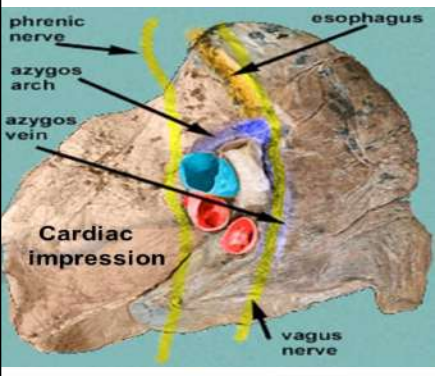
On the mediastinal surface of the right lung, you find these structures:

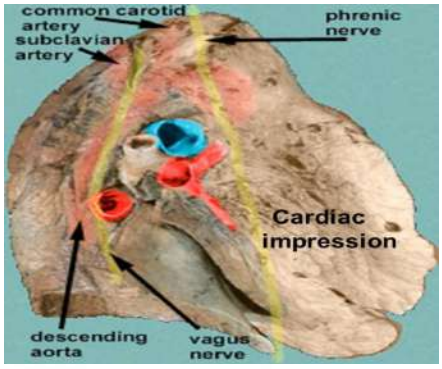
- Vagus nerve posterior to the root of the lung.
- Phrenic nerve anterior to the root of the lung.
- Cardiac impression: related to right atrium.
- Azygos vein and its arch (posterior and over the root of the lung).
- Esophagus posterior to the root.
- Below hilum and in front of pulmonary ligament : groove for Inferior vena cava

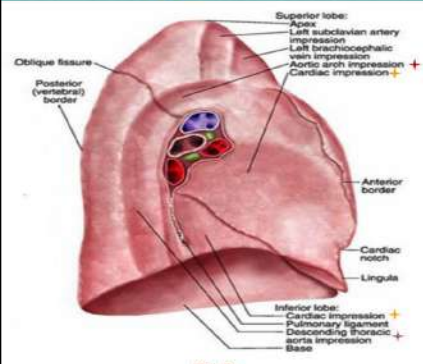
❖ Mediastinal surface of left lung:

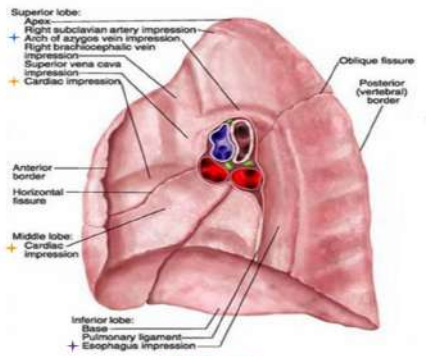
On the mediastinal surface of the left lung, you will find these structures:

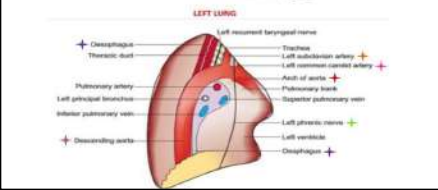
- Vagus nerve posterior to the root of the lung & over the root.
- Phrenic nerve anterior to the root of the lung.
- Cardiac impression: related to left ventricle.
- Descending aorta posterior to the root.
- Arch of the aorta over the root of the lung.
- Groove for left common carotid and left subclavian arteries.

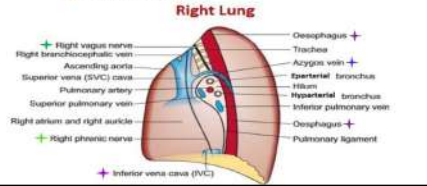












Surface anatomy of Lung

Costal & Mediastina surface :

❖ Costal surface:

- Convex and Covered by costal pleura which separates lung from:

  ribs, costal cartilages & intercostal muscles

❖ Medial surface:

It is divided into 2 parts:

- Anterior (mediastinal)

Contains a hilum in the middle (it is a depression in which bronchi, vessels, & nerves forming the root of lung).

- Posterior (vertebral)

It is related to:

- Bodies of thoracic vertebrae.
- Intervertebral discs
- Posterior intercostal vessels
- Sympathetic trunk.

Blood supply of lung

❖ Arteries

- On the Bronchial arteries (From descending aorta) It supplies oxygenated blood to bronchi , lung tissue & visceral pleura.
- Pulmonary artery which carries non-oxygenated blood from right ventricle to the lung alveoli.

❖ Veins

- Bronchial veins drain into azygos & hemiazygos veins.
- pulmonary veins carry oxygenated blood from lung alveoli to the left atrium of the heart.

Nerve supply of lung

❖ Pulmonary plexus:

At the root of lung is formed of autonomic N.S. from sympathetic & parasympatheticfibers.

❖ Sympathetic Fibers

- From : sympathetic trunk
- Action: broncho-dilatation & vasoconstriction

❖ Parasympathetic Fibers

- From : Vagus nerve
- Action: Broncho-constriction & vasodilatation & secretomotor to Bronchial glands.

Bronchopulmonary segments

Bronchi :

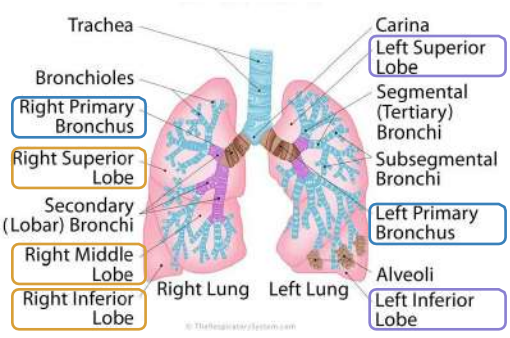
The trachea divides into 2 main bronchi:

❖ Right main bronchus

- which divides before entering the hilum, it gives: superior lobar (secondary) bronchus.
- On entering hilum, it divides into middle & inferior lobar bronchi

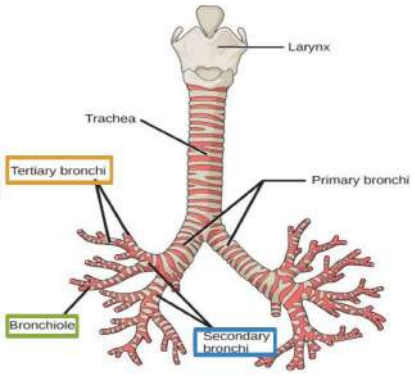
❖ Right main bronchus

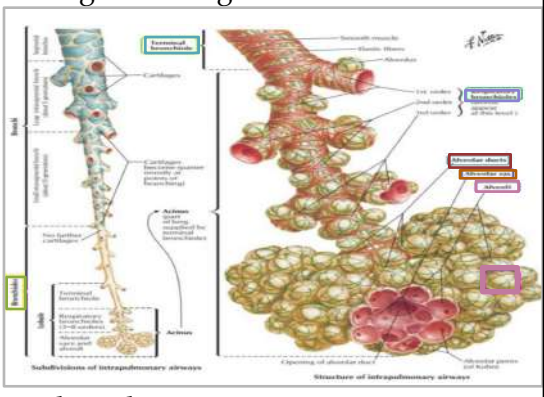
- On entering hilum, it divides into superior & inferior lobar bronchi



They are the anatomic, functional, and surgical units of the lungs.

- Each lobar (secondary) bronchus gives segmental (tertiary) bronchi.
- Each segmental bronchus divides repeatedly into bronchioles.
- Bronchioles divide into terminal bronchioles, which show delicate outpouchings "the respiratory bronchioles"
- The respiratory bronchioles end by branching into alveolar ducts, which lead into alveolar sacs.
- The alveolar sacs consist of several alveoli, each alveolus is surrounded by a network of blood capillaries for gas exchange.

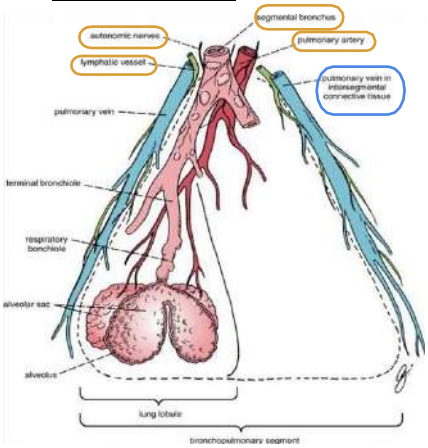


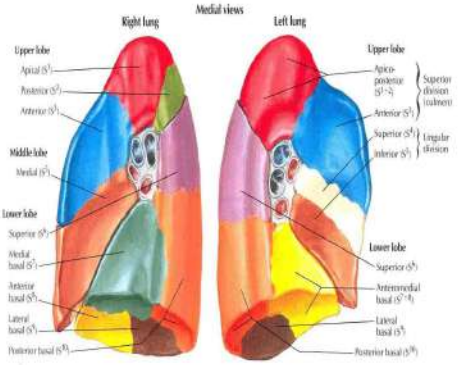


The main characteristics of a bronchopulmonary segment:

- It is a subdivision of a lung lobe.
- It is pyramidal shaped, its apex toward the lung root.
- It is surrounded by connective tissue septa.
- It has a segmental bronchus, a segmental artery, lymph vessels, and autonomicnerves.
- The segmental vein lies in the inter- segmental C.T. septa between the segments.
- Adiseased segment can be removed surgically, because it is a structuralunit.

Note:
Segmental vein can't be removed, since it also gives the neighbor segment





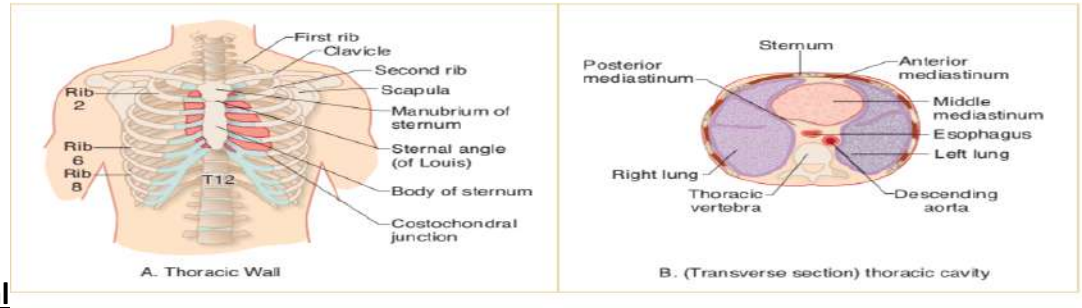


Figure II-2-4. Thoracic Cavity

Clinical

Passage of instruments through the intercostal space is done in the **lower part** of the space to avoid the intercostal neurovascular structures (as during a thoracentesis).
An intercostal nerve block is done in the **upper portion** of the intercostal space

Pleura and pleural cavity

- Within the thoracic and abdominal cavities there are 3 serous mesodermal derived membranes which form a covering for the lungs (**pleura**), heart (**pericardium**), and abdominal viscera (**peritoneum**).
- Each of these double-layered membranes permits friction-reducing movements of the viscera against adjacent structures.
- The outer layer of the serous membranes is referred to as the **parietal layer**; and the inner layer which is applied directly to the surface of the organ is called the **visceral layer**. The 2 layers are continuous and there is a potential space (pleural cavity) between the parietal and visceral layers containing a thin layer of serous fluid.

Pleura

- The **pleura** is the serous membrane that invests the lungs in the lateral compartments of the thorac cavity (Figure II-2-5). The **external parietal pleura** lines and attaches to the inner surfaces of the ch wall, diaphragm, and mediastinum. The innermost **visceral** layer reflects from the parietal layer at th hilum of the lungs and is firmly attached to and follows the contours of the lung. Visceral and parietal pleura are continuous at the root of the lung.
- The **parietal pleura** is regionally named by its relationship to the thoracic wall and mediastinum (Figu II-2-5):
    - **Costal parietal pleura** is lateral and lines the inner surfaces of the ribs and intercostal spaces
    - **Diaphragmatic parietal pleura** lines the thoracic surface of the diaphragm.
    - **Mediastinal parietal pleura** is medial and lines the mediastinum. The mediastinal pleura refle and becomes continuous with the visceral pleura at the hilum.
    - **Cervical parietal pleura** extends into the neck above the first rib where it covers the apex the lung.
- The **visceral pleura** tightly invests the surface of the lungs, following all of the fissures and lobes the lung.

Clinical Correlate

inflammation of the parietal pleural layers (pleurisy) produces sharp pain upon respiration. Costal inflammation produces local dermatome pain of the chest wall via the intercostal nerves; whereby mediastinal irritation produces referred pain via the phrenic nerve to the shoulder dermatomes of C3–5.

Innervation of Pleura

- The parietal pleura has extensive **somatic** sensory innervation provided by nerves closely related to different aspects of the pleura.
    - The **intercostal nerves** supply the costal and peripheral portions of the **diaphragmatic** pleura.
    - The phrenic nerve supplies the central portion of the **diaphragmatic** pleura and the **mediastinal** pleura.
- The **visceral pleura** is supplied by visceral sensory nerves that course with the autonomic nerves.

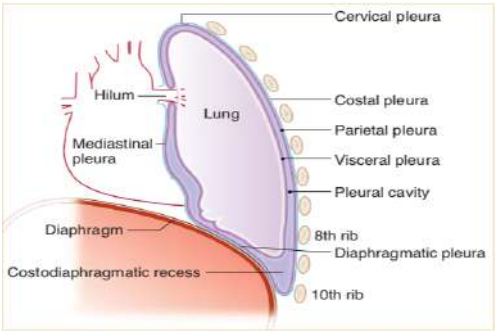


Figure II-2-5. Layers of the Pleura

- The **pleural cavity** is th nd visceral layers of the pleura. It is a closed space which contains a small amount of serous fluid that lubricates the opposing parietal and visceral layers.
- The introduction of air into the pleural cavity may cause the lung to collapse, resulting in a **pneumothorax** which causes shortness of breath and painful respiration. The lung collapses due to the loss of the negative pressure of the pleural cavity during a pneumothorax.

Clinical Correlate

- **Open pneumothorax** occurs when air enters the pleural cavity following a penetrating wound of the chest cavity. Air moves freely through the wound during inspiration and expiration. During inspiration, air enters the chest wall and the mediastinum will shift toward other side and compress the opposite lung. During expiration, air exits the wound and the mediastinum moves back toward the affected side.
- **Tension pneumothorax** occurs when a piece of tissue covers and forms a flap over the wound. During inspiration, air enters the chest cavity, which results in a shift of the mediastinum toward the other side, compressing the opposite lung. During expiration, the piece of tissue prevents the air from escaping the wound, which increases the pressure and the shift toward the opposite side is enhanced. This severely reduces the opposite lung function and venous return to the heart and can be life-threatening.

KAPLAN CORNER

Pleural Reflections

Pleural reflections are the areas where the parietal pleura abruptly changes direction from one wall to the other, outlining the extent of the pleural cavities.

- The sternal line of reflection is where the costal pleura is continuous with the mediastinal pleura posterior to the sternum (from costal cartilages 2–4). The pleural margin then passes inferiorly to the level of the sixth costal cartilage.
- Around the chest wall, there are 2 **rib interspaces separating** the inferior limit of parietal pleural reflections from the inferior border of the lungs and visceral pleura: between ribs 6–8 in the **midclavicular line**, ribs 8–10 in the **midaxillary line**, and ribs 10–12 at the vertebral column (**paravertebral line**), respectively.

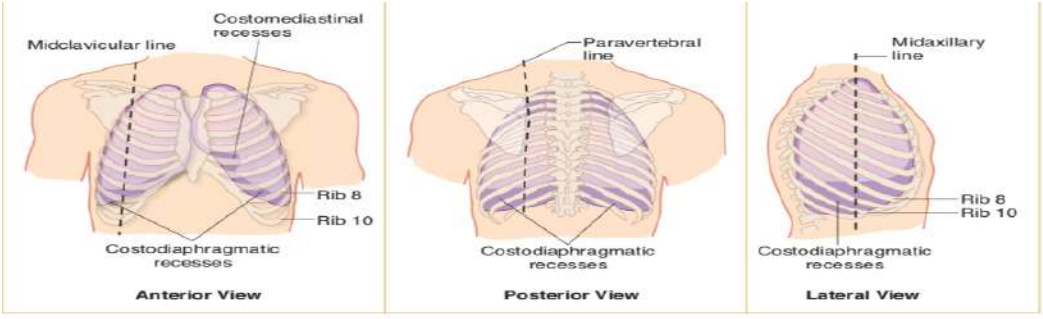


Figure II-2-6. Pleural Reflections and Recesses

Pleural

Pleural recesses are potential spaces not occupied by lung tissue except during deep inspiration.

- **Costodiaphragmatic recesses** are spaces below the inferior borders of the lungs where costal and diaphragmatic pleura are in contact.
- The **costomediastinal recess** is a space where the left costal and mediastinal parietal pleura meet, leaving a space caused by the cardiac notch of the left lung. This space is occupied by the lingual of the left lung during inspiration.

	Visceral Pleura	Parietal Pleura
Midclavicular line	6th rib	8th rib
Midaxillary line	8th rib	10th rib
Paravertebral line	10th rib	12th rib

Lungs

The lungs and the pleural membranes are located in the lateral compartment of the thoracic cavity. The lungs are separated from each other in the midline by the mediastinum. The **hilum** of the lung is on the medial surface and serves for passage of structures in the root of the lung: the pulmonary vessels, primary bronchi, nerves, and lymphatics.

Lung and Pleura

Surfaces and Regions

Each lung has 3 surfaces:

1. The **costal surface** is smooth and convex and is related laterally to the ribs and tissues of the chest wall.
2. The **mediastinal surface** is concave and is related medially to the middle mediastinum and the heart. The mediastinal surfaces contain the root of the lung and a deep **cardiac impression**, more pronounced on the left lung.
3. The **diaphragmatic surface** (base) is concave and rests on the superior surface of the diaphragm. It is more superior on the right owing to the presence of the liver.

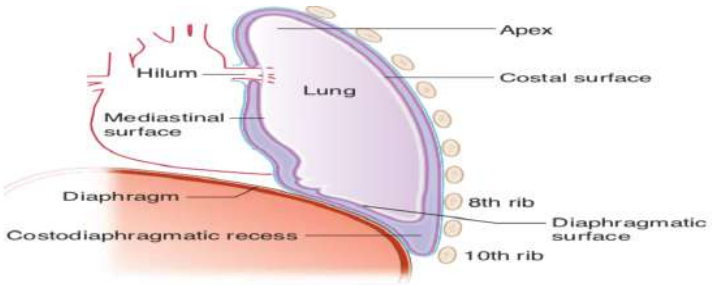


Figure II-2-7. Surfaces of the Lung

The apex (cupola) of th l of the first rib and is crossed anteriorly by the subclavian artery and vein.

Clinical Correlate: A tumor at the apex of the lung (Pancoast tumor) may result in thoracic outlet syndrome

Lobes and Fissures

- The **right lung** is divided into 3 lobes (**superior**, **middle**, **inferior**) separated by 2 fissures, the **horizontal** and **oblique fissures**. The horizontal fissure separates the superior from the middle lobe and the oblique fissure separates the middle from the inferior lobe.
- The left lung is divided into 2 lobes (superior, inferior) separated by an oblique fissure. The lingula of the upper lobe of the left lung corresponds to the middle lobe of the right lung.
    - The oblique fissure of both lungs projects anteriorly at approximately the 5th intercostal space in the midclavicular line, ending medially deep to the 6th costal cartilage.
    - The horizontal fissure runs horizontally from the oblique fissure in the right 5th intercostal space to the right 4th costal cartilage.

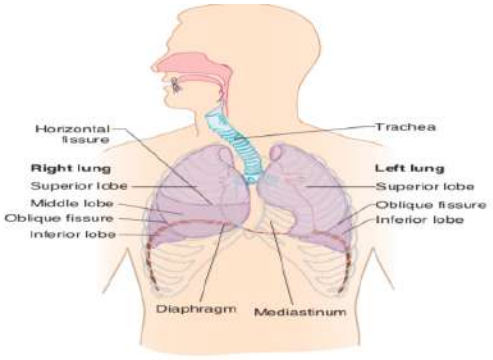


Figure II-2-8. Lobes and Fissures of Lungs

KAPLAN CORNER

Lung and Pleura

Clinical Correlate

- The superior lobe of the **right lung** projects anteriorly on the chest wall above the **4th rib** and the middle lobe projects anteriorly **below** the 4th rib.
- A small portion of the inferior lobe of both lungs projects **below** the 6th rib anteriorly but primarily projects to the **posterior chest** wall.
- To listen to **breath sounds** of the **superior lobes** of the right and left lungs, the stethoscope is placed on the superior area of the anterior chest wall (**above the 4th rib** for the right lung).
- For **breath sounds** from the **middle lobe of the right lung**, the stethoscope is placed on the anterior chest wall inferior to the **4th rib** and medially toward the sternum.
- For **the inferior lobes** of both lungs, **breath sounds** are primarily heard on the **posterior** chest wall.
- Aspiration of a foreign body will more often enter **the right primary bronchus**, which is shorter, wider, and more vertical than the left primary bronchus. When the individual is vertical, the foreign body usually falls into the **posterior basal segment** of the **right inferior lobe.**

Lymphatic System

- The **lymphatic system** consists of an extensive network of lymph capillaries, vessels, and nodes that drain extracellular fluid from most of the body tissues and organs. The lymph flow will return to the blood venous system by 2 major lymphatic vessels, **the right lymphatic duct** and the **thoracic duct** on the left (Figure II-2-10A). These 2 vessels drain into the junction of the internal jugular and the subclavian veins on their respective sides
    - **The thoracic duct** carries all lymphatic drainage from the body below the diaphragm and on the left side of the trunk and head above the diaphragm (Figure II-2-10B).
    - **The right lymphatic duct** drains lymph flow from the right head and neck and the right side of the trunk above the diaphragm (Figure II2-10B).

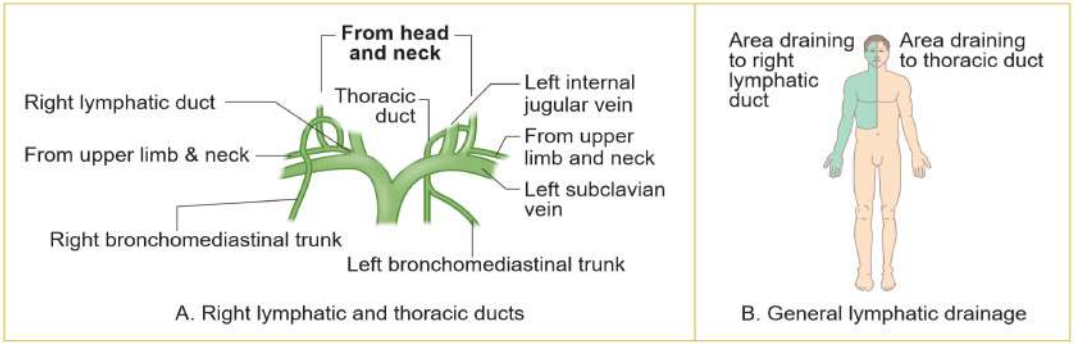


Figure II-2-10. Lymphatic Drainage

KAPLAN CORNER

Lung and Pleura

Lymphatic Drainage

The lymphatic drainage of the lungs is extensive and drains by way of **superficial** and **deep** lymphatic plexuses. The superficial plexus is immediately deep to the visceral pleura. The deep plexus begins deeply in the lungs and drains through **pulmonary nodes** which follow the bronchial tree toward the hilum.

The major nodes involved in the lymphatic drainage of these 2 plexuses are:

- **Bronchopulmonary (hilar) nodes** are located at the hilum of the lungs. They receive lymph drainage from both superficial and deep lymphatic plexuses, and they drain into the tracheobronchial nodes.
- **Tracheobronchial nodes** are located at the bifurcation of the trachea, and they drain into the right and left bronchomediastinal nodes and trunk.
- **Bronchomediastinal nodes** and trunk are located on the right and left sides of the trachea, and they drain superiorly into either the right lymphatic duct or the thoracic duct on the left.

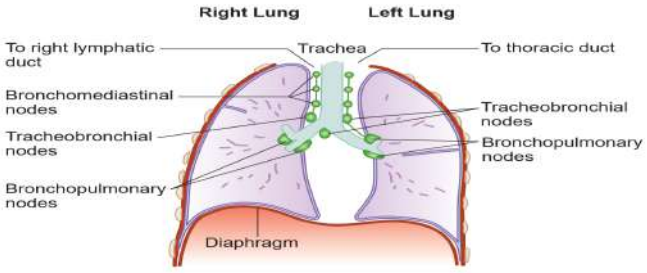


Figure II-2-9. Lymphatics of the Lungs

Clinical Correlate

The lymphatic drainage from the **lower lobe of the left lung** also drains across the midline into the **right bronchomediastinal** lymphatic trunk and nodes, then continues along the right pathway to the right lymphatic duct. This is important to consider with metastasis of lung cancer.

Microbacterium Tuberculosis

Distinguishing Features

- Auramine-rhodamine staining bacilli (fluorescent apple green); no antibody involved (sensitive but not specific)
- Acid fast
- Aerobic, slow growing on Lowenstein-Jensen medium; new culture systems (broths with palmitic acid) faster
- Produces niacin
- Produces a heat-sensitive catalase: catalase-negative at 68.0°C (154.4 F) (standard catalase test); catalase active at body temperature Reservoir: human lungs Transmission: respiratory droplets

Pleura

Describe anatomy of pleura?

- It's lined by mesothelial cells
- It produces pleural fluid

What are differences between spontaneous and tension pneumothorax?

Spontaneous pneumothorax	Tension pneumothorax
Often due to rupture of emphysematous bleb	Often due to penetrating chest wall injury
Often seen in young adults	
X-ray: trachea deviates to side of collapse	X-ray: trachea pushed to opposite side of injury; medical emergency; put chest tube

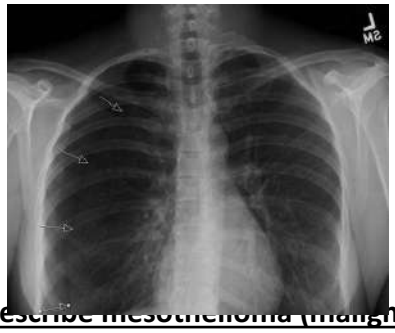


Fig: spontaneous pneumothorax (no tracheal shift)

Describe mesothelioma (malignant neoplasm of mesothelial cells).

- Presentation:
  - Recurrent pleural effusion (mesothelial cells make pleural fluid)
  - Tumor encases the lung
- Risk factor:
  - Asbestos (lung cancer far more likely)

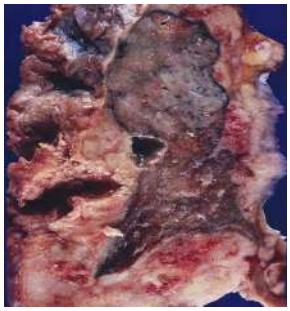


Fig: mesothelioma (tumor encasing the lung)

Objective

- Define tuberculosis & Know the epidemiology of tuberculosis (TB).
- List the diseases caused by Mycobacteria & conditions associated with increased risk of Tuberculosis and factors predisposing to extension of the infection
- Recognize the morphology of Mycobacteria and its special stain (the Ziehl-Neelsen) as well as the morphology of granulomas in TB (tubercles).
- In regards to Mycobacterial lung infection: Compare and contrast the following in relation to their gross and histologic lung pathology: 1. Primary tuberculosis (include a definition of the Ghon complex). 2. Secondary or reactivation tuberculosis. 3. Miliary tuberculosis.
- List organs other than lung that are commonly affected by tuberculosis.
- Know the basis and use of tuberculin skin (Mantoux) test.
- List the common clinical presentation of tuberculosis & List the complication and prognosis of tuberculosis.

Objective

Microbiology:

- Define tuberculosis as a chronic disease mainly affecting the respiratory system, AND Recognize roughly the epidemiology of tuberculosis worldwide and in the kingdom of Saudi Arabia
- Understand the methods of transmission of tuberculosis and the people at risk, AND Understand the pathogenesis of tuberculosis.
- Know the causative agents and their characteristic and classification and methods of detection.
- Differentiate between primary and secondary tuberculosis and the clinical features of each.
- Understand and describe and explain the methods of tuberculin test, tuberculin skin test (TST) and its different results, AND Know the radiological and laboratory diagnostic methods.
- Know the chemotherapeutic and other methods of management of tuberculosis cases.
- Describe the methods of prevention and control of tuberculosis.

Objective

IMMUNOLOGY:

- To know how M. tuberculosis infection is contracted and its initial encounter with the immune system
- To understand delayed type of hypersensitivity reaction against M. tuberculosis
- To identify possible outcomes of the infection with M. tuberculosis in immunocompetent and immuno-compromised hosts.
- To know the basis of interferon gamma release assay and its potential to detect latent tuberculosis.
- To identify the basis of tuberculin test and its importance in gauging immunity against M. tuberculosis

TB pathogenesis | Infectious diseases | NCLEX-RN | Khan Academy by khanacademymedicine

Introduction

Mycobacterium tuberculosis is the **second** most common infectious cause of death in adults worldwide, with an increasing incidence due to HIV. TB is transmitted through aerosols (airborne transmission) by coughing or sneezing and acquired mainly through **inhalation**. The clinical development of the disease depends solely on the effectiveness of the host's **innate and adaptive** immune response to the infection. If the immune response is functioning well, the clinical disease has little to no chance of developing.

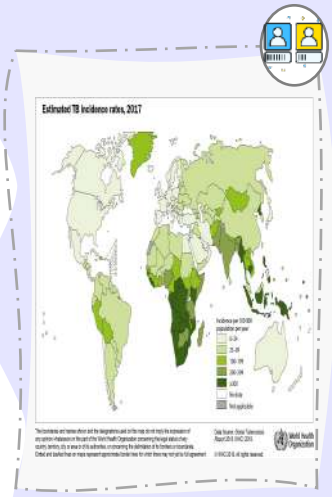
Note :
Infection Vs clinical disease:
Infection, the patient will have the bacteria but he's asymptomatic, but when he develop symptoms, we can say he has the disease (clinical disease).

Definition

Tuberculosis is a communicable chronic granulomatous disease caused by **Mycobacterium tuberculosis**. It usually involves the lungs but may affect any organ or tissue in the body. Typically, the centers of tuberculous granulomas undergo caseous necrosis.

Epidemiology

The World Health Organization (WHO) considers tuberculosis to be the most common cause of death resulting from a single infectious agent. TB affects 1/3 of human race, It is estimated that 1.7 billion individuals are infected by tuberculosis worldwide, with 8 to 10 million new cases in 2014 and 1.5 million deaths per year. Incidence among HIV 20 times. 1.3million deaths from TB among HIV-negative people in 2017 and an additional 300000 deaths From TB among HIV-positive people. It's a worldwide disease, more common in developing countries like India, china, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Affects all age groups who are subject to get the infection. If properly treated is curable, but fatal if untreated in most cases.



Tuberculosis flourishes under conditions of:

1. Poverty
2. Crowding
3. Chronic debilitating illness
4. Malnutrition

It is considered as to be one of the major endemic diseases in the kingdom, particularly involving: Elderly, AIDS patients, Diabetes mellitus, Hodgkin's lymphoma, Silicosis patients, The urban poor and Alcoholism.

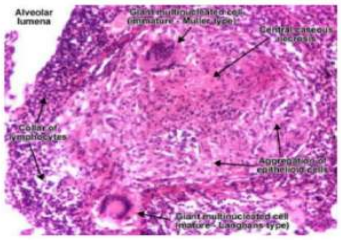
Common sites of infections

Usually affects the apical areas of lung, but other organs can be affected in one third of cases. Non-pulmonary TB may spreads from **pulmonary infections** to other organs. For example:

- TB of lymph node, cervical mesenteric
- TB meningitis , especially in children.
- TB bone and joints
- TB of the genitourinary system
- TB miliary (Blood)
- TB of soft tissue (cold abscess) with caseation, which means lacks inflammation like hotness and redness.
- Renal parenchyma.

Note :

- Caseation: due to delayed hypersensitivity reaction. Contains many bacilli ,enzymes, O2,N2 intermediates → necrotic center of granuloma (cheesy material.
- No inflammation this is usually Cold abscess TB , if inflammatory infiltrate present the this is other type of TB.



HISTOLOGY

Caseous necrosis in lung tissue

Transmission

Tuberculosis transmitted mainly through **direct person-to-person** transmission by **inhalation** of airborne **droplet** (tiny and wet) nuclei (< 5 µm) in pulmonary diseases case and rarely through GIT & skin. It reaches the alveolar macrophages intracellular and are able to survive their' main virulence factor. It can affect Young children and adults.

People at risk:

- Lab Technicians (risk of exposure)
- Workers in mines (risk of developing)
- Immunosuppressed patients (risk of developing as secondary)
- Contacts with index case (People around the infected person)

Species of Mycobacteria

Mycobacterium tuberculosis complex :

Cause tuberculosis, such M. tuberculosis, M. bovis , M. Africanum and BCG strains

Mycobacterium leprae:

Causes leprosy

Atypical Mycobacteria, Mycobacteria other than tuberculosis (MOTT):

Cause infections in immunosuppressed patients

Etiology

Mycobacterium tuberculosis hominies	It is very aerophilic (strict aerobe, acid fast). Responsible for most cases of tuberculosis, endemic in KSA; the reservoir of infection typically is found in individuals with active pulmonary disease. Transmission usually is direct, by inhalation of airborne organisms in aerosols generated by expectoration or by exposure to contaminated secretions of infected individuals.
Mycobacterium Avium	Atypical bacteria, seen only in **immunocompromised.** There's no formation of granulomas.
Mycobacterium bovis	Acquired through drinking unpasteurized milk (from cows), usually starts in the tonsils or Peyer's patches, can cause gastrointestinal tuberculosis in human. It may go to lymph node.

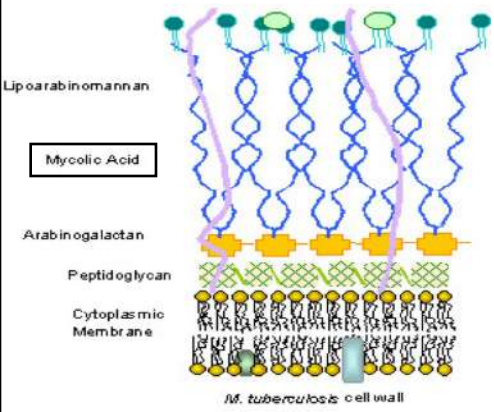
Note :

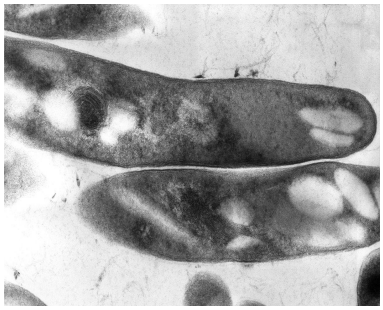
- M. tuberculosis is a human type and very common.
- M. bovis is a bovine type and rare because of pasteurization of milk.
- BCG strains used for vaccination because it's a weak bacteria but in rare cases it can cause TB in immunocompromised children

Characteristics of the Genus Mycobacteria

It's unusual Gram positive, slim, and rod in shape (bacilli), non-motile, non-spore forming, and it's strict aerobes (loves and need Oxygen). Do not stain by Gram stain because it Contain high lipid conc. **(Mycolic acid)** in the cell wall which resist staining. (prevent crystal violet to reach Peptidoglycan)

Called **Acid- alcohol fast bacilli (AFB),** because it resists decolorization with up to 3% HCL, 5% ethanol or both. So, it is Stained by **Ziehl-Neelsen (Z-N) and Auramine staining.** Mycobacterium species appear tiny red bacilli acid fast bacilli (AFB) by Z-N stain.





Mycobacterium under electroscope

Pathogenesis of TB

Droplet reaches the alveolar macrophages intracellular, This starts cell mediated immune response; which controls the multiplication of the organism but does not kill it. Patient show evidence of delayed cell mediated immunity (CMI). Disease result due to destructive effect of CMI.

1. Entry into macrophages:

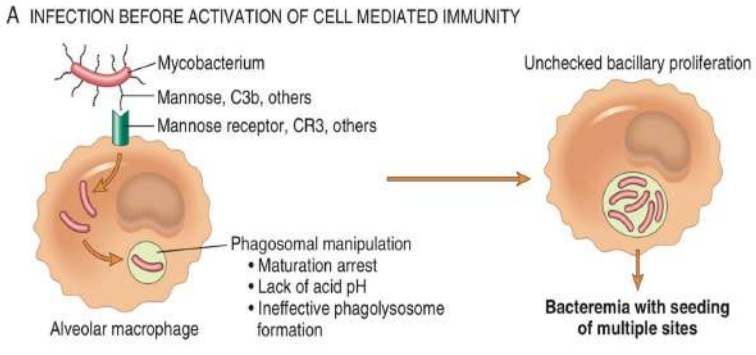
A virulent strain of mycobacteria gains entry to macrophage endosomes, a process mediated by several macrophage receptors, including the macrophage mannose receptor and complement receptors that recognize several components of the mycobacterial cell walls. Once internalized, the organisms inhibit normal microbicidal responses by producing a protein (cord factor) preventing the fusion of the lysosomes with the phagocytic vacuole. allowing the mycobacterium to persist and proliferate. Thus, the earliest phase of primary tuberculosis (the first 3 weeks) in the non-sensitized patient is characterized by bacillary proliferation within the pulmonary alveolar macrophages and air spaces, eventually resulting in bacteremia and seeding of the organisms to multiple sites. Despite the bacteremia, most individuals at this stage are asymptomatic or have a mild flu-like illness. **Tuberculosis is able to withstand the body's immune response after being phagocytosed by several ways, including:**

Virulence factors	Host factors
○ The lipid-rich waxy outer coat blocks phagocytic enzymes. ○ Catalase-peroxidase resists the host cell oxidative response. ○ The glycolipid Lipoarabinomannan (LAM) Stimulates cytokines, resists the host oxidative stress and interferes with MHC Class II expression to CD4 cells	○ Resistance to reactive oxygen intermediates. ○ Inhibition of phagosome-lysosome fusion ○ Inhibition of phagosome acidification. (prevents digestion in an acidic environment) ○ Escape from the phagosomal compartment of the cytoplasmic space

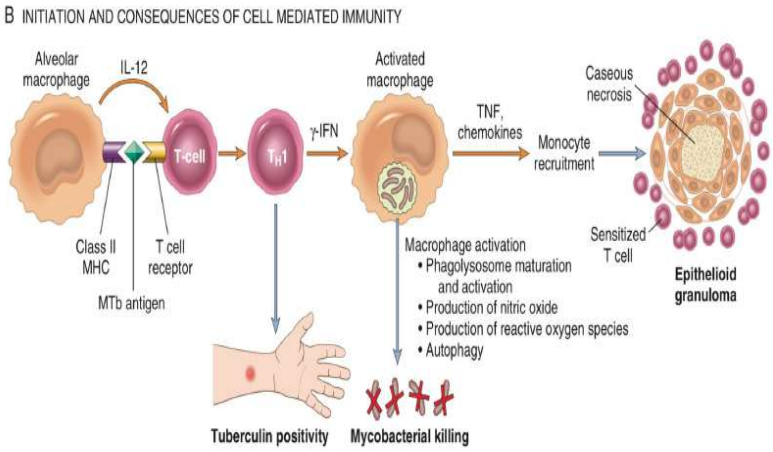
Note :
How can we differentiate between Septicemia and Bacteremia?
- Septicemia: Proliferation of the organism within the blood causing an infection & activating a systemic immune response (not caused by TB).
- Bacteremia: Presence of the bacteria within the blood, without causing an infection (caused by TB).

2. First time exposure to TB:

A. Events occurring in the first 3 weeks after exposure



B. Events thereafter, formation of granuloma occur



3. Development of cell-mediated:

This occurs approximately 3 weeks after exposure. Processed mycobacterial antigens reach the draining lymph nodes and are presented to CD4 T cells by dendritic cells and macrophages. Under the influence of macrophage-secreted IL-12, CD4+ T cells of the TH1 subset that are capable of secreting IFN-γ are generated

4. T cell–mediated macrophage activation and killing of bacteria:

IFN-γ released by the CD4+ T cells of the TH1 subset is crucial in activating macrophages. Activated macrophages, in turn, release a variety of mediators + chemokines and upregulate expression of genes with important downstream effects including:

- TNF: responsible for recruitment of monocytes.
- Nitric Oxide synthase (iNOS): raises NO levels.
- Defensin: anti-microbial peptides which is toxic to M.TB.

5. Granulomatous inflammation and tissue damage:

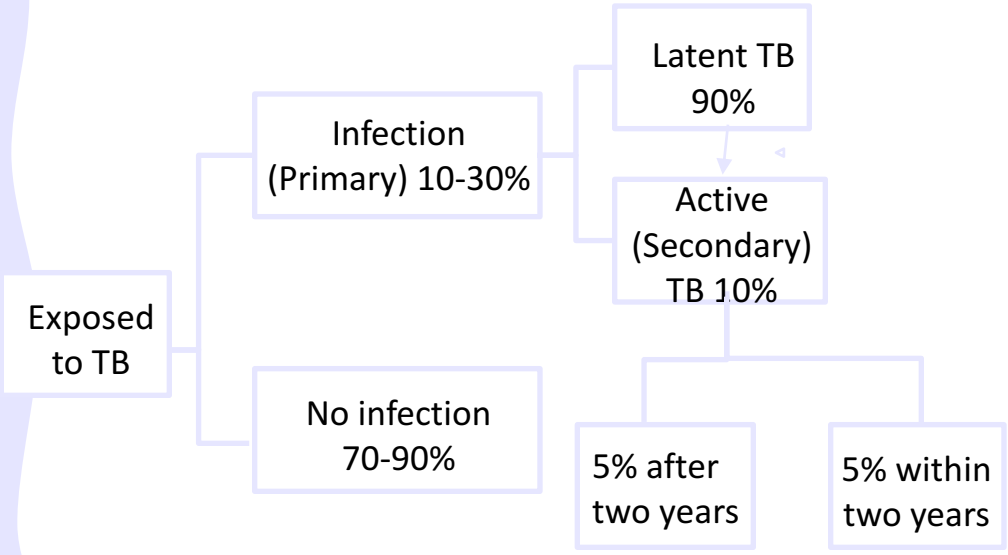
TH1 response orchestrates (organize) the formation of granulomas and caseous necrosis by releasing IFN-γ which cause macrophages to differentiate into epithelioid histiocytes that aggregate to form granulomas. Granuloma is formed three weeks after primary TB exposure

Extra Explanation :

- Defects in any of the steps of a TH1 T cell response (including IL-12, IFN-γ, TNF, or NO production) result in poorly formed granulomas, absence of resistance, and disease progression.
- Individuals with inherited mutations in any component of the TH1 pathway are extremely susceptible to infections with mycobacteria.
- Reactivation of the infection or re-exposure to the bacilli in a previously sensitized host results in rapid mobilization of a defensive reaction but also increased tissue necrosis. Just as hypersensitivity and resistance appear in parallel, so, too, the loss of hypersensitivity is an ominous sign of fading resistance to the organism.

Note :

Histiocytes Vs macrophages: Histiocytes are inactive in phagocytosis while macrophages are active



Possible outcomes of TB infection

Immediate clearance	Immediate onset (primary & secondary)
Latent	Onset after many years (Reactivation)

Primary TB

Definition:

Primary tuberculosis is the form of disease that develops in a previously unexposed and therefore unsensitized patient. Happens within the first three weeks of exposure. The majority of cases are Asymptomatic.

Site:

Distal air spaces of the lower part of the upper lobe or in the upper part of the lower lobe, typically close to the pleura

Pathogenesis:

1. **Inhalation:** The bacteria **enters the body** via inhalation.
2. **Phagocytosis:** The alveolar macrophages phagocytose the bacteria but cannot kill it.
3. **Recruitment:** The infected macrophages send out a distress signal in the form of chemokines, attracting other macrophages.

4. **Ghon's focus:** The newly recruited macrophages surround the bacteria, this eventually forms a nodular granuloma called a **tubercle**. This whole structure is known as a Ghon's focus.

5. **Ghon's complex:** If the replication isn't controlled, it spreads to the draining **lymph nodes**, forming a Ghon's complex.

6. **Ranke's complex:** In some cases, the tubercles become **fibrotic and heal**, forming a Ranke's complex. This type of fibrosis never goes away.

2-6 weeks after the infection, the bacilli trigger a Cell Mediated Immunity response. This leads to:

1. **Th1 cells:** Weeks after the infection, the CMI response causes Th1 cells to release:
   A. IFN-ɣ: activates more macrophages and enhances its ability to kill phagocytosed bacilli.
   B. TNF: induces local inflammation and activates more macrophages.

2. **CMI response:** If the CMI response is not effective, the lung gets destroyed by:
   A. Nitrogen intermediates
   B. TNF-α
   C. Reactive oxygen
   D. Contents of cytotoxic cells (Perforin, granzymes)

3. **Outcome:** The destructive substances lead to **caseous** necrosis, a major characteristic of TB. Eventually, the caseating lesions start to erode, spreading to the airways and becoming infectious. If left untreated, the disease can become chronic or even lead to death (80% of cases).

4. **Chronic Disease:** It is characterized by episodes of healing by fibrotic changes around the lesion and tissue breakdown. Recovery is possible(20%) at this stage, but complete eradication of the bacilli is rare.

Morphology:

Stage I: Ghon focus

- 1 to 1.5 cm area of gray-white inflammatory consolidation.
- Emerges during the development of sensitization.
- Usually, the center of this focus undergoes caseous necrosis (Located peripherally).

Stage II: Ghon complex

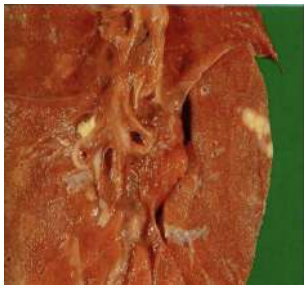
Tubercle bacilli, either free or within phagocytes, travel via the lymphatic vessels to the regional lymph nodes which also often caseate. It located subpleural area. Upper parts of the lower lobes or lower parts of upper lo (mid lung)

Stage III: Ranke complex

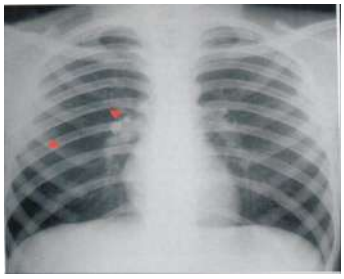
Development of cell-mediated immunity controls the infection in approximately 95% of cases, therefore the ghon complex undergoes progressive fibrosis, followed by calcification.

Note :

Foci of scarring may harbor a small number of organisms that remain viable for years and later, if immune mechanisms wane or fail, these bacilli may multiply and cause secondary TB.



Ghon focus + Nodal lesions

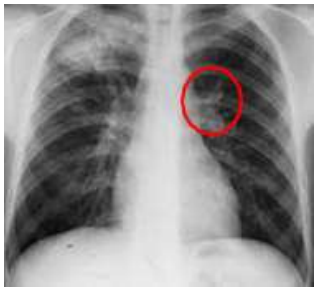


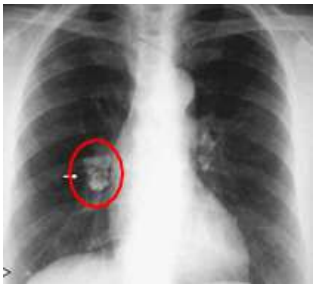
Healed primary pulmonary tuberculosis

Note :

- Uncommonly, new infection leads to progressive primary tuberculosis.
- The incidence of progressive primary tuberculosis is particularly high in HIV-positive patients with significant immunosuppression (i.e., CD4+ T-cell counts below 200 cells/µl).
- Why? Immunosuppression results in an inability to mount a CD4+ T cell–mediated response that would contain the primary focus.*

Ghon's focus in chest x-ray:



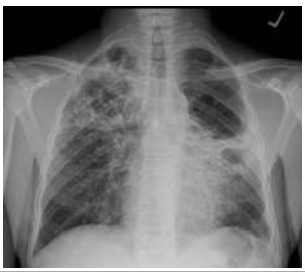


Microscopy of lesion shows → **Granuloma.**

Clinically → primary TB usually **asymptomatic** or minor illness and rarely transmitted.

Chest radiographic of Primary TB:

Middle or lower lobe consolidation



Secondary TB

Definition:

Secondary tuberculosis is the pattern of disease that arises in a previously sensitized host, it arises due to reactivation of dormant primary lesions or due to reinfection.

It forms Cavitary foci of caseous necrosis: The risk of spread of infection to non-infected persons from individuals with cavitary tuberculosis is very high. Why? because the patient now coughs sputum that contains bacilli, therefore patient should be isolated for 10-14 days from starting treatment.

Site:

Classically localized to the apex of one or both upper lobes. The reason is obscure but may relate to high oxygen tension in the apices. The regional lymph nodes are less prominently involved early in the disease than they are in primary TB.

Complication :

It may progress to Miliary Tuberculosis, which can rupture the macrophages and escape into the bloodstream via lymphatic vessels. The word miliary is derived from the resemblance of these foci to millet seeds. It can go anywhere & symptoms depend on the location, E.g. Liver, bone marrow, meninges fallopian tubes and epididymis.

Miliary TB

Miliary TB (disseminated TB) can occur if the primary infection is not properly contained. This develops when the TB bacilli spreads throughout the lung and/or to other organs through hematogenous lymphatic spread. Its most common presentation is **meningeal TB.**

Pulmonary MTB:

Occurs when organisms reach the bloodstream through lymphatic vessels and then **recirculate to the lung** via the pulmonary arteries. The lesions appear as small (2-mm) foci of yellow-white consolidation scattered through the lung parenchyma

Systemic MTB:

- Ensues when the organisms disseminate hematogenously **throughout the body.**
- Systemic miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenal glands, meninges, kidneys, fallopian tubes, and epididymis.
- Multiple small yellow nodular lesions in several organs . Almost every organ in the body may be seeded. Lesions resemble those in the lungs

Isolated-organ TB (Extrapulmonary TB):

May appear in any **one of the organs** or tissues seeded hematogenously. Organs typically involved include:

- **Lymph nodes** (tuberculous lymphadenitis): are the most frequent form of extrapulmonary tuberculosis esp. in the cervical region "Scrofula".
- Pleura with pleural effusion (exudate).
- Liver, spleen, kidneys and Adrenals glands.
- Fallopian tube (Tuberculous salpingitis) and endometrium.
- Epididymis and prostate.
- Meninges (tuberculous meningitis).
- Bone marrow and Vertebrae (Pott's disease).
- Intestinal tuberculosis.

Latent TB

Pathogenesis:

1. Presentation of antigens by APCs in the lymph nodes. Delayed-type hypersensitivity (Type IV).
2. Activation of CD4+ (Th1) lymphocytes. This phase coincides with high rate of replication of bacilli.
3. Low induction of CD8+ lymphocytes. CD8+ lymphocytes recognize the antigen and produce IFN-γ, leading to macrophage activation.
4. Induction of high number of CD8 + Increased production of IFN-γ and cytotoxic activity. This phase coincides with bacterial growth stabilization.
5. Bacterial load remains constant and infection is kept in a dormant state.

Note :
The immune response and Anti-MTB drugs are directed towards the **growing** bacilli, therefore making the **non-replicating** bacilli in latent TB somewhat invisible to the body (resistant).

Reactivation

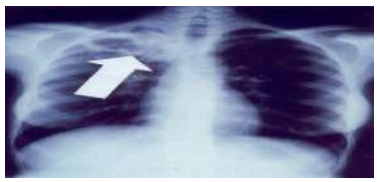
The dormant bacteria that were stopped during primary infection can start proliferating again (5-10% of cases). It tends to be **localized** with much **less caseation** and **little lymph node involvement.** It usually only affects the lung **apices.** Dissemination here is **usually uncommon.**

Factors contributing to reactivation:

- Immunosuppression
- End-stage renal disease
- Diabetes
- Malignant Lymphoma
- Corticosteroids
- Aging
- HIV/AIDS
- Anti TNF-α drugs

Chest radiographic In reactivation of TB:

Classically fibro-cavitary apical disease



Clinical features

- Localized secondary tuberculosis may be asymptomatic.
- Manifestations are usually insidious in onset.
- Systemic manifestations, probably related to the release of cytokines by activated macrophages (e.g., TNF and IL-1). Which can be:
  - Malaise
  - Weight loss
  - Night sweats
  - Anorexia
  - Fever: Commonly, the fever is low grade and remittent. With progressive pulmonary involvement, increasing amounts of sputum, at first mucoid and later purulent appear.
  - Cough or/and hemoptysis
  - Pleuritic pain: Due to extension of infection to the pleural surfaces.

Extra Explanation :
What if the mycobacterium spread, will the manifestations change?
Yes, extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved, For example:
- Tuberculous salpingitis may present as infertility.
- Tuberculous meningitis may present as headache and neurologic deficits.
- Pott disease may present with back pain and paraplegia.

Investigations

Ways in which we can obtain a specimen:

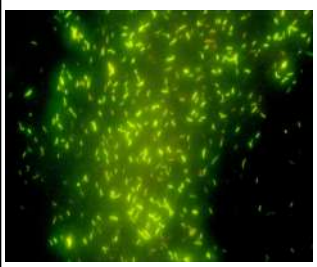
- Bronchoalveolar lavage
- CSF
- 3 Early morning sputum or urine
- lymph nodes, Pus or tissue not swab
- Joint, bone aspiration

Acid-Fast Bacilli (AFB)

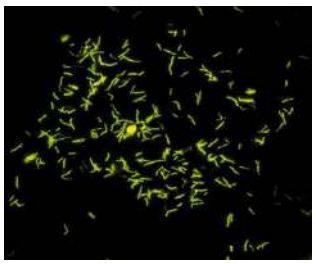
Stains used: Ziehl-Neelsen stain (ZN stain) and Auramine Rhodamine stain. Its strict aerobes and multiply intracellularly (inside the cells, macrophages, and other tissues). Because of that it cause delayed hypersensitivity reaction type 4 of immune response. Slowly growing (between 2 - 8 weeks) due to the thick layer of mycolic acid that surrounds the cell wall preventing nutrition's to reach the cell.

The Acid-fast bacilli appear pink in a contrasting background (Methylene Blue of Brilliant Green).

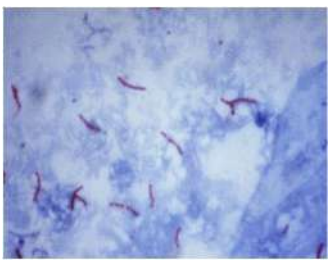
Note :
Auramine rhodamine is a Fluorescence stain



Fluorescence stain



Auramine



ZN stain

Tests for TB

Mantoux

Also called **tuberculin** test or heaf test.

It is a delayed-type hypersensitivity(DTH) skin test. A cell-mediated immunity will occur and that will result in a localized delayed **hypersensitivity reaction type 4**. Resulting from macrophage reaction and interaction with CD4 T cells which got transformed to TH2 cells Through IL-12 at 3rd week. So we can you use this reaction to our advantage to test for TB by using 0.1ml PPD **Intradermal injection** of antigenic protein particles from killed MTB which causes the area to swell. The same area is inspected 2-3 days later and the results depend on the diameter of the induration. This response (DTH), however, is not reliable in diagnosis because it cannot distinguish between a reaction from the BCG vaccine and the actual bacteria. Moreover, being immunocompromised can also affect the results of the test. If the test is positive will result in localized skin **induration** (5+mm) and erythema 3 days after injection. The size of induration is measured 48– 72 hours later.

False-negative reactions may be produced by certain viral infections, sarcoidosis, malnutrition, Hodgkin lymphoma, immunosuppression and AIDS. False-positive reactions may result from infection by atypical mycobacteria. This test doesn't differentiate between infection and disease.

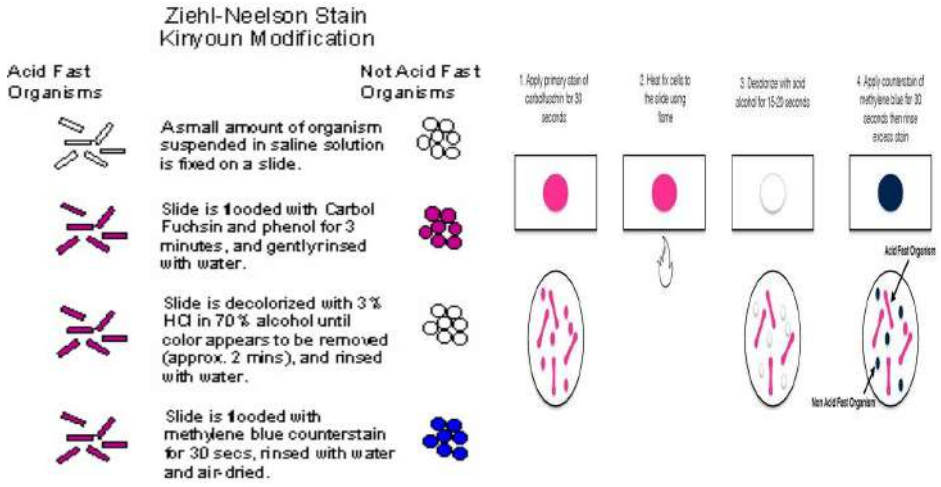
Results:

- **Positive:** induces a visible and palpable induration at least 5 mm in diameter:
  - A person who has been vaccinated against TB.
  - Patient who have been exposed to TB before
- **Negative:**
  - Patient who haven't been exposed to TB before.
  - Severely immunocompromised patients

- Uses purified protein derivative
- Activity expressed by Tuberculin unit
- Activates synthesized lymphocytes to produce CMI which appear as skin induration.
- May not distinguish between active and past infection except in an individual with recent contact with infected case.
- Low level activity induced by environmental mycobacteria, previous vaccination.

Acid Fast Bacilli AFB or (carbol fuchsin) Ziehl-Neelsen:

We don't use gram stain because M.TB contain high lipid concentration (Mycolic acid) in their cell wall, which resists staining. It has an atypical cell wall. Therefore After taking a smear we'll use either Ziehl Neelsen method or the auramine stain.



Auramine stain:

A stain that involves staining the antibody with an immunofluorescence dye and then reacting it with the antigen of the bacteria. If there is a reaction then it is positive.

Lowenstein – Jensen (culture):

We can test the susceptibility to different antibiotics. LJ is a medium that we can culture M.TB on. It takes 2-12 weeks (10 weeks). liquid media can give results in 2 weeks.

Polymerase chain reaction PCR:

It is a method that recognize the DNA of the bacteria via molecular means. this is very accurate. it might give false positive because it's sensitivity. there are no limiting factors such as a time, amount of specimen, or even deterioration of the tissue. It takes around two days or so to obtain the results.

IFN-ɣ release assay:

This test measures the IFN released by T cells when Mycobacterium antigens are injected. Early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) antigens are used since they are not found in BCG vaccines. If a reaction occurs, this means the body has already been exposed to these antigens prior to this test. This helps differentiate between people with latent TB and people who have taken the BCG vaccine, unlike the Mantoux test.

Extra Explanation :

1. Staining by using carbon fusion stain (red color)
2. Fixation (using the heat to allow the dye to go inside the wall)
3. Decolorization by strong acid (methanol 3-5% or hydrochloric acid)
   - We use a very powerful acid to make sure that the bacteria can handle the decolorization with acid that's way it was named Acid Fast Bacilli.
   - So no matter how powerful is the acid, the bacteria will not lose the dye In case of TB it will keep its red color and it won't change

Note :

ESAT-6 and CFP-10 are found in the bacteria. So if the bacteria was already in the blood and the antigen was injected, the IFN levels would increase

Granuloma

Definition:

A Granuloma is a microscopic aggregation of macrophages that are transformed into epithelium-like cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells. **Tuberculosis is a granulomatous disease**

Note :
Granuloma: the predominant cell type is an activated macrophage with a modified epithelial-like (epithelioid) appearance. Also seen are lymphocytes, multinucleated giant cells and occasional plasma cells.

Caseation:

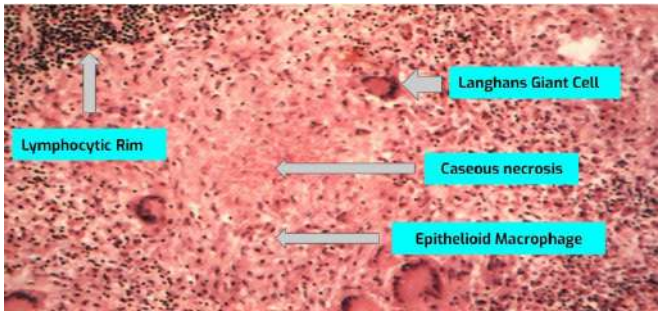
Fibrous connective tissue often surrounds granulomas (as remodelling of tissue). In TB areas within the granuloma can undergo necrosis **(caseous necrosis).** Necrosis can lead to **calcification**. TB granulomas are called tubercles, and if they are caseating in the center, they are called soft tubercles.

Caseation:

Epithelioid cells fuse to form giant cells containing 20 or more nuclei. The giant cells can be found either at periphery or at the center of the granuloma. The nuclei are arranged either **peripherally** (langhans-type giant cells) or **haphazardly** (foreign body-type giant cells). Both Langhans (Classic TB) and foreign-body giant cells are common.

Note :
After biopsy and seeing granulomas, recall that sarcoidosis and crohn's disease both form granuloma. So, ask for where the patient is from and look for other risk factor to determine if it's TB or not .

Morphology of Granulomas in TB (Tubercles):

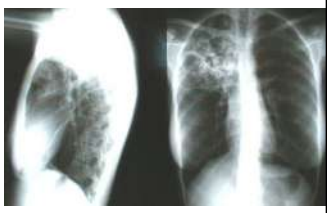


Radiology

Chest radiology:

- **No chest X-ray pattern is absolutely typical of TB.**
- 10-15% of culture-positive TB patients not diagnosed by X-ray.
- 40% of patients diagnosed as having TB on the basis of x-ray alone do not have active TB
- Chest x-Ray can be anything even nothing (normal X-Ray), but that doesn't rule out TB.

Chest radiographic appearance:



- Infiltration
- Cavitation
- Fibrosis with traction
- Pleural thickening
- Enlargement of hilar and mediastinal lymph node

Summary

	Tuberculosis
General considerations	Tuberculosis occurs worldwide, with greatest frequency in disadvantaged groups. In the pulmonary form, it is spread by inhalation of droplets containing the organism Mycobacterium tuberculosis (also referred to as the tubercle bacillus).
Types of tuberculosis	**Primary TB:** It's the initial infection, characterized by the Ghon complex, the combination of a peripheral subpleural parenchymal lesion and involved hilar lymph nodes. Primary tuberculosis is most often asymptomatic. It usually does not progress to clinically evident disease. **Secondary TB:** Usually results from activation of a prior Ghon complex, with spread to a new pulmonary or extrapulmonary site.
Pathologic changes	**A. Localized lesions:** usually in the apical or posterior segments of the upper lobes. Involvement of hilar lymph nodes is also common. **B. Tubercle formation:** The lesions frequently coalesce and rupture into the bronchi. The caseous contents may liquefy and be expelled, resulting in cavitary lesions. Cavitation is a characteristic of secondary, but not primary, tuberculosis; caseation (a manifestation of partial immunity) is seen in both. **C. Scarring and calcification.**
Spread of disease	Secondary tuberculosis may be complicated by lymphatic and hematogenous spread, resulting in miliary tuberculosis, which is seeding of distal organs with innumerable small millet seed-like lesions. Hematogenous spread may also result in larger lesions, which may involve almost any organ. Organs typically involved include: Meninges, fallopian tube" Tuberculous salpingitis", vertebrae"Pott disease", Lymphadenitis in the cervical region "Scrofula".

Tuberculosis

Describe presentation of primary TB.

- Caused by inhalation of bacteria.
- **Presentation:**
  - Focal caseating necrosis classically in lower lobe and hilar lymph nodes
  - The foci undergo fibrosis and calcification resulting in **Ghon complex**
  - Mostly asymptomatic
  - Leads to positive PPD

Fig: Ghon complex (calcified and fibrosed lung): classic location is subpleural region near hylar nodes

Describe presentation of secondary TB (aka reactivated TB).

- Commonly seen due to immunosuppression, AIDS, or old age
- **Presentation:**
  - Usually affects upper lobes
  - Forms many focal caseating necrosis, or miliary TB or TB bronchopneumonia
- **Symptoms:**
  - Fevers and night sweats
  - Cough with hemoptysis
  - Weight loss

What are classic locations for spread of miliary TB?

- Kidney - most common organ to be involved - gives sterile pyura
- Meninges (classic location is base of brain)
- Cervical lymph nodes
- Lumbar vertebrae (pott disease)

Mycobacterium tuberculosis - Shoot out at the TB Corral

1. Pink Gun leaving a pink finish - Acid fast is represented by the mycolic acids (carbol fuschien stain), ie the 2 branched tassels representing mycolic acids.
2. Lowenstein General Store - Lowenstein Medium
3. Billows - Obligate Aerobe
4. Cart - Transmission - Human to Human respiratory droplets and proliferates in macrophages
5. Cart - Macrophage Cage
6. Glycolipid are responsible for Clumping of bacteria into a serpentine formation – Virulence factor - called cord factor
7. Lasso wrapping up the driver of the macrophage cart - Cord factor will increases granuloma formation by increasing TNF-a activating other macrophages walling itself off in a granuloma – this will protect the bacteria
8. Spurs kicking up Dust clouds behind cowboy - Sulfatides - prevent phagolysosome fusion. Allow TB to survive in macrophages by creating incompetent secondary lysosomes preventing fusion to hydrolyzes
9. Cactus with holes in the middle lobe and red cactus fruit near hilum, Gun complex - Primary infection - healed infection, Affects lungs and will form a GHON complex, visual calcification, right middle lobular, Hilar lymph node involvement.
10. Carts that are broken down - Caseation Granulomas - tubers - tuberculosis resides in broken down necrotic macrophages (Langerhans giant cells)
11. Sick Child in burlap sack- Primary infection symptoms, long fever and in children, resolves by fibrosis (burlap sack)
12. Shovel with Dirt - Test for TB with PPD, BCG vaccine will always show positive skin test
13. Millet seed pouring out of the cart and cow skull- Milliary TB – Multi-organ failure - Millet seeds from the macrophage cart - Lethal
14. Guy strapped to barrels of TNF - Latent Infection - Associated with immunosuppression through downregulation of TNF-a release
    Immune system is defenseless if TNF is inhibited. Always screen for PPD before using a TNF inhibitor like infliximab
15. Right Cactus with holes in upper lung scene takes place at night- Reactivation is on the upper lungs, look for cough, night sweats, Bloody cough hemoptysis
16. Prisoner in the MΦ cage - Reactivation occurs in macrophages
17. Coughing out blood on handkerchief - Promotes body wasting
18. Broken Pots - Pots disease is demineralization of the bone, spinal weakness,
19. Bullet hole going through the hat - CNS involvement is also seen as meningitis or tuberculoma. "Hat being shot off"
20. Treatment - combination of RIPE, rifampin, isoniazid, Pyrazinamide, ethambutol
21. Prophylaxis - Rifampin or isoniazid - 9 months

SKETCHY CORNER

Microbacterium Tuberculosis

Pathogenesis

- Facultative intracellular organism (most important)
- Sulfatides (sulfolipids in cell envelope): inhibit phagosome-lysosome fusion, allowing intracellular survival (if fusion occurs, waxy nature of cell envelope reduces killing effect)
- Cord factor (trehalose dimycolate): causes serpentine growth in vitro; inhibits leukocyte migration; disrupts mitochondrial respiration and oxidative phosphorylation
- Tuberculin (surface protein) along with mycolic acid → delayed hypersensitivity and cell-mediated immunity (CMI): granulomas and caseation mediated by CMI; no exotoxins or endotoxin; damage done by immune system

Disease(s)

- Primary pulmonary TB
  - Symptoms can include fever, dry cough
  - Organisms replicate in naive alveolar macrophages, killing the macrophages until CMI is set up (Ghon focus)
  - Macrophages transport the bacilli to the regional lymph node (Ghon complex) and most people heal without disease
  - Organisms that are walled off within the Ghon complex remain viable unless treated
- Reactivational TB
  - Symptoms can include fever, hemoptysis, night sweats, weight loss
  - Erosion of granulomas into airways (high oxygen) later in life under conditions of reduced T-cell immunity can lead to mycobacterial replication and disease symptoms

Diagnosis

- Microscopy of sputum: screen with auramine-rhodamine stain (fluorescent apple-green); no antibody involved; very sensitive; if positive, confirm with
- acid fast stain
- PPD skin test (Mantoux): measure zone of induration at 48–72 hours; positive if:
  - – ≥5 mm in HIV+ or anyone with recent TB exposure; AIDS patients have reduced ability to mount skin test.
  - ≥10 mm in high-risk population: IV drug abusers, people living in poverty, or immigrants from high TB area
  - – ≥15 mm in low-risk population
  - Positive skin test indicates only exposure but not necessarily active disease.
- Quantiferon-TB Gold Test: measures interferon-gamma production when leukocytes exposed to TB antigens
- Slow-growing (3–6 weeks) colonies on Lowenstein-Jensen medium (faster new systems)
- Organisms produce niacin and are catalase-negative (68°C).
- No serodiagnosis

Microbacterium Tuberculosis

Treatment

- Multiple drugs critical to treat infection
- Standard observed short-term therapy for uncomplicated pulmonary TB (rate where acquired resistance <4%):
    - First 2 months: rifampin + isoniazid + pyrazinamide + ethambutol (RIPE)
    - Next 4 months: rifampin and isoniazid
- Streptomycin added for possible drug-resistant cases until susceptibility tests are back (if area acquired has >4% drug-resistant mycobacteria)
- For MDR TB, use 3−5 previously unused drugs: aminoglycosides, fluoroquinolones, thioamide, cycloserine, bedaquiline

Prevention

- Isoniazid taken for 9 months can prevent TB in persons with infection but no clinical symptoms
- Bacille Calmette-Guérin (BCG) vaccine containing live, attenuated organisms may prevent disseminated disease; not used in U.S
- UV light or HEPA filter used to treat potentially contaminated air

Objective

1. Discuss the etiology of tuberculosis.
2. Discuss the common route for transmission of the disease.
3. Discusses the outline for treatment of tuberculosis.
4. Discuss the drugs used in the first & second line Regarding :
   - The mechanism of action.
   - Adverse effects.
   - Drug interactions.
   - Contraindications.
5. Discuss tuberculosis & pregnancy.
6. Discuss tuberculosis & breast feeding

Note :
Pyridoxine (Vit B6)
pyridoxine is the precursor for Vitamin B6 and should be prescribed with INH. Because INH is antagonist to Vitamin B6 and inhibit pyridoxine metabolism to its active form the metabolite Vitamin B6. as a result of that nerves are affected. (pyridoxine) is essential for neurological functions,

Note :
INH & Hepatitis
Hepatitis with INH, is age dependent; it is rare in persons younger than 20 years, risk increases with age & alcohol use. We should check liver function and enzymes before and during treatment.

Note :
Acetylating is a process of metabolism by adding acetyl group to enhance excretion of the drug, some or slow acetylators
- Fast acetylators → high toxic metabolites
- Slow acetylators individuals are genetically fast tors → neuropathy

Treatment : Anti-TB

Drugs combination is important to prevent development of drug resistance.
Periods of treatment is minimum 6 months.

1st line treatment:

	Isoniazid (INH)
Overview	○ Bacteriostatic works on resting bacilli ○ Bactericidal works on rapidly growing bacilli
Site of action	Intracellular & extracellular bacilli
MOA	○ **Inhibits** the synthesis of **mycolic acid**, an important component of mycobacterial cell wall. ○ **Penetrates** macrophages.
Clinical uses	○ Treatment of TB. ○ Treatment of **Latent TB** in patients **with Positive tuberculin skin test.** ○ **Prophylaxis** against active TB **in individuals who are in great risk.**
ADRs	○ Peripheral neuritis, i.e. loss pin & needles sensation in the feet. ○ Optic neuritis & atrophy***. ○ Hepatitis (toxic metabolites) ****.
Drug interaction	○ INH inhibits cytochrome P450 **2C19** isoform **(enzyme inhibitor).** It prevents the metabolism of drugs that are metabolized by 2C19 which leads to accumulation of these drugs and then toxicity ○ Slow & fast acetylators.

	Rifampin (Rifampicin) (RIF)
Overview	Bactericidal
Site of action	Intracellular & extracellular bacilli
MOA	Binds to bacterial DNA- dependent RNA polymerase enzyme & thus **inhibits RNA synthesis.**
Clinical uses	○ Treatment of TB. ○ Prophylaxis, such as in case of meningococcal & staphylococcal infections.
ADRs	○ Harmless red-orange discoloration of body secretions: saliva, sweat, urine, tears. ○ Hepatitis. Less common compared to INH. ○ Flu-like syndrome ○ Hemolytic anemia
Drug interaction	○ RIF strongly **induces** most cytochrome P450 isoforms **2C19,2C9,3A4.** ○ Clinically significant drug interactions: warfarin, methadone will be metabolized faster, therefore their activity is reduced.

Note :
Tell the patient about this effect can permanently stain contact lenses.

	Ethambutol
Overview	Bacteriostatic
Site of action	Intracellular & extracellular bacilli
MOA	Inhibits mycobacterial **arabinosyl transferase;** essential enzyme for mycobacterial cell wall synthesis ,thus disrupts the assembly of mycobacterial cell wall.
Clinical uses	Treatment of TB in combination with other drugs.
ADRs	○ Impaired visual acuity. ○ Red-green color blindness.
Contraindication	It is contraindicated in children under 5 years old.

Note :
Streptomycin
It should be preserved for severe cases only, never used as a first option. Streptomycin is added to first line regimens because patients that have previously been treated for TB are more likely to have developed some drug resistance.

	Streptomycin
Overview	Bactericidal
Site of action	Extracellular bacilli
MOA	**Inhibitor of protein synthesis** by binding to **30S** ribosomal subunit. It is an aminoglycoside; this is their mechanism of action.
Clinical uses	Injectable drug used in severe, life-threatening form of TB as meningitis, disseminated disease.
ADRs	○ Ototoxicity like vertigo & hearing loss may be permanent. ○ Nephrotoxicity. ○ Neuromuscular block.

	Pyrazinamide (PZA)
Overview	Bacteriostatic
Site of action	Intracellular bacilli
MOA	Pyrazinamide is converted to **pyrazinoic acid** (the active form) which **disrupts mycobacterial cell membrane metabolism & transport functions.**
Clinical uses	○ Mycobacterial infections mainly in multidrug resistance cases. ○ It is important in short course (6 months) regimen. ○ Prophylaxis of TB .
ADRs	○ **Hepatotoxicity.** ○ Hyperuricemia → gouty arthritis. ○ Drug fever & skin rash

Treatment : Anti-TB

2nd line treatment:

	Ethionamide
MOA	**Inhibit mycolic acid synthesis.**
Clinical uses	2ND line treatment of TB orally.
ADRs	○ Teratogenic. ○ Poorly tolerated due to severe gastric irritation & neurological manifestation.

Note :
Ethionamide
It causes deformities in the fetus, so it's contraindicated in pregnancy

	Aminosalicylic acid (PAS)
Overview	Bacteriostatic
MOA	**Inhibits folic acid synthesis** thus slows bacterial cell growth & multiplication.
Clinical uses	○ As a 2nd line agent is used in the treatment of chronic pulmonary & other forms of TB. ○ Help to slow development of resistance to other drugs, especially INH & streptomycin.
ADRs	○ GIT upset ○ Crystalluria

Treatment in pregnancy:

- Untreated TB represents a great risk to the pregnant woman & her fetus than the treatment itself.
- First line: INH, ethambutol & rifampicin drugs are given for 9 months in normal doses. **Streptomycin is not used** because it can cross the placenta.

Treatment in breastfeeding :

- It is not a contraindication to receive drugs, but caution is recommended.

Antituberculad Drugs

Combination drug therapy is the rule to delay or prevent the emergence of resistance and to provide additive (possibly synergistic) effects against *Mycobacterium tuberculosis.*

- The primary drugs in combination regimens are isoniazid (INH), rifampin, ethambutol, and pyrazinamide. Regiments may include 2-4 of these drugs, but in the case of highly resistant organisms, other agents may also be required. Backup drugs include aminoglycosides (streptomycin, amikacin, kanamycin), fluroquinolone, capreomycin, (marked hearing loss), and cycloserine (neurotoxic).
- Prophylaxis: usually INH, but rifampin if intolerant. In suspected multidrug resistance, both drugs may be used in combination.

Features of antitubercular drugs

Drug	Mechanism of action and resistance	Side effect
Isoniazid (INH)	• Inhibit myocolic synthesis • Produce requiring conversion by catalase • High level resistance-deletions in *kat*G gene (encodes catalase needed for INH bioactivation)	• Hepatitis (age-dependent) • Peripheral neuritis (use vitamin B6) • Sideroblastic anemia (use vitamin B6) • SLE in slow acetylatros (rare)
Rifampin	Inhibit DNA-dependent RNA polymerase (nucleic acid synthesis inhibitor)	• Hepatitis • Induction of P450 • Red-orange metabolites
Ethambutol	Inhibit synthesis of arabinogalactan (cell-wall component)	Dose-dependent retrobulbar neuritis → ↓visual acuity and red-green discrimination
Pyrazinamide		• Hepatitis • Hyperuricemia
Streptomycin	Protein synthesis inhibiton	• Deafness • Vestibular dysfunction • Nephrotoxicity

Objective

1. Understand that pneumonia is an inflammatory condition of the lung characterized by consolidation (solidification) of the pulmonary tissue.
2. Is aware of the pathogenesis of pneumonia and its classification which principally include bronchopneumonia, lobar pneumonia and atypical pneumonia.
3. Is able to appreciate the etiology and pathogenesis of lung abscess.

Note :
Streptomycin

- X-ray which shows lobe consolidation
- CBC. In CBC you not be able to see the histiocyte and macrophages in the circulation, so you won't see them in CBC. You will just notice an increase in neutrophils. If High Neutrophils bacterial pneumonia while if you notice high Lymphocytes Viral pneumonia
- ESR & CRP
- Sputum culture

Pneumonia

Definition

Pneumonia can be very broadly defined as **any infection** in the lung.

Predisposing factors :

- Old age.
- Diabetes and CVS.
- Debilitated diseases (rheumatoid arthritis, COPD, renal failure).
- **Immunologic deficiencies**, treatment with immunosuppressive agents, leukopenia, autoimmune disease (SLE).
- Chemotherapy.
- Retention and accumulation of secretions: e.g. cystic fibrosis and bronchial obstruction.
- Pulmonary congestion and edema.
- **Decreased function of alveolar macrophages**: by alcohol, tobacco smoke, anoxia, or oxygen intoxication.
- **Injury to the mucociliary apparatus**: by either impairment of ciliary function or destruction of ciliated epithelium e.g. cigarette smoke, inhalation of hot or corrosive gases, viral diseases, chronic diseases or genetic disturbances.
- **Loss or suppression of the cough reflex**: coma, anesthesia, neuromuscular disorders, drugs, or chest pain.

Portal of entry for most pneumonias is:

- Inhalation of air droplets
- Aspiration of infected secretions or objects
- Hematogenous spread from one organ to other organs can occur.

Respiratory tract infections are more frequent than infections of any other organ. Why?

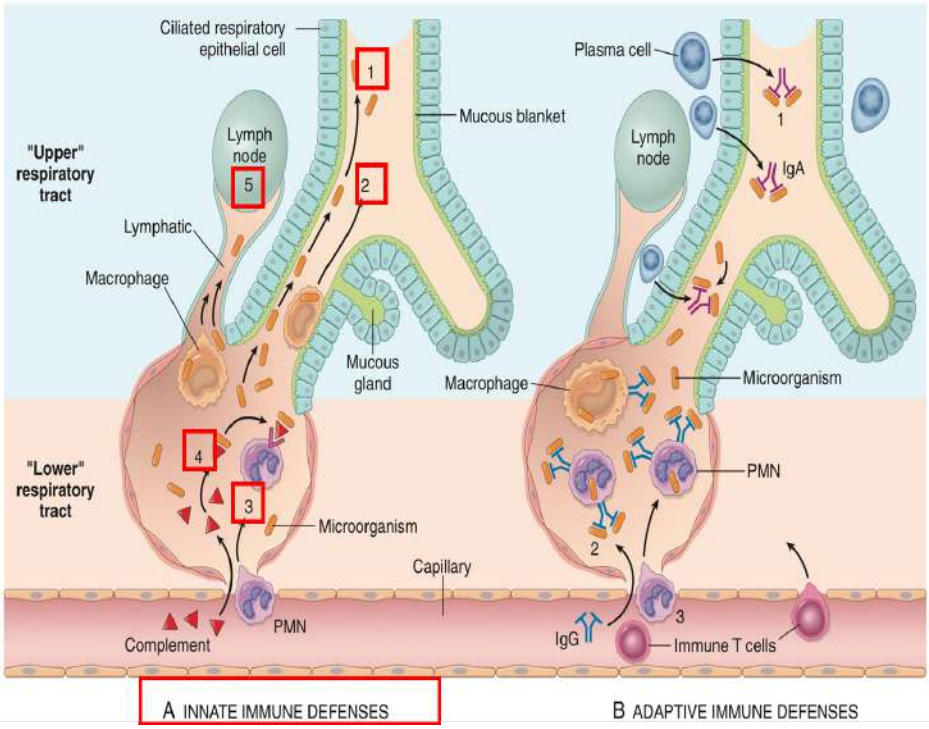
- The vulnerability of the lung to infection despite these defenses is not surprising because many microbes are airborne and readily inhaled into the lungs.
- Nasopharyngeal flora are regularly aspirated during sleep, even by healthy individuals.
- Lung diseases often lower local immune defenses.

Defense mechanisms in the respiratory system

Normally, the lung parenchyma remains sterile because of a number of highly effective immune and non-immune defense mechanisms that extend throughout the respiratory system from the nasopharynx to the alveolar air spaces. Failure in any of these mechanisms can lead to the development of pneumonia.

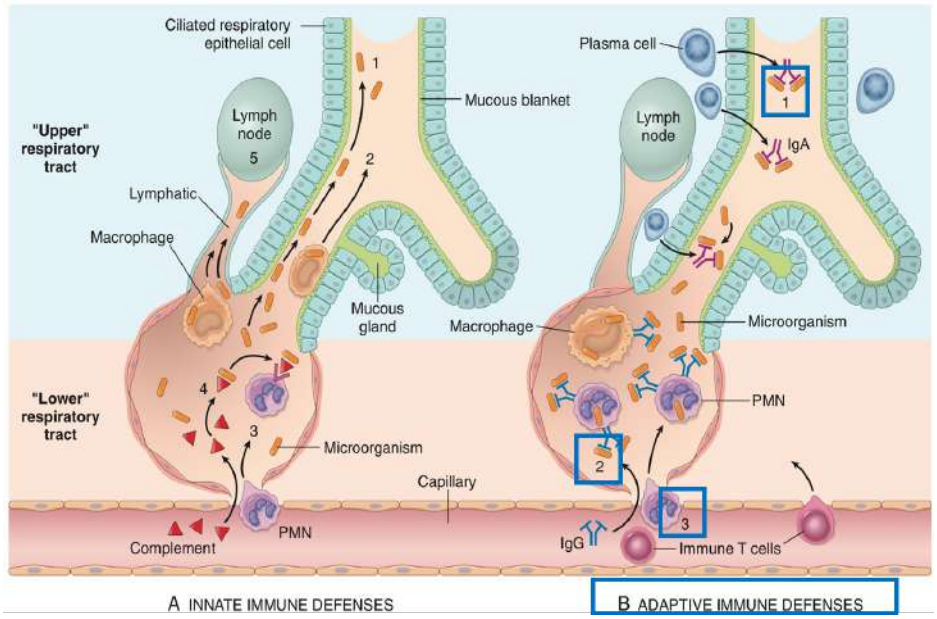
Note :
It causes deformities in the fetus, so it's contraindicated in pregnancy

Immunological defense mechanisms of the lung:



A. Innate immune defenses:

1. Inhalation of droplets.
2. Phagocytosis by alveolar macrophages to remove them from the air spaces.
3. Phagocytosis and killing by neutrophils recruited by macrophage factors.
4. Complement activation may occur through the alternative pathway, producing opsonin C3b to enhance phagocytosis.
5. Organisms (including those ingested by phagocytes), may reach the draining lymph nodes to initiate immune responses.



B. Adaptive immune defenses:

1. Secreted IgA can block attachment of the microorganism to epithelium in the upper-respiratory tract.
2. Serum antibodies (IgM, IgG) are present in the alveolar lining fluid, they activate the complement system by the classic pathway, yielding C3b (not shown). In addition, IgG is an opsonin.
3. The accumulation of immune T cells is controlling infections by viruses and other intracellular microorganisms.

- Patients with inherited or acquired defects in innate immunity or adaptive immunity have an increased incidence of infections with pyogenic bacteria. The lifestyle choices may also interfere with host immune defense mechanisms and facilitate infections. For example, cigarette smoke compromises mucociliary clearance and pulmonary macrophage activity, and alcohol impairs neutrophile function as well as cough and epiglottic reflexes.
- Patients with mutations in MYD88 (an adaptor protein required for signaling by Toll-like receptors), are extremely susceptible to severe necrotizing pneumococcal infections.
- Patients with congenital defects in IgA production are at increased risk for pneumonias caused by encapsulated organisms such as pneumococcus and H. influenzae.
- Defects in TH1 cell–mediated immunity lead mainly to increased infections with intracellular microbes such as atypical mycobacteria.

Pneumonia classification

Based on the etiology:

- **Streptococcus pneumoniae (Pneumococcal)**
- **Klebsiella pneumoniae:**

in chronic alcoholic people and who are debilitated.

- **Legionella pneumonia:**

Especially in immunocompromised post transplant. the bacteria loves water tanks or any wet things.

- **Haemophilus influenzae:**

is the most common bacterial cause of acute exacerbations of COPD.

- **Moraxella catarrhalis organisms:**

It is the second most common bacterial cause of acute exacerbation of COPD in adults.

- **Staphylococcal species.**
- **streptococcus pyogenes.**

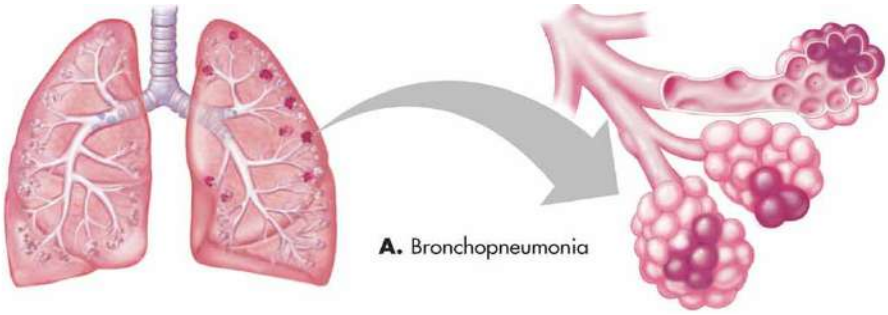
Note :
Bacterial pneumonias are classified according to the specific etiologic agent or, if no pathogen can be isolated, by the clinical setting in which the infection occurs.

Clinically:

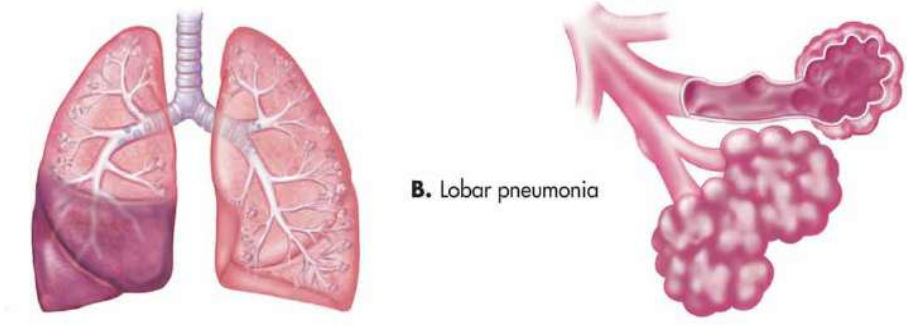
- Community Acquired acute Pneumonia.
- Community Acquired Atypical Pneumonia.
- Hospital Acquired (Nosocomial) Pneumonia.
- Aspiration Pneumonia
- Chronic Pneumonia
- Necrotizing Pneumonia and Lung Abscess
- Opportunistic pneumonias (Pneumonia in the Immunocompromised Host)

Based on the morphology:

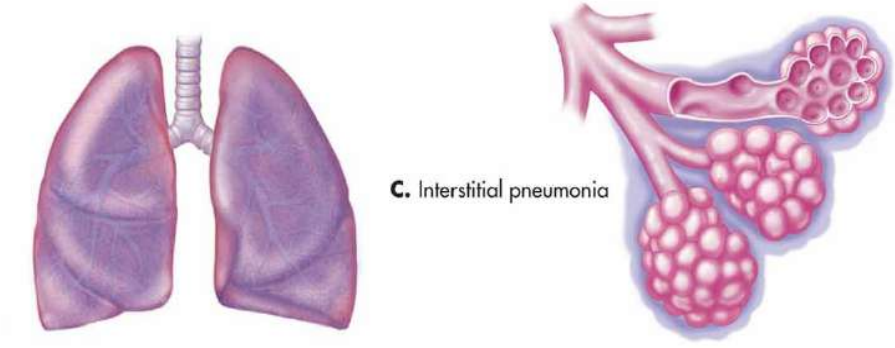
A. **Bronchopneumonia:** Multifocal and patchy Infection inflammation of the bronchi, and surrounding the alveoli. Streptococcus pneumoniae, Haemophilus influenza, Staphylococcus aureus represent an extension from preexisting bronchitis or bronchiolitis. Extremely common tends to occur in two extremes of life.



B. **Lobar pneumonia:** It happens to one lobe in the lung or sometimes two lobes. Streptococcus pneumonia, Acute bacterial infection of a large portion of a lobe or entire lobe. Classic lobar pneumonia is now infrequent.



C. **Interstitial (Atypical or Viral) pneumonia:** It doesn't affect the alveoli. It appears as linear density in X-RAY. It caused by Influenza virus in children, Mycoplasma pneumoniae. The major inflammatory is cell is Lymphocyte, so when we find neutrophils it means there's a secondary infection.



Community-Acquired Acute Pnemonia

Community-Acquired Acute Pneumonia can be Lobar or Bronchopneumonia, it's usually bacterial and can follow URT infections.

Causing organisms:

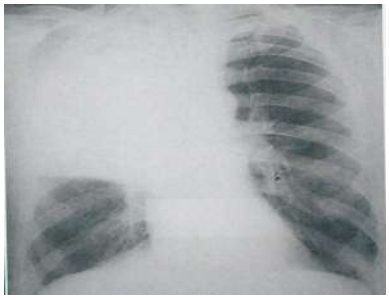
- **Most common:** Streptococcus pneumonia
- **Intravenous drug abuser:** Staphylococcus aureus
- **Others:** Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Legionella pneumophila, Klebsiella pneumoniae and Pseudomonas aeruginosa spp.

Signs & Symptoms

- Hypoxia, Pleuritic chest pain, chills & sudden high fever.
- Dyspnea & reduced air entry and dullness by percussion
- Productive rusty brownish cough may be with hemoptysis

Investigation:

- Culture
- Clinical
- Blood test: Leukocytosis with a predominance of neutrophils
- Radiology: In lobar pneumonia there is a radio opaque (consolidation) well circumscribed lobe. While in bronchopneumonia there are multiple small opacities usually basal and bilateral.



Note :
Bacterial pneumonia. Radiological chest x-ray showed consolidation of the upper lobe in Right lung

Complications:

- Tissue destruction and necrosis (abscess).
- Spread of infection to the pleura leading to empyema.
- Organization of the exudate which converts the lung into solid tissue.
- Bacteremic dissemination to heart valves (infective endocarditis), pericardium, brain (meningitis), kidneys, spleen or joints (arthritis).

Lobar Pneumonia

It happens to one lobe in the lung or sometimes two lobes. It is usually community acquired.

Causing organisms:

90-95% are caused by Streptococcus Pneumoniae (Pneumococci) type 1,2,3&7. Rarely by K. pneumoniae (in elderly), H. influenza, Pseudomonas, Proteus, Legionella pneumophila.

Stages of Lobar Pneumonia:

Stage I: Congestion hepatization, lung is heavy, boggy and red. The intra alveolar space is filled with fluid, few scattered neutrophils and numerous bacteria. There is vascular dilatation + exudate and fibrin.

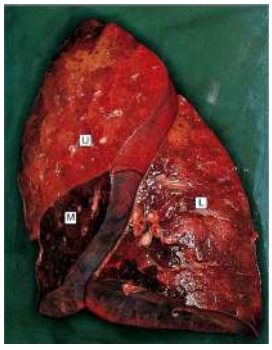
Stage II: Red hepatization, alveolar spaces are filled withneutrophils, red cells (congestion) and fibrin. Grossly the lung is firm/solid red and liver-like. The lung will look like the liver because of the red inflammatory exudate.

Stage III: Gray hepatization, here the red cells are reduced but neutrophils and fibrin are still present. Grossly the lung is still firm/solid and liver-like but gray to brown cut surface. More macrophages, less neutrophils and fibrin.

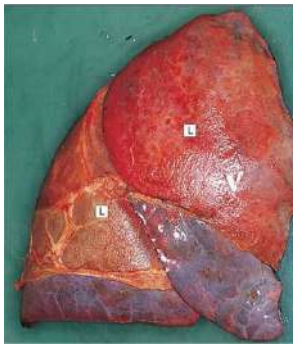
Stage IV: Resolution, exudates within the alveoli are being enzymatically digested, resorbed, ingested by macrophages or coughed up. Exudate is broken down ⍰ debris

Note :
Why it's called hepatization? Because of the consolidation it won't be spongy anymore, it will be firm and looks like the liver (Hepatic).

Red hepatization.
Alveoli are filled with fibrin, RBC's and neutrophils



Lobar pneumonia.
The upper (U) and lower (L) lobes are consolidated compared to the congested but uninvolved middle lobe (M).



Acute pleurisy in lobar pneumonia.
The pleural surfaces over consolidated lobes (L) are covered by a patchy, white, fibrinous exudate, causing acute pleurisy.

Bronchopneumonia

Multifocal and patchy inflammation of the bronchi, and surrounding the alveoli. It can affect more than one lobe in the same lung or both lungs. It can be caused by any organism.
Usually it involves lower lobes (basal) because there is a tendency of the secretions to gravitate into the lower lobes. Well developed lesions are 3 to 4 cm dry grey red ill defined nodules.

Etiology:

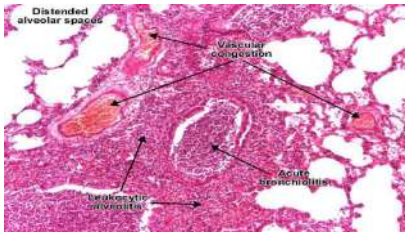
- Usually **Streptococcus pneumoniae**, also almost there's a **predisposing cause (DM,COPD,Age)**
- Staphylococci after URTI
- Haemophilus Influenzae In COPD
- Pseudomonas Aeruginosa in cystic fibrosis
- It can be secondary to TB
- Staphylococcus aureus is an important cause of secondary bacterial pneumonia after viral respiratory illnesses (e.g., measles in children and influenza in both children and adults)

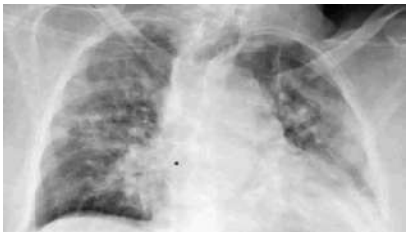
Diagnose:

Microscopy: neutrophil rich exudate filling the bronchi, bronchioles and adjacent alveolar spaces

BAL (Bronchoalveolar lavage) test: which is conducted with 3 steps:

1. Use a bronchoscope to reach the lungs then squirt a fluid and collect it for examination. When you perform BAL test you find soup bubble exudate but you don't find any inflammatory cells in the lungs. Why? Because he is immunosuppressed.
2. do **Silver Stain** -for the bacteria- and you find an organism called **pneumocystis jiroveci** (Fungus). Pneumocystis jiroveci is the most common cause of pneumonia in HIV patients.
3. test his blood and you find a decrease in WBC's level. Then you take the serum & do a molecular testing for HIV virus. The test will be positive for sure.





Multiple small opacities (consolidation)

Community-Acquired Atypical Pneumonia

Also called Primary atypical pneumonia or interstitial pneumonitis.

Note :
Streptomycin
It should be preserved for severe cases only, never used as a first option. Streptomycin is added to first line regimens because patients that have previously been treated for TB are more likely to have developed some drug resistance.

Characteristics & features:

- Characterized by patchy inflammation in the lungs confined to the alveolar septae and pulmonary interstitium and therefore it is called interstitial pneumonitis. .
- The major inflammatory cell is lymphocyte , so when we find neutrophils it means there's a secondary infection.
- It's called atypical pneumonia because it not the typical pneumonia in which the inflammation is primarily in the alveolar spaces.

Clinical course:

Extremely variable course. Patient usually present with flu like symptoms which may progress to life threatening situations. Identification of the organism is difficult and prognosis in uncomplicated patient is good.

Predisposing factors:

Malnutrition, alcoholism and any underlying debilitating disease.

How to diagnose it:

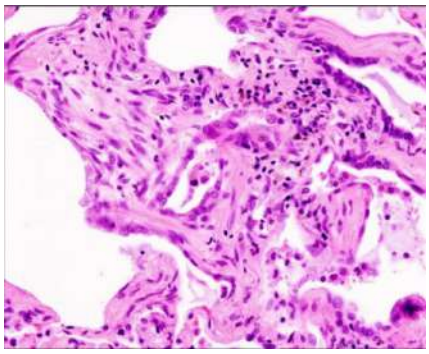
- By Cold **Agglutinin Test**. It's called cold because we do the test under a low temperature. The mycoplasma will lead to the formation of some **IgM** in the circulation. We take a blood sample from the patient and add RBC's form a sheep (lamb) to it. The RBC's of the lamb will **agglutinate** because of the IgM.
- **Serological** assays.
- Polymerase chain reaction (**PCR**).

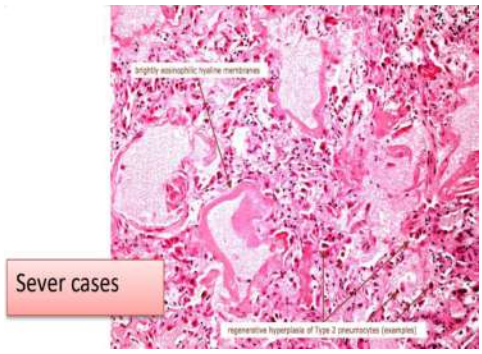
Gross view:

Pneumonic involvement may be **patchy**, or involve whole lobes bilaterally or unilaterally. Affected areas are red-blue congested.

Microscopy:

- Predominantly there is inflammation in the interstitium/alveolar wall.
- Alveolar septa are widened and edematous with mononuclear inflammatory infiltrate (and neutrophils in acute cases only)
- Severe cases: Intra-alveolar proteinaceous material with pink hyaline membrane lining the alveolar walls (diffuse alveolar damage)





Mycoplasma pneumonia

This is the most common form of interstitial (atypical) pneumonia; it usually occurs in children and young adults, and it may occur in epidemics. it can also cause Mycoplasma pneumonia (it's a community acquired disease).

Onset is more insidious compared to bacterial pneumonia and usually follows a mild, self-limited course.

Characteristics & features:

Characteristics include an inflammatory reaction confined to the interstitium, with no exudate in alveolar spaces, and intra-alveolar hyaline membranes.

How to diagnose it:

Diagnosis is by sputum cultures, requiring several weeks of incubation, and by complement-fixing antibodies. Mycoplasma pneumonia may be associated with nonspecific cold agglutinins reactive to red cells. This phenomenon is the basis for a facile laboratory test that can provide early diagnostic information.

Viral pneumonias

Viral pneumonias are the most common types of pneumonia in childhood. They are cause most commonly by:

- Influenza virus (children)
- Influenza A and B (adults)
- Adenoviruses
- Rhinovirus
- Respiratory syncytial virus
- SARS virus.

May also arise after childhood exanthems (viral eruptions) such as rubeola (measles) or varicella (chicken pox); the measles virus produces giant cell pneumonia, marked by numerous giant cells and often complicated by tracheobronchitis.

Coxiella burnetti

Q fever is the most common rickettsial pneumonia. It is caused by Coxiella burnetti. It may infect persons working with infected cattle or sheep, who inhale dust particles containing the organism, or those who drink unpasteurized milk from infected animals.

Chlamydia

Causes **Ornithosis (psittacosis),** which is transmitted by inhalation of dried excreta of infected birds.

Nosocomial pneumonia

(Hospital acquired Pneumonia)

Patient status	Causes
- Severe underlying conditions, e.g. **Immunosuppression**. - Prolonged antibiotic therapy. - Intravascular catheter. - Patients with mechanical ventilator.	Gram-negative organisms like Klebsiella, Pseudomonas aeruginosa and E.coli.

Aspiration pneumonia

A necrotizing pneumonia with fulminant clinical course, common complication (abscess) and frequent cause of death.

Patient status	Causes
- Debilitated patients - Comatose - Alcoholic - **Those who aspirated gastric contents.**	Chemical injury due gastric acid and bacterial infection (anaerobic bacteria admixed with aerobic bacteria, e.g. Bacteroides, Fusobacterium and Peptococcus).

Chronic pneumonia

Patient status	Causes
Often a localized lesion in **Immunocompetent person**, with or without regional lymph node involvement. In the immunocompromised, there is usually systemic dissemination of the causative organism, accompanied by widespread disease.	**There is typically granulomatous inflammation**, which may be due to bacteria (M.Tuberculosis) or Fungi (Histoplasma capsulatum, coccidioides immitis, blastomyces. **Tuberculosis** is the most important entity within the spectrum of chronic pneumonias.

Opportunistic pneumonia

Patient status	Causes
Immunosuppressed patients (AIDS, cancer patients and transplant recipients).	Cytomegalovirus , **Pneumocystis jiroveci** (carinii), Mycobacterium avium-intracellulare , Invasive aspergillosis , Invasive candidiasis and "Usual" bacterial, viral, and fungal organisms.

Effective methods of diagnosis are:

identify the organism in bronchoalveolar lavage fluids or in a transbronchial biopsy specimen. immunofluorescence antibody kits and PCR-based assays

Causative agents of pneumonia

Community-Acquired Bacterial Pneumonia

Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Legionella pneumophila
Enterobacteriaceae *(Klebsiella pneumoniae)* and *Pseudomonas spp.*
Mycoplasma pneumoniae
Chlamydia pneumoniae
Coxiella burnetii (Q fever)

Community-Acquired Viral Pneumonia

Respiratory syncytial virus, human metapneumovirus, parainfluenza virus (children); influenza A and B (adults); adenovirus (military recruits)

Nosocomial Pneumonia

Gram-negative rods belonging to *Enterobacteriaceae* (*Klebsiella* spp., *Serratia marcescens, Escherichia coli*) and *Pseudomonas* spp.
S. aureus (usually methicillin-resistant)

Aspiration Pneumonia

Anaerobic oral flora (*Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus*), admixed with aerobic bacteria (*S. pneumoniae, S. aureus, H. influenzae,* and *Pseudomonas aeruginosa*)

Chronic Pneumonia

Nocardia
Actinomyces
Granulomatous: Mycobacterium tuberculosis and atypical mycobacteria, *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis*

Necrotizing Pneumonia and Lung Abscess

Anaerobic bacteria (extremely common), with or without mixed aerobic infection
S. aureus, K. pneumoniae, Streptococcus pyogenes, and type 3 pneumococcus (uncommon)

Pneumonia in the Immunocompromised Host

Cytomegalovirus
Pneumocystis jiroveci
Mycobacterium avium complex (MAC)
Invasive aspergillosis
Invasive candidiasis
"Usual" bacterial, viral, and fungal organisms (listed above)

Lung Abscess

Definition:

Localized suppurative necrotic process within the pulmonary parenchyma.

Features:

- Tissue necrosis
- Marked acute inflammation

Causative organisms:

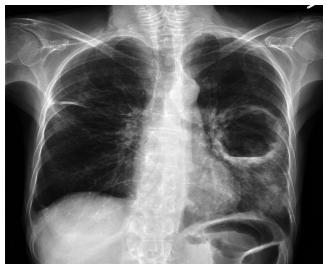
- Staphylococci
- Streptococci
- Gram-negative organisms
- Anaerobes

Pathogenesis:

- Can follow aspiration
- As a complication of bronchopneumonia
- Septic emboli
- Tumors or Direct infection

Clinical features:

- Prominent cough producing copious amount of foul smelling and bad-tasting purulent sputum.
- Change in position evoke paroxysm of cough.
- Fever malaise and clubbing of fingers.
- Radiology shows fluid filled cavity.



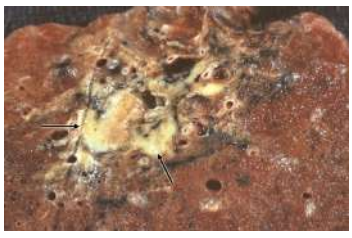
Single fluid filled cavity

Complications:

- Bronchopleural fistula and pleural involvement resulting in empyema which is accumulation of pus and purulent material in the pleural cavity.
- Massive hemoptysis, spontaneous rupture into uninvolved lung segments.
- Non-resolution of abscess cavity.
- Bacteremia could result in brain abscess and meningitis.

Prognosis:

With antibiotic therapy, 75% of abscess resolve. If it is not resolving, surgery is needed.



Abscess is filled with necrotic suppurative debris

Pulmonary Infections

What is pneumonia? What causes it?

- It's infection of lung parenchyma.
- **Causes:**
    - Lack of cough reflex
    - Damage to mucociliary escalator
    - Mucus plugging

What are presentation of pneumonia?

- Fevers and chills (organism usually leak out to blood)
- Cough with yellow-green (pus) or rusty (blood) sputum
- Tachypnea with pleuritic chest pain (inflammation produces bradykinin and PGE2 which causes pain)
- Decreased breath sounds and dullness to percussion (loss of air volume due to exudates will result in dullness to percussion)
- Elevated WBC count (due to infection)

How do you diagnose pneumonia?

- X-ray
- Blood culture/ sputum stain and culture

What are patterns of pneumonia seen on X-ray?

Lobar pneumonia	Bronchopneumonia	Interstitial pneumonia (aka atypical pneumonia)
Affects whole lobe	Affects area around bronchioles (mostly multifocal)	Inflammation of interstitium without consolidation of air sacks (see increased lung markings in X-ray)
Cause is mostly bacterial	Cause is mostly bacterial	Called atypical because need special media to grow the bacteria. Viruses also cause it
Most common cause: • Strep. Pneumoniae (95%) • Klebsiella pneumoniae • H influenziae		Bacterial causes: • Mycoplasm pneumoniae • Chlamydophilla • Legionella (pathoma puts legionella in broncho)
Treat: ceftriaxone		Treatment:

Pulmonary Infections

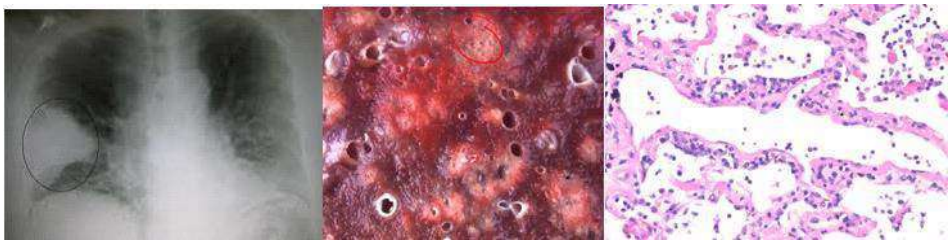


Fig : lobar pneumonia (right), bronchopneumonia (middle), interstitial pneumonia (left). Note lack of alveolar Exudate in interstitial pneumonia

Lobar pneumonia Bacteria	Association
Strep pneumo	Most common cause of community acquired pneumonia
Klebsiella pneumoniae	• enteric flora that's aspirated. • Common seen in alcoholics, nursing home pt. • Bacteria has thick mucoid capsule, so see currant jelly sputum. • Often complicated by **lung abscess**

Broncho pneumonia bacteria	Association
Staph aureus	• **Most common cause of secondary pneumonia** (pneumonia superimposed on viral upper respiratory tract infection) • Often complicated by **abscess or emphyema** (free pus in pleural space)
Haemophilus influenzae	• **Common cause of secondary pneumonia** • Associated with **COPD**
Pseduomonas aeruginosa	Associated with **cystic fibrosis patients**
Moxarella catarrhalis	• Associated with **COPD** • Community acquired
Legionella pneumophila	• Transmitted from water source • Associated with **COPD** and immunocompromised states • Intracellular organism visualized by silver stain • Pt. Presents with pneumonia, diarrhea, and hyponatremia

Atypical pne organism	Association
Mycoplasma pneumoniae	• **Most common cause of atypical pneumonia** • Affects young adult in close quarters (military recruits, dorm students) • Complications: **autoimmune hemolytic anemia** (IgM against I antigen on RBC), erythema multiforme
Chlamydia pneumoniae	**2nd most common** cause of atypical pneumonia in young adults
Respiratory syncytial virus (RSV)	Most common cause of pneumonia in **infants**
Cytomegalovirus (CMV)	Associated with **posttransplant immunosuppressive therapy**
Influenza virus	• Commonly seen in **elderly**, immunocompromised, or people with preexisting lung disease • **Increases risk for S aureus or H influenza secondary pneumonia**
Coxiella burnetti	• Pneumonia with high fever (Q fever; generally, pneumonia has low fever) • Associated with farmers and veterinarians • Coxiella is different from rickettsia in 3 ways: causes pneumonia, does not require arthropod for transmission (transmitted as spores), does not produce rash

What are four classic phases of lobar pneumonia?

- Congestion - due to edema
- Red hepatization - due to neutrophil and RBC exudate. Hepatization because previously spongy lung is now tough due to fluid
- Grey hepatization - breaking down of RBC makes lung gray.
- Resolution - lung tissue is regenerated by type II pneumocytes

What is aspiration pneumonia? What are it's causes? What's it's presentation?

- Seen in patients at risk for aspiration (ex - comatose, alcoholics)
- Causes: anaerobic bacteria of oropharynx:
  - Bacteroides
  - Fusobacterium
  - Peptococcus
  - Kliebsiella (is it anaerobic?)
- Classic presentation:
  - Right lower lobe abscess

Objective

1. Define the terms, pneumonia, community acquired pneumonia, health care associated pneumonia (HCAP) and ventilator associated pneumonia (VAP).
2. Describe the pathogenesis of the health care associated pneumonia (hospital associated pneumonia) and VAP.
3. Classify HCAP according to the time of onset & Name the different causative bacterial agents
4. Classify and describe types of VAP.
5. Recognize the ways by which VAP is prevented.
6. Describe the different chemotherapeutic antimicrobial agents used for the treatment of health care associated pneumonia.
7. Evaluate response to treatment and recognize reasons for failure of treatment

Pneumonia

Definition: infection of the pulmonary parenchyma.

Types:

- **Community acquired pneumonia:**

Acquired in the community. The organisms causing it usually susceptible to antibiotics.. Example: streptococcus pneumonia.

- **Health care associated pneumonia (Nosocomial pneumonia):** Acquired at least 48 hours (and not incubating) after admission to health care institutions. The organisms causing it usually resistant to antibiotics. Example: Pseudomonas Aeruginosa. If the symptoms occur before 48 hours, then the infection is acquired from the community not the hospital.
  - Hospital Acquired Pneumonia (HAP)
  - Ventilator Associated Pneumonia (VAP): in patients with assisted respiration (mechanical ventilation) for a period at least 48 hours.

Epidemiology of Nosocomial Pneumonia :

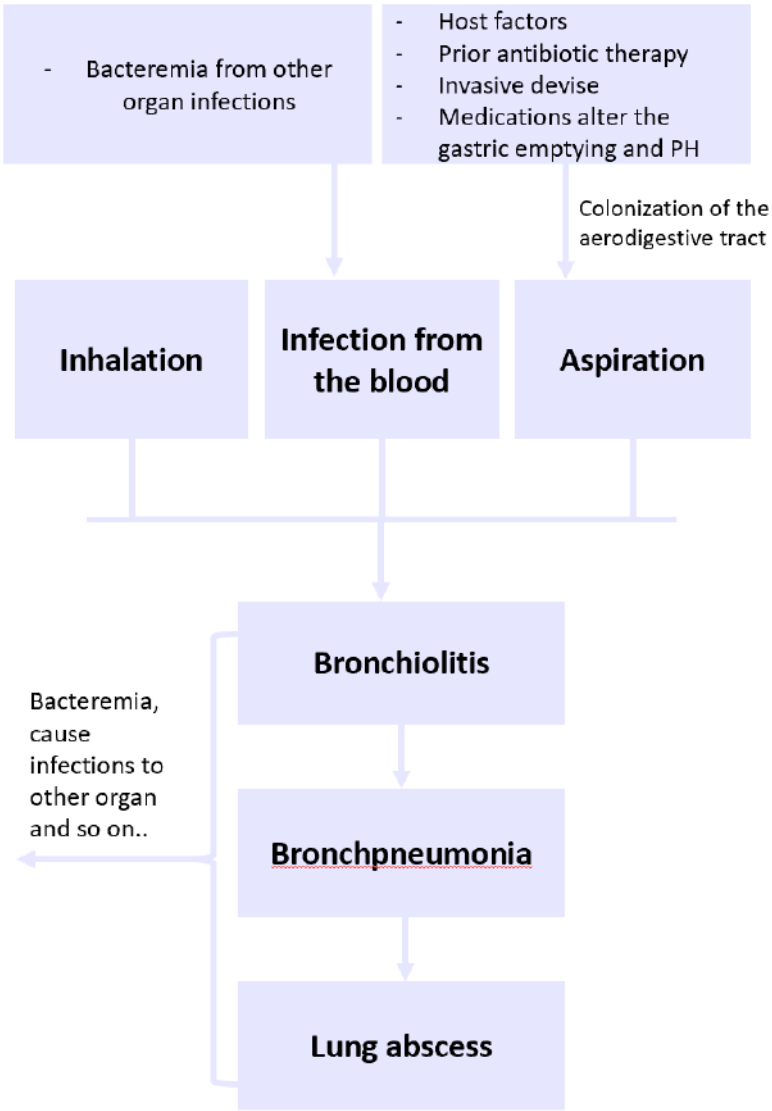
- Nosocomial pneumonia is the **2nd** most common hospital-acquired infections after urinary tract infection
- Nosocomial pneumonia is the **leading cause** of death from hospital-acquired infections.
- The incidence of nosocomial pneumonia is highest in **ICU** patients.
- The incidence of nosocomial pneumonia in ventilated patients is 10-fold **higher** than non-ventilated patients.
- The reported crude **mortality** for HAP is 30% to greater than 70%.

Pathogenesis of Nosocomial Pneumonia

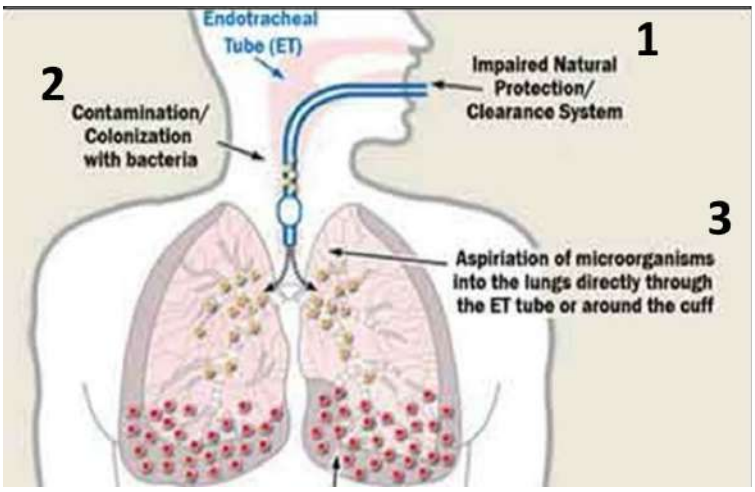
For **pneumonia** to occur, at least **one of the following three conditions must occur**:

1. Significant impairment of host defenses.
2. Introduction of highly virulent organisms into the lower respiratory tract.
3. Introduction of a sufficient-size (high amount) inoculum to overwhelm the host's lower respiratory tract defenses.

The introduction caused most commonly by microaspiration of oropharyngeal secretions colonized with pathogenic bacteria.



Pathogenesis of Ventilator Associated Pneumonia:



1. Mechanical ventilation prevents mechanical clearance by cough and the mucociliary escalator.
2. Bacterial colonization of the aerodigestive tract.
3. Aspiration of contaminated secretion into the Lower airway.

Prevention For VAP:

When we have patients with assisted respiration, we should do some of these procedures to prevent VAP:

A. By oral decontamination:

By oral regimen: Gentamicin, Colistin,Vancomycin cream (treating oropharyngeal colonization could prevent VAP**)**

B. Non-pharmacologic strategies:

- Effective hand washing and use of protective gowns and gloves.
- Semirecumbent positioning to prevention of aspiration.
- Avoidance of large gastric volume.
- Oral (non-nasal) intubation.
- Continuous subglottic suctioning.
- Humidification with heat and moisture exchanger**.**

C. Pharmacologic strategies:

- Stress-ulcer prophylaxis.
- Combination antibiotic therapy.
- Prophylactic antibiotic therapy.
- Chlorhexidine oral rinse.
- Prophylactic treatment of neutropenic patients Vaccines.

Classification of nosocomial pneumonia:

By Classifying Pneumonia according to the onset, we can identify the group of organisms causing it.

A. **Early-onset nosocomial pneumonia:** Occurs during the first 4 days of admission.
- S. pneumonia
- Methicillin sensitive S.Aureus
- H.Influenza
- Anaerobes

B. **Late-onset nosocomial pneumonia:** occurs more than 4 days of admission.
- Gram negative organisms like: Pseudomonas aeruginosa, Acinetobacter.
- Enterobacteriaceae like: Klebsiella, Enterobacter, serratia.
- Methicillin resistance S.Aureus

In the case of VAP, the Classification is:

The same Principle applied to VAP , but we start counting the days of The onset of the disease **from the tracheal intubation**, not from the admission to the hospital.

A. **Early-onset VAP:** within 48-72 hours **after tracheal intubation.**

B. **Late-onset VAP:** after 72 hours **after tracheal intubation.**

Causative Agents:

A. Enteric Gram negative bacilli:

Most frequently in patients:

- With late-onset disease
- with serious underlying disease often already on broad-spectrum antibiotics. Prior use of broad-spectrum antibiotics and an immunocompromised state make resistant Gram-negative organisms more likely.

B. S. aureus:

Most frequently in patients:

- Ventilated patients after head trauma, neurosurgery and wound infection.
- Received prior antibiotics.
- Prolonged care in ICU.

Specially methicillin resistant S.aureus is commonly in patients who:

- Received corticosteroids.
- Undergone mechanical ventilation >5 days.
- Presented with chronic lung disease.

C. Pseudomonas aeruginosa , Acinetobacter

Most frequently in patients:

- With late-onset pneumonia.
- In ventilated patients.

The frequency of ICU-acquired P. aeruginosa carriage or colonization/infection was 23.4% at 7 days and 57.8% at 14 days.

D. Anaerobes:

Most frequently in patients:

- Predisposed to aspiration ..
- Anaerobes occurred more often with oropharyngeal intubation than nasopharyngeal intubation.

Treatment of Nosocomial Pneumonia:

Most initial therapy is empiric , because the pathogen is not identified or results are not available when antimicrobial decisions are made in most patients, so initially be treated with a broad- spectrum antibiotic regimen aimed at covering all likely bacterial pathogens . This regimen should subsequently be narrowed, according to the result of culture.

American Thoracic Society has divided patients into three groups, each with a set of probable pathogens:

1. Mild to moderate HAP with **no** risk factor
2. Mild to moderate HAP **with** risk factor
3. A. severe HAP, early-onset with **no** risk factor
3. b. severe HAP, late-onset or **with** risk factor

Mild to moderate HAP, monotherapy has been shown to be effective. Severe HAP in which infection with resistant organisms is likely, **combination** therapy probably should be instituted until culture result are available.

- **Vancomycin + Linezolid** (better due to less nephrotoxicity) for Patients with **S. aureus infection.**
- **Combination** of Antipseudomonal drugs. There is controversy in the combination of Antipseudomonal drugs:
    - Antipseudomonal Beta-lactam with an Aminoglycoside. Synergy but potential nephrotoxicity.
    - Antipseudomonal Beta-lactam with a Fluoroquinolone. No synergy but reduced nephrotoxicity.

Response to the therapy:

If no clinical response is noted or deterioration occurs, we need to consider:

Infectious causes:

- Resistant pathogen
- Resistant pathogen
- Superinfection
- Unusual pathogens
- Lung abscess
- Extrapulmonary infection

Noninfectious events:

- Heart: congestive heart failure.
- Lung: fibroproliferative acute respiratory distress syndrome (ARDS), pulmonary emboli, Atelectesis.

Some Bacteria causing hospital acquired pneumonia

Gram-negative bacilli

Genus: pseudomonas

Genus Features

- Gram-negative rod
- Oxidase-positive, catalase-positive
- Aerobic (nonfermenting)

Species of Medical Importance: Pseudomonas aeruginosa

Pseudomonas aeruginosa

Distinguishing Features

- Oxidase-positive, Gram-negative rods, nonfermenting
- Pigments: pyocyanin (blue-green) and f luorescein
- Grape-like odor
- Slime layer
- Non–lactose fermenting colonies on EMB or MacConkey
- Biofilm Reservoir: ubiquitous in water Transmission: water aerosols, raw vegetables, lowers

Pseudomonas

- Gram (−), oxidase (+), aerobic Bacillus
- Blue-green pigments, fruity odor
- Burn infections—blue-green pus, fruity odor
- Typical pneumonia—CGD or CF

Patnogenesis

- Endotoxin causes inf lammation in tissues and gram-negative shock in Septicemia
- Pseudomonas exotoxin A ADP ribosylates eEF-2, inhibiting protein synthesis (like diphtheria toxin)
- Liver is primary target
- Capsule/slime layer allows formation of pulmonary microcolonies; difficult to remove by phagocytosis

Disease(s)

- Healthy people: transient GI tract colonization (loose stool 10% popu- lation); hot tub folliculitis; eye ulcer (trauma, coma, prolonged contact wear)
- Burn patients: GI tract colonization → skin → colonization of eschar→ cellulitis (blue-green pus) → septicemia
- Neutropenic patients: pneumonia and septicemia (of t en superinfection, i.e., infection while on antibiotics)
- Chronic granulomatous disease: pneumonias, septicemias (Pseudomo-nas is catalase-positive); [diabetic] osteomyelitis (diabetic foot)
- Otitis externa: swimmers, diabetics, those with pierced ears
- Septicemias: fever, shock ± skin lesions (black, necrotic center, erythematous margin, ecthyma gangrenosum)
- Catheterized patients: urinary tract infection
- Cystic fibrosis: early pulmonary colonization, recurrent pneumonia;always high slime-producing strain

Some Bacteria causing hospital acquired pneumonia

Diagnosis: Gram stain and culture

Treatment: antipseudomonal penicillin and an aminoglycoside or luoroquinolones

Prevention: pasteurize or disinfect water-related equipment, hand washing; and drug prompt removal of catheters; avoid lowers and raw vegetables in burn units

Acinetobacter baumannii

Distinguishing Features:
- oxidase-negative; non-fermenting; bioilm

Transmission: wound infection or nosocomial

Disease(s): wound infection and pneumonia in military personnel; 'Iraqibacter'

Treatment: highly drug-resistant; carbapenem or polymyxin

Genus: staphylococcus

Genus Features
- Gram-positive cocci in clusters
- Catalase positive (streptococci are catalase negative)

Species of Medical Importance
- S. aureus
- S. epidermidis
- S. saprophyticus

Staphylococcus aureus

Distinguishing Features
- Small, yellow Staphylococcus aureuscolonies on blood agar
- β-hemolytic
- Coagulase positive (all other Staphylococcus species are negative)
- Ferments mannitol on mannitol salt agar

Reservoir
- Normal flora
- Nasal mucosa (25% of population are carriers)
- Skin

Transmission
- Hands
- Sneezing
- Surgical wounds
- Contaminated food
    - Custard pastries
    - Potato salad
    - Canned meats

Some Bacteria causing hospital acquired pneumonia

Predisposing Factors for Infection

- Surgery/wounds
- Foreign body (tampons, surgical packing, sutures)
- Severe neutropenia (<50 0/μ L)
- Intravenous drug abuse
- Chronic granulomatous disease
- Cystic fibrosis

Pathogenesis

- Protein A binds Fc component of IgG, inhibits phagocytosis
- Enterotoxins: fast acting, heat stable
- Toxic shock syndrome toxin-1 (TSST-1): superantigen (see kaplan Immunology book for further explanation of a superantigen)
- Coagulase: converts fibrinogen to fibrin clot
- Cytolytic toxin (α toxin): pore-forming toxin, Panton-Valentine leukocidin (PVL), forms pores in infected cells and is acquired by bacteriophage; associated with increased virulence, MRSA strains
- Exfoliatins: skin-exfoliating toxins (involved in scalded skin syndrome [SSS]) and bullous impetigo

Diseases

Disease	Clinical symptoms	Pathogenicity factor
Gastroenteritis (food poising)–toxin ingested preformed in food	**2-6 hours** after ingesting toxin: nausea, abdominal pain, vomiting, followed by diarrhea	Enterotoxin A-E preformed in food
Infective endocarditis (acute) **(most common cause)**	Fever, malaise, leukocytosis, heart murmur (may be absent initially)	Fibrin-platelet mesh, cytolytic toxin
Abscesses and mastitis	Subcutaneous tenderness, redness and swelling; hot	Coagulase, cytolysins
Toxic shock syndrome	Fever, hypotension, **scarlatiniform rash that desquamates (particularly on palms and soles)**, multiorgan failure	TSST-1
Impetigo	Erythematous papules to bullae	Coagulase, exofoliatins
Scalded skin syndrome	Diffuse epidermal peeling	Coagulase, exofoliatins

Some Bacteria causing hospital acquired pneumonia

Disease	Clinical symptoms	Pathogenicity factor
Pneumonia	Productive pneumonia with rapid onset, high rate of necrosis, and high fatality; nosocomial, ventilator, postinfluenza, IV drug abuse, cystic fibrosis, chronic granulomatous disease, etc. Salmon-colored sputum	Coagulase, cytolysins
Surgical infection	Fever with cellulitis and/or abcesses	Coagulase, exofoliatins ± TSSTs
Osteomylitis (most common cause)	Bone pain, fever ± tissue swelling, redness, lytic bone lesions on imaging	Cytolysins, coagulase
Septic arthritis	Monoarticular joint pain; inflamation	Cytolysins, coagulase

Treatment

- Gastroenteritis is self-limiting.
- Nafcillin/oxacillin are drugs of choice because of widespread penicillinase-producing stains.
- Mupirocin for topical treatment.
- For methicillin-resistant Staphylococcus aureus (MRSA): vancomycin
- For vancomycin-resistant Staphylococcus aureus (VRSA) or vancomycin-intermediate S. aureus (VISA): quinupristin/dalfopristin

Pseudomonas - The suiters of pseudo Mona

1. Red theme - Gram Negative rod
2. Bathtub - Thrives in aquatic environments, hot tub folliculitis
3. Blue Ring - Oxidase Positive
4. Cat - Catalase Positive -
5. Chronic Granulomatous Disease heightened risk
6. Blue Green on tub - Produces a blue green pigment when plated may even turn wounds blue. It's from Pyocyanin and pyoverdin
7. Grapes being eaten - Fruity grape like odor
8. Air bellow Billowing the flames - Obligate Aerobe
9. Nurse pouring chlorine to remind us of the dysfunctional channel of CF patients - Most common Gram Neg Nosocomial Pneumonia, respiratory failure in CF patients. Chlorine channels in CF
10. Nurse Coughing – Causes pneumonia
11. Mortar and pestle w/ Fish bones - Osteomyelitis in the IV drug users and Diabetics.
12. Glass Capsule - Encapsulated
13. Maid on fire - Burn patients are especially susceptible.
14. Chamber Pot - Indwelling catheter infections from UTI's, chamber pot, nosocomial UIT's
15. Pruritic folliculitis (Hot tub folliculitis)
16. Dalmatian Dog - Can lead to ecthyma gangrenosom (black spots on the Dalmatian)
17. ear trumpet maid listening - Otitis Externa (swimmers ear)
18. 1st suiter in green - Exotoxin A - Ribosolation of elongation factor 2, leads to inhibition of protein synthesis and cell death
19. Piper suiter and Suiter with a Sai and flower - Treatment - Piperacillin (penicillin) , aminoglycosides and Fluoroquinolones

SKETCHY CORNER

Staphylococcus (grape like) **aureus** (gold in color) – The golden staff of Moses

1. Moses Robes are violet – Gram Positive cocci
2. Cat – Catalase Positive
3. Parting of the red sea – Coagulase Positive (will change fibrin to fibrinogen)
4. Bright red B lightbulb – Beta Hemolytic
5. Tail man – Ferments Mannitol Salt Agar turns yellow.
6. Large letter A on Moses Staff – Protein A, Main virulence factor on staph aureus. Protein A is a component of S. Aureus cell wall and it can bind to the FC region of antibodies and this will prevent compliment from occurring. Preventing opsonization and phagocytosis.
7. Nose missing from the sphinx – S. Aureus will colonize the nares
8. Guy pulling the camel down to his knees
    a. Coughing – Pneumonia
    b. Patchwork quilt – Patchy infiltrate on x-ray
    c. Icosahedron shaped lamps – Icosahedron shaped capsule of the virus that will infect after a S. Aureus infection.
    d. Bandages on the knees – S. Aureus is the most common cause of Septic Arthritis in adults.
    e. Humps with red cloth – Really large erythematous abscesses
9. Spooked camel running to the edge of the cliff – Rapid onset that just happened out of nowhere
    a. Clutching chest with hearts – Rapid onset Bacterial Endocarditis
    b. Mortar and pestle – IV drug use
    c. 3 pyramids in background – Tricuspid valve endocarditis
    d. 2 Fish bones – most common cause of osteomyelitis in adults
10. Bald man w/o turban that is all red – Scalded skin syndrome mediated by a protease
    a. Super Cape on Man - Toxic Shock Syndrome, commonly caused by leaving a bandage in or a tampon, causes nonspecific binding of MHC II to T cell receptors causing over reaction and Cytokine storm.
11. Running Camel with woman holding her mouth – Leads to Food Poisoning. This one is die to preformed toxins not the actual organisms. Usually from meats and mayonnaise. Also comes with salad and cream filled pastries. Usually in 6 hours they will be sick
12. Pharaoh raising hand showing mercy – MRSA – resistant to penicillin Binding proteins
    a. Anubis building pyramids – altered builders of the pyramid signifying altered cell walls
13. Van or Caravan – Vancomycin, TXT for S. Aureus.
14. Nafcillin – TXT for methicillin sensitive S. Aureus *Naf for Staph

SKETCHY CORNER

Objective

1. Discuss the epidemiology and pathophysiology of pneumonia and CAP
2. Explain the different classifications of pneumonia
3. Recognize clinical presentations associated with CAP
4. Discuss the diagnosis and treatment of CAP
5. Identify common etiological agents causing CAP and discuss their laboratory work up
6. Discuss virulence factors and prevention of Streptococcus pneumoniae

Pneumonia

Definition:

It's is an infection that leads to inflammation of the **parenchyma** of the lung (the alveoli) → consolidation and exudation.

Epidemiology:

Overall the rate of CAP 5-6 cases per 1000 persons per year. Mortality 23% – High, especially **in old people**. Almost 1 million annual episodes of CAP in adults > 65 years in the US.

Risk factors :

- **Age < 2yrs and > 65yrs**
- Alcoholism and Smoking
- **Asthma and COPD**
- Aspiration
- Dementia
- Prior influenza
- Immunosuppression and HIV
- Institutionalization
- Recent hotel: Legionella
- Travel, pets, occupational exposures- birds owner (C.psittaci)

Note :
Aspiration means inhaling the secretion of nasopharynx to the lung directly which is abnormal. the person might have aspiration when they lose their conscious like alcoholic and intubation.

Note :
Histology:
- Fibrinopurulent alveolar exudate is seen in acute bacterial pneumonias.
- Mononuclear interstitial infiltrates in viral and other atypical pneumonias.
- Granulomas and cavitation seen in chronic pneumonias.

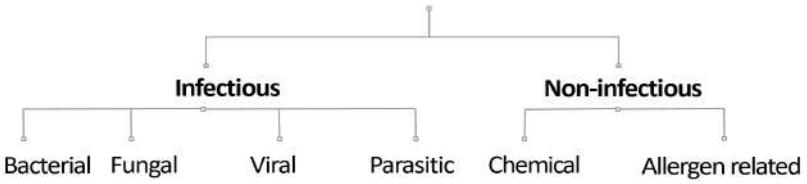
Course of disease:

It may present as:
- Acute, fulminant clinical disease → very severe.
- Chronic disease with a more prolonged course.

Etiological agents:

- **Two factors involved in the formation of pneumonia:**

1. Pathogens
2. Host defenses



Community Acquired Pneumonia

Definition:

pneumonia acquired outside of hospitals or extended-care facilities for >14 days before the onset of symptoms.

Causative organisms:

- Strep pneumonia (most common cause of CAP) = 48%
- Viral (most common cause of URTI) = 23%
- Atypical organ: mycoplasma pneumonia, Legionella pneumophila, Chlamydia pneumophila =22%
- Haemophilus influenza (Gram -ve coccobacilli) =7%
- Moraxella catarrhalis (Gram -ve diplococci) = 2%
- Staph aureus (Gram +ve cocci in clusters) = 15%
- Gram –ve organs: mainly in hospital acquired pneumonia =14%
- Anaerobes

Typical pneumonia

The onset is acute. (2-3 days). Prior viral upper respiratory infection.

Causative organisms:

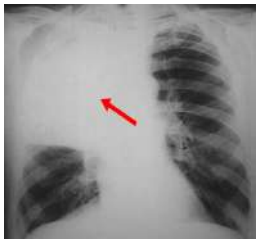
- Streptococcus pneumoniae → lobar pneumonia
- Haemophilus influenzae
- Moraxella catarrhalis
- S.aureus
- Gram-negative organisms

Clinical features:

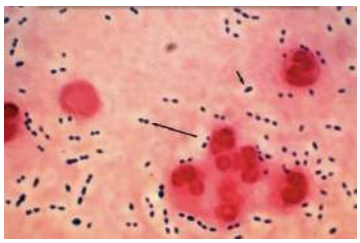
- **Respiratory symptoms:** Fever, Shaking chills, Shortness of breath, Chest pain or pleurisy (happens during inspiration they cannot take a full breath because of the pain).
- Cough with sputum production (rusty-sputum)

Diagnosis:

- **Clinical:** History & physical
- **X-ray examination**
- **Laboratory:** CBC → leukocytosis, seputum, Gram stain- 15% → Culture, Blood Culture 5-14%, Pleural Effusion Gram+culture.



upper lobe lobar pneumonia



Pneumococcpneumonia

Culture

Streptococcus pneumonia

The most common bacteria causes CAP. It's a Gram-positive diplococci.

- Alpha hemolytic streptococci
- Catalase negative
- Normal flora of upper respiratory tract in 20- 40% of people

Note :
Sensitive to Optochin
We use this test to differentiate between the Alpha hemolytic organisms S.pneumonia which is sensitive and other Alpha organisms S.viridans which have resistance.
some drug resistance.

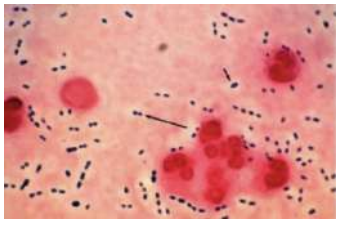
May cause:

- Respiratory infections
- Non respiratory infections
- Pneumonia, sinusitis, otitis
- Non respiratory infections
- Bacteremia, meningitis

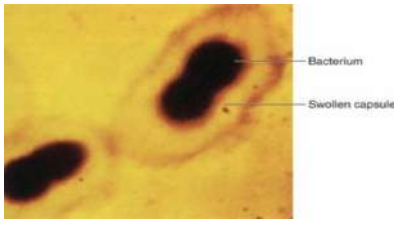
Note :
Pneumolysin
We use this test to differentiate between the Alpha hemolytic organisms S.pneumonia which is sensitive and other Alpha organisms S.viridans which have resistance.
some drug resistance.

Virulence factors:

- **Capsule:** More than 90 capsular types
- **Pneumolysin**
- **Autolysin** Similar to lysozyme.
- **Neuraminidase:** help them to spread.



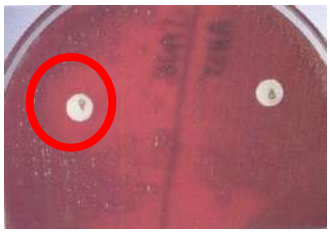
Pneumococcal pneumonia



Capsule

Characteristics:

- **Sensitive to Optochin:**
- Lysed by bile: usually mild soluble, after a while its will disappear.
- Prevention: vaccination.



1. zone of inhibition because it's sensitive to optochin .
2. desk to identify 100% that this a P.coccus

Atypical pneumonia

Features:

- Not detectable on gram stain
- Won't grow on standard media
- Most don't have a bacterial cell wall → Don't respond to β-lactams.
- Usually less severe than Typical Pneumonia with some exceptions.

Causative organisms:

- Chlamydia pneumonia
- Mycoplasma pneumonia
- Legionella spp
- Q fever (Coxiella burnetii)
- Psittacosis (Chlamydia psittaci)
- Viral (Influenza, Adenovirus, Rhinovirus)
- Pneumocystis Jiroveci

Note :
Often they present with extra-pulmonary manifestations:
Mycoplasma: otitis, non-exudative pharyngitis, watery diarrhea, erythema multiform, increased cold agglutinin titer
Chlamydophilla: laryngitis

Symptoms:

Insidious onset , and Usually mild in all typical organisms except L egionella it is the most severe

- Headache
- Malaise
- Fever
- Dry cough
- Arthralgia / myalgia

Signs:

- Minimal
- Low grade fever
- Few crackles

Note :
Rhonchi a continuous sound consisting of a dry whistle like noise with a lower pitch than that of a wheeze, produced in the throat or bronchial tube due to a partial obstruction

Diagnosis:

- X-ray
- CBC: Mild elevation WBC
- Urea & Electrolytes: Low serum Na →Legionella
- Liver Function Tests: ↑ ALanine aminotransferase and ↑ Anaplastic Lymphoma Kinase.
- Sputum Culture on special media: Buffered Charcoal Yeast Extract for Legionella
- Urine antigen for Legionella
- Serology for detecting antibodies
- DNA detection

Treatment:

- Macrolide
- Quinolones
- Tetracycline: B lactams have no activity

Treat for 10-14 days

Mycoplasma pneumonia

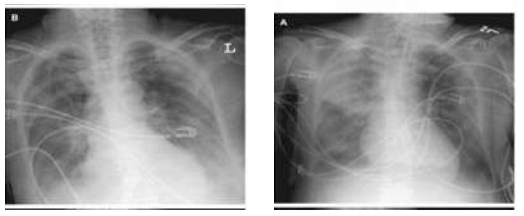
Features:

- Eaton's agent (1944) a bacterium of the genus (M. pneumoniae) that is the causative agent of primary atypical pneumonia.
- No cell wall thus no response to β-lactams.
- Common but rare in children and in > 65
- People younger than 40
- Crowded places like schools, homeless shelters, prisons
- Can cause URT symptoms
- Usually mild and responds well to antibiotics and can be very serious.

Symptoms & signs:

May be associated with extrapulmonary findings:

- Skin rash
- Hemolysis
- Myocarditis
- Pancreatitis
- Encephalitis



Mycoplasma pneumonia Cx-ray

Diagnosis:

- Serology
- Nucleic Acid Amplification Test
- Culture can be done but requires special media and slow grower (weeks)

Chlamydia pneumonia

Features:

- Obligate intracellular organism
- 50% of adults sero-positive
- Mild disease
- Subclinical infections are common
- 5-10% of community acquired pneumonia
- Have a cell wall but no peptidoglycan, thus no response to b-lactant.

Diagnosis:

- Serology
- Nucleic Acid Amplification Test

Psittacosis

Features:

- The cause is Chlamydia psittaci.
- Who affected are bird owners, pet shop employees, vets Parrots, pigeons and poultry.
- Birds often asymptomatic

Note :
This atypical bacterium commonly causes pharyngitis, bronchitis, coronary artery disease and atypical pneumonia in addition to several other possible diseases with other subtypes. So mainly the most important are (atypical pneumonia, urethritis and trachomatis).

Q fever (Coxiella burnetii)

Features:

- Pneumonia is acute form of infection
- Exposure to farm animals mainly sheep
- Spread by inhalation of infected animal birth products

Diagnosis:

- Serology

Legionella pneumophila

Features:

- The Most severe one. Can be very severe and lead to ICU admission.
- Can cause Legionnaires disease.
- Serious outbreaks linked to exposure to cooling towers. People usually get infected from the air conditioning system of hotels
- It's a waterborne bacteria, and usually target the immunosuppressed patient

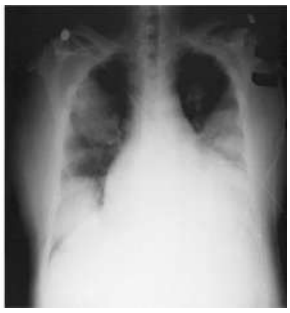
Symptoms & signs:

Can cause:

- Hyponatraemia: < 130 mMol and WBC < 15,000
- Bradycardia
- Abnormal Liver Function Tests
- Raised Creatine PhosphoKinase
- Acute Renal failure

Diagnosis:

- **Specimen:** sputum
  - Culture on specialized media (BCYE)
  - Direct Fluorescent Antibody
  - Nucleic Acid Amplification Test
- Urine antigen testing



Legionella presents on X-Ray as: interstitial pneumonia but can present as lobar or any other type

Pontiac fever

Features:

- Non pneumonic
- **Influenza like illness**
- **Self limiting**
- Related to exposure to environmental aerosols containing Legionella (potentially reaction to bacterial endotoxins).

Antibiotic Treatment of CAP

Factors to consider in selection of antibiotic:

- Co morbidities.
- Previous antibiotic exposure in last 3 months
- Severity. Outpatient management vs requiring inpatient admission vs requiring ICU.

	Outpatient, healthy patient with no exposure to antibiotics in the last 3 months	Outpatient, patient with comorbidity or exposure to antibiotics in the last 3 months	Inpatient: Not in ICU	Inpatient: in ICU
	- S. pneumonia - Atypical pathogens - Viral	- S. pneumonia - Atypical pathogens - Viral - Anaerobes - S. aureus	- S. pneumonia - Atypical pathogens - Viral - Anaerobes - S. aureus - coliforms	- S. pneumonia - Atypical pathogens - Viral - Anaerobes - S. aureus - Coliforms - Pseudomonas
Macrolides	√			
Doxycycline	√			
Levofloxacin		√	√	
B-lactam & Macrolide		√	√	√
B-lactam & Levo				√

Some Bacteria causing hospital acquired pneumonia

Streptococcus pneumoniae

Distinguishing Features

- α hemolytic
- Optochin sensitive
- Lancet-shaped diplococci
- Lysed by bile (bile soluble)

Reservoir: human upper respiratory tract pneumoniae

Transmission: respiratory droplets (not considered highly communicable; otencolonize the nasopharynx without causing disease)

Predisposing Factors

- Antecedent inf luenza or measles infection
- Chronic obstructive pulmonary disease (COPD)
- Congestive heart failure (CHF)
- Alcoholism
- Asplenia predisposes to septicemia

Pathogenesis

- Polysaccharide capsule is the major virulence factor
- IgA protease
- Teichoic acid
- Pneumolysin O: hemolysin/cytolysin: damages respiratory epithelium; inhibits leukocyte respiratory burst and inhibits classical complement fixation

Diseases

- Typical pneumonia: most common cause (especially in decade 6 of life); shaking chills, high fever, lobar consolidation, blood-tinged, “rusty” sputum
- Adult meningitis: most common cause; peptidoglycan and teichoicacids are highly inf lammatory in CNS; CSF reveals high WBCs (neu- trophils) and low glucose, high protein
- Otitis media and sinusitis in children most common cause

Laboratory Diagnosis

- Gram stain and culture of CSF or sputum
- Quellung reaction: positive (swelling of the capsule with the addition of type-specific antiserum, no longer used but still tested!)
- Latex particle agglutination: test for capsular antigen in CSF
- Urinary antigen test

Treatment: beta lactams for bacterial pneumonia; cetriaxone or cefotaxime for adult meningitis (add vancomycin if penicillin-resistant S. pneumoniae has been reported in community); amoxicillin for otitis media and sinusitis in children (erythromycin in cases of allergy)

Some Bacteria causing hospital acquired pneumonia

Prevention

- Antibody to capsule (>80 capsular serotypes) provides type-specific immunity
- Vaccine
    - Pediatric (PCV, pneumococcal conjugate vaccine): 13 of most common serotypes; conjugated to diphtheria toxoid; prevents invasive disease
    - Adult (PPV, pneumococcal polysaccharide vaccine): 23 of most common capsular serotypes; recommended for all adults age ≥65 plus at-risk individuals

Mycoplasma pneumoniae

Distinguishing Features

- Extracellular, tiny, flexible
- No cell wall; not seen on Gram-stained smear
- Membrane with cholesterol but does not synthesize cholesterol
- Requires cholesterol for in vitro culture Reservoir: human respiratory tract Transmission: respiratory droplets; close contact: families, military recruits, medical school classes, college dorms

Pathogenesis

- Surface parasite: not invasive
- Attaches to respiratory epithelium via P1 protein
- Inhibits ciliary action
- Produces hydrogen peroxide, superoxide radicals, and cytolytic enzymes, which damage the respiratory epithelium, leading to necrosis and a bad, hacking cough (walking pneumonia)
- M. pneumoniae functions as superantigen, elicits production of IL-1,IL-6, and TNF-α

Disease: walking pneumonia

- Pharyngitis
- May develop into atypical pneumonia with persistent hack (little sputum produced)
- Most common atypical pneumonia (along with viruses) in young adults

Diagnosis

- Primarily clinical diagnosis; PCR/nucleic acid probes
- ELISA and immunof luorescence sensitive and specific
- Fried-egg-shaped colonies on sterol-containing media, 10 days
- Positive cold agglutinins (autoantibody to RBCs) test is nonspecific and is positive in only 65% of cases

Treatment: erythromycin, azithromycin, clarithromycin; no cephalosporin or penicillin

Prevention: none

Some Bacteria causing hospital acquired pneumonia

Coxiella burnetii

Distinguishing Features:
- obligate intracellular, spore-like characteristics

Transmission: inhalation from dried placental material; zoonosis (sheep and goats); possible bioterrorism agent

Pathogenesis: obligate intracellular, live inside phagolysosomes

Disease(s): Q fever: atypical pneumonia, hepatitis, or endocarditis

Diagnosis: serologic detection of Phase II LPS antigen (for acute disease) and Phase I and Phase II LPS antigens (for chronic disease)

Treatment: doxycycline

Family: chlamydiaceae

Family Features
- Obligate intracellular bacteria
- Elementary body/reticulate body
- Not seen on Gram stain
- Cannot make ATP
- Cell wall lacks muramic acid

Genera of Medical Importance
- Chlamydia trachomatis
- Chlamydophila pneumoniae
- Chlamydophila psittaci

Chlamydia trachomatis

Distinguishing Features
- Obligate intracellular bacterium; cannot make ATP
- Found in cells as metabolically active, replicating reticulate bodies
- Infective form: inactive, extracellular elementary body
- Not seen on Gram stain; peptidoglycan layer lacks muramic acid

Reservoir: human genital tract and eyes

Transmission: sexual contact and at birth; trachoma is transmitted by hand- to-eye contact and lies.

Pathogenesis: infection of nonciliated columnar or cuboidal epithelial cells of mucosal surfaces leads to granulomatous response and damage

Some Bacteria causing hospital acquired pneumonia

Diseases

- STDs in U.S.
  - Serotypes D-K (most common bacterial STD in U.S., though overall herpes and HPV are more common in prevalence)
  - Nongonococcal urethritis, cervicitis, PID, and major portion of infertility (no resistance to reinfection)
  - Inclusion conjunctivitis in adults (with NGU and reactive arthritis)
  - Inclusion conjunctivitis a nd /or pneumonia in neonates/infants (staccato cough) with eosinophilic infiltrate
- Lymphogranuloma venereum
  - Serotypes L1, 2, 3 (prevalent in Africa, Asia, South America); painless ulcer at site of contact; swollen lymph nodes (buboes) around inguinal ligament (groove sign); tertiary includes ulcers, fistulas, genital elephantiasis
- Trachoma
  - Leading cause of preventable infectious blindness: serotypes A, B, Ba, and C
  - Follicular conjunctivitis leading to conjunctival scarring, and inturned eyelashes leading to corneal scarring and blindness

Diagnosis

- NAAT; DNA probes in U.S. (rRNA) and PCR
- Cytoplasmic inclusions seen on Giemsa-, iodine-, or f luorescent-antibody-stained smear or scrapings
- Cannot be cultured on inert media
- Is cultured in tissue cultures or embryonated eggs
- Serodiagnosis: DFA, ELISA

Treatment: azithromycin or doxycycline

Prevention: erythromycin for infected mothers to prevent neonatal disease; systemic erythromycin neonatal conjunctivitis to prevent pneumonia

KAPLAN CORNER

Some Bacteria causing hospital acquired pneumonia

Genus: legionella

Legionella pneumophila

Distinguishing Features

- Stain poorly with standard Gram stain; gram-negative
- Fastidious requiring increased iron and cysteine for laboratory culture (BCYE, buffered charcoal, yeast extract)
- Facultative intracellular
- **Reservoir**: rivers/streams/amebae; air-conditioning water cooling tanks
- **Transmission**: aerosols from contaminated air-conditioning; no human-to-human transmission

Predisposing Factors: smokers age >55 with high alcohol intake; immunosuppressed patients such as renal transplant patients

Pathogenesis: facultative intracellular pathogen; endotoxin

Disease(s)

- Legionnaires disease ("atypical pneumonia"): associated with air- conditioning systems (now routinely decontaminated); pneumonia; hyponatremia; mental confusion; diarrhea (no Legionella in GI tract)
- Pontiac fever: pneumonitis; no fatalities

Diagnosis

- Urinary antigen test (serogroup 1)
- DFA (direct f luorescent antibody) on biopsy, (+) by Dieterle silver stain
- Fourfold increase in antibody

Treatment: luoroquinolone (levoloxacin) or macrolide (azithromycin) with rifampin (immunocompromised patients); drug must penetrate human cells.

Prevention: routine decontamination of air-conditioner cooling tanks

Strep Pneumonia "the alpha knight tournament"

1. Purple Background - G+
2. α knight tournament – α hemolytic, partial hemolysis where the surrounding zone is a green hue
3. **Strep Pneumonia Knight**
4. Armor – Polysaccharide Capsule is major virulence factor
5. Chin is exposed – Optochin sensitive, optochin inhibits the growth of strep pneumo
6. Double Lance – Lancet shaped diplococci
7. Mud on horses legs - Bile soluble, meaning it does not grow in Bile
8. Rust Colored single lobe on chest – Rust colored sputum and lobar pneumonia
9. Squire mopping up muddy mess MOPS - Meningitides, Otitis Media, Pneumonia, Sinusitis
10. Number 1 sign – number one cause of all these diseases.
11. Cracked Shield with the symbol of IgA dimer molecule - Protease that cleaves IgA that allows invasion of mucosa reducing host defenses
12. Sickle - Removal of spleen leads to susceptibility of infection by encapsulated organisms like in sickle cell anemia.
13. Crows – azithromycin Macrolides
14. 3 Axes - Ceftriaxone
15. **Adults** in the **M**ezzanine, **Children** on the **G**round - 2 pneumococcal vaccines, adult is a 23 valiant polysaccharide vaccine, children is 7 valent but conjugated to a protein. Adults will have a T-Cell independent response creating IgM that does not last long. Adding the protein adds a more robust antigen response leading to a production of IgG in children.

Strep Viridians

1. No Armor – Not encapsulated
2. Jesters mask protects face including the chin – optochin resistant
3. Donkey with bile resistant boots – Bile resistant
4. Foul Yellow teeth on donkey – associated with dental carries
5. Deck of cards with plate shield - Synthesizes Dextran's from glucose which allows strep viridians to adhere to any fibrin from platelets that has been damaged in the heart.
6. Strep Sanguineous adheres to fibrin platelet aggregates in damaged heart valves, most commonly occurs in mitral valve.

SKETCHY CORNER

Mycoplasma pneumonia - "walking on thin ice"

1. No stain color - Gram indeterminate
2. No walls on the pond for the hockey game - No cell walls, like the pond, so cant appear on gram stain
3. Net with ringed structures resembling sterols - Cholesterol in the cell membrane, sterols in the membrane
4. Referee walking around with no issues - Atypical pneumonia because can't readily culture a microbe - walking pneumonia. X ray much worse than patients do clinically
5. Patchy collection of clouds in the sky -Patchy infiltrate in the x ray
6. Young players - Young adults, commonly in military recruits. Less than 30 y/o
7. Camouflage goalie <30 – military recruits <30
8. Hockey pucks that are stuck together - IgM molecules that agglutinate red blood cells in cold temperatures, lysis of RBC's
9. IgM Snowflakes - IgM
10. Do not EAT ON ice - Grown on eatons agar, "do not eat on ice"
11. Crows - Treatment - Macrolides - Zpack

SKETCHY CORNER

Coxiella burnetii - "Curly Q the Ram"

1. Causes Q fever -
2. Red Barn - Gram Negative
3. Pristine white - means that coxiella does not cause a rash, IE NO RASH
4. Exaggerated horns to look like curly Q's - q fever
5. Ram is never allowed to leave the barn - Obligate intracellular organism
6. Walnuts and Animal Droppings - Transmission - spore like structure that comes in animal droppings
7. Dust everywhere from the pissed off Ram - It gets into humans through aerosol transmission - outbreaks from farm animals to farmers or placental excretions
8. Coughing and hitting head on rafter - Clinical presentation - pneumonia and headache
9. Sick Farmer sweating profusely- Fever
10. **spots on the cow resemble a liver - Also causes hepatitis**
11. Antibiotics are not needed, self-limiting
12. Prevention is pasteurization of milk
13. Hemorrhage on fingers

SKETCHY CORNER

Chlamydia Trachomatis, Pneumonia, philapsittaci: the pirates of Calam Island

1. White island - Gram Indeterminate - does not gram stain
2. stuck on an island - Obligate intracellular bacteria -
3. Stuck on an island - Cannot create its own ATP which is why it is intracellular
4. "No mermaid sign" - Lack of muramic acid in the cell wall
5. Pearls outside of the cell - Elementary bodies - 1st stage of life cycle outside of the cell. This is the **INFECTIOUS** form Elementary enters the eukaryotic cell and are taken up by phagosomes. Elementary Enters
6. Pearl inside the clam - Reticulate body - 2nd stage and is active and multiply, aka the **DIVIDING** form. Reticular Replicates to form Inclusion Bodies seen under microscope in cells when infected. Reticulate Replicates
7. Pearls spread everywhere – inclusion bodies seen when under a microscope
8. Treasure chest of gems - Visualized using Giemsa stain
9. Gnats around treasure chest - Diagnose with NAAT test. Aka PCR.
10. Monkeys and pirate slapping the knee - Reiter's syndrome: reactive arthritis, cross react of antibodies fighting chlamydia hits knee or sacroiliac joint. "can't see, cant pee, cant climb a tree"
11. Symptoms of trachomatous – 3 types
    i. A-C: Blindness - Pirate is blind - Trachoma: leading cause of blindness in world
    ii. Hand shield sun from eye -Transmission: hand to eye contact, possibly from fomites

a. Mermaid at head of ship - D-K: STI
    i. **Scene takes place in water and leak in the ship - Most common Bacterial STI in US, watery discharge, Ghon has a mucopurulent discharge**
    ii. Flying the Jolley roger uterus flag - Can turn into PID w/o symptoms, ectopic pregnancies as well
    iii. Mermaid shielding babies eyes wearing a clamshell bra - Baby can get infection if mother has it during delivery giving it neonatal conjunctivitis and pneumonia. Baby will present w/ in 1-2 weeks with a possible cough (Staccato cough) or conjunctivitis. Gonorrhea will present 2-4 days

b. L1-L3: LGV
    i. Mermaid w/ barnacles around inguinal region Lymphogranuloma Venerum - infection of inguinal nodes, Presents as a tender lymphadenopathy with draining lymph nodes.

12. Clam Shell bra on adult mermaid - Chlamydia Pneumonia: Walking pneumonia, more common in the elderly
13. Parrot - Chlamydia Psittaci: Transmitted by Birds, causes pneumonia and transmitted by bird droppings
14. Treatment:

a. Crows - Macrolides - azithromycin
b. Bicycle wheel - Tetracycline -
c. Confection of Chlamydia and gonorrhea treat with cephtriaxone

SKETCHY CORNER

Legionella - "The SS cysteine joins the legion"

1. Red and Rusty ship due it to being gram neg - but visualized under silver stain
2. Silver Ship – Silver stain to visualize
3. Heaping piles of coal on the ship - Agar requirement is charcoal yeast extract in presence of cysteine and iron
4. SS Cysteine and Iron anchor – Cysteine and iron need to be added to agar
5. Pontiac car broke down - Pontiac Fever - fever and malaise usually is self-limiting
6. Sailor smoking - Legionnaire's Disease - common in smokers and elderly men
7. Blue print of the ships layout with lobar infiltrate - Atypical pneumonia patchy unilobed infiltrate
8. Sailor spilling salt into the sea - Clinical presentation - Hyponatremia - excess HNO3 ammonia Na. wasting salt
9. Falling paint can hitting sailor below - Neurologic symptoms, headache with confusion
10. Brown paint spilled over - Diarrhea
11. Sweating sailor - High fever over 104 F
12. Fresh Water
13. Sailor pissing in the river - Lab test to confirm - rapid urine antigen test to confirm
14. Crow or Sailor giving away a flower - Treat with macrolides and fluoroquinolones
15. Girl wearing the ring - Oxidase Positive
16. **Zinc Melloprotease is the main virulence factor, its cytotoxic and inhibits PMN production, inhibits superoxide reduction, deactivates il-1 and CD4 and TNF.**

SKETCHY CORNER

Objective

1. The types of respiratory tract infections (RTI).
2. The antibiotics that are commonly used to treat RTI & their side effects.
3. Understand the mechanism of action & pharmacokinetics of individual drugs.

Classification of Respiratory Tract Infections

Upper Respiratory Tract Infections:

Viruses:
Most URTIs are of viral etiology. Should NOT be treated with antibiotics. Rest and plenty of fluids, over the counter cold and pain relievers.

Bacteria: Mainly group A streptococcus and H. Influenza. Should treated by Antibiotics, type depends on:

- Type of bacteria.
- Sensitivity test.

Lower Respiratory Tract Infections

Costly and more difficult to treat.

Bronchitis: inflammation of major bronchi & trachea. Could be Acute, Chronic or Acute exacerbation of chronic bronchitis. The causes of could be Viruses or bacteria: H. Influenza, Streptococcus pneumonia & Moraxella catarrhalis.

Pneumonia: serious infection of bronchioles & alveoli. It divided into Community-acquired & Hospital-acquired. The causes could be Bacteria: S. pneumoniae (66%) & H. Influenza (20%).

Antibiotics commonly used in the treatment of RTIs

	Beta-lactam antibiotics (Penicillins)
Overview	- Amoxicillin-Clavulanic acid. Beta Lactams are sometimes combined with beta lactamase inhibitors such as: clavulanic acid. - Ampicillin-Sulbactam sulbactam, tazobactam, this is because some strains of bacteria have evolved into species that Piperacillin-Tazobactam can cleave beta lactam ring through an enzyme called beta lactamase. - Act on both gram +ve and gram –ve microorganisms.
MOA	- Inhibit bacterial wall synthesis through inhibition of peptidoglycan layer on the cell wall. - Bactericidal
Pharmacokinetics	- Given orally or parenterally - Not metabolized in human - Relatively lipid insoluble - Excreted mostly unchanged in urine - Probenecid slows their elimination and prolongs their half life by inhibiting the renal excretion of penicillin. - Half-life: 30-60 min (increased in renal failure)
Clinical uses	- URTIs & LRTIs
ADRs	- Hypersensitivity reactions nausea and vomiting as a start , followed by urticaria, laryngeal edema, and finally anaphylactic shock and cardiovascular collapse. - Diarrhea - Superinfections an infection that occurs as a result of killing the normal. - Nephritis flora along with the pathogen after using antibiotics (especially broad spectrum antibiotics) - Convulsions (after high I.V dose or in renal failure)

Beta-lactam antibiotics (Cephalosporins)

MOA	- Inhibit bacterial cell wall synthesis. - Bactericidal (similar to Penicillins) more stable than penicillins to β-lactamase.. - Classified into 3 generations.		
Generation	1st	2nd	3rd
Drug	Cephalexin	Cefuroxime, Cefaclor	Ceftriaxone, Cefotaxime, Cefixime
Route of administration	Orally	Orally well absorbed	IV
Spectrum	Gram +ve bacteria	Gram -ve bacteria	Gram -ve bacilli
Uses	URTIs	URTIs & LRTIs	Pneumonia
Pharmacokinetics	- Given parenterally & orally. - Relatively lipid insoluble (like penicillins). - Do not penetrate cells or the CNS except for 3rd generation. - Mostly excreted unchanged by the kidney (glomerular & tubular secretion). - Probenecid slows their elimination & prolongs their half lives. - Half-life: 30-90 min except ceftriaxone (4-7 hr).		
Clinical uses	- URTIs & LRTIs		
ADRs	- Hypersensitivity reactions. - Thrombophlebitis an inflammation that forms a blood clot which blocks a vein therefore injections are given slowly - Superinfections. - Diarrhea.		

	Macrolide (Erythromycin)	
Drugs	Clarithromycin	Azithromycin
MOA	- Inhibits bacterial protein synthesis by binding to 50S subunit of the bacterial ribosomal RNA. - They are bacteriostatic, but when used at higher concentration → bactericidal.	
Half life	6-8 hours	3 days
Dose	Twice a day	One dialy
Antibacterial Spectrum	More effective on G+ve bacteria	More effective on G-ve bacteria
Pharmacokinetics	- Stable at gastric acidity. - Inhibition cytochrome P450 system. - Metabolized in liver to active metabolites. - Biliary route is the major route of elimination. - Only 10-15% excreted unchanged in the urine.	- Stable at Gastric Acidity. - No effect on cytochrome P-430. - Undergo Some Hepatic Metabolism (inactive metabolite) - Biliary route Is The major route of elimination. - Only 10-15% excreted unchanged the urine
Clinical uses	Chlamydial & Legionella Pneumonia	
ADRs	- GI Disturbances: Nausea,Vomiting,abdominal cramps, diarrhea. - Hypersensitivity Reaction	

	Fluoroquinolones	
Drugs	Ciprofloxacin	Moxifloxacin Gatifloxacin
MOA	- Block bacterial DNA synthesis by inhibiting DNA Gyrase enzyme (an enzyme involved in DNA supercoiling).	
Dose	Twice a day	One dialy
Antibacterial Spectrum	G –ve bacteria highly active against Pseudomonas species	G –ve & G +ve. highly active against Pseudomonas species
Pharmacokinetics	- Given orally or parenterally. - Di & tri-valent cations interfere with its absorption. (divalent cation is a cation with +2 charge, like calcium, trivalent with +3 like aluminium). - Concentrate in many tissues (kidney, prostate, lung & bones/joints) which means it can treat infections in these organs. - Excretion mainly through the kidney. - Long half-life	
Clinical uses	- Acute exacerbation of chronic obstructive pulmonary disease. - Community-acquired pneumonia. - Legionella pneumonia	
ADRs	- GI Disturbances: Nausea,Vomiting,abdominal cramps, diarrhea. - Hypersensitivity Reaction	
Contraindicat-ions	- Not recommended for patients younger than 18 years. - Pregnancy & Breastfeeding Women	

Aminoglycosides

Drugs	Gentamicin
MOA	- Bactericidal antibiotics. - inhibits protein synthesis by binding to 30S ribosomal subunits
Antibacterial Spectrum	Only active against Gram –Ve Aerobic organisms
Pharmacokinetics	- Given parenterally (IM, IV) poorly absorbed orally. - Cross placenta contraindicated in pregnancy, may cause hearing loss. - Excreted unchanged in urine. - Half-life: 2-3 h & increased to 24-48 h in renal impairment
Clinical uses	evere infection caused by gram -ve organisms
ADRs	- Ototoxicity - Nephrotoxicity - In very high doses → neuromuscular blockade that results in respiratory paralysis

Note :
Other types of Aminoglycosides: Neomycin, streptomycin

Tetracyclines

Drugs	Doxycycline
MOA	It inhibit protein synthesis by binding reversibly to 30-S subunit of the bacterial ribosome.
Antibacterial Spectrum	Broad Spectrum Bacteriostatic. Active against many gram +ve and gram -ve bacteria
Pharmacokinetics	- long acting - Usually given orally - Absorption is 90-100%. Absorbed in the upper small intestine & best in absence of food. - Food & di & tri-valent cations (Ca, Mg, Fe, AL) impair absorption it binds with Ca decreasing the absorption, patients should avoid dairy products. - Protein binding 40-80 % - Distributed well, including CSF - Cross placenta and excreted in milk. - Largely metabolized in the live
Clinical uses	Treatment of URTIs caused by S.pyogenes, S.pneumonia & H.influenza.
ADRs	- Nausea, vomiting ,diarrhea & epigastric pain (given with food that doesn't contain dairy products) - Thrombophlebitis if given IV - Hepatic toxicity (prolonged therapy with high dose) - Brown discolouration of teeth in children - Deformity or growth inhibition of bones in children - Phototoxicity in sun or light exposure - Vertigo - Superinfections.
Contraindicat-ions	- Pregnancy & breastfeeding - Children (below 10 years) because it causes bone deformities in newborns.

Note :
Other types of Tetracyclines: minocycline, chlortetracycline

Objective

1. Acquire the basic knowledge about fungal infections of the respiratory system
2. Know the main fungi that affects the respiratory system.
3. Identify the clinical settings of such infections.
4. Know the laboratory diagnosis, and treatment of these infections.

Respiratory fungal infection

Introduction:

- Inhalation (airborne), and Aspiration (oral route), are mostly the rout of Respiratory infections.
- Respiratory fungal infections are less common than viral and bacterial infections. Viruses > bacteria > fungi.
- Invasive diseases have significant difficulties in diagnosis and treatment.

Note :
Cryptococcosis Usually seen in meningitis rather than respiratory

Etiology:

Opportunistic

Yeast

- Candida → Candidiasis
- Cryptococcus neoformans and C. gattii → Cryptococcosis

Mould fungi

- Aspergillus species → Aspergillosis
- Zygomycetes, Rhizopus and Mucor → Zygomycosis
- Other mould

Primary infections

Dimorphic fungi:

- Histoplasma capsulatum
- Blastomyces dermatitidis
- Paracoccidioides brasiliensis
- Coccidioides immitis

Primary Systemic Mycoses

Definition: Infections of the respiratory system.

Epidemiology: Common in North America to a lesser extent in South America. Not common in other parts of the World.

Transmission: Inhalation.

Where can we see it? Dissemination. It can spread to more than organ. seen in immunocompromised hosts.

Etiology:

In nature found in soil of restricted habitats. Primary pathogens. They are highly infectious. If you inhaled just few of it you will get infected unlike others. It include:

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis

Note :
Aspergillosis include Mycotoxicosis, Colonization (without invasion and extension) in preformed cavities, Invasive disease of lungs, Systemic and disseminated disease, Allergy.

Aspergillosis

Definition: Aspergillosis is a spectrum of diseases of humans and animals caused by members of the genus Aspergillus (mould fungi).

Etiology:

Aspergillus species, common species are:

- A.fumigatu → most virulent
- A. flavus → most common in Riyadh
- A. niger
- A. terreusand
- A. nidulans

Risk factor:

- **Bone marrow & Organ transplantation**

Because we gave them immunosuppressants to decrease their immunity

- Cancer: Leukemia, lymphoma
- AIDS
- Drugs: Cytotoxic drugs, steroids
- Diabetes

Diagnosis:

Specimen:

- Respiratory specimens: Sputum, BronchoAlveolar Lavage Second, **Lung biopsy.**
- Other samples: Blood

Lab Investigations:

- Direct Microscopy: Giemsa Stain, Grocott Methenamine Silver Stain. **Will show fungal septate hyphae.**
- Culture on SDA.

Serology:

- Test for Antibody.
- ELISA test for galactomannan Antigen. specific for Aspergillus.

PCR: Detection of Aspergillus DNA in clinical samples.

Note :
Sputum is NOT the best because it's full with normal flora while BronchoAlveolar Lavage Second is the best method and lung biopsy is the test for choice because it's sterile + you can check if the disease is invasive or not.

Treatment:

Antifungal: Voriconazole → the drug of choice. Alternative therapy: Amphotericin B, Itraconazole, Caspofungin

+ surgery to remove aspergilloma.

Pneumocystosis (PCP)

Pneumocystis pneumonia (PCP) is Opportunistic fungal pneumonia. It is interstitial pneumonia of the alveolar area. Affect compromised host especially common in AIDS patients.

Etiology:

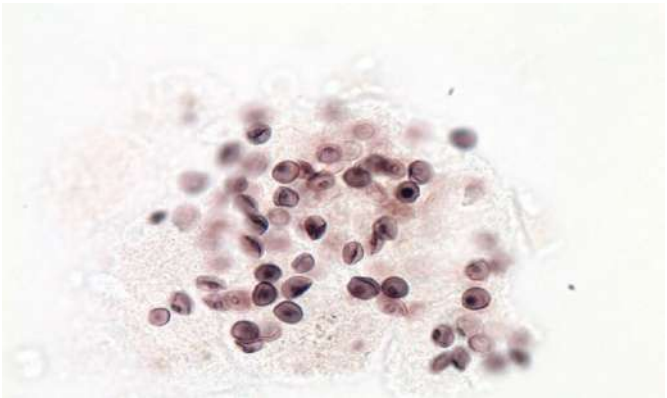
Pneumocystis jiroveci. Naturally found in rodents (rats), other animals(goats, horses), Humans may contract it during childhood.

Diagnosis:

- Does not grow in laboratory media e.g. SDA.
- Laboratory Diagnosis:
  - **Specimen:**
    - Bronchoscopic specimens (BAL) BronchoAlveolar Lavage.
    - Sputum
    - Lung biopsy
- Histological sections or smears stained by GMS stain.
- Immunofluorescence (better sensitivity) If positive —> will see cysts of hat-shape, cup shape, crescent.

Treatment:

- Trimethoprim (sulfamethoxazole) → the drug of choice
- Dapsone



Classification of Aspergillosis

Invasive pulmonary Aspergillosis

Signs & symptom	- Cough - Hemoptysis - Fever - Leukocytosis
Diagnosis	Radiology: will show lesions with halo sign.

Note :
Invasive pulmonary Aspergillosis
In immunocompromised patient

Chronic Aspergillosis (Colonizing Aspergillosis)

Types	- Aspergilloma of lung - Maxillary (sinus) aspergilloma
Causes	Aspergilloma, which is also known as (Aspergillus fungus ball).
Signs & symptom	- Dry cough - Hemoptysis - Variable fever
Diagnosis	Radiology: will show mass in the lung. radiolucent crescent air surround the mass.

Allergic

Types	- Allergic bronchopulmonary Aspergillosis (ABPA) - Allergic Aspergillus sinusitis
Signs & symptom	- Symptoms of Asthma - Bronchial obstruction - Eosinophilia - Wheezing +/-
Diagnosis	- Skin test reactivity to Aspergillus - **Serum antibodies to Aspergillus.** - Serum IgE> 1000 ng/m

Note :
Allergic Aspergillosis
In healthy patient
usually common in KSA

Note :
Serum antibodies to Aspergillus is used to differentiate between asthma and allergic aspergillosis.

Persistence without disease

Signs & symptom	Colonisation of the airways or nose/ sinuses.

Fungal sinusitis

Aspergillus sinusitis has the same spectrum of aspergillus disease in the lung. Common in KSA especially allergic sinusitis

Etiology:

Aspergillus flavus and other fungi.

Symptoms:

Nasal polyps and other symptoms of sinusitis.

Diagnosis:

- Clinical and Radiology
- Histology
- Culture
- Precipitating antibodies are useful in diagnosis
- Measurement of IgE level, RAST test

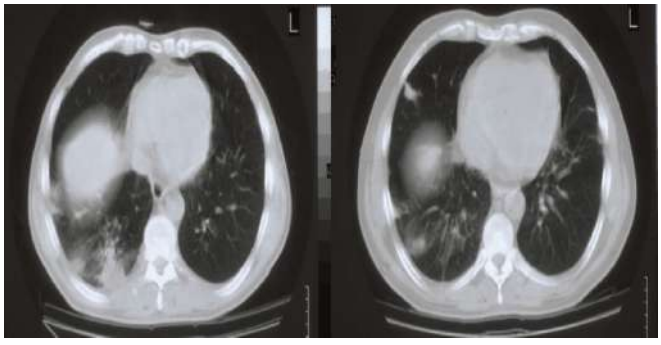
Treatment:

Depends on :

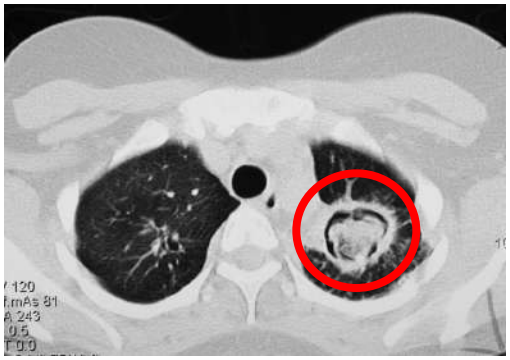
- the type and severity of the disease.
- the immunological status of the patient

Complication:

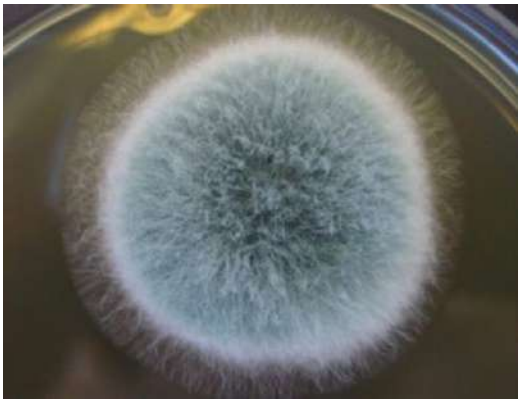
In immunocompromised, could disseminate to eye lead to craneum (Rhinocerebral).



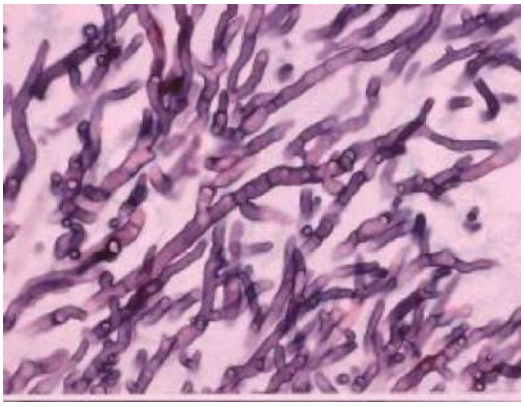
Invasive pulmonary aspergillosis, Note the Halo sign



Chronic Aspergillosis, Note the Air crescent



Cultures of Aspergillus fumigatus greenish-yellow



Smear: Septate fungal, hyphae Aspergillosis

Aspergillus niger black-brownish

Zygomycosis

Zygomycosis is acute infection marked by: Consolidation , nodules, cavitation , pleural effusion, hemoptysis. Infection may extend to chest wall, diaphragm , pericardium causing: Pulmonary infarction, hemorrhage and Rapid evolving clinical course.

Early recognition and intervention are critical. If it's in the form of sinusitis it will extends into the brain in 10 days.

Types:

- Pulmonary zygomycosis
- Rhinocerebral zygomycosis

Pulmonary zygomycosis

Etiology:

Zygomycetes: Non-septate hyphae. e.g. Rhizopus

Risk factors:

- Transplant patients
- Malignancy
- AIDS
- Diabetic ketoacidosis

Diagnosis:

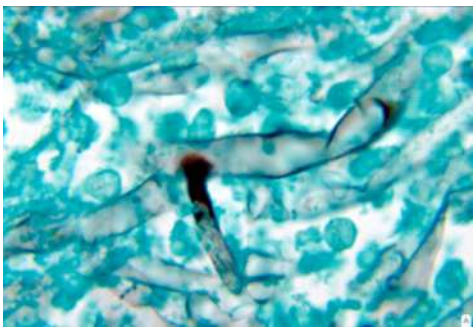
Specimen:

- Respiratory specimens: Sputum, BAL, Lung biopsy.

Laboratory Investigations:

- Direct Microscopy: Giemsa stain, GMS stain → Will show broad non- septate fungal hyphae
- Culture on SDA.

Serology: Not available



GMS stain for zygomycetes

Treatment:

- Amphotericin B
- Surgery

Fungi causing Opportunistic pulmonary infection

Aspergillus fumigatus

- Opportunistic Fungi
- Monomorphic filamentous fungus
- Dichotomously branching
- Generally acute angles
- Frequent septate hyphae with 45° angles
- One of our major recyclers: compost pits, moldy marijuana

Disease.

Predisposing conditions include the following:

- Allergic bronchopulmonary aspergillosis (ABPA)/asthma, cystic fibrosis (growing in mucous plugs in the lung but not penetrating the lung tissue)
- Fungus ball: free in preformed lung cavities (surgical removal to reduce coughing, which may induce pulmonary hemorrhage)
- Invasive aspergillosis/severe neutropenia, CGD, CF, burns
    - Invades tissues causing infarcts and hemorrhage
    - Nasal colonization, leading to pneumonia or meningitis
    - Cellulitis/in burn patients; may also disseminate

Treatment is voriconazole for invasive aspergillosis and aspergilloma; glucocorticoids and itraconazole for ABPA.

Mucor, Rhizopus, Abs

- Opportunistic Fungi
- Nonseptate filamentous fungi
- Environmental Source: soil; sporangiospores are inhaled Disease.
- These fungi penetrate without respect to anatomical barriers, progress into the brain tissue.
- Rhinocerebral infection caused by Mucor (or other zygomycophyta) [old names included mucormycosis = phycomycosis = zygomycosis]
- Characterized by paranasal swelling, necrotic tissues, hemorrhagic exudates from nose and eyes, mental lethargy
- Occurs in ketoacidotic diabetic and leukemic patients
- Diagnosis is made with KOH of tissue; broad ribbon-like nonseptate hyphae with about 90° angles on branches.
- Treatment is debridement of necrotic tissue and amphotericin B started imme- diately. Fatality rate is high due to rapid growth and invasion

KAPLAN CORNER

Fungi causing Opportunistic pulmonary infection

Pneumocystis jirovecii (formerly P. carinii)

- Fungus (based on molecular techniques like ribotyping)
- Obligate extracellular parasite
- Silver-stained cysts in tissues Disease: interstitial pneumonia
- Pneumonia in AIDS patients even with prophylaxis (mean CD4+/mm^3 of 26), malnourished babies, premature neonates, and some other IC adults and kids
- Symptoms: fever, cough, shortness of breath; sputum nonproductive except in smokers
- Serum leaks into alveoli, producing an exudate with foamy or honeycomb appearance on H&E stain (silver stain reveals the holes in exudate are actually the cysts and trophozoites, which do not stain with H&E)
- X-ray : patchy infiltrative (ground glass appearance); lower lobe periphery may be spared
- Diagnosis is made with silver-staining cysts in bronchial alveolar lavage luids or biopsy.
- Treatment is trimethoprim/sulfamethoxazole for mild disease and dapsone for moderate/severe disease.

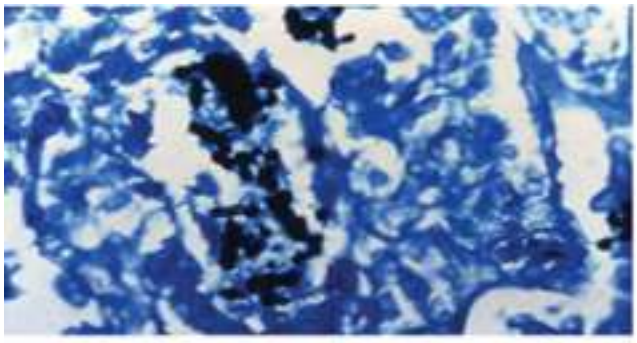
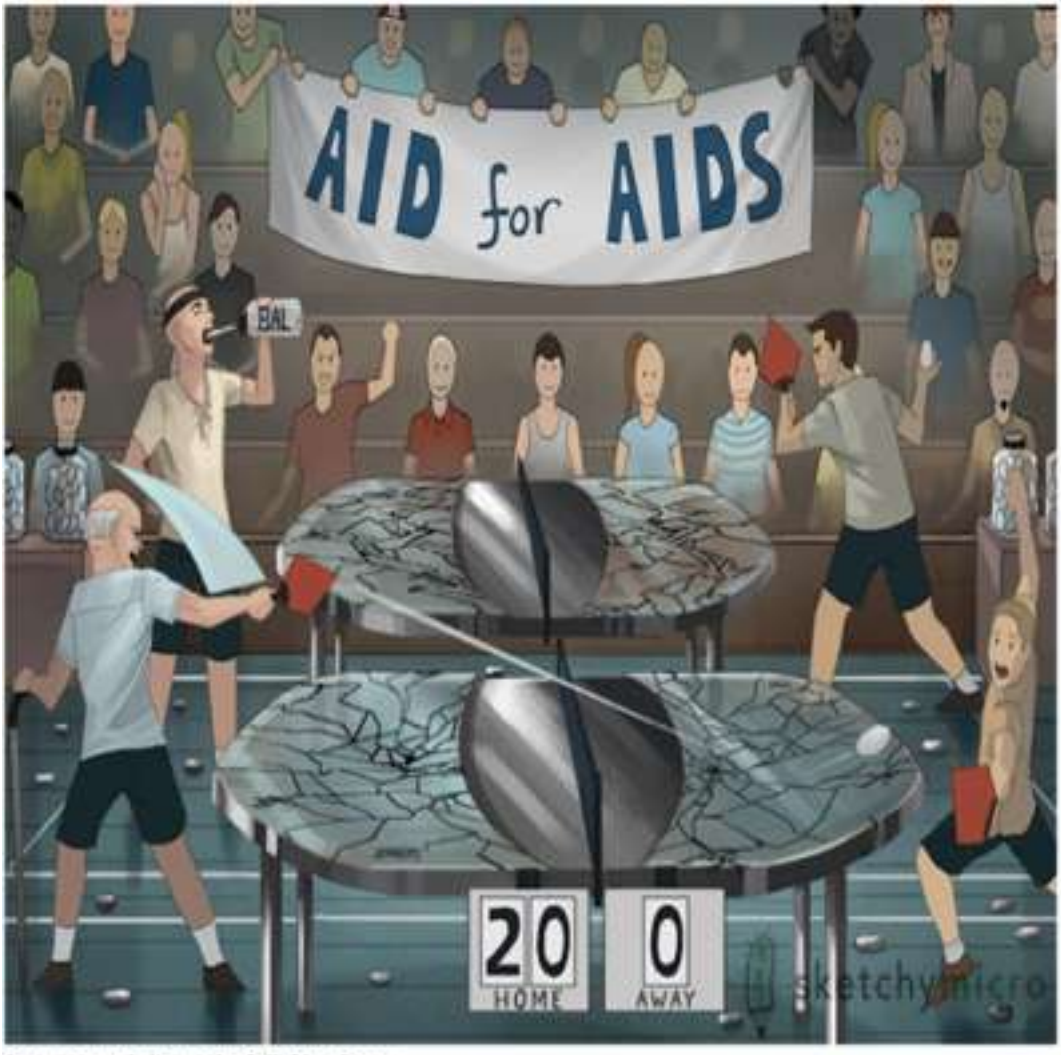


Figure II-5-23. *Pneumocystis, Silver Stain, Exudate*



Pneumocystis jiroveci – PCP Ping Pong

1. Aid for Aids – Associated with Aids CD4 counts below 200
2. 20-0 – CD4 counts below 200
3. Immunocompromised Cane player and young player – Symptoms are evident in immunocompromised individuals
4. Cracked glass ping pong tables - Will have a ground glass appearance in both lungs
5. BAL water bottle - Broncheolavar lavage for diagnosis
6. Silver discs on the table and ovoid ping pong balls - Methamine silver stain to identify fungus that looks like disc shaped yeasts
7. Backhand, and the jar of ping pong sulfa bottle- Prophylaxis begins when CD4 count is below 200, Bactrim (TMP/SMX)
8. Pentagon paddles – Pentadamine can be used with sulfa allergies

SKETCHY CORNER

Aspergillus fumigatus – Asparagus Farm

1. Cat on scarecrow - Catalase Positive
2. Peanut plant in the front – Peanuts are associated with **aflatoxins produced by Aspergillus flavus**
3. Wheat field – aflatoxins associates with grain
4. Cow with liver and Crab on the tractor - Hepatocellular carcinoma
5. Plant has acute angles and septations – Aspergillus is Acute branching with septations ASpergillus
6. Fruiting bodies on the peanut plant - Condiophores with fruiting bodies, those will be inhaled by humans
7. 3 types of infection
    a. Crop duster with Sweaty, running, farmer running with inhaler below- Allergic bronchopulmonary aspergillus (ABPA), causing wheezing, fever, and a migratory pulmonary infiltrate.
        i. Inhaler says IgE on it - Type I hypersensitivity, IgE response
    b. Farmer that is coughing with a handkerchief and TB Cactus – Susceptibility increases with TB cavities. Aspergillosis causing aspergillomas
        i. Peanuts under the ground - Aspergillomas are gravity dependent so fungus balls will be at the bottom of the cavity
    c. Farmer on the right w/immunocompromised cane – Angioinvasive aspergillosis - Patients with neutropenia from leukemia or lymphoma –
        i. Red sprinkler system throughout the crops - invades blood vessels and the surrounding tissues
        ii. Scarecrow with a straw heart, kidneys, and black dots on head, black dot on nose – Kidney failure, endocarditis, ring enhancing lesions in the brain. Invades nasal sinus
8. Pine cones and vortex – Voriconazole for less serious infections
9. Frogs – Amphotericin B for angioinvasive disease

SKETCHY CORNER

Mucormycoses – Mu Car Auto Shop

1. Cain – Immunocompromised
2. Jar of candy – Diabetes patients are susceptible
3. Baguette – Rhizopus is a bread mold
4. Mechanic is coughing from fumes in exhaust pipe - Transmitted via spore inhalation
5. Ketone auto parts - **Diabetic Ketone acidosis** predisposes infection of this fungus
6. **Tire iron - Hyphae are non-septate and have 90 degree angle branching**
7. Red jumper cables - Fungus like to proliferate in blood vessels
8. Oil pan that has several holes it is leaking through - Invade through cribriform plate in the skull then will continue to cause necrosis of tissues and frontal cortex abscesses
9. Mechanic with oil dripping on face – will present as a black eschar and necrosis of nasal cavity and eyes, causing neuro deficits and death
10. Treatments – debridement first
11. Frog car – Amphotericin B
12. Biopsy is needed for diagnosis

SKETCHY CORNER

Middle and Lower Respiratory System Infections

Type Infection	Case Vignette/Key Clues	Most Common Causal Agents
Respiratory difficulty or obstruction	Inflamed epiglottis; patient often 2–3 and unvaccinated	*Haemophilus influenzae* (epiglottitis)
	Infant with fever, sharp barking cough, inspiratory stridor, hoarse phonation	Parainfluenza virus (Croup)
Pneumonia Typical: high fever, productive cough, diffuse infiltrates	Poorly nourished, unvaccinated baby/child; giant cell pneumonia with hemorrhagic rash	Measles: malnourishment ↑ risk of pneumonia and blindness
	Adults (including alcoholics) #1 CA Rusty sputum, often follows influenza	*Streptococcus pneumoniae*
	Neutropenic pts, burn pts, CGD, CF	*Pseudomonas*
	Foul smelling sputum, aspiration possible	Anaerobes, mixed infection (*Bacteroides, Fusobacterium, Peptococcus*)
	Alcoholic, abscess formation, aspiration, faculta- tive anaerobic, gram-negative bacterium with huge capsule, currant jelly sputum	*Klebsiella pneumoniae*
	Nosocomial, ventilator, post-influenza, Abscess formation, Gram +, catalase +, coagulase + Salmon-colored sputum	*Staphylococcus aureus*
Atypical: low fever, dry cough, diffuse infiltrates	Pneumonia teens/young adults; bad hacking cough; initially non-productive cough	*Mycoplasma pneumoniae* (most common cause of pneumonia in school age children)
	Atypical with air conditioning exposure especially >50 yr, heavy smoker, drinker	*Legionella* spp.
	Atypical with bird exposure, hepatitis	*Chlamydophila psittaci*
	AIDS patients with staccato cough; “ground glass” x-ray; biopsy: honeycomb exudate with silver staining cysts, progressive hypoxia	*Pneumocystis jirovecii*

Middle and Lower Respiratory System Infections

Type Infection	Case Vignette/Key Clues	Most Common Causal Agents
Acute respiratory distress	Travel to Far East, winter, early spring, hypoxia	SARS-CoV
	Spring, 4 corners region, exposure to rodents	Hanta virus
Acute pneumonia or chronic cough with weight loss, night sweats, calcifying lesions	Over 55, HIV+, or immigrant from developing country	*Mycobacterium tuberculosis*
	Dusty environment with bird or bat fecal contami- nation (Missouri chicken farmers), yeasts packed into phagocytic cells	*Histoplasma capsulatum*
	Desert sand, SW U.S.	*Coccidioides immitis*
	Rotting contaminated wood, North and South Carolina	*Blastomyces dermatitidis*

Objective

1. Know the epidemiology of lung cancer
2. Know the classification of bronchogenic carcinoma which include: squamous carcinoma, adenocarcinoma, small cell and large cell (anaplastic) carcinomas.
3. Understand the predisposing factors of bronchogenic carcinoma.
4. Understands the clinical features and gross pathology of bronchogenic carcinoma.
5. Know the precursors of squamous carcinoma (squamous dysplasia) and adenocarcinoma (adenocarcinoma in situ and atypical adenomatous hyperplasia).
6. Know about neuroendocrine tumors with special emphasis on small cell carcinoma and bronchial carcinoid.
7. Know that the lung is a frequent site for metastatic neoplasms.

Lung tumors

Overview:

Most lung tumors are malignant. The Primary lung cancer is a common disease but metastatic tumors are the most common lung carcinoma seen in clinical practice. 95% of primary lung tumors are carcinomas, 5% carcinoids, mesenchymal malignancies (fibrosarcomas, leiomyomas) and lymphomas.

Note:

- Carcinoma → malignant tumor of epithelial origin.
- Teratoma→ benign/malignant tumor where tissues arise from the 3 embryogenic layers.
- Hamartoma → abnormal mass of tissue consisting of various indigenous tissue.
- Sarcoma→ malignant tumor of mesenchymal origin

Metastatic → (secondary) tumors are more common in the lung and the the tumor have multiple nodules.

Epidemiology:

- Primary lung cancer is the most common fatal cancer in both men and women worldwide.
  - Accounts for >30% of cancer deaths in men.
  - Accounts for >25% of cancer deaths in women.
- Incidence of lung cancer is declining in men but increasing in women, and peak incidence is at 55-65 years of age.

Symptoms :

- **General:**

1. Unexplained weight loss
2. Unexplained anemia
3. Unexplained fever (usually lymphoma)
4. Unexplained fatigue

- **Lung-specific:**

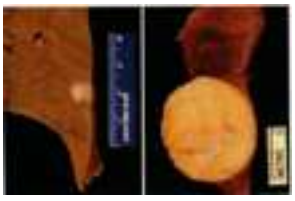
1. Unexplained cough.
2. Hemoptysis.
3. Chest pain
4. Cyanosis
5. Cachexia (TNF-a and IL-1)

Benign Lung Tumor

Hamartoma:

Most common benign tumor, spherical, small (1 to 4 cm), discrete (hamartoma) that often shows up as a so-called (coin lesion) or (leave me alone lesion) on chest imaging. It consists mainly of mature cartilage admixed with fat, fibrous tissue, and blood vessels in various proportions. Hamartoma simply is normal tissue but in a disorganized fashion.

- **Gross**: Well-circumscribed, rounded solid lesion (coin) with yellowish pale cut surface.
- **Histopathology**: Cartilage, blood vessels, glands, inflammatory cells, mesenchymal tissue, fat.



Hamartoma, gross

Hamartoma, microscopic

Hamartoma, radiograph (rounded coin-like mass)

Note:
The majority of lung cancers are NSCLC and SCLC, and the most common lung cancer out of bronchogenic carcinomas is adenocarcinoma

Malignant Lung Tumor

Lung Tumours

- Non-Small Cell Lung Carcinoma(70%-75%)
  - Squamous cell carcinoma (25%-35%)
  - Adenocarcinoma, including bronchioloalveolar carcinoma (30%-35%)
  - Large cell carcinoma (10%-15%)
- Small cell lung carcinoma (20%-25%)
- Combine patterns (5%-10%)
  - Mixed squamous cell carcinoma and adenocarcinoma
  - Mixed squamous cell carcinoma & SCLC
- Carcinoid tumours — Benign cancer arising from Neuroendocrine cells

Bronchogenic carcinoma:

A common cause of cancer death in both men and women.
For therapeutic purposes, bronchogenic carcinoma are classified into:

	NSCLC	SCLC
Therapy	○ **Surgical**: offers the best chance for curing. ○ **Radiation**: controls local disease. It's used to palliate symptoms. ○ **Chemotherapy**: not effective ○ Monoclonal therapy nowadays.	○ **Chemotherapy** is very effective because SCLC are highly responsive to chemotherapy ○ **Surgery** is not effective because it's usually detected late, after metastasis.

Central tumors (related to smoking)	Peripheral tumors (related to scar)
○ Squamous cell carcinoma ○ Small cell carcinoma	○ Adenocarcinoma: - Bronchial derived - Bronchioalveolar CA ○ Large cell carcinoma

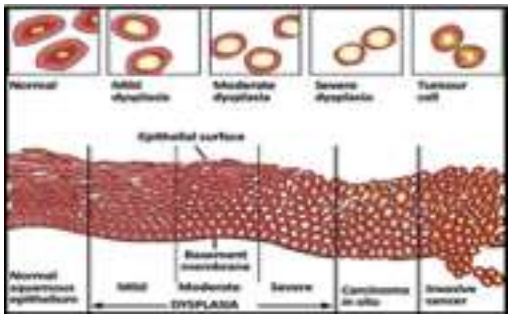
Central carcinoma of the bronchus:
appear as friable white masses of tissue (L), extended into the lumen of bronchi and invaded into the adjacent lung.

Peripheral carcinoma of the lung:
appear as ill-defined masses (C), often occurring **in relation to scars,** and frequently extend to the pleural surface.

Predisposing factors of bronchogenic carcinoma:

Tobacco smoking:

- 85% of lung cancers occur in cigarette smokers. Most types are linked to cigarette smoking, but the strongest association is with **squamous cell carcinoma and small cell carcinoma.**
- The **nonsmoker** who develops cancer of the lung usually has an **adenocarcinoma**.
- It's directly proportional to the number of cigarettes smoked daily and the number of years of smoking.
- Cessation of cigarette smoking for at least 15 years brings the risk down.
- Passive smoking increases the risk to approximately **twice** than non-smokers.
- Cigarette smokers show various gradual histologic changes, including squamous **metaplasia** of the respiratory epithelium which may progress to dysplasia, **carcinoma in situ** and ultimately **invasive carcinoma .**



Radiation:

All types of radiation may be carcinogenic and increase the risk of developing lung cancer. **radium** and **uranium** workers are at risk.

Asbestos:

Increases incidence, especially in combination with cigarette smoking.

Industrial exposure:

Exposure to nickel and chromates, coal, mustard gas, arsenic, iron etc.

Air pollution

Increases incidence, especially in combination with cigarette smoking.

Asbestos:

May play some role in increased incidence. Indoor air pollution especially by **radon**.

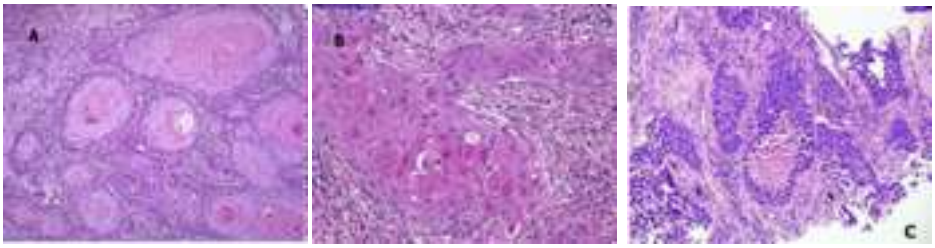
Scarring:

Sometimes old infarcts, wounds, scar, granulomatous infections are associated with **adenocarcinoma**.

Non-small cell carcinoma (NSCC):

A. Squamous cell carcinoma

Degrees of squamous differentiation in squamous cell carcinoma:



Well-differentiated | Moderately differentiated | Poorly differentiated

B. Adenocarcinoma

Epidemiology:

- **Most frequent** histologic subtype of bronchogenic carcinoma; more common in **women**, & patients **under the age of 40.**
- They **do not have a clear link to smoking** history
- They are classically **peripheral tumors** arising from the peripheral airways and alveoli.
- Peripheral adenocarcinomas are sometimes associated with **pulmonary scars** (from a previous pulmonary inflammation/infection) and therefore is also referred to as **scar carcinoma.**

Etiology:

20% of adenocarcinoma of the lung are associated with mutation of epidermal growth factor receptor **(EGFR)** and respond to its anti therapy.

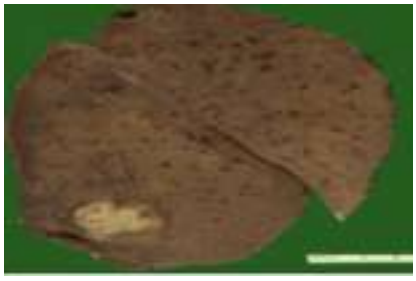
Morphology:

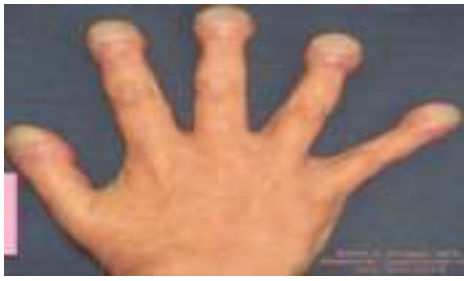
The hallmark of adenocarcinomas is the **tendency to form glands** that may or may not produce mucin.

- More mucous → well differentiated (grade I)
- Less mucous → poorly differentiated (grade III)

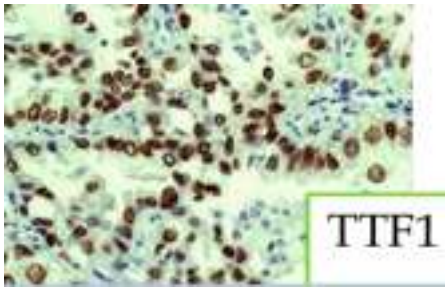
Clinical features:

- Associated with hypertrophic pulmonary osteoarthropathy (Clubbing of the fingers)
- Rarely cavitate

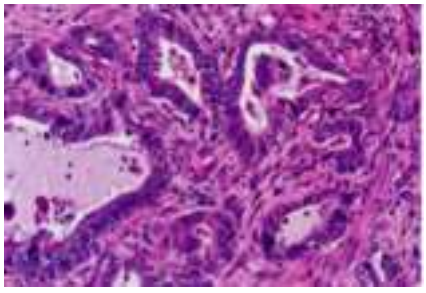




Clubbing of the fingers



Thyroid Transcription Factor 1 (TTF-1) → Special stain for adenocarcinoma

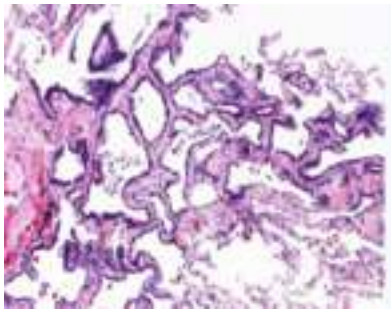


Tendency to form glands

Adenocarcinoma Precursor Lesions:

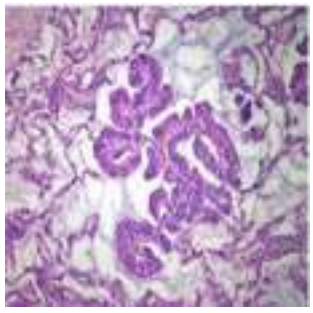
1. Atypical adenomatous hyperplasia (AAH):

- Small lesion (≤5 mm)
- Characterized by: dysplastic pneumocytes lining alveolar walls that are mildly fibrotic.



2. Adenocarcinoma in situ (AIS)

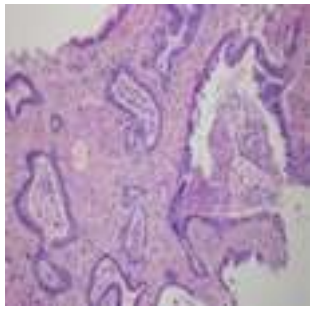
- Used to be called Bronchioloalveolar carcinoma.
- Lesion 3 cm or less.
- Composed **entirely of dysplastic cells** growing along preexisting alveolar septa
- Lepidic growth pattern but once invasive (>3cm) it forms desmoplasia (fibrosis).
- No feature of necrosis or invasion.



Note :
Adenocarcinoma in situ (AIS)
Composed entirely of dysplastic cells growing along preexisting alveolar septa without rupturing it (Atypical glandular cells line the alveoli along the basement membrane → hyperplasia)

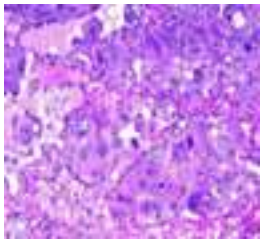
2. Minimally invasive adenocarcinoma of lung (MIA)

- Lesion ≤3 cm.
- Describes small solitary adenocarcinomas with either pure lepidic growth or predominant lepidic growth with ≤5 mm of stromal invasion.



C. Large cell carcinoma

- Frequency: 10 %
- strongly associated with **smoking**
- **Undifferentiated** malignant epithelial tumors.
- They made up of **large and anaplastic cells.**
- They may exhibit **neuroendocrine or glandular differentiation markers** when studied by immunohistochemistry or electron microscopy.
- **Poor prognosis**



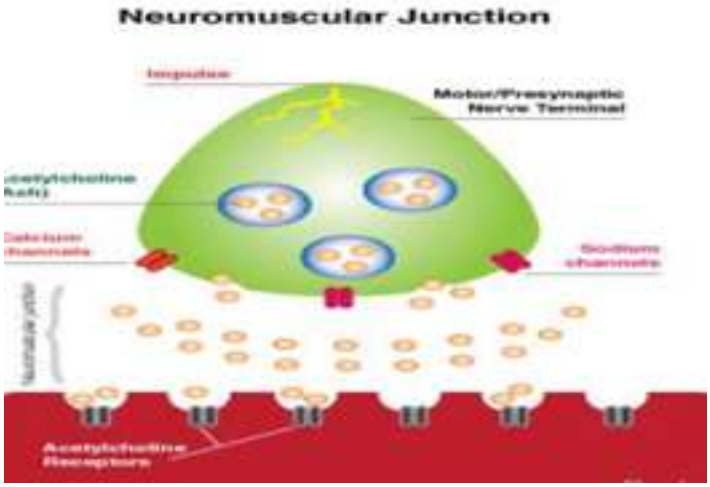
Small cell carcinomas

Epidemiology:

- Also known as: oat cell carcinoma.
- Type of poorly differentiated **neuroendocrine tumors** arising from neuroendocrine cells.
- common in **men**.
- Strongly associated with **cigarette smoking**, 95% of patients are smokers.
- Centrally located perihilar mass with **early metastases** (Early involvement of the hilar and mediastinal nodes).
- Ability to secrete a host of **polypeptide hormones** like ACTH, ADH, calcitonin, gastrin-releasing peptide and chromogranin. ACTH: Adrenocorticotropic hormone (usually from the pituitary) → stimulates adrenal cortex to release cortisone. Moonface, Hirsutism, Obesity → caused by cortisone released from the adrenal cortex. Inappropriate secretion of ADH →hyponatremia.
- Paraneoplastic syndromes related to small cell carcinoma: Cushing's & **Eaton-Lambert syndrome.**

Eaton-Lambert syndrome.

Autoimmune disease. **The immune system attacks the connection between nerve and muscle** (the neuromuscular junction) and interferes with the ability of nerve cells to send signals to muscle cells leading to **muscle weakness**



Clinical features of bronchogenic carcinoma:

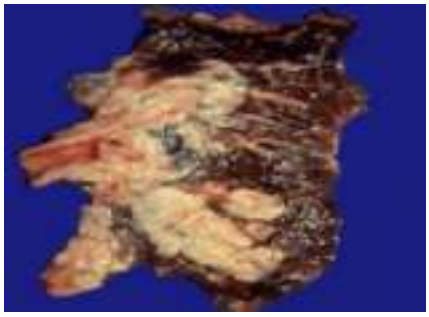
- Chest pain (30% of cases)
- Can be silent in early stage, no symptoms or insidious lesions.
- Weight loss (40% of cases)
- Cough, when the tumor gets larger. Most common symptom (75% of cases)
- Dyspnea, when it's enlarged and obstructing the lung.
- Hemoptysis (25%– 30% of cases) especially when cavitation starts.
- Symptoms due to invasion and metastatic spread.
- Hoarseness, because of invasion of hilum, recurrent laryngeal nerve paralysis, chest pain especially when it reaches pleura, pericardial or pleural effusion.
- **Superior vena cava syndrome:** invasion leads to **obstruction of venous drainage** which leads to dilation of veins in the upper part of the chest and neck resulting in swelling and cyanosis of the face, neck, and arms.
- **Pancoast tumor (superior sulcus tumor): Apical** Bronchogenic carcinoma (could be either squamous or adenocarcinoma) neoplasms may invade the **brachial sympathetic plexus** to cause severe pain, numbness and weakness in the distribution of the ulnar nerve. Pancoast tumor is often accompanied by d**estruction of the first and second ribs and thoracic vertebrae.** It often coexists with Horner syndrome.
- **Horner syndrome:** invasion of the cervical thoracic sympathetic nerves and it leads to ipsilateral enophthalmos (displacement of the eyeball within the orbit –eyes goes inside-). miosis, ptosis, and facial anhidrosis.

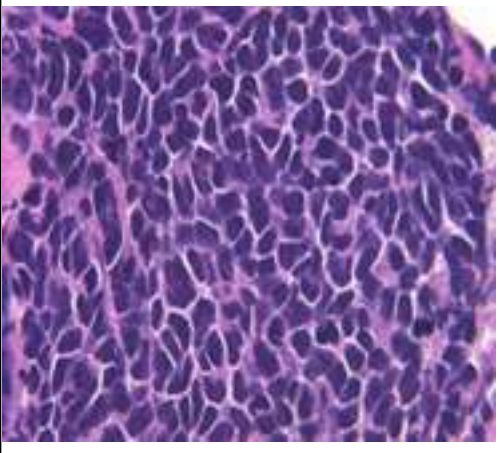
The combination of Pancoast tumor & Horner syndrome is known as Pancoast syndrome.

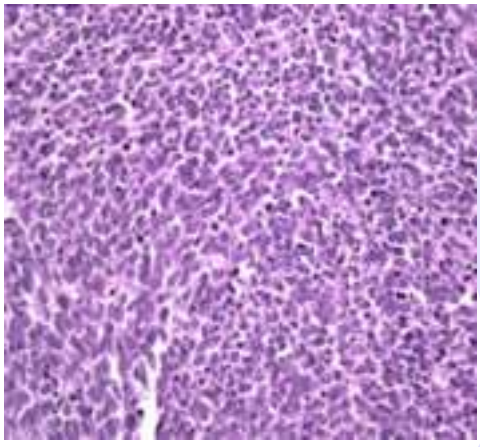
Note :

- **Haemoptysis**: the coughing up of blood.
- **Hoarseness** Of the voice : abnormal voice changes.
- **Anhidrosis** is the inability to sweat normally –leads to dryness in facial areas

- **Morphology:**



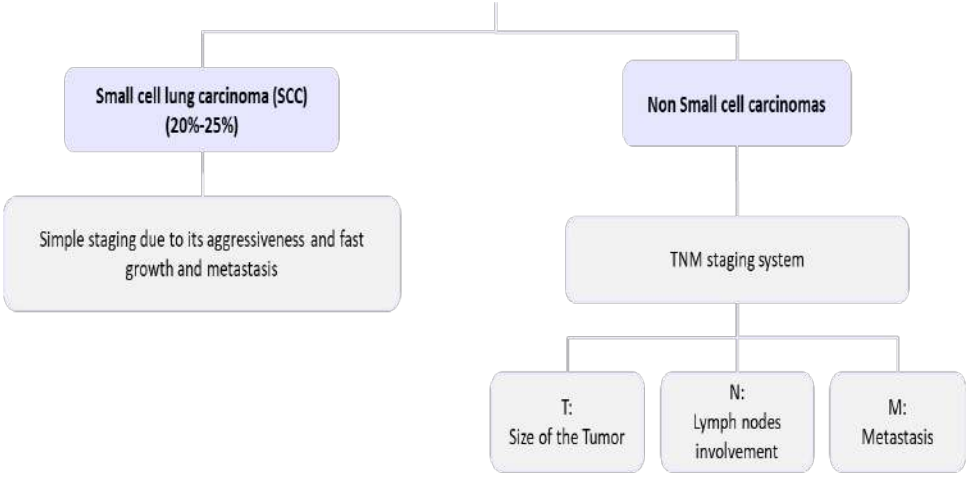




Electron microscopy: dense-core **neurosecretory granules**

Microscopically composed of small, dark, round to oval, **lymphocyte-like** cells with little cytoplasm

Staging of Bronchogenic Carcinoma



Complications of bronchogenic carcinoma

- Bronchiectasis
- Obstructive pneumonia
- Paraneoplastic syndrome
- Pleural effusion, bloody
- Hoarseness from recurrent laryngeal nerve paralysis

Spread of bronchogenic carcinoma

- Lymphatic spread
  - Successive chains of nodes (scalene nodes).
  - Involvement of the supraclavicular node (Virchow's node).
- Extend into the pericardial or pleural spaces → Infiltrate the **superior vena cava.**
- A tumor may extend directly into the esophagus, producing obstruction, sometimes complicated by a **fistula**.
- Phrenic nerve invasion usually causes **diaphragmatic paralysis.**
- May invade the **brachial or cervical sympathetic plexus.**
- Distant metastasis to liver (30-50%), adrenals (>50%), brain (20%) and bone (20%).

Note :
If we check the X-Ray and found a mass in the lung. And the abdominal scan shows bilateral adrenal gland enlargement. Then it is bronchogenic carcinoma with metastasis to adrenals.

Treatment:

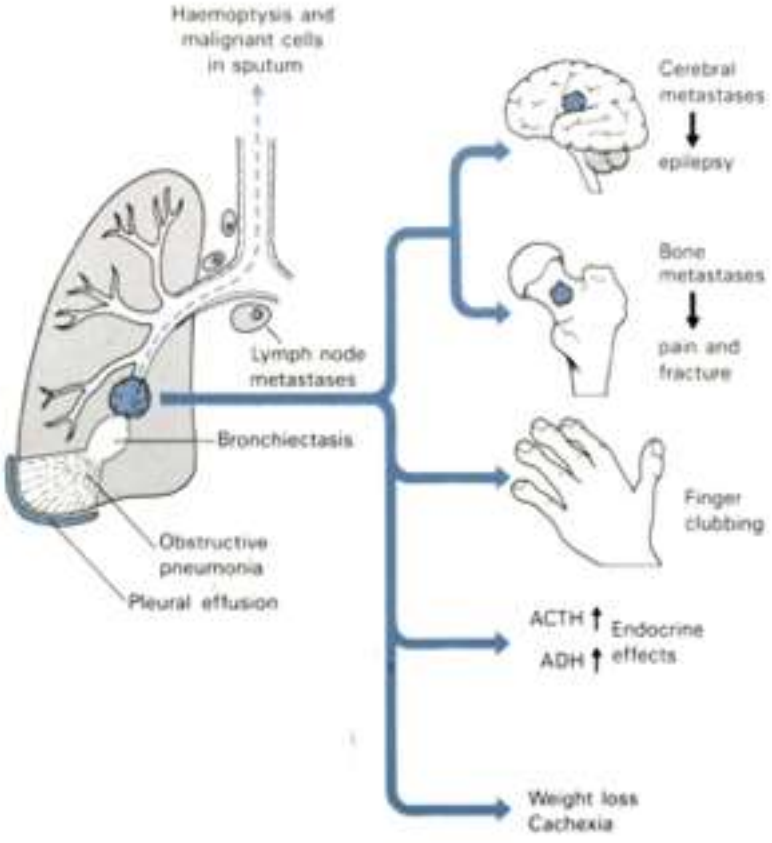
- Chemotherapy responsive
- Least likely form to be cured by surgery; usually already metastatic at diagnosis

Prognosis:

- Highly malignant and aggressive tumor, **poor prognosis**, rarely resectable.
- Histological types and the stage of lung cancer determine the outcome.
- Survival is better for early stage disease, except **for small cell carcinoma** (very early metastases)
- Non small cell cancers fare better than small cell carcinoma
- Overall combined 5-year survival rate is ~15%

Paraneoplastic syndrome

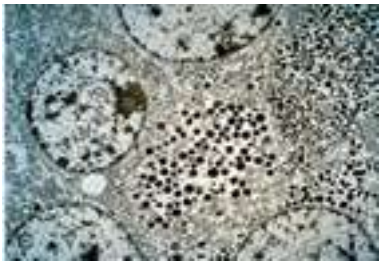
- Are extrapulmonary, remote effects of the tumor.
- 3% to 10% of lung cancers develop paraneoplastic syndromes.
    1. Squamous cell carcinomas may secrete **parathyroid hormone-like** peptide leading to hypercalcemia.
    2. Adenocarcinomas can lead to **hematologic manifestations,** repeated coagulations, thrombosis in different parts of the body) and **digital clubbing** due to reactive periosteal changes
    3. Small cell carcinomas. **ACTH** → leading to Cushing's syndrome. **ADH**→ lead to (water retention and hyponatremia.



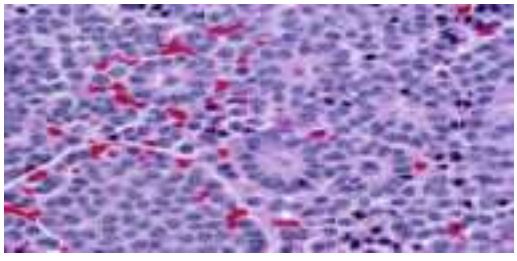
Carcinoid tumors

- Carcinoid tumors of the lung are Very well differentiated
- neuroendocrine neoplasms.
- These neoplasms account for 2% of all primary lung cancers.
- (localized and can be excised)
- It shows no sex predilection, and are not related to cigarette smoking or other environmental factors.
- Usually seen in **adults**
- Can be central or peripheral in location.
- Tumor cells produce serotonin and bradykinin leading to carcinoid syndrome
- Can occur in patients with **Multiple Endocrine Neoplasia (MEN-I)**
- Low grade malignancy, Often resectable and curable
- Spreads by direct extension into adjacent tissue
- Can lead to carcinoid syndrome (due to vasoactive amines→palpitations, diarrhea, abdominal pain, heart changes)

Morphology of typical carcinoid tumors:

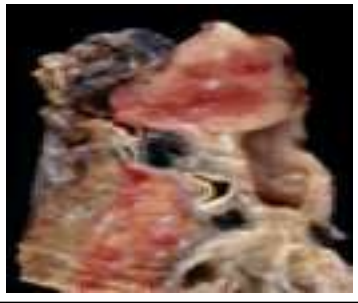


Electron microscopy: dense-core neurosecretory granules.



Composed of uniform cuboidal cells that have regular round nuclei with few mitoses and little or no anaplasia.

Note :
Both small cell carcinoma (high grade) and carcinoids,(low grade) are neuroendocrine tumors as both arise from the neuroendocrine cells (from bronchial epithelium) normally present in the lung.



Mesothelioma

- **Malignant tumor** of mesothelial cells lining the **pleura**
- Highly malignant neoplasm
- Most patients (70%) have a history of exposure to **asbestos**
- **Smoking is not related to mesothelioma**
- The age of patients with mesothelioma is 60 years.
- Pleural mesotheliomas tend to spread locally within the chest cavity, invading and compressing major structures.
- Metastases can occur to the lung parenchyma and mediastinal lymph nodes, liver, bones, peritoneum etc.
- Treatment is largely ineffective and prognosis is poor
- Few patients survive longer than 18 months after diagnosis

Carcinoma metastases to the lung:

1. Pulmonary metastases are more common than Primary Lung Tumors.
2. Metastatic tumors in the lung are typically multiple and circumscribed. When large nodules are seen in the lungs radiologically, they are called cannon-ball metastases
3. The common primary sites are: the breast, stomach, pancreas, kidney and colon.

Type of infusion	Pathogenesis	Causes
Transudate → Less than 30g protein/L	Increased hydrostatic P	Cardiac failure
	Decreased oncotic P	○ Vena caval obstruction ○ Hypoalbuminemia
Exudate → More than 30g protein /L	Infections	Bacterial (e.g. TB)
	Neoplasm	Metastatic carcinoma
	Pulmonary infarction	Thromboembolism disease
	Autoimmune disease	Rheumatoid disease Systemic lupus erythematosus
	Abdominal disease	Pancreatitis Subphrenic abscesses

Lung Cancer

What are key risk factors for lung cancer?

- **Cigarette smoking (85% of lung cancer)**
  - Risk directly linked to duration and amount of smoking (pack years)
- **Radon (2nd most common cause) - most common ionizing radiation exposure in USA**
  - Colorless, odorless gas
  - Decay product of uranium
  - Found in soil, accumulates in closed space (basement)
- **Asbestos**

What is carcinogenicity of cigarette smoking?

- Contains > 60 carcinogens
- **Polycyclic aromatic hydrocarbons and arsenic** are particularly carcinogenic
- Cancer risk directly increases with duration and amount of smoking (pack years)

What is presentation of lung cancer?

- Average age at presentation is 60.
- Most common cause of cancer death in USA
- Nonspecific presentation
  - Cough, wt loss, hemoptysis, post obstructive pneumonia

How do you diagnose lung cancer?

- Diagnosis requires biopsy
- Imaging reveals solitary nodule (coin-lesion) - growing lesion concerning
- Coin lesions also seen in (HY):
  - Granulomas - TB, fungus (ex - histoplasma in midwest)
  - Bronchial hamartoma - benign tumor of lung tissue + cartilage; often calcified in imaging
  - *Harmartoma - disorganized mass that grows at same rate as surrounding tissue; made of same cells that makes the tissue*

Describe the TNM staging of lung cancer.

- T - tumor size
  - I. Pleural involvement classically seen in adenocarcinoma (adenocarcinoma is peripheral)
  - II. Obstruction of SVC (superior vena cava syndrome) - distended head and neck veins with edema and blue discoloration of arms and face
  - III. Involvement of recurrent laryngeal nerve (hoarseness) or phrenic nerve (diaphragmatic paralysis)
  - IV. Horner's - compression of sympathetic chain (ptosis, anhydrosis - in skin, miosis) - especially if tumor is at apex of lung (pancoast tumor)
- N –
  - Spread to hilar and mediastinal lymph nodes
- M -
  - Unique site of distant metastasis is adrenals (HY)
  - Others - brain, bone, liver

Lung Cancer

What's prognosis of lung cancer?

Poor (no effective screening method) - 5 year survival rate is 15%

What are two categories of lung cancer?

Small cell carcinoma (15% of all lung carcinoma)	Non-small cell carcinoma (85% of all lung carcinoma)
	• Adenocarcinoma (40%) - glands or mucus production • Squamous cell carcinoma (30%) - keratin pearls or intercellular bridges • Large cell carcinoma (10%) - none of above features seen • Carcinoid tumor (5%)
Usually no amenable to surgery (treat with chemotherapy and radiation)	Treat upfront with surgery (doesn't respond well to chemotherapy)

What are different types of lung cancer?

S.N	Cancer type	Remarks
1	Small Cell carcinoma	Treat with chemotherapy
2	Non-small cell carcinoma	**Subtype** • Squamous cell carcinoma • Adenocarcinoma • Broncheoalveolar carcinoma (Adenocarcinoma in situ) • Large cell carcinoma • (Bronchial) carcinoid tumor
3	Mesothelioma	related to asbestos
4	Metastasis	Common origin of metastasis - breast, colon

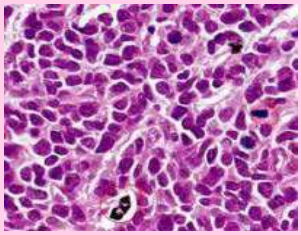
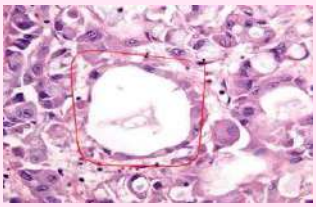
Lung Cancer

Classify the different types of lung cancer

Neuroendocre (NE) tumor	Adenocarcinoma	Related to smoking: small, large, squamous, adeno	Paraneoplastic syndrome	Undifferentiated and poor prognosis	Excellent prognosis
Small cell carcinoma (poorly differentiatd NE cells)	Adenocarcinoma	Squamous cell carcinoma (most common in male smokers	Squamous cell carcinoma (PTHrp)	Small cell carcinoma	Bronchoalveolar carcinoma
(Bronchial) carcinoid tumor (well differentiated NE cells)	Bronchioalveolar carcinoma (adenocarcinoma in situ)	Small cell carcinoma (male smokers)	Small cell carcinoma (ADH, ACTH, Ab for Ca channel)	Large cell carcinoma	
		• Adenocarcinoma (most common in female smokers and non-smokers) • broncheoalveolar carcinoma not associated with smoking	Large cell carcinoma (B-HCG)		
		Large cellcarcinoma			

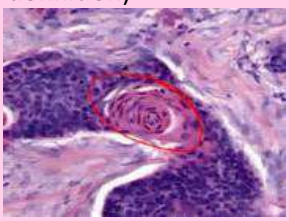
Lung Cancer

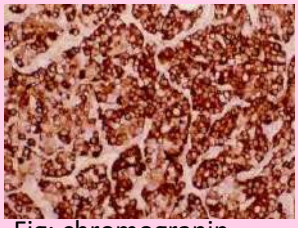
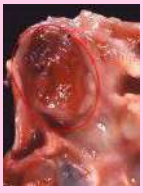
Describe the following types of cancer

Cancer	Histology	Association	Location	Remarks
Small cell carcinoma	• Poorly differentiated small cell and very aggressive • Arise from neuroendocrine cells (Kulchitsky cells) • Chromogranin +ve (less +ve than carcinoid tumor) 	Male smokers (99% of small cell carcinoma pt are smokers)	Central	• Associated with 5A and 1B • Produces **A**CTH • Produces **A**DH • Produces **A**b for Eaton-Lambert syndrome (presynaptic Ca channel Ab) (paraneoplastic syndromes) • **A**nti-neuronal antibody syndrome (limbic encephalitis, cerebellar degeneration, opsoclonus, GI dysmotility, poly radiculopathy) • **A**mplification of myc oncogene • LOVES TO GO TO **B**RAIN - give prophylactic cranial irraditation • MOST AGGRESSIVE TYPE OF LUNG CANCER
Adenocarcinoma	Glands or mucin  Fig: glandular structure in adenocarcinoma	Most common tumor in nonsmokers and female smokers	Peripheral	

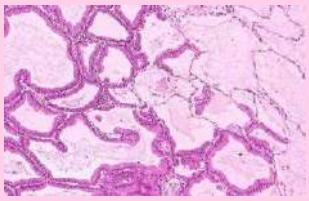
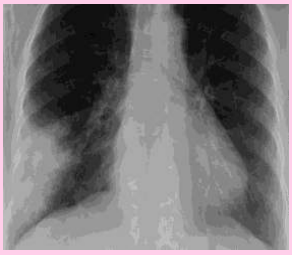
Lung Cancer

Cancer	Histology	Association	Location	Remarks

Squamous cell carcinoma	Keratin pearls or intercellular bridges (by definition)
	 
	Fig: keratin pearl
		Most common tumor in male smoker	Central
			 
			Fig- intracellular bridge
				• May produce PTHrp (paraneoplastic syndrome)
				• Hilar mass from bronchus
				• Associated with double C
				  ○ Hyper**C**alcemia- due to PTHrp
				  ○ **C**avitation

Large cell carcinoma	Poorly differentiated and highly anaplastic cells (no keratin pearls, intercellular bridges, glands or mucin)	Smoking	Central or peripheral	• Poor prognosis • Poor response to chemotherapy; remove surgically • Paraneoplastic – may secrete B-HCG
(Bronchial) Carcinoid tumor	Well differentiated neuroendocrine cells; chromogranin positive  Fig: chromogranin positivity	Not related to smoking	Central or peripheral (when central, makes polyp like mass in bronchus) 	• **MOST COMMON PRIMARY LUNG CANCER IN CHILDREN** • Low grade malignancy; rarely, can cause carcinoid Syndrome - caused due to release of vasoactive substance (mainly serotonin) - flushing, diarrhea, restrictive cardiomyopathy due to endocardial fibrosis

Lung Cancer

Cancer	Histology	Association	Location	Remarks
Bronchiol oalveolar carcinoma (adenocar cinoma in situ)	Columnar cells that grow along preexisting bronchioles and alveoli; arise from **clara cells**  Fig: normal alveoli top right; columnar cells on rest	Not related to smoking	Peripheral	• Excellent prognosis • **Pneumonia like consolidation on imaging** 
Metastasis	Most common source are breast and colon carcinoma		Canon-ball nodules on imaging 	More common than primary
Mesotheli oma	See **psammoma bodies** in biopsy (concentric calcifications - other HY cancer - papillary thyroid, meningioma, papillary serous ovarian)	Highly associated with asbestos exposure (lung cancer more common in asbestos exposure)		• Malignant tumor of mesothelial cells (mesothelium is a membrane of simple squamous cells that lines body cavities: pleura , peritoneum, mediastinum and pericardium) • Tumor encases the lung

- Small cell carcinoma is poorly differentiated neuroendocrine tumor; carcinoid tumor is well differentiated neuroendocrine tumor.
- Neuroendocrine cells have neurosecretory granules; chromogranin stains positive for neurosecretory granule.

Lung Pathology

3.1 - Lung Carcinoma

1. METropolitan bus:: metastases are the MC cancers in the lung
2. Crab bra, kidney purse & colon belt: breast, renal and colon CAs commonly metastasize

Risk Factors

3. Risky red dice: risk factors for developing lung CA (e.g. smoking, radiation, pulmonary fibrosis, toxins (, i.e. asbestos, radon, metals, and aromatic hydrocarbons)
4. Smoking: **most important** risk factor (20x increased risk)

Presentation

5. Clutching chest: **chest pain** (esp in younger patients); Thin arm: **weight loss**; Falling food: ¯ **appetite**; Gasping: **dyspnea**
6. Coughing warden & wheezy party blower: **coughing & wheezing** (especially central tumors)
7. Recurrent bacterial lanterns & bloody air duct: **recurrent pneumonia & hemoptysis** (especially central tumors)

Small cell lung carcinoma – Small prison cell

8. "Sentral Cell Block": centrally located tumors include Small cell and Squamous cell carcinoma
9. Sheets of bubble wrap: contains sheets of round blue (basophilic) cells with scant cytoplasm
10. Granite cell: granular chromatin ("salt & pepper") and stains **chromogranin** + (neuroendocrine marker)
11. Neuroendocrine wiring: neuroendocrine tumor
12. Escaping prisoner: metastasizes early (discovered diffusely in both lungs)
13. Radiation window & chemistry set: sensitive to radiation & **chemotherapy**

Paraneoplastic syndromes

14. Inappropriately wet head: **SIADH** (ADH release from tumor)
15. Antibody keys & empty calci-yum cups: **Lambert Eaton Myasthenic Syndrome (LEMS)** (Ab against voltage-gates Ca+ channels)
16. Acetyl-cola trash bin & struggling to get up: LEMS causes decreased ACh release due to blocked presynaptic Ca+ channels → proximal muscle weakness
17. Antibody keys under cerebral turban: **neurological syndromes** (e.g. cerebellar degeneration, encephalomyelitis) which are due to autoimmune responses against antigens in neural tissue
18. Cushion: **Cushing's syndrome** (ACTH-like substance release from tumor)

Squamous cell carcinoma (non-small cell) – Squamous epithelial tile

19. Columnar cells: normal respiratory epithelium is pseudostratified columnar
20. Temporary metal plates: replaced with resistant stratified squamous (reversible squamous metaplasia)
21. Disgusting squamous tiles: squamous metaplasia can progress to dysplasia (disordered squamous cells with hyperchromasia & mitotic figures)
22. Cells breaking through floor: SCC in situ can progress to invasive carcinoma (invades BM)
23. Pearl necklaces: well-differentiated SCC exhibits **keratin pearls & intercellular bridges**
24. Necrotic skull in cavity: may exhibit central necrosis & cavitation

Paraneoplastic syndromes

25. Raised calcium cup: **humoral hypercalcemia of malignancy** (s"ca++"mous CC) (PTHrP release from tumor)
26. Knocked out PhD & PhD in disguise: humoral hypercalcemia of malignancy is assoc. w. suppressed PTH levels (PTH-independent hypercalcemia) and is caused by PTH related protein (PTHrP) release from tumor

Adenocarcinoma (non-small cell lung carcinoma) – "Dining Den"

27. "No smoking" in Dining Den: MC type of lung CA in non-smokers
28. Young lunch lady: MC lung CA in women and patients < 40 y/o
29. Smoker in Dining Den: MC type of lung CA (in smokers and non-smokers)
30. Glandular hair net: glandular characteristics on histology (e.g. acinar, papillary, mucinous)
31. Behind the glass plate: adenocarcinoma in situ (AIS) has not yet crossed the basement membrane (BM)
32. Layer lining food containers: AIS consists of tall columnar cells spreading along alveolar septae (appears to thicken alveolar walls)
33. Leopard print: surface alveolar growth (as seen in AIS) is called LEPIDIC growth pattern
34. Coughing up mucus: cells in AIS and adenocarcinoma can be mucinous → mucus production, copious sputum production
35. Mucus blob on chest: AIS may present like pneumonia on CXR (hazy consolidation)
36. Jello cubes beyond glass barrier: adenocarcinoma has cuboidal to **low columnar cells** (hyperchromatic with prominent nuclei)

Paraneoplastic syndromes

37. Clubbed fingers: **hypertrophic osteoarthropathy** (HOA) (digital clubbing)
38. Wrapped joints: HOA causes sudden arthropathy of the hands and wrists (less commonly elbows, knees, ankles)

Large cell carcinoma (non-small cell) – Large prison inmate contains large undifferentiated anaplastic cells (with large nuclei & prominent nucleoli)

Regional tumor spread to mediastinum

39. Wet pleural shirt & pericardial case: lung CA can cause **pleural & pericardial effusions**
40. "Pancoast Airlines": **Pancoast syndrome** occurs with regional tumor spread to superior pulmonary sulcus
41. Electric plexus fence: Pancoast tumors can invade the medial roots of the brachial plexus causing shoulder pain, arm/neck pain, hand muscle wasting
42. Air raid horn: **Horner's syndrome** occurs with regional tumor spread to the sympathetic chain ganglia
43. Droopy search light & constrictive horn: ptosis, miosis (and anhydrosis) in Horner's
44. Mediastinal mast: lung CA may extend medially involving mediastinal structures
45. Horse with laryngeal reigns: hoarseness due to **recurrent laryngeal nerve involvement**
46. Red balloon face: **SCV syndrome** → compression of superior vena cava causes swelling of face, neck & UE

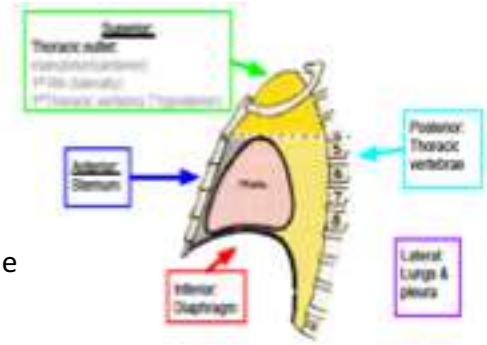
SKETCHY CORNER

Objective

1. Define the mediastinum.
2. Differentiate between the divisions of the mediastinum.
3. List the boundaries and contents of each division.
4. Describe the relations between the important structures in each division.

The Mediastinum

The mediastinum is a thick movable partition between right & left pleural sacs & lungs. It includes all the structures which lie in the intermediate compartments of the thoracic cavity



Boundaries :

- **Superior**: Thoracic outlet: (manubrium, 1st rib &T1)
- **Inferior**: Diaphragm
- **Anterior**: Sternum
- **Posterior**: 12 Thoracic vertebrae
- **Lateral**: Lungs & pleura

Note:

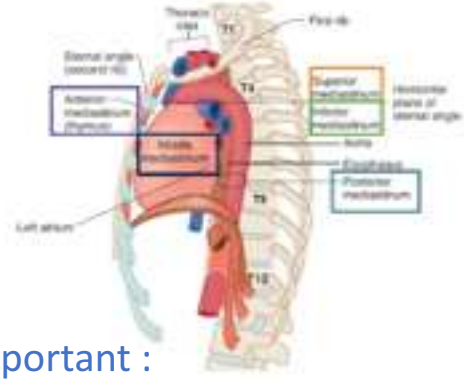
- Carcinoma → malignant tumor of epithelial origin.
- Teratoma→ benign/malignant tumor where tissues arise from the 3 embryogenic layers.
- Hamartoma → abnormal mass of tissue consisting of various indigenous tissue.
- Sarcoma→ malignant tumor of mesenchymal origin

Metastatic → (secondary) tumors are more common in the lung and the the tumor have multiple nodules.

Divisions :

By a horizontal plane from sternal angle to lower border of T4 into:

- Superior mediastinum (1 part): above the plane
- Inferior mediastinum (3 parts): below the plane, subdivided into:
  - Posterior mediastinum: behind the heart.
  - Middle mediastinum: contains the heart.
  - Anterior mediastinum: in front of the heart.



Level of T4

It is the Level of:

- Sternal angle
- Second costal cartilage

Why the Level of T4 is important :

- Bifurcation of trachea
- Bifurcation of pulmonary trunk
- Beginning & termination of arch of aorta

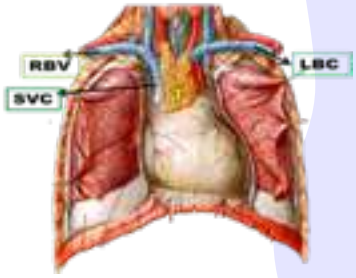
Superior Mediastinum

Boundaries :

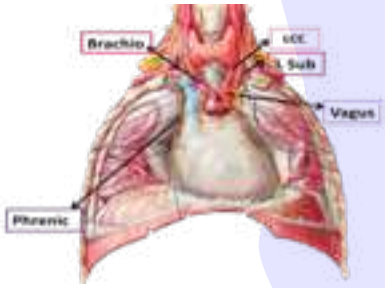
- **Superior**: Thoracic outlet
- **Inferior**: Horizontal plane
- **Anterior**: Manubrium of sternum
- **Posterior**: Upper 4 thoracic vertebrae
- **Lateral**: Lungs & pleura

Content :

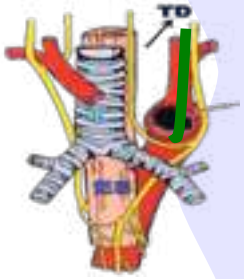
- **Superficial:**
  - Thymus Gland.
  - Three Veins: Left brachiocephalic v. (LBC), Right brachiocephalic v.(RBV), Superior vena cava (SVC).



- **Intermediate**
  - Arch of aorta & its three branches: Brachiocephalic artery (right side), Left common carotid artery, Left Subclavian artery
  - Nerves: Right & Left Phrenic, Right & Left Vagus.



- **Deep**
  - Trachea
  - Esophagus (most posterior)
  - Thoracic Duct (beside the esophagus)
  - Lymph Nodes



Anterior Mediastinum

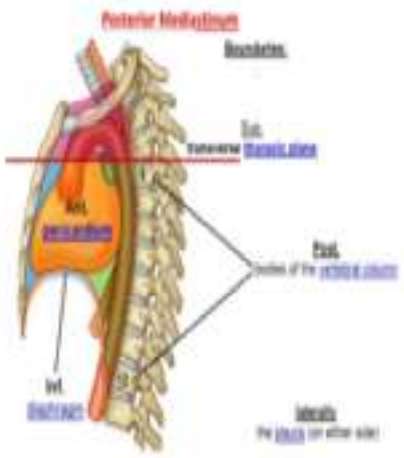
Boundaries

- **Superior:** Horizontal plane
- **Inferior:** Diaphragm
- **Anterior:** Body & xiphoid of sternum
- **Posterior:** Heart
- **Lateral:** Lungs & pleurae

Content

- Thymus gland
- Lymph nodes

Posterior Mediastinum

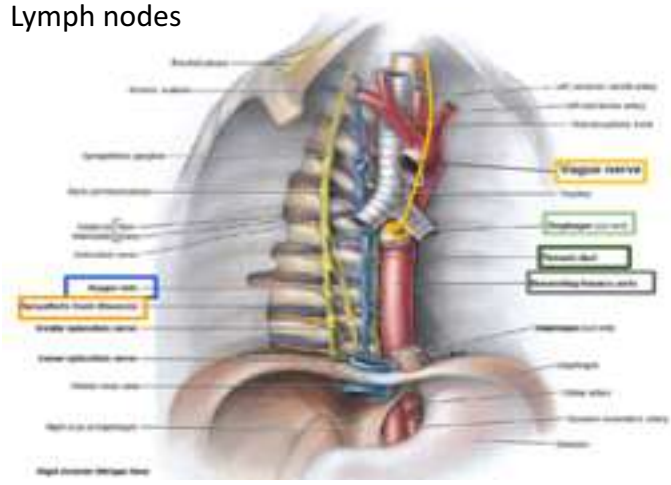


Boundaries :

- **Superior:** Horizontal plane
- **Inferior:** Diaphragm
- **Anterior:** Heart
- **Posterior:** Thoracic vertebrae from T5 to T12
- **Lateral:** Lungs & pleurae

Content :

- Esophagus
- Right & left Vagus nerves: around esophagus
- Thoracic duct: posterior to esophagus
- Azygos vein: posterior & to the right of esophagus
- Descending aorta: posterior & to the left of esophagus
- Right & left sympathetic trunk
- Lymph nodes



Middle Mediastinum

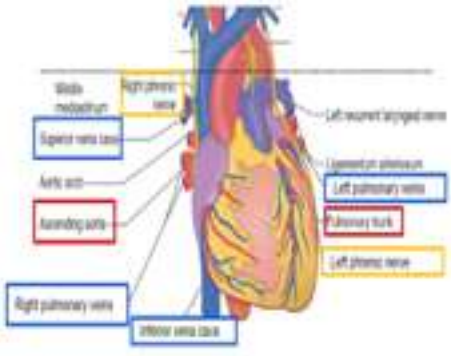
The largest and it contains the heart.

Site

- Between anterior & posterior mediastinum

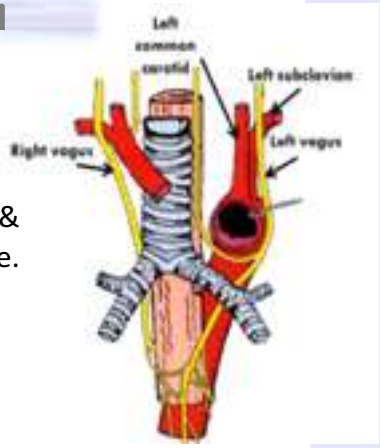
Content

- Heart & pericardium
- Ascending Aorta
- Pulmonary trunk
- Superior & inferior vena cava
- Right & left pulmonary veins
- Right & left phrenic nerves
- Lymph nodes



Important structures in Mediastinum

Vagus nerve



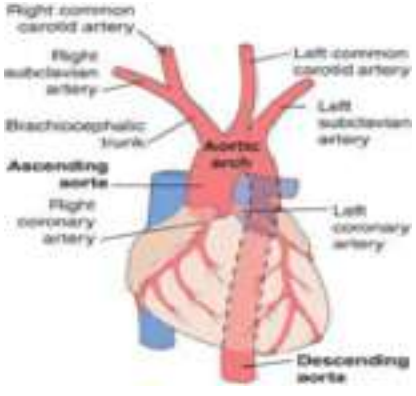
- It is the 10th cranial nerve.
- The right vagus descends to the right side of trachea, forms the posterior esophageal plexus & continues in abdomen as posterior gastric nerve.
- The left vagus descends between left common carotid & left subclavian arteries, forms the anterior esophageal plexus & continues in abdomen as anterior gastric nerve.

Phrenic nerve

- Root value: C3,4,5
- Course in thorax: They pass through the superior & middle mediastinum.
- The right phrenic descends on the right side of SVC (superior vena cava) & heart.
- The left phrenic descends on the left side of heart.
- Both nerves terminate in the diaphragm.
- Supply:
  - Motor & sensory fibers to diaphragm
  - Sensory fibers to pleurae & pericardium

Aorta

- Ascending aorta:
  - Beginning: at aortic orifice of left ventricle.
  - Course: in middle mediastinum
  - End: continues as arch of aorta (at level of T4)
- Arch of aorta:
  - Course: in superior mediastinum
  - End: continues as descending thoracic aorta (at level of T4)
- Descending aorta:
  - Course: in posterior mediastinum
  - End: continues as abdominal aorta through diaphragm

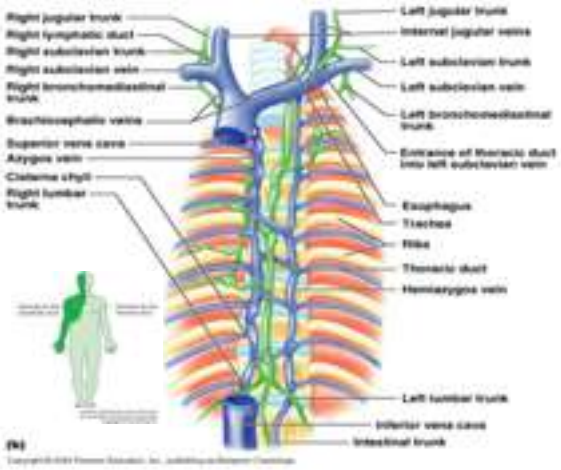


Lymphatic vessels in thorax

- Lymph from the right side of the head, nech, thorax, & upper limb drains into the Right lymphatic duct and ends in the right brachiocephalic vein
- Lymph from the lower half of the body drains into the Cisterna chyli then to the Thoracic duct
- Lymph from the left side of the head, nech, thorax, & upper limb drains directly into the Thoracic duct

Thoracic Duct

- Beginning:
  It is the continuation of Cisterna chyli at the level of L1
- Course:
  - It passes through the aortic opening of diaphragm.
  - It ascends in the posterior mediastinum (posterior to esophagus).
  - It ascends in the superior mediastinum (to the left of esophagus).
- Tributaries:
  It receives Lymphatics from all body EXCEPT right side of (head & neck, thorax, upper limb) as we mentioned before
- End:
  in the left brachiocephalic vein.



IMPORTANT NOTE

There are **six** structure present in more than one region in mediastinum

- **Three** in superior and posterior mediastinum:
  Thoracic duct ,Esophagus , vagus nerves
- **Two** in superior and middle mediastinum:
  Phrenic nerves ,superior vena cava
- **One** in superior and anterior mediastinum:
  Thymus gland

Mediastinum

The **mediastinum** is the central, midline compartment of the thoracic cavity. It is bounded anteriorly by the sternum, posteriorly by the 12 thoracic vertebrae, and laterally by the pleural cavities

- Superiorly, the mediastinum is continuous with the neck through the thoracic inlet; and inferiorly, is closed by the diaphragm. The mediastinum contains most of the viscera of the thoracic cavities except from the lungs (and pleura) and the sympathetic trunk.
- The sympathetic trunks are primarily located paravertebrally, just outside the posterior mediastinum. However, the greater, lesser, and least thoracic splanchnic nerves, which convey preganglionic sympathetic fibers to the collateral (prevertebral) ganglia below the diaphragm, enter the posterior mediastinum after leaving the sympathetic trunks.
- The mediastinum is divided into superior and inferior mediastina by a plane passing from the sternal angle (of Louis) anteriorly to the intervertebral disc between T4 and T5 posteriorly. The sternal angle and plane are important clinical landmarks. The inferior mediastinum is classically subdivided into anterior, middle, and posterior mediastina.

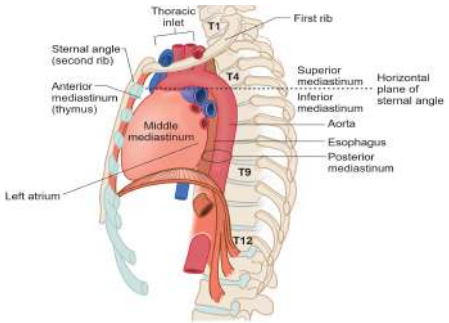


Figure II-2-29. Divisions of the Mediastinum

Anterior Mediastinum

The anterior mediastinum is the small interval between the sternum and the anterior surface of the pericardium. It contains fat and areolar tissue and the inferior part of the thymus gland. A tumor of the thymus (thymoma) can develop in the anterior or superior mediastinum.

Posterior Mediastinum

The **posterior mediastinum** is located between the posterior surface of the pericardium and the T5-T12 thoracic vertebrae. Inferiorly, it is closed by the diaphragm. There are 4 vertically oriented structu coursing within the posterior mediastinum:

- **Thoracic (descending) aorta**
    - Important branches are the **bronchial, esophageal, and posterior intercostal arteries**
    - Passes through the **aortic hiatus** (with the thoracic duct) at the T12 vertebral level to become the abdominal aorta
- **Esophagus**
    - Lies immediately posterior to the left primary bronchus and the **left atrium**, forming an important radiological relationship.
    - Covered by the **anterior and posterior esophageal plexuses**, which are derived from the left and right vagus nerves, respectively
    - Passes through the **esophageal hiatus** (with the vagal nerve trunks) at the T10 vertebral level
    - Is constricted (1) at its origin from the pharynx, (2) posterior to the arch of the aorta, (3) posterior to the left primary bronchus, and (4) at the esophageal hiatus of the diaphragm

KAPLAN CORNER

Mediastinum

- **Thoracic duct**
  - posterior to the esophagus and between the thoracic aorta and azygos vein.
  - Ascends the posterior and superior mediastina and drains into the junction of the left subclavian and internal jugular veins.
  - Arises from the cisterna chyli in the abdomen (at vertebral level L1) and enters the mediastinum through the **aortic hiatus** of the diaphragm.
- **Azygos system of veins**
  - Drains the posterior and thoracic lateral wall
  - Communicates with the inferior vena cava in the abdomen and terminates by arching over the root of the right lung to empty into the **superior vena cava** above the pericardium
  - Forms **a collateral venous circulation** between the inferior and superior vena cava

Middle Mediastinum

The middle mediastinum contains the pericardium, the heart, parts of the great vessels, and the phrenic nerves.

Superior Mediastinum

The **superior mediastinum** is located between the manubrium of the sternum, anteriorly, and the thoracic vertebrae 1-4, posteriorly. As with all mediastina, the parietal pleura and the lungs form the lateral boundary. The thoracic inlet connects superiorly with the neck and the horizontal plane through the sternal angle forms the inferior boundary.

- The superior mediastinum contains the thymus, great arteries and veins associated with the upper aspect of the heart, trachea, and esophagus.
- The vagus and phrenic nerves and the thoracic duct also course through the mediastinum.
- The pulmonary trunk and arteries are located completely in the middle mediastinum and are not found in the superior mediastinum.

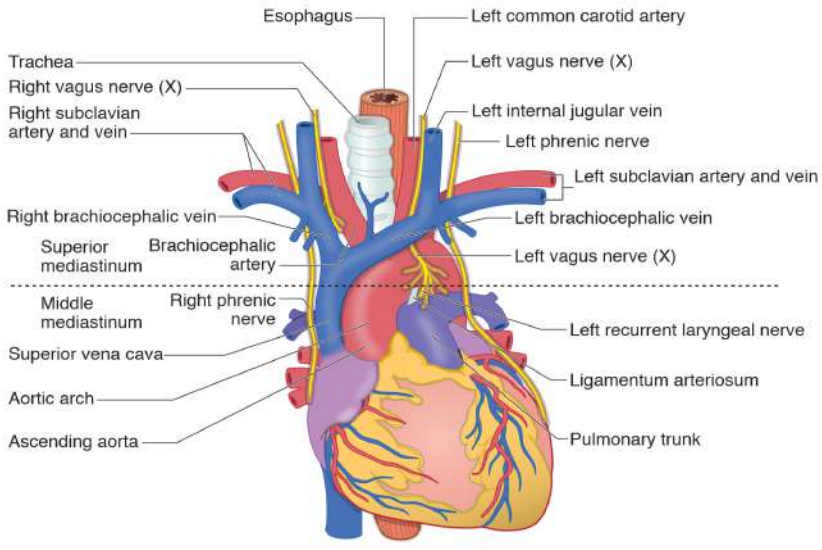


Figure II-2-30. Structures of the Mediastinum

KAPLAN CORNER

Mediastinum

The relationships of these structures in the superior mediastinum are best visualized in **a ventral to dorsal** orientation between the sternum anteriorly and the vertebrae posteriorly:

- **Thymus**: located posterior to the manubrium, usually atrophies in the adult and remains as fatty tissue
- **Right and left brachiocephalic veins:** right vein descends almost vertically and left vein obliquely crosses the superior mediastinum posterior to the thymic remnants
    - The 2 veins join to form the **superior vena cava posterior** to the **right first costal cartilage.**
    - The superior vena cava descends and drains into the right atrium **deep to the right third costal cartilage**.
- **Aortic arch and its 3 branches**: aortic arch begins and ends at the plane of the sternal angle and is located just **inferior** to the left brachiocephalic vein.
    - As a very important radiological landmark, the origins of the 3 branches of the aortic arch **(brachiocephalic, left common carotid, and left subclavian)** are directly **posterior** to the left brachiocephalic vein.
- **Trachea**: lies posterior to the aortic arch and bifurcates at the level of T4 vertebra to form right and left primary bronchi
    - The **carina** is an internal projection of cartilage at the bifurcation.
- Esophagus: lies posterior to the trachea and courses posterior to left primary bronchus to enter the posterior mediastinum.

In addition to these structures, the superior mediastinum also contains the **right and left vagus** and **phrenic nerves** and the superior end of the **thoracic duct.**

- Right and left **vagus nerves** contribute to the pulmonary and cardiac plexuses. In the neck, the right vagus nerve gives rise to the **right recurrent laryngeal nerve**, which passes under the right subclavian artery to ascend in the groove between the esophagus and the trachea to reach the larynx. **Note:** The right recurrent laryngeal nerve is not in the mediastinum. The left vagus nerve gives rise to the **left recurrent laryngeal nerve** in the superior mediastinum, which passes under the aortic arch and ligamentum arteriosum to ascend to the larynx.
- The **thoracic duct** is the largest lymphatic channel in the body. It returns lymph to the venous circulation at the junction of the left internal jugular vein and the left subclavian vein.
- **Phrenic nerves** arise from the ventral rami of **cervical nerves 3, 4, and 5**. The nerves are the sole motor supply of the diaphragm and convey sensory information from the central portion of both the superior and inferior portions of the diaphragm and parietal pleura. Both phrenic nerves pass through the middle mediastinum lateral between the fibrous pericardium and pleura, and anterior to the root of the lung.

Clinical Correlate

- The **left recurrent laryngeal nerve** (Figure II-2-30) curves under the aortic arch distal to the ligamentum arteriosum where it may be damaged by pathology (e.g., malignancy or aneurysm of the aortic arch), resulting in paralysis of the left vocal folds. The right laryngeal nerve is not affected because it arises from the right vagus nerve in the root of the neck and passes under the subclavian artery.
- Either the right or the left recurrent laryngeal nerve may be lesioned with thyroid gland surgery.

KAPLAN CORNER

Objective

1. Identify the development of the laryngotracheal (respiratory) diverticulum.
2. Identify the bones of the thoracic cage.
3. Identify superficial soft tissues.
4. Identify the trachea and lung fields.
5. Describe the mediastinum and the cardiac shadows. Describe brief knowledge about Bronchography.
6. Describe brief knowledge about Coronary Angiography

Radiography

Different views of the chest can be obtained by changing the orientation of the body and the direction of the x-ray beams.
The most common views are:

1. **Posteroanterior (PA):**
   - The x-rays enter through the posterior aspect of the chest, and exit out of the anterior aspect where they are detected by an x-ray film.
   - It avoids magnification of the heart as the film is close to the anterior chest wall. Thus Gives a good assessment of the Cardiac Size.
   - It is identified by the presence of the fundal gas bubble and the absence of the scapulae in the lung fields.
2. **Anteroposterior (AP):**
   - The x-rays enter through the anterior aspect and exit through the posterior aspect of the chest.
   - Done where it is difficult for the patient to obtain a normal chest x-ray, such as when the patient cannot get out of bed.
3. **Lateral:** Indicated only for further interpretation.
4. **Decubitus:** lying at the side.


Posteroanterior


Anteroposterior


Lateral


Decubitus

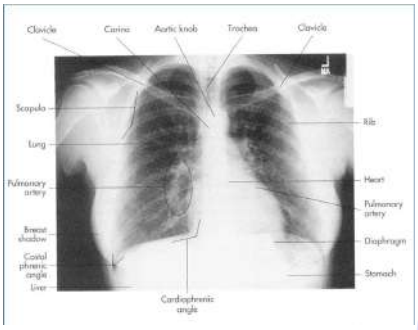
A chest x-ray may be used to diagnose, plan treatment and follow up for various conditions, including:

- Fractures of the chest bones, including ribs, sternum, clavicle, vertebrae, and scapula.
- Lung disorders such as pneumonia, emphysema, pleural effusion, tuberculosis and lung cancer.*
- Heart disorders such as congestive heart failure ,which causes cardiomegaly (heart enlargement)*
- Screen for job-related lung diseases in industries such as mining where workers are exposed to dust, (asbestosis, silicosis).
- Sometime its Requested as pre-employment demand.

Posteroanterior Radiograph

For Posteroanterior radiograph (PA), the following systems must be examined in order:

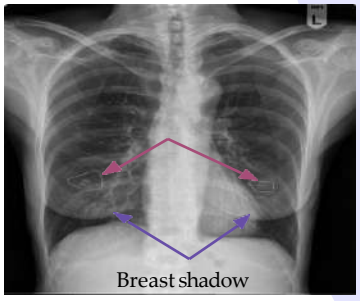
1. Superficial soft tissues
2. Bones
3. Diaphragm
4. Trachea
5. Lungs
6. Mediastinum



1- Superficial soft tissues

The superficial soft tissues that can be seen are:

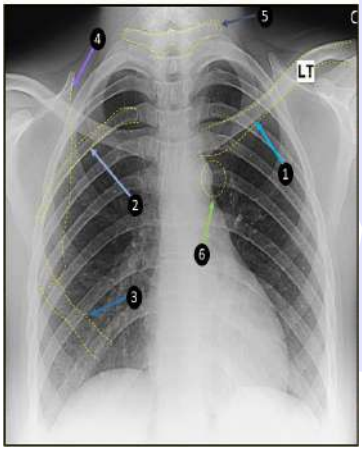
- The nipples in both sexes
- The breast in female are seen superimposed on the lung fields



2- Bones

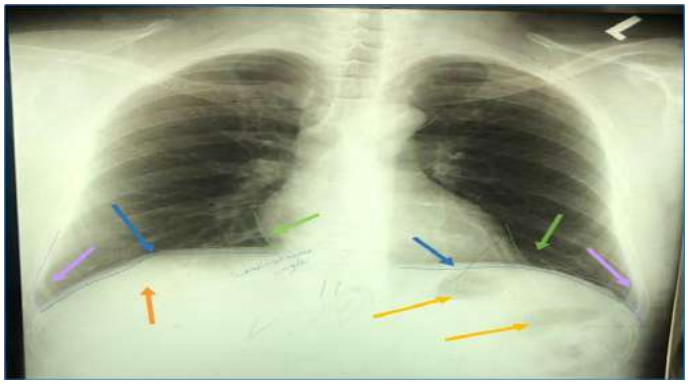
Bones of the thoracic cage, e.g:

1. Clavicle : are seen clearly crossing the upper part of each lung field.
2. Posterior rib.
3. Anterior rib.
4. Medial border of scapula: may overlap the periphery of each lung field.
5. Thoracic vertebrae: are imperfectly seen.
6. Costotransverse joints and each Rib should be examined in order from above downward and compared to their fellows of the opposite side, The Costal Cartilages are not usually seen, but if calcified (abnormal), they will be visible.



3- Diaphragm

- The diaphragm appears as a dome-shaped shadow on each side.
- The right side is slightly higher than the left.
- Beneath the right dome is the homogeneous, dense shadow of the liver.
- Beneath the left dome a gas bubble mostly seen in the fundus of the stomach.
- Notice the Costophrenic or Costodiaphragmatic angle, where the diaphragm meets the thoracic wall.
- The angle becomes blunt or obscured due to minimal pleural fluid (effusion) or fibrosis.
- Also note the cardiophrenic angle where the diaphragm meet the heart.



4- Trachea

- The radio-translucent, air-filled shadow of the trachea is seen in the midline of the neck as a dark area.
- This is superimposed by the lower cervical and upper thoracic vertebrae.
- Tracheal shift : Tracheal air column is seen shifted to right on X-ray chest PA view. It indicates:
  - A loss of volume of the right upper lobe of the lung, either due to collapse or fibrosis.

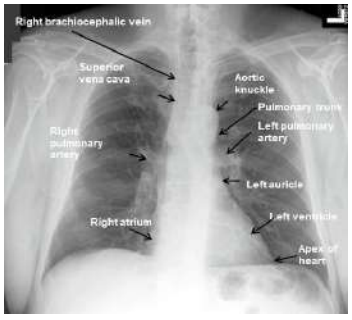
  OR
  - A massive pleural effusion on the left side

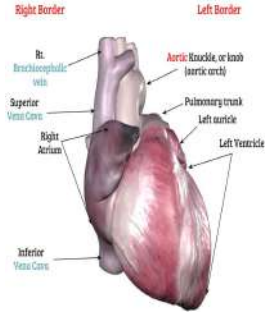
5- Lungs

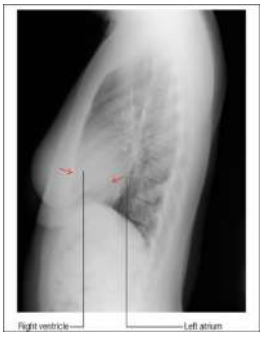
- Lung roots: relatively dense shadows caused by the presence of:
  - Blood-filled pulmonary and bronchial vessels
  - Large bronchi.
  - Lymph nodes.
- Notice that the lower margin of left hilum lies at the level of the upper margin of right hilum.
- The lung fields, by the air so they are more translucent on full inspiration than on expiration.
- The pulmonary blood vessels are seen as a series of small, rounded, white shadows radiating from the lung root.
- The large bronchi, are seen as similar round shadows.
- The smaller bronchi are not seen.

6- Mediastinum

- The shadow is produced by the various structures within the mediastinum, superimposed one on the other.
- Note the outline of the heart and great vessels.

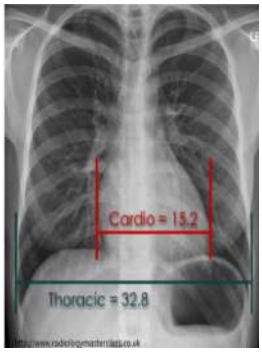






Note:
Right ventricle & left atrium appear only in lateral view

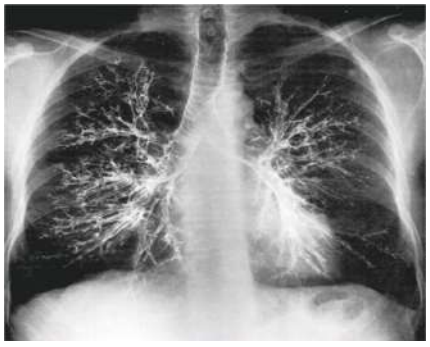
- The right border of mediastinum; consists of:
  - Right brachiocephalic vein
  - Superior vena cava
  - Right atrium
  - Inferior vena cava (sometimes)
- The left border of mediastinum consists of:
  - Aortic knuckle, or aortic knob (aortic arch)
  - Pulmonary trunk
  - Left auricle
  - Left ventricle and apex of heart.
- The inferior border (lower border of the heart) blends with the diaphragm and liver shadow.
- Normally the transverse diameter of the heart should not exceed half of the width of thoracic cage.
- On deep inspiration, when the diaphragm descends, the vertical length of the heart increases and the transverse diameter is narrowed.
- In infants, the heart is always wider and more globular in shape than in adults.

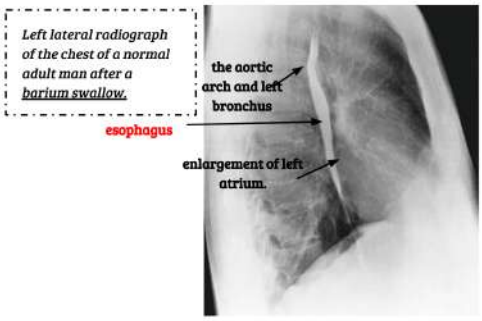


Other uses of chest X-ray

Bronchography

- Bronchography is special study of the bronchial tree by introduction of contrast medium into a particular bronchus usually under fluoroscopic control.
- The contrast media are non irritating and sufficiently radiopaque to allow good visualization of the bronchi. After the radiographic examination is completed, the patient is asked to cough and expectorate the contrast medium





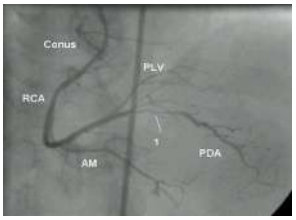
Contrast visualization of Esophagus

- Contrast visualization of the esophagus by swallowing a contrast media, (barium swallow).
- Other barium contrast studies:
  - Barium meal: stomach
  - Barium follow through: small intestine
  - Barium enema: large intestine

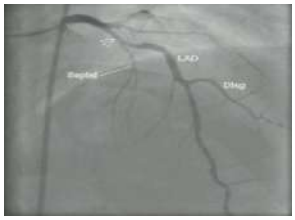
Coronary Angiography

- An X-ray with radio-opaque contrast in the coronary arteries.
- The coronary arteries are visualized by introduction of radio-opaque material into their lumen
- Pathological narrowing or blockage of coronary artery can be identified.

Right



Left



Radiological Anatomy of The Thorax

X-ray

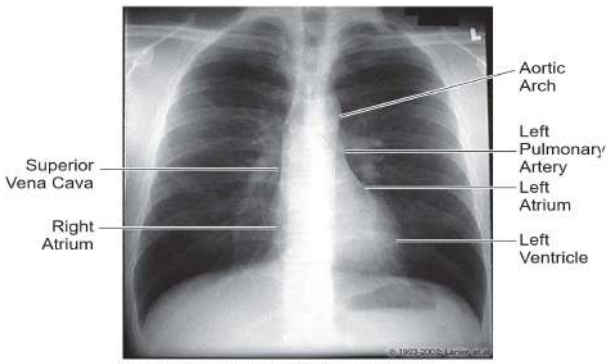


Figure II-2-46. Anterior Projection of Chest, Male

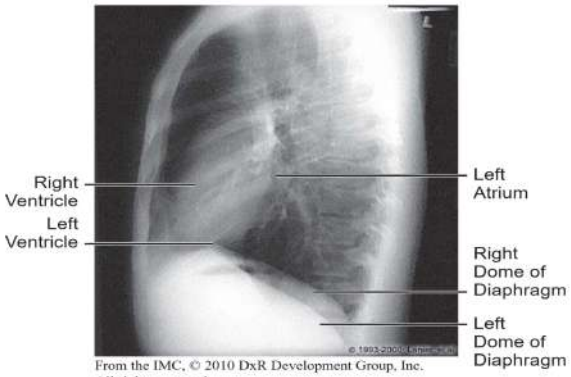


Figure II-2-47. Lateral Projection of Chest, Male

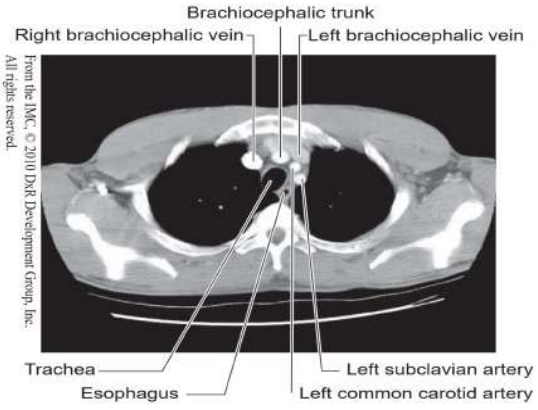


Figure II-2-48. Chest: CT, T2

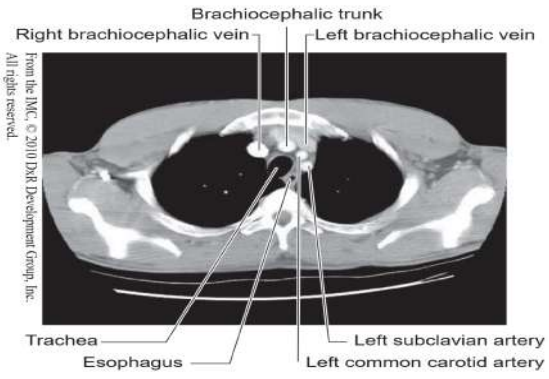


Figure II-2-48. Chest: CT, T2

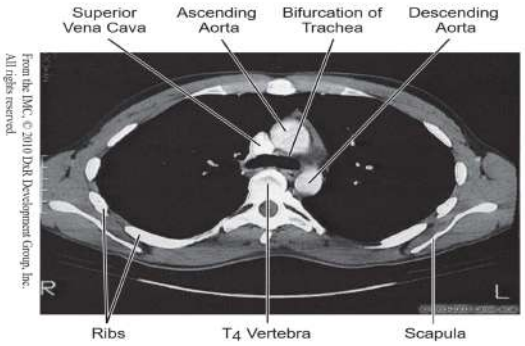


Figure II-2-50. Chest: CT, T4

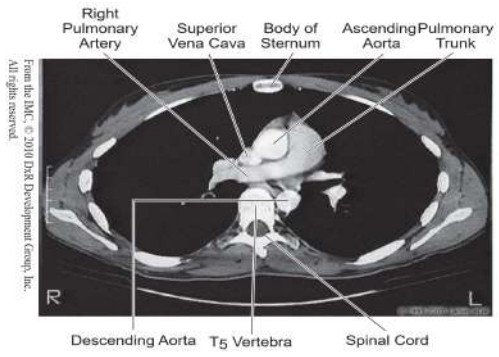
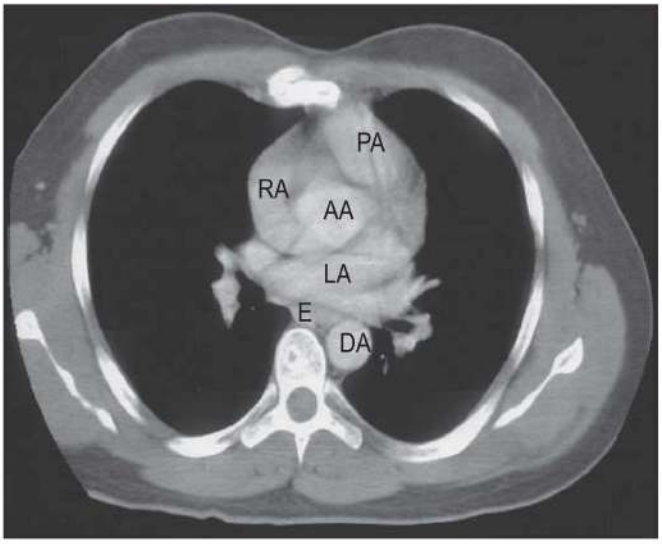


Figure II-2-51. Chest: CT, T5

KAPLAN CORNER

Radiological Anatomy of The Thorax

CT scan



PA = pulmonary artery
RA = right atrium
AA = ascending aorta
LA = left atrium
E = esophagus
DA = descending aorta

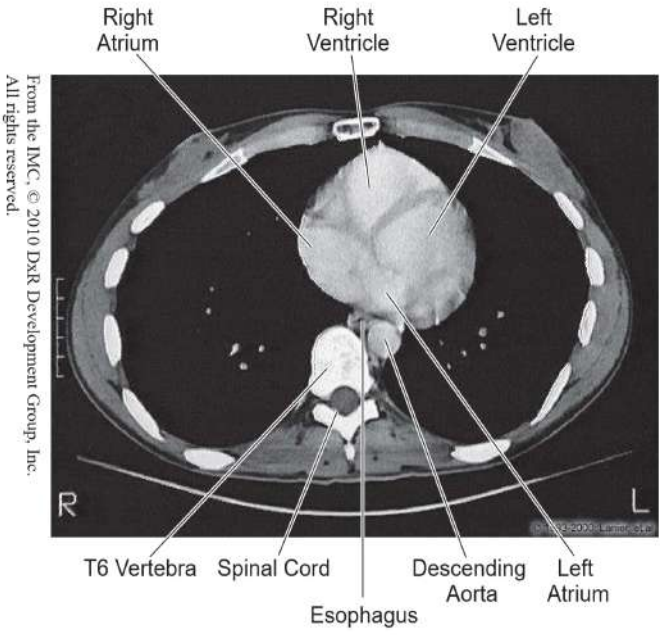


Figure II-2-53. Chest: CT, T6

KAPLAN CORNER

SECTION 4 :

MISCELLANEOUS

282 **BIOCHEMISTERY:** Phospholipids of physiological significance

289 **BIOCHEMISTERY** Respiratory chain

295 **PHYSIOLOGY:** Effects of low and high gas pressure on the body

302 **PHYSIOLOGY:** Effect of Exercise on respiratory

307 **PHARMACOLOGY:** Antibiotics

311 **PHARMACOLOGY:** Anti-cholinergic drugs

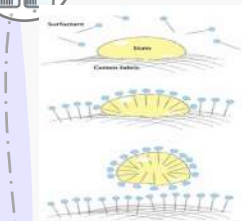
315 **PHARMACOLOGY:** Adrenergic drugs

324 **PHARMACOLOGY:** Anaphylactic shock

330 **FAMILY MEDICINE:** Tobacco smoking

Objective

1. Identify the types and functions of phospholipids
2. Discuss the physiological importance of phospholipids
3. Understand the Types, functions and role of glycerophospholipids in cell signaling, protein anchoring, lung surfactant and their clinical implications in respiratory distress syndrome (RDS)
4. Identify the classes and physiological functions of phospholipase enzymes



What is a detergent?
A molecule with a nonpolar end that attaches to the lipid, and a polar end that attaches to water. Because of this property, it can solubilize lipid in water "as Shown in the picture"

Phospholipids :

What are phospholipids?

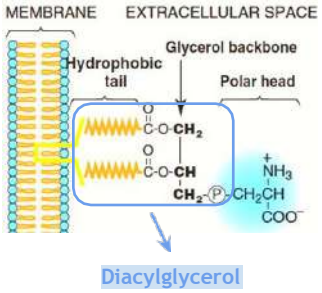
Major lipids of cell membranes, they are polar, ionic compounds that contain an alcohol group attached either to:
Diacylglycerol → Glycerophospholipids
Sphingosine →Sphingophospholipids.

Properties:

They are Amphipathic which have two component

- Phospho=Hydrophilic = polar which mean interacting with the aqueous environment
- Lipid = Hydrophobic = non-polar which attached to the membrane .

Its Function : selectivity in permeability (only lipid soluble can cross).



Functions:

Membrane-bound phospholipids:

- Reservoir for intracellular messengers (signaling)
- Anchors to cell membranes

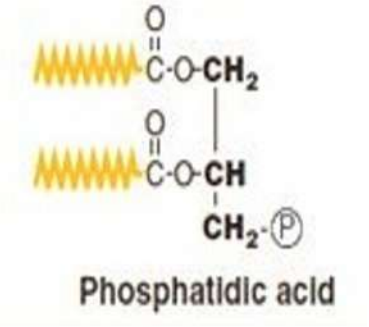
Nonmembrane-bound phospholipids:

- Lung surfactant
- Components of bile (as detergents)

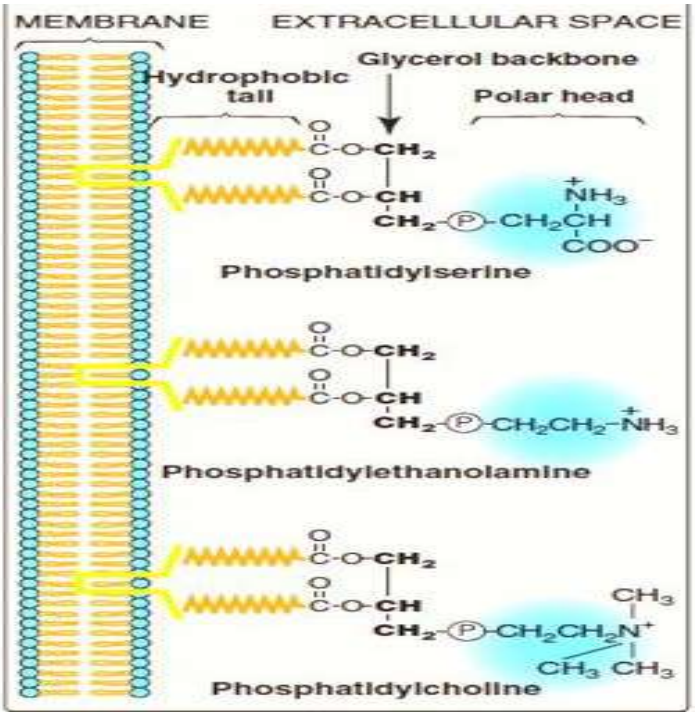
Glycerophospholipids "Also called phosphoglycerides

What are they ?

- A major class of phospholipids
- Contain glycerol (Backbone)
- All contain (derived from) phosphatidic acid which is the simplest phospholipid (precursor)



	Consist of	Function
Phosphatidylserine (PS)	Serine + PA	Cell signaling - Blood clotting
Phosphatidylethanolamine (PE) (cephalin)	Ethanolamine + PA	Play a role in membrane fusion
Phosphatidylcholine (PC) (lecithin)	Choline + PA	Lung surfactant
Phosphatidylinositol (PI)	Inositol + PA	Cell signaling
Phosphatidylglycerol (PG)	Glycerol + PA * by phosphodiester bond	Lung surfactant



Some Example of glycerophospholipids

Platelet activating factor (PAF)

- **Structure** :

In general other phosphoglycerides, the fatty acids are attached to glycerol by Ester linkages, while in PAF:

1- it is bound by an Ether linkage

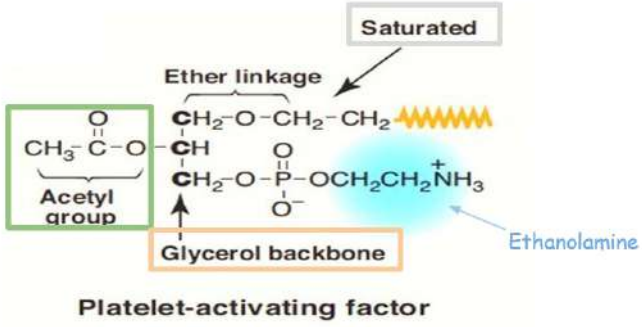
2- it has an acetyl group at carbon number 2

- **Location :**

attached to cell surface receptors of platelets (mainly) or other cells

- **Function:**

Activates platelets to aggregate and triggers thrombotic and acute inflammatory reaction (hypersensitivity) which can cause tissue damage



Platelet-activating factor

Cardiolipin

- **Structure** :

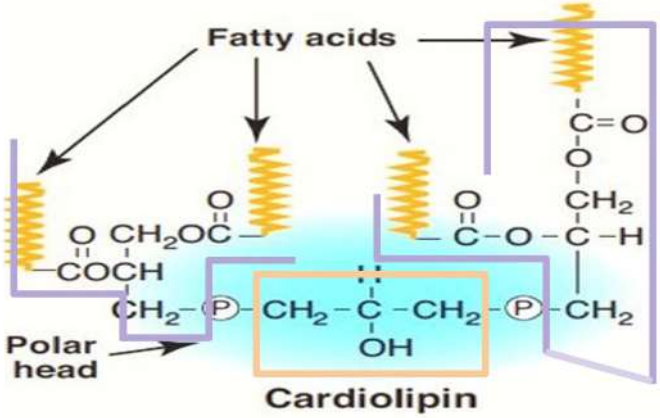
2 molecules of PA + additional molecule of glycerol through PO4 groups

- **Location** :

the inner mitochondrial membrane.

- **Function**:

maintenance of respiratory complexes of electron transport chain



Cardiolipin

Role of Phosphatidylcholine (lecithin) in lung surfactant

Alveolar cells of lungs :

- lined by the extracellular fluid layer, which has tendency to develop surface tension.
- Type 2 alveolar cells secrete lipid such as Dipalmitoylphosphatidylcholine

lung surfactant complex:

- lipids (90%)

The major is Dipalmitoylphosphatidylcholine (DPPC), and Other Phosphatidylglycerol.

- Proteins (10%)

help in distributing the surfactant in between the water molecules, preventing them from sticking together (reduce the surface tension)

Function of surfactant:

Decreases the surface tension of the fluid layer:

- reduces the pressure needed to re-inflate the alveoli.
- prevents alveolar collapse (atelectasis)

Respiratory distress syndrome (RDS) :

- Adults:

Due to damaged alveoli by infection, trauma or smoking

- Preterm infants:

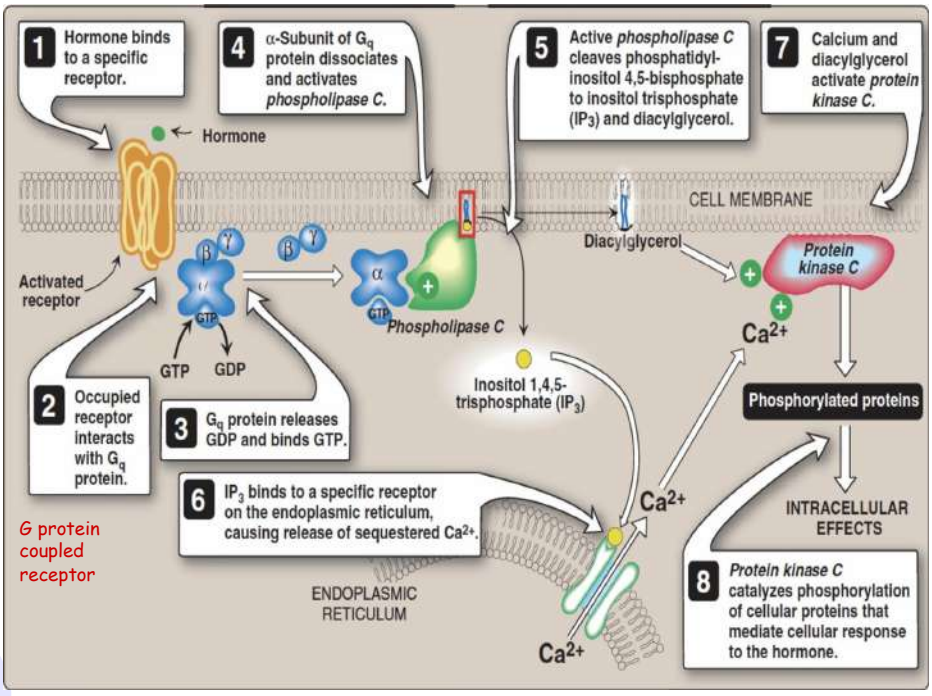
It is due to deficiency of lung surfactant. It is a major cause of neonatal death. Can be Treated or prevented by given Glucocorticoids to mother to promote lung maturation prior to delivery .

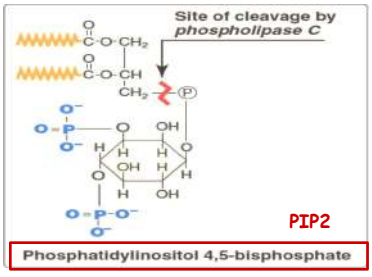
Note:
How to assist the lung maturity of the fetus by: target for the Amniotic fluid and measure the ratio of DPPC and sphingomyelin.
علاقة الاثنين عكسية بحيث الجنين يصنع واحد أكثر من الثاني

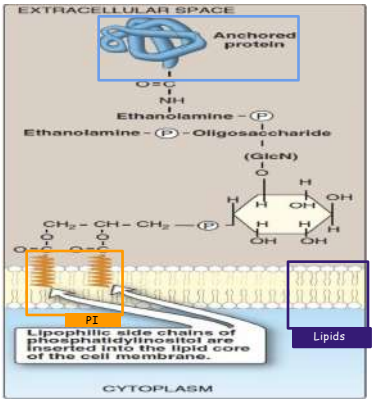
Main Role of Phosphatidylinositol (PI)

Intracellular signaling

- It is a part of calcium-phosphatidyl inositol system
- In the membrane it is phosphorylated at two positions.







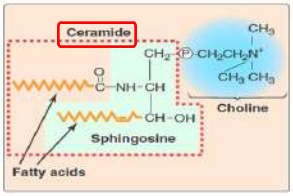
Protein anchoring to membranes

- Attaching of protein to the embedded lipid. By carbohydrate-PI bridge
- Can be cleaved by phospholipase C enzyme
- Common proteins that are anchored :

1- Alkaline phosphatase located at the surface of small intestine
2- Acetylcholine esterase located at postsynaptic membrane of neurons

Sphingophospholipids

Precursor of sphingophospholipids



- Structure :

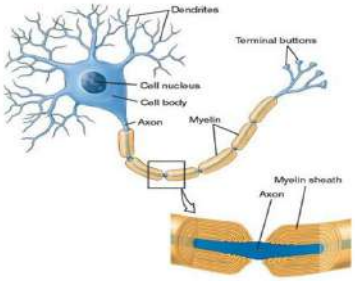
A long-chain fatty acid attached to sphingosine.

- Example:

Sphingomyelin

- Importance :

An important component of myelin that protects and insulates nerve fibers which increase conduction velocity



Phospholipids in lipoprotein particles

- The outer core of lipoprotein particles is hydrophilic Contains

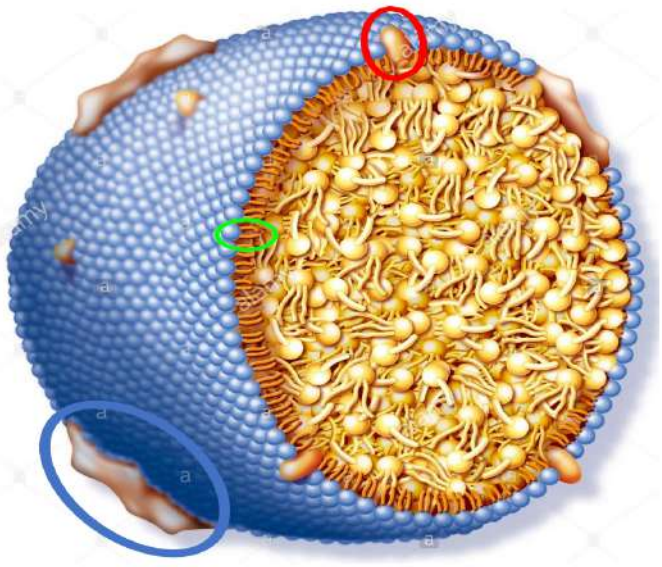
- Phospholipids
- Free cholesterol (Unesterified) “polar”

Allows transport of core lipids in aqueous plasma

- Inner core contains:

- Triacylglycerol
- Cholesteryl esters

- Apolipoprotein



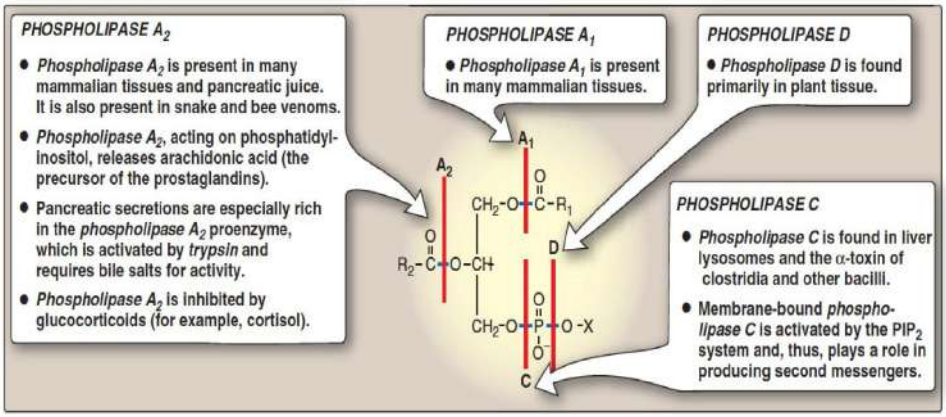
Phospholipases

What are they ?

- Present in all tissues including pancreatic juice

- They work on Degradation of phospholipids
  - Degradation of Glycerophospholipids by Phospholipase A1 ,A2, C, D
  - Degradation of sphingophospholipids by Sphingomyelinase, Present in lysosomes especially hepatocytes (liver)

Extra Explanation:
Phospholipases D : involved in signal transduction , generating phosphatidic acid and choline from phosphatidylcholine and diacylglycerol



Functions of phospholipases ?

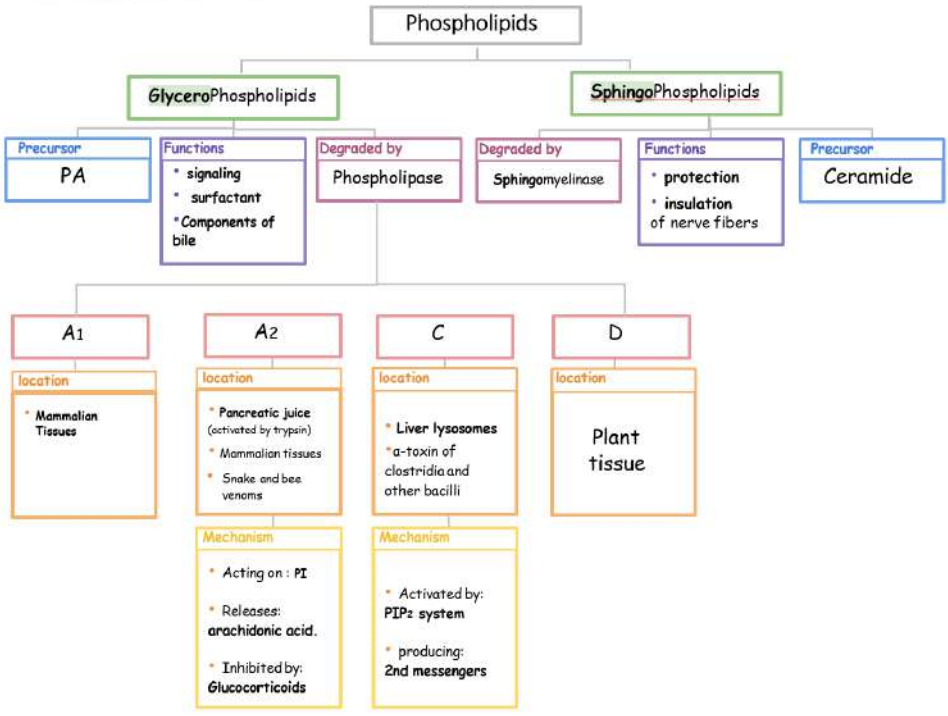
- **Digestion** of phospholipids by pancreatic juice.

- Production of **second messengers.**

- **Remodeling** of phospholipids (from one kind of phospholipid to another kind).

- Pathogenic **bacteria produce** phospholipases to dissolve cell membranes and spread infection.

In Summary :



Take home message:

- Phospholipids are complex lipids that perform important physiological functions in the body.
- Membrane-bound phospholipids are involved in cell signaling, protein anchoring and myelin protective functions.
- Nonmembrane-bound phospholipids function as lung surfactant and as detergent in the bile.
- Phospholipases are enzymes that degrade phospholipids.
- They are important for remodeling of phospholipids.

Objective

1. Understand how energy-rich molecules including glucose are metabolized by series of oxidation-reduction reactions ultimately yielding CO_2 and water.
2. Explain the process of electron transport chain that releases free energy, which is used for ATP synthesis and heat production.
3. Recognize the reaction taking place in mitochondria that are coupled to oxidative phosphorylation.

Structure of the mitochondria

Outer membrane:

- Contains special channels (formed by the protein porin).
- Highly permeable.

Inner membrane:

- Impermeable to most small ions, small and large molecules.
- Highly selective.

Intermembrane space:

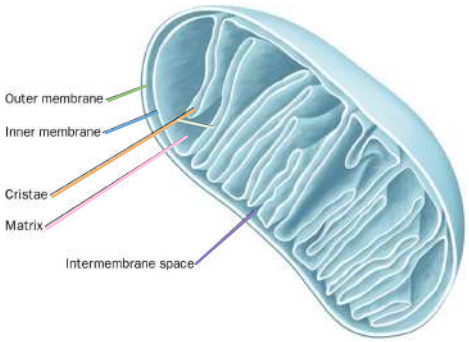
- The space between the outer and the inner membrane.

Matrix:

- Gel like solution in the interior of the Mitochondria.
- Contains:
  - TCA cycle enzymes.
  - Fatty acid oxidation enzymes
  - Mitochondrial ribosomes.
  - mtDNA & mtRNA

Cristae:

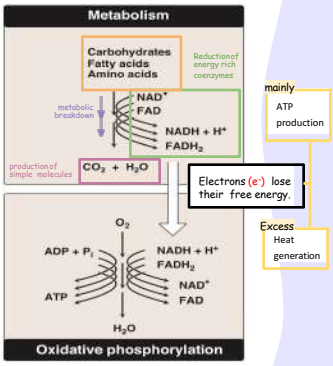
- Folding of the inner membrane.
- Increase the surface area.



Electron Transport chain (ETC)

Definition:

A system of electron transport that uses respiratory O2 to finally produce ATP (energy).



Location:

The inner mitochondrial membrane (IMM).

Characteristics:

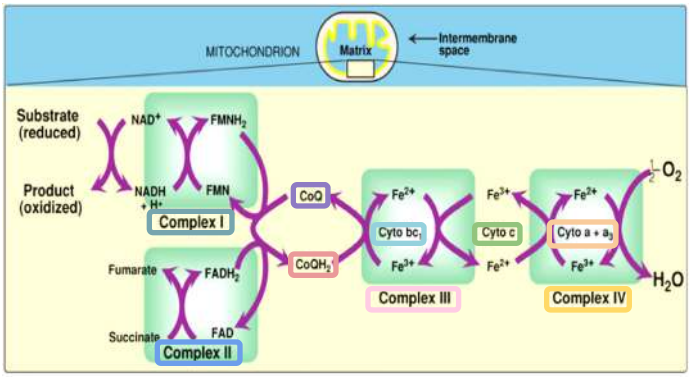
- Final common pathway of metabolism.
- Uses the maximum amount of O2.

Mechanism:

Electrons from food metabolism Transported to O2.

Process of Electron Transport Chain:

- Each complex accepts or donates electrons to mobile carriers.
- Carriers accept electrons from donors and then donate to the next carrier in chain.
- Notice that no ATP has been generated yet from this process.
- The Sequence : CoQ → Complex III → Cytochrome C → Complex IV



- **Explain the figure above :**

1- Co-Enzyme Q receives an electron from Complex I and complex II, then it gets reduced and become CoQH2.

2- Then it gives the electron to cytochrome bc1 "in complex III", then CoQH2 gets oxidized back to CoQ to do another round of taking the electron.

3- Complex III is a combination of two cytochromes cytochrome B and cytochrome C1, which gives electrons to mobile carrier Cytochrome C.

4- Cytochrome C receives the electron and gives it to Cytochrome a + a3 "in complex IV".

5- The **final acceptor** is the **oxygen** which gets combined with electrons & protons to form **water.**

Components of Electron transport Chain

Complex I (NADH Dehydrogenase) :

- It is a Proton pumps.
- Collects the pair of electrons from NADH and passes them to CoQ.

Complex II (Succinate dehydrogenase)

- Transfers electrons to CoQ From FADH
- Part of the TCA cycle

Co-Enzyme Q

- It is Mobile electron carriers
- Also called ubiquinone "present in all biological systems"
- The only non-protein member of the ETC
- Lipid soluble and mobile

Complex III

- It is a Proton pumps.
- Cytochrome bc_1

Complex IV

- It is a Proton pumps.
- Cytochrome a+a3
- Also called cytochrome c oxidase

Cytochrome C

- It is Mobile electron carriers

Complex V (ATP synthase)

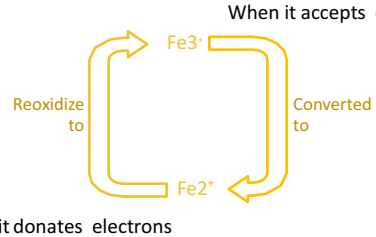
- It is a Proton pumps.
- Catalyzes ATP synthesis
- **"Not a part of ETC"**

Electrons flow:

complexes I&II → CoQ → Complex III → Cytochrome C → Complex IV

Cytochromes:

Each cytochrome is a protein that contains (Porphyrin ring + iron in Fe3+ state= Heme group)

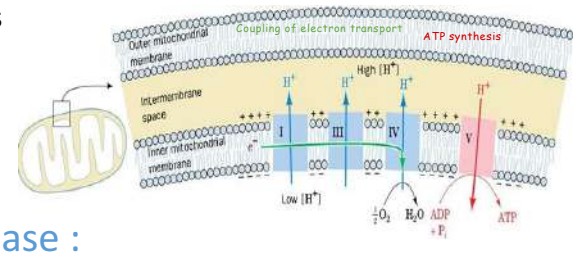


ATP synthesis

ETC is coupled to proton transport for ATP synthesis

- The energy of electron transfer is used to drive the protons out of the matrix (proton pump)
- Creates a proton gradient across the Inner Mitochondrial Membrane :

  1- Electrical gradient
  (more positive charges in the intermembrane space than on the matrix)
  2- PH (chemical) gradient
  (the intermembrane space is at a lower pH than the matrix)
- The energy (proton-motive force) generated by the gradient drive ATP synthesis



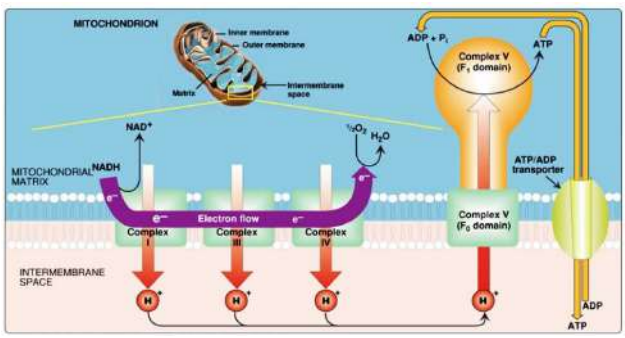
ATP synthase :

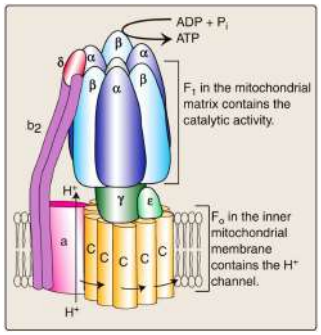
- ATP Synthase (complex V) synthesizes ATP by "using the energy of the proton gradient generated by the electron transport chain"
- The inner mitochondrial membrane has high selectivity so the only way protons can return is through ATP synthase
- Consist of two domains:

  - F_1 : Extra- membranous domain (In the mitochondrial matrix)
  - F_0 : Membrane spanning domain (In the intermembrane space) , it is called Fo because it can be inhibited by **o**ligomycin)

Transport of protons :

- H+ ion re-enter the matrix by passing through a H+ channel in the F0 domain
- Rotation of the c ring of F0
- Conformational changes in the three β subunits of F1
- In F1 domain, Binding of ADP + P
- In F1 domain, Phosphorylation of ADP to ATP and release ATP





Energetics of ATP synthesis

- Energy produced from the transport of a pair of electrons from NADH to O2 = 52.58 kcal.
- Energy required for phosphorylation of ADP → ATP = 7.3kcal/mol, and it is the energy is needed to form the Phosphate bond.
- NO. Of ATP molecules produced is 3 (NADH→O2). 3 x 7.3 = 21.9 kcal
- Excess energy is used for other reactions or released as heat. 52.58 - 21.9 = 30.78 kcal.
- Ratio :
  - NADH (3:1) : which mean 3 ATP are made per oxygen atom reduced.
  - FADH2 (2:1) : which mean 2 ATP are made per oxygen atom reduced.

Extra Explanation:

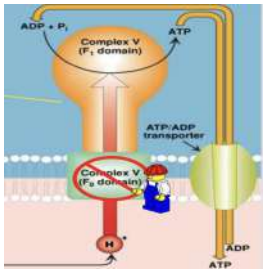
Why does FADH2 produces less ATP than NADH?

- NADH transfers its electrons in complex I so it passes through 3 pumps (complexes I, III and IV).
- FADH2 transfers its electrons in complex II so it passes only through 2 pumps (complexes III and IV)

Inhibitors of ATP synthesis :

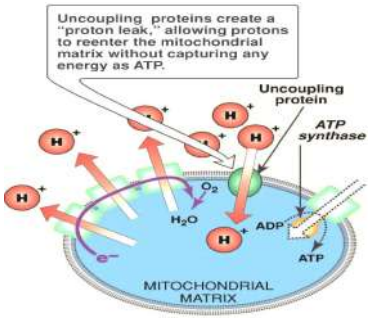
- Oligomycin:

Binds to F0 domain of ATP, synthase and closes the H+ channel



- Uncoupling proteins (UCPs):

Energy is released as heat (non- shivering thermogenesis)



From Lippincott:

Responsible for heat production in the mitochondria-rich brown adipocytes of mammals.

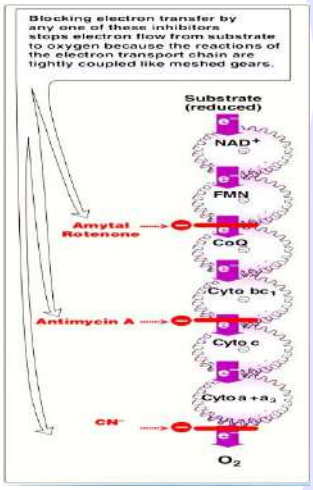
In brown fat, unlike the more abundant white fat, ~90% of its respiratory energy is used for thermogenesis in infants in response to cold.

Thus, brown fat is involved in energy expenditure, whereas white fat is involved in energy storage.

Site-specific inhibitors of ETC

- These respiratory inhibitors prevent the passage of electrons by binding to a component of the chain, blocking the oxidation-reduction reaction. Therefore, all electron carriers before the block are fully reduced, whereas those located after the block are oxidized.
- Inhibition of electron transport inhibits ATP synthesis because these processes are tightly coupled.
  So, there's No production of ATP and energy dissipated as heat. known as non-shivering thermogenesis.

Site-specific inhibitors of ETC



Rotenone:

Inhibits between FMN (complex I) and CoQ.

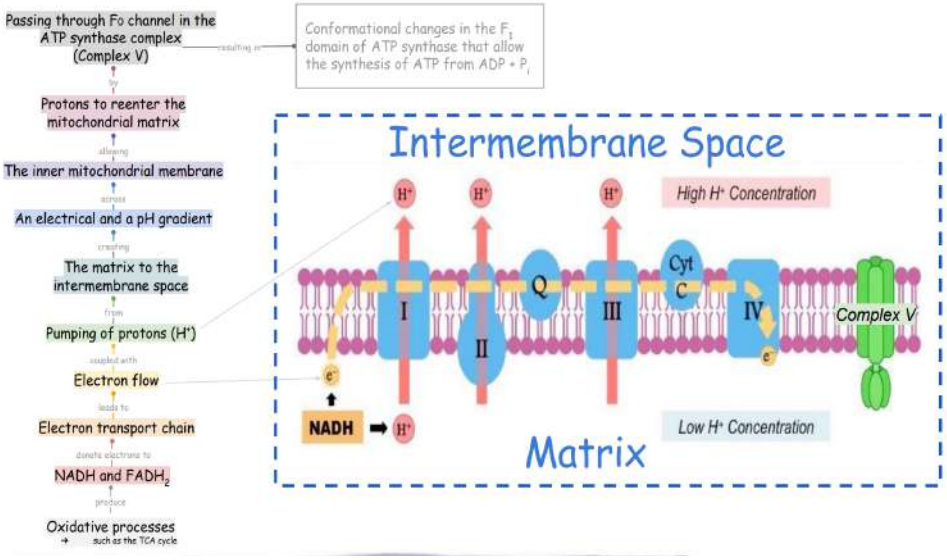
Antimycin A:

Poison which inhibits between cyto bc1 (complex III) and cyto c.

Cyanide (CN):

When there is cyanide (CN-) or CO or sodium azide poisoning they will inhibit the Cycle (oxidative phosphorylation) at the last step before the oxygen gets oxidized (complex IV).

In Summary



Take home message :

- ETC is a common pathway of transferring energy-rich electrons from metabolism finally yielding CO2 and water
- The energy of the electrons transferred is used for ATP synthesis and heat production.

Objective

1. Describe the effects of exposure to low and high barometric pressures on the body.
2. Describe the body acclimatization to low barometric pressure.
3. Define decompression sickness and explain how it can be avoided.
4. Understand the effects of high nitrogen pressure, and nitrogen narcosis.

Effect of Increased Barometric Pressure (Deep Sea Diving)

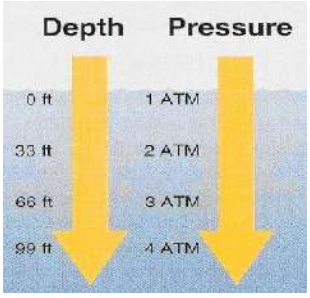
Introduction :

- The atmospheric pressure is 760 mmHg.

When human descend below the sea, the pressure around them INCREASES. To prevent the lungs from collapse air must be supplied also under high pressure this exposes the blood in the lungs to extremely high alveolar gas pressure (hyperbarism). Under certain limits these high pressures cause tremendous alterations in the physiology of the body.

Note :
Therefore, a person 33 feet beneath the ocean surface is exposed to 2 atmosphere pressure, one is the atmospheric pressure caused by the weight of the air above the water and the second atmosphere by the weight of the water itself.

- The surrounding pressure increases by 1 atmosphere for every 10 meters (33 feet) of depth in sea water. For example, at a depth of 31 meter (100 feet) in the ocean the diver is exposed to a pressure of 4 atmospheres (1 atm “from air” +3 atm “1 for each 10m” = 4).



- These problems confront SCUBA (**S**elf **C**ontained **U**nderwater Breathing Apparatus.)

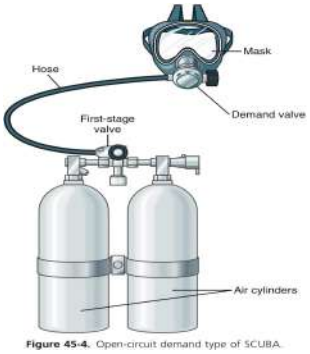
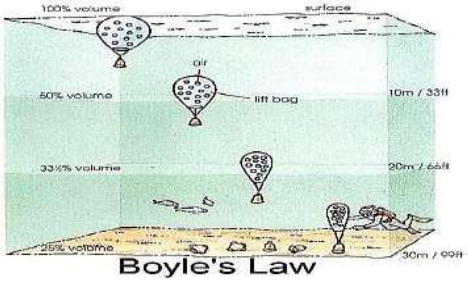


Figure 45-4. Open-circuit demand type of SCUBA.

Effect of depth on the volume of the gases:

- At depth there is compression of gases to smaller and smaller volumes. For example, 1L (sea level) →1/2 L at 33 feet and so on.
- Boyle's law: Volume to which a given quantity of gas is compressed is inversely proportional to the pressure.



Effect of depth on density of gases:

- Increase in the density of gas and hence increased work of breathing.
- Increase air resistance in the airway is like swallowing jelly instead of water.
- Increase in pressure causes the gas molecules to be more close to each other so the space will decrease between the molecules, and this decrease in space makes the gas too thick and like liquids.

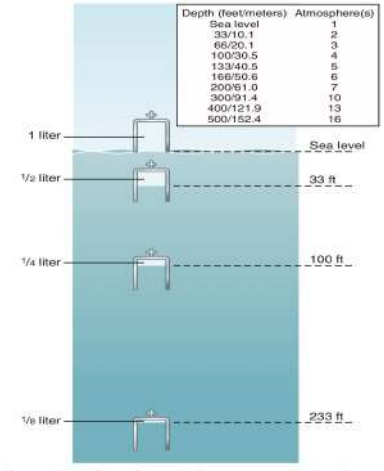
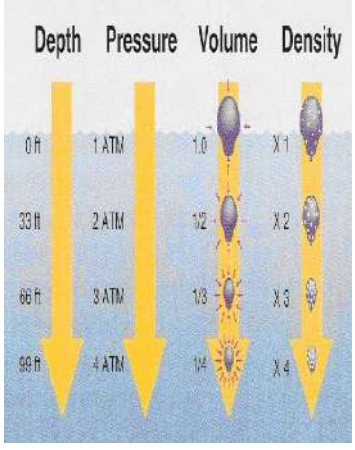


Figure 45-1. Effect of sea depth on pressure (*top*) and on gas volume (*bottom*).



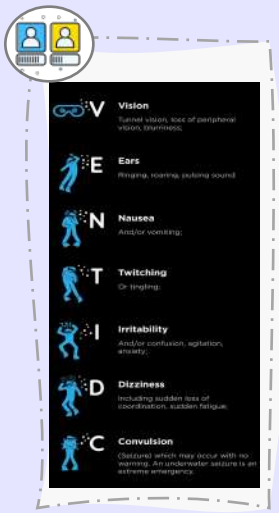
Nitrogen effect at high pressure:

Nitrogen is the most element among respiratory elements that's affected by Henry's law .

- Henry' law: " the amount of dissolved gas (is proportional to its partial pressure in the gas phase".
- Has 2 principle effects:

- Decompression sickness.
- Nitrogen narcosis (anesthetic effect)

Oxygen toxicity when breathing hyperbaric air



Effect of Very High PO2 on Blood Oxygen Transport :

When the Po2 in the blood rises above 100 mmHg. the amount of oxygen dissolved in the blood increases markedly.

Acute Oxygen Poisoning

Acute Oxygen Poisoning is a Condition resulting from the harmful effects of breathing molecular Oxygen (O2) at increased partial pressure.

At 4 atmospheres pressure of oxygen (Po2 = 3040 mm Hg) will cause :

- Brain seizures:
  followed by coma in most people within 30 to 60 minutes.
- Other symptoms include:
  Nausea, muscle twitching, dizziness, disturbances of vision, irritability and disorientation.

How does it happen ?

Molecular oxygen (O2) has little capability of oxidizing other chemical compounds. Instead, it must first be converted into an active form of oxygen. Called oxygen free radicals. e,g superoxide and hydrogen peroxide.

- So the cause of oxygen toxicity is not the oxygen itself but the active form of it which is the free radicals.

- At high levels, these oxygen free radicals can have serious destructive and even lethal effects on the cells.

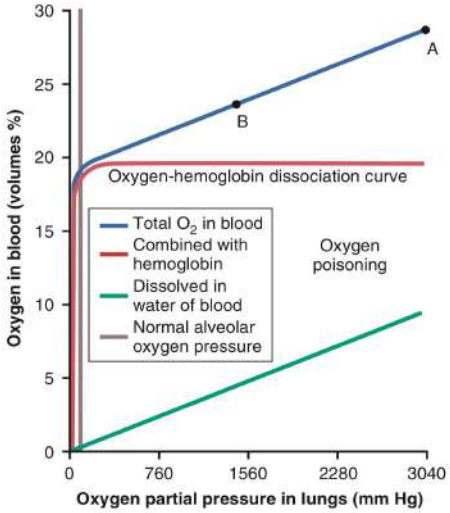
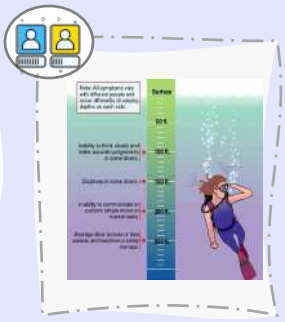


Figure 45-2. Quantity of O_2 dissolved in the fluid of the blood and in combination with hemoglobin at very high P_{O_2} values.

Nitrogen Narcosis

Introduction:

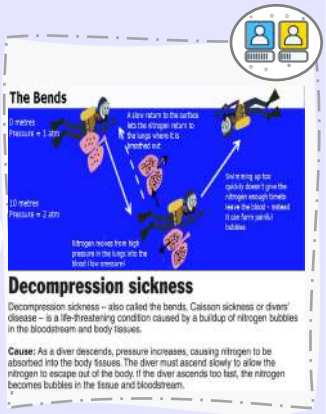


- Nitrogen like most other anesthetic gases, dissolve freely in the fats of the body including the membranes and other lipid structures of the neurons.
- This leads to alteration of the electrical conductance of the membranes and reduces their excitability and subsequent narcosis develops.
- Nitrogen diffuse into blood only in high pressure altitudes and it can cross BBB and has an anesthetic response.
- Nitrogen is five times as soluble in fat as in water.
- The signs and symptoms are varied dependent on the feet :
  - **At 120 feet:** The diver loses many of his cares.
  - **At 150 feet:** There is a feeling of euphoria, drowsiness and impaired performance.
  - **At higher pressure than 150 Feet** : Loss of coordination and finally coma might develop.

Feet	Liters
0	1
33	2
100	4
200	7
300	10

Decompression Sickness (Caisson's Disease)

It is a syndrome caused by a decrease in the ambient (surrounding) pressure which occur in animal and men when the tissues of the body contain an excess of physically inert (does not undergo chemical reactions) gas. Some other names: Bends, Compressed Air Sickness, Caisson Disease, Diver's Paralysis, Dysbarism.



On Ascending :

Inert gas comes out of physical solution forming a gaseous phase (bubbles), leading to symptoms and signs.

- During slow ascent:

N2 is slowly removed from the tissues since the partial pressure there is higher than that in the arterial blood and alveolar gas. To avoid getting caisson's disease.

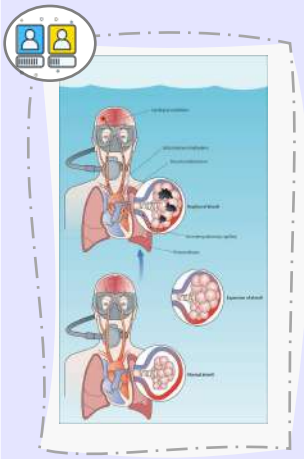
- If decompression is rapid:

Bubbles of gaseous nitrogen are released, in tissues and blood, causing the symptoms of decompression sickness (the bends or caisson disease). It Happens when the diver gets out of the water fast. Under the sea (under high pressure) the nitrogen inside our body is in a liquid like that's why when ascending too fast the nitrogen is converted quickly into gas and forms bubbles in the blood.

During Descending :

The high partial pressure of nitrogen (encountered when breathing compressed air at depth) forces this gas into solution in body tissue particularly in fat (it has a high N2 solubility).

Symptoms and signs of Decompression Sickness (DS)

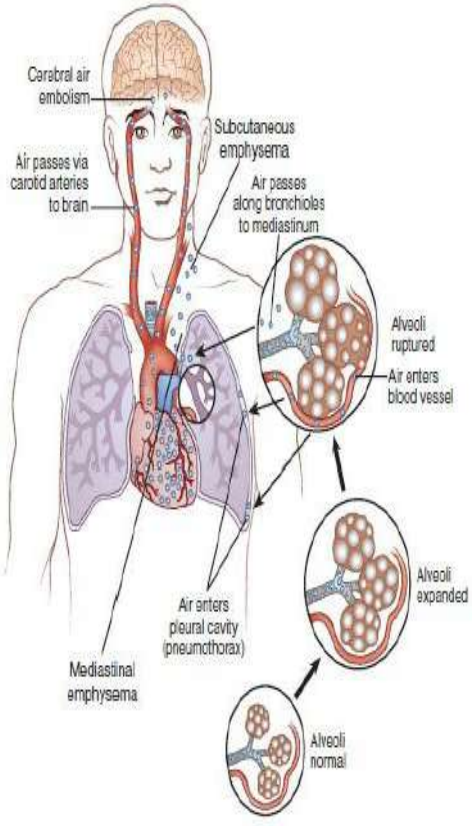


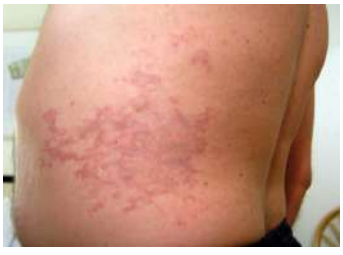
Mild symptoms:

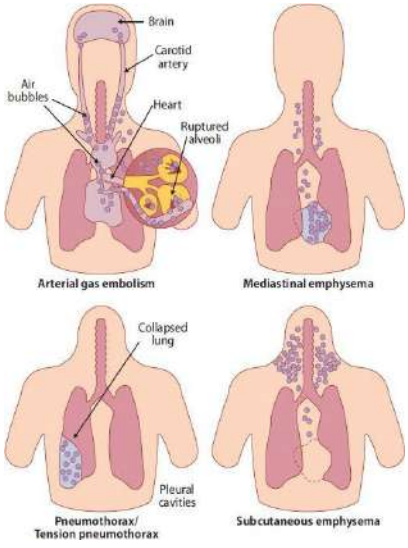
- fatigue or drowsiness after decompression.
- Locally there is a skin itch.

Severe symptoms:

- bubbles in the tissues cause severe pains particularly around the joints.
- Neurological symptoms include paresthesia, paralysis, and inner ear disturbances.
- Thoracic pains: dyspnea, substernal pain, cyanosis, and cough.
- Bubbles in the coronary arteries may cause myocardial damage “the bubbles will block the blood vessels”.
- Decompression sickness shock, capillaries become permeable to plasma and hypovolemia (decrease in blood volume) rapidly develop.
- Edema may be prominent and shock is also usually complicated by pulmonary edema.







Treatment of decompression symptoms

A- Rapid recompression :

Rapid recompression in a pressure chamber followed by slower decompression. Thus stimulating what would have happened if the diver was decompressed slowly

- This reduces the volume of the bubbles and forces them back into solution.
- In a very deep dives, the risk of decompression sickness can be reduced if a helium-O2 mixture is breathed during the dive.
- Also it is important to reduce the oxygen concentration in the gaseous mixture to avoid oxygen toxicity that would cause seizures .

B- Helium:

It is more desirable than nitrogen in deep dives because :

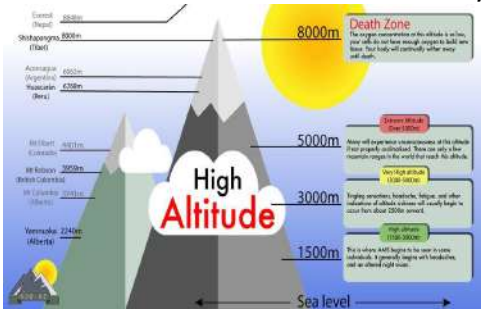
- It has 1/4 - 1/5 the narcotic effect of nitrogen on CNS.
- It is 1/7 the molecular weight of nitrogen.
- Low density leading to decreased airway resistance of diver.
- Helium is about 1/2 as soluble as nitrogen in body fluids. This reduces the quantity of bubbles that can form in tissues when the diver is decompressed after diving.

Diffuses out of the tissues during decompression several times as rapidly as does nitrogen, thus reducing the problem of decompression sickness. so it easily diffuses from capillary to alveoli and leaves the body. The advantage of Nitrogen in the gas mixture is to dilate so we replace it with Helium which is also has a dilating effect

Effects of low oxygen pressure on the body (Aviation-ascend to high altitude)

Introduction :

- At the sea level the barometric (atmospheric) pressure is 760 mmHg. While at 10,000 feet is 523 mmHg and it is 87 mmHg at 50,000 feet.
- The decreasing in barometric pressure is the basic cause of all the problems of hypoxia in high altitude physiologically. Because that's mean decreasing in O2 concentration which lead to Hypoxia.



From Guyton :

girl's doctor recommended us to read this part from Guyton Chronic Breathing of Low Oxygen Stimulates Respiration Even More—The Phenomenon of "Acclimatization"

Mountain climbers have found that when they ascend a mountain slowly, over a period of days rather than a period of hours, they breathe much more deeply and therefore can withstand far lower atmospheric oxygen concentrations than when they ascend rapidly. This is called acclimatization.

The reason for acclimatization is that, within 2 to 3 days, the respiratory center in the brain stem loses about four fifths of its sensitivity to changes in Pco2 and hydrogen ions.

Therefore, the excess ventilatory blow-off of carbon dioxide that normally would inhibit an increase in respiration fails to occur, and low oxygen can drive the respiratory system to a much higher level of alveolar ventilation than under acute conditions. Instead of the 70 percent increase in ventilation that might occur after acute exposure to low oxygen, the alveolar ventilation often increases 400 to 500 percent after 2 to 3 days of low oxygen; this helps immensely in supplying additional oxygen to the mountain climber.

Alveolar PO_2 at different altitudes :

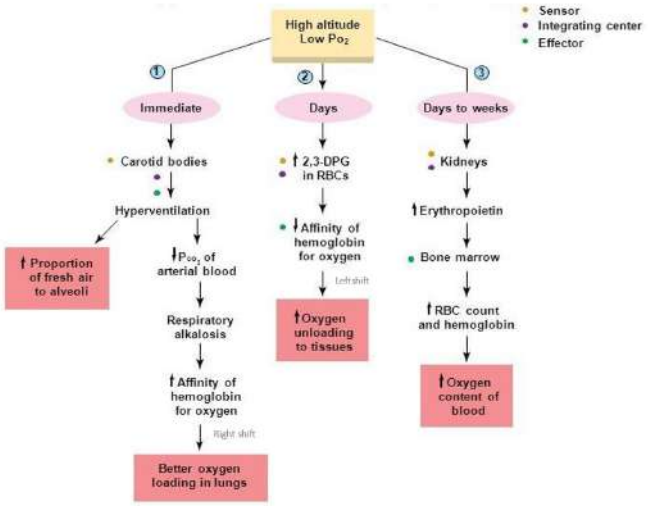
- As the barometric pressure decreases, the oxygen partial pressure (PO_2) decreases proportionally, and remaining less than 21% of the total barometric pressure.
- At the sea level the oxygen partial pressure is 159 mmHg. While at 20,000 feet is 40 mmHg and it is only 18 mmHg at 50,000 feet.
- Even at high altitude CO2 is continuously excreted from the pulmonary blood into the alveoli. Also, water vaporizes into the inspired air from the respiratory surfaces.
- Therefore, these two gases dilute the oxygen in the alveoli, thus reducing the oxygen concentration and therefore hypoxia develops.

Acclimatization to Low PO_2 :

A person remaining at high altitudes for days , weeks or years becomes more and more acclimatized to low PO2. So that it causes fewer deleterious effects on the body and it becomes possible for the person to work harder without hypoxic effects or to ascend to still higher altitude.

- **Principle means of acclimatization ;**
  - Increased pulmonary ventilation.
  - Increased diffusing capacity of the lungs.
  - Increased vascularity of the tissues.
  - Increased ability of the cells to utilize oxygen despite the low PO through increased number of mitochondria and oxidative enzymes activity.
  - Increased red blood cells.

(if there is decrease in O2 the kidney will respond by producing Erythropoietin which will go to the bone marrow and synthesize RBCs + Hb, so more O2 will be carried on Hb and more O2 will be transferred to the tissue).



Low and High Altitude

High Altitude

At high altitude, atmospheric pressure is reduced from 760 mm Hg of sea level. Because atmospheric pressure is a factor that determines room air and alveolarPO2, those 2 values are also reduced; they are permanently depressed unless enriched oxygen is inspired.
Therefore, PAO_2 <100 mm Hg, PaO_2 <100 mm Hg, and the low arterial PO_2 stimulates the peripheral chemoreceptors and increases alveolar ventilation. At high altitude, then, the main drive for ventilation changes from CO_2 on the central chemoreceptors at sea level to a low PO_2 drive of the peripheral chemo-receptors, and hyperventilation ensues.

	Acute Changes	Acclimatization
PAO_2 and PaO_2	decreased	remains decreased
$PACO_2$ and $PaCO_2$	decreased	remains decreased
Systemic arterial pH	increased	decreases to normal via renal compensation
Hb concentration	no change	increases (polycythemia)
Hb % sat	decreased	remains decreased
Systemic arterial O_2 content	decreased	increases to normal

At high altitude, hypoxia can develop, resulting in increased circulating levels of erythropoietin and red cell concentration of 2,3-bisphosphoglycerate (right shifts the oxygen-hemoglobin dissociation curve). Erythropoietin increases red blood cell production and eventually causes an adaptive polycythemia.

High-Pressure Environment

In a hyperbaric environment breathing room air (21% O_2 and 79% N_2), the partial pressure of O_2 and N_2 increase in the alveoli and systemic arterial blood. The pressure of nitrogen also increases in other body compartments.

Oxygen

- Adverse effect is oxygen toxicity due to the production of oxygen radicals.
- Clinical uses include carbon monoxide poisoning, compromised tissue grafts, and gas gangrene.

Nitrogen

- **Rapture of the deep**: a feeling of euphoria associated with high nitrogen levels
- **The bends** (Caisson's disease, or decompression sickness) too-rapid decompression after exposure to high nitrogen pressures. It can result in nitrogen coming out of solution in joints (bends) or in the blood, resulting in air emboli in the vasculature.

Low and High Altitude

Note

What principle explains the physiology of why nitrogen will be forced into solution? Answer: Henry's law. The amount of gas that will dissolve in a liquid varies directly with the pressure above that liquid. High pressures force gas into solution. However, solubilities and temperature also come into play when considering Henry's law. Even though a huge N_2 gradient may exist between the air and plasma, nitrogen is barely soluble at all.

Clinical Correlate

High altitude is sometimes categorized as a fifth cause of hypoxemia. High altitude causes low PAO_2, similar to hypoventilation. All the observations described here apply, except for PCO_2. At high altitude, a subject hyperventilates, and thus $PACO_2$ and $PACO_2$ are reduced.

Objective

1. Identify the development of the laryngotracheal (respiratory) diverticulum.
2. Describe the effects of moderate and severe exercise on oxygen consumption, and ventilation volumes.
3. Interpret the effects of exercise on arterial PO2 PCO2
4. Define the diffusing capacity of the respiratory membrane, and its typical values at rest, and explain its changes in exercise.
5. Explain causes of hyperventilation in exercise

The respiratory system and exercise

Introduction :

Oxygen uptake during exercise can be up to twenty times a person's normal oxygen uptake. When we exercise, More oxygen is needed for muscles to work and more carbon dioxide must be removed from muscles. As a result:

- The rate of breathing increase
- The depth of breathing increase up to our vital capacity
- The flow of blood through the lung increase (cardiac output increase)
- The oxygen taken up and used by the body increase (metabolic reactions

Effect of Exercise on the respiratory system :

Respiration usually stimulated when the blood gases are abnormal. However, They do not always have to become abnormal for respiration to be stimulated. Instead, in exercise, respiration is mainly stimulated by neurogenic mechanisms.

Regulation of respiration during strenuous exercise :

- O2 consumption and CO2 formation may increase 20 folds.
- The arterial PO2, PCO2, PH all remain almost exactly normal.
- Alveolar ventilation increases almost exactly in step with the increased levels of metabolism.

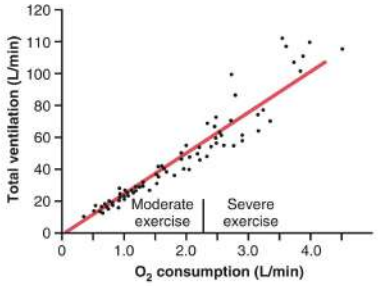


Figure 42-9. Effect of exercise on oxygen consumption and ventilatory rate. *(From Gray JS: Pulmonary Ventilation and Its Physiological Regulation. Springfield, Ill: Charles C Thomas, 1950.)*

What causes intense ventilation during exercise?

The brain, on transmitting motor impulses to the exercising muscles, transmits at the same time collateral impulses into the brain stem to excite the respiratory center.

A large share of the total increase in ventilation begins immediately on initiation of the exercise, before any blood chemicals have had time to change. This is mostly due to neurogenic signals:

- Neural signals from the motor areas of the brain to the respiratory center.
- The joint proprioceptors
- Body temperature (hypothalamus).
- Possibility that the neurogenic factor for control of ventilation during exercise is

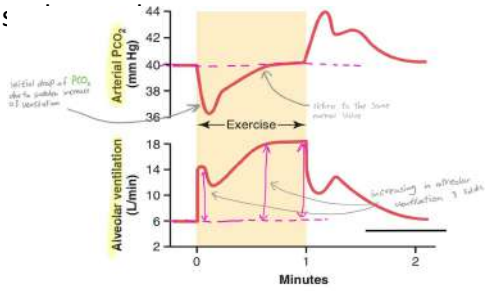
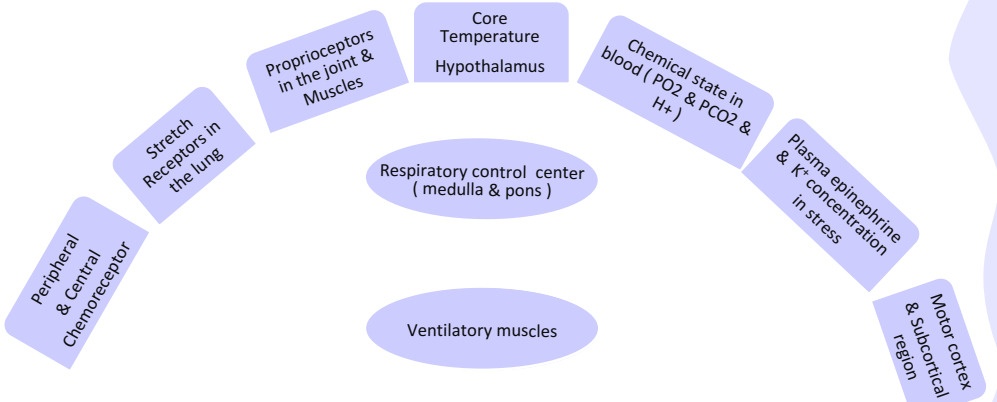


Figure 42-10. Changes in alveolar ventilation (*bottom curve*) and arterial P_{CO_2} (*top curve*) during a 1-minute period of exercise and also after termination of exercise.

From Guyton :

At the onset of exercise, the alveolar ventilation increases almost instantaneously without an initial increase in arterial PCO2. In fact, this increase in ventilation is usually great enough so that at first it actually decreases arterial PCO2 below normal. The presumed reason that the ventilation forges ahead of the buildup of blood CO2 is that" This is at least partly learned response"

Summary of factors stimulate ventilation during exercise



Relation Between Chemical and Nervous Factors in the Control of Respiration During Exercise.

Brain :

Direct nervous signal stimulate the respiratory center almost the proper amount to supply the extra oxygen required for exercise and to blow off extra carbon dioxide

Nervous respiratory system :

Occasionally, the nervous respiratory control signals are either: too strong or too weak.

Chemical factors :

Then chemical factors play a significant role in bringing about the final adjustment of respiration required to keep the O2, CO2, and H+ ion concentrations of the body fluids as nearly normal as possible.

Note :
Sometimes we see weight lifters take few deep breaths unconsciously before even try to rise the load, so the ventilation rate increase immediately with the beginning of exercise . Also that might happen when we see the exam hall, our heart rate increase even though we don't have an exam.

The Neurogenic Factor for Control of Ventilation during Exercise Is a Learned Response:

- The ventilatory response during exercise, is at least partly a learned response. With repeated periods of exercise, the brain becomes more able to provide the proper signals required to keep the blood PCO2 at its normal level.
- The cerebral cortex is involved in this learning, because experiments show that blocking the cortex also block the learned response.

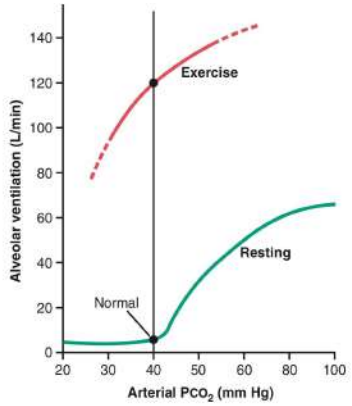


Figure 42-11. Approximate effect of maximum exercise in an athlete to shift the alveolar P_{CO_2}-ventilation response curve to a level much higher than normal. The shift, believed to be caused by neurogenic factors, is almost exactly the right amount to maintain arterial P_{CO_2} at the normal level of 40 mm Hg both in the resting state and during heavy exercise.

Diffusion capacity of the respiratory membrane

O_2 diffusing capacity

- During Rest :

Even if the oxygen pressure difference across the respiratory membrane is 11 mmHg —>11x21= 230ml oxygen diffusing through the membrane each minute. So, 11 mmHg is the minimal pressure difference we need to maintain normal O_2 consumption. During rest tissues consume 250 ml O_2/min =12x21. In conclusion, it is 21 ml/min/mmHg.

- During Exercise :

It is around 65 ml/min/mmHg. This is due to :
increased number of open pulmonary capillaries which was dormant, thereby increasing the surface area for gas exchange.
In addition to increased alveolar ventilation.

CO_2 diffusing capacity:

It diffuses 20 times greater than oxygen due to greater diffusion coefficient which is 20 times that for oxygen.

- During Rest :

Tissues consume, 20x21 = 400 ml CO_2/min /mmHg.

- During Exercise :

The diffusing capacity increase 3 times during exercise
65 x 20 = 1300 ml/min/mmHg.

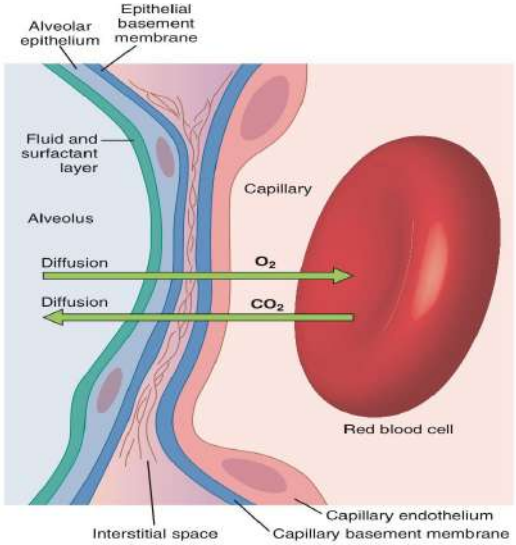


Figure 40-9. Ultrastructure of the alveolar respiratory membrane, shown in cross section.

Note :
Factors affecting diffusing capacity:
1- surface area
2- thickness of respiratory membrane

From Guyton :
How to measure the diffusion capacity of O_{2and} CO_2 ?
The diffusing capacity for CO2 has never been measured because CO2 diffuses through the respiratory membrane so rapidly that the average PCO2 in the pulmonary blood is not far different from the PCO2 in the alveoli—the average difference is less than 1 mm Hg

It is not practical to measure the O2-diffusing capacity directly because it is not possible to accurately measure the O2 tension of the pulmonary capillary blood.

However, the diffusing capacity for CO can be measured accurately because the CO tension in pulmonary capillary blood is zero under normal conditions. So, we measure O_2 capacity using CO.

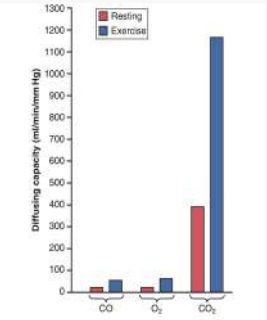


Figure 40-10. Diffusing capacities for carbon monoxide, oxygen, and carbon dioxide in the normal lungs under resting conditions and during exercise.

During Exercise :

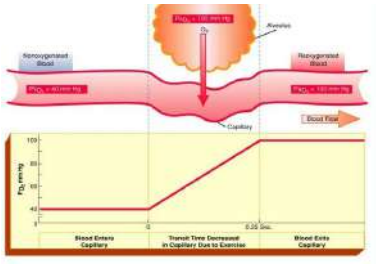
- During exercise the oxygen requirement increased 20 times, and cardiac output increased and so the time blood remained in the pulmonary capillaries becomes less than half normal despite the fact that additional capillaries open up.

- But the blood is almost completely saturated with oxygen when it leaves the pulmonary capillaries.

- The reasons for that :

1- The diffusing capacity for oxygen increases almost three fold during exercise, this results mainly from increasing numbers of capillaries participating in the diffusion, and a more even V/Q ratio all over the lung.

2- At rest the blood normally stays in the lung capillaries about three times as long as necessary to cause full oxygenation. Therefore, even with shortened time of exposure in exercise, the blood is still fully oxygenated or nearly so.



The curve show how the blood speed increase when it enter the pulmonary capillaries But that doesn't affect the saturation of O_2 and the blood maintain normal PO_2

Oxygen Consumption and Pulmonary Ventilation in Exercise

- Normal oxygen consumption for a young man at rest is about 250 ml/min.
- Under maximal conditions, It could increase to approximately the following average levels:

- Untrained average male = 3600 ml/min.
- Athletically trained average male = 4000 ml/min.
- Male marathon runner = 5100 ml/min

The pictures show: Gasping for air after race to repay oxygen debt

Objective

1. Classification of antibiotics.
2. Misuses of antibiotics.
3. Choice of antibiotics
4. Bacterial resistance and ways to prevent it.
5. General principles of antibiotic therapy.
6. Indications for antibiotics prophylaxis

Note :
They will not cure infections caused by viruses.

Antibiotics

- They are chemical substances produced by various microorganisms (bacteria, fungi, actinomycetes) that have the capacity to inhibit the growth or destroy other microorganisms.
- They are either **bactericidal** which kill the bacteria or **bacteriostatic** hold bacteria from growing.

CLASSIFICATION OF ANTIBIOTICS:

classified according to:

- **Spectrum**
  - **Narrow spectrum**: penicillin G, aminoglycosides
  - **Broad spectrum**: ampicillin, amoxicillin
- **Mechanism of action**
  - **Inhibition of cell wall synthesis:** e.g Penicillins, Cephalosporins
  - **Inhibition of DNA synthesis:** e.g Quinolones
  - **Inhibition of folate metabolism:** e.g Sulfonamides, Trimethoprim
  - **Inhibition of RNA synthesis by binding to RNA polymerase:** e.g Rifampicin
  - **Inhibition of protein synthesis:** Macrolides, Tetracyclines, Aminoglycosides

Note :

Folate is important for nucleic acid synthesis

AMINOGLYCOSIDES:
works on either gram -ve or +ve bacteria

AMOXICILLIN:
works on both gram -ve and +ve bacteria

Choice of Antibiotic

1 Clinical diagnosis:

e.g. Syphilis

2 Microbiological information:

✖ Disadvantages:

- The bacteria isolated may not be the prime cause of the disease.
- do not take in consideration site of infection.
- some bacteria cannot be cultivated or take time to grow (e.g. M. Leprae, M. Tuberculosis)
- Bacteriological services are not available at all hospitals.

✓ Advantages:

- The exact antibiotic to be used.
- The most effective and reject the one with little or no activity.
- The least toxic.
- The cheapest.

Note :
Microbiological information:
a culture for the bacteria is done to test the sensitivity

3 Pharmacological consideration:

1-Site of infection.

- **Immune system:**
  e.g. Alcoholism, diabetes, HIV, malnutrition, anticancer drugs, advanced age (higher than usual doses or longer courses are required).
- **Liver function:**
  e.g. **Erythromycin** (hepatic failure)

3-Host factors :

- **Genetic factors:**
  e.g. Patients with G-6-PD deficiency treated with **sulfonamides** (Hemolysis).
- **Extreme Age:**
  Neonates and elderly

2-Drug & Allergy.

- **Pregnancy and Lactation:**
  e.g - **Aminoglycosides** (hearing loss) "ototoxicity"

  - Tetracyclines (bone deformity in the child)
- **Renal function:**
  e,g **Aminoglycosides** (renal failure)

Note :
It's very important to know whether the antibiotic can reach the site of infection or not.
E.: 1st and 2nd generations of cephalosporins can't cross BBB so can't treat meningitis

Note :
Tetracyclines
Cause bone deformity in the child, because tetracycline bind to calcium and affects the bones and teeth

Bacterial resistance

Definition:

Concentration of antibiotic required to inhibit or kill the bacteria is greater than the concentration that can safely be achieved in the plasma.

When does bacterial resistance emerge?

One result of the widespread use of antibiotics has been the emergence of resistant pathogens that have been sensitive in the past.

Reasons for Misuse of Antibiotics :

- Availability of a very wide selection.
- Limitation of physician's time.
- Physician shortage and expenses.
- Availability without prescriptions in pharmacies.
- Public demand (pressure to prescribe)

Note :
Presence of pus or necrotic tissue , or blood at the surgical site, can prevent the absorption of antibiotics so drainage should be done first

Mechanism of Acquired Antibiotic Resistance :

- **Inactivation by enzyme** produced by bacteria: **Bacterial β-lactamase** inactivates penicillin's & cephalosporins by cleaving the β-lactam ring of the drug.
- Or Bacteria develops an **altered receptor** for the drug .
- Or Bacteria develops an **altered metabolic pathway.**
- Or **Reduced bacterial permeability** to antibiotic through cell membrane.
- Or Actively **transporting the drug out** of the bacterial cell.

Prevention of bacterial resistance:

- Use antibiotic only when absolutely required.
- Use antibiotics in adequate dosage for sufficient period of time.
- Not too brief therapy.
- Not too prolonged therapy (exceptions, e.g. TB → 6 months).
- Combination of antibiotics may be required to delay resistance. (e.g. TB).

Misuse of Antibiotics

- Treatment of diseases caused by viruses.
- Improper dosage.
- Therapy of fever of unknown origin.
- Presence of pus or necrotic tissue , or blood at the surgical site.
- Lack of adequate bacteriological information.
- Excessive use of prophylactic antibiotics in travelers.
- Overuse as growth promoters in animals and agriculture.
- Patients do not take them according to their doctor's instructions.
- Some patients save unused antibiotics for another illness, or pass to others

General principles of Antibacterial therapy

- Administer drug in full dose, at proper interval and by the best route
- When apparent cure achieved, continue for about 3 days further to avoid relapse
- Skipping doses may decrease effectiveness of antibiotics & increase the incidence of bacterial resistance.
- Measurement of plasma conc. of antibiotics is seldom (rarely) needed, except for systemic Aminoglycosides e.g. streptomycin, gentamicin.
- In some infections, bacteriological proof of cure is desirable (e.g. TB, UTI).

1 disadvantages:

2 Exceptions where combining antibiotics is a good option:

Usage of multiple antimicrobial

- **Higher cost**
- **Possibility of antagonism**
- **Increased risk of sensitivity or toxicity**
- **Increased risk of colonization and infection with a resistant bacteria**
- **Desperately ill patient of unknown etiology**
- **To prevent emergence of resistance (e.g. TB)**
- **To achieve synergism e.g. piperacillin + gentamicin (pseudomonas aeruginosa)**

Note :
Antibiotic synergy is when two or more antibiotics are used simultaneously to treat an infection. In the synergistic response, the applied antibiotics work together to produce an effect more potent than if each antibiotic were applied singly.

Note :
Frequent and inappropriate use of antibiotics can cause bacteria or other microbes to change so antibiotics don't work against them.

Indications for Antibiotics Prophylaxis:

Surgical prophylaxis	**Immunosuppressed Patients**	**Dental extractions** controversial
bowel surgery, joint replacement, etc. to prevent postoperative infections.	○ Very old ○ Very young ○ Diabetics ○ Anaemics ○ AIDS ○ Cancer pts	○ Pts with total joint replacements ○ Pts with cardiac abnormalities

Objective

1. Describe the structures and functions of the conductive and respiratory zones of airways.
2. Identify the classification of anticholinergic drugs.
3. Describe pharmacokinetics and dynamics of muscarinic antagonists.
4. Identify the effects of atropine on the major organ systems. list the clinical uses of muscarinic antagonists.
5. Know adverse effects & contraindications of anticholinergic drugs.
6. Identify at least one antimuscarinic agent for each of the following special uses: mydriasis, cyclopedia, peptic ulcer & parkinsonism

Classification Anticholinergic drugs

According to Source:

Natural	Synthetic / Semisynthetic
Atropine (Hyoscyamine)	Homatropine (Semisynthetic)
Hyoscine (Scopolamine)	Tropicamide
Pharmacokinetics of Atropine and Hyoscine: • Lipid soluble • Good Oral absorption • Good distribution • Can cross BBB (have CNS effect) • Hyoscine has better BBB penetration • 50% of ATROPINE is metabolized in liver and 50% excreted unchanged in urine. • HYOSCINE is more completely metabolized. • ATROPINE has t1/2 of 3–4 h.	Ipratropium Pirenzepine Benztropine Oxybutynin Darifenacin Glycopyrrolate

According to Structure:

Tertiary amines "Lipid soluble"	Quaternary ammonium "Water soluble"
Atropine (Hyoscyamine)	Glycopyrrolate
Hyoscine (Scopolamine)	Ipratropium

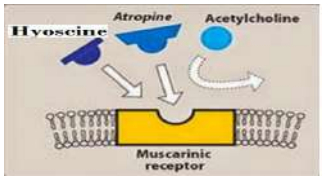
According to selectivity:

Non-selective	Selective
Atropine (Hyoscine)	Pirenzepine (M1)
Hyoscine (Scopolamine)	Darifenacin (M3)
Ipratropium	

Mechanism of action

Reversible competitive blockade of muscarinic receptors, (reverses muscarinic effects of cholinergic drugs).

- Salivary, bronchial, and sweat glands are most sensitive
- Gastric glands and gastric smooth muscles are the least.
- Smooth muscle and heartare intermediate.
- Atropine &hyoscine can block all muscarinic receptors because they are (not selective).



Note :
some Anticholinergic like atropine block nicotinic receptors also in toxic doses.

Pharmacodynamics Actions

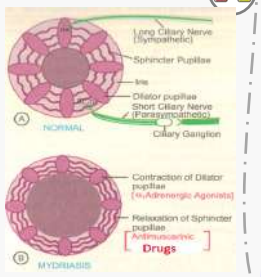
CVS & RESPIRATORY:

- Bradycardia followed by tachycardia (blocks M2 receptors in SA node)
- ↑AV conduction
- No BP influence, but decreases vasodilation caused by cholinergic agonists
- Toxic dose → Cutaneous vasodilation (atropine flush)
- Bronchodilation + ↓ Secretion (leads to viscosity).

Note :
Why initial bradycardia?
At low doses, atropine (non-selective) inhibits pre-synaptic M1 receptors that inhibit Ach release. This "double" inhibition leads to an increase of Ach-->bradycardia

EYE:

- Passive mydriasis (circular muscle paralysis) (active mydriasis is due to radial muscle contraction)
- Cycloplegia (ciliary muscle paralysis→ loss of near accommodation → blur)
- ↑IOP (not suitable for glaucoma) + ↓Lacrimal secretion (sandy eye).

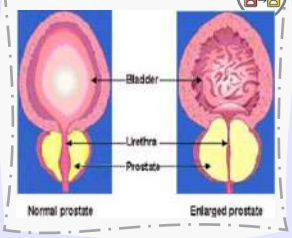


GIT:

- ↓ Motility (antispasmodic) → constipation
- ↓ Gastric acid production, and ↓ Salivary secretions (dry mouth)
- ↑ Sphincter contraction
- Smooth muscle relaxation

GENITOURINARY TRACT:

- Sphincter contraction → that's why it is contraindication in elderly men with prostatic hyperplasia can cause urinary retention
- Relaxation of urinary bladder smooth muscles



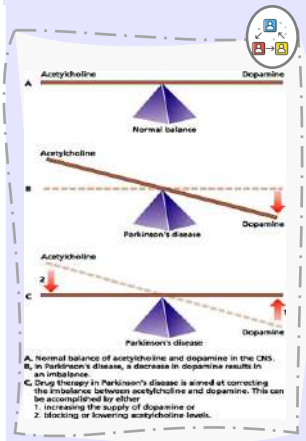
SECERETIONS:

- ↓ Sweating (dry skin), and in children, a modest dose can cause atropine fever

CNS:

- Atropine (clinical dose) → stimulation followed by sedation
  - It stimulates medullary centers including vagal, vasomotor, and respiratory
  - High dose: cortical excitation, restlessness, hallucinations, disorientation,

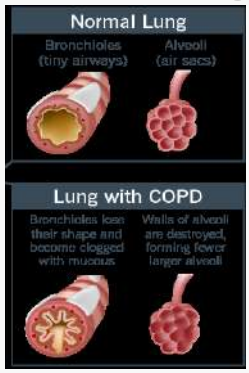
  and delirium followed by respiratory depression and coma
- Hyoscine → Sedation (both drugs are pre-anesthetics)
- Antiemetic (block vomit center) and Antiparkinsonian effects (block basal ganglia)



Note :

Pirenzepine & Peptic Ulcer:

because pirenzepine acts on M1 receptors, which are responsible for gastric acid secretion from stomach parietal cells, inhibiting those receptors leads to reduced secretion of gastric acid)



Note :

Atropine IV/IM

Used to increase heart rate through vagolytic effects, causing increase in cardiac output.

Drugs	Organ	Clinical uses
Benztropine & Benzhexol	CNS	Parkinsonism
Hyoscine		Vomiting (Motionsicknes) Preanesthetic
Tropicamide & homatropine **Atropine substitute with short duration of action**	Ophthalmic disorders	Ophthalmoscopic examination (fundus examunation) of retina
Glycopyrrolate & Hyoscine butyl bromide	GIT	○ Intestinal spasm. ○ Biliary and renal colics. ○ Irritable bowel syndrome.
Pirenzepine		Peptic Ulcer
Dicyclomine		Irritable bowel syndrome, colonic diverticular disease
Atropine & diphenoxylate		Used for treatment of Traveler's diarrhea with opioid, because Opioid drugs cause constipation.
Oxybutynin & Darifenacin	GUT	Urinary incontinence &Urinary urgency caused by minor inflammatory bladder disorders.
Ipratropium (inhalation)	Respiratory disorders	Bronchial asthma &chronic obstructive pulmonary disease (COPD).
Atropine	CVS andCNS	Preanesthetic Sinus bradycardia
	Cholinergic poisoning	Mushroom poisoning. Atropine reverses muscarinic effects of cholinergic poisoning. Cholinesterase inhibitors (insecticides)
	Sweating gland	Hyperhydrosis “excessive sweating”

Anticholinergics Adverse effects

CAN'T PEE, CAN'T SEE, CAN'T SPIT, CAN'T SHIT

CNS:

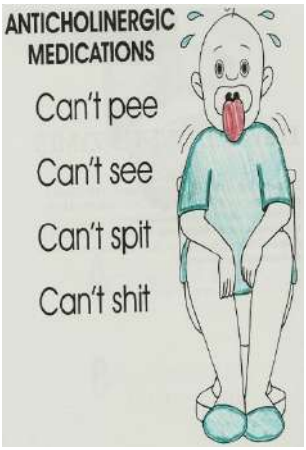
- Confusion, agitation and delirium.

CVS:

- Tachycardia and Hot flushed skin(dilation of cutaneous blood vessels).

EYE:

- Blurred vision and mydriasis (pupil dilation).



GIT:

- Constipation

GUT:

- Urinary retention.

SECERETIONS

- Dryness of mouth, sandy eyes and Hyperthermia.

Anticholinergics Adverse effects

- Tachycardia : (secondary to thyrotoxicosis or cardiac insufficiency)
- Prostate Hypertrophy : (urinary retention)
- Glaucoma : (angle closure glaucoma)
- Constipation
- Paralytic ileus
- Children in case of Atropine (Atropine flush)

In Summary

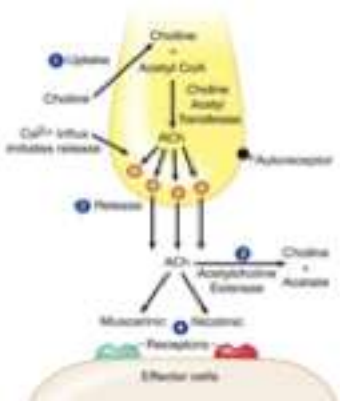
- Antimuscarinics reverse action of cholinomimetics on muscarinic receptors.
- Are useful in many applications including intestinal spasm, urinary urgency,

vomiting, parkinsonism, asthma and peptic ulcer.

- Are contraindicated in constipation, Prostate hypertrophy, tachycardia and glaucoma.

Anti-cholinergic drugs

Cholinergic neuroeffector junctions synthesis and release of ACH



Drugs that works on:

1. Hemicholinium
2. Botulinum toxin
3. Acetylcholinesterase (AChE) inhibitors
4. Receptor agonists and antagonists

Explanation

Choline is accumulated in cholinergic presynaptic nerve endings via an active transport mechanism linked to a Na+ pump and similar to the sodium-dependent glucose transporter.
Choline uptake is inhibited by **hemicholinium** (① in Figure II-2-1). ACh is synthesized from choline and acetyl-CoA via choline acetyltransferase (ChAT) and accumulates in synaptic vesicles. Presynaptic membrane depolarization opens voltage-dependent Ca^{2+} channels, and the influx of this ion causes fusion of the synaptic vesicle membranes with the presynaptic membrane, leading to exocytosis of ACh. H **Botulinum toxin** (② in Figure II-2-1) interacts with synaptobrevin and other proteins to prevent ACh release and is used in blepharospasm, strabismus/hyperhidrosis, dystonia, and cosmetics.
Some cholinergic nerve endings have presynaptic autoreceptors for ACh that on activation may elicit a negative feedback of transmitter release.

Note:

- M receptor activation → ↓ CV function
- ↑ secretions and ↑ smooth muscle contraction
- All M receptor activators and blockers are nonspecific.

Anti-cholinergic drugs

M receptor location and function ,,,,, figure out

Target		receptor	Response
Eye	Sphincter Ciliary muscle	M_3 M_3	Contraction- miosis Contraction- accumediation for near vision
Heart	SA node AV node	M_2 M_2	↓ heart rate (HR)-negative chronotrophy ↓ conduction velocity-negative dromotropy No effects on ventricles, Purkinje system
Lung	Bronchioles Glands	M_3 M_3	Contraction-bronchospasm ↑ secretion
GI tract	Stomach Gland Intestine	M_3 M_1 M_3	↑ motility-cramps ↑ secretion Contraction-diarrhea, involuntary defecation
Bladder		M_3	Contraction (detrusor), relaxation (triagone/sphincter), voiding, urinary incontinece
Sphincter		M_3	Relaxation, except lower esophageal, which contract
Glands		M_3	↑ secretion-sweat (thermoregulatory), salivation, and lacrimation
Blood vessels (edothelium)		M_3	Dilation (via NO/endothelium-derived relaxing factor)-no innervation, no effects of indirect agonists

M_1 and M_3	G_q coupled	↑ phospholipase C → ↑ IP_3, DAG, Ca^{2+}
M_2	G_i coupled	↓ adenylyl cyclase → ↓ cAMP
N_N and N_M	No 2^{nd} messengers	Activation (opening) of Na/K channel

Anti-cholinergic drugs

Muscarinic receptor antagonists

Atropine

- Prototype of the class
- As a tertiary amine, it enters CNS
- Other M blockers differ mainly in their pharmacokinetic properties

Pharmacologic effects :

Atropine effects in order of increasing dose

- Decreased secretions (salivary, bronchiolar, sweat)
- Mydriasis and cycloplegia
- Hyperthermia (with resulting vasodilation)
- Tachycardia
- Sedation
- Urinary retention and constipation
- Behavioral: excitation and hallucinations

Other classes of drugs with antimuscarinic pharmacology

- Antihistamines
- Tricyclic antidepressants
- Antipsychotics
- Quinidine
- Amantadine
- Meperidine

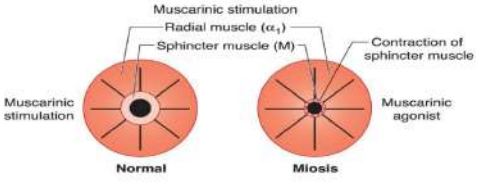
Treatment of acute intoxication: symptomatic ± physostigmin

Drug	Clinical and/or characteristics
Atropine	Antispasmodic, antisecretory, management of AChE inhibitor OD, antidiarrheal, ophthalmology (but long action)
Tropicamide	Ophthalmology (topical)
Ipratropium, tiotropium	Asthma and COPD (inhalational)-no CNS entry, no change in mucus viscosity
Scopolamine	Used in motion sickness, causes sedation and short-term memory block
Benztropine, trihexyphenidyl	Lipid-soluble (CNS entry) used in parkinsonism and in acute extrapyramidal symptoms included by antipsychotics
Oxybutynin	Used in overactive bladder (urge incontinence)

Anti-cholinergic drugs

Note:
Both the ANS (neural) and endocrine feedback loops are invoked when patients are treated with antihypertensive drugs. Such compensatory mechanisms may result in tachycardia and both salt and water retention.

Pupillary size and accommodation mechanisms



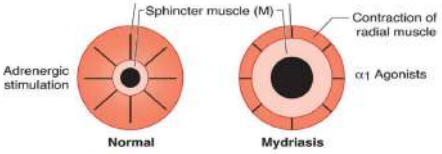
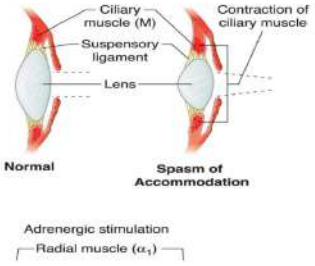


Figure II-1-5. Effect of ANS Drugs on the Eye



Muscarinic stimulation
1. Miosis
2. Accommodation (near vision)

Muscarinic antagonism
1. Mydriasis
2. Accommodation to far vision, leading to cycloplegia (paralysis of accommodation)

α_1-agonists
1. Mydriasis
2. No cycloplegia

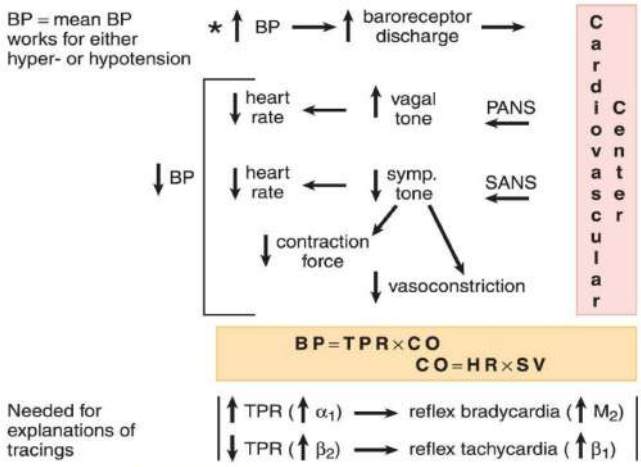
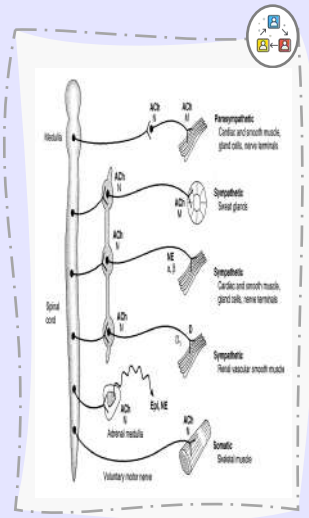


Figure II-1-2. Autonomic Feedback Loop

KAPLAN CORNER

Objective

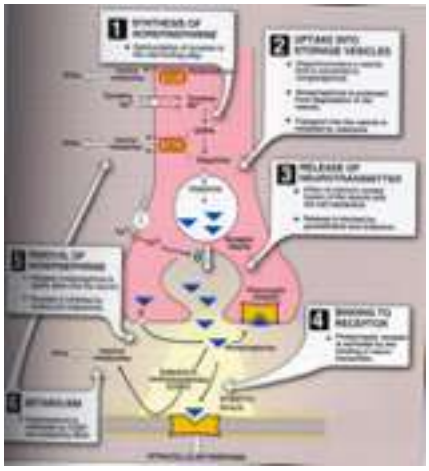
1. classify adrenergic agonists according to chemical structure, receptor selectivity and mode of action.
2. Discuss pharmacodynamics actions, ADRs, indications and contraindication of adrenergic agonists.



Neurotransmission at adrenergic neurons:

Adrenergic transmission:

1. Synthesis of norepinephrine (hydroxylation of tyrosine → rate limiting step)
2. Storage of norepinephrine in vesicles
3. Release of norepinephrine
4. Binding to post-synaptic receptors
5. Ending of action by:
   - Neuronal reuptake into neuron.
   - Monoamine oxidase (MAO) in neuronal mitochondria.
   - Catechol-O-methyl transferase (COMT) in synaptic space



Adrenergic Receptors

- α-adrenoceptors (α1 | α2)
- β-adrenoceptors (β1 | β2 | β3)
- Dopaminergic receptors (e.g. D1)

Pre-synaptic:

α2	β2
Pre-synaptic	
○ Inhibition of norepinephrine release (negative feedback mechanism) ○ How? this mainly happen by an Auto-receptor 'presynaptic receptor' which is present on the neuron releasing the neurotransmitter itself, the neurotransmitter bind to the receptor of the same neuron it was released by and inhibiting further release of the neurotransmitter, producing a negative feedback mechanism)	○ Increase release of norepinephrine (Positive feedback mechanism)

Post-synaptic:

α1	β2
Post-synaptic located in tissue (meaning it is mediated by a neuron which received a signal from a preganglionic neuron by synapsis)	
excitatory in function (cause contraction) except in GIT	inhibitory in function (cause relaxation)
Present mainly in smooth muscles	
Contraction of pregnant uterus	Relaxation of the uterus (Delay premature labor) also called tocolytic effect
Vasoconstriction of skin & peripheral blood vessels → increased peripheral resistance (resistance to blood flow due to constriction of blood vessels)→ hypertension. Agonists used as nasal decongestants.	Relaxation of skeletal & coronary blood vessels (vasodilatation)
Relaxation of GIT muscles & urinary bladder's muscles. Contraction of GIT sphincter (constipation) & urinary bladder's sphincter urinary retention	
Contraction of radial muscle of eye causes active mydriasis, (dilation of pupil, cholinergic agents have no effect on this muscle)	.Relaxation of bronchial smooth muscles (bronchodilation) .Tremor of skeletal muscles
Increase blood glucose level (hyperglycemia), by:	
.↑ glycogenolysis	.↑ glucagon release from pancreas .↑ liver & muscle glycogenolysis

β1	β3
Post-synaptic located in tissue (meaning it is mediated by a neuron which received a signal from a preganglionic neuron by synapsis)	
excitatory in function, present mainly in heart, juxtaglomerular cells of the kidney	In adipose tissue
↑ heart rate: chronotropic effect (Tachycardia) ↑ force of contraction : + inotropic effect Increase cardiac output ↑ conduction velocity: + dromotropic effect (via A.V. node)(dromotropic effect means an effect in the speed of conduction of electrical impulses) ↑ blood pressure ↑ renin release (this is an enzyme produced by the kidney in response to stretch receptors found on blood vessels, its function is to increase blood pressure)	↑ lipolysis ↑ free fatty acids

Adrenergic Agonists "sympathomimetics"

Main Actions :

- Increase heart rate
- Bronchodilation
- Inhibit peristalsis of GIT and secretion + Relaxation of GIT muscles (constipation)
- Relaxation of the uterus (Delay premature labor) tocolytic
- Mydriasis (dilatation of eye pupil)
- Relaxation of urinary bladder
- Increase conversion of glycogen to glucose (hyperglycemia)

Classification :

- **According to CHEMISTRY :**

Catecholamines	Non-Catecholamines
Rapidly acting Have short half-life, due to rapid degradation by MAO (Monoamine Oxidase) & COMT (Catechol-O-MethylTransferase) in GIT	Delayed action Have Long half-life, because they resist degradation by MOA & COMT in GIT
Have catechol ring water soluble (polar) ,thus not effective orally and have Poor penetration to CNS	Lack catechol ring Lipid soluble , thus Effective orally and Cross BBB well , have Prominent CNS effects
Parenterally administered	Orally administered
Natural: Adrenaline, Noradrenaline, Dopamine Synthetic: Isoprenaline.	e.g. Ephedrine, amphetamine, phenylephrine.

- **According to MODE OF ACTION :**

Direct-Acting	Indirect-Acting	Dual-Acting (Mixed)
Stimulate adrenergic receptors directly e.g. adrenaline, noradrenaline, dopamine, isoprenaline, phenylephrine, clonidine, dobutamine, salbutamol, methoxamine	Stimulate adrenergic receptors by: ↑noradrenaline release from presynaptic adrenergic nerve endings. e.g. amphetamine, Tyramine Or Inhibit uptake of noradrenaline e.g. Cocaine & antidepressants	Direct and indirect stimulation of adrenergic receptors (mixed) e.g. ephedrine, pseudoephedrine

- **According to SPECTRUM OF ACTION :**

Non-selective adrenergic agonist:	selective adrenergic agonist:
• Adrenaline (α1, α2 , β1 , β2, β3) • Noradrenaline (α1, α2 , β1) • Isoprenaline (β1, β2, β3) • Dopamine (D1, β1, α1) • Ephedrine	• Phenylephrine (α1) • α-Methyldopa - clonidine (α2) • Dobutamine (β1) • Salbutamol, terbutaline, ritodrine (β2)

Adrenaline

Receptor:

Non-selective **α1; α2; β1 ; β2; β3**

Overview:

- Natural catecholamine. It has fast onset & Short duration of action.
- Direct acting Adrenergic Agonists:

Administration:

Given I.V, S.C, inhalation.
Not effective orally (inactivated by intestinal enzymes).

Action:

- **Heart:** inotropic,chronotropic,dromotropic (β1).
- **Blood pressure:**
  - ↑systolic (β1) (α1)
  - ↓diastolic (β2) and vasorelaxation.
- **Vascular:**
  - Vasoconstriction of blood vessels in skin + peripheral (α1).
  - Vasodilatation of blood vessels of skeletal muscles and coronaries (β2).
- **Eye:** mydriasis (α1) → no effect on accommodation
- **Lung:** bronchodilatation (β2)
- **GIT:** ↓motility (β2) / contract sphincter (α1)
- **Bladder:**
  - relaxation of detrusor muscle (β2)
  - contraction of sphincter (α1)
- **CNS:** little (rare), headache, tremors & restlessness due to vasoconstrictor effects, less oxygen to brain cells)
- **Pregnant uterus:** relaxation tocolytic effect (β2), and cause relaxation of uterus "suppresses contractions" to prevent premature labor)
- **Metabolism:**
  - ↓ insulin (α2),↑ glucagon (β2)
  - ↑ liver glycogenolysis +skeletal muscle glycolysis (β2)
  - ↑ adipose lipolysis (β3)

Note :

Adrenaline

- always know the actions of the receptors, and which receptors the drug acts on. This helps in guessing the probable actions of the drug).
- Adrenaline has a more dominant action on β2 receptors, followed mainly by α1 and β1, remembering their respective actions is helpful in studying this drug's effects

Explanation :

- Systolic: the phase of heartbeat when the heart contracts and pumps blood.
- Diastolic: the phase of heartbeat when the heart relaxes and allows the chambers of the heart to be refilled with blood

Indication:

1. Locally
    - **Haemostatic** (control bleeding): By vasoconstriction
        - Nasal pack (stuffing) in epistaxis and in dental practice.
    - **Combined with local anesthetic to:**
        - ↓ absorption of L.A. & ↑ duration of action
        - ↓ side effects of local anesthetic
        - ↓ bleeding from the incision
2. Systemically

- **In acute asthma (status asthma)** S.C.,Inhalation, emergency bronchodilatation (β2) + ↓mucosal edema (α1)
- **Anaphylactic shock** (Hypersensitivity reactions) is the drug of choice as it is the physiological antagonist of histamine (↑BP & bronchodilation)
- **Cardiac arrest (i.v.)**

Note :
Histamine
- is a vasodilator and decreases blood pressure

ADRs:

- Tachycardia, palpitation, arrhythmias, angina pains (chest pains) .
- Headache, weakness, tremors, anxiety and restlessness.
- Hypertension → cerebral hemorrhage and pulmonary edema.
- Coldness of extremities → tissue necrosis due to vasoconstriction and reduced blood flow which lead to necrosis.
- Nasal stuffiness: rebound congestion if used as decongestant.

Note :
Adrenaline
has similar effects to thyroid gland hormones, such as increased metabolism rate and tachycardia therefore injecting adrenaline will only intensify the effects making them unwanted

Contraindications:

- Coronary heart diseases (CHD), Ischemic heart disease (angina).
- Arrhythmia, Myocardial infarction •Hypertension, peripheral arterial disease.
- Hyperthyroidism
- Closed-angle glaucoma (ciliary relaxation ↓filtration angle) →↑ IOP.

Note :
remember that iris sphincter muscle " aka: constrictor pupillae, circular muscle of iris" decreases IOP when contracted

Direct acting Adrenergic Agonists

	Noradrenaline (Norepinephrine)	Isoprenaline
overview	Catecholamine non-selective agonist	○ Synthetic direct acting catecholamine, and , has very similar effects of Adrenaline ○ shows no reuptake nor breakdown by MAO which leads to longer action.
Administr-ation	○ only administered by I.V ○ may cause necrosis using IM or SC	○ Parenteral in cardiac arrest ○ inhalation rarely in acute attack of asthma
Receptor	mainly on α adrenoceptors (α1, α2, β1, weak action on β2).	non-selective β agonist It Acts on β1, β2, β3
Pharmacological Action	○ Severe vasoconstriction (α1) ○ Increase force of contraction but decrease H.R. ○ Reflex bradycardia due to severe vasoconstriction	❖ **β1:** ○ + inotropic effect ○ + chronotropic effect ○ increase cardiac output ❖ **β2:** ○ Vasodilatation of blood vessels of ○ skeletal muscles and coronaries ○ Bronchodilatation ○ Relaxation of uterus ○ Hyperglycemia ❖ **β3:** ○ lipolysis
Indication	❖ **Locally:** as a local haemostatic with local anesthetic to reduce tachycardia & irritability, but as side effect, may produce necrosis & sloughing of the skin ❖ **Systemically:** hypotensive states : ○ in spinal anesthesia, especially in birth via C-section. ○ in septic shock (hypotension) if fluid replacement and inotropic fail.	❖ **Uses:** ○ Used mainly in cardiac arrest (Parenteral). ○ Rarely in acute attack of asthma (inhalation). ❖ **Contraindications:** ○ In hyperthyroidism & Congestive heart disease CHD

Note :
Baroreceptors in blood vessels detect change in pressure of blood vessels due to sympathetic stimulation, this triggers a parasympathetic stimulation "vagus nerve" to restore the blood vessels to their dilated appropriate diameter, hence the tone will be maintained

Note :
Fluid replacement is a therapeutic way to compensate for the slowing and loss of adequate blood circulation during anesthesia for example. This can be compensated by giving IV fluids. However, at times this does not work and we might need the heart to increase its activity by the use of stimulants of heart activity like adrenaline, this way the circulation can return back to normal

Note :
Phenylephrine
Hypertension is one of its Adverse effects. Thus, another drug is more preferable to produce hypertension that doesn't last for long.

Direct acting Adrenergic Agonists

	Dopamine	Dobutamine	Phenylephrine
overview	• Natural catecholamine & CNS neurotransmitter. • Direct acting. • Released from postganglionic adrenergic fibres.	○ Synthetic catecholamine. ○ Direct acting. ○ Metabolized by COMT, thus has a short duration	• Synthetic non catecholamine • Direct acting • Has prolonged duration of action, since it's Not inactivated by COMT
Administration	Given parenterally by infusion	IV	Orally
Receptor	**D1 > β1>α1** (in order)	Selective **β1**–agonist	Selective **α1**
Pharmacological Action	❖ **D1**: Low dose: • Vasodilatation of mesenteric, coronary, renal blood vessels. Thus improves blood flow to viscera. • Diuresis (increase excretion of urine) • Decrease BP ❖ **β1**: intermediate dose: • +ve inotropic • +ve chronotropic effects • Increase BP ❖ **α1**: high dose: • Vasoconstriction	○ On heart: ○ +ve Inotropic with little chronotropic effect. as it increases cardiac output and heart contractility. ○ **On BP**: Hardly any effect; β1 & β2 counterbalance + no α1. since β1 agonists ○ increase BP, and β2 decrease it by vasodilatory effect)	○ ↑ increased both systolic & diastolic blood pressure (hypertension) due to vasoconstriction (α1) ○ Reflex Bradycardia due to ↑ BP ❖ **Adverse effects:** ○ Hypertension. ○ Midodrine. It peaks in 20 min, duration 30 minonly.
Uses	• Drug of choice in treatment of shocks: septic, Hypovolemic (after fluid replacement), cardiogenic (I.V). It increases the BP & CO by β1 receptor but without causing renal impairment (D1) • Can be given in acute heart failure (HF) but Dobutamine is better.	○ Short term management of Cardiac decompensation after cardiac surgery, in acute myocardial infarction(AMI) & heart failure. ○ It does not increase oxygen demand which made it preferred.	❖Systemically: Vasopressor (anti-hypotensive) agent in hypotension &terminates atrial tachycardia by its reflex bradycardia action. ❖ Topically: • Haemostatic with Local anesthesia. • Mydriatic (in ophthalmic solutions to facilitate eye examination). • Nasal decongestant "vasoconstriction" topically, nasal drops in allergic rhinitis, cold.

Note :
remember that iris sphincter muscle " aka: constrictor pupillae, circular muscle of iris" decreases IOP when contracted

Direct acting Adrenergic Agonists

	Clonidine	Brimonidine
overview	Synthetic Imidazoline	Imidazoline
Administration	Orally or patch	———
Receptor	**Presynaptic α2 agonist**	**α2 agonist**
Pharmacological Action	• Acts centrally (α2) at nucleus tractus solitarius to decrease sympathetic outflow to heart & vessels. • Inhibit sympathetic vasomotor centers.	Used in **glaucoma** as it reduces formation of **aqueous humor** and therefore decrease intraocular pressure (IOP)
Uses	**Antihypertensive drug:** used in essential hypertension to lower BP.	

Note :
Remember, that α2 agonist ac on Presynaptic receptor which inhibits NE release

	Salbutamol	Terbutaline	Ritodrine
overview	Synthetic non catecholamines		
Administration	Orally, inhalation or injection	———	Orally or injection
Receptor	**Selective β2 agonists**		
Pharmacological Action	**Bronchodilator** for **acute attacks of asthma & COPD.**	**Bronchodilator & Tocolytic**	**Tocolytic** relaxation of uterus to treat premature labor
Uses	N.B. Salmeterol & Formoterol act longer		

Indirect acting Adrenergic Agonists

Amphetamine (Indirect acting)	
P.K	• Synthetic non-catecholamine. • give orally, long duration of action (not destroyed by MAO) • Excreted mostly unchanged (increases by acidification of urine)
M.O.A	It acts indirectly by releasing NE from adrenergic nerve endings. It depletes vesicles from stored NE and thus causes Tachyphylaxis.
Selectivity	Acts on α & β similar to epinephrine but has CNS stimulant effects
CNS effects	Mental alertness, wakefulness, concentration & self-confidence followed by depression and fatigue on continued use
ADRS	• Euphoria* & abuse in use • Loss of appetite & decreased weight • Increased energy expenditure *a feeling or state of intense excitement and happiness which is what cause its addiction
Extra information	Not used therapeutically anymore, because it induces psychic & physical dependence & psychosis

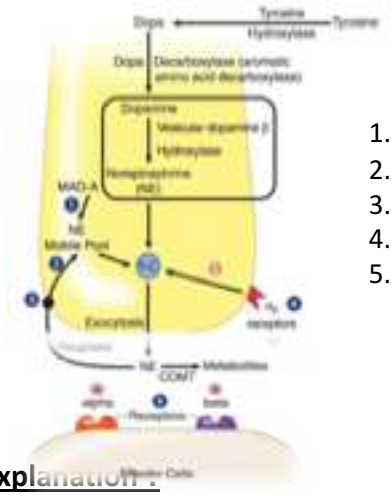
Dual acting Adrenergic Agonists

Ephedrine (Dual Acting)	
Overview	Plant alkaloid, synthetic, non-catecholamine, dual (mixed) acting
Spectrum of Action	Non selective , Acts on α & β
Pharmacokinetics	Absorbed orally, not destroyed by MAO or COMT → prolonged action
Mechanism of action	- Directly: direct action on receptors → down-regulation of receptors. - Indirectly: Release NE from adrenergic nerve endings → depletion of stores → Tachyphylaxis
Action	- Facilitation of neuromuscular transmission & retention of urine - It has CNS stimulant effects (less than amphetamine)
ADRS	- Drugs of abuse by athletes and prohibited during games, thus Not used therapeutically anymore - Bi folded effect: activation followed by dropping; Because it depletes vesicles of stored NE and causes tachyphylaxis
Pseudoephedrine	Dual acting , acts on CNS & has less pressor effects compared to ephedrine. Produces vasoconstriction in nasal passages thus Used as nasal & ocular decongestant & in flu remedies

Adrenergic Neuroeffector Junctions

Synthesis and release of NE

The important aspects of the adrenergic neuroeffector junction are summarized below.



1. MAO inhibitors
2. Releasers
3. Reuptake blockers
4. α_2 agonists and antagonists
5. Agonists and blockers of α_1 and β_1 receptors

Explanation :

- Tyrosine is actively transported into nerve endings and is converted to dihydroxyphenylalanine (DOPA) via tyrosine hydroxylase. This step is rate limiting in the synthesis of NE. DOPA is converted to dopamine (DA) via Laromatic amino acid decarboxylase (DOPA decarboxylase). DA is taken up into storage vesicles where it is metabolized to NE via DA beta hydroxylase. Inactivation of NE via monoamine oxidase A (MAO-A) (1) may regulate prejunctional levels of transmitter in the mobile pool (2) but not the NE stored in granules.
- Presynaptic membrane depolarization opens voltage-dependent Ca^{2+} channels. Influx of this ion causes fusion of the synaptic granular membranes, with the presynaptic membrane leading to NE exocytosis into the neuroeffector junction. NE then activates postjunctional receptors (5), leading to tissue-specific responses depending on the adrenoceptor subtype activated.
- Termination of NE actions is mainly due to removal from the neuroeffector junction back into the sympathetic nerve ending via an NE reuptake transporter system (3). At some sympathetic nerve endings, the NE released may activate prejunctional alpha adrenoceptors (4) involved in feedback regulation, which results in decreased release of the neurotransmitter. Metabolism of NE is by catechol-O-methyltransferase (COMT) in the synapse or MAOA in the prejunctional nerve terminal.

Adrenergic Neuroeffector Junctions

Adrenergic receptor location and function

Receptors	Response
α_1	
Eye: radial (dilator) muscle Arterioles (skin, viscera)	Contraction: mydriasis Contraction: ↑ TPR, ↑ diastolic pressure, ↑ afterload
Veins Bladder trigone and sphincter and prostatic urethra Male sex organ Liver Kidney	Contraction: ↑ venous return, ↑ preload Contraction: urinary retention Vas deferens: ejaculation ↑ glycogenolysis ↓ renin release
α_2	
Prejunctional nerve terminals Platelets pancreas	↓ transmitter release and NE synthesis Aggregation ↓ insulin secretion
β_1	
Heart SA node AV node Arterial and ventricular muscle His-Purkinje Kidney	↑ HR (positive chronotrophy) ↑ conduction velocity (positive dromotropy) ↑ force of contraction (positive inotropy), conduction velocity, CO and oxygen consumption ↑ automaticity and conduction velocity ↑ renin release
β_2	
Blood vessels (all) Ureter Bronchioles Skeletal muscle	Vasodilation: ↓ TPR: ↓ diastolic pressure, ↓ afterload Relaxation Dilatation ↑ glycogenolysis: contractility (tremor)
D_1 (peripheral)	
Renal, mesenteric, coronary, vasculature	Vasodilation: in kidney ↑ RBF, ↑ GFR, ↑ Na^+ secretion

KAPLAN CORNER

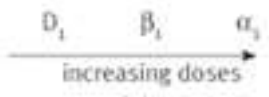
Adrenergic Neuroeffector Junctions

Notes:

Adrenoceptor Sensitivity:

Beta receptors are usually more sensitive to activators than alpha receptors. With drugs that exert both effects, the beta responses are dominant at low doses; at higher doses, the alpha responses will predominate.

Dopamine Use in Shock



F[illegible]t used for severe hypertension.

α_1	G_q coupled	↑ phospholipase → ↑ IP_3, DAG, Ca^{2+}
α_2	G_i coupled	↓ adenylyl cyclase → ↓ cAMP
β_1 β_2 D_1	G_S coupled	↓ adenylyl cyclase → ↓ cAMP

α_1 agonists:

- Systemically, alpha-1 agonists increase mean BP via vasoconstriction.
- Increased BP may elicit a reflex bradycardia Cardiac output may be ↓ but also offset by ↑ venous return.

Drugs and uses:

- **Phenylephrine:** nasal decongestant and ophthalmologic use (mydriasis without cycloplegia), hypotensive states

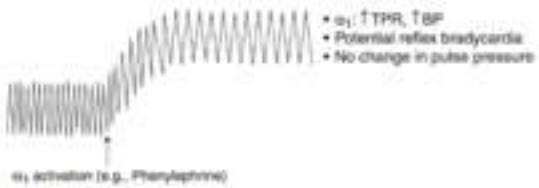


Figure II-3-2. Effect of Alpha Activators on Heart Rate and Blood Pressure

$\alpha_2$agonists

Alpha-2 agonists stimulate prejunctional receptors in the CNS to decrease sympathetic outflow. Their primary use is for mild to moderate HTN.

Drugs and uses:

clonidine and methyldopa (mild to moderate hypertension)

KAPLAN CORNER

β agonist

Systemically, beta-agonists decrease mean BP via vasodilation (β_2)and and increase HR (β_1)

Figure II-3-3. Effect of Beta Receptor Activation on Heart Rate and Blood Pressure

Drugs and us

- Isoproterenol ($\beta_1 = \beta_2$)
- Dobutamine ($\beta_1 > \beta_2$): congestive heart failure
- Selective β_2 agonists: salmeterol, albuterol, terbutaline (asthma); terbutaline (premature labor)

Mixed-acting agonists:

Norepinephrine Vs. Epinephrine

- **Norepinephrine (α1, α2, β1)**

Figure II-3-4. Effect of Norepinephrine on Heart Rate and Blood Pressure

- **Epinephrine (α1, α2, β1, β**

Dose-dependent effects:
Low-dose: β_1, β_2 stimulation (see Figure II-3-5a)
High-dose: α_1, β_1(β_2) (see Figure II-3-5c)

Figure II-3-5a. Effect of Low-dose Epinephrine on Heart Rate and Blood Pressure

Figure II-3-5b. Effect of Medium-Dose Epinephrine on Heart Rate and Blood Pressure

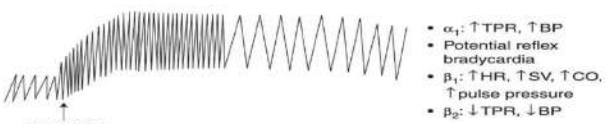


Figure II-3-5c. Effect of High-dose Epinephrine Is Similar to Norepinephrine

KAPLAN CORNER

Adrenergic Neuroeffector Junctions

ß2-specific effects

Smooth muscle relaxation: bronchioles, uterus, blood vessels

Metabolic effects:

- ↑ glycogenolysis (muscle and liver)
- ↑ gluconeogenesis
- ↑ mobilization and use of fat

Differentiation of high-dose epinephrine versus norepinephrine:

Epinephrine reversal: Use of α1 blocker to reverse hypertension to hypotension in a patient receiving too much epinephrine

Hypertension was due to predominant α_1 tone on the vasculature

Hypotension results from unmasking β_2 receptors

Uses of norepinephrine and epinephrine

- Cardiac arrest
- Adjunct to local anesthetic
- Hypotension
- Anaphylaxis (epinephrine only)
- Asthma (epinephrine only)

Indirect-acting adrenergic receptor agonists

RELEASERS

Releasers displace norepinephrine from the mobile pool.

- Releasers displace norepinephrine from the mobile pool
- Drug interaction: MAO_A inhibitors (hypertensive crisis)
- **Tyramine** (red wine, cheese) Oral bioavailability is limited by MAO-A metabolism in gut and liver MAO-A inhibition ↑ bioavailability, resulting in hypertensive crisis
- Amphetamine: Clinical use of methylphenidate in narcolepsy and ADHD Psychostimulant due to central release of DA, NE, 5HT
- Ephedrine (cold medication)

Clinical correlate:

- Indirect-acting adrenoceptor agonists act only on effector tissues innervated by SANS.
- Denervated effector tissues are nonresponsive because these drugs act either to release transmitter from nerve terminals or to inhibit neurotransmitter reuptake.

Forms of MAO:

MAO type A: mainly in liver, but **A**nywhere (metabolizes NE, 5HT, and tyramine)

MAO type B: mainly in **B**rain (metabolizes DA)

KAPLAN CORNER

Reuptake Inhibitors

- Cocaine
- Tricyclic antidepressant (in part)

Adrenergic Antagonists

α receptor antagonists

Alpha-receptor antagonists decrease TPR and decrease mean BP.

- May cause reflex tachycardia and salt and water retention
- Major uses:
  - Hypertension
  - Pheochromocytoma (nonselective α blocker)
  - Benign prostatic hyperplasia (BPH; selective α_1 blocker)

Drugs:

- Nonselective blocker: phentolamine (competitive inhibitor)
- phenoxybenzamine (noncompetitive inhibitor)
- Selective α_1 blocker: prazosin, doxazosin, terazosin, tamsulosin
- Selective α_2 blocker: mirtazapine (used as antidepressant)

β receptor antagonists

- **β_1 blockade**
  - ↓ HR, ↓ SV, ↓ CO
  - ↓ renin release
- **β_2 blockade**
  - May precipitate bronchospasm (in asthmatics) and vasospasm (inpatients with vasospastic disorders)
  - ↓ aqueous humor production

Metabolic effects

- Blocks glycogenolysis, gluconeogenesis
- ↑ LDLs, TGs

Clinical correlate

Chronic use of beta blockers (e.g., in angina, HTN) leads to receptor upregulation.
During withdrawal from use, it is important to taper dose to avoid excessive cardiovascular effects (rebound effects) of endogenous amines.

Clinical correlate

Glucagon and the Heart

Positive inotropic and chronotropic, not via activation of β_1 receptors, but through glucagon receptors that are G-protein linked to adenylyl cyclase → basis for its use in beta-blocker overdose.

KAPLAN CORNER

Adrenergic Antagonists

Cardioselectivity (β_1):

- Less effect on vasculature, bronchioles, uterus, and metabolism
- Safer in asthma, diabetes, peripheral vascular diseases

Intrinsic sympathomimetic activity (ISA):

- Act as partial agonists
- Less bradycardia (β_1)
- Slight vasodilation or bronchodilation (β_2)
- Minimal change in plasma lipids (β_2)
- Pharmacokinetic properties: no CNS entry of atenolol

General uses of beta-blockers:

- Angina, hypertension, post-MI (all drugs)
- Antiarrhythmics (class II: propranolol, acebutolol, esmolol)
- Glaucoma (timolol)
- Migraine, thyrotoxicosis, performance anxiety, essentialtremor (propranolol)

Combined alpha-1 and beta blocking activity:

- Labetalol and carvedilol
- Use in CHF (carvedilol) and in hypertensive emergencies (labetalol)
- K^+-channel blockade and β-blocking activity: sotalol

Drugs	β_1 -selective	ISA	Sedation	Blood lipids
Acebutolol	+	++	+	-
Atenolol	+	-	-	↑↑
Metoprolol	+	-	+	↑↑
Pindolol	-	++	+	-
Propranolol	-	-	+++	↑↑
Timolol	-	-	++	↑↑

Re

Which of the following directly results from activation of the beta 2 receptor?

A) Decrease in blood pressure
B) Increase in cardiac output
C) Increase in heart rate
D) Increase in stroke volume

Answer: A

KAPLAN CORNER

Objective

1. Perceive the differences between anaphylactic shock and other types of shock.
2. Recognize its nature, causes & characteristics.
3. Specify its diagnostic features.
4. Identify its standard emergency management protocol.
5. Justify the mechanism of action and method of administration of each of the different used drugs to limit its morbid outcomes

Anaphylaxis

Anaphylaxis Is a sudden, severe allergic reaction affecting the whole body (generalized or systemic) in response to allergen

Symptoms:

- Rash
- Mucosal swelling
- Difficulty in breathing
- Hypotension

Shock:

- It is Generalized circulatory derangement causing multiple organ HYPOPERFUSION & strong sympathetic activation.
- Hypoperfusion is Inadequate oxygen delivery to meet metabolic demands.
- If the shock is intense or sustained long enough, it will lead to irreversible derangements sets then to permanent functional deficit or death.

Types of shocks :

- **Hypovolemic**
  - Hemorrhage.
  - Fluid loss (plasma,EFC).
- **Obstructive**
  - Extra-cardiac obstruction.
    E.g. Cardiac tamponade ,Pulmonary embolism
- **Cardiogenic**
  - Inability to contract &pump.
    E.g. myocardial infarction.
- **Distributive**
  - Decreased Peripheral Resistance.
    E.g. septic shock,Neurogenic shock (Anaphylactic shock).

ANAPHYLACTIC SHOCK

Definition:

A life-threatening allergic reaction that causes shock (hypoperfusion) and airway swelling. it is a medical emergency where immediate treatment is needed to prevent potential death.

The Nature of anaphylactic shock:

Immunologic Anaphylaxis

- Known as ANAPHYLAXIS
- It belongs to type I hypersensitivity reaction
- Occurs after exposure to foreign substances (antigen) such as food, insect or animal venom, drugs, blood products.
- The immune system will then develop antibodies for this antigen and it will remain in the body for a while.
- After a 2nd exposure to the same
- antigen in previously sensitized persons (antigen-specific IgE are present), IgE binds with mast cell causing its degranulation.

Non-Immunologic Anaphylaxis

- Known as (ANAPHYLACTOID)
- Directly act on mast cells (Not IgE-mediated)
- Exogenous substances directly degranulate mast cells.
- E.g. Radiocontrast dye, Opiates , Depolarizing drugs, Dextrans

- Anaphylaxis because anaphylactic and anaphylactoid reactions produce the same clinical manifestations and are treated exactly the same way, we use the term anaphylaxis to refer to both conditions.
- The degranulation of the mast cells will release Histamine, Leukotrienes and other inflammatory substances and will lead to :

- **Lungs**
  - Bronchospasm
  - Vasoconstriction
  - Shortness in breath
- **Blood vessels**
  - Vasodilation
  - Leakiness
  - Hypo-perfusion
- **Skins**
  - Pruritus
  - Urticaria
  - Edema
- **Mucous swelling**
  - Rhinitis 16%
  - Airway 56%
  - Angioedema 88%
  - GIT 30%
- **Heart**
  - ↓Output
  - ↓Coronary flow
  - Circulatory Collapse

characters of anaphylactic shock:

- Rapidly developing [5/30 min. → can be hours]
- Severe, life-threatening
- Multisystem involvement
- Mortality: due to respiratory (70%) or cardiovascular deficits (25%)

Anaphylactic Shock Therapy Protocol

When the diagnosis is made as an anaphylactic shock (after calling the ambulance), emergency treatment should be immediately start as follows:

	Life Threatening Problems	Management
Rescue	○ **Airway**: swelling, hoarseness, stridor . ○ **Breathing:** rapid breathing, wheezing, cyanosis, fatigue, confusion, oxygenated Hb (SpO2) <92% ○ **Circulation:** pale, clammy, low BP, faintness, drowsy /coma.	**Respiratory support** • Open airway for O2 inhalation **Circulatory support** • Lay down and raise legs up • Fluid replacement
1st Line Therapy	• **Adrenaline** (give IM by Auto injector or by syringe, unless there is a specialist to give IV) • **IV fluid** challenge , Crystalloid is given for children to increase the blood plasma level.	
2nd line	○ **Chlorpheniramine** (first generation H1 blocker) (IM or slow IV). ○ **Hydrocortisone** (Glucocorticoid) (IM or slow IV).	
Adjuvant to 2nd line	• **Bronchodilators:** Salbutamol (nebulizer), Ipratropium (nebulizer), Aminophylline (IV). • **Glucagon:** For patients taking beta blockers &with refractory hypotension to increase cardiac output • **H2 blocker:** we mainly want to block H1 so we give H2 blocker to support the action of H1 antagonist • **Ranitidine:** I.V • **Cimetidine:** contraindicated in elderly renal/hepatic failure, or if on beta-blockers.	**Why do we use the 2nd line adjuvants?** ❖ **Objective of Therapy:** • To support the respiratory & circulatory deficits. • To halt the existing hyper-reaction. • To prevent further hyper-reaction of immune system (prevent biphasic phenomenon). ❖ **Biphasic Phenomenon:** • 2nd release of mediators without re-exposure to antigen in up to 20%). • leukotrienes and histamines are still active • Clinically evident 3-4h after the initial manifestations clear.

1st line Therapy

	Adrenaline (A Sympathomimetic)
Mechanism	**nonselective** Adrenergic agonist (α1, α2, β1, β2, β3).
Actions	• **α agonist:** -Reverses peripheral vasodilation , thus maintains BP and directs blood flow to major organs. - Vasoconstriction leads to decreasing edema → reverse hives, swelling around face &lips &angioedema in nasopharynx & larynx. • **β agonist:** -β2 :Dilates bronchial airways +↓ histamine &leukotriene release from mast cells . -β1 :↑ force of myocardial contraction. ➢ **Adrenaline is the physiological antagonist of histamine:** -Attenuates "reduce "the severity of **IgE-mediated** allergic reactions.
Indications	**Drug of choice for anaphylactic shock.**
Contraindications	• Rare in a setting of anaphylaxis • Not given for cardiac patient who are older than 40 years • Patients taking **β-blockers** either are: why? because of the **β blocking action** o **Refractory;** as it may antagonize β effects of adrenaline. (β2 receptors won't be stimulated since they're blocked, no ↑ cAMP, no effect) o **Rebound hypertension** (unopposed **α** effect), specially when adrenaline is repeated (glucagon is used in this case).
ARDs	**Causes dysrhythmias if given IV.**
Administration	**IM: why?** 1. Easily accessible by using Auto-injectors Kits, they are disposable prefilled devices,automatically administer a single dose of epinephrine in emergency. 2. Greater margin of safety → no dysrhythmias as with IV. 3. No need to wait for IV line, if present, it should be given by physician under monitoring. 4. Repeat every 5-10 min as needed 5. Patient should be observed for 4-6 hours **(fear of biphasic anaphylaxis)**

Note :

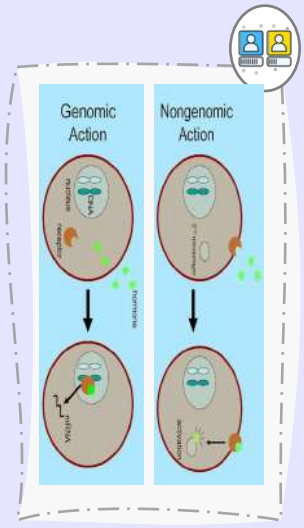
- If hypotension persists, start Dopamine, To protect the kidney.
- Why not noradrenaline? Noradrenaline is nonselective on (α1, α2, β1). It has no effect on β2 stimulation of α1 (vasoconstriction) causes hypertension, but this vasoconstriction is not opposed by the stimulation of β2 (vasodilatation) Therefore, noradrenaline will cause a very severe vasoconstriction, much more than what is required in the case of anaphylactic shock.

Note :

Adrenaline

It could also be administered subcutaneously, which is safer, but won't produce as rapid effect as IM injection for the rescue of anaphylaxis..

2nd line Therapy and Adjuvant 2nd line therapy



	Corticosteroids (anti- inflammatory)
Mechanism	❖ **Genomic Action: *For chronic use.** • Intracellular receptors (cytosol or nucleus) • Takes hours to days to be activated. • Used for maintenance of asthma as it suppresses airway inflammation ❖ **Non-genomic actions:** • Immediate Glucocorticoids actions on **Membrane-bound receptors**, which leads to modulating 2nd messengers levels. • Rapid onset of action (seconds or minutes). *That's why we use it in anaphylactic shock.
Action	**Non-genomic action in anaphylactic shock:** • Reverse hypotension & bronchoconstriction. • ↓ release of inflammatory and allergic mediators (anti-chemotactic & mast cell stabilizing effects.) • ↓ mucosal swelling and skin reaction. • May help to limit biphasic reactions by decreasing allergic mediators.
Administration	• Given slowly IV or IM. • Not used alone **(not life saving).**

Note :

H2 Blockers

Such as Cimetidine shouldn't be given to elderly, renal/ hepatic failure, or if on b-blockers.

Why? Because it inhibits cytochrome P450 which controls drug-drug interactions. So when given it may increase the toxicity of other drugs , therefore it's replaced by ranitidine.

	❖ 2nd line therapy	❖ Adjuvant 2nd line therapy
	H1 Blockers	**H2 Blockers**
Examples	Pheniramine	Ranitidine, Cimetidine, Pantorole
Action	• Though mast cells have already de-granulated, yet these drugs can still help to counteract histamine-mediated vasodilation & bronchoconstriction. • May help to limit biphasic reactions by blocking histamine receptors.	• The significance of H2 blockers is not established, these drugs are associated with serious adverse drug interactions. • Pantoprazole is a Proton pump inhibitor it is safer and given once. to decrease GIT acidity, it's safer than H2 blockers
Administration	• Given slowly I.V or I.M • It can not be used alone (not life saving).	-
Contra-indication	-	Cimetidine shouldn't be given to elderly, renal/ hepatic failure, or if on b-blockers.

Adjuvant 2nd line

Bronchodilators (used for asthma as well)		
Salbutamol	**Ipratropium**	**Aminophylline**
Inhalation		Parenteral IV
β2 agonist	Anticholinergic Antimuscarinic	Methylxanthine
• Short acting. • Rapid onset of acting. • Relaxation of bronchial smooth muscle. (Bronchodilation) • Decrease mediators released from mast cell and basophils. . • Inhibit airway microvascular leakage.	• Longer acting. • Less rapid in action. • Slower onset of action. • Decrease secretion • Decreases cGMP , therefore decreases the contractility of smooth muscles.	• IV is useful for anaphylactic shock. • may be useful in the treatment of anaphylaxis when inhaled bronchodilators are not effective & bronchospasm is persistent. • Given in hospital setting as levels of drug should be therapeutically monitored because it has narrow therapeutic index. • Increase cAMP • Smooth muscle relaxation
Not effective in Patients taking β blockers	• Effective for bronchodilation in spite of β-adrenergic blockade.	

	Glucagon
Mechanism	• Main action: act on glucagon receptors in the heart.
Action	• Has both positive inotropic &chronotropic effect on heart→ increase cardiac cyclic AMP. • This effect is completely independent of Adrenergic Receptors, That is why effective in spite of β-adrenergic blockade. • Efficacy of acting on bronchi is less prominent than thatof the heart → no evident bronchodilation
Clinical uses	• Drug of choice for severe anaphylaxis in patients taking β-blockers, because adrenaline won't be effective

Note :

Important question

How a patient will benefit if he took beta blockers and developed allergic reaction, what will be the role of glucagon? Glucagon works the same way it increases cAMP BUT independent of adrenergic receptors.

H_2 Antagonists

Cimetidine, Ranitidine, Famotidine

Mechanisms of action

- Suppress secretory responses to food stimulation and nocturnal secretion of gastric acid via their ability to decrease (indirectly) the activity of the proton pump.
- Also partially antagonize HCl secretion caused by vagally or gastrininduced release of histamine from ECL-like cells (GI mast cells)
- No effects on gastric emptying time

Uses

- PUD (overall less effective than proton pump inhibitors)
- Gastroesophageal reflux disease (GERD)
- Zollinger-Ellison syndrome

Side effects

- Cimetidine is a major inhibitor of P450 isoforms → drug interaction
- via ↑ effects
    - Cimetidine → ↓ androgens → gynecomastia and ↓ libido

Objective

1. Epidemiology of smoking in Saudi Arabia.
2. Risks of smoking (Morbidity and Mortality).
3. Effect of passive smoking on pregnancy, children
4. How are you going to help the smoker to quit and how to overcome withdrawal symptoms.
5. Update in pharmacological management, smoking cessation medication.
6. Nicotine preparations, varniciline, bupropion

Magnitude of the problem

Prevalence of Tobacco smoking among persons aged 15 years and above % (Male) 2015 WHO "SA 27.9%" Saudi is the 34th in ranking of most cigarettes smoked by adult/year, at a rate of 1395.14 cigarettes/adult/year

Global prevalence:

- In 2012, 21% of the global population aged 15 and above smoked tobacco.
- Men smoked at five times the rate of women. the average rates were 36% and 7% respectively.

Saudi Arabia:

- In 2010, WHO estimates that about 16% of Saudi Arabia's population smoked (3,092,300 persons).

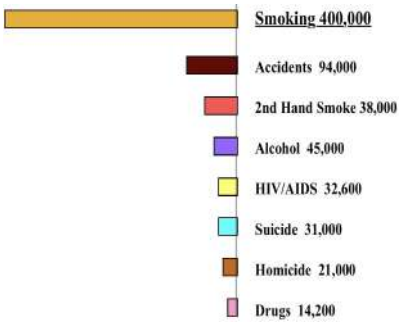
- If tobacco control efforts continue at the same intensity, WHO projects that in 2025 around 24% of the population (approximately 6,268,400 persons) will be smokers.

- 26% of men and about 3% of women smoked in Saudi Arabia .
- The highest rate of smoking among men was seen in the age -group 25 – 39 and among women in the age-group 70+.

Morbidity and Mortality :

- Cigarette smoking causes more than 4oo,oo0 deaths each year in the United States, Smoking causes more deaths each year than all of these combined:

- Human immunodeficiency virus (HIV).
- Illegal drug use.
- Alcohol use.
- Motor vehicle injuries.
- Firearm-related incidents.



What is Tobacco ?

Content of Cigarette :

More than 4,000 substances, including:

- **Tar**: black sticky substance used to pave roads
- **Nicotine**: Insecticide
- **Carbon Monoxide**: Car exhaust
- 210 Polonium: radio-active substance
- Acetone: Fingernail polish remover
- Ammonia: Toilet Cleaner
- Cadmium: used batteries
- Ethanol: Alcohol
- Arsenic: Rat poison
- Butane: Lighter Fluid

From Guyton :

At the onset of exercise, the alveolar ventilation increases almost instantaneously without an initial increase in arterial PCO_2. In fact, this increase in ventilation is usually great enough so that at first it actually decreases arterial PCO_2 below normal. The presumed reason that the ventilation forges ahead of the buildup of blood CO_2 is that" This is at least partly learned response"

Is tobacco Addictive ?

- Nicotine Found naturally in tobacco, which is addictive . Tobacco dependence has been classified as a mental and behavioral disorder.
- The dependence "addiction" make it hard to stay away from it and causes unpleasant withdrawal symptoms.
- People who stop smoking before age 50 cut their risk of dying in the next 15 years in half. Ex-smokers enjoy a higher quality of life with fewer illnesses.
- Smoking typically begins in adolescence if a person remains smoke-free throughout adolescence, it is highly unlikely that he or she will ever begin smoking thus intensive efforts be made to help young people stay smoke-free.

Smoking:

What is it ? :

It refers to the inhalation and exhalation of fumes from burning tobacco in cigars, cigarettes and pipe.

Ways of smoking :

- **Cigarettes:**

are uniform in size and contain less than 1g of tobacco each.

- **Cigar:**

are composed primarily of a single type of tobacco, and they have a tobacco wrapper. They contain between 1 gram and 20 grams of tobacco.

- **Electronic Cigarette:**

It is a battery-powered vaporizer which has a similar feel to tobacco smoking, but do not contain tobacco, although they do use nicotine from tobacco plants. They do not produce cigarette smoke but rather an aerosol, which is referred to as vapor.

- **Water-Pipe (Shisha):**

Not safer than regular tobacco smoke, Causes the same diseases but more Polycythemia which is increase in RBCs and Hemoglobin. It Raises the risk of lip cancer, spreading infections like Tuberculosis. Users can inhale the same amount of smoke as from more than 100 cigarettes.

Types:

- Active (Conventional smoking).
- Passive (Secondhand smoking).
- Third hand smoking.

Smoking Effects :

Active smoking :

- **Mainstream smoke:** The smoke exhaled by a smoker.
- **Side stream smoke:**
  - Smoke from the lighted end of a cigarette, pipe, or cigar.
  - Side stream smoke has higher concentrations of cancer-causing agents (carcinogens) and is more toxic than mainstream smoke.
  - it has smaller particles than mainstream smoke. These smaller particles make their way into the lungs and the body's cells more easily.

The combination of both is the second-hand smoke (SHS).

From Guyton :

At the onset of exercise, the alveolar ventilation increases almost instantaneously without an initial increase in arterial PCO_2. In fact, this increase in ventilation is usually great enough so that at first it actually decreases arterial PCO_2 below normal. The presumed reason that the ventilation forges ahead of the buildup of blood CO_2 is that" This is at least partly learned response"

Passive smoking :

- **Secondhand smoking :**

It is dangerous. Secondhand smoke is a mixture of gases and fine particles that includes:

1- Smoke from a burning cigarette, cigar, or pipe tip

2- Smoke that has been exhaled or breathed out by the person or people smoking.

- **Third hand smoking :**

Smoke exposure refers to exposure to smoke components and their metabolic by-products from contact with surfaces that have adsorbed smoke. The smoke leaves a residue of nicotine and other toxic substances in household dust and on surfaces. Although not yet well studied, there is concern that contact with third hand smoke will result in absorption of toxins through the skin or ingestion from contamination of the hands.

Effects on Specific population:

- **Smoking during pregnancy can lead to:**
  - Premature delivery.
  - Low birth weight.
  - Sudden infant death syndrome.
  - Limited mental ability.
  - trouble with learning.

The more cigarettes a mother-to-be smokes, the greater the danger to her baby causing 5 % of infant deaths and 10% of preterm births.

- **Conditions have been linked to secondhand smoke exposure in children:**
  - Sudden infant death syndrome (SIDS)
  - More respiratory infections (such as 436,000 episodes of bronchitis and 190,000 cases of pneumonia)
  - More severe and frequent Asthma attacks, nearly 530,000 doctor visits.
  - Up to 2,000,000 of ear infections each year.
  - Chronic cough

38% of children aged 2 months to 5 years are exposed to SHS. and they are particularly at risk because their bodies are still growing, and they breathe at a faster rate than adult.

Consequences of tobacco use :

- Health (short term, long term)
- Economic (individual, family, community)
- Social (family, community)
- Development (community)
- Religious (individual, community)
- Premature death

Effect on health In general :

Causes more than 25 different diseases. Smoking can cause cancer almost anywhere in your body. Affects different body-systems, especially:

- Gastro-intestinal system.
- Respiratory tract.
- Cardio-vascular system.
- Urinary system.
- Others, such as

Skin : wrinkles, premature scaring and aging.

Oro-dental problems : stained teeth, gum inflammation, black hairy tounge, oral cancer, Leukoplakia.

Fetal Smoking Syndrome :

If the mother were smoker the baby will develop this syndrome which include: (Birth defects, Premature stillbirth, Low birth weight, Lowered immune capacity and Proneness to Sudden Infant Death Syndrome (SIDS).

Effect of Smoking on Respiratory:

- **Laryngeal cancer:**

Over 80% of deaths from laryngeal cancer are linked to smoking, some of its Symptoms: (Persistent hoarseness, Chronic sore throat, Painful swallowing, Pain in the ear and Lump in the neck.

- **Emphysema chronic bronchitis :**

Its symptoms include o Shortness of breath, chronic cough, Wheezing, anxiety, fatigue, weight loss, and swelling of ankle, feet and leg.

- **Lung cancer:**

Kills more people than any other type of cancer, Cigarette smoking causes most cases of lung cancer by 25 times

Effect of Smoking on Cardiovascular:

- **Arteriosclerosis & atherosclerosis.**
- **Peripheral vascular disease.**
- **Heart attack:**

Smokers are twice as likely as Nonsmokers to have a heart attack. Quitting smoking rapidly reduces the risk of coronary heart disease.

- **Stroke:**

Which can cause death or severe mental or physical disability.

Prevention & Control ?

Globally :

WHO-MPOWER (first launched in 2008), Monitoring tobacco use, and prevention policies, Banning tobacco advertising, Increasing taxing on tobacco, and health education .

From Guyton :

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Nationally :

- Tobacco Control Program; Ministry of Health
- Purity Organization; Ministry of Social Affairs

Conceptually:

- **Primary prevention** = tobacco use [smoking] prevention By:
  - Strengthening religious beliefs / "fatwas"
  - Legislations for banning smoking in public places
  - Banning advertising, especially to youngsters
  - Increasing taxation on tobacco products
  - Public health education through:

  1- Health warning labeling on tobacco products
  2- Using mini and mass media
  3- Banning smoking in drama

- **Secondary prevention** = tobacco use [smoking] cessation (quitting smoking), Personal advice can help the patient to quit smoking.
- **Tertiary prevention** = dealing with its consequences Tobacco Use.

Why targeting youth ?

The younger the age when smoking begins, the longer the smoking cycle. Young persons are also more vulnerable because they are likely to be less aware of the addictive nature of nicotine and the harmful effects of tobacco consumption.

Why do people smoke ?

- Parental influences
- Influence of peer
- Low socioeconomic status
- Social rewards
- Stress reliever
- Curiosity
- Weight control.
- Availability

Smoking cessation

Dramatically reduces the risk of most smoking-related diseases.

- Picking a quit date
- Keeping a record of why, when, where and with whom you smoke
- Getting support and encouragement from your family,friends, and health providers.
- Joining a quit group, counseling
- Quitting Clinics available.

Withdrawal symptoms:

Symptoms peak in the first two weeks, where relapse is high:

- Dizziness (which may last 1 to 2 days after quitting).
- Feelings of frustration, impatience, and anger.
- Depression, Anxiety.
- Sleep disturbances and Restlessness.
- Trouble concentrating and headaches.
- Increased appetite and Weight gain.
- Constipation and gas.
- Cough, dry mouth, sore throat, and nasal drip.
- Chest tightness.

Tips to overcome withdrawal:

- Avoid temptation: Stay away from people and places that tempt you to smoke.
- Change your habits: Take a brisk walk instead of a smoke break.
- Choose other things for your mouth: Use substitutes such as sugarless gum.
- Get active with your hands: Do something to reduce your stress such as woodworking.
- Breathe deeply: imagine you breathed deeply as you inhaled the smoke.
- Delay: If you feel that you're about to light up, hold off. Tell yourself you must wait at least 10 minutes.
- Reward yourself.

Immediate rewards of quitting smoking:

- Breath smells better, Bad smell in clothes and hair go away.
- Stained teeth get whiter, and Yellow fingernails disappear.
- Food tastes better.
- Sense of smell returns to normal.
- Everyday activities no longer leave them out of breath.
- Reduce the Cost
- Social acceptance

Models help in smoking cessation

The model of 5 A's

This model allowing physicians to incorporate smoking cessation counseling into busy clinical practices :

- **Ask:**

All patients should be asked about tobacco use and assessed for motivation to quit at every clinical encounter.

- **Advise**:

Advice to patients should be clear, strong, personalized.

- **Assess:**

Smoking history, Willingness to quit, Patients should be asked about their timeline for quitting and about previous attempts.

- **Assist**:

Offer support and help patients to anticipate difficulties (Nicotine withdrawal symptom, depression) and encourage them to prepare their social support systems.

- **Arrange:**

Follow-up plans should be set.

From Guyton :

At the onset of exercise, the alveolar ventilation increases almost instantaneously without an initial increase in arterial PCO_2. In fact, this increase in ventilation is usually great enough so that at first it actually decreases arterial PCO_2 below normal. The presumed reason that the ventilation forges ahead of the buildup of blood CO_2 is that" This is at least partly learned response"

The model of 5 R's:

This model allowing physicians to incorporate smoking cessation counseling into busy clinical practices :

- **Relevance:**

Motivational information has a great impact when it is relevant to the patient

- **Risks**:

Ask the patient to identify potential negative consequences associated with tobacco use.

- **Rewards:**

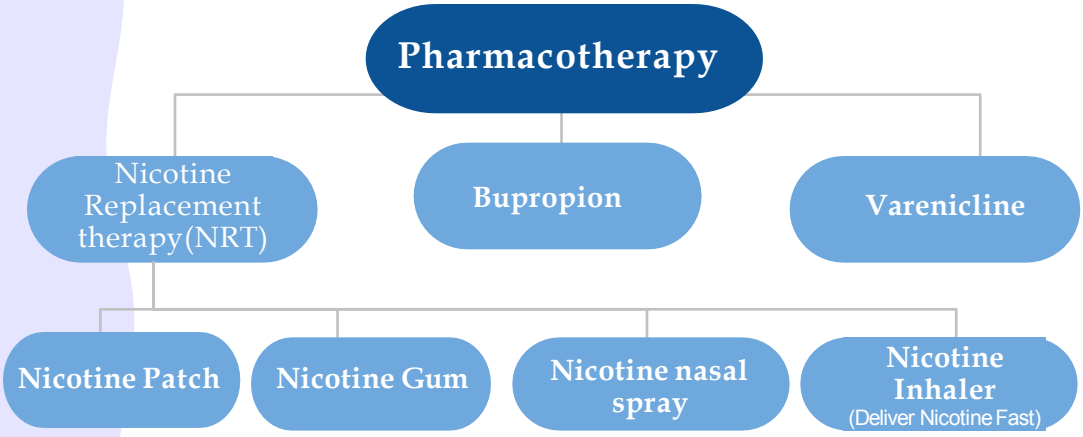
Encourage the patient to identify potential benefits of quitting smoking and highlight those most relevant to the patient.

- **Roadblocks**

Invite the patient to identify barriers or impediments to quitting and suggest treatments

- **Repetition**

Repeat the motivational intervention every time an unmotivated patient visits the clinic setting.



Nicotine Replacement Therapy (NRT)

NRT provides nicotine without using tobacco to relieve withdrawal symptoms as the patient stops cigarette smoking, The initial dose is based on the number of cigarettes smoked/day.

Transdermal nicotine patch:

- Simplest to use and High compliance
- Long acting and slow onset, which provides constant relief over 24hrs
- It is available over the counter.
- How to use: Place patch over hairless site, changed the next morning.

Starting on the quit day, patients who smoke >10 cigarettes/day: use highest dose of patch (21 mg/day) for 4-6 weeks, followed by 14 mg/day for 2 weeks, and finish with 7 mg/day for 2 weeks.

Smokers who weigh less than 45 kg or smoke ≤10 cigarettes per day are advised to begin with the 14 mg/day strength for 6 weeks, followed by 7 mg/day for 2 weeks.

Nicotine gum:

- very common and short-acting NRT.
- Chewing the gum releases nicotine, and absorbed through the oral mucosa, peak of nicotine in blood within 20 min of chewing.

4 mg dose of gum is for smokers who smoke ≥ 20 cigarettes per day 2 mg dose is recommended for lighter smokers. They can chew one piece of gum every 1 to 2 hours for six weeks. gradual reduction over the second six weeks (total duration should be 3 months).

- Acidic beverages (eg, coffee, carbonated drinks) should be avoided before and during gum use, as they lower the oral pH, causing nicotine to ionize and reducing nicotine absorption.

Bupropion and Varenicline

	Bupropion	Varenicline
M.O.A	inhibits the uptake of norepinephrine, serotonin, and dopamine reducing the urge of smoking.	○ It blocks the nicotine in tobacco smoke from binding to the receptor, thereby reducing the rewarding aspects of cigarette smoking, resulting in moderate levels of dopamine in the terminal synapse. ○ It reduces the withdrawal symptoms
Features	The quit date should be set for one to two weeks after bupropion therapy is initiated. And the therapy is usually continued for eight to 12 weeks after the patient has quit smoking	○ It increases the chances of a successful quit attempt 2-3-fold compared with non pharmacologic assistance. ○ Varenicline is superior to bupropion in promoting abstinence.
ADRs	The quit date should be set for one to two weeks after bupropion therapy is initiated. And the therapy is usually continued for eight to 12 weeks after the patient has quit smoking	increased risk of coronary events.
Contraindications	○ A history of seizure disorder. ○ The presence of eating disorders. ○ Uncontrolled hypertension	

From Guyton :

At the onset of exercise, the alveolar ventilation increases almost instantaneously without an initial increase in arterial PCO_2. In fact, this increase in ventilation is usually great enough so that at first it actually decreases arterial PCO_2 below normal. The presumed reason that the ventilation forges ahead of the buildup of blood CO_2 is that" This is at least partly learned response"

Appendix

Mind Maps

By Olivia Smith

What is pneumonia?

Pneumonia is inflammation of the lung parenchyma caused by a lower respiratory tract infection.
It often occurs after a viral infection in the upper respiratory tract. It is uncertain how the bacteria reach the lower respiratory tract after attaching to disaccharide receptors on pharyngeal epithelial cells.

Pathophysiology

Debatable methods of invasion include:

- The inhibition of IgA.
- Pneumolysins, which inhibit ciliary beating.
- Damage of the epithelial cells by prior infection.
- Hijacking the platelet aggregating factor receptor pathway to reach the alveoli.

Symptoms

- Fever.
- Cough with purulent sputum.
- Dyspnoea.
- Pleuritic pain.

Signs

- Percussion: dull.
- Auscultation: crackles, bronchial breathing.
- Respiratory failure: cyanosis, tachypnoea.
- Septicaemia: rigors.

Causative organisms

Children	Community acquired pneumonia	Hospital acquired pneumonia	HIV patients or immunocompromised patients
Viruses	*Streptococcus pneumoniae*	Gram-negative bacteria	*Pneumocystis jirovecii*
Pneumococcus	*Haemophilus influenzae*	*Staphylococcus aureus*	Cytomegalovirus
Mycoplasma	*Moraxella catarrhalis*	*Streptococcus pneumoniae*	Adenovirus
	Chlamydia pneumoniae (A)	Anaerobes	Herpes simplex virus
	Mycoplasma pneumoniae (A)	Fungi	*Mycobacterium tuberculosis*
	Legionella pneumophila (A)	*Legionella pneumophila*	Bacterial infection, e.g. *Staphylococcus aureus*
	Viruses		

A = Atypical

MAP 2.1 **Pneumonia**

Treatment

Remember this as **BAPP**:

- **B**reathing: maintain oxygen saturation levels.
- **A**ntibiotics: treat the underlying cause (check hospital guidelines).
- **P**ain: give analgesics.
- **P**neumococcal vaccines for those at risk, e.g. diabetics, the immunosuppressed and those over 65 years old.

Complications

- Respiratory failure: by causing acute respiratory distress syndrome (ARDS).
- Septic shock: the causative agent enters the patient's bloodstream, releasing cytokines.
- Pleural effusion.
- Empyema.
- Lung abscess.
- Hypotension: sepsis or dehydration is usually the underlying cause.

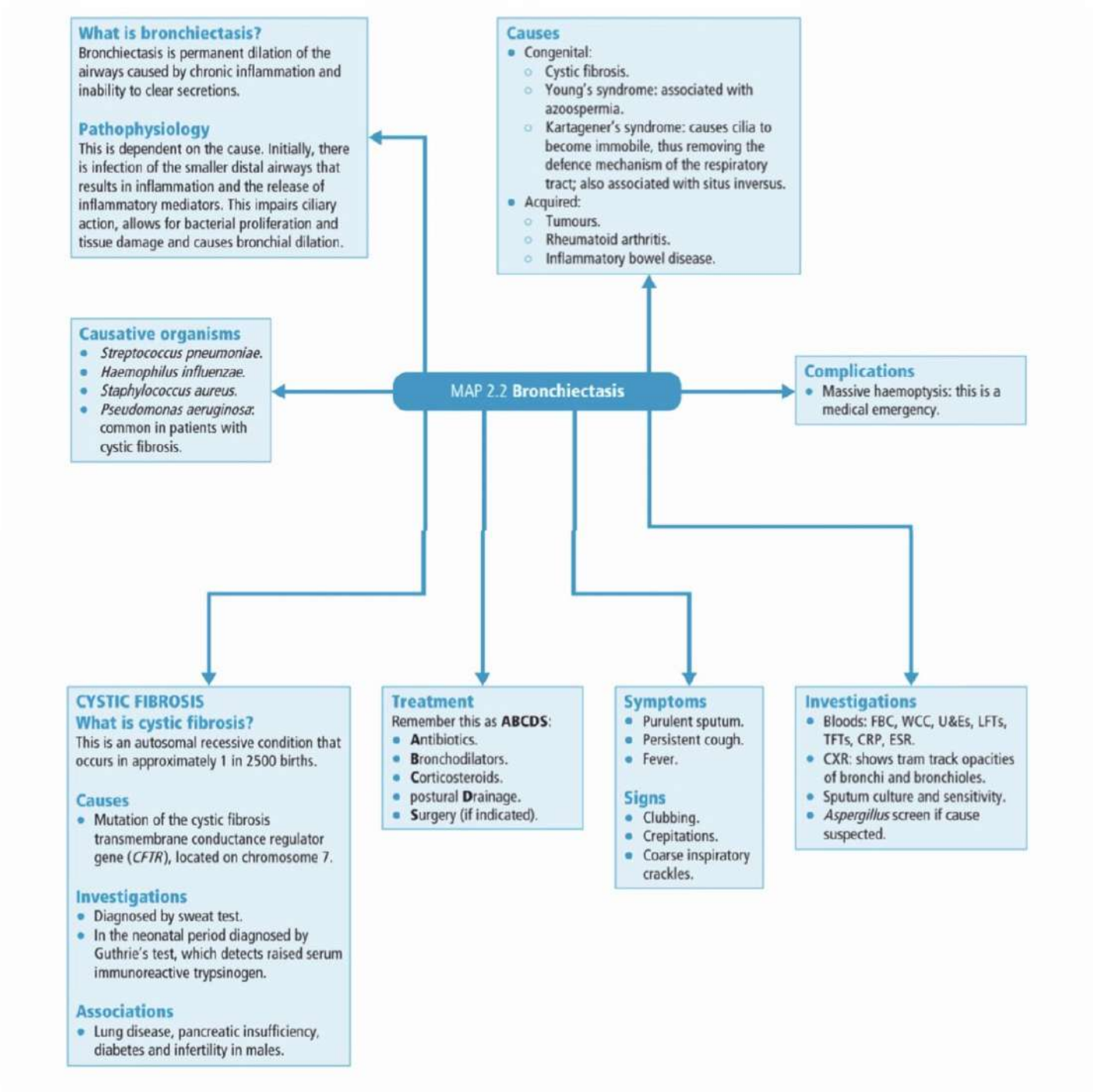
Investigations

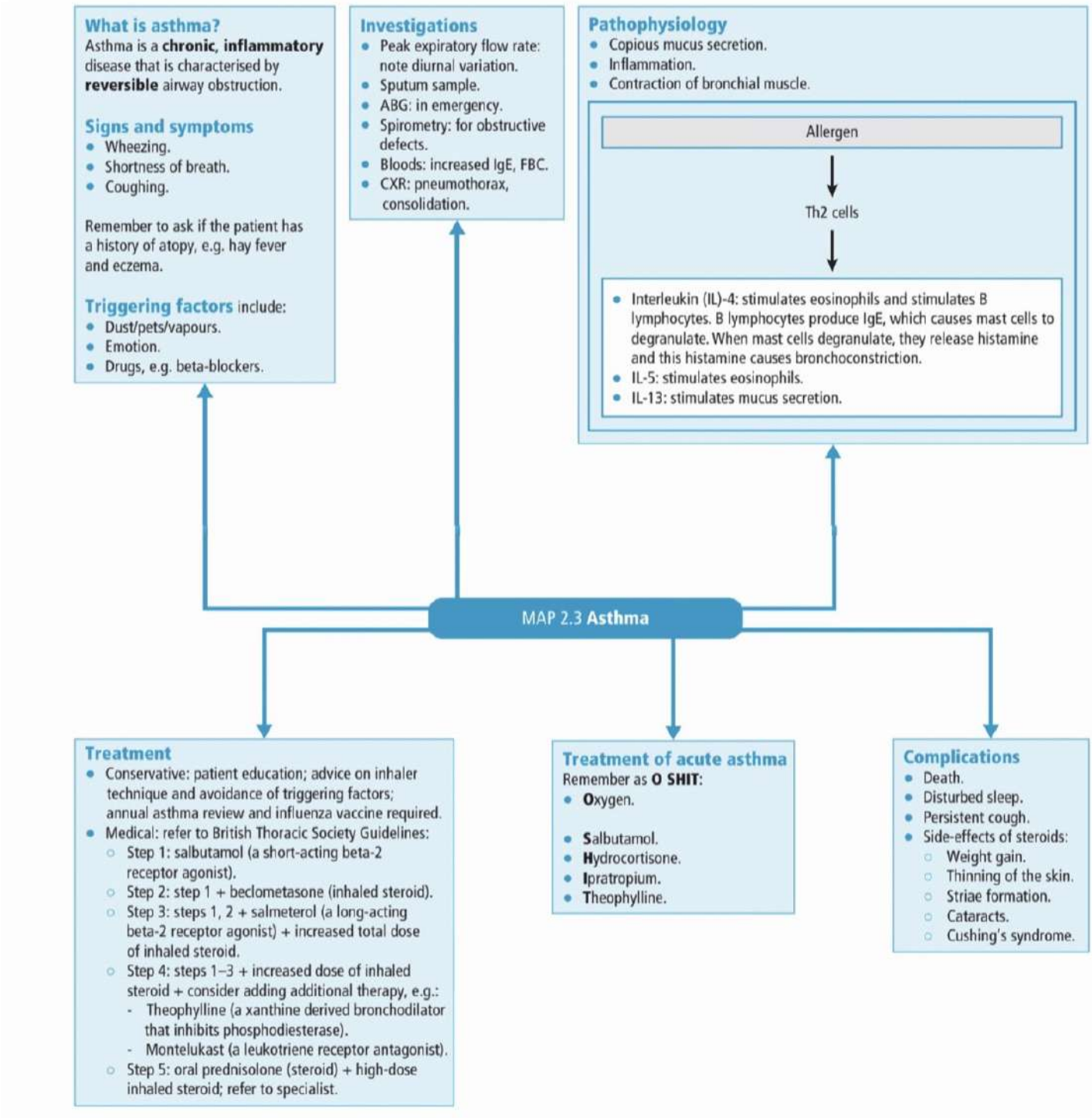
- CXR: look for infiltrates.
- Identify the causative organism by assessing a sputum sample.
- Monitor oxygen saturation.
- Bloods: look for raised WCC and raised inflammatory markers.
- Urinary antigen test: for pneumococcal or *Legionella* antigen.
- Arterial blood gas (ABG).

Assess **severity** using **CURB-65**

- **C**onfusion.
- **U**rea >7 mmol/L.
- **R**espiratory rate >30/min.
- **B**P <90/<60 mmHg.
- >**65** years old.

Each section of the CURB-65 is worth 1 point:
1 = Outpatient care.
2 = Admission.
>3 = Requires ICU admission.


MAP 2.2 Bronchiectasis
What is bronchiectasis?
Bronchiectasis is permanent dilation of the airways caused by chronic inflammation and inability to clear secretions.
Pathophysiology
This is dependent on the cause. Initially, there is infection of the smaller distal airways that results in inflammation and the release of inflammatory mediators. This impairs ciliary action, allows for bacterial proliferation and tissue damage and causes bronchial dilation.
Causes
Congenital:
Cystic fibrosis.
Young's syndrome: associated with azoospermia.
Kartagener's syndrome: causes cilia to become immobile, thus removing the defence mechanism of the respiratory tract; also associated with situs inversus.
Acquired:
Tumours.
Rheumatoid arthritis.
Inflammatory bowel disease.
Causative organisms
Streptococcus pneumoniae.
Haemophilus influenzae.
Staphylococcus aureus.
Pseudomonas aeruginosa: common in patients with cystic fibrosis.
Complications
Massive haemoptysis: this is a medical emergency.
CYSTIC FIBROSIS
What is cystic fibrosis?
This is an autosomal recessive condition that occurs in approximately 1 in 2500 births.
Causes
Mutation of the cystic fibrosis transmembrane conductance regulator gene (CFTR), located on chromosome 7.
Investigations
Diagnosed by sweat test.
In the neonatal period diagnosed by Guthrie's test, which detects raised serum immunoreactive trypsinogen.
Associations
Lung disease, pancreatic insufficiency, diabetes and infertility in males.
Treatment
Remember this as ABCDS:
Antibiotics.
Bronchodilators.
Corticosteroids.
postural Drainage.
Surgery (if indicated).
Symptoms
Purulent sputum.
Persistent cough.
Fever.
Signs
Clubbing.
Crepitations.
Coarse inspiratory crackles.
Investigations
Bloods: FBC, WCC, U&Es, LFTs, TFTs, CRP, ESR.
CXR: shows tram track opacities of bronchi and bronchioles.
Sputum culture and sensitivity.
Aspergillus screen if cause suspected.


What is asthma?
Asthma is a chronic, inflammatory disease that is characterised by reversible airway obstruction.
Signs and symptoms
Wheezing.
Shortness of breath.
Coughing.
Remember to ask if the patient has a history of atopy, e.g. hay fever and eczema.
Triggering factors include:
Dust/pets/vapours.
Emotion.
Drugs, e.g. beta-blockers.
Investigations
Peak expiratory flow rate: note diurnal variation.
Sputum sample.
ABG: in emergency.
Spirometry: for obstructive defects.
Bloods: increased IgE, FBC.
CXR: pneumothorax, consolidation.
Pathophysiology
Copious mucus secretion.
Inflammation.
Contraction of bronchial muscle.
Allergen
Th2 cells
Interleukin (IL)-4: stimulates eosinophils and stimulates B lymphocytes. B lymphocytes produce IgE, which causes mast cells to degranulate. When mast cells degranulate, they release histamine and this histamine causes bronchoconstriction.
IL-5: stimulates eosinophils.
IL-13: stimulates mucus secretion.
MAP 2.3 Asthma
Treatment
Conservative: patient education; advice on inhaler technique and avoidance of triggering factors; annual asthma review and influenza vaccine required.
Medical: refer to British Thoracic Society Guidelines:
Step 1: salbutamol (a short-acting beta-2 receptor agonist).
Step 2: step 1 + beclometasone (inhaled steroid).
Step 3: steps 1, 2 + salmeterol (a long-acting beta-2 receptor agonist) + increased total dose of inhaled steroid.
Step 4: steps 1–3 + increased dose of inhaled steroid + consider adding additional therapy, e.g.:
- Theophylline (a xanthine derived bronchodilator that inhibits phosphodiesterase).
- Montelukast (a leukotriene receptor antagonist).
Step 5: oral prednisolone (steroid) + high-dose inhaled steroid; refer to specialist.
Treatment of acute asthma
Remember as O SHIT:
Oxygen.
Salbutamol.
Hydrocortisone.
Ipratropium.
Theophylline.
Complications
Death.
Disturbed sleep.
Persistent cough.
Side-effects of steroids:
Weight gain.
Thinning of the skin.
Striae formation.
Cataracts.
Cushing's syndrome.

MAP 2.4 Chronic Obstructive Pulmonary Disease (COPD)

What is COPD?

This is a chronic obstructive airway disease that is characterised by its irreversibility.
It is closely linked to smoking.
It is made up of:

- Chronic bronchitis: cough with sputum production for at least 3 months in 2 consecutive years.
- Emphysema: this encompasses permanently dilated airways distal to the terminal bronchioles with alveolar destruction and bullae formation. It is defined histologically and is associated with alpha-1 antitrypsin deficiency and increased elastase activity.

Causes

Remember this as **GASES**:

- **G**enetics: alpha-1 antitrypsin deficiency results in the loss of protection against proteases.
- **A**ir pollution.
- **S**moking.
- **E**xposure through occupation, e.g. coal mining.
- **S**econdhand smoke exposure.

Pathophysiology

- Chronic bronchitis: chronic infection results in the chronic infiltration of the respiratory submucosa by inflammatory cells. This results in mucous gland hyperplasia and smooth muscle hypertrophy, causing bronchial lumen narrowing. 'Blue bloaters' are patients where this pathology dominates.
- Emphysema: alveolar walls are destroyed resulting in bullae formation and the fusion of adjacent alveoli. This ultimately results in a decreased surface area for gas exchange and decreased elastic recoil with subsequent air trapping. 'Pink puffers' are patients where this pathology dominates.

Investigations

- Diagnosis is confirmed by spirometry, which has a FEV_1 value <80% predicted and FEV_1/FVC <0.7.
- CXR shows lung hyperinflation, emphysematous change and diaphragmatic flattening.
- Bloods: FBC, U&Es, WCC, ESR, CRP, alpha-1 antitrypsin levels.
- ECG: for cor pulmonale.
- Sputum culture.

The **GOLD scale** assesses severity of COPD:
Stage I: mild COPD.
Stage II: moderate COPD.
Stage III: severe COPD.
Stage IV: very severe COPD.

Complications

Remember this as **CLIPPeR**:

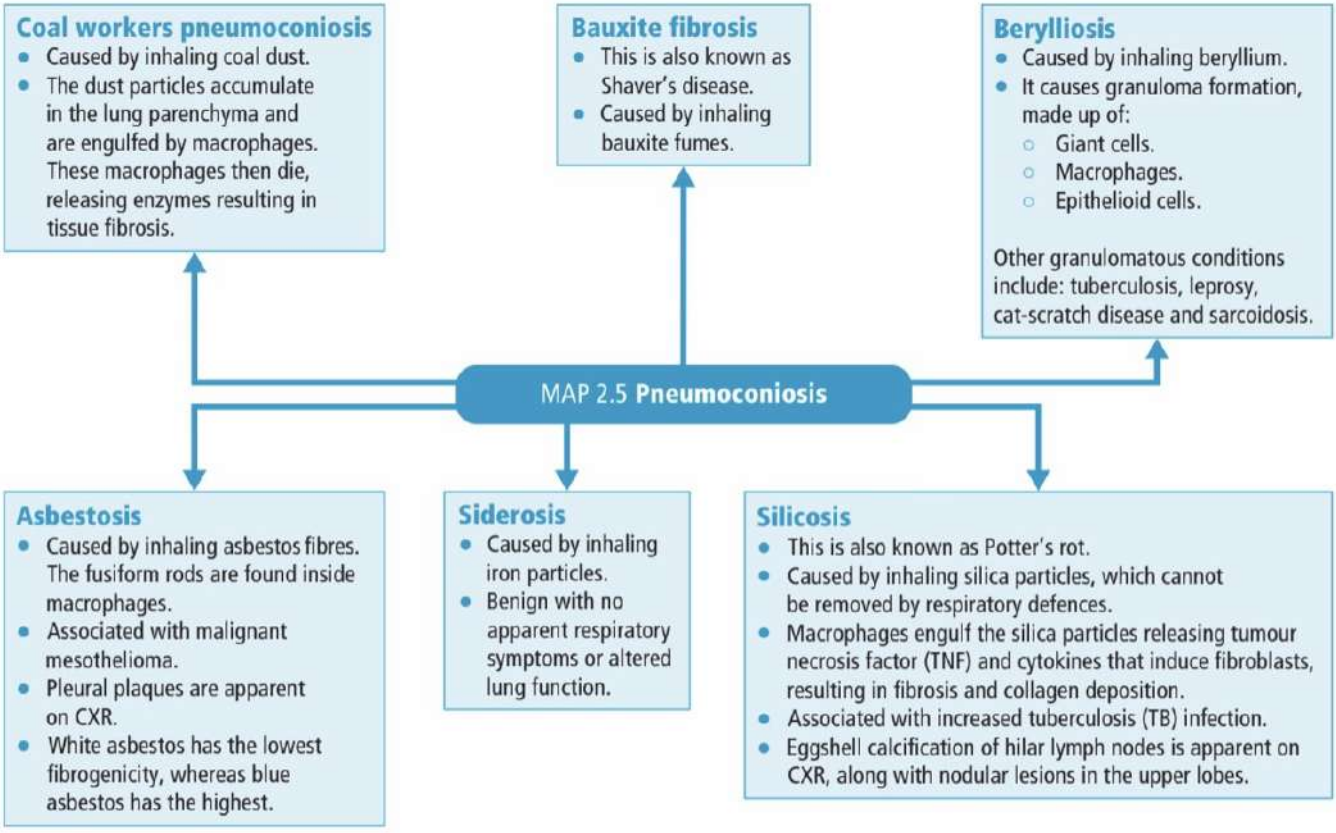
- **C**or pulmonale: right-sided heart failure due to chronic pulmonary hypertension.
- **L**ung cancer.
- **I**nfections: usually treat with macrolide antibiotics.
- **P**neumothorax.
- **P**olycythaemia.
- **e**
- **R**espiratory failure.

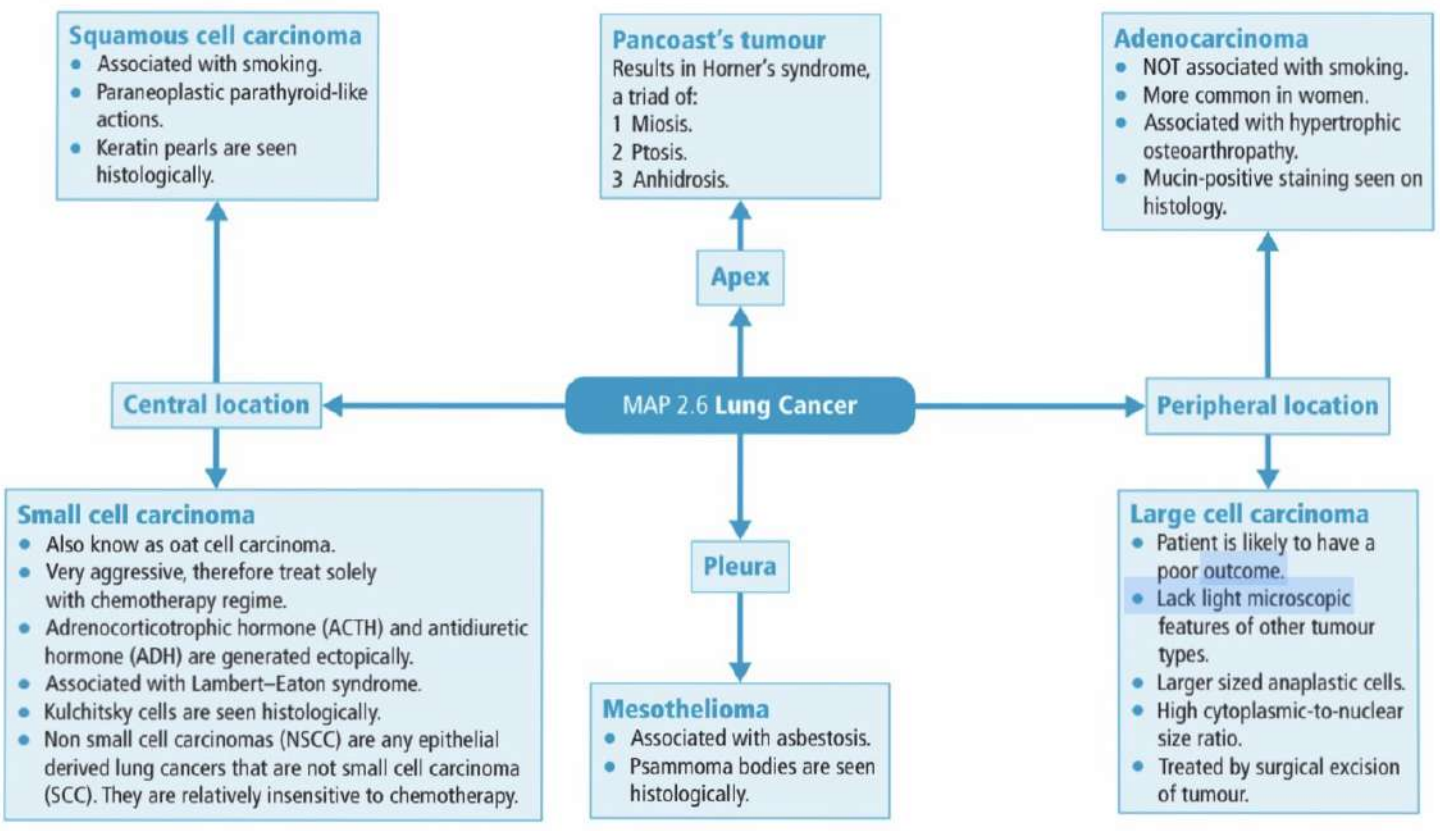
Treatment

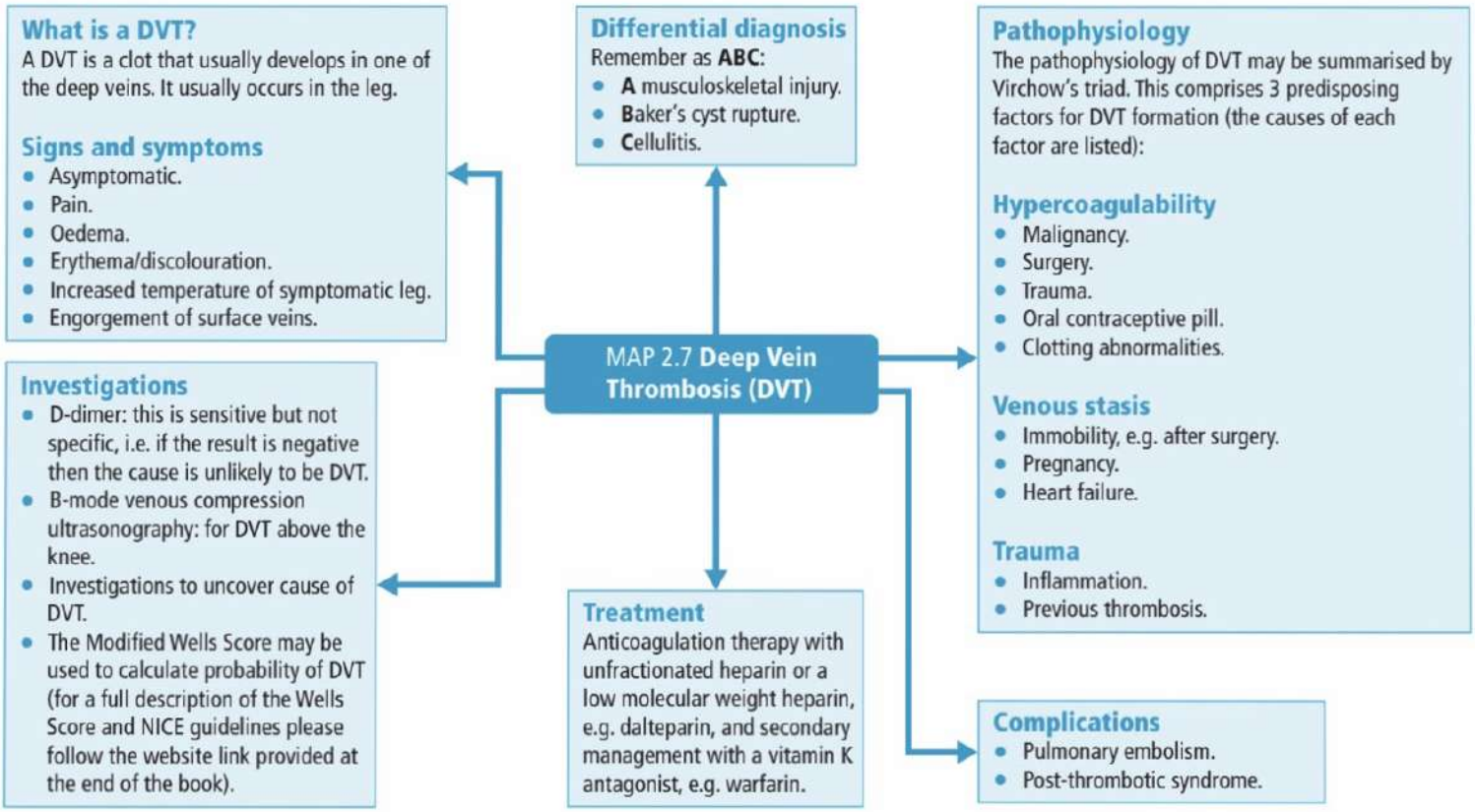
Remember this as **ABCS, oxygen therapy and pulmonary rehabilitation**:

- **A**nticholinergics, e.g. ipratropium.
- **B**ronchodilators, e.g. salmeterol.
- **C**orticosteroids.
- **S**moking cessation is imperative.

- **Oxygen therapy**: long-term oxygen therapy (LTOT) or noninvasive ventilation (NIV).


Coal workers pneumoconiosis
Caused by inhaling coal dust.
The dust particles accumulate in the lung parenchyma and are engulfed by macrophages. These macrophages then die, releasing enzymes resulting in tissue fibrosis.
Bauxite fibrosis
This is also known as Shaver's disease.
Caused by inhaling bauxite fumes.
Berylliosis
Caused by inhaling beryllium.
It causes granuloma formation, made up of:
Giant cells.
Macrophages.
Epithelioid cells.
Other granulomatous conditions include: tuberculosis, leprosy, cat-scratch disease and sarcoidosis.
MAP 2.5 Pneumoconiosis
Asbestosis
Caused by inhaling asbestos fibres. The fusiform rods are found inside macrophages.
Associated with malignant mesothelioma.
Pleural plaques are apparent on CXR.
White asbestos has the lowest fibrogenicity, whereas blue asbestos has the highest.
Siderosis
Caused by inhaling iron particles.
Benign with no apparent respiratory symptoms or altered lung function.
Silicosis
This is also known as Potter's rot.
Caused by inhaling silica particles, which cannot be removed by respiratory defences.
Macrophages engulf the silica particles releasing tumour necrosis factor (TNF) and cytokines that induce fibroblasts, resulting in fibrosis and collagen deposition.
Associated with increased tuberculosis (TB) infection.
Eggshell calcification of hilar lymph nodes is apparent on CXR, along with nodular lesions in the upper lobes.


MAP 2.6 Lung Cancer
Central location
Apex
Pleura
Peripheral location
Squamous cell carcinoma
Associated with smoking.
Paraneoplastic parathyroid-like actions.
Keratin pearls are seen histologically.
Pancoast's tumour
Results in Horner's syndrome, a triad of:
1 Miosis.
2 Ptosis.
3 Anhidrosis.
Adenocarcinoma
NOT associated with smoking.
More common in women.
Associated with hypertrophic osteoarthropathy.
Mucin-positive staining seen on histology.
Small cell carcinoma
Also know as oat cell carcinoma.
Very aggressive, therefore treat solely with chemotherapy regime.
Adrenocorticotrophic hormone (ACTH) and antidiuretic hormone (ADH) are generated ectopically.
Associated with Lambert–Eaton syndrome.
Kulchitsky cells are seen histologically.
Non small cell carcinomas (NSCC) are any epithelial derived lung cancers that are not small cell carcinoma (SCC). They are relatively insensitive to chemotherapy.
Mesothelioma
Associated with asbestosis.
Psammoma bodies are seen histologically.
Large cell carcinoma
Patient is likely to have a poor outcome.
Lack light microscopic features of other tumour types.
Larger sized anaplastic cells.
High cytoplasmic-to-nuclear size ratio.
Treated by surgical excision of tumour.


MAP 2.7 Deep Vein Thrombosis (DVT)
What is a DVT?
A DVT is a clot that usually develops in one of the deep veins. It usually occurs in the leg.
Signs and symptoms
Asymptomatic.
Pain.
Oedema.
Erythema/discolouration.
Increased temperature of symptomatic leg.
Engorgement of surface veins.
Differential diagnosis
Remember as ABC:
A musculoskeletal injury.
Baker's cyst rupture.
Cellulitis.
Pathophysiology
The pathophysiology of DVT may be summarised by Virchow's triad. This comprises 3 predisposing factors for DVT formation (the causes of each factor are listed):
Hypercoagulability
Malignancy.
Surgery.
Trauma.
Oral contraceptive pill.
Clotting abnormalities.
Venous stasis
Immobility, e.g. after surgery.
Pregnancy.
Heart failure.
Trauma
Inflammation.
Previous thrombosis.
Investigations
D-dimer: this is sensitive but not specific, i.e. if the result is negative then the cause is unlikely to be DVT.
B-mode venous compression ultrasonography: for DVT above the knee.
Investigations to uncover cause of DVT.
The Modified Wells Score may be used to calculate probability of DVT (for a full description of the Wells Score and NICE guidelines please follow the website link provided at the end of the book).
Treatment
Anticoagulation therapy with unfractionated heparin or a low molecular weight heparin, e.g. dalteparin, and secondary management with a vitamin K antagonist, e.g. warfarin.
Complications
Pulmonary embolism.
Post-thrombotic syndrome.

MAP 2.8 Pulmonary Embolism (PE)

What is a PE?

This is occlusion of the pulmonary vasculature by a clot. Often it occurs from a deep vein thrombosis (DVT) that has become dislodged and forms an embolus that lodges in the pulmonary arterial vasculature, blocking the vessels.

Signs and symptoms

- Breathlessness: this may be of sudden onset or progressive.
- Tachypnoea.
- Pleuritic chest pain.
- Cyanosis.
- Haemoptysis.

Causes

- DVT.
- Air embolus.
- Fat embolus.
- Amniotic fluid embolus.
- Foreign material introduced via IV drug use.

Pathophysiology

The extent of thrombus may be classified into small-medium, multiple and massive PE. Symptom correlation depends on where the pulmonary circulation is occluded.

There are 3 pathways involved in the pathophysiology of PE:

1. Platelet factor release: serotonin and thromboxane A_2 cause vasoconstriction.
2. Decreased alveolar perfusion: lung is underperfused and this leads to diminished gas exchange.
3. Decreased surfactant: this leads to ventilation/perfusion mismatch, hypoxaemia and dyspnoea.

Investigations

- D-dimer: sensitive but not specific; negative result used to rule out PE.
- Thrombophilia screening: in patients <50 years with recurrent PE.
- CXR: usually normal.
- ECG: sinus tachycardia, S1Q3T3 pattern is classical but rare; excludes MI.
- ABG: hypoxaemia.
- CT, pulmonary angiography.
- V/Q scan.
- The Wells Score may be used to calculate risk of PE.

Treatment

- Acute:
  - Oxygen.
  - IV fluids.
  - Thrombolysis therapy if indicated, e.g. alteplase if massive PE or haemodynamically unstable.
  - Low molecular weight heparin.
- Long-term management:
  - Anticoagulation.
  - Inferior vena cava filter.

Complications

- Sudden death.
- Arrhythmia.
- Pulmonary infarction.
- Pleural effusion.
- Paradoxical embolism.
- Pulmonary hypertension.

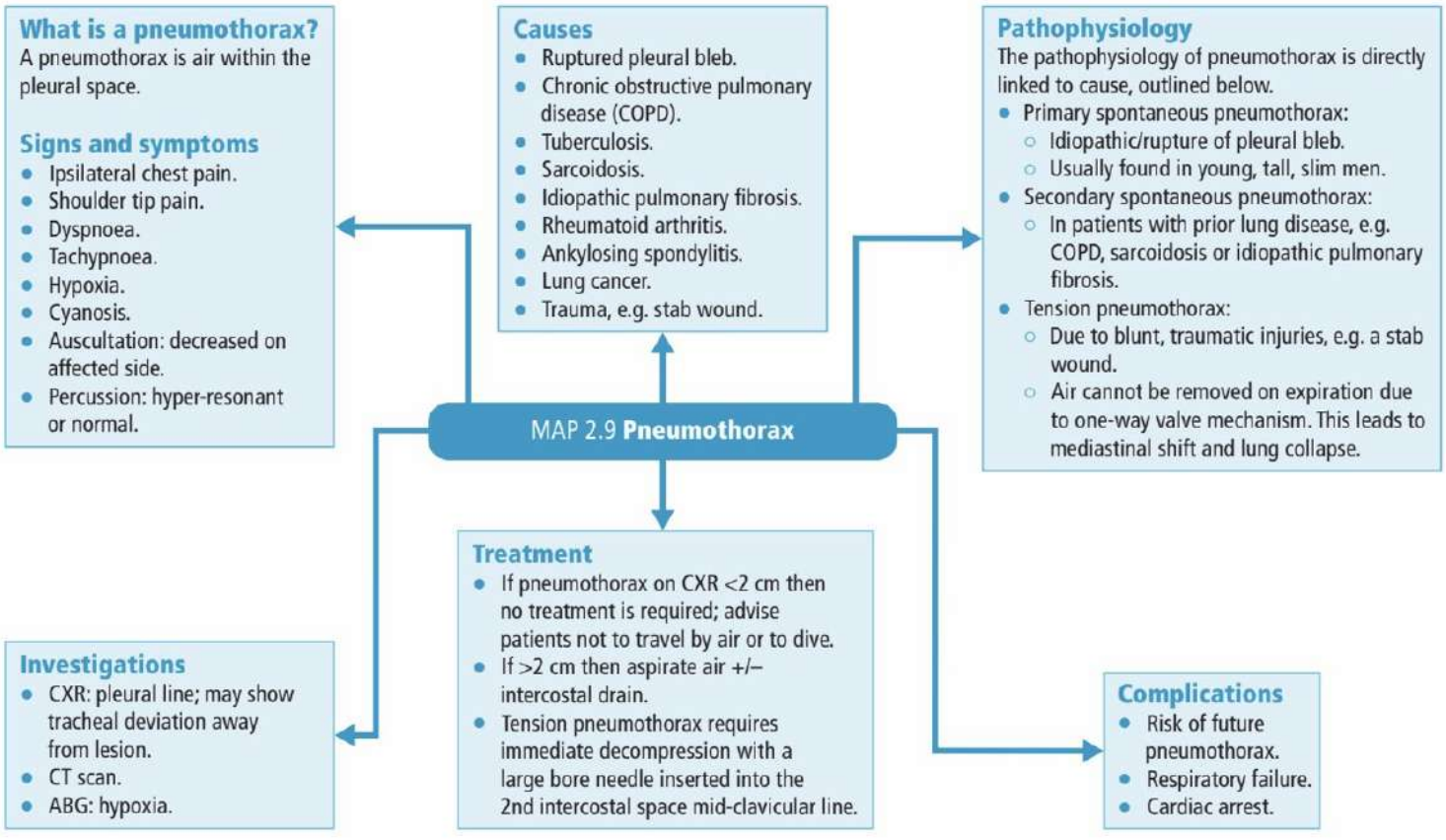

What is a pneumothorax?
A pneumothorax is air within the pleural space.
Signs and symptoms
Ipsilateral chest pain.
Shoulder tip pain.
Dyspnoea.
Tachypnoea.
Hypoxia.
Cyanosis.
Auscultation: decreased on affected side.
Percussion: hyper-resonant or normal.
Causes
Ruptured pleural bleb.
Chronic obstructive pulmonary disease (COPD).
Tuberculosis.
Sarcoidosis.
Idiopathic pulmonary fibrosis.
Rheumatoid arthritis.
Ankylosing spondylitis.
Lung cancer.
Trauma, e.g. stab wound.
Pathophysiology
The pathophysiology of pneumothorax is directly linked to cause, outlined below.
Primary spontaneous pneumothorax:
Idiopathic/rupture of pleural bleb.
Usually found in young, tall, slim men.
Secondary spontaneous pneumothorax:
In patients with prior lung disease, e.g. COPD, sarcoidosis or idiopathic pulmonary fibrosis.
Tension pneumothorax:
Due to blunt, traumatic injuries, e.g. a stab wound.
Air cannot be removed on expiration due to one-way valve mechanism. This leads to mediastinal shift and lung collapse.
MAP 2.9 Pneumothorax
Investigations
CXR: pleural line; may show tracheal deviation away from lesion.
CT scan.
ABG: hypoxia.
Treatment
If pneumothorax on CXR <2 cm then no treatment is required; advise patients not to travel by air or to dive.
If >2 cm then aspirate air +/– intercostal drain.
Tension pneumothorax requires immediate decompression with a large bore needle inserted into the 2nd intercostal space mid-clavicular line.
Complications
Risk of future pneumothorax.
Respiratory failure.
Cardiac arrest.

TABLE 2.1 **Type 1 vs. Type 2 Respiratory Failure**		
	Type 1: hypoventilation with V/Q mismatch 'Pink puffer' – thin and hyperinflated	**Type 2: hypoventilation with or without V/Q mismatch** 'Blue bloater' – strong build and wheezy
Cause	Pneumonia Pulmonary embolism Pulmonary oedema Fibrosing alveolitis	Chronic obstructive pulmonary disease (COPD) and asthma Cerebrovascular disease Opiate overdose Myasthenia gravis Motor neuron disease
Symptoms	Remember this as **ABCD**: **A**gitation **B**reathlessness **C**onfusion **D**rowsiness and fatigue	Remember this as **ABCD**: **A**gitation **B**reathlessness **C**onfusion **D**rowsiness and fatigue
Signs	Central cyanosis	Remember this as **ABC**: **A** flapping tremor **B**ounding pulse **C**yanosis
PaO_2	↓ (<8.0 kPa)	↓ (<8.0 kPa)
$PaCO_2$	Normal (~6.7 kPa)	↑ (>6.7 kPa)
Treatment	Oxygen replacement therapy Treatment of underlying cause	Noninvasive ventilation Treatment of underlying cause
Complications	Nosocomial infections, e.g. pneumonia Heart failure Arrhythmia Pericarditis	Nosocomial infections, e.g. pneumonia Heart failure Arrhythmia Pericarditis

Appendix :

Medcomics

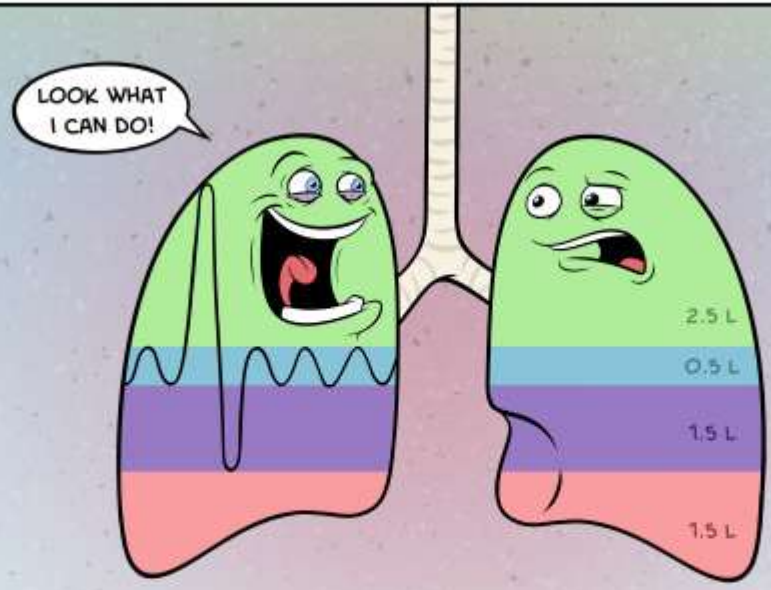
LUNG VOLUMES AND CAPACITIES

IRV
INSPIRATORY
RESERVE VOLUME

V_T
TIDAL VOLUME

ERV
EXPIRATORY
RESERVE VOLUME

RV
RESIDUAL VOLUME

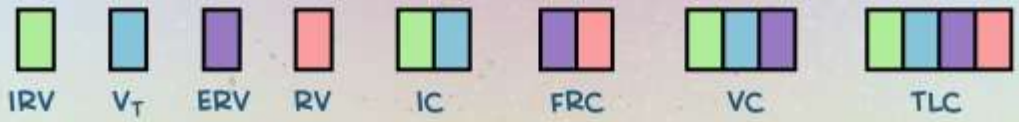


IC
INSPIRATORY
CAPACITY

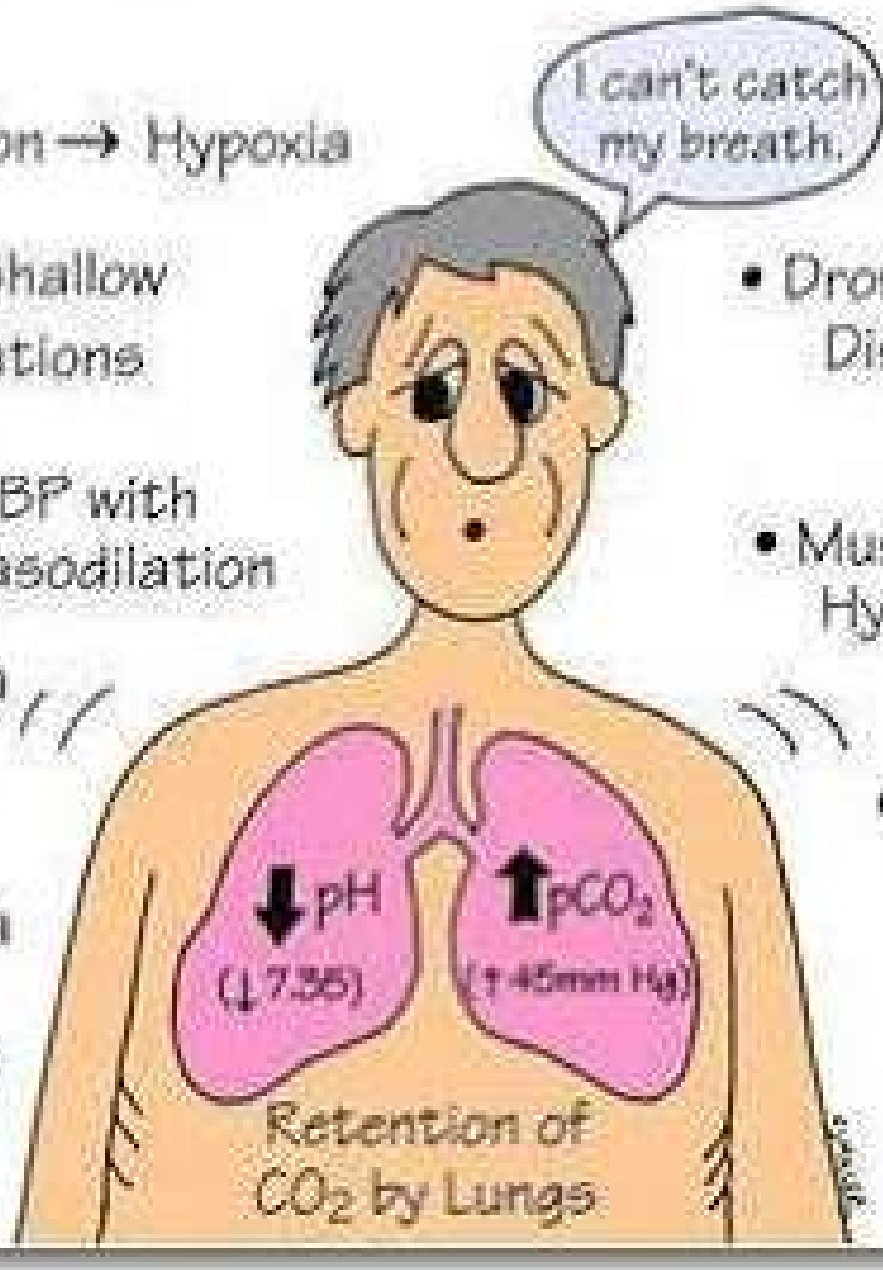
FRC
FUNCTIONAL
RESIDUAL CAPACITY

VC
VITAL CAPACITY

TLC
TOTAL LUNG
CAPACITY



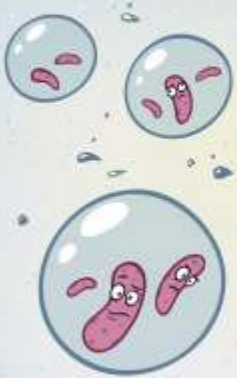
RESPIRATORY ACIDOSIS



- Hypoventilation → Hypoxia
- Rapid, Shallow Respirations
- ↓ BP with Vasodilation
- Dyspnea
- Headache
- Hyperkalemia
- Dysrhythmias (↑K)
- Drowsiness, Dizziness, Disorientation
- Muscle Weakness, Hyperreflexia
- Causes:
  - ↓ Respiratory Stimuli (Anesthesia, Drug Overdose)
  - COPD
  - Pneumonia
  - Atelectasis

TUBERCULOSIS

MYCOBACTERIUM TUBERCULOSIS IS CARRIED THROUGH THE AIR IN INFECTIOUS DROPLETS PRODUCED WHEN INFECTED INDIVIDUALS COUGH



NIGHT SWEATS

THE PPD TEST CONSISTS OF A SUBCUTANEOUS INJECTION OF TUBERCULIN ANTIGEN WITH A SUBSEQUENT READING IN 48 TO 72 HOURS

FEVER, FATIGUE, WEIGHT LOSS, PRODUCTIVE COUGH, AND BLOOD-STREAKED SPUTUM

THE REACTION IS REPORTED ACCORDING TO THE DIAMETER OF THE INDURATION, NOT ERYTHEMA

Infectious Mononucleosis
"Mono"

Transmission:
Most common age 15-24 yrs. Contracted through saliva, mucus and tears...Known as the "Kissing Disease"

Cause:
Epstein Barr Virus (EBV)

- Fever "101°-104°"
- Sore Throat
- Pain Mid-Epigastric and LUQ With Spleen Enlargement
- Loss of Appetite
- Body Aches
- Headache
- Chills
- Swollen Lymph Glands
- Pain in RUQ With Liver Involvement
- Fatigue
- Decreased Energy

Diagnostic:
- Mono Spot
- Liver Enzymes
- CMV - Ab Cytomegalovirus Can Mimic Mono Symptoms

Treatment:
- Rest
- Throat Soothing Measures
- Acetaminophen / Ibuprofen
- Low Energy / Impact Activity
- Gradual ↑ Activity

RUBEOLA

ORDINARY MEASLES

CONJUNCTIVITUS
COUGH
CORYZA
FEVER

KOPLIK SPOTS ON BUCCAL MUCOSA

RASH APPEARS AT THE HAIRLINE AND SPREADS CEPHALOCAUDALLY OVER 3 DAYS

RUBELLA

GERMAN MEASLES

HEADACHE
LOW GRADE FEVER
SORE THROAT
CORYZA

FORCHHEIMER SPOTS ON SOFT PALATE

LYMPHADENOPATHY

RASH BEGINS ON THE FACE AND SPREADS CEPHALOCAUDALLY

ROSEOLA INFANTUM

EXANTHEM SUBITUM

AFFECTS YOUNG CHILDREN 6-36 MONTHS OLD

CAUSED BY HUMAN HERPES VIRUS 6

ABRUPT HIGH FEVER

AFTER FEVER SUBSIDES, A RASH DEVELOPS, STARTING ON THE NECK AND TRUNK AND SPREADING TO THE FACE AND EXTREMITIES

CLASSIFICATION OF ASTHMA

PERSISTENT

RESCUE MEDICATION
< 2 DAYS PER WEEK

NIGHTTIME SYMPTOMS
≤ 2 TIMES PER MONTH

FEV1 > 80% PREDICTED
FEV1/FVC NORMAL

INTERMITTENT

RESCUE MEDICATION
> 2 DAYS PER WEEK

NIGHTTIME SYMPTOMS
3-4 TIMES PER MONTH

FEV1 > 80% PREDICTED
FEV1/FVC NORMAL

MILD

RESCUE MEDICATION
DAILY

NIGHTTIME SYMPTOMS
> 1 TIME PER WEEK

FEV1 > 60% BUT < 80% PREDICTED
FEV1/FVC REDUCED 5%

MODERATE

RESCUE MEDICATION
SEVERAL TIMES PER DAY

NIGHTTIME SYMPTOMS
OFTEN > 7 TIMES PER WEEK

FEV1 < 60% PREDICTED
FEV1/FVC REDUCED > 5%

SEVERE

CHRONIC BRONCHITIS

CLINICAL DIAGNOSIS: DAILY PRODUCTIVE COUGH FOR THREE MONTHS OR MORE, IN AT LEAST TWO CONSECUTIVE YEARS

OVERWEIGHT AND CYANOTIC

ELEVATED HEMOGLOBIN

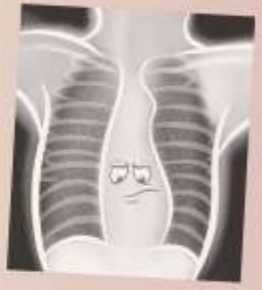
PERIPHERAL EDEMA

RHONCHI AND WHEEZING

EMPHYSEMA

PATHOLOGIC DIAGNOSIS: PERMANENT ENLARGEMENT AND DESTRUCTION OF AIRSPACES DISTAL TO THE TERMINAL BRONCHIOLE

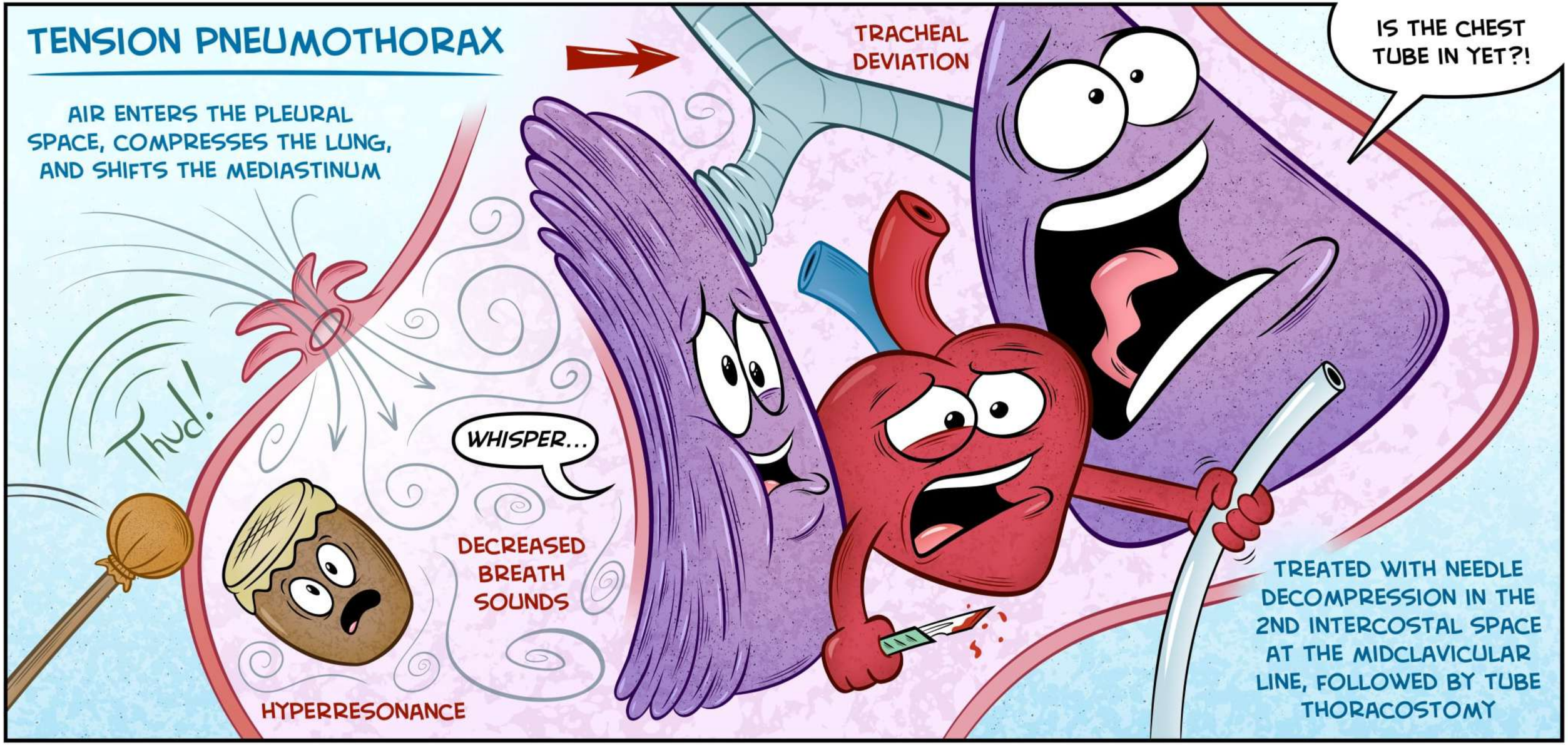
OLDER AND THIN



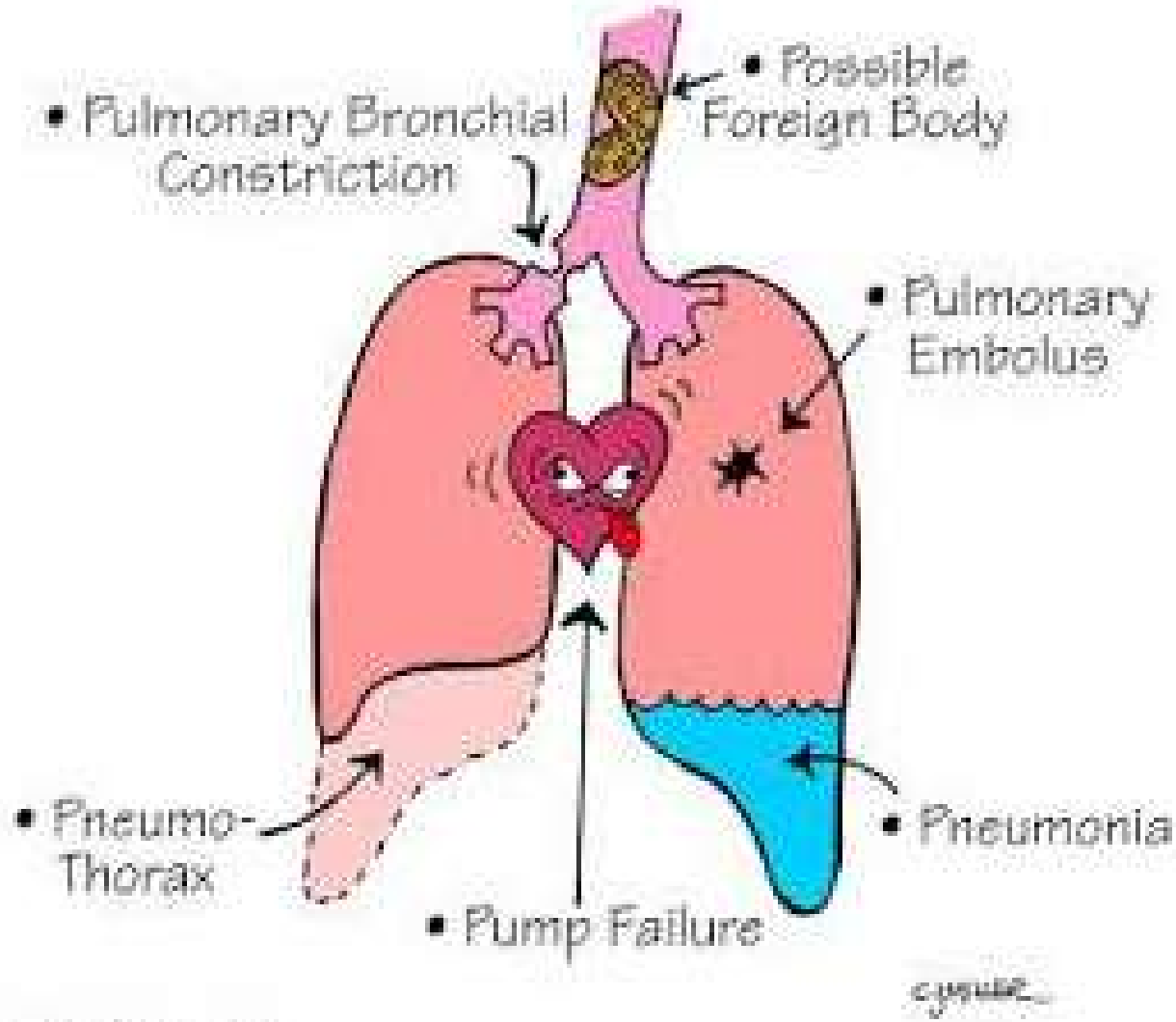
SEVERE DYSPNEA

QUIET CHEST

X-RAY: HYPERINFLATION WITH FLATTENED DIAPHRAGMS



6-Ps OF DYSPNEA



neuroscharts

BREATH SOUNDS

EASY TO REMEMBER STUDENT EDITION

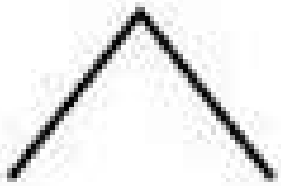
VESICULAR SOUNDS

Normal - heard over periphery
Gentle rustling sound
Fades on expiration

BRONCHIAL SOUNDS

Normal - heard over substernal notch
LOUDER - Expiratory lasts longer
Silent internal

BRONCHOVESICULAR



Normal - heard 1st & 2nd inter coastal space anteriorly and between scapulae posteriorly
Intermediate intensity

FINE CRACKLES

Abnormal - discontinous
High pitched
Popping quality

COARSE CRACKLES

Abnormal - discontinous
Low pitched
Louder & Longer

WHEEZE

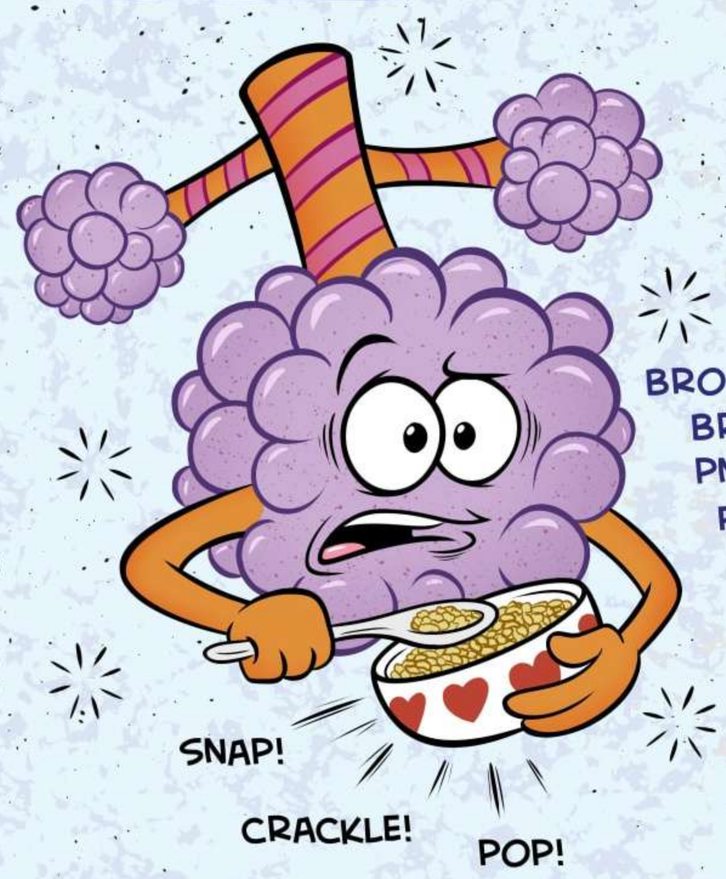
Abnormal - continous
High pitched
Musical quality

RHONCHI

Abnormal - continous
Low pitched
Gurgling quality

ADVENTITIOUS BREATH SOUNDS

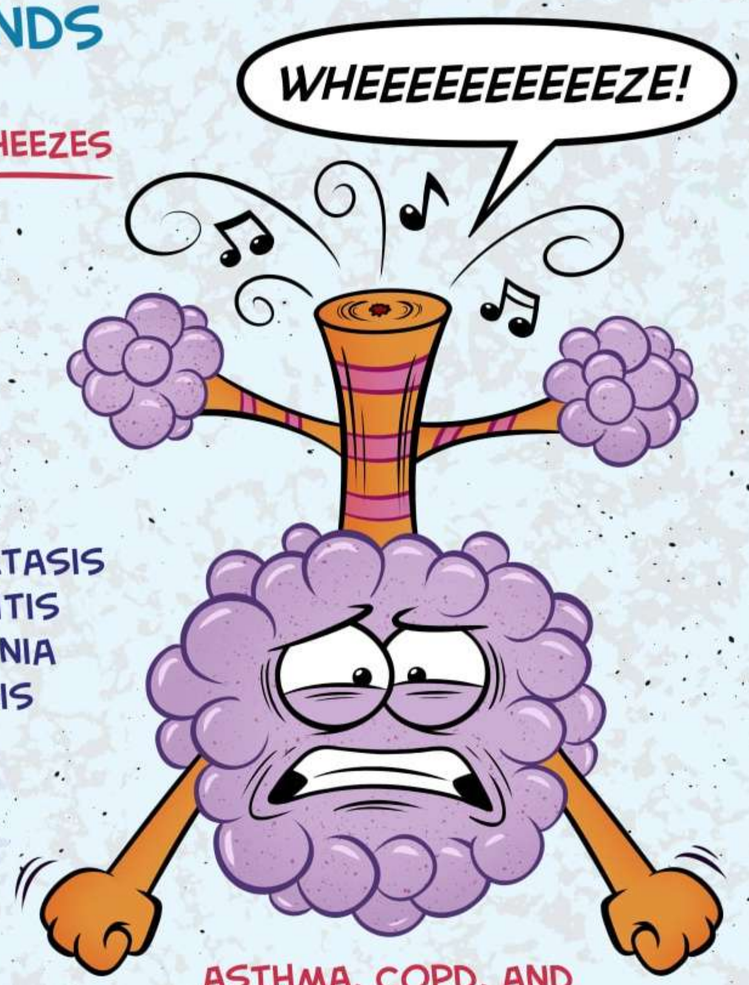
CRACKLES (RALES)



BRONCHIECTASIS
BRONCHITIS
PNEUMONIA
FIBROSIS
CHF

DISCONTINUOUS

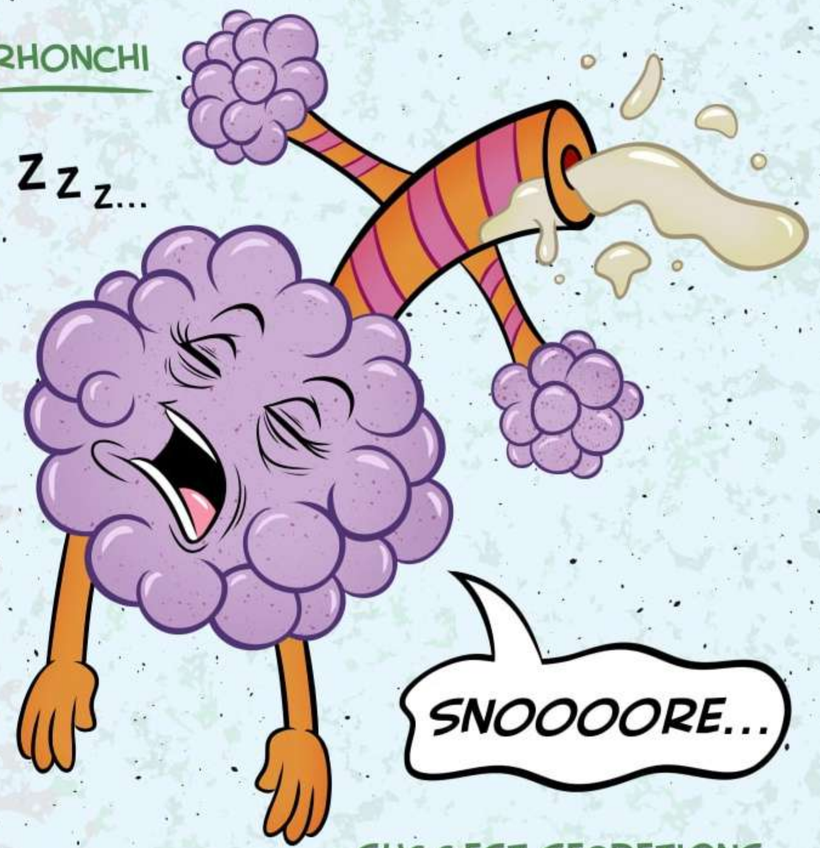
WHEEZES



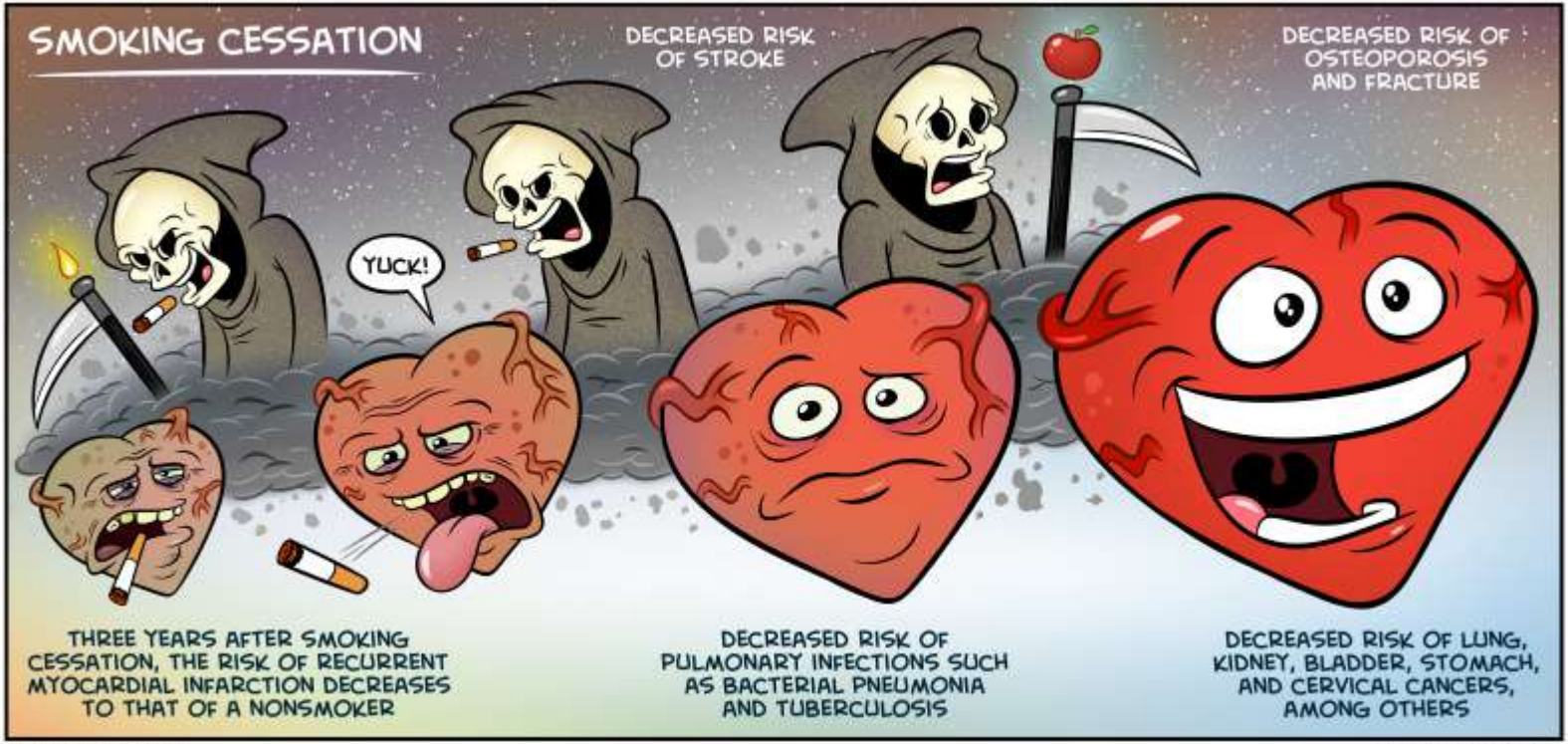
ASTHMA, COPD, AND
OTHER CAUSES OF AIRWAY OBSTRUCTION

CONTINUOUS

RHONCHI



SUGGEST SECRETIONS
IN THE LARGE AIRWAYS



Appendix :

First Aid

For USMLE STEP 1 2019

Respiratory

"There's so much pollution in the air now that if it weren't for our lungs, there'd be no place to put it all."

—Robert Orben

"Freedom is the oxygen of the soul."

—Moshe Dayan

"Whenever I feel blue, I start breathing again."

—L. Frank Baum

"Life is not the amount of breaths you take; it's the moments that take your breath away."

—Will Smith, *Hitch*

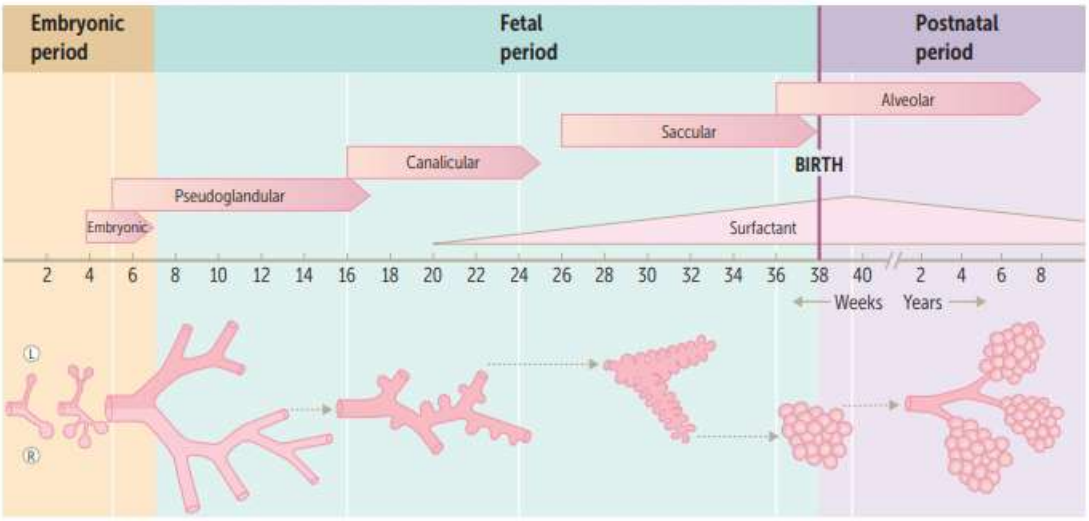
Group key respiratory, cardiovascular, and renal concepts together for study whenever possible. Know obstructive vs restrictive lung disorders, $\dot{V}/\dot{Q}$ mismatch, lung volumes, mechanics of respiration, and hemoglobin physiology. Lung cancers and other causes of lung masses are high yield. Be comfortable reading basic chest x-rays, CT scans, and PFTs.

▸ RESPIRATORY—EMBRYOLOGY

Lung development

Occurs in five stages. Initial development includes development of lung bud from distal end of respiratory diverticulum during week 4. Every Pulmonologist Can See Alveoli.

STAGE	STRUCTURAL DEVELOPMENT	NOTES
Embryonic (weeks 4–7)	Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.	Errors at this stage can lead to tracheoesophageal fistula.
Pseudoglandular (weeks 5–17)	Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.	Respiration impossible, incompatible with life.
Canalicular (weeks 16–25)	Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.	Airways increase in diameter. Respiration capable at 25 weeks. Pneumocytes develop starting at 20 weeks.
Saccular (week 26–birth)	Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae.	
Alveolar (week 36–8 years)	Terminal sacs → adult alveoli (due to 2° septation). In utero, "breathing" occurs via aspiration and expulsion of amniotic fluid → ↑ vascular resistance through gestation. At birth, fluid gets replaced with air → ↓ in pulmonary vascular resistance.	At birth: 20–70 million alveoli. By 8 years: 300–400 million alveoli.



Congenital lung malformations

Pulmonary hypoplasia	Poorly developed bronchial tree with abnormal histology. Associated with congenital diaphragmatic hernia (usually left-sided), bilateral renal agenesis (Potter sequence).
Bronchogenic cysts	Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined, fluid-filled densities on CXR (air-filled if infected). Generally asymptomatic but can drain poorly, causing airway compression and/or recurrent respiratory infections.

Club cells

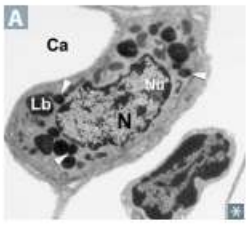
Nonciliated; low columnar/cuboidal with secretory granules. Located in bronchioles. Degrade toxins; secrete component of surfactant; act as reserve cells.

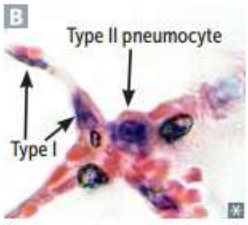
Alveolar cell types

Type I pneumocytes

97% of alveolar surfaces. Line the alveoli. Squamous; thin for optimal gas diffusion.

Type II pneumocytes





Secrete surfactant from lamellar bodies (white arrowheads in A) → ↓ alveolar surface tension, prevents alveolar collapse, ↓ lung recoil, and ↑ compliance. Cuboidal and clustered B. Also serve as precursors to type I cells and other type II cells. Proliferate during lung damage.

$$\text{Collapsing pressure } (P) = \frac{2\,(\text{surface tension})}{\text{radius}}$$

Law of Laplace—Alveoli have ↑ tendency to collapse on expiration as radius ↓.

Pulmonary surfactant is a complex mix of lecithins, the most important of which is dipalmitoylphosphatidylcholine (DPPC).

Surfactant synthesis begins around week 20 of gestation, but mature levels are not achieved until around week 35.

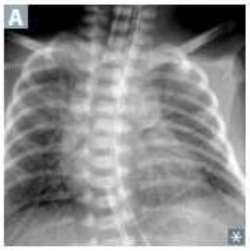
Corticosteroids important for fetus surfactant production and lung development.

Type II pneumocytes produce 2 cell types and have 2 functions (surfactant and stem cell functions).

Alveolar macrophages

Phagocytose foreign materials; release cytokines and alveolar proteases. Hemosiderin-laden macrophages may be found in the setting of pulmonary edema or alveolar hemorrhage.

Neonatal respiratory distress syndrome



Surfactant deficiency → ↑ surface tension → alveolar collapse ("ground-glass" appearance of lung fields) A.

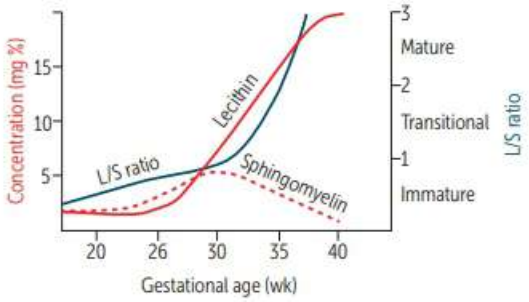
Risk factors: prematurity, maternal diabetes (due to ↑ fetal insulin), C-section delivery (↓ release of fetal glucocorticoids; less stressful than vaginal delivery).

Treatment: maternal steroids before birth; exogenous surfactant for infant.

Therapeutic supplemental O_2 can result in Retinopathy of prematurity, Intraventricular hemorrhage, Bronchopulmonary dysplasia (RIB).

Screening tests for fetal lung maturity: lecithin-sphingomyelin (L/S) ratio in amniotic fluid (≥ 2 is healthy; < 1.5 predictive of NRDS), foam stability index, surfactant-albumin ratio.

Persistently low O_2 tension → risk of PDA.



▸ RESPIRATORY—ANATOMY

Respiratory tree

Conducting zone

Large airways consist of nose, pharynx, larynx, trachea, and bronchi. Airway resistance highest in the large- to medium-sized bronchi. Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance).

Warms, humidifies, and filters air but does not participate in gas exchange → "anatomic dead space."

Cartilage and goblet cells extend to the end of bronchi.

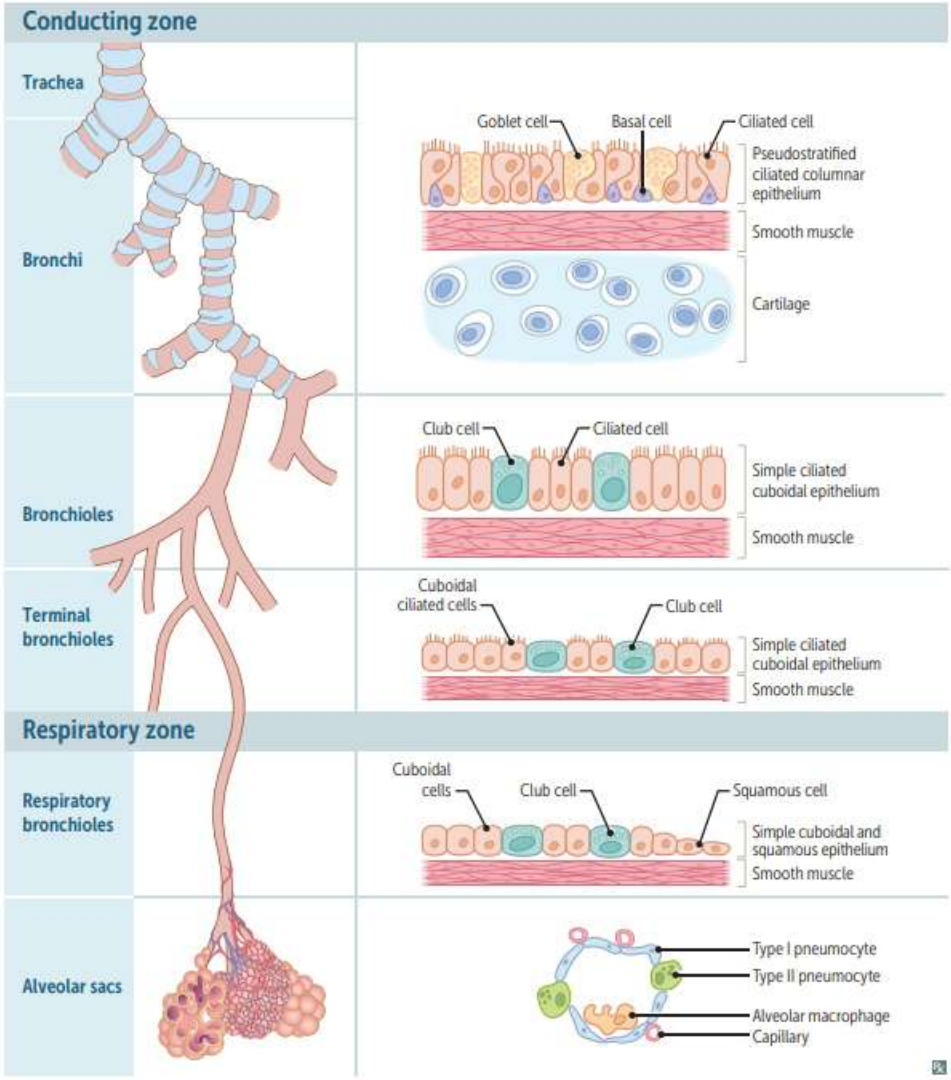
Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells. Clear mucus and debris from lungs (mucociliary escalator).

Airway smooth muscle cells extend to end of terminal bronchioles (sparse beyond this point).

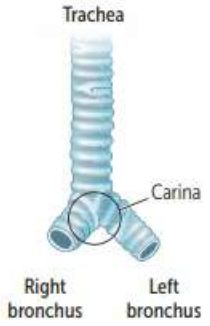
Respiratory zone

Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange.

Mostly cuboidal cells in respiratory bronchioles, then simple squamous cells up to alveoli. Cilia terminate in respiratory bronchioles. Alveolar macrophages clear debris and participate in immune response.



Lung anatomy

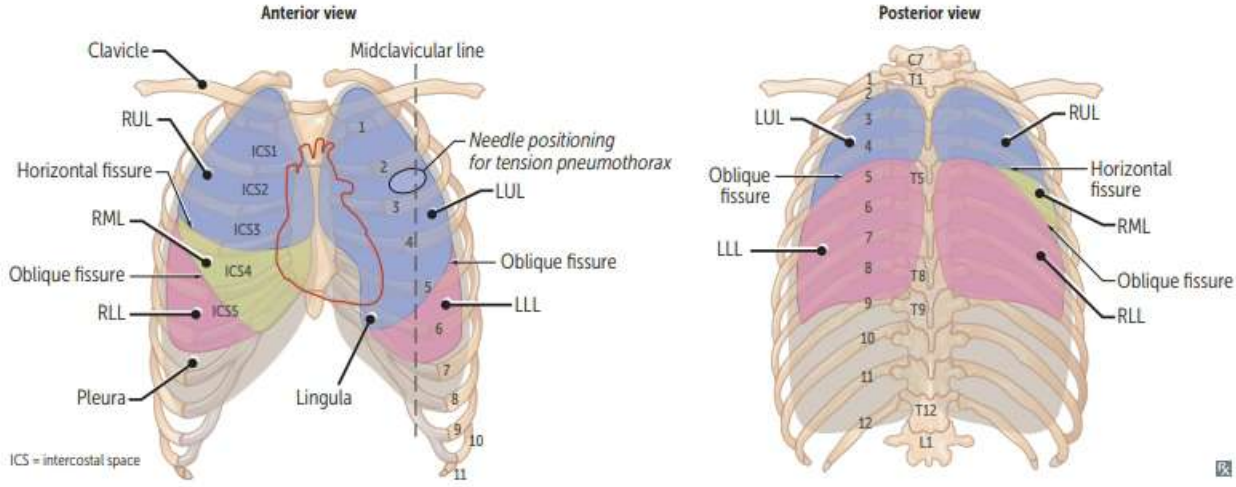


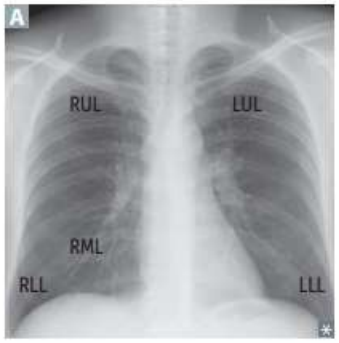
Right lung has 3 lobes; **L**eft has **L**ess **L**obes (2) and **L**ingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart A.

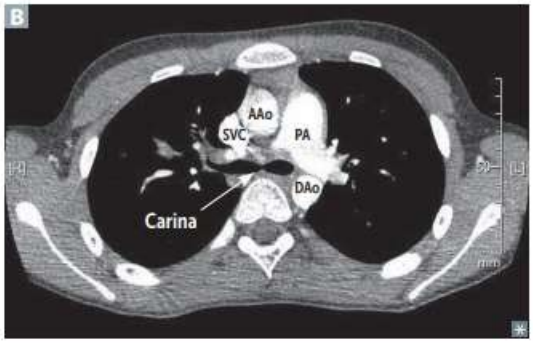
Relation of the pulmonary artery to the bronchus at each lung hilum is described by **RALS**—**R**ight **A**nterior; **L**eft **S**uperior. Carina is posterior to ascending aorta and anteromedial to descending aorta B.

Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:

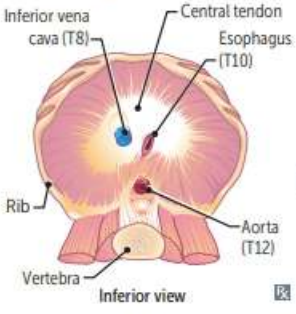
- While supine—usually enters superior segment of right lower lobe.
- While lying on right side—usually enters right upper lobe.
- While upright—usually enters right lower lobe.







Diaphragm structures



Structures perforating diaphragm:

- At T8: IVC, right phrenic nerve
- At T10: esophagus, vagus (CN 10; 2 trunks)
- At T12: aorta (red), thoracic duct (white), azygos vein (blue) ("At T-1-2 it's the red, white, and blue")

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

Number of letters = T level:
T8: vena cava
T10: "0esophagus"
T12: aortic hiatus

I (IVC) ate (8) ten (10) eggs (esophagus) at (aorta) twelve (12).

C3, 4, 5 keeps the diaphragm alive.

Other bifurcations:

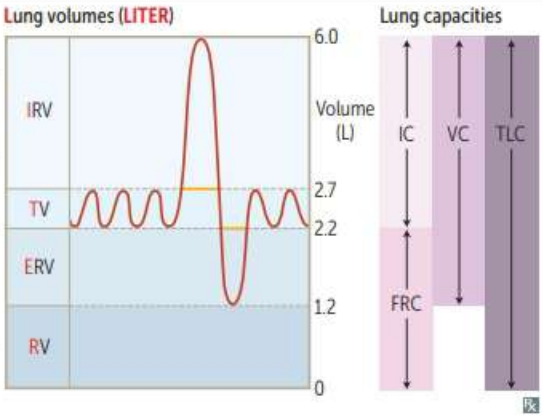
- The common carotid bifourcates at C4.
- The trachea bifourcates at T4.
- The abdominal aorta bifourcates at L4.

▸ RESPIRATORY—PHYSIOLOGY

Lung volumes

Note: a **capacity** is a sum of ≥ 2 physiologic **volumes.**

Inspiratory reserve volume	Air that can still be breathed in after normal inspiration
Tidal volume	Air that moves into lung with each quiet inspiration, typically 500 mL
Expiratory reserve volume	Air that can still be breathed out after normal expiration
Residual volume	Air in lung after maximal expiration; RV and any lung capacity that includes RV cannot be measured by spirometry
Inspiratory capacity	IRV + TV Air that can be breathed in after normal exhalation
Functional residual capacity	RV + ERV Volume of gas in lungs after normal expiration
Vital capacity	TV + IRV + ERV Maximum volume of gas that can be expired after a maximal inspiration
Total lung capacity	IRV + TV + ERV + RV Volume of gas present in lungs after a maximal inspiration



Determination of physiologic dead space

$$V_D = V_T \times \frac{Paco_2 - Peco_2}{Paco_2}$$

V_D = physiologic dead space = anatomic dead space of conducting airways plus alveolar dead space; apex of healthy lung is largest contributor of alveolar dead space. Volume of inspired air that does not take part in gas exchange.

V_T = tidal volume.

$Paco_2$ = arterial Pco_2.

$Peco_2$ = expired air Pco_2.

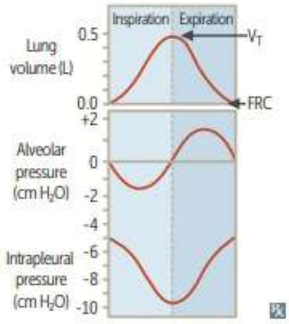
Taco, Paco, Peco, Paco (refers to order of variables in equation)

Physiologic dead space—approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with $\dot{V}/\dot{Q}$ defects.

Ventilation

Minute ventilation	Total volume of gas entering lungs per minute $V_E = V_T \times RR$	Normal values: Respiratory rate (RR) = 12–20 breaths/min V_T = 500 mL/breath V_D = 150 mL/breath
Alveolar ventilation	Volume of gas that reaches alveoli each minute $V_A = (V_T - V_D) \times RR$	

Lung and chest wall



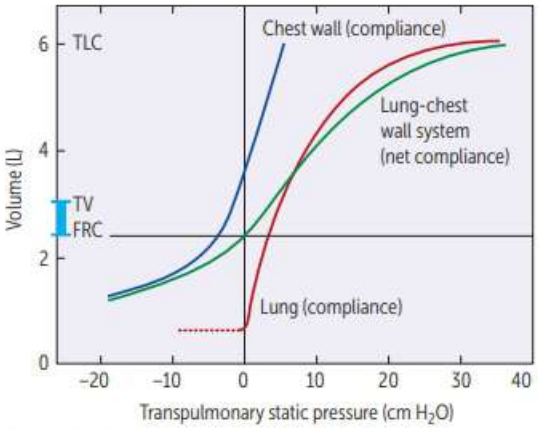
Elastic recoil—tendency for lungs to collapse inward and chest wall to spring outward.

At FRC, inward pull of lung is balanced by outward pull of chest wall, and system pressure is atmospheric.

At FRC, airway and alveolar pressures equal atmospheric pressure (called zero), and intrapleural pressure is negative (prevents atelectasis). The inward pull of the lung is balanced by the outward pull of the chest wall. System pressure is atmospheric. Pulmonary vascular resistance (PVR) is at a minimum.

Compliance—change in lung volume for a change in pressure; expressed as $\Delta V/\Delta P$ and is inversely proportional to wall stiffness. High compliance = lung easier to fill (emphysema, normal aging), lower compliance = lung harder to fill (pulmonary fibrosis, pneumonia, NRDS, pulmonary edema). Surfactant increases compliance.

Hysteresis—lung inflation curve follows a different curve than the lung deflation curve due to need to overcome surface tension forces in inflation.



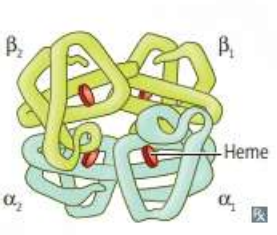
Compliant lungs **comply** (cooperate) and fill easily with air.

Respiratory system changes in the elderly

Aging is associated with progressive ↓ in lung function. TLC remains the same.

INCREASED	DECREASED
Lung compliance (loss of elastic recoil)	Chest wall compliance (↑ chest wall stiffness)
RV	FVC and FEV_1
$\dot{V}/\dot{Q}$ mismatch	Respiratory muscle strength (can impair cough)
A-a gradient	Ventilatory response to hypoxia/hypercapnia

Hemoglobin



Hemoglobin (Hb) is composed of 4 polypeptide subunits (2 α and 2 β) and exists in 2 forms:

- Deoxygenated form has low affinity for O_2, thus promoting release/unloading of O_2.
- Oxygenated form has high affinity for O_2 (300×). Hb exhibits positive cooperativity and negative allostery.

↑ Cl^-, H^+, CO_2, 2,3-BPG, and temperature favor deoxygenated form over oxygenated form (shifts dissociation curve right → ↑ O_2 unloading).

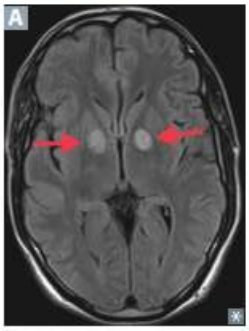
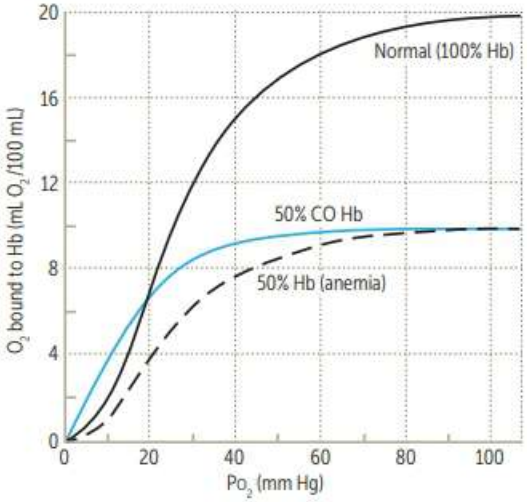
Fetal Hb (2α and 2γ subunits) has a higher affinity for O_2 than adult Hb, driving diffusion of oxygen across the placenta from mother to fetus. ↑ O_2 affinity results from ↓ affinity of HbF for 2,3-BPG.

Hemoglobin acts as buffer for H^+ ions.

Myoglobin is composed of a single polypeptide chain associated with one heme moiety. Higher affinity for oxygen than Hb.

Cyanide vs carbon monoxide poisoning

Both inhibit aerobic metabolism via inhibition of complex IV (cytochrome c oxidase) → hypoxia unresponsive to supplemental O_2 and ↑ anaerobic metabolism.
Both can lead to pink or cherry red skin (usually postmortem finding), seizures, and coma.

	Cyanide	Carbon monoxide
SOURCE	Byproduct of synthetic product combustion, ingestion of amygdalin (cyanogenic glucoside found in apricot seeds) or cyanide.	Odorless gas from fires, car exhaust, or gas heaters.
TREATMENT	Hydroxocobalamin (forms cyanocobalamin) or induced methemoglobinemia with nitrites and sodium thiosulfate.	100% O_2, hyperbaric O_2.
SIGNS/SYMPTOMS 	Breath has bitter almond odor; cardiovascular collapse.	Headache, dizziness. Multiple individuals may be involved (eg, family with similar symptoms in winter). Classically associated with bilateral globus pallidus lesions on MRI A, although rarely seen with cyanide toxicity as well.
EFFECT ON OXYGEN-HEMOGLOBIN DISSOCIATION CURVE	Curve normal; oxygen saturation may appear normal initially.	↓ oxygen-binding capacity with left shift in curve, ↓ O_2 unloading in tissues. Binds competitively to Hb with 200× greater affinity than O_2 to form carboxyhemoglobin. 

Methemoglobin

Oxidized form of Hb (ferric, Fe^{3+}), does not bind O_2 as readily as Fe^{2+}, but has ↑ affinity for cyanide. Fe^{2+} binds O_2.

Iron in Hb is normally in a reduced state (ferrous, Fe^{2+}; "just the 2 of us").

Leads to tissue hypoxia from ↓ O_2 saturation and ↓ O_2 content.

Methemoglobinemia may present with cyanosis and chocolate-colored blood.

Nitrites (eg, from dietary intake or polluted/high-altitude water sources) and benzocaine cause poisoning by oxidizing Fe^{2+} to Fe^{3+}.

Methemoglobinemia can be treated with methylene blue and vitamin C.

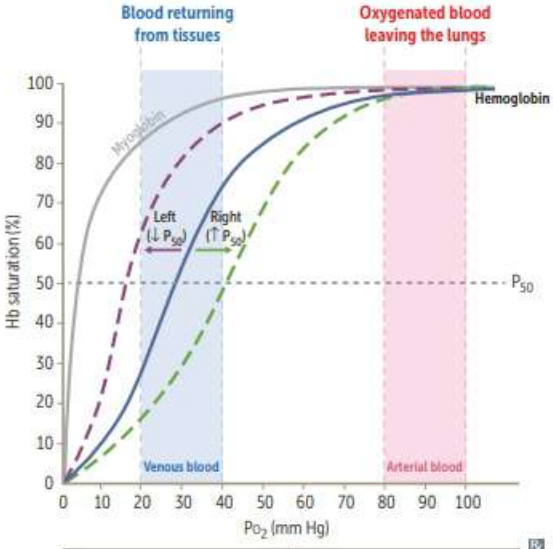
Oxygen-hemoglobin dissociation curve

ODC has a sigmoidal shape due to positive cooperativity (ie, tetrameric Hb molecule can bind 4 O_2 molecules and has higher affinity for each subsequent O_2 molecule bound). Myoglobin is monomeric and thus does not show positive cooperativity; curve lacks sigmoidal appearance.

Shifting the curve to the right → ↓ Hb affinity for O_2 (facilitates unloading of O_2 to tissue) → ↑ P_{50} (higher Po_2 required to maintain 50% saturation).

Shifting the curve to the left → ↓ O_2 unloading → renal hypoxia → ↑ EPO synthesis → compensatory erythrocytosis.

Fetal Hb has higher affinity for O_2 than adult Hb (due to low affinity for 2,3-BPG), so its dissociation curve is shifted left.



Left shift (↓ O_2 unloading to tissue) Left = Lower	Right shift (↑ O_2 unloading to tissues) ACE Bats right handed
↓ H^+ (↑ pH, base)	↑ H^+ (↓ pH, Acid)
↓ Pco_2	↑ Pco_2
↓ 2,3-BPG	Exercise
↓ Temperature	↑ 2,3-BPG
↑ CO	High Altitude
↑ MetHb	↑ Temperature
↑ HbF	

Oxygen content of blood

O_2 content = $(1.34 \times Hb \times Sao_2) + (0.003 \times Pao_2)$

Hb = hemoglobin concentration; Sao_2 = arterial O_2 saturation

Pao_2 = partial pressure of O_2 in arterial blood

Normally 1 g Hb can bind 1.34 mL O_2; normal Hb amount in blood is 15 g/dL.

O_2 binding capacity ≈ 20 mL O_2/dL of blood.

With ↓ Hb there is ↓ O_2 content of arterial blood, but no change in O_2 saturation and Pao_2.

O_2 delivery to tissues = cardiac output × O_2 content of blood.

	Hb CONCENTRATION	% O_2 SAT OF Hb	DISSOLVED O_2 (Pao_2)	TOTAL O_2 CONTENT
CO poisoning	Normal	↓ (CO competes with O_2)	Normal	↓
Anemia	↓	Normal	Normal	↓
Polycythemia	↑	Normal	Normal	↑

Pulmonary circulation

Normally a low-resistance, high-compliance system. P_{O_2} and P_{CO_2} exert opposite effects on pulmonary and systemic circulation. A ↓ in P_{AO_2} causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited—O_2 (normal health), CO_2, N_2O. Gas equilibrates early along the length of the capillary. Exchange can be ↑ only if blood flow ↑.

Diffusion limited—O_2 (emphysema, fibrosis, exercise), CO. Gas does not equilibrate by the time blood reaches the end of the capillary.

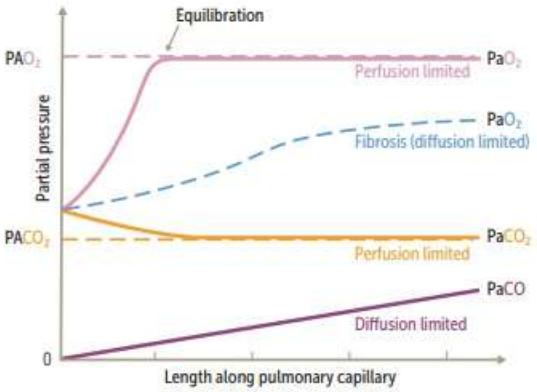
A consequence of pulmonary hypertension is cor pulmonale and subsequent right ventricular failure.

Diffusion: $\dot{V}_{gas} = A \times D_k \times \frac{P_1 - P_2}{\Delta_x}$ where

A = area, Δ_x = alveolar wall thickness, D_k = diffusion coefficient of gas, $P_1 - P_2$ = difference in partial pressures.

- A ↓ in emphysema.
- T ↑ in pulmonary fibrosis.

D_{LCO} is the extent to which CO, a surrogate for O_2, passes from air sacs of lungs into blood.



Pa = partial pressure of gas in pulmonary capillary blood
PA = partial pressure of gas in alveolar air

Pulmonary vascular resistance

$$PVR = \frac{P_{pulm\ artery} - P_{L\ atrium}}{\text{cardiac output}}$$

Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$

$$R = \frac{8\eta l}{\pi r^4}$$

$P_{pulm\ artery}$ = pressure in pulmonary artery
$P_{L\ atrium}$ ≈ pulmonary capillary wedge pressure
Q = cardiac output (flow)
R = resistance
η = viscosity of blood
l = vessel length
r = vessel radius

Alveolar gas equation

$$P_{AO_2} = PI_{O_2} - \frac{P_{aCO_2}}{R}$$

$$\approx 150 \text{ mm Hg}^a - \frac{P_{aCO_2}}{0.8}$$

[a]At sea level breathing room air

P_{AO_2} = alveolar P_{O_2} (mm Hg)
PI_{O_2} = P_{O_2} in inspired air (mm Hg)
P_{aCO_2} = arterial P_{CO_2} (mm Hg)
R = respiratory quotient = CO_2 produced/O_2 consumed
A-a gradient = $P_{AO_2} - P_{aO_2}$. Normal A-a gradient estimated as (age/4) + 4; eg, for a person < 40 years old, gradient should be < 14.

Oxygen deprivation

Hypoxia (↓ O_2 delivery to tissue)	Hypoxemia (↓ Pao_2)	Ischemia (loss of blood flow)
↓ cardiac output Hypoxemia Anemia CO poisoning	Normal A-a gradient ▪ High altitude ▪ Hypoventilation (eg, opioid use, obesity hypoventilation syndrome) ↑ A-a gradient ▪ $\dot{V}/\dot{Q}$ mismatch ▪ Diffusion limitation (eg, fibrosis) ▪ Right-to-left shunt	Impeded arterial flow ↓ venous drainage

Ventilation/perfusion mismatch

Ideally, ventilation is matched to perfusion (ie, $\dot{V}/\dot{Q} = 1$) for adequate gas exchange.

Lung zones:
- $\dot{V}/\dot{Q}$ at apex of lung = 3 (wasted ventilation)
- $\dot{V}/\dot{Q}$ at base of lung = 0.6 (wasted perfusion)

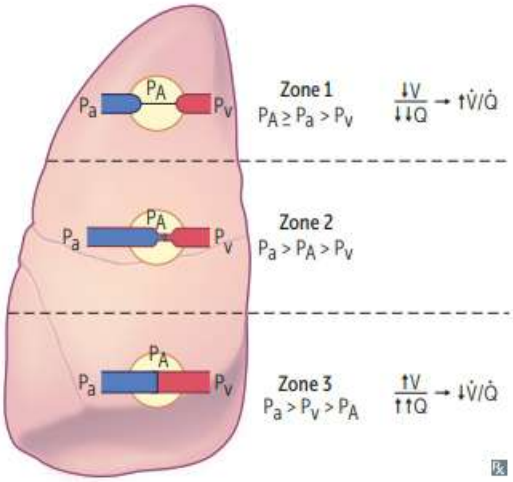
Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.

With exercise (↑ cardiac output), there is vasodilation of apical capillaries → $\dot{V}/\dot{Q}$ ratio approaches 1.

Certain organisms that thrive in high O_2 (eg, TB) flourish in the apex.

$\dot{V}/\dot{Q} = 0$ = "oirway" obstruction (shunt). In shunt, 100% O_2 does not improve Pao_2 (eg, foreign body aspiration).

$\dot{V}/\dot{Q} = \infty$ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O_2 improves Pao_2 (eg, pulmonary embolus).



Carbon dioxide transport

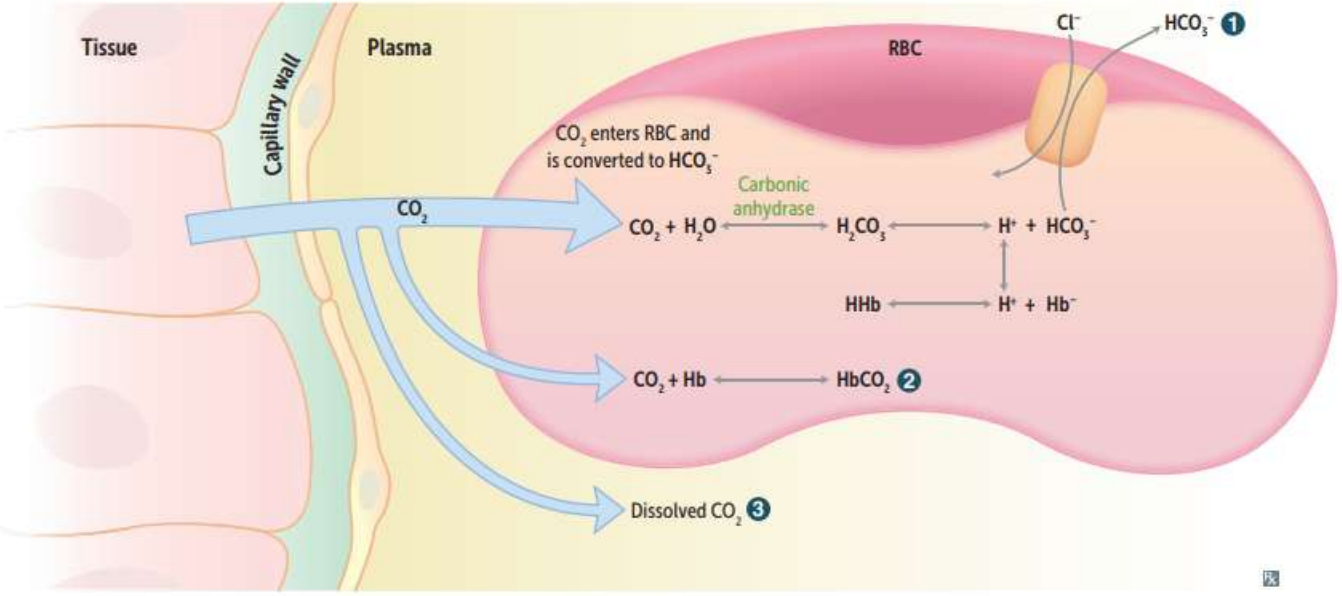
CO_2 is transported from tissues to lungs in 3 forms:

1. HCO_3^- (70%).
2. Carbaminohemoglobin or $HbCO_2$ (21–25%). CO_2 bound to Hb at N-terminus of globin (not heme). CO_2 favors deoxygenated form (O_2 unloaded).
3. Dissolved CO_2 (5–9%).

In lungs, oxygenation of Hb promotes dissociation of H^+ from Hb. This shifts equilibrium toward CO_2 formation; therefore, CO_2 is released from RBCs (Haldane effect).

In peripheral tissue, ↑ H^+ from tissue metabolism shifts curve to right, unloading O_2 (Bohr effect).

Majority of blood CO_2 is carried as HCO_3^- in the plasma.



Response to high altitude

↓ atmospheric oxygen (PiO_2) → ↓ Pao_2 → ↑ ventilation → ↓ $Paco_2$ → respiratory alkalosis → altitude sickness.

Chronic ↑ in ventilation.

↑ erythropoietin → ↑ Hct and Hb (due to chronic hypoxia).

↑ 2,3-BPG (binds to Hb causing rightward shift of the ODC so that Hb releases more O_2).

Cellular changes (↑ mitochondria).

↑ renal excretion of HCO_3^- to compensate for respiratory alkalosis (can augment with acetazolamide).

Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

Response to exercise

↑ CO_2 production.

↑ O_2 consumption.

↑ ventilation rate to meet O_2 demand.

$\dot{V}/\dot{Q}$ ratio from apex to base becomes more uniform.

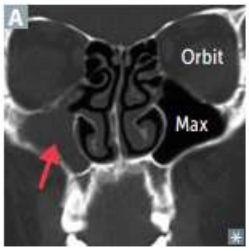
↑ pulmonary blood flow due to ↑ cardiac output.

↓ pH during strenuous exercise (2° to lactic acidosis).

No change in Pao_2 and $Paco_2$, but ↑ in venous CO_2 content and ↓ in venous O_2 content.

▸ RESPIRATORY—PATHOLOGY

Rhinosinusitis



Obstruction of sinus drainage into nasal cavity → inflammation and pain over affected area. Typically affects maxillary sinuses, which drain against gravity due to ostia located superomedially (red arrow points to fluid-filled right maxillary sinus in A).

Superior meatus—drains sphenoid, posterior ethmoid; middle meatus—drains frontal, maxillary, and anterior ethmoid; inferior meatus—drains nasolacrimal duct.

Most common acute cause is viral URI; may lead to superimposed bacterial infection, most commonly *S pneumoniae, H influenzae, M catarrhalis.*

Infections in sphenoid or ethmoid sinuses may extend to cavernous sinus and cause complications (eg, cavernous sinus syndrome).

Epistaxis

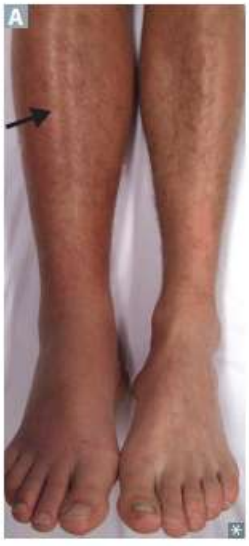
Nose bleed. Most commonly occurs in anterior segment of nostril (Kiesselbach plexus). Life-threatening hemorrhages occur in posterior segment (sphenopalatine artery, a branch of maxillary artery). Common causes include foreign body, trauma, allergic rhinitis, and nasal angiofibromas (common in adolescent males).

Kiesselbach drives his Lexus with his LEGS: superior Labial artery, anterior and posterior Ethmoidal arteries, Greater palatine artery, Sphenopalatine artery.

Head and neck cancer

Mostly squamous cell carcinoma. Risk factors include tobacco, alcohol, HPV-16 (oropharyngeal), EBV (nasopharyngeal). Field cancerization: carcinogen damages wide mucosal area → multiple tumors that develop independently after exposure.

Deep venous thrombosis



Blood clot within a deep vein → swelling, redness A, warmth, pain. Predisposed by Virchow triad (SHE):

- Stasis (eg, post-op, long drive/flight)
- Hypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden; oral contraceptive use, pregnancy)
- Endothelial damage (exposed collagen triggers clotting cascade)

D-dimer lab test used clinically to rule out DVT in low-to-moderate risk patients (high sensitivity, low specificity).

Most pulmonary emboli arise from proximal deep veins of lower extremity.

Use unfractionated heparin or low-molecular-weight heparins (eg, enoxaparin) for prophylaxis and acute management.

Use oral anticoagulants (eg, warfarin, rivaroxaban) for treatment (long-term prevention).

Imaging test of choice is compression ultrasound with Doppler.

Pulmonary emboli

V̇/Q̇ mismatch, hypoxemia, respiratory alkalosis. Sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia. Large emboli or saddle embolus A may cause sudden death due to electromechanical dissociation (pulseless electrical activity). CT pulmonary angiography is imaging test of choice for PE (look for filling defects) C. May have S1Q3T3 abnormality on ECG.

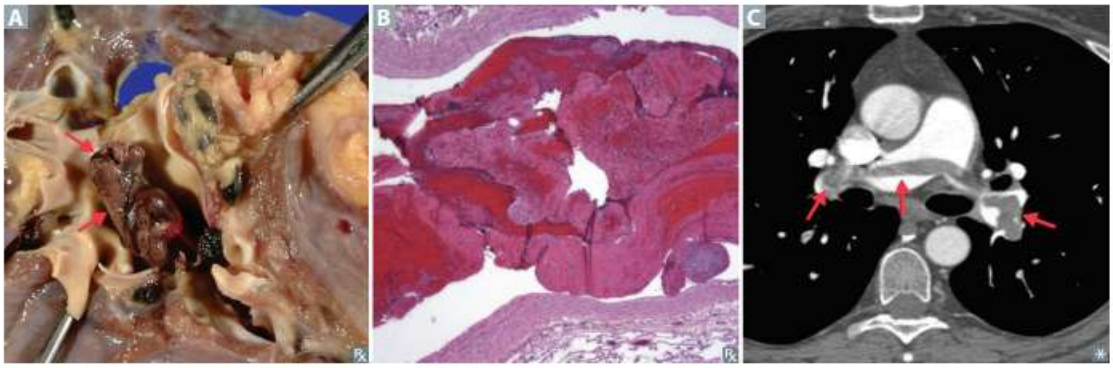
Lines of Zahn are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi B.

Types: **F**at, **A**ir, **T**hrombus, **B**acteria, **A**mniotic fluid, **T**umor. An embolus moves like a **FAT BAT**.

Fat emboli—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash.

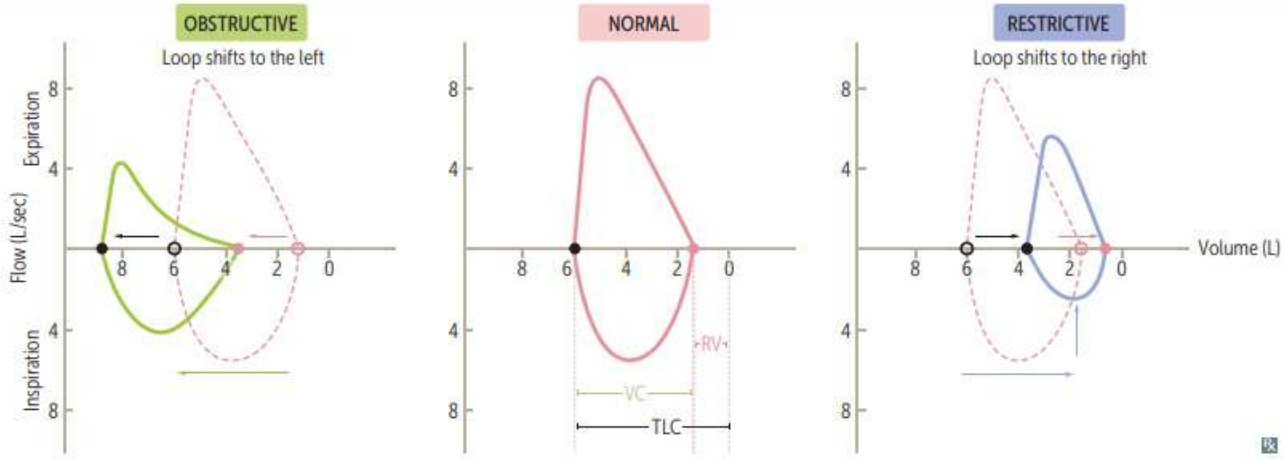
Air emboli—nitrogen bubbles precipitate in ascending divers (caisson disease/decompression sickness); treat with hyperbaric O_2; or, can be iatrogenic 2° to invasive procedures (eg, central line placement).

Amniotic fluid emboli—typically occurs during labor or postpartum, but can be due to uterine trauma. Can lead to DIC. Rare, but high mortality.



Flow-volume loops

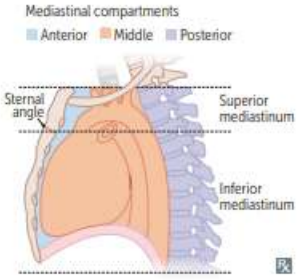
FLOW-VOLUME PARAMETER	Obstructive lung disease	Restrictive lung disease
RV	↑	↓
FRC	↑	↓
TLC	↑	↓
FEV_1	↓↓	↓
FVC	↓	↓
FEV_1/FVC	↓ FEV_1 decreased more than FVC	Normal or ↑ FEV_1 decreased proportionately to FVC



Mediastinal pathology

Normal mediastinum contains heart, thymus, lymph nodes, esophagus, and aorta. Divided into compartments.

Mediastinal masses



Some pathologies (eg, lymphoma, lung cancer, abscess) can occur in any compartment, but there are common associations:

- Anterior—4Ts: Thyroid, Thymic neoplasm, Teratoma, "Terrible" lymphoma.
- Middle—esophageal carcinoma, metastases, hiatal hernia, bronchogenic cysts.
- Posterior—neurogenic tumor (eg, neurofibroma), multiple myeloma.

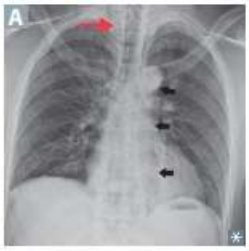
Mediastinitis

Inflammation of tissues in the mediastinum. Commonly due to postoperative complications of cardiothoracic procedures (pathology ≤ 14 days), esophageal perforation, or contiguous spread of odontogenic/retropharyngeal infection.

Chronic mediastinitis—also known as fibrosing mediastinitis; due to ↑ formation of connective tissue in mediastinum. *Histoplasma capsulatum* is common cause.

Clinical features: fever, tachycardia, leukocytosis, chest pain, and (especially with cardiac procedures) sternal wound drainage.

Pneumomediastinum



Presence of gas (usually air) in the mediastinum (black arrows show air around the aorta, red arrow shows air dissecting into the neck A). Can either be spontaneous (due to rupture of pulmonary bleb) or 2° (eg, trauma, iatrogenic, Boerhaave syndrome).

Ruptured alveoli allow tracking of air into the mediastinum via peribronchial and perivascular sheaths.

Clinical features: chest pain, dyspnea, voice change, subcutaneous emphysema, ⊕ Hamman sign (crepitus on cardiac auscultation).

Can be associated with pneumothoraces.

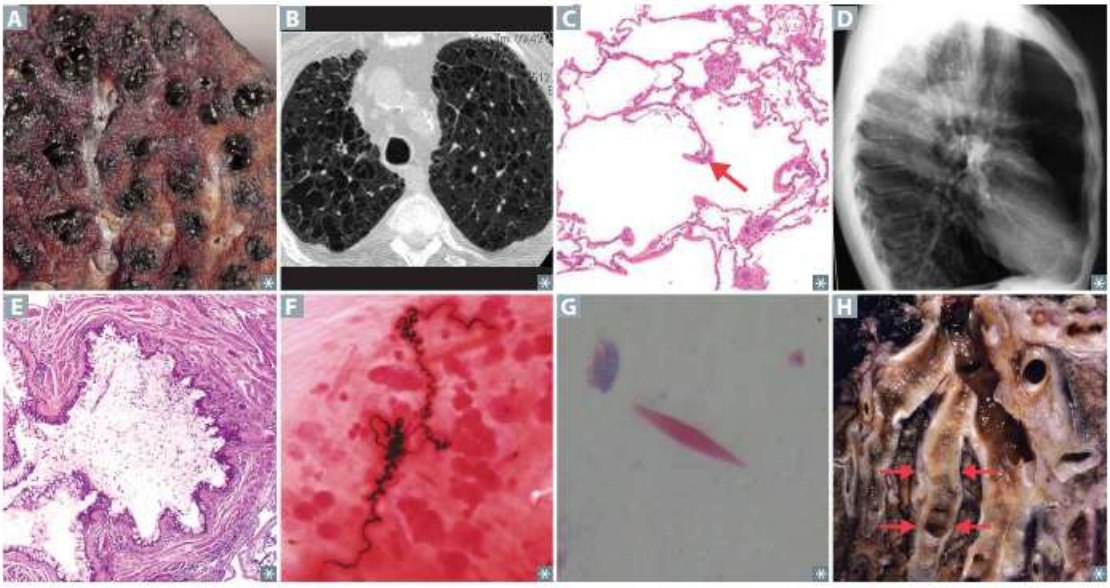
Obstructive lung diseases

Obstruction of air flow → air trapping in lungs. Airways close prematurely at high lung volumes → ↑ FRC, ↑ RV, ↑ TLC. PFTs: ↓↓ FEV_1, ↓ FVC → ↓ FEV_1/FVC ratio (hallmark), $\dot{V}/\dot{Q}$ mismatch. Chronic, hypoxic pulmonary vasoconstriction can lead to cor pulmonale. Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis and emphysema. "FRiCkin' RV needs some increased TLC, but it's hard with COPD!"

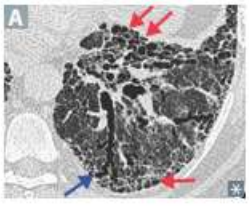
TYPE	PRESENTATION	PATHOLOGY	OTHER
Chronic bronchitis ("blue bloater")	Findings: wheezing, crackles, cyanosis (hypoxemia due to shunting), dyspnea, CO_2 retention, 2° polycythemia.	Hypertrophy and hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) > 50%. D_{LCO} usually normal.	Diagnostic criteria: productive cough for > 3 months in a year for > 2 consecutive years.
Emphysema ("pink puffer")	Findings: barrel-shaped chest D, exhalation through pursed lips (increases airway pressure and prevents airway collapse).	Centriacinar—associated with smoking A B. Frequently in upper lobes (smoke rises up). Panacinar—associated with α_1-antitrypsin deficiency. Frequently in lower lobes. Enlargement of air spaces ↓ recoil, ↑ compliance, ↓ D_{LCO} from destruction of alveolar walls (arrow in C). Imbalance of proteases and antiproteases → ↑ elastase activity → ↑ loss of elastic fibers → ↑ lung compliance.	CXR: ↑ AP diameter, flattened diaphragm, ↑ lung field lucency.
Asthma	Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, ↓ inspiratory/expiratory ratio, pulsus paradoxus, mucus plugging E. Triggers: viral URIs, allergens, stress. Diagnosis supported by spirometry and methacholine challenge.	Hyperresponsive bronchi → reversible bronchoconstriction. Smooth muscle hypertrophy and hyperplasia, Curschmann spirals F (shed epithelium forms whorled mucous plugs), and Charcot-Leyden crystals G (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum). D_{LCO} normal or ↑.	Type I hypersensitivity reaction. Aspirin-induced asthma is a combination of COX inhibition (leukotriene overproduction → airway constriction), chronic sinusitis with nasal polyps, and asthma symptoms.

Obstructive lung diseases *(continued)*

TYPE	PRESENTATION	PATHOLOGY	OTHER
Bronchiectasis	Findings: purulent sputum, recurrent infections, hemoptysis, digital clubbing.	Chronic necrotizing infection of bronchi or obstruction → permanently dilated airways.	Associated with bronchial obstruction, poor ciliary motility (eg, smoking, Kartagener syndrome), cystic fibrosis H, allergic bronchopulmonary aspergillosis.



Restrictive lung diseases



Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). PFTs: ↑ FEV_1/FVC ratio. Patient presents with short, shallow breaths.

Types:

- Poor breathing mechanics (extrapulmonary, normal D_{LCO}, normal A-a gradient):
  - Poor muscular effort—polio, myasthenia gravis, Guillain-Barré syndrome
  - Poor structural apparatus—scoliosis, morbid obesity
- Interstitial lung diseases (pulmonary, ↓ D_{LCO}, ↑ A-a gradient):
  - Pneumoconioses (eg, coal workers' pneumoconiosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granuloma; ↑ ACE and Ca^{2+}
  - Idiopathic pulmonary fibrosis (repeated cycles of lung injury and wound healing with ↑ collagen deposition, "honeycomb" lung appearance (red arrows in A), traction bronchiectasis (blue arrow in A) and digital clubbing).
  - Goodpasture syndrome
  - Granulomatosis with polyangiitis (Wegener)
  - Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (bleomycin, busulfan, amiodarone, methotrexate)

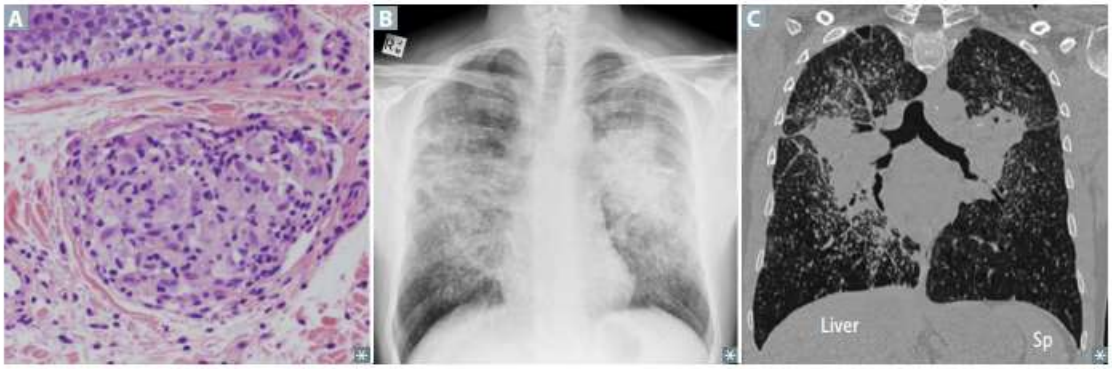
Hypersensitivity pneumonitis—mixed type III/IV hypersensitivity reaction to environmental antigen. Causes dyspnea, cough, chest tightness, headache. Often seen in farmers and those exposed to birds. Reversible in early stages if stimulus is avoided.

Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas A, elevated serum ACE levels, and elevated CD4/CD8 ratio in bronchoalveolar lavage fluid. More common in African-American females. Often asymptomatic except for enlarged lymph nodes. CXR shows bilateral adenopathy and coarse reticular opacities B; CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy C.

Associated with **B**ell palsy, **U**veitis, **G**ranulomas (noncaseating epithelioid, containing microscopic Schaumann and asteroid bodies), **L**upus pernio (skin lesions on face resembling lupus), **I**nterstitial fibrosis (restrictive lung disease), **E**rythema nodosum, **R**heumatoid arthritis-like arthropathy, hypercalcemia (due to ↑ 1α-hydroxylase–mediated vitamin D activation in macrophages). A **facial droop** is **UGLIER**.

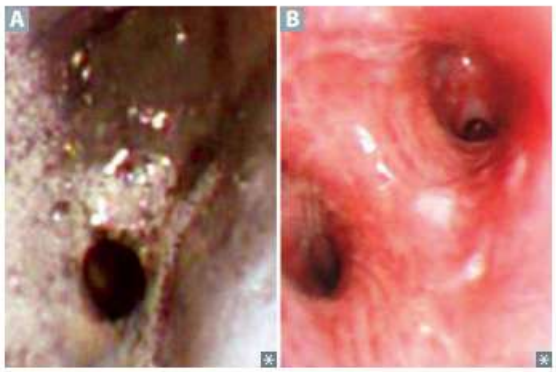
Treatment: steroids (if symptomatic).



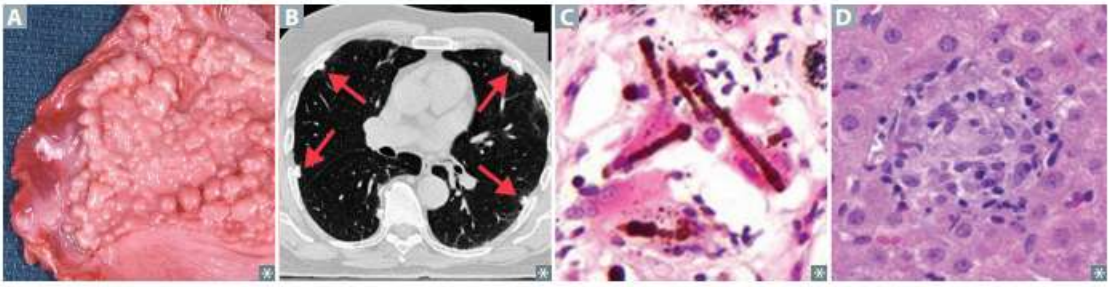
Inhalation injury and sequelae

Complication of inhalation of noxious stimuli (eg, smoke). Caused by heat, particulates (< 1 μm diameter), or irritants (eg, NH_3) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, cyanide poisoning, or arsenic poisoning. Singed nasal hairs or soot in oropharynx common on exam.

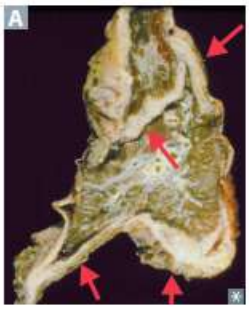
Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (A, 18 hours after inhalation injury; B, resolution at 11 days after injury).



Pneumoconioses	Asbestos is from the roof (was common in insulation), but affects the base (lower lobes). Silica and coal are from the base (earth), but affect the roof (upper lobes).	
Asbestosis	Associated with shipbuilding, roofing, plumbing. "Ivory white," calcified, supradiaphragmatic A and pleural B plaques are pathognomonic of asbestosis. Risk of bronchogenic carcinoma > risk of mesothelioma. ↑ risk of Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).	Affects lower lobes. Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells C, found in alveolar sputum sample, visualized using Prussian blue stain, often obtained by bronchoalveolar lavage. ↑ risk of pleural effusions.
Berylliosis	Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous (noncaseating) D on histology and therefore occasionally responsive to steroids. ↑ risk of cancer and cor pulmonale.	Affects upper lobes.
Coal workers' pneumoconiosis	Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis. Also known as black lung disease. ↑ risk of Caplan syndrome.	Affects upper lobes. Small, rounded nodular opacities seen on imaging. Anthracosis—asymptomatic condition found in many urban dwellers exposed to sooty air.
Silicosis	Associated with sandblasting, foundries, mines. Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB. ↑ risk of cancer, cor pulmonale, and Caplan syndrome.	Affects upper lobes. "Eggshell" calcification of hilar lymph nodes on CXR. The silly egg sandwich I found is mine!



Mesothelioma



Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening A.

Psammoma bodies seen on histology.
Calretinin ⊕ in almost all mesotheliomas, ⊖ in most carcinomas.
Smoking not a risk factor.

Acute respiratory distress syndrome

PATHOPHYSIOLOGY

Alveolar insult → release of pro-inflammatory cytokines → neutrophil recruitment, activation, and release of toxic mediators (eg, reactive oxygen species, proteases, etc) → capillary endothelial damage and ↑ vessel permeability → leakage of protein-rich fluid into alveoli → formation of intra-alveolar hyaline membranes (arrows in A) and noncardiogenic pulmonary edema (normal PCWP).

Loss of surfactant also contributes to alveolar collapse.

CAUSES

Sepsis (most common), aspiration, pneumonia, trauma, pancreatitis.

DIAGNOSIS

Diagnosis of exclusion with the following criteria (**ARDS**):

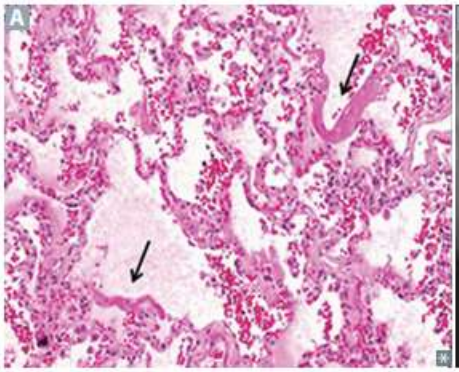
- **A**bnormal chest X-ray (bilateral lung opacities) B
- **R**espiratory failure within 1 week of alveolar insult
- **D**ecreased Pao_2/Fio_2 (ratio < 300, hypoxemia due to ↑ intrapulmonary shunting and diffusion abnormalities)
- **S**ymptoms of respiratory failure are not due to HF/fluid overload

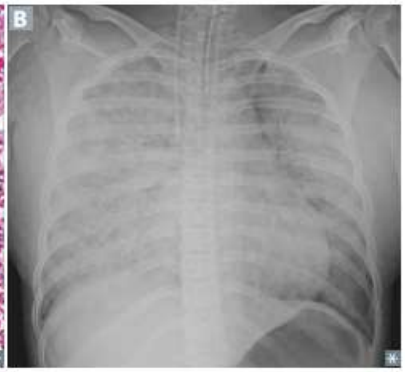
CONSEQUENCES

Impaired gas exchange, ↓ lung compliance; pulmonary hypertension.

MANAGEMENT

Treat the underlying cause.
Mechanical ventilation: ↓ tidal volumes, ↑ PEEP.





Sleep apnea	Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. Diagnosis confirmed by sleep study. Normal Pao_2 during the day. Nocturnal hypoxia → systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death. Hypoxia → ↑ EPO release → ↑ erythropoiesis.
Obstructive sleep apnea	Respiratory effort against airway obstruction. Associated with obesity, loud snoring, daytime sleepiness. Caused by excess parapharyngeal tissue in adults, adenotonsillar hypertrophy in children. Treatment: weight loss, CPAP, surgery.
Central sleep apnea	Impaired respiratory effort due to CNS injury/toxicity, HF, opioids. May be associated with Cheyne-Stokes respirations (oscillations between apnea and hyperpnea). Think 3 C's: Congestive HF, CNS toxicity, Cheyne-Stokes respirations. Treat with positive airway pressure.
Obesity hypoventilation syndrome	Obesity (BMI ≥ 30 kg/m^2) → hypoventilation → ↑ $Paco_2$ during waking hours (retention); ↓ Pao_2 and ↑ $Paco_2$ during sleep. Also known as Pickwickian syndrome.

Pulmonary hypertension	Normal mean pulmonary artery pressure = 10–14 mm Hg; pulmonary hypertension ≥ 25 mm Hg at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions. Course: severe respiratory distress → cyanosis and RVH → death from decompensated cor pulmonale.
ETIOLOGIES	
Pulmonary arterial hypertension	Often idiopathic. Heritable PAH can be due to an inactivating mutation in *BMPR2* gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Pulmonary vasculature endothelial dysfunction results in ↑ vasoconstrictors (eg, endothelin) and ↓ vasodilators (eg, NO and prostacyclins). Other causes include drugs (eg, amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis.
Left heart disease	Causes include systolic/diastolic dysfunction and valvular disease.
Lung diseases or hypoxia	Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).
Chronic thromboembolic	Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed.
Multifactorial	Causes include hematologic, systemic, and metabolic disorders, along with compression of the pulmonary vasculature by a tumor.

Lung—physical findings in select lung diseases

ABNORMALITY	BREATH SOUNDS	PERCUSSION	FREMITUS	TRACHEAL DEVIATION
Pleural effusion	↓	Dull	↓	None if small Away from side of lesion if large
Atelectasis	↓	Dull	↓	Toward side of lesion
Simple pneumothorax	↓	Hyperresonant	↓	None
Tension pneumothorax	↓	Hyperresonant	↓	Away from side of lesion
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy	Dull	↑	None

Atelectasis

Alveolar collapse, which can be due to multiple etiologies:

- Obstructive—airway obstruction prevents new air from reaching distal airways, old air is resorbed (eg, foreign body, mucous plug, tumor)
- Compressive—external compression on lung decreases lung volumes (eg, space-occupying lesion, pleural effusion)
- Contraction (cicatrization)—scarring of lung parenchyma that distorts alveoli (eg, sarcoidosis)
- Adhesive—due to lack of surfactant (eg, NRDS in premature babies)

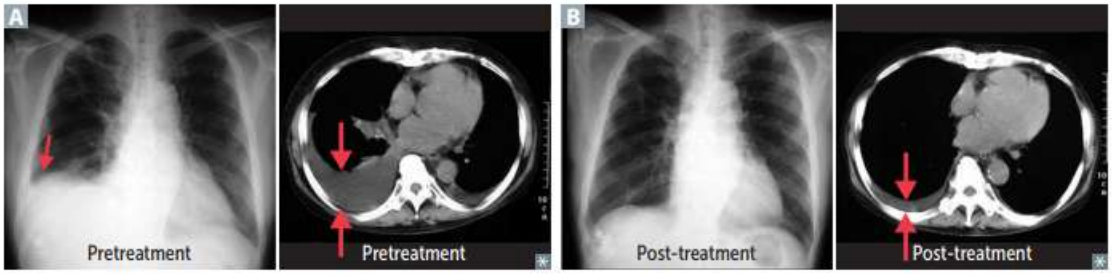
Pleural effusions

Excess accumulation of fluid A between pleural layers → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid B.

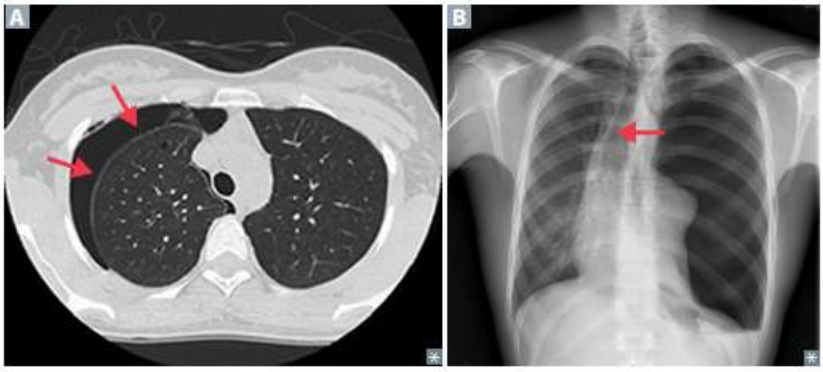
Transudate: ↓ protein content. Due to ↑ hydrostatic pressure (eg, HF) or ↓ oncotic pressure (eg, nephrotic syndrome, cirrhosis).

Exudate: ↑ protein content, cloudy. Due to malignancy, pneumonia, collagen vascular disease, trauma (occurs in states of ↑ vascular permeability). Must be drained due to risk of infection.

Lymphatic: Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milky-appearing fluid; ↑ triglycerides.

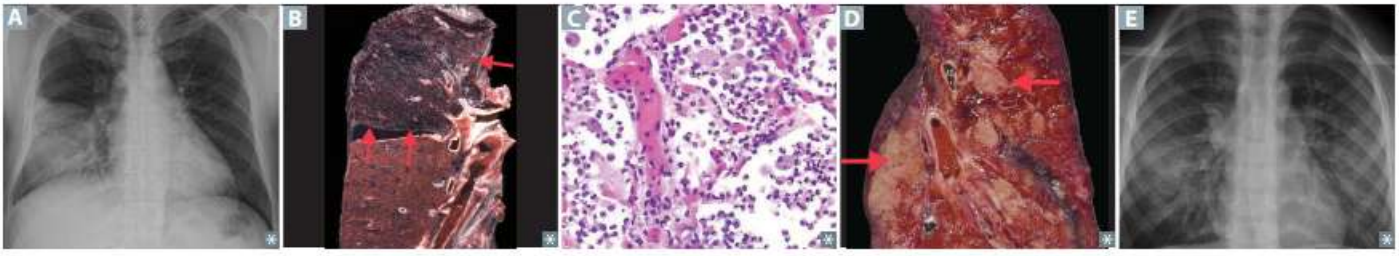


Pneumothorax	Accumulation of air in pleural space A. Dyspnea, uneven chest expansion. Chest pain, ↓ tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.
Primary spontaneous pneumothorax	Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males and smokers.
Secondary spontaneous pneumothorax	Due to diseased lung (eg, bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.
Traumatic pneumothorax	Caused by blunt (eg, rib fracture), penetrating (eg, gunshot), or iatrogenic (eg, central line placement, lung biopsy, barotrauma due to mechanical ventilation) trauma.
Tension pneumothorax	Can be from any of the above. Air enters pleural space but cannot exit. Increasing trapped air → tension pneumothorax. Trachea deviates away from affected lung B. May lead to increased intrathoracic pressure → mediastinal displacement → kinking of IVC → ↓ venous return → ↓ cardiac output. Needs immediate needle decompression and chest tube placement.



Pneumonia

TYPE	TYPICAL ORGANISMS	CHARACTERISTICS
Lobar pneumonia	*S pneumoniae* most frequently, also *Legionella*, *Klebsiella*	Intra-alveolar exudate → consolidation A; may involve entire lobe B or the whole lung.
Bronchopneumonia	*S pneumoniae*, *S aureus*, *H influenzae*, *Klebsiella*	Acute inflammatory infiltrates C from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe D.
Interstitial (atypical) pneumonia	*Mycoplasma*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Legionella*, viruses (RSV, CMV, influenza, adenovirus)	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; CXR shows bilateral multifocal opacities E. Generally follows a more indolent course ("walking" pneumonia).
Cryptogenic organizing pneumonia	Etiology unknown. Secondary organizing pneumonia caused by chronic inflammatory diseases (eg, rheumatoid arthritis) or medication side effects (eg, amiodarone). ⊖ sputum and blood cultures, no response to antibiotics.	Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure.



Natural history of lobar pneumonia

	Congestion	Red hepatization	Gray hepatization	Resolution
DAYS	1–2	3–4	5–7	8+
FINDINGS	Red-purple, partial consolidation of parenchyma Exudate with mostly bacteria	Red-brown, consolidated Exudate with fibrin, bacteria, RBCs, and WBCs	Uniformly gray Exudate full of WBCs, lysed RBCs, and fibrin	Enzymes digest components of exudate

Lung cancer

Leading cause of cancer death.

Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic "coin" lesion on CXR or noncalcified nodule on CT.

Sites of metastases from lung cancer: **L**iver (jaundice, hepatomegaly), **A**drenals, **B**one (pathologic fracture), **B**rain; "Lung 'mets' **L**ove **A**ffective **B**oneheads and **B**rainiacs."

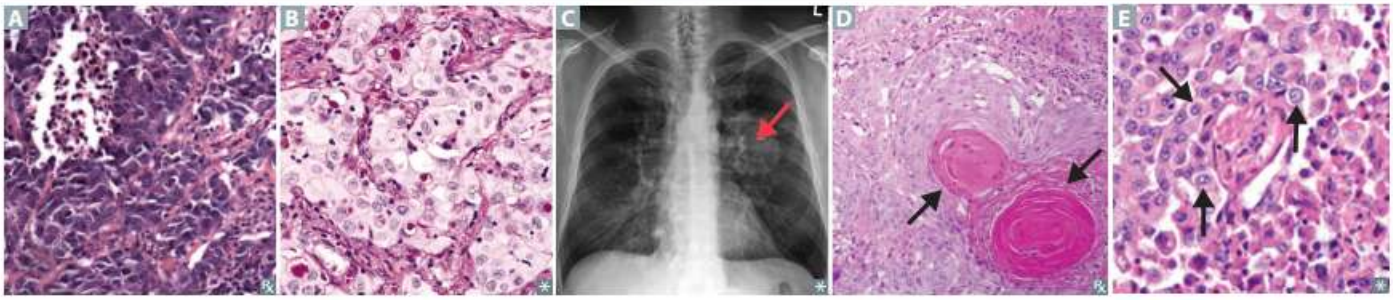
In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

SPHERE of complications:
- **S**uperior vena cava/thoracic outlet syndromes
- **P**ancoast tumor
- **H**orner syndrome
- **E**ndocrine (paraneoplastic)
- **R**ecurrent laryngeal nerve compression (hoarseness)
- **E**ffusions (pleural or pericardial)

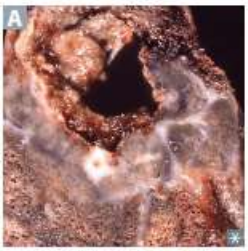
Risk factors include smoking, secondhand smoke, radon, asbestos, family history.

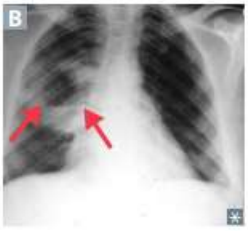
Squamous and **S**mall cell carcinomas are **S**entral (central) and often caused by **S**moking.

TYPE	LOCATION	CHARACTERISTICS	HISTOLOGY
Small cell			
Small cell (oat cell) carcinoma	Central	Undifferentiated → very aggressive. May produce **A**CTH (Cushing syndrome), SI**A**DH, or **A**ntibodies against presynaptic Ca^{2+} channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encephalitis, subacute cerebellar degeneration). **A**mplification of *myc* oncogenes common. Managed with chemotherapy +/– radiation.	Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells **A**. Chromogranin **A** ⊕, neuron-specific enolase ⊕, synaptophysin ⊕.
Non–small cell			
Adenocarcinoma	Peripheral	Most common 1° lung cancer. More common in women than men, most likely to arise in nonsmokers. Activating mutations include *KRAS*, *EGFR*, and *ALK*. Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis.	Glandular pattern on histology, often stains mucin ⊕ **B**. Bronchioloalveolar subtype: grows along alveolar septa → apparent "thickening" of alveolar walls. Tall, columnar cells containing mucus.
Squamous cell carcinoma	**C**entral	Hilar mass **C** arising from bronchus; **C**avitation; **C**igarettes; hyper**C**alcemia (produces PTHrP).	Keratin pearls **D** and intercellular bridges.
Large cell carcinoma	Peripheral	Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically. Strong association with smoking.	Pleomorphic giant cells **E**.
Bronchial carcinoid tumor	Central or peripheral	Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).	Nests of neuroendocrine cells; chromogranin A ⊕.



Lung abscess





Localized collection of pus within parenchyma A. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcoholics, epileptics]) or bronchial obstruction (eg, cancer).

Air-fluid levels B often seen on CXR; presence suggests cavitation. Due to anaerobes (eg, *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*) or *S aureus*.

Treatment: antibiotics, drainage, or surgery.

Lung abscess 2° to aspiration is most often found in right lung. Location depends on patient's position during aspiration: RLL if upright, RUL or RML if recumbent.

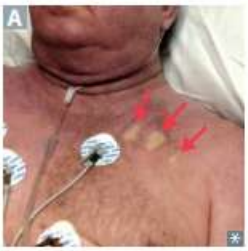
Pancoast tumor

Also known as superior sulcus tumor. Carcinoma that occurs in the apex of lung A may cause Pancoast syndrome by invading/compressing local structures.

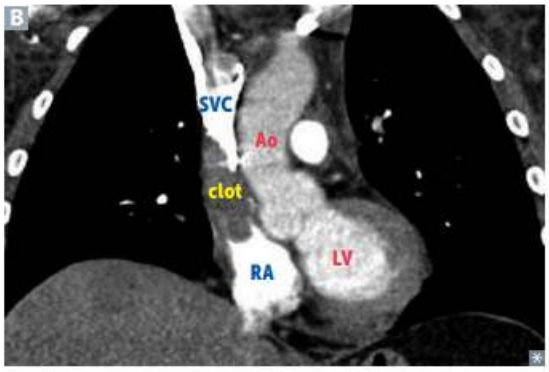
Compression of locoregional structures may cause array of findings:

- Recurrent laryngeal nerve → hoarseness
- Stellate ganglion → Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava → SVC syndrome
- Brachiocephalic vein → brachiocephalic syndrome (unilateral symptoms)
- Brachial plexus → sensorimotor deficits

Superior vena cava syndrome



An obstruction of the SVC that impairs blood drainage from the head ("facial plethora"; note blanching after fingertip pressure in A), neck (jugular venous distention), and upper extremities (edema). Commonly caused by malignancy (eg, mediastinal mass, Pancoast tumor) and thrombosis from indwelling catheters B. Medical emergency. Can raise intracranial pressure (if obstruction is severe) → headaches, dizziness, ↑ risk of aneurysm/rupture of intracranial arteries.



▸ RESPIRATORY—PHARMACOLOGY

Histamine-1 blockers	Reversible inhibitors of H_1 histamine receptors.	
First generation	Diphenhydramine, dimenhydrinate, chlorpheniramine, doxylamine.	Names usually contain "-en/-ine" or "-en/-ate."
CLINICAL USE	Allergy, motion sickness, sleep aid.	
ADVERSE EFFECTS	Sedation, antimuscarinic, anti-α-adrenergic.	
Second generation	Loratadine, fexofenadine, desloratadine, cetirizine.	Names usually end in "-adine."
CLINICAL USE	Allergy.	
ADVERSE EFFECTS	Far less sedating than 1st generation because of ↓ entry into CNS.	

Guaifenesin — Expectorant—thins respiratory secretions; does not suppress cough reflex.

***N*-acetylcysteine** — Mucolytic—liquifies mucus in chronic bronchopulmonary diseases (eg, COPD, CF) by disrupting disulfide bonds. Also used as an antidote for acetaminophen overdose.

Dextromethorphan — Antitussive (antagonizes NMDA glutamate receptors). Synthetic codeine analog. Has mild opioid effect when used in excess. Naloxone can be given for overdose. Mild abuse potential. May cause serotonin syndrome if combined with other serotonergic agents.

Pseudoephedrine, phenylephrine

MECHANISM	α-adrenergic agonists.
CLINICAL USE	Reduce hyperemia, edema (used as nasal decongestants); open obstructed eustachian tubes.
ADVERSE EFFECTS	Hypertension. Rebound congestion if used more than 4–6 days. Can also cause CNS stimulation/anxiety (pseudoephedrine).

Pulmonary hypertension drugs

DRUG	MECHANISM	CLINICAL NOTES
Endothelin receptor antagonists	Competitively antagonizes endothelin-1 receptors → ↓ pulmonary vascular resistance.	Hepatotoxic (monitor LFTs). Example: bosentan.
PDE-5 inhibitors	Inhibits PDE-5 → ↑ cGMP → prolonged vasodilatory effect of NO.	Also used to treat erectile dysfunction. Contraindicated when taking nitroglycerin or other nitrates (due to risk of severe hypotension). Example: sildenafil.
Prostacyclin analogs	PGI_2 (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.	Side effects: flushing, jaw pain. Examples: epoprostenol, iloprost.

Asthma drugs — Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.

β_2-agonists — **Albuterol**—relaxes bronchial smooth muscle (short acting β_2-agonist). For acute exacerbations. Can cause tremor, arrhythmia.

Salmeterol, formoterol—long-acting agents for prophylaxis. Can cause tremor, arrhythmia.

Inhaled corticosteroids — **Fluticasone, budesonide**—inhibit the synthesis of virtually all cytokines. Inactivate NF-κB, the transcription factor that induces production of TNF-α and other inflammatory agents. 1st-line therapy for chronic asthma. Use a spacer or rinse mouth after use to prevent oral thrush.

Muscarinic antagonists — **Tiotropium, ipratropium**—competitively block muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting.

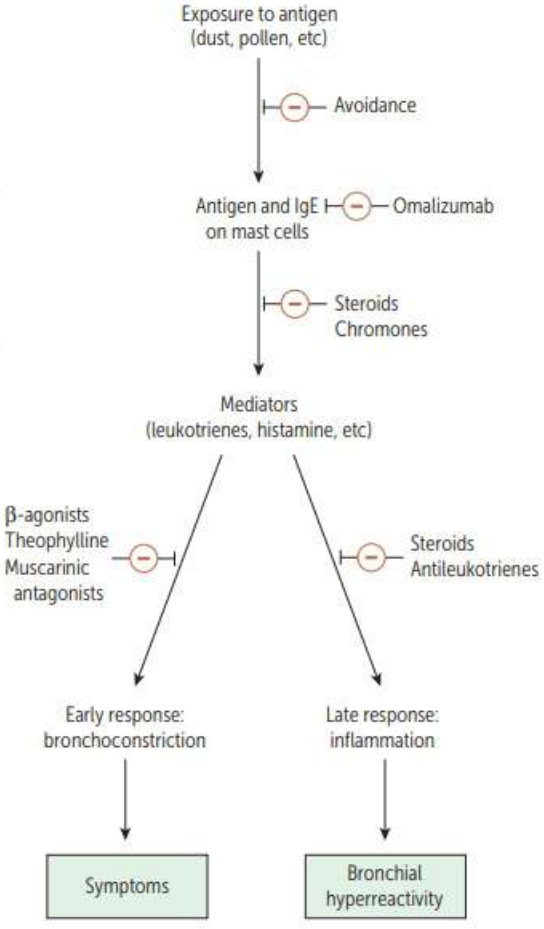
Antileukotrienes — **Montelukast, zafirlukast**—block leukotriene receptors (CysLT1). Especially good for aspirin-induced and exercise-induced asthma.

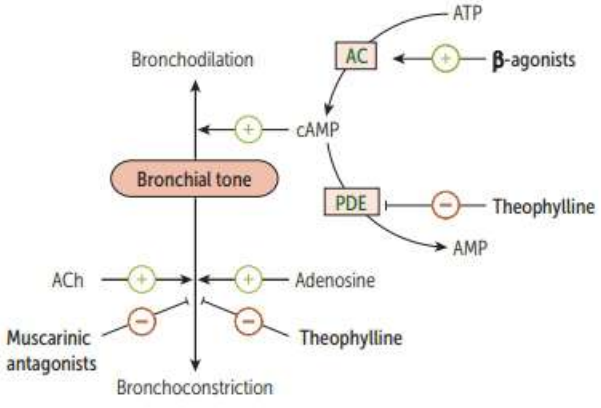
Zileuton—5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. Hepatotoxic.

Anti-IgE monoclonal therapy — **Omalizumab**—binds mostly unbound serum IgE and blocks binding to FcεRI. Used in allergic asthma with ↑ IgE levels resistant to inhaled steroids and long-acting β_2-agonists.

Methylxanthines — **Theophylline**—likely causes bronchodilation by inhibiting phosphodiesterase → ↑ cAMP levels due to ↓ cAMP hydrolysis. Limited use due to narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450. Blocks actions of adenosine.

Chromones — **Cromolyn**—prevents mast cell degranulation. Prevents acute asthma symptoms. Rarely used.





Methacholine — Nonselective muscarinic receptor (M_3) agonist. Used in bronchial challenge test to help diagnose asthma.

Appendix :

First Aid

for Basic Sciences (ORGAN SYSTEMS)

CHAPTER 10

Respiratory

KEY FACT

The larynx, trachea, and lung buds develop as an outpouching of the esophagus.

FLASH BACK

Humans have five pharyngeal arches derived from ectoderm, endoderm, mesoderm, and neural crest. Recall that the 4th and 6th arches give rise to multiple muscle and cartilage structures in the oropharynx and larynx, critical for respiration.

Embryology

RESPIRATORY DEVELOPMENT

The respiratory system allows for blood oxygenation and clearance of carbon dioxide (CO_2), sustains aerobic metabolism, and maintains acid-base balance. The respiratory system develops in the fluid-filled womb, devoid of air. Development occurs in a cranial-to-caudal fashion. The upper respiratory tract (larynx to trachea) develops first, followed by the lower respiratory tract (bronchi and lungs). Lung development is further subdivided into pseudoglandular, canalicular, saccular, and alveolar stages (Figure 10-1).

The respiratory system develops from the laryngotracheal groove on the ventral foregut during gestational weeks 3 and 4 (Figure 10-2). The groove develops into a diverticulum (outpouching) and elongates to form the laryngotracheal tube. The developing respiratory system is partitioned off from the esophagus by the tracheoesophageal septum. The proximal end of this tube becomes the larynx, the middle becomes the trachea, and the distal end forms the lung buds.

Larynx

The larynx is a musculocartilaginous structure in the anterior neck that protects the airway, aids in respiration, and produces sound (vocalization). Located just below the pharynx, it marks the division between the respiratory and digestive systems. It is suspended from the hyoid bone by muscle and ligaments and attached to the trachea inferiorly. The laryngeal cartilage and musculature are derived from the fourth and sixth

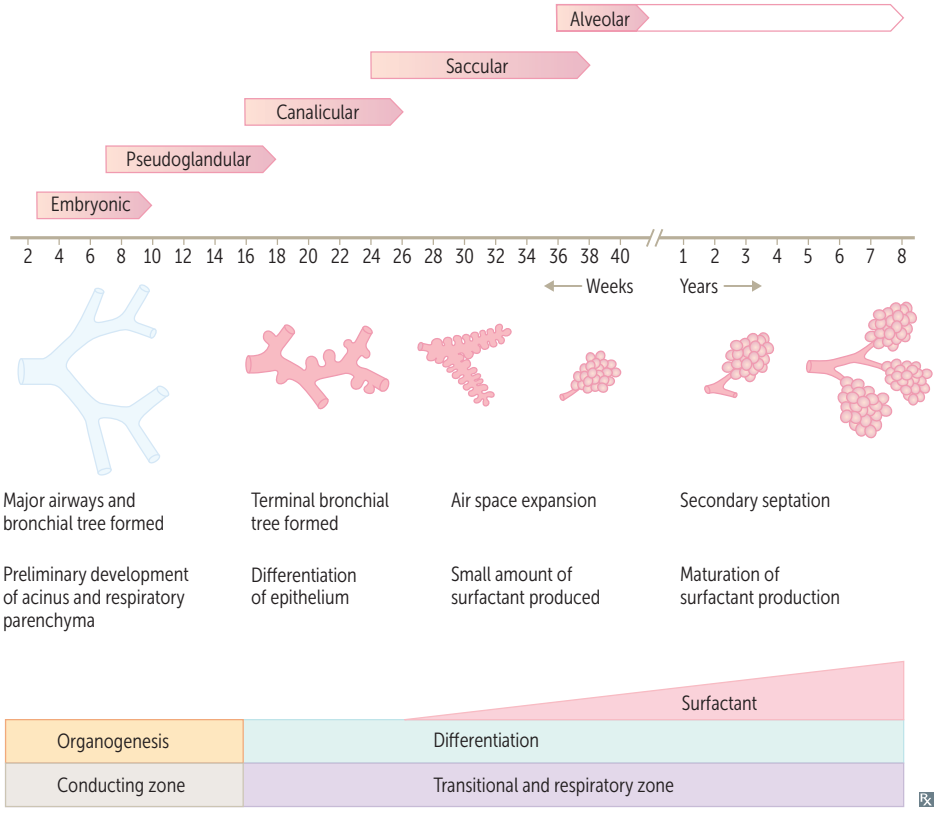


FIGURE 10-1. Overview of respiratory system development. After development of the larynx and trachea, the other conducting zones develop through branching. The transitional and respiratory zones develop after the conducting zone.

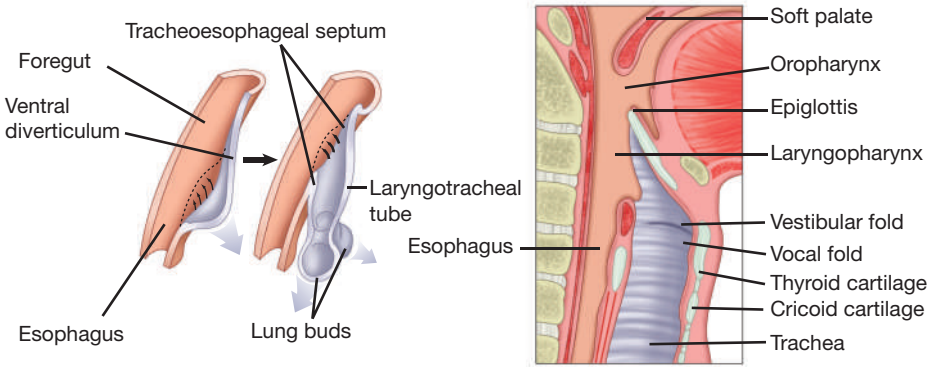


FIGURE 10-2. Larynx and trachea development. The larynx begins as the ventral diverticulum. As the diverticulum lengthens, lung buds form at its distal end. This will ultimately give rise to the trachea and lungs.

pharyngeal arches and are innervated by the superior laryngeal nerve (CN X) and recurrent laryngeal nerve (CN X), respectively. As the pharyngeal arches develop, a primitive laryngeal orifice arises below the fourth arch. During week 5, swellings develop lateral to the orifice and eventually form the arytenoid cartilages. An anterior swelling becomes the epiglottis. During week 6, this region develops into a T-shaped orifice (Figure 10-3). Epithelial tissue occluding the orifice breaks down during week 10, with surrounding epithelial folds differentiating into the false and true vocal folds.

Trachea

The trachea is a conducting airway derived from the middle portion of the laryngotracheal tube. The epithelium and glands are derived from the tube endoderm; cartilage, smooth muscle, and connective tissue are derived from splanchnic mesoderm (the ventral part of the lateral mesoderm).

Bronchi and Bronchioles

The lower laryngotracheal tube divides into bronchi, which further divide into bronchioles. The first division is asymmetrical, accompanied by movement of the **smaller left bud** to a **more lateral position** than the **larger right bud.** The second division of the bronchi is also asymmetrical, with three branches on the right and two branches on the left. The tertiary bronchi continue to divide dichotomously until terminal bronchioles with distal alveoli are formed.

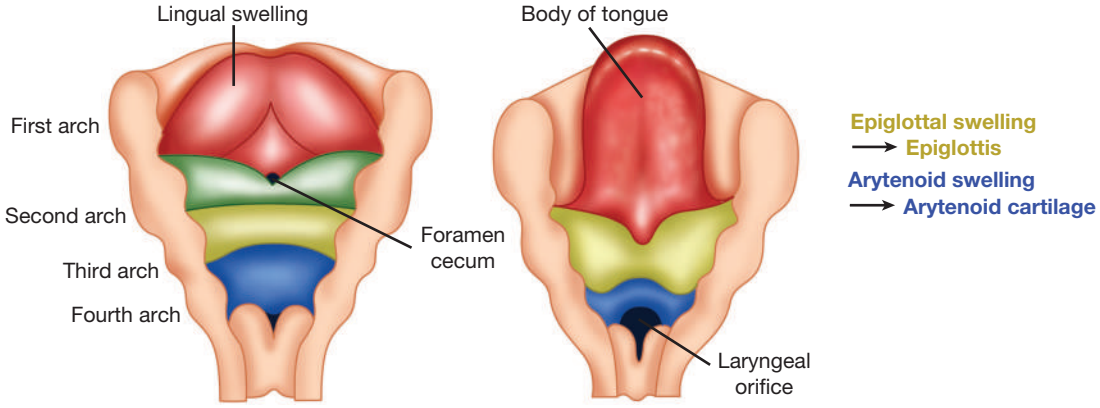


FIGURE 10-3. Larynx development from pharyngeal arches. The cartilage and musculature of the larynx are derived from the pharyngeal arches. An epiglottic swelling will give rise to the epiglottis, and an arytenoid swelling will give rise to the arytenoid cartilages. The foramen cecum is a depression along the groove that divides the tongue into two symmetric halves.

Lungs

At the end of week 4, the laryngotracheal diverticulum forms the lung buds as two lateral outpouchings (Figure 10-1). The two lung buds go on to develop the bronchi and bronchial tree between 2 and 7 months of gestation (the **pseudoglandular** and **canalicular** periods). The lungs mature relatively late compared to many other organs. The terminal sacs and eventually alveoli begin to form in week 26 when the bronchial tree is completed, and **surfactant production begins between weeks 25 and 28** with a rise in production over time (the **saccular** and **alveolar** periods). As a result, the developmental maturity of the lungs is one of the most critical determinants of survival in premature neonates.

Pseudoglandular Period (Weeks 5–16)

Branching continues and all major parts of the lung are formed, except for the gas-exchange elements—respiratory bronchioles and alveoli (Figure 10-1).

Canalicular Period (Weeks 16–26)

The **airways increase in diameter and lung vasculature** develops. **Primitive end-respiratory units,** consisting of a respiratory bronchiole, alveolar duct, and terminal sac, are formed (Figure 10-1).

Saccular Period (Week 26–Birth)

Terminal sacs develop, distinguished by their **thin epithelial lining.** Type I squamous epithelial cells form the gas-exchange surface; type II secretory pneumocytes produce surfactant (Figure 10-1).

Alveolar Period (Prenatal–Childhood)

Clusters of primitive alveoli form, allowing "breathing" in utero via aspiration and expulsion of amniotic fluid. The fluid in the lungs keeps the pulmonary vascular resistance high throughout gestation. At birth, the lungs are half-filled with liquid that must be expelled through the mouth or absorbed into the blood and lymph. The replacement of fluid with air results in a decrease in pulmonary vascular resistance at birth. The alveoli continue to mature after birth, growing in number for the first 3 years and then increasing in both number and size for the next 5 years (Figure 10-1).

MNEMONIC

C3, 4, 5 keep the diaphragm alive.

MNEMONIC

Several **P**arts **B**uild a **D**iaphragm:
Septum transversum
Pleuroperitoneal folds
Body wall
Dorsal mesentery of the esophagus

Pleural Cavities

The lungs invaginate to penetrate part of the intraembryonic coelom, or body cavity, as they grow and branch. This leaves a layer of **visceral pleura** from the splanchnic mesoderm covering the lung, and a layer of **parietal pleura** from the somatic mesoderm directly abutting the body wall (Figure 10-4).

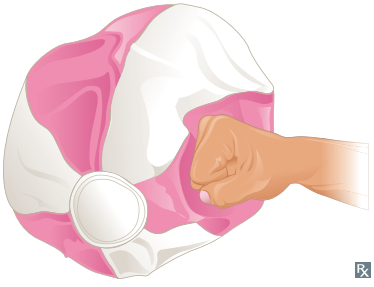


FIGURE 10-4. Pleural cavity development. Imagine pushing on a partially inflated beach ball. As the ball invaginates over your fist, it creates two juxtaposed layers. The surface in contact with your fist is the visceral pleura, and the outer surface is the parietal pleura. The pleural cavity is a potential space that normally contains < 10 mL fluid and lies between the visceral and parietal pleura.

Diaphragm

The diaphragm develops more superiorly than its postnatal location but maintains its innervation from cervical roots C3, **C4,** and C5. It is formed from four embryologic structures that fuse by week 7 (Figure 10-5):

- The **septum transversum** is formed by mesodermal tissue that projects from the ventral body wall to partially separate the thoracic cavity and abdominal cavity. In the adult, the septum transversum forms the **central tendon** of the diaphragm.
- The **pleuroperitoneal folds** extend from the dorsolateral sides of the body wall to form the pleuroperitoneal membranes, which then fuse with the septum transversum.
- The **body wall** also extends from the dorsal and lateral sides (after the pleuroperitoneal folds have closed the thoracic cavity) to form the peripheral, muscular portion of the adult diaphragm.
- The **dorsal mesentery of the esophagus** forms the portion that is dorsal to the esophagus and ventral to the aorta.

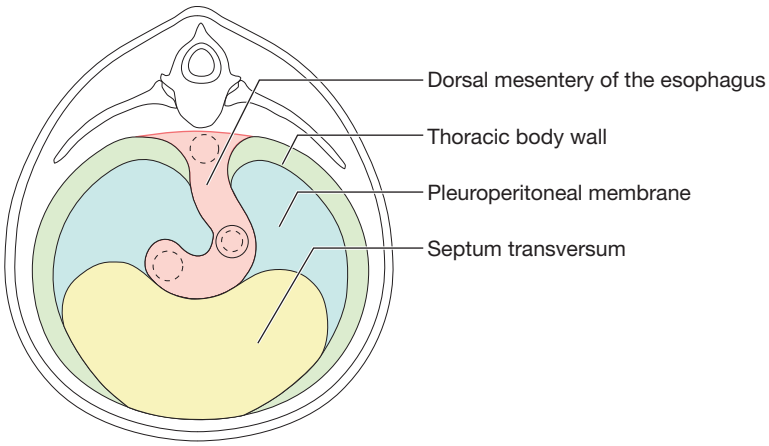


FIGURE 10-5. Embryonic origins of the diaphragm.

CONGENITAL MALFORMATIONS

Esophageal Atresia and Tracheoesophageal Fistula

The ventral laryngotracheal diverticulum is separated from the dorsal gut tube (esophagus at this region) by the **tracheoesophageal septum** (mesoderm-derived tissue). Anomalies in the tracheoesophageal septum can lead to **esophageal atresia** (EA) and/or **tracheoesophageal fistula** (TEF) (see also Chapter 3). A fistula is an abnormal communication between two body cavities. Atresia refers to an absence or abnormal narrowing of an opening in the body.

The most common combination of findings is a proximal EA with a distal TEF. However, other variants have been described (Figure 10-6).

Esophageal closure can form as a result of posterior deviation of the tracheoesophageal septum (see Figure 10-6). Embryos in whom there is an EA with no proximal TEF are unable to swallow amniotic fluid, leading to fluid accumulation, polyhydramnios, and an enlarged uterus.

Infants with a TEF have a conduit that allows oral and/or acidic gastric contents to communicate with the lungs, which can cause coughing during feedings. Chemical irritation of the airway mucosa by gastric contents is termed **aspiration pneumonitis.** Infection of the lungs by this process is called **aspiration pneumonia.** In addition, pas-

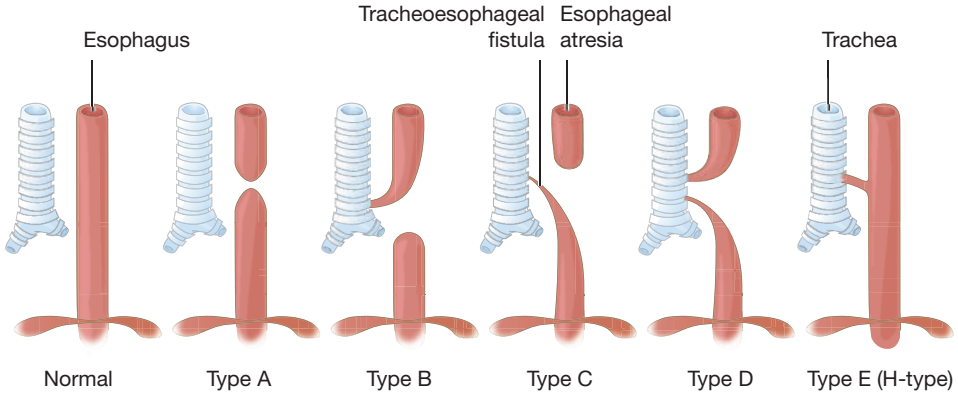


FIGURE 10-6. Congenital malformations of the trachea and esophagus. Normal. Type A (8%): esophageal atresia (EA) only. Type B (1%): proximal tracheoesophageal fistula (TEF) and distal EA. Type C (86%): proximal EA and distal TEF. Type D (1%): proximal TEF and distal TEF. Type H (4%): TEF only.

CLINICAL CORRELATION

The aspiration of amniotic fluid during gestation is essential for lung development, and fetal breathing movements are important for respiratory muscle development. **Pulmonary hypoplasia** may result from **oligohydramnios** (too little amniotic fluid), which may be caused by renal malformation in **Potter syndrome.**

sage of air into the stomach (via the trachea to esophagus during breathing) causes gastric dilation, elevation of the diaphragm, and impaired breathing. Air may be seen in the stomach on a chest radiograph.

TEF and EA may be part of a larger pattern of congenital anomalies known by the acronym **VACTERL,** which includes **V**ertebral defects, **A**nal atresia or imperforate anus, **C**ardiac defects, **T**EF, **E**sophageal atresia, **R**enal agenesis/obstruction, and **L**imb hypoplasia.

Laryngeal Atresia

Discontinuity of the larynx is thought to be due to failed recanalization during development. Although rare, it is considered a medical emergency. A neonate with laryngeal atresia will asphyxiate unless tracheostomy is performed.

Laryngomalacia

Laryngomalacia is a congenital laxity (weakness) of immature laryngeal cartilages that leads to collapse of the larynx during inspiration, audible as a "wet" inspiratory stridor. It is common in neonates and usually resolves spontaneously without treatment.

CLINICAL CORRELATION

Congenital diaphragmatic hernia is most commonly found on the left side because the liver prevents herniation of bowel into the thorax on the right.

Congenital Diaphragmatic Hernia

A **congenital diaphragmatic hernia** (CDH) may result if the components of the developing diaphragm fail to properly fuse. The newborn presents with respiratory distress and bowel sounds in the thoracic cavity. A chest radiograph will show abdominal contents (loops of bowel) within the thoracic cavity (Figure 10-7). CDH is the most common cause of pulmonary hypoplasia.

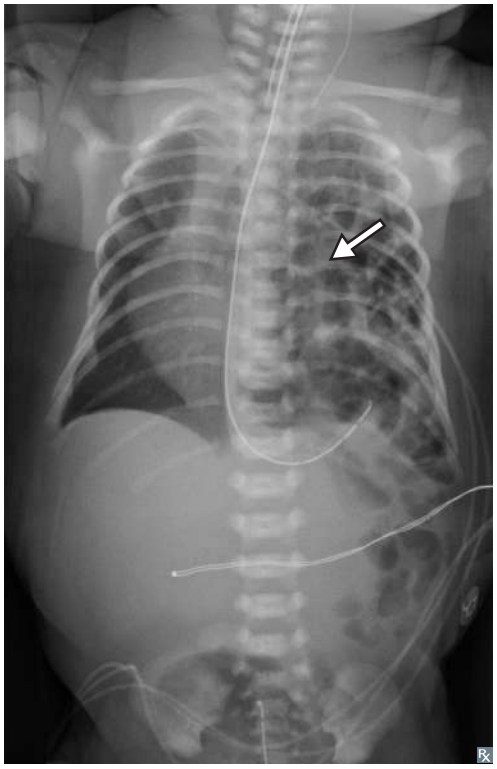


FIGURE 10-7. Congenital diaphragmatic hernia. Anteroposterior portable chest and abdomen film shows numerous air-filled loops of bowel (indicated by the arrow) in the left hemithorax in this neonate with a congenital diaphragmatic hernia. There is a shift of mediastinal structures to the right. An orogastric tube lies within the stomach.

Pulmonary Hypoplasia

Failure of the lungs to develop fully may be primary or, more commonly, secondary to another defect such as oligohydramnios, or due to compression by a CDH or tumor (Figure 10-8). The hypoplastic lung lacks respiratory exchange capacity and has overgrowth of smooth muscle elements, which leads to pulmonary hypertension. Unilateral hypoplasia is compatible with life; bilateral usually results in early death. In rare cases, the lungs may fail to develop entirely, termed **pulmonary aplasia.**

Congenital Cysts

Congenital cysts are saccular enlargements of the terminal bronchiole. They are usually solitary and can be associated with chronic infection secondary to poor drainage.

Respiratory Distress Syndrome

During weeks 25–28, type II pneumocytes begin to produce surfactant, a phospholipoprotein fluid that facilitates alveolar opening by reducing surface tension during expiration. Due to the absence of surfactant, a fetus delivered prior to 25 weeks of gestation may not be viable. A baby delivered prematurely during the period between the onset of surfactant secretion and term gestation has some degree of surfactant deficiency (Figure 10-9). The static surface tension of surfactant-deficient alveoli results in collapse of some air spaces and hyperexpansion of others due to LaPlace's law ($P = 2T/r$). The impaired ventilation contributes to vascular congestion and leakage of proteins, resulting in formation of hyaline membranes. Respiratory distress syndrome (RDS) is further discussed under Interstitial Lung Diseases. Clinically, the infant exhibits superficial, rapid breathing (**tachypnea**) and **cyanosis.** The incidence of RDS is inversely related to gestational age at birth. The most important intervention for RDS is to prevent premature birth, if possible. The first-line treatment is administration of antenatal corticosteroids (stimulates fetal surfactant production) to all pregnant women who are at risk of delivery between 23 and 34 weeks' gestation. Initial postnatal treatment includes nasal continuous positive airway pressure (CPAP). Exogenous surfactant replacement, endotracheal intubation, and mechanical ventilation are used for more severe RDS.

Anatomy

The respiratory system consists of the nasal passages and mouth, pharynx, trachea, bronchi, bronchioles, lungs, and the muscles that control respiration, as shown in Figure 10-10.

KEY FACT

The conducting airways are surrounded by a layer of smooth muscle that hypertrophies and undergoes spastic contractions in **asthma,** an obstructive lung disease.

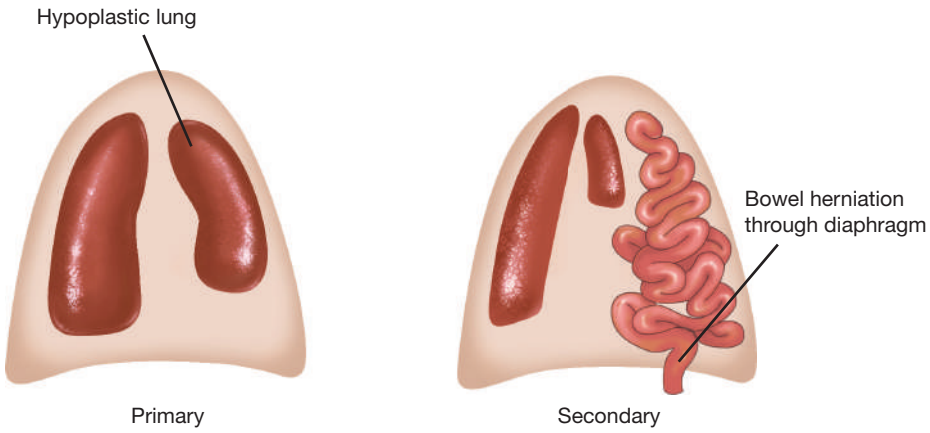


FIGURE 10-8. Lung hypoplasia and congenital diaphragmatic hernia (CDH). Failure of a lung to fully develop may occur as an isolated event (left) or secondary to another defect such as bowel herniation through the diaphragm (right).

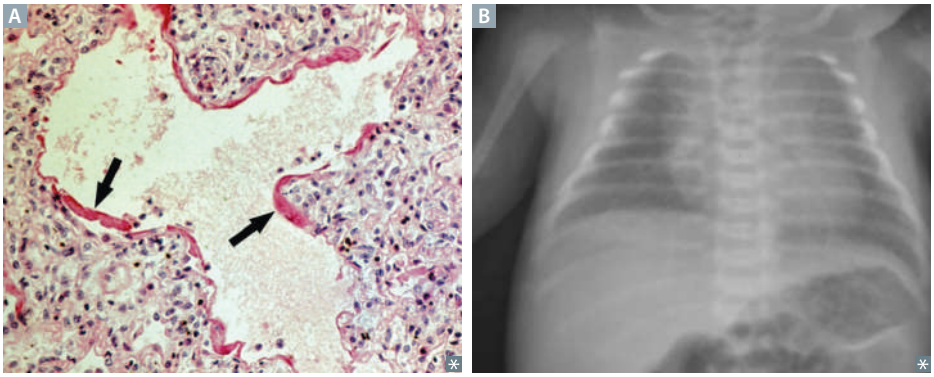


FIGURE 10-9. **Indications of surfactant deficiency in a premature infant.** A Photomicrograph shows collapsed alveoli surrounding dilated alveolar ducts lined by smooth homogeneous hyaline membranes (arrows). B X-ray of the chest shows diffuse ground-glass opacities and prominent air bronchograms consistent with neonatal respiratory distress syndrome.

AIRWAYS

The passages that transmit air from the environment to the lungs can be divided into conducting and respiratory airways (Table 10-1).

MNEMONIC

RALS:

Right pulmonary artery is **A**nterior, **L**eft pulmonary artery is **S**uperior to the bronchi.

LUNGS

The right and left lungs are structurally distinct (Table 10-2).

Blood Supply of the Lungs

- The right and left **pulmonary arteries** transport relatively deoxygenated blood from the right ventricle to the lungs.
- The **bronchial arteries** branch from the descending aorta to supply the bronchi and pulmonary connective tissues with nourishing, O_2-rich blood. In reality, the perfusion provided by these vessels is not clinically significant. They are not commonly reanastomosed during lung transplantation.
- Branches of the pulmonary and bronchial arteries enter the **bronchopulmonary segments** centrally alongside the **segmental (tertiary) bronchi.**

KEY FACT

An aspirated foreign object is more likely to lodge in the right mainstem bronchus than the left mainstem bronchus due to the smaller angle of entry and wider diameter of the right mainstem bronchus (see Figure 10-10).

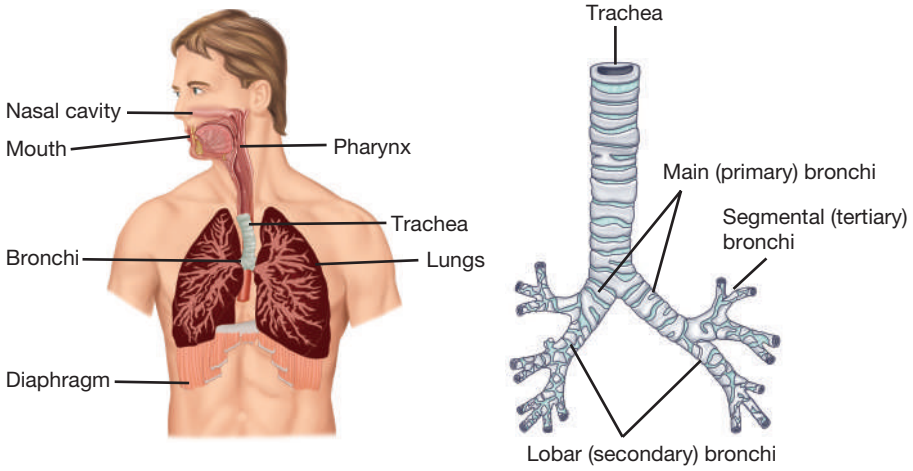


FIGURE 10-10. **Gross anatomy of the respiratory system.** Overview (left) and conducting airways (right).

TABLE 10-1. Conducting and Respiratory Airways

	CONDUCTING AIRWAYS	RESPIRATORY AIRWAYS
Function	Warm, humidify, and filter air; no gas exchange (anatomic dead space)	Gas exchange
Structures	Nose/mouth, pharynx Trachea Bronchi Bronchioles Terminal bronchioles	Respiratory bronchioles Alveolar ducts Alveoli

- Small **bronchial veins** unite to form a single vessel in each lung that empties into the **azygos vein** on the right and the **hemiazygos vein** on the left.
- The **pulmonary veins** transport highly oxygenated blood from the alveoli to the left atrium.

The relationship among the conducting airways, respiratory airways, and blood supply to the alveoli is shown in Figure 10-11.

Pleura

The lungs are located within a bilayered pleural sac in the thoracic cavity.

- The **visceral pleura,** or **pulmonary pleura,** adheres tightly to the outer surface of the lungs.
- The **parietal pleura** covers the inside of the thoracic cavity, including the diaphragm, chest wall, and the mediastinum.
- The **pleural reflections** are the angled boundaries between the parietal pleura lining one surface and the parietal pleura lining another. For example, the costal pleura is continuous with the diaphragmatic pleura, forming the costal line of pleural reflection at the boundary between the ribs and the diaphragm, also called the **costophrenic angle.**

Between the visceral and parietal pleura is a potential space, the **pleural cavity,** which normally contains < 10 mL of fluid. In some disease states, fluid accumulates in the pleural cavity, forming a **pleural effusion.** When the patient is erect, the fluid fills the **costodiaphragmatic recess** located at the inferior part of the thoracic cavity. On a chest radiograph, the costophrenic angles are normally sharply demarcated and unoccupied by tissue or fluid, but pleural effusions blunt these angles, as seen in Figure 10-12.

TABLE 10-2. Anatomy of the Right and Left Lungs

	RIGHT	LEFT
Lobes	Three (upper, middle, and lower)	Two (upper with lingula, and lower)
Main bronchus entry	Smaller angle (more continuous with trachea)	Sharper angle (greater deviation from trachea)
Main bronchus shape	Shorter and wider	Longer and narrower
Pulmonary artery entry	Anterior to right mainstem bronchus	Superior to left mainstem bronchus

KEY FACT

The visceral pleura lacks sensory innervation. The parietal pleura is innervated by branches of the intercostal and phrenic nerves, and is thus highly sensitive to pain, but the visceral pleura is not.

MNEMONIC

The **P**arietal pleura feels **P**ain.

FLASH BACK

A pleural effusion may be classified as **transudative** or **exudative.**

- **Transudate:** increased capillary pressure or decreased oncotic pressure secondary to congestive heart failure (CHF), cirrhosis, or nephrotic syndrome.
- **Exudate:** increased vascular permeability and inflammation secondary to lung infection, malignancy, or pulmonary embolism (PE), although some PEs produce a transudative pleural effusion.

CLINICAL CORRELATION

A pneumothorax occurs when air fills the pleural cavity due to compromise of one or both of the pleurae (often caused by trauma or ruptured blebs). Positive pleural pressure resulting from air entering the thorax leads to collapse of the ipsilateral lung, as well as dissociation of the lung–chest wall system. These events may manifest as shortness of breath (dyspnea), particularly when the pneumothorax is large.

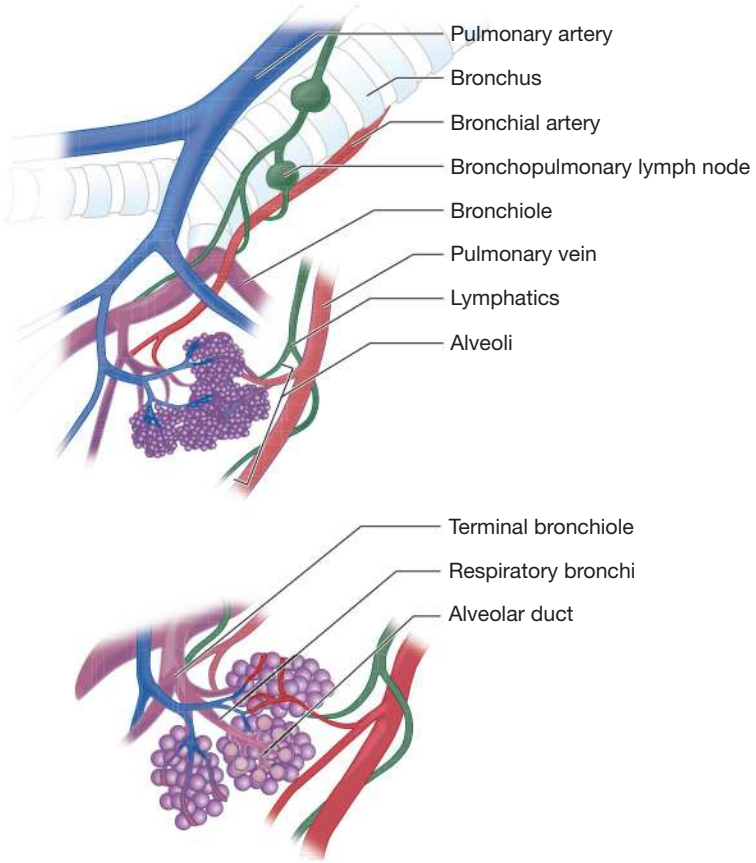


FIGURE 10-11. Anatomy of the bronchopulmonary segments. Each lobe of the lung is subdivided into several functional bronchopulmonary segments, each supplied by its own artery and tertiary bronchus. The pulmonary and bronchial arteries approach the alveoli alongside the bronchi, and the pulmonary vein drains blood separately.

DIAPHRAGM

The thoracic diaphragm is a domed, musculotendinous structure that forms the inferior border of the thoracic cavity. During physiologic inspiration, the central part of the diaphragm descends, decreasing intrathoracic pressure and increasing lung volume.

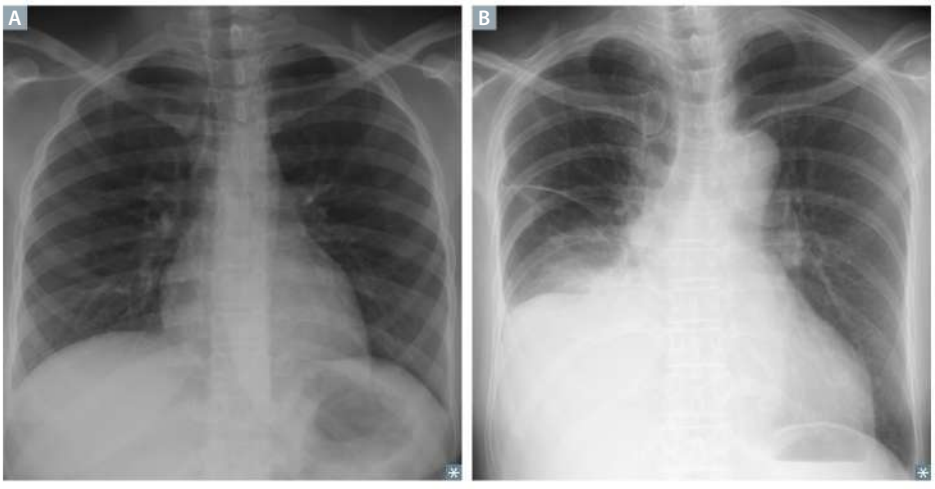


FIGURE 10-12. Chest radiographs. A Normal chest radiograph. B Plain chest radiograph shows pleural effusion in the right hemithorax.

The peripheral parts of the diaphragm are fused to the thoracic wall and are thus immobile. The left and right crura (singular: crus) affix the diaphragm posteriorly to the vertebral column.

The diaphragm is a useful landmark in radiographs, as it has three openings at specific vertebral levels, which allow structures to penetrate: (1) the inferior vena cava (IVC) through the caval opening at T8; (2) the esophagus and vagus nerve through the esophageal hiatus at T10; and (3) the aorta, azygos vein, and thoracic duct through the aortic hiatus at T12 (Figure 10-13).

EXTERNAL ANATOMY

Landmarks outline the location of the lungs and surrounding pleural cavities (Figure 10-14).

- The lung apices are superior to the first rib, extending into the **supraclavicular fossa.** This is of clinical significance in penetrating trauma to the lower neck and upper thoracic regions, as the lung apex can be damaged and a pneumothorax can result.
- At full exhalation, the lower lung borders extend to the sixth rib anteriorly, eighth rib at the midaxillary line, and 10th rib posteriorly.
- The pleural reflection extends to the eighth rib anteriorly, descending to the 10th rib at the midaxillary line, and to the 12th rib posteriorly.

These landmarks are important when performing thoracic procedures. A **thoracentesis** allows for sampling of pleural effusions by introducing a needle into the pleural space. The needle is typically inserted against the superior border of the corresponding rib, because the intercostal vein, artery, and nerve lie at the inferior rib margin (Figure 10-15).

MUSCLES OF RESPIRATION

The diaphragm is the primary muscle of respiration. It is innervated by the **phrenic nerve,** which is formed by branches of the C3, C4, and C5 nerve roots.

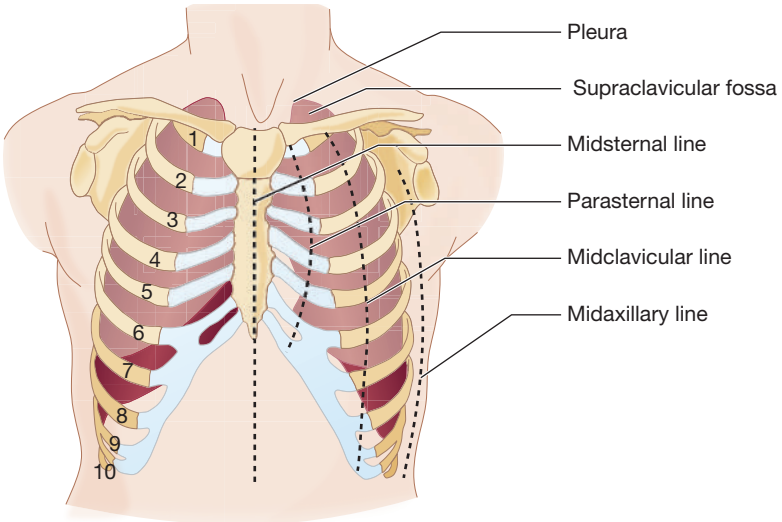


FIGURE 10-14. External landmarks of the thoracic cavity. Note the difference between the extent of the lungs at normal inflation (pink) and at full inspiration (dark red). The floating ribs (11 and 12) are not illustrated.

FLASH BACK

The **right crus** of the diaphragm wraps around the esophagus to prevent the formation of a **hiatal hernia,** in which the stomach begins to slide into the thoracic cavity (refer to the Pathology section in Chapter 3 for details).

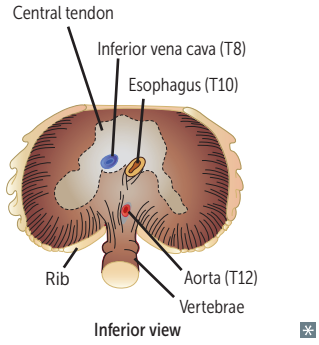


FIGURE 10-13. The diaphragm and penetrating structures.

MNEMONIC

I 8 10 EGGs AAT 12 ("I ate ten eggs at twelve"):

Inferior vena cava: T**8**
Esopha**G**us, va**G**us nerve: T**10**
Aorta, **A**zygos vein, **T**horacic duct: T**12**

MNEMONIC

The intercostal **V**ein, **A**rtery, and **N**erve travel in a **VAN** inferior to the rib, in a superior-to-inferior direction: V → A → N.

CLINICAL CORRELATION

A lesion of the phrenic nerve results in ipsilateral paralysis of the diaphragm. On a chest radiograph, this can be seen as elevation of the ipsilateral diaphragm.

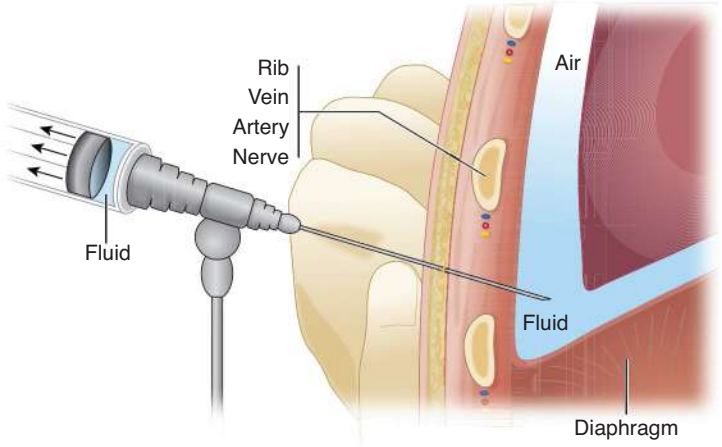


FIGURE 10-15. **Thoracentesis.**

The diaphragm (and to a lesser extent, the external intercostals and scalenes) is involved in **quiet inspiration** (inspiration at rest), while **quiet expiration** is a passive activity. Multiple additional accessory muscles are involved in **forced respiration,** which occurs during heavy activity (Table 10-3).

FLAIL CHEST

Flail chest is usually due to significant blunt trauma and is defined as three or more adjacent ribs with fractures at two or more locations. The result is an unstable chest wall segment with **paradoxical breathing motion.** The flail segment moves inward during inspiration and outward during expiration—opposite from the surrounding uninjured chest wall. Crepitus may be present as well. Pulmonary contusion underlying the flail segment often results in respiratory compromise. Treatment is beyond the scope of this text but may include pain control, incentive spirometry, and mechanical ventilation.

Histology

Within the lungs, there are two distinct functional regions: the **conducting airways,** which partition, humidify, and filter the air, and the **respiratory airways,** which allow for

TABLE 10-3. **Respiratory Muscles**

	QUIET RESPIRATION	FORCED RESPIRATION
Inspiration	Diaphragm External intercostals Internal intercostals (interchondral part)	Diaphragm External intercostals Internal intercostals (interchondral part) Scalenes Sternocleidomastoids
Expiration	None (passive)	Rectus abdominis Internal/external obliques Transversus abdominis Transversus thoracis Internal intercostals (interosseous part)

gas exchange. Specialized epithelial cell layers along these different airways contribute to their distinct functional capacities. The conducting airways are lined by thick pseudostratified columnar epithelium, and the alveoli are lined by exceedingly thin type I pneumocytes and interspersed surfactant-secreting type II pneumocytes.

RESPIRATORY EPITHELIUM

The proximal portion of the upper respiratory tract consists of **stratified squamous epithelium,** which lines the following:

- Oropharynx
- Laryngopharynx
- Anterior epiglottis
- Upper half of posterior epiglottis
- True vocal cords

The remainder of the conducting portion of the respiratory tract is lined mostly by **ciliated pseudostratified columnar epithelium ("respiratory epithelium")** from the nasal cavity to the terminal bronchioles, where the lining transitions to ciliated simple cuboidal (respiratory bronchioles) and then simple squamous (alveolar ducts and alveoli) epithelium.

Cilia of the respiratory epithelium sweep mucus and foreign particles toward the mouth, thereby protecting the lower respiratory tract. **Goblet cells,** which secrete mucus, are interspersed in the respiratory epithelium from the nasopharynx to the primary bronchioles. These cells can be identified by their distinct shape and pale-staining cytoplasm.

Clara cells lack cilia, are located in the terminal bronchioles, and secrete protein to help protect the airway lining from damage. Microscopically, Clara cells can be identified by secretory granules in the apical cytoplasm.

ALVEOLI

The alveoli are composed of multiple cell types. These cells are described in Table 10-4 and illustrated in Figure 10-16.

TABLE 10-4. Types of Alveolar Cells

	TYPE I CELLS	TYPE II CELLS	ENDOTHELIAL CELLS	MACROPHAGES	CLARA CELLS
Prevalence	Cover 95% of alveolar surface area. Comprise 10% of cell population	Cover 5% of alveolar surface area. Comprise 12% of the cell population	40% of the cell population	Variable	11% in terminal bronchioles; 22% in respiratory bronchioles
Structure	Flat and extremely thin (< 500 nm)	Cuboidal	Thin, wrapped into cylinders to form capillaries	Amorphous	Nonciliated; low-columnar/cuboidal with secretory granules
Function(s)	Allow for gas exchange with the adjacent capillaries Nonproliferative	Secrete surfactant Proliferate after lung damage Are source of precursors for new alveolar cells (types I and II)	Allow for gas exchange with the alveolus	Engulf debris ("dust cells")	Secrete component of surfactant; degrade toxins; act as reserve cells

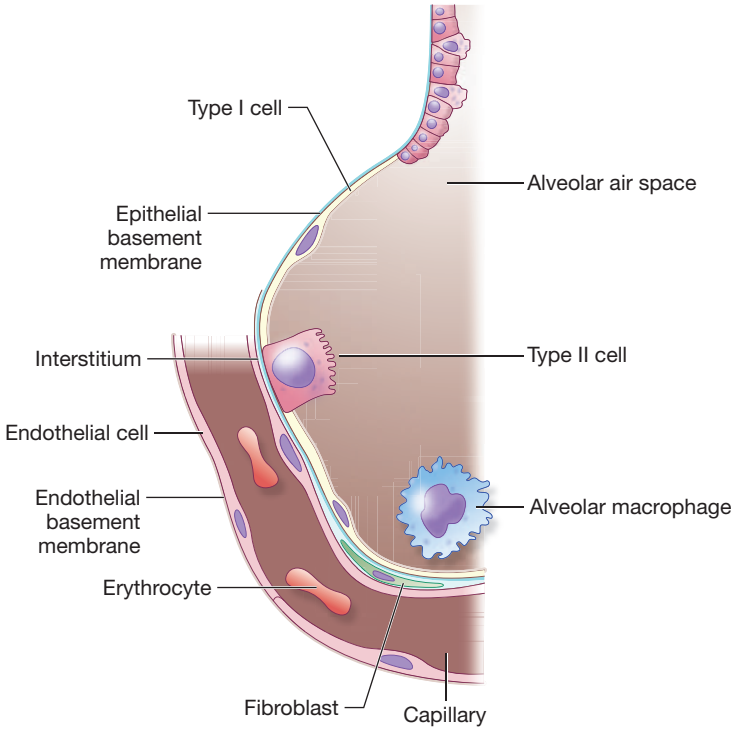


FIGURE 10-16. Alveolar structure.

Pulmonary surfactant is a mixture of phospholipids (80%, primarily dipalmitoylphosphatidylcholine [DPPC], which is a type of lecithin), surfactant-associated proteins (12%), and lipids (8%). Surfactant is stored in the whorled cytoplasmic **lamellar bodies** of type II alveolar cells (Figure 10-17).

Pulmonary capillary endothelial cells are joined by tight junctions to form a continuous endothelium without fenestrations. This configuration prevents fluid leakage but still permits gas exchange across the thin cell bodies.

FLASH BACK

In **Kartagener syndrome** (immotile cilia syndrome or primary ciliary dyskinesia), a defect in the protein dynein prevents cilia from moving properly. This results in impaired clearance of secretions and **frequent respiratory infections,** as well as **infertility** and **situs inversus** or **situs ambiguus (heterotaxy).**

FLASH BACK

Alveolar macrophages, which phagocytize RBCs that leak into alveoli in CHF, are also called "heart failure cells." See Left-Sided Heart Failure in Chapter 1 for more details.

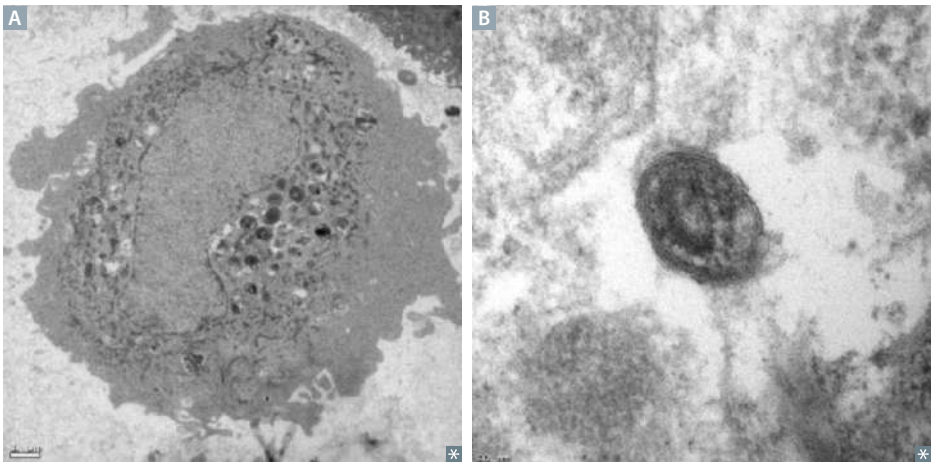


FIGURE 10-17. Type II pneumocytes. A Electron micrograph of type II pneumocytes. B Higher magnification electron micrograph showing lamellar bodies.

OLFACTORY CELLS

In the nasal cavity, the **pseudostratified olfactory epithelium** is found in the superior conchae. Among other supportive cells in this epithelium, **olfactory cells** are bipolar neurons that generate action potentials in response to specific odor molecules. Each olfactory cell has a single dendrite containing a few nonmotile cilia that function to increase the surface area for olfactory receptors.

FLASH BACK

Increased capillary hydrostatic pressure within the lungs, as occurs in severe left ventricular systolic failure, can cause leakage of fluid into the lungs **(pulmonary edema).**

Physiology

The respiratory system is a means for inspiring air, facilitating gas exchange between the air and blood, and expelling air. As illustrated by the ideal gas law and Boyle's law, air and its component gases are characterized by their quantity, volume, and pressure. Likewise, respiratory physiology may be described as a series of **pressure-driven changes in the volume of gas in the lung** that enables the **regulation of oxygen, carbon dioxide, and pH in the blood.** This section introduces lung volumes and capacities and then discusses in detail (1) the movement of gas into and out of the lungs **(ventilation)** and (2) the regulation of O_2 and CO_2 transport (the **blood gases**).

KEY FACT

Ideal Gas Law

$PV = nRT$

where

P = absolute pressure (pascals)

V = volume (m^3)

n = number of gas molecules (moles)

R = universal gas constant (8.314 J/[K * mol])

T = temperature (Kelvin)

LUNG VOLUMES AND CAPACITIES

Important lung volumes and capacities are defined in Table 10-5 and depicted graphically in Figure 10-18.

- Forced expiratory volume in 1 second (FEV_1) is normally 70–80% of the forced vital capacity (FVC), or **FEV_1/FVC = 0.7–0.8.**
- In obstructive lung diseases, like **asthma** or **emphysema,** FEV_1 is decreased more than FVC, so **FEV_1/FVC < 0.7** (Figure 10-19 and Table 10-6).

KEY FACT

Boyle's Law

Special case of the ideal gas law that states: For a fixed amount of an ideal gas at a constant temperature, the pressure and volume of the gas are inversely proportional.

$PV = k$, where k is a constant.

TABLE 10-5. Lung Volumes and Capacities

NAME	DESCRIPTION
Volumes	
Tidal volume (TV or V_T)	Volume of air taken into the lungs during resting inspiration after a resting expiration.
Inspiratory reserve volume (IRV)	Maximal additional volume of air that can be inspired beyond tidal inspiration.
Expiratory reserve volume (ERV)	Maximal volume of air that can be expired beyond resting expiration.
Residual volume (RV)	Volume of air in lungs that cannot be expired regardless of effort.
Capacities (Sums of 2 or more volumes)	
Inspiratory capacity (IC)	Maximal volume of air inhaled after a quiet expiration at rest. IC = IRV + TV
Functional residual capacity (FRC)	Volume of air remaining after tidal expiration. FRC = ERV + RV
Vital capacity (VC) Forced vital capacity (FVC)	Maximum expiratory volume after a maximal inspiration. The FVC is the *measured* VC when the patient exhales forcefully after maximal inspiration. VC = IRV + TV + ERV = TLC – RV
Forced expiratory volume in 1 second (FEV_1)	Volume of air forcefully expired in 1 second following a maximal inspiration.
Total lung capacity (TLC)	Total volume of air contained in the lungs after maximal inspiration.

*For 70-kg male.

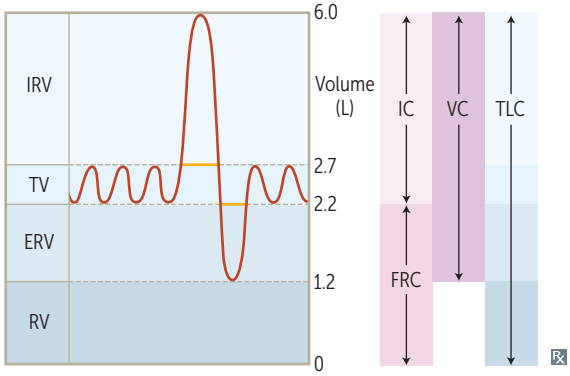


FIGURE 10-18. Lung volumes and capacities. A spirometry tracing showing all of the lung volumes (left) and capacities (right). Values are typical for a 70-kg male. ERV, expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity; TV, tidal volume; VC, vital capacity.

- In restrictive lung diseases, like **pulmonary fibrosis,** FEV_1 is decreased to the same extent as, or less than, FVC, so $\mathbf{FEV_1/FVC \geq 0.7}$.

Measurement of Lung Volumes and Capacities

Some lung volumes and capacities can be measured simply by having a patient perform various breathing maneuvers into a spirometer. For example, having a patient take a maximal inspiration to total lung capacity (TLC) followed by a maximal expiration to residual volume (RV) generates a volume equivalent to the VC. However, since RV, functional residual capacity (FRC), and TLC cannot, by definition, be measured as expired volumes on spirometry, other methods are used. They include:

CLINICAL CORRELATION

Pulmonary vascular resistance is lowest at FRC and increases at both higher and lower volumes.

- **Dilution tests:** A known volume and concentration of an inert gas such as helium is inhaled at the end of a tidal expiration. This inert gas is diluted by the air already in the lungs, so the change in concentration of the gas that is expired can be used to calculate the FRC. Specifically, if *X* is the unknown lung volume of the patient, then

$$X = \frac{V_o \cdot (C_o - C)}{C}$$

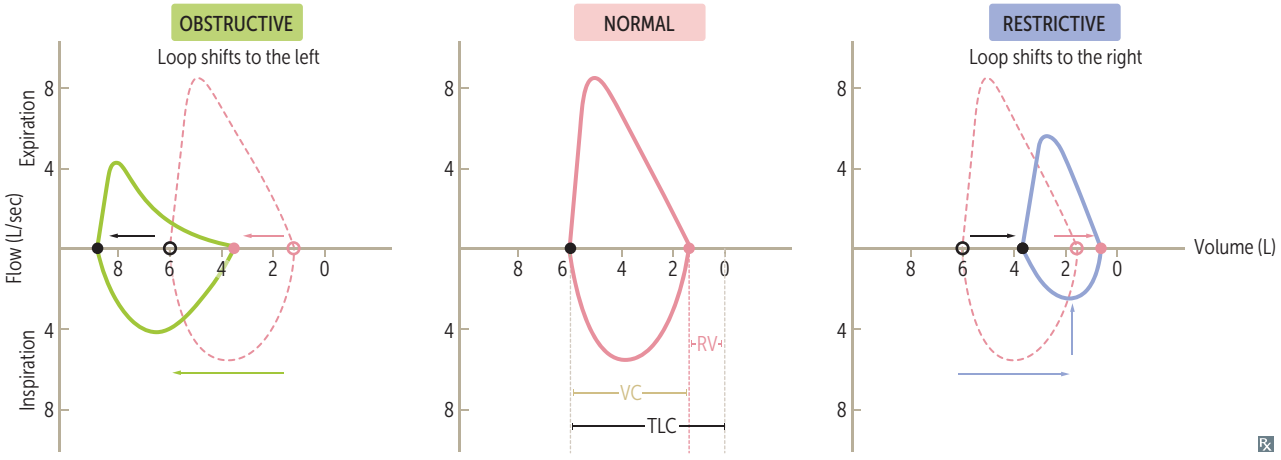


FIGURE 10-19. Obstructive versus restrictive lung diseases. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) in normal subjects and patients with lung disease. RV, residual volume; TLC, total lung capacity; VC, vital capacity.

TABLE 10-6. Lung Volumes in Restrictive Versus Obstructive Disease

	RV	FRC	TLC	FVC	FEV_1	FEV_1/FVC
Obstructive	↑↑	↑	↑	↓	↓↓	↓
Restrictive	↓	↓	↓	↓↓	↓	↑ or normal

FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

where V_o and C_o are the original volume and concentration of helium in the spirometer, and C is the final concentration of the helium after equilibration with the patient's lungs.

- **Body plethysmography:** The patient sits in an airtight box with a known pressure and breathes through a mouthpiece. At end expiration, the mouthpiece is closed and the patient attempts to inhale. Chest expansion against the closed system increases the measured pressure within the box. The FRC volume can thus be computed by Boyle's law. In contrast to dilution tests, body plethysmography can detect air that is not in communication with the airways.

Anatomic Dead Space

The volume of air in the conducting airways that does not participate in gas exchange (ie, everything but the respiratory bronchioles, alveolar ducts, and alveoli). It is **normally ~150 mL** and should not change for a given individual under different respiratory conditions.

Physiologic Dead Space (Total Dead Space)

The total volume of inspired air that does not participate in gas exchange, comprised of the **anatomic dead space** and the **alveolar dead space.** The alveolar dead space represents the alveoli that are filled with air but not perfused by blood ($\dot{V}/\dot{Q}$ mismatch, where $\dot{V}$ is ventilation rate and $\dot{Q}$ is blood flow; see Hypoxemia section under Blood Gases). Conceptually, dead space (or more specifically V_D/V_T) is proportional to the fraction of tidal volume that reaches areas that do not contribute expired CO_2 (no gas exchange due to absence of perfusion). Thus, in healthy lungs, the total dead space is essentially equal to the anatomic dead space, while diseased lungs may have elevated physiologic dead space. The Bohr equation computes the physiologic dead space:

$$V_D = V_T \cdot \frac{Paco_2 - Peco_2}{Paco_2}$$

where V_D is the physiologic dead space (mL); V_T is the tidal volume (mL); $Paco_2$ is the arterial partial pressure of carbon dioxide (mm Hg); and $Peco_2$ is the partial pressure of carbon dioxide in expired air (mm Hg).

MNEMONIC

To remember order of variables in Bohr equation:
Taco, **Pa**co, **Pe**co, **Pa**co

VENTILATION

Alveolar Function

Gas Exchange

The alveolus enables robust gas exchange, even during rigorous exercise. To accomplish this, the approximately spherical alveolar surface is criss-crossed by a network of narrow capillaries barely wider than a single red blood cell, or about 10 µm. Oxygen and CO_2 must diffuse across a trilaminar barrier: the endothelial cell wall, the basement membrane, and a type I pneumocyte. The total thickness of this barrier is approximately

500 nm in a healthy human lung. At normal respiratory rates, RBCs are fully saturated with O_2 after traversing a quarter of the length of an alveolar capillary. The remaining length provides the capacity to accommodate increased cardiac output during exertion.

Surface Tension

The collapsing pressure of the alveoli is governed by Laplace's law:

$$P = (2T)/r$$

where P is collapsing pressure (the pressure required to hold the alveolus open); T is surface tension; and r is the alveolar radius.

When r is small, greater pressure is required to keep the alveolus open. Thus, alveoli are most likely to collapse on expiration, when their radii are at a minimum; this alveolar collapse is called **atelectasis. Surfactant** reduces the surface tension to protect small alveoli from collapsing.

Surfactant

As described previously (see Alveoli in the Histology section), surfactant is synthesized by **type II alveolar cells** and is composed primarily of **DPPC.**

- Surfactant lines alveoli and acts as a detergent, reducing surface tension during expiration. This helps prevent alveolar collapse.
- Surfactant production in the fetus may begin as early as week 24, and is usually present by week 35. A **lecithin (DPPC):sphingomyelin ratio > 2:1** indicates mature surfactant production.
- **Neonatal respiratory distress syndrome** can occur in premature infants due to a low level of surfactant. These infants have **atelectasis, decreased compliance,** trouble with inspiration, and **hypoxemia** due to $\dot{V}/\dot{Q}$ mismatch and shunting.

KEY FACT

Decreased or dysfunctional surfactant in acute respiratory distress syndrome (ARDS) and the lack of surfactant in neonatal RDS contribute to decreased lung compliance and atelectasis.

Other Lung Products

The lung produces many important substances besides surfactant, including:

- **Prostaglandins:** Various functions, including contraction or relaxation of vascular smooth muscle.
- **Histamine:** Promotes vascular permeability and exudative processes.
- **Kallikrein:** Activates bradykinin.
- **Angiotensin-converting enzyme (ACE):** Converts angiotensin I to angiotensin II (see also Renin-Angiotensin-Aldosterone System in the Physiology section of Chapter 8); inactivates bradykinin.

KEY FACT

Angiotensin-converting enzyme (ACE) not only converts angiotensin I to angiotensin II but is also responsible for breaking down bradykinin. Hence, ACE inhibitors increase bradykinin levels, potentially causing cough and angioedema as adverse effects.

Ventilation Rate

Minute Ventilation

The total amount of air inspired in 1 minute.

$$\text{Minute ventilation} = (\text{Dead space ventilation} + \text{alveolar ventilation}) \times \text{Breaths/min}$$

Alveolar Ventilation

The total amount of air reaching the alveoli (air that participates in gas exchange) in 1 minute. It is different from minute ventilation due to dead space.

$$\text{Alveolar ventilation} = (V_T - V_D) \times \text{Breaths/min}$$

$$\dot{V}_A = \dot{V}CO_2/FACO_2 = 0.863\ \dot{V}CO_2/PaCO_2$$

where $\dot{V}_A$ is alveolar ventilation (L/min), $\dot{V}CO_2$ is the rate of CO_2 production in the body (mL/min), $FACO_2$ is the fraction of alveolar CO_2, $PaCO_2$ is the partial pressure of CO_2 in the arterial blood, and 0.863 is the temperature and pressure-adjusted conversion between $FACO_2$ and $PaCO_2$.

Increasing alveolar ventilation through increased depth (tidal volume) or rate of breathing results in a proportionate decrease in $PaCO_2$.

Inspiration

Inspiration is an active process that always requires at least some muscle activity (see also Table 10-3).

- **Diaphragm:** The most important muscle of inspiration. When the diaphragm contracts, the volume of the thoracic cavity increases vertically. This creates negative intrathoracic pressure, thus drawing air into the lungs.
- **External intercostals, scalenes, and sternocleidomastoids:** Normally used only during times of increased work of breathing, such as **exercise,** but may be used **at rest in patients with lung disease.** The actions of these muscles on the upper and lower ribs are different because the upper ribs are firmly attached to the sternum and relatively parallel to the horizontal plane, whereas the lower ribs descend as they curve around the body anteriorly. As a result, movement of the upper ribs is often compared to a pump-handle, where the ribs and sternum move up and out as a unit and increase the anteroposterior (AP) diameter of the chest. In contrast, movement of the lower ribs is more like lifting bucket handles from either side of the thorax, resulting in an increased transverse diameter (Figure 10-20).

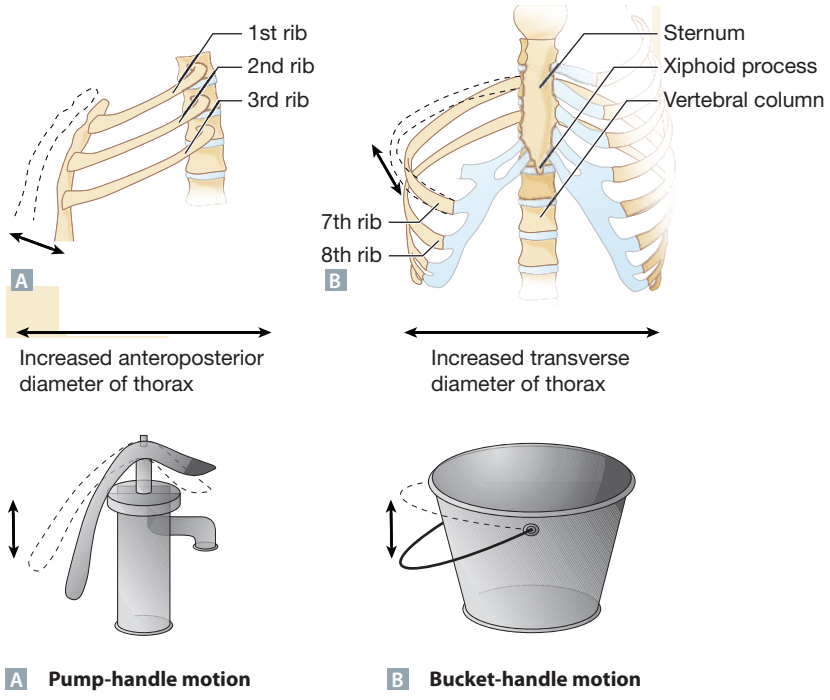


FIGURE 10-20. Pump-handle versus bucket-handle movement. A When accessory muscles lift the upper ribs, which are directly affixed to the sternum, the sternum lifts up and out as if it were a water pump, thereby increasing the anteroposterior diameter of the thorax. B When accessory muscles lift the lower ribs, which have a significant downward angle and indirect attachment to the sternum, they primarily lift up like the handle of a bucket, thereby increasing the transverse diameter of the thorax.

Expiration

Expiration is normally passive, secondary to the elastic recoil of the lung–chest wall system. The lung–chest wall system is minimally distended at FRC, so once the active muscle activity of inspiration is removed, the lungs recoil back to FRC.

Expiratory muscles are used during **exercise,** coughing, or when airway resistance is elevated in disease (eg, **asthma**). Such muscles include the interosseous part of the internal intercostals, rectus abdominis, transversus abdominis, and internal/external obliques.

Lung Compliance

Compliance (C) is the distensibility of an object; in other words, the volume change that results per unit of pressure applied. The more compliant the lung, the easier it is to inflate and deflate it. Compliance is the reciprocal of elastance and is therefore inversely proportional to the amount of elastic tissue.

$$\text{Compliance } (C) = \Delta \text{ Volume } (V) / \Delta \text{ Pressure } (P)$$

where C is in mL/cm H_2O, V is in mL, and P is in cm H_2O (1 cm H_2O = 0.74 mm Hg).

KEY FACT

In **emphysema,** there is destruction of elastic tissue, so ***C*** ↑.
In **fibrotic lung disease,** the lungs become stiffer, so ***C*** ↓.

When inspiration and expiration are plotted on a volume-versus-pressure graph (Figure 10-21), the slope of the curve is the compliance (this is a **static** compliance curve, meaning that the points correspond to measurements made after airflow is halted at different stages of inspiration or expiration). Notice that the compliance changes as a function of pressure and according to whether a person is breathing in or out (this path-dependence is termed *hysteresis*).

Compliance of the Lung–Chest Wall System

Since the act of breathing involves both the lungs and the chest wall, the separate compliance curves for both must be summed in order to understand the mechanics of the respiratory cycle (Figure 10-22).

Mechanics of Breathing During the Respiratory Cycle

The respiratory cycle involves the repeating pattern of inspiration → expiration → rest. The volumes and key pressures during a prototypical tidal breath are graphed in Figure 10-23 and described in detail in the following sections.

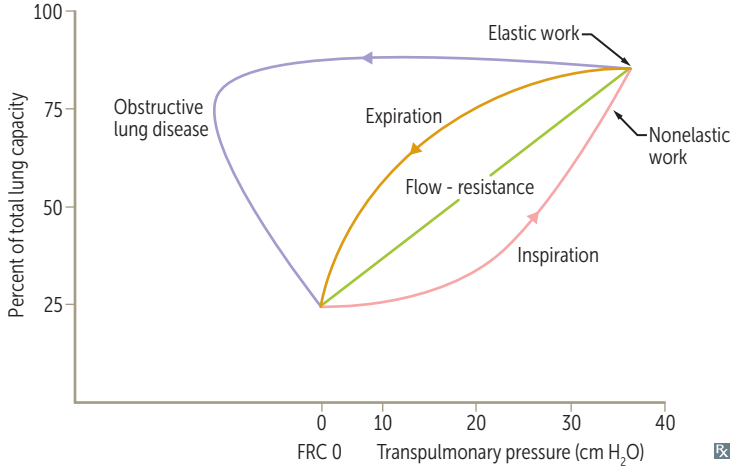


FIGURE 10-21. Hysteresis curve. Percent of total lung capacity versus transpulmonary pressure.

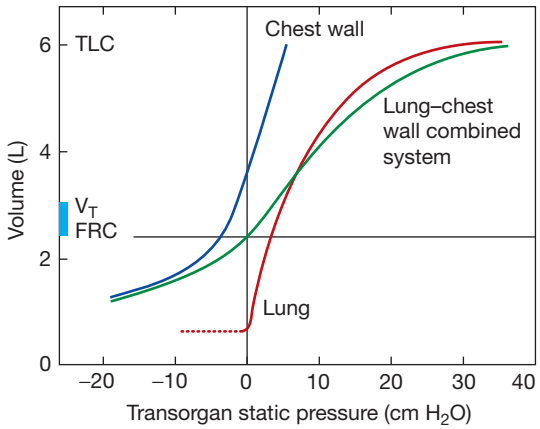


FIGURE 10-22. Lung–chest wall system. Pressure and volume tracings for the lung, chest wall, and the combined system. FRC, functional residual capacity; TLC, total lung capacity; V_T, tidal volume.

Forces Defined

- **Inward recoil of the lungs:** Inward-directed force created by the elastic tissue in the lungs. In isolation, the lungs always collapse to a minimal volume, regardless of how much air they contain.
- **Outward recoil of the chest wall:** Outward-directed force created by the chest wall's tendency to expand to its resting state (~70% of TLC).
- **Intrapleural pressure:** The pressure within the pleural cavity.
- **Intra-alveolar pressure:** The pressure within the alveoli of the lungs; the major determinant of air flow between the lungs and the environment. Varies from negative during inspiration to positive during expiration.
- **Transpulmonary pressure:** Intra-alveolar pressure minus intrapleural pressure, ie, the pressure difference across the lung wall.
- **Negative pressure:** When the intra-alveolar pressure is lower than the ambient pressure at the airway opening, air flows down the pressure gradient into the lungs.
- **Positive pressure:** When the intra-alveolar pressure is greater than the airway opening pressure, air flows down the pressure gradient out of the lungs.

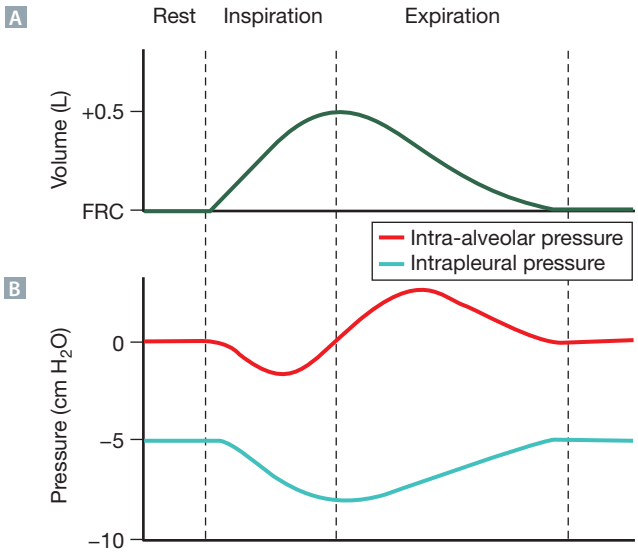


FIGURE 10-23. Spontaneous respiration. A Volume of the lung relative to functional residual capacity (FRC) during spontaneous respiration. B Intrapleural (blue) and intra-alveolar (red) pressures during spontaneous respiration.

At Rest

At rest, when the gas volume in the lungs is equal to FRC, the pressures created by the lungs (inward recoil) and the chest wall (outward recoil) are equal and opposite (Figure 10-22). The lungs create positive pressure because they tend to collapse due to their elasticity. At the same time, the chest wall generates negative pressure because the ribcage and the rest of the thoracic wall to which the lungs are affixed resist deformation from their natural shape. These opposing forces cancel out, establishing a distending pressure (alveolar pressure) of 0 (Figure 10-23). The respiratory muscles are not involved in this process.

Intrapleural pressure = –5 cm H_2O
Intra-alveolar pressure = 0 cm H_2O

In **emphysema,** the lungs have a decreased tendency to collapse due to a loss of elasticity (compliance ↑). As a result, the lung–chest wall system recalibrates to a new, **higher FRC** at which the forces balance. This is why patients with emphysema are **barrel-chested.**

In **lung fibrosis,** the lungs have an increased tendency to collapse (compliance ↓), so the system equilibrates to a new, **lower FRC** at which the forces balance.

During Inspiration

The muscles of inspiration contract, generating negative pressure. The intra-alveolar pressure is therefore negative. However, inspiration does not continue indefinitely because the pressure exerted by the chest wall becomes positive as it expands beyond its natural shape, thus opposing the muscles of inspiration. Approximate values for a young, healthy subject are given below; note that there can be significant variation based on age, weight, or health:

Intrapleural pressure: Decreases from –5 to –8 cm H_2O
Intra-alveolar pressure < 0 cm H_2O, so air flows into the lungs

At Maximum Inspiration

At TLC, the positive inward pressures due to the distension of the chest wall and lungs have increased to the point where they exactly cancel out the negative outward pressure generated by the muscles of inspiration. Thus, the lungs are held at full capacity, neither expanding nor contracting.

Intrapleural pressure = –8 cm H_2O
Intra-alveolar pressure = 0 cm H_2O, so no air flows

During Expiration

The muscles of inspiration relax, removing their strong negative outward force and allowing the intra-alveolar pressure to become positive. This allows the lung–chest wall complex to return to its equilibrium at FRC.

Intrapleural pressure: Increases from –8 to –5 cm H_2O (may increase into positive range, depending on the patient)
Intra-alveolar pressure > 0 cm H_2O, so air flows out of the lungs

At Maximum Expiration

At RV, there is still some gas left in the lungs. That is, **we can never exhale enough to fully collapse the lungs.** At RV, the chest wall exerts such a strong negative outward pressure (due to its tendency to recoil outward to its resting shape) that the expiratory muscles are unable to create enough positive inward pressure to exhale any further.

Intrapleural pressure = –5 cm H_2O
Intra-alveolar pressure = 0 cm H_2O, so no air flows

Mechanical Ventilation

Mechanical ventilators allow physicians to manipulate the pressures and volumes that govern inspiration and expiration. A detailed explanation of mechanical ventilation is beyond the scope of this text, but a brief discussion of the most common modes of mechanical ventilation and how they work may be useful.

Positive end-expiratory pressure (PEEP): With this setting, airway pressure at the end of expiration does not fall to 0, but is instead maintained at a fixed value (eg, 10 cm H_2O). This helps to maintain airway patency during expiration and is particularly useful in hypoxemic states such as acute respiratory distress syndrome (ARDS). In a patient who is initiating all breaths, the equivalent of PEEP is continuous positive airway pressure (CPAP), which may be applied by mask or endotracheal tube in order to maintain airway patency. CPAP is commonly used in the treatment of obstructive sleep apnea.

CLINICAL CORRELATION

Obstructive sleep apnea occurs when excess body weight, extra pharyngeal tissue, or abnormal anatomy (eg, tonsillar hypertrophy or short mandible) blocks the upper airway passages when the patient is sleeping. This obstruction causes periods of hypoventilation and hypoxia, resulting in nocturnal awakenings, poor sleep, and daytime somnolence. Treatment includes continuous positive airway pressure (CPAP), which is the equivalent in spontaneous breathers of PEEP.

Airways

Flow

Airflow is proportional to the pressure difference between the mouth (or nose) and the alveoli and is inversely proportional to the resistance of the airway.

$$\dot{V} = \Delta P/R$$

where $\dot{V}$ is the ventilation rate (airflow); ΔP is the pressure gradient; and R is resistance.

Note that the dot over the $\dot{V}$ in the ventilation rate indicates that it is the change in volume with respect to time (ie, dV/dt).

Resistance

Governed by Poiseuille's law:

$$R = (8\eta l)/(\pi r^4)$$

where R is resistance, η is the viscosity of the gas, l is airway length, and r is airway radius.

Since airway radius is the major determinant of resistance (r^4), the major source of airway resistance is the **medium-sized bronchi** (the smaller bronchi have greater numbers arranged in parallel, thus offering less net resistance than the medium-sized bronchi).

CLINICAL CORRELATION

For a mechanically ventilated patient, hypoxia (low O_2) can be corrected by increasing FiO_2 or PEEP, whereas hypercarbia (high CO_2) can be corrected by increasing minute ventilation or tidal volume.

CLINICAL CORRELATION

Patients with ARDS are routinely treated with PEEP at low tidal volumes to protect the lungs. CO_2 is lowered by increasing the respiratory rate rather than the tidal volume.

Factors That Influence Pulmonary Resistance

- Contraction of bronchial smooth muscle:
  - **Sympathetic stimulation:** Airways dilate via β_2-adrenergic receptors, thus decreasing resistance. **Albuterol** is a common β_2 agonist and is used in an inhaled form by patients with asthma or chronic obstructive pulmonary disease (COPD).
  - **Parasympathetic stimulation:** Airways constrict via M_3-cholinergic receptors, thus increasing resistance. This is seen in **asthma** as part of the immune response. **Ipratropium** is a common anticholinergic drug used to counter this parasympathetic bronchoconstriction in asthma or COPD.
- **Secretions:** Increased and/or thickened airway secretions, a hallmark of chronic bronchitis and cystic fibrosis (CF), lead to increased airway obstruction and resistance.

- **Lung volumes:**
  - **High lung volumes:** The lung tissue surrounding and attached to the airways expands, pulling the airways open, so resistance is decreased.
  - **Low lung volumes:** When the lung volume is low, there is less traction and increased resistance. Airways are more prone to collapse.

BLOOD GASES

Oxygen Transport

Hemoglobin

- **Structure:** Hemoglobin is a globular protein composed of four subunits (two α-family chains and two β-family chains). Each subunit contains a **heme moiety,** which is a porphyrin ring containing a single iron atom at its core. The iron in hemoglobin is in the **ferrous** (Fe^{2+}) state and can bind O_2. If the iron is in the **ferric** (Fe^{3+}) state, it is called **methemoglobin** and **is unable to bind O_2.** Hemoglobin can exist in two forms: **taut,** which has low affinity for O_2, and **relaxed,** which has high affinity for O_2.
- **O_2 saturation (Spo_2):** The percentage of total oxygen-binding sites on hemoglobin that are actually occupied by oxygen, also called the saturation of peripheral oxygen.
- **O_2 content:** The total amount of O_2 in the blood, both dissolved and bound to hemoglobin. Measured in mL of O_2 per deciliter of blood. Depends on hemoglobin concentration, partial pressure of O_2 (Po_2), and the 50% hemoglobin capacity (P_{50}). Calculated by the equation:
  - O_2 content = O_2 bound to hemoglobin + O_2 dissolved in blood
  - O_2 content (mL/dL blood) = (1.34 mL O_2/dL blood × [Hemoglobin] × **Spo_2**) + (0.0031 mL/mm Hg O_2 × Pao_2)
  - Using typical values of hemoglobin = 14 g/dL, Spo_2 = 1.00 (100%), and partial arterial pressure of oxygen (Pao_2) = 100 mm Hg, one finds that the vast majority (98.5%) of oxygen in the blood is bound to hemoglobin.
- **O_2 capacity:** The maximum amount of O_2 that can be bound to hemoglobin (in mL/dL blood), computed as 1.34 mL O_2/dL blood × [Hemoglobin]. This is approximately equal to the O_2 content of blood at 100% saturation.

Oxygen-Hemoglobin Dissociation Curve

The oxygen-hemoglobin dissociation curve describes how the oxygen saturation of hemoglobin varies with the Po_2 in the blood (Figure 10-24). Its sigmoidal shape reflects positive cooperativity among the four subunits, such that the more oxygen molecules that are bound, the easier it is for an additional oxygen molecule to bind. Factors that decrease the affinity of hemoglobin for oxygen cause the curve to shift right, leading to greater oxygen unloading. On the other hand, a left shift causes more oxygen to become bound in the blood.

- Increases in Pco_2, altitude, 2,3-bisphosphoglycerate (2,3-BPG), or temperature, or a decrease in pH, will cause a rightward shift of the curve.
- Decreases in Pco_2, altitude, 2,3-diphosphoglycerate, or temperature, or an increase in pH, will cause a leftward shift of the curve.
- During exercise, Pco_2 and temperature rise, and pH falls in the active muscle tissue. This promotes a right shift and greater O_2 unloading to the tissues. This is known as the Bohr effect.
- At high altitudes, 2,3-DPG synthesis is increased, facilitating O_2 unloading.
- Fetal hemoglobin ($\alpha_2\gamma_2$) does not bind 2,3-DPG as strongly as adult hemoglobin ($\alpha_2\beta_2$), shifting the curve to the left. This helps the fetus obtain O_2 from the mother's RBCs.

KEY FACT

Fe_2 binds O_2.

MNEMONIC

Hemoglobin:
Taut in **T**issues, **R**elaxed in **R**espiratory tract.

KEY FACT

Methemoglobinemia may result from treatment with nitrites and is thus sometimes induced when amyl nitrite or sodium nitrite is given to treat cyanide poisoning. Methemoglobinemia is treated with **methylene blue,** which reduces the ferric iron reducing agent that converts ferric iron (Fe^{3+}) in methemoglobin to ferrous iron (Fe^{2+}). Remember that only reduced Fe can bind O_2.

MNEMONIC

Causes of a right-shifted hemoglobin dissociation curve—
BAT ACES
BPG (2,3-BPG)
Altitude
Temperature
Acid
CO_2
Exercise
Sickle cell

MNEMONIC

A rule of thumb for translating between Po_2 and Spo_2 is the 40–50–60: 70–80–90 rule, where Po_2s of 40, 50, and 60 mm Hg translate to 70%, 80%, and 90% saturation, respectively.

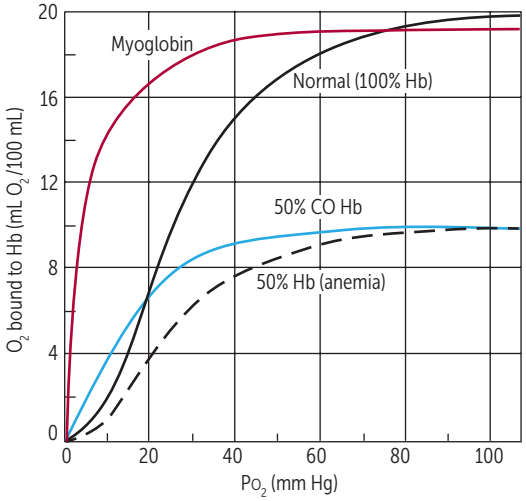


FIGURE 10-24. Oxygen dissociation curves. Normal hemoglobin vs carbon monoxide poisoning (blue line), anemia (dashed line), and myoglobin (red line). Graph illustrates O_2 bound to hemoglobin relative to Po_2. CO, carbon monoxide; Hb, hemoglobin; Po_2, partial pressure of oxygen.

There are several important regions of the oxygen-hemoglobin dissociation curve worth remembering:

- At a **Po_2 of > 70 mm Hg,** hemoglobin is essentially 100% saturated. **Arterial blood** has a Po_2 of around 100 mm Hg.
- At a **Po_2 of 40 mm Hg,** hemoglobin is 70% saturated. **Venous blood** is at this level of oxygenation.
- At a **Po_2 of 25 mm Hg,** hemoglobin is 50% saturated. This is the **P_{50}** (50% saturation point) of hemoglobin.

Carbon Dioxide Transport

CO_2 is produced in the body's tissues and carried to the lungs via the venous blood. It is transported in three forms:

- **HCO_3^- (bicarbonate),** formed by the combination of CO_2 and H_2O by the enzyme **carbonic anhydrase,** is the **major mode** of carbon dioxide transportation, making up 70% of CO_2 in the blood. This reaction reverses in the lungs, where HCO_3^- enters RBCs in exchange for Cl^-, and CO_2 is reformed by carbonic anhydrase and expired (Figure 10-25).
- Dissolved CO_2, 5–9% which is free in the bloodstream.
- Carbaminohemoglobin, 21–25% which is CO_2 bound to hemoglobin. In the lungs, the oxygenation of hemoglobin promotes the dissociation of CO_2 from hemoglobin. This is known as the **Haldane effect** (Figure 10-26).

Respiratory Acid-Base Disturbances

The lungs, kidneys, and molecular buffers are the major determinants of acid-base balance within the body. The kidneys can eliminate and reabsorb both base (HCO_3^-) and acid (H^+ and fixed [nonvolatile] acids) in the urine, whereas the lungs remove volatile acid from the circulation in the form of exhaled CO_2. Molecular buffers are involved with short-term compensation for acidosis.

- **Respiratory acidosis** (Table 10-7): Caused by a **decrease in alveolar ventilation** (hypoventilation) and retention of CO_2 **($Paco_2$ > 40 mm Hg),** leading to an increase in blood [H^+] and [HCO_3^-].
  - **Renal compensation:** Increased excretion of H^+ and NH_4^+ and increased reabsorption of HCO_3^-.

MNEMONIC

Factors that cause a right shift of the oxygen-hemoglobin dissociation curve—

CADET

↑ Pco_2
Higher **A**ltitude
↑ 2,3-**D**PG
Exercise (buildup of lactic acid and CO_2 → ↓ pH)
↑ **T**emperature

KEY FACT

Carbon monoxide (CO) binds to hemoglobin with 240 times greater affinity than O_2 does, thus creating an allosteric change in the hemoglobin that prevents the unloading of O_2 from other binding sites. This causes a left shift of the curve and results in hypoxemia in CO poisoning. Treatment includes high-flow O_2 to competitively remove the CO from hemoglobin.

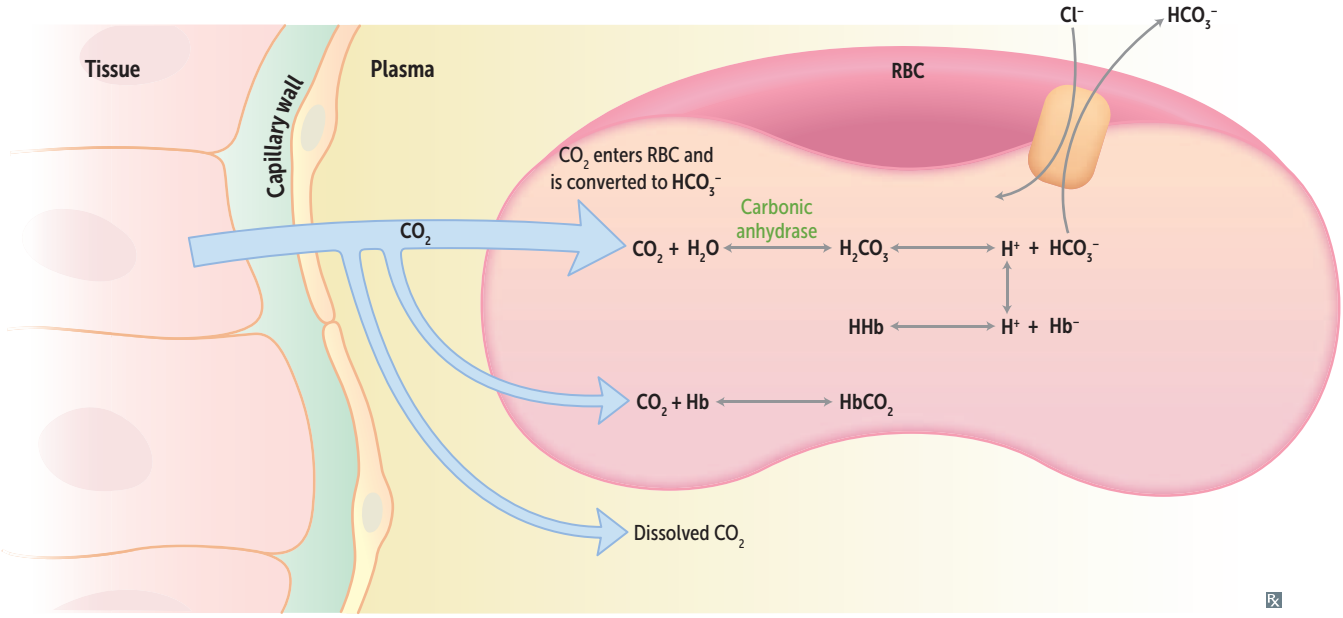


FIGURE 10-25. Carbon dioxide transport. CO_2 handling in the RBC. Hb^-, ionized hemoglobin; HHb, deionized hemoglobin.

FLASH BACK

The kidneys play a vital role in acid-base disturbances. In the case of metabolic acidosis and alkalosis, the role of the respiratory system is to try to compensate for the skewed pH. Hyperventilation helps blow off excess carbon dioxide and therefore compensates for metabolic acidosis. Hypoventilation helps to retain carbon dioxide and therefore compensates for metabolic alkalosis.

- **Acute respiratory acidosis:** Renal compensation has not yet occurred (intracellular fluid buffering only). Each 10 mm Hg increase in $Paco_2$ leads to a 1 mEq/L rise in HCO_3^- and a 0.08 decrease in pH.
- **Chronic respiratory acidosis:** Renal compensation has occurred. Each 10 mm Hg increase in $Paco_2$ leads to a 3.5 mEq/L rise in HCO_3^- and a 0.03 decrease in pH.
- Causes of respiratory acidosis include opiates, sedatives, and anesthetics (due to inhibition of the medullary respiratory center), Guillain-Barré syndrome, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) (due to weakening of respiratory muscles), airway obstruction, ARDS, and COPD (due to decreased CO_2 exchange).

- **Respiratory alkalosis** (Table 10-7): Caused by an **increase in alveolar ventilation** (hyperventilation) and a loss of CO_2 **($Paco_2$ < 40 mm Hg)**, leading to a decrease in blood $[H^+]$ and $[HCO_3^-]$.
  - **Renal compensation:** Decreased excretion of H^+ and NH_4^+, decreased reabsorption of HCO_3^-.

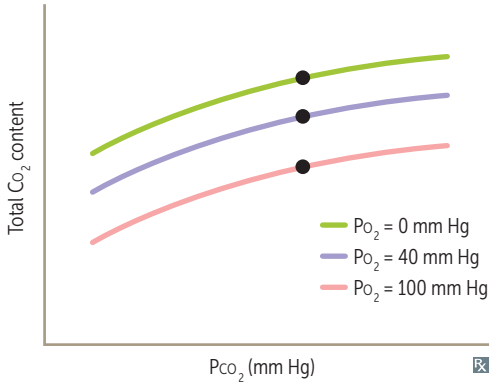


FIGURE 10-26. Haldane effect. As RBCs pass through the alveolar capillaries and the partial pressure of oxygen (Po_2) increases from 70% to almost 100%, the CO_2 dissociation curve shifts downward. This promotes the dissociation of CO_2 from the RBCs.

TABLE 10-7. Acid-Base Disturbances

	RESPIRATORY			
	ACIDOSIS		ALKALOSIS	
	CHANGE IN HCO_3^-	CHANGE IN PH	CHANGE IN HCO_3^-	CHANGE IN PH
Acute	↑ 1 mEq/L	↓ 0.08	↓ 2 mEq/L	↑ 0.08
Chronic	↑ 3.5 mEq/L	↓ 0.03	↓ 5 mEq/L	↑ 0.03

- **Acute respiratory alkalosis:** Renal compensation has not yet occurred (intracellular fluid buffering only). Each 10 mm Hg decrease in $Paco_2$ leads to a 2 mEq/L decrease in HCO_3^- and a 0.08 rise in pH.
- **Chronic respiratory alkalosis:** Renal compensation has occurred. Each 10 mm Hg decrease in $Paco_2$ leads to a 5 mEq/L decrease in HCO_3^- and a 0.03 rise in pH.
- Causes of respiratory alkalosis include pulmonary embolism (PE), high altitude (due to hypoxemia and increased ventilation rate), anxiety, pregnancy, cirrhosis, and salicylate intoxication (due to direct stimulation of the medullary respiratory center).

CLINICAL CORRELATION

Treat altitude sickness with acetazolamide, a carbonic anhydrase inhibitor that increases the renal excretion of HCO_3^-.

The lungs play a compensatory role in the cases of metabolic acidosis and alkalosis, which are discussed in greater detail in Chapter 8.

- In **metabolic acidosis,** hyperventilation occurs to blow off excess CO_2 and thus carbonic acid, although this cannot completely compensate for the acidosis.
- Conversely, in **metabolic alkalosis,** hypoventilation occurs to retain CO_2 and thus carbonic acid, although this cannot completely compensate for the alkalosis.

KEY FACT

Normal pH in the presence of abnormal HCO_3^- or CO_2 suggests a mixed disorder.

Pulmonary Circulation

Characteristics

The pulmonary vasculature has unique characteristics that set it apart from the rest of the vascular system. These properties relate directly to the physiologic function of the respiratory system (Figure 10-27).

- **Pressures** are much **lower** in the pulmonary circulation than in the systemic circulation (normal pulmonary arterial pressure = 25 mm Hg systolic and 10 mm Hg diastolic).
- **Resistance** is much **lower** than in the systemic circulation.

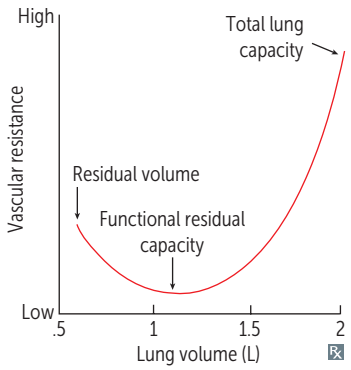


FIGURE 10-27. Lung volume and pulmonary vascular resistance (PVR). As the lung volume increases from residual volume (RV) to total lung capacity (TLC), PVR changes as shown in the graph. PVR is the sum of the resistance in all pulmonary vessels. PVR is typically lowest at functional residual capacity (FRC).

- Normal pulmonary vascular resistance (PVR) = 20–120 dynes · s · cm^{-5}. This is ~1/10 of systemic vascular resistance (SVR) (Table 10-8).
- PVR changes with lung volume. At high volumes, the **alveolar vessels** are compressed by stretched alveolar walls and contribute more to PVR. At low volumes, larger extra-alveolar pulmonary vessels are compressed due to decreased elastic traction and increased positive intrathoracic pressure, contributing to an increased PVR.
- Total PVR is at its minimum at FRC.

Distribution of Pulmonary Blood Flow

When a person is supine, blood flow is nearly uniform throughout the entire lung. When standing, however, the lungs are divided into three zones based on blood flow and ventilation as affected by gravity, with zone 1 at the apices, zone 2 in the middle, and zone 3 at the bases. Both blood flow and ventilation are increased as one moves down the lung due to gravity, but blood flow increases to a greater degree than ventilation, resulting in a mismatch between ventilation ($\dot{V}$) and perfusion ($\dot{Q}$). This is known as $\dot{V}/\dot{Q}$ mismatch (Figure 10-28).

- **Zone 1 (apices):** Ventilation exceeds perfusion.
  - Alveolar pressure > arterial pressure > venous pressure.
  - High alveolar pressures compress the capillaries and reduce blood flow.
  - $\dot{Q}$ is reduced relative to $\dot{V}$; therefore, $\dot{V}/\dot{Q}$ is increased. In extreme cases, zone 1 can approximate dead space ($\dot{Q} = 0$, so $\dot{V}/\dot{Q} = \infty$).
  - P_{O_2} is the highest and P_{CO_2} is the lowest in zone 1 due to having greater ventilation relative to blood flow; there is unspent (wasted) ventilation left over even after full oxygenation of the blood.
- **Zone 2 (middle):** Well-matched.
  - Arterial pressure > alveolar pressure > venous pressure.
  - Blood flow here is driven by the difference between arterial and alveolar pressures.
- **Zone 3 (bases):** Perfusion exceeds ventilation.
  - Arterial pressure > venous pressure > alveolar pressure.
  - Blood flow here is driven by the difference between arterial and venous pressures, as in the systemic circulation.
  - $\dot{Q}$ is increased relative to $\dot{V}$, so $\dot{V}/\dot{Q}$ is decreased. In extreme cases, zone 3 can approximate shunt ($\dot{Q} >> \dot{V}$, so $\dot{V}/\dot{Q} \rightarrow 0$).
  - P_{O_2} is the lowest and P_{CO_2} is the highest in zone 3 due to decreased gas exchange and airway closure.

CLINICAL CORRELATION

Reactivated pulmonary TB usually occurs in the lung apices due to the high $\dot{V}/\dot{Q}$ and thus high O_2 concentrations in this region of the lung.

KEY FACT

Pulmonary blood flow can be measured using radioactive isotopes. This method, called **$\dot{V}/\dot{Q}$ scanning,** can detect areas of decreased perfusion and is useful for evaluating for pulmonary embolism (PE) and assessing regional lung function. CT pulmonary angiograms can also be used to identify PEs.

TABLE 10-8. Calculating Cardiac Output, Pulmonary Vascular Resistance, and Systemic Vascular Resistance

	CALCULATION	NORMAL VALUE
CO	SV × HR	5–6 L/min
PVR	[(MPAP – MLAP)/(CO)] × 80 **Note:** Units for pressure and CO should be mm Hg and L/min, respectively. The factor of 80 converts the units to dynes • s • cm^{-5}.	20–120 dynes • s • cm^{-5}
SVR	[(MAP – MRAP)/(CO)] × 80	770–1500 dynes • s • cm^{-5}

CO, cardiac output; MAP, mean arterial pressure; MLAP, mean left atrial pressure; MPAP, mean pulmonary artery pressure; MRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

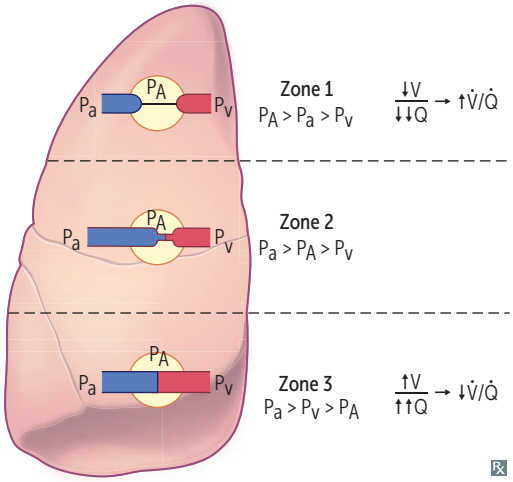


FIGURE 10-28. Degrees of ventilation and perfusion in the zones of the lung. Zone 1 (apex) has increased ventilation relative to perfusion due to the negative pleural pressures holding alveoli open and impeding blood flow. Zone 2 (mid lung) has a proportionate amount of ventilation relative to perfusion. Zone 3 (lower lung) has relatively more perfusion due to a less negative pleural pressure from the weight of the lung. P_A, alveolar pressure; P_a, arterial pressure, P_v, venous pressure.

Regulation of Pulmonary Blood Flow

- **Hypoxia:** In the lungs, hypoxia leads to **vasoconstriction.** This phenomenon serves to shunt blood to areas of better ventilation. In chronic hypoxia, pulmonary hypertension can result from prolonged vasoconstriction. This is in contrast to other organs, in which hypoxia leads to vasodilation. Hypoxic vasoconstriction allows blood to be redirected away from poorly ventilated regions and toward well-ventilated areas.
- Several other factors also affect pulmonary blood flow (Table 10-9).

Hypoxemia

Hypoxemia is defined as a below-normal O_2 content in the arterial blood (as opposed to **hypoxia,** which means low O_2 in tissues), usually indicated by a reduced Pao_2. In a normal individual, the blood leaving the lungs should have an O_2 tension (Pao_2) approximately equal to the O_2 tension within the alveoli (PAo_2).

$$PAo_2 = FIo_2(PB - PH_2O) - (PaCo_2/R)$$

where FIo_2 is the fraction of inspired air that is O_2 (0.21 on room air, 1.00 for pure oxygen); PB is the barometric pressure (760 torr at sea level, where 1 torr = 1 mm Hg = 133 Pa); PH_2O is the vapor pressure of H_2O in the alveoli (47 torr at 37°C); $PaCo_2$ is the arterial CO_2 tension; and *R* is the respiratory quotient.

The respiratory quotient, *R*, which represents the number of molecules of CO_2 produced for every molecule of O_2 consumed, depends on diet. *R* = 0.7 for fat metabolism, 0.8 for protein metabolism, and 1.0 for carbohydrate metabolism. The typical Western diet is assumed to have an *R* of about 0.8.

CLINICAL CORRELATION

Bosentan, a nonselective competitive antagonist of endothelin-1 at the ET-A and ET-B receptors on vascular endothelium, lowers PVR by relaxing blood vessels and is one of the pharmacologic treatments for primary pulmonary hypertension.

TABLE 10-9. Factors Regulating Pulmonary Blood Flow and Pulmonary Vascular Resistance

	LOW O_2	LOW PH	HISTAMINE	PROSTAGLANDINS	NITRIC OXIDE	ENDOTHELIN	SYMPATHETIC TONE	PARASYMPATHETIC TONE
Vasoconstriction	X	X				X	X	
Vasodilation			X	X	X			X

KEY FACT

In the fetus, PVR is very high due to hypoxic vasoconstriction. This allows blood to be diverted away from the developing lungs via the ductus arteriosus and foramen ovale. When the infant is born and begins to breathe, PVR decreases due to the action of vasodilators while the ductus arteriosus closes up. This results in increased blood flow to the lungs.

For a patient breathing room air, this can be simplified to:

$$P_{AO_2} = 150 - 1.25(P_{aCO_2})$$

Once P_{AO_2} is calculated, the actual P_{aO_2} can be measured via arterial blood gas testing. The difference between the P_{AO_2} and P_{aO_2} is the **alveolar-arterial O_2 gradient** (A-a gradient, or $AaDO_2$), and should be < **15 torr,** although this value can increase with normal aging. A good rule of thumb is that the gradient should be less than the patient's age/4 + 4. For example, a 60-year-old should have an A-a gradient no greater than 19 torr. The A-a gradient is important for determining the cause(s) of hypoxemia, discussed in greater detail later and diagrammed in Figure 10-29. In particular, the A-a gradient is increased in the case of shunt, $\dot{V}/\dot{Q}$ mismatch, and diffusion impairment, but it is unchanged in the case of pure hypoventilation or low F_{IO_2}.

Etiology

There are five main causes of hypoxemia (Figure 10-29). They include:

1. **Hypoventilation:** Hypoventilation is relatively common in lung disease. It is characterized by a reduced P_{aO_2} and an **increased P_{aCO_2}.** Since alveolar ventilation is also reduced, there is **no increase in A-a gradient.**
2. **Decreased inspired O_2:** This occurs most commonly at high altitudes, where the P_B is decreased. This causes a reduction in P_{aO_2} due to the decrease in P_{AO_2}. Thus, there is **no increase in A-a gradient.** There are several physiologic adaptations to high altitude (Table 10-10).
3. **Poor gas exchange (diffusion impairment):** Diffusion impairment occurs due to a failure of P_{O_2} in the pulmonary capillary blood to equilibrate with alveolar gas. This is a rare cause of hypoxemia because most abnormalities in diffusion are too mild to cause hypoxemia unless the patient is exercising. The **A-a gradient is increased.**
   - O_2 is normally a **perfusion-limited** gas. This means that O_2 equilibrates early along the length of the pulmonary capillary (within the first third). This leaves a lot of room for compensation in disease states; thus, a failure in O_2 diffusion is a very rare cause of hypoxemia.
   - O_2 can become a **diffusion-limited** gas under certain circumstances, in which case it does not equilibrate by the end of the pulmonary capillary, resulting in the maintenance of a partial pressure gradient between the alveolus and the capillary. This can occur in **strenuous exercise** (due to increased cardiac output), **pulmonary fibrosis** and ARDS (due to alveolar membrane thickening), and **emphysema** (due to decreased surface area for gas diffusion).
   - Diffusion capacity can be measured using carbon monoxide, resulting in a D_{LCO} (diffusion capacity of the lung for carbon monoxide) value. CO is used in place

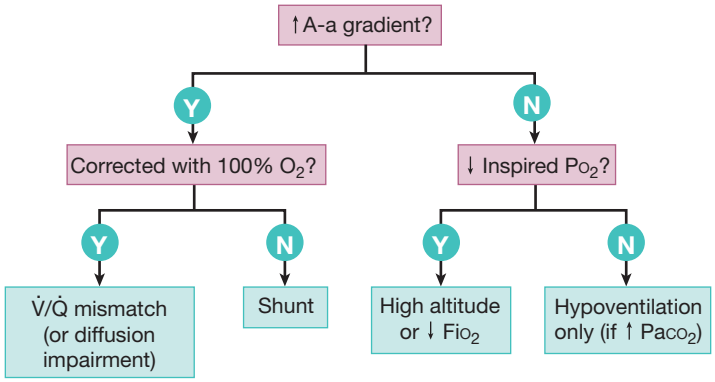


FIGURE 10-29. Hypoxemia decision tree. The different causes of hypoxemia can be distinguished as shown. Note, however, that combinations of different mechanisms are common.

TABLE 10-10. Response to High Altitude

PARAMETER	RESPONSE
Pa_{O_2}	Decreased (hypoxemia)
P_{AO_2}	Decreased (due to ↓ barometric pressure)
Ventilation rate	Increased (hyperventilation due to hypoxemia)
Arterial pH	Increased (respiratory alkalosis)
Hemoglobin concentration	Increased (polycythemia)
2,3-DPG concentration	Increased
Hemoglobin-O_2 curve	Right shift
PVR	Increased (hypoxic vasoconstriction)

2,3-DPG, 2-3-diphosphoglycerate; P_{AO_2}, partial alveolar pressure of oxygen; Pa_{O_2}, partial arterial pressure of oxygen; PVR, pulmonary vascular resistance.

of oxygen because of the very high affinity of hemoglobin for CO. D_{LCO} is a surrogate for the surface area available for gas exchange.

- D_{LCO} is decreased when useful surface area for gas exchange is lost, such as in emphysema, interstitial lung disease, and pulmonary vascular disease.
- D_{LCO} may be increased in the presence of intraparenchymal hemorrhage, increased blood volume due to CHF, or polycythemia (increased hematocrit).

4. **$\dot{V}/\dot{Q}$ mismatch:** The $\dot{V}/\dot{Q}$ ratio is the ratio of ventilation to pulmonary blood flow. Under normal circumstances, $\dot{V}/\dot{Q} \approx 0.8$, although it varies with position in the lungs (see previous discussion of lung zones). When the $\dot{V}/\dot{Q}$ ratio is altered, hypoxemia can result. There is also an **increased A-a gradient.** Deviation of the $\dot{V}/\dot{Q}$ ratio from normal indicates the presence of a shunt (Figure 10-30).
   - **$\dot{V}/\dot{Q}$ mismatch in airway obstruction:** If the airway is completely blocked and blood flow remains, then $\dot{V} = 0$, so $\dot{V}/\dot{Q} = 0$, and there is a **shunt.** Since there is no gas exchange, the values of P_{O_2} and P_{CO_2} for pulmonary capillary blood approach the values of mixed venous blood (Pa_{O_2} = 40 mm Hg, Pa_{CO_2} = 46 mm Hg).
   - **$\dot{V}/\dot{Q}$ mismatch in pulmonary embolism:** If blood flow is completely blocked, then $\dot{Q} = 0$, so $\dot{V}/\dot{Q} = \infty$ and there is **complete dead space.** This results in increased CO_2 retention, although this is rarely seen since patients with PE often hyperventilate and may even become hypocapnic as a result. Local bron-

KEY FACT

$\dot{V}/\dot{Q}$ of 0 suggests airway obstruction (shunt); 100% O_2 does not improve PO_2.
$\dot{V}/\dot{Q}$ of ∞ suggests a blood flow obstruction (physiologic dead space); 100% O_2 improves PO_2.

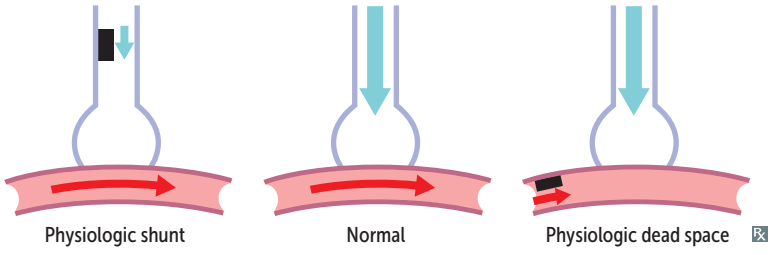


FIGURE 10-30. Physiologic dead space. Under normal circumstances, both ventilation and perfusion are adequate. A physiologic dead space is created when ventilation is greater than perfusion. This may be caused by pulmonary embolism, pulmonary arteritis, necrosis, or fibrosis. A physiologic shunt is created when perfusion is greater than ventilation. In this situation, blood passes through pulmonary vasculature without optimal gas exchange. This may be caused by asthma, COPD, atelectasis, or diseases of the chest wall.

QUESTION

A man at sea level suffers from dyspnea. His ABG shows PaO_2 of 70 mm Hg and Pa_{CO_2} of 35 mm Hg. What is the equation for A-a gradient and P_{AO_2}?

chospasm due to the PE can also contribute to hypoxemia. If the blood flow is low but not zero, the values of P_{O_2} and P_{CO_2} for pulmonary capillary blood approach that of inspired air (P_{AO_2} = 150 mm Hg, P_{ACO_2} = 0 mm Hg).
   - In most cases of $\dot{V}/\dot{Q}$ mismatch, there is neither true shunt nor complete dead space, but simply an **abnormal $\dot{V}/\dot{Q}$ ratio.** Blood from well-ventilated areas is already saturated at baseline, so no amount of effort from well-ventilated areas can compensate for the desaturated blood emerging from areas that are poorly ventilated. Giving the patient **100% O_2 increases the patient's P_{AO_2}.**
5. **Shunt:** As mentioned previously, shunt is an extreme case of $\dot{V}/\dot{Q}$ mismatch that occurs when some blood reaches the systemic circulation without being oxygenated, reducing P_{AO_2}. Since the P_{AO_2} is unaffected, the **A-a gradient is increased.**
   - **Right-to-left shunt:** Occurs when blood from the right side of the heart enters the systemic circulation without passing through the lungs. It is seen in **tetralogy of Fallot** (and other congenital heart conditions causing right-to-left shunts) and always causes a reduction in P_{AO_2}.
   - **Left-to-right shunt:** More common than right-to-left shunt because pressures are higher on the left side of the heart. It is seen with several congenital abnormalities, including patent ductus arteriosus (PDA), atrial septal defect, and ventricular septal defect, as well as with traumatic injury. Left-to-right shunts **do not decrease P_{AO_2}** since oxygenated blood is returning to the right side of the heart, raising the P_{O_2}.
   - True shunt can be differentiated from $\dot{V}/\dot{Q}$ mismatch by giving the hypoxemic patient 100% O_2. This increases P_{AO_2} in the case of $\dot{V}/\dot{Q}$ mismatch but not in the case of a shunt, since in the latter, the blood never communicates with the alveolar gas, regardless of its composition. A patient without a shunt should achieve a P_{AO_2} of at least 400 torr on 100% oxygen.

CLINICAL CORRELATION

Over time, left-to-right shunts can cause pressures on the **right side** of the heart to become greater than those on the **left.** This leads to a reversal of the shunt to right-to-left, causing hypoxemia. This is called **Eisenmenger syndrome.**

Hypercapnia

Alveolar ventilation is the main determinant of P_{ACO_2}. Hypercapnia occurs when alveolar ventilation is reduced, which can happen in a number of ways:

- Decreased total minute ventilation without a change in the V_D/V_T ratio.
- Constant minute ventilation with increasing V_D/V_T. This can occur with decreased V_T (eg, a greater percentage of the V_T is taken up by dead space) and increased respiratory rate.
- $\dot{V}/\dot{Q}$ mismatch. Well-perfused areas may be underventilated, whereas underperfused areas may be overventilated. When a large amount of ventilation is "wasted" on underperfused sections of lung, the effect is similar to increasing the dead space: less air is available to exchange gases with the blood, and CO_2 levels in the blood increase.

KEY FACT

CO_2 is the most potent cerebral vasodilator. Increased CO_2 decreases cerebral vascular resistance, resulting in increased perfusion and intracranial pressure.

The response of the body to hypercapnia is often to increase alveolar ventilation by hyperventilating and blowing off more CO_2. Thus, CO_2 retention may not occur even if the preceding criteria are met as long as the body is able to compensate.

Control of Respiration

Central Control of Respiration

- **Medullary respiratory center:** Located in the reticular formation. Damage to or suppression of this region due to stroke, opioid overdose, or other causes can lead to respiratory failure and death.
   - **Dorsal respiratory group:** Responsible for **inspiration** and determines the **rhythm of breathing** (normally 12–20 breaths/minute with an I:E [inspiration-to-expiration] ratio of 1:2). The dorsal respiratory group receives sensory input from peripheral chemoreceptors and lung mechanoreceptors via the vagus and glossopharyngeal nerves. Output travels via the phrenic nerve (C3–C5) and

ANSWER

A-a gradient = 35.25, P_{AO_2} = 106.25
A-a = $P_{AO_2} - P_{aO_2}$
$P_{AO_2} = 150 - 1.25\ (P_{aCO_2})$
$P_{AO_2} = 150 - 1.25\ (35)$
$P_{AO_2} = 150 - 43.75$
$P_{AO_2} = 106.25$
A-a = 106.25 – 70 = 35.25
A-a > 15 is abnormal

the intercostal nerves (T1–T11) to the diaphragm and the external intercostal muscles, respectively.
    - **Ventral respiratory group:** Responsible for **forced expiration;** not active during ordinary passive expiration. Also involved with increased inspiratory effort (eg, during exercise).
- **Pons:**
    - **Pneumotaxic center:** Located in the upper pons. **Inhibits inspiration,** helping to regulate inspiratory volume and rate.
    - **Apneustic center:** Located in the lower pons. **Stimulates inspiration.**
- **Cerebral cortex:** Exerts voluntary control over breathing.

Chemoreceptors

- **Central chemoreceptors in the medulla:** Respond to the pH of the cerebrospinal fluid (CSF), with decreases in pH causing hyperventilation. CO_2 from arterial blood diffuses into the CSF and combines with H_2O to form H^+ and HCO_3^-.
- **Peripheral chemoreceptors in the carotid and aortic bodies:** Increased $Paco_2$ or decreased pH or Pao_2 stimulate these chemoreceptors to increase respiratory rate. Pao_2 must reach low levels (< 60 mm Hg) before breathing is stimulated.

Other Receptors

- **Lung stretch receptors:** Mechanoreceptors located in the airway smooth muscle that are stimulated by distention of the lungs and produce reflex inspiratory time shortening and Hering-Breuer inflation and deflation reflexes. In the Hering-Breuer inflation reflex, excessive stretching of the lungs during a large inspiratory effort leads to inhibition of the dorsal respiratory group and the apneustic center to promote expiration. The deflation reflex acts during expiration to activate the inspiratory control areas.
- **Irritant receptors (nociceptors):** Located between airway epithelial cells and stimulated by noxious substances.
- **Juxtacapillary (J) receptors:** Located close to the capillaries in the alveolar walls. Increases in interstitial fluid, such as during pulmonary edema, PE, or pneumonia, stimulate these receptors, causing rapid, shallow breathing.
- **Joint and muscle receptors:** These are activated by limb movement and help to stimulate breathing early in exercise.

Pathology

Discussion of respiratory pathology will begin with an overview of physical examination findings commonly associated with respiratory dysfunction. Pathologic conditions of the upper airways (eg, nasopharynx, oropharynx, larynx) are then covered, followed by those of the lower airways (eg, tracheobronchial tree, lung parenchyma).

PATHOLOGY ON PHYSICAL EXAMINATION

The pulmonary physical examination has four components: inspection, auscultation, percussion, palpation. This section provides an overview of each component in the context of the USMLE Step 1. The technical aspects of the physical examination are beyond the scope of this text.

KEY FACT

Suspect foreign body aspiration in a child who presents with acute onset wheezing.

Inspection

Signs of respiratory distress include dyspnea (labored breathing), tachypnea (respiratory rate > 20 breaths/min), cyanosis, grunting, nasal flaring, retractions, and using accessory muscles of respiration. Retractions refer to the inward "pulling" of muscles during

inspiration and are commonly seen in the intercostal, subcostal, suprasternal, and abdominal areas. Accessory muscles refer to the muscles primarily involved in forced breathing rather than unlabored diaphragmatic breathing. Increased work of breathing not in the context of exercise or physical exertion is concerning.

Hyperinflated lungs can be a sign of COPD, in particular the "**barrel chest**" seen in emphysema.

Auscultation

On a normal physical examination, breath sounds can be heard differently depending on the auscultated region. Physiologic breath sounds can be described as tracheal (auscultated over the trachea), bronchial (over the manubrium), vesicular (over most of the lung), and bronchovesicular (between the scapulae and in the first and second intercostal spaces anteriorly). Although physiologic breath sounds are usually not directly tested on board exams, it is important to be familiar with the terminology, as it does show up in question stems. On the other hand, adventitious (pathologic) breath sounds are high yield for exams and are described in Table 10-11.

Egophony describes modified voice transmission on lung auscultation. It is classically detected by having the patient produce and hold an "E" sound. In cases of egophony, transmission will be such that the examiner hears an "A" sound through the stethoscope. This finding is highly specific for lung consolidation (ie, lobar pneumonia).

CLINICAL CORRELATION

To become more familiar with percussion sounds, you can generate different tones by percussing over certain areas:

- Flatness—thigh
- Dullness—liver
- Resonance—normal lung
- Tympany—puffed out cheek

Percussion

Lung percussion provides the examiner with information regarding the nature of the underlying tissue (ie, air-filled, fluid-filled, solid). In general, percussion over solid or fluid-filled cavities tends to generate duller tones, whereas percussion over air-filled cavities produces more resonant or "drum-like" tones. In order of increasing resonance, the five tones generated by percussion are flatness, dullness, resonance, hyperresonance, and tympany (Table 10-12).

TABLE 10-11. Adventitious Lung Sounds

SOUND	DESCRIPTION	COMMON ETIOLOGIES
Crackles (rales)	Often equated to the sound of rubbing strands of hair between the fingers or the sound produced by velcro. Due to fluid/consolidation within the lung parenchyma **(wet crackles)** or pulmonary fibrosis **(dry crackles).**	Wet crackles: pneumonia, pulmonary edema (eg, congestive heart failure) Dry crackles: pulmonary fibrosis
Wheezes	Whistling sound. Can be heard during inspiration or expiration. Caused by air passing through **narrowed airways.**	Obstructive diseases: asthma, chronic obstructive pulmonary disease (COPD), bronchitis, foreign body aspiration (FBA)
Rhonchi	Low-pitched **"snoring"** sound. Suggests secretions in large airways.	Asthma, COPD, bronchitis
Stridor	Similar to a wheeze, but louder (often heard without auscultation) and almost entirely inspiratory. High pitch, best heard over trachea, **loudest in the neck.** Indicates partial obstruction of **laryngeal or trachea;** often a medical emergency.	Laryngotracheitis (croup), FBA
Pleural rub	**Scratching** sound when **inflamed parietal and visceral pleura** rub against one another during respiration. Usually heard during both inspiration and expiration. Often localized to a small area of the chest wall.	Connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis) Infections (viral, bacterial, fungal)

TABLE 10-12. Lung Percussion Findings

SOUND	DESCRIPTION	COMMON ETIOLOGIES
Dullness, flatness	**Fluid** in pleural cavity or lung parenchyma	Pleural effusion, lobar pneumonia
Resonance	Normal lung finding	Normal lung
Hyperresonance, tympany	**Excess air** in pleural cavity or lung parenchyma	Emphysema, pneumothorax

Palpation

The chest wall can be palpated to check for symmetrical chest wall expansion, tenderness, crepitus, as well as tactile fremitus. The patient's neck can also be palpated to check for tracheal deviation. Refer to Table 10-13 for more details.

NASOPHARYNX

Rhinosinusitis

Inflammation of the paranasal sinuses. The paranasal sinuses refer to the hollow, air-filled cavities surrounding the nose, which are lined with mucus and drain into the nasal cavity. They serve to humidify inspired air. The four groups of paranasal sinuses are the frontal, sphenoid, ethmoid, and maxillary sinuses, illustrated in Figure 10-31.

When sinus drainage into the nasal cavity becomes obstructed (typically by mucus), the sinuses can become infected. The vast majority of infectious rhinosinusitis is caused by viral upper respiratory tract infections (URIs). In certain cases, viral URIs can be superimposed by bacterial infections, with the most common organisms being *Streptococcus pneumoniae* (40%), *Haemophilus influenzae* (35%), and *Moraxella catarrhalis* (5%). The widespread use of conjugated pneumococcal vaccination in children is changing the incidence rate of the major pathogens. The percentage of bacterial sinusitis due to *S pneumoniae* is decreasing, while the number of cases caused by nontypeable

TABLE 10-13. Lung Palpation Findings

FEATURE	DESCRIPTION	COMMON ETIOLOGIES
Chest wall expansion	Assessed by placing your hands on each side of the patient's back with thumbs pointed toward the spine and fingers wrapped around each hemithorax. Have the patient take a deep breath and feel for equal movement of your hands away from the midline as the chest expands.	**Asymmetrical expansion:** hemidiaphragmatic paralysis, large pleural effusion, pneumothorax
Tenderness		Trauma, costochondritis
Crepitus	Crackles sensation or "rice krispies" felt under the skin. Indicative of **subcutaneous air.**	Pneumothorax, pneumomediastinum
Tactile fremitus	Vibrations palpated as the patient vocalizes. Detected by placing the ulnar surface of your hands just medial to each of the patient's scapulae and having him/her vocalize.	**Decreased tactile fremitus:** nonspecific (eg, chronic obstructive pulmonary disease, pleural effusion, pneumothorax, atelectasis, thick chest wall) **Increased tactile fremitus:** lobar pneumonia
Tracheal positioning	Palpated along the patient's neck. Tracheal deviation can be ipsilateral or contralateral to the affected lung; can also be confirmed on chest x-ray.	**Ipsilateral deviation:** atelectasis, spontaneous (simple) pneumothorax **Contralateral deviation:** pneumothorax, large pleural effusion

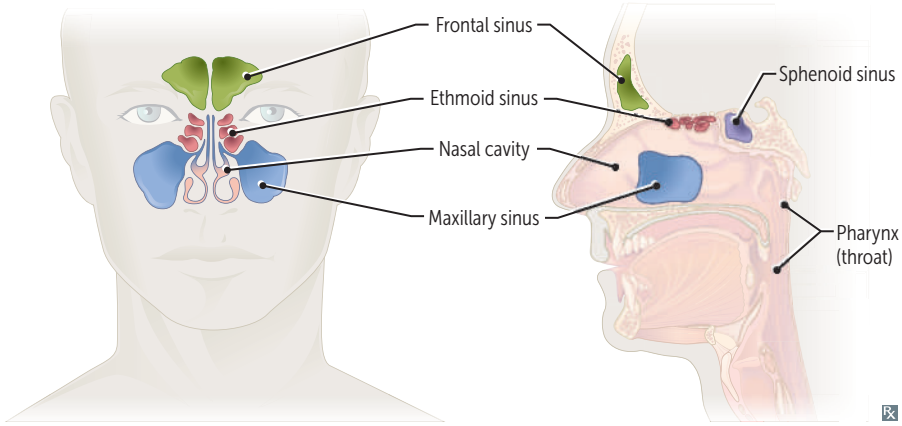


FIGURE 10-31. Paranasal sinuses

H influenzae is increasing. If indicated, empiric treatment with antibiotics is generally directed toward these agents.

Presentation

- Sinus inflammation presents with tenderness to palpation, a sensation of "fullness" in the affected paranasal regions (may mimic toothache), and, rarely, earache. These symptoms are often associated with viral URI symptoms (eg, rhinorrhea, nonproductive cough).
- When rhinosinusitis is superimposed by bacterial infections, patients present with fever and purulent nasal discharge, in addition to their pre-existing symptoms. Bacterial infections can also be suspected when viral URI symptoms persist or worsen after 1–2 weeks. Antibiotics are generally not indicated for sinusitis, unless symptoms have persisted longer than 10 days, although exceptions exist.

Diagnosis

- Primarily clinical suspicion based on patient history and physical examination.
- CT scan (coronal view) can show air-fluid levels (Figure 10-32). CT is the imaging method of choice but is rarely clinically indicated in uncomplicated sinusitis.
- Nasal swabs for culture are not reliable and almost never indicated.

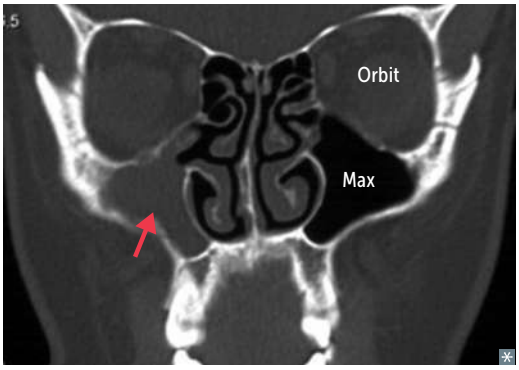


FIGURE 10-32. Rhinosinusitis. Coronal CT of sinus showing maxillary sinusitis (arrow).

Treatment

- Rhinosinusitis due to viral URI is typically self-limiting.
- If complicated by bacterial infections, antibiotics are indicated.
- Amoxicillin-clavulanate is first-line pharmacologic treatment; use doxycycline, ciprofloxacin, or moxifloxacin if patient is allergic to penicillin.

Epistaxis

Epistaxis is a nose bleed; the nasopharynx receives its blood supply from four arteries listed below (origins in parentheses) and illustrated in Figure 10-33:

- Anterior ethmoidal arteries (ophthalmic artery)
- Septal branch of the superior labial artery (facial artery)
- Greater palatine artery (maxillary artery)
- Nasopalatine branch of the sphenopalatine artery (maxillary artery)

The terminal branches of these arteries form an anastomotic network in the anterior segment of the nasopharynx called **Kiesselbach plexus.** Epistaxis most commonly arises from vascular damage within this plexus. Although less common, epistaxis arising from the posterior segment of the nasopharynx (sphenopalatine artery) can be life threatening. If a board question describes a patient who "picks their nose" and presents with persistent large-volume epistaxis, and no other localizing information is given, Kiesselbach plexus or sphenopalatine artery is the likely injured vessel.

OBSTRUCTIVE LUNG DISEASES

The three major obstructive disorders are **COPD** (includes emphysema and chronic bronchitis), **asthma,** and **bronchiectasis.** These diseases are characterized by air outflow obstruction (+/– inflow obstruction) and subsequent air trapping within the lungs. Obstruction can occur from the bronchioles to the mainstem bronchi. Spirometry (pulmonary function tests [PFTs]) shows a markedly decreased FEV_1 and decreased (although possibly normal) FVC. As such, a decreased **FEV_1:FVC ratio** is the hallmark of obstructive disease. RV is increased because of air trapping. Impaired ventilation results in a decreased $\dot{V}/\dot{Q}$ ratio on ventilation-perfusion scan.

FLASH BACK

FEV_1/FVC ratio < 0.7 is characteristic of obstructive lung disease. While FEV_1/FVC is used to diagnose obstructive lung disease, FEV_1 is used to determine the severity of disease.

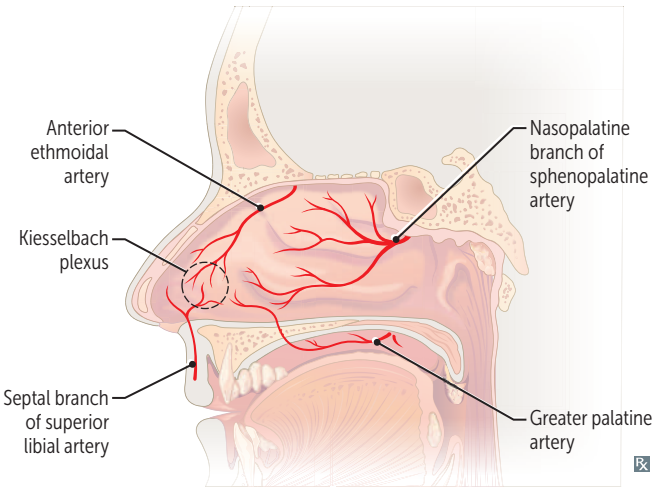


FIGURE 10-33. **Blood supply of nasopharynx.**

FLASH BACK

Lung compliance describes how much the lung volume increases for any given increase in pressure. Imagine how large you can inflate a balloon with a single breath. Now imagine how much larger you can inflate a plastic bag with a single breath. The plastic bag is more compliant than the balloon.

Emphysema

Emphysema is abnormal and permanent airway enlargement distal to the terminal bronchiole, accompanied by progressive destruction of alveolar walls and surrounding interstitium. The result is loss of elastic recoil, **increased lung compliance,** dilation of the terminal air spaces, and air trapping. The loss of elastic recoil in the lung parenchyma shifts the compliance curve of the lung upward and to the left (Figure 10-34).

Normally, alveolar neutrophils and macrophages produce **elastase** in response to air pollutants. Elastase is a proteolytic enzyme that digests elastin (the component responsible for elastic recoil of alveolar walls). **α_1-Antitrypsin** is an anti-proteolytic enzyme (protease inhibitor) that neutralizes elastase, thus maintaining the elastic properties of alveolar walls. **Emphysema develops from either excess elastase or deficient α_1-antitrypsin production.**

Two major causes of emphysema:

- **Smoking:** The most significant risk factor across the population for developing emphysema, so significant that those who do not smoke rarely develop emphysema unless an underlying genetic disorder or uncommon environmental exposure is present. Ash particles in cigarette smoke enter alveoli and attract increased numbers of neutrophils and macrophages, which produce elastase. Over time, excess elastase overwhelms local production of α_1-antitrypsin.
- **Hereditary α_1-antitrypsin deficiency:** Autosomal dominant. Accounts for 1% of emphysema cases. Emphysema develops secondary to unopposed elastase activity. Patients with α_1-antitrypsin deficiency often develop emphysema at a much younger age than smokers, often younger than 45 years.

CLINICAL CORRELATION

Air resistance decreases with inhalation and increases with exhalation. This difference in resistance explains why it takes longer to fully exhale than it does to fully inhale (normal I:E ratio is 1:2).

Air trapping develops in emphysema secondary to **loss of radial traction.** Radial traction is the outward pull on airway walls by lung interstitium. Normally, as the lungs deflate during expiration, the interstitial tissues pull the airways open (ie, increase radial traction), allowing airflow. In emphysema, radial traction is lost (ability to expire is compromised) as the interstitium is destroyed, leading to airway collapse and subsequent air trapping during expiration.

This loss of elastic recoil also explains the **prolonged expiration time** needed to completely empty the lungs. This increases the overall duration of a single respiratory cycle. Because of the ongoing need to ventilate at a high-enough rate to maintain oxygenation, patients often begin inhaling their next breath before exhaling all of the air from the previous breath. This traps nonventilated air in the lungs. As a result, the volume of trapped air increases over the course of several breaths (**dynamic hyperinflation**).

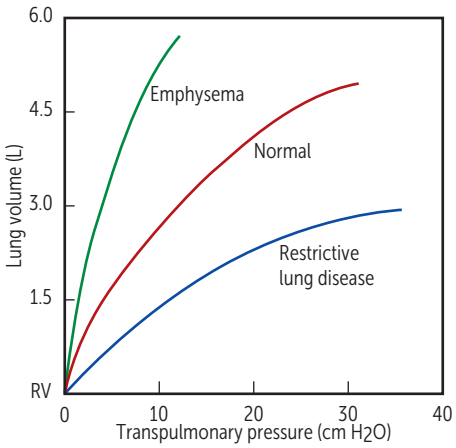


FIGURE 10-34. Lung compliance in pulmonary disease. The lung compliance curve shifts up and to the left in emphysema and down and to the right in restrictive lung disease.

Presentation

- Chronic dyspnea with or without cough. Dyspnea and desaturation are often worsened by exertion and can be exacerbated by respiratory tract infections, air pollutants, bronchospasm, or CHF.
- **"Pink puffer":** Pa_{O_2} is well preserved, so patients are not cyanotic ("pink"). Although ventilation and perfusion are both decreased, they are often well matched (alveoli and pulmonary capillaries are destroyed equally), so $\dot{V}/\dot{Q}$ mismatch is not severe. Patients require a high minute ventilation to maintain normal levels of P_{O_2} and P_{CO_2}, so they "puff," working hard to get air in. Although this is the classic presentation, many patients do not fit this description.

Diagnosis

- **Physical exam:**
  - Thin or cachectic.
  - Leaning forward on extended arms ("tripoding"), using accessory muscles of respiration.
  - Signs of hyperinflation: Resonance to percussion; diminished breath sounds bilaterally.
  - Breathing through pursed lips. This increases pressure within the airways and prevents airway collapse during expiration.
  - Prolonged expiration and associated **wheezing** on auscultation.
- **Chest film:** Barrel-shaped chest due to hyperinflated lungs and flattened diaphragm (Figure 10-35). Classic emphysema (smoking related) has decreased vascular markings (arterial deficiency) in the upper lobes with or without bullae. These changes can be seen in the lower lobes in α_1-antitrypsin deficiency.
- **Pulmonary function testing:**
  - **Spirometry:** Decreased FEV_1 and FEV_1:FVC ratio. FVC is often preserved.
  - **Lung volumes:** Increased TLC, FRC, and RV due to hyperinflation and air trapping.
  - **Diffusing capacity (DL_{CO}):** DL_{CO} is directly proportional to the surface area available to participate in gas exchange. Thus, the DL_{CO} is reduced in emphysema due to destruction of alveolar walls and associated capillary beds.
- **Arterial blood gas testing:** Early in the disease, Pa_{O_2} may be mildly decreased or normal but decreases as alveolar damage progresses. More severely affected patients often chronically retain CO_2, resulting in compensated respiratory acidosis (elevated P_{CO_2}, elevated HCO_3, and slightly decreased pH). During an acute exacerbation, Pa_{O_2} drops and Pa_{CO_2} increases, resulting in acute respiratory acidosis.
- **Pathology:** Two major subtypes of emphysema.
  - **Panacinar (panlobar) emphysema:** Characterized by dilation of the entire acinus (includes the respiratory bronchioles, alveolar ducts, and alveolar sacs). Primarily affects the lower lobes. **Associated with α_1-antitrypsin deficiency.**
  - **Centriacinar (centrilobular) emphysema (Figure 10-36):** Characterized by dilation of the proximal part of the acinus (the respiratory bronchioles). The pattern of involvement is more irregular and is often localized to the upper parts of the lungs. **Associated with smoking**.

Treatment

- **Smoking cessation is most important.**
- Supplemental oxygen is useful in patients with severe hypoxemia.
- Only smoking cessation and supplemental oxygen are proven to reduce mortality. All other treatments, including pharmacotherapy, only reduce symptoms.
- If hospitalization is required for an acute exacerbation, appropriate antibiotics, such as levofloxacin, improve outcome.
- Inhaled bronchodilators can reduce airflow obstruction. These include:
  - β_2-agonists (albuterol, salmeterol, formeterol)
  - Anticholinergics (ipratropium, tiotropium)
- Corticosteroids are used in acute exacerbations (PO/IV) and for long-term control (inhaled).

KEY FACT

Recognizing emphysema on a lateral chest x-ray is high yield. Look for an enlarged retrocardiac clear space (increased distance between sternum and heart) and flattened diaphragm.

KEY FACT

Common nonallergic causes of asthma include aspirin, exercise, occupational exposure, and viral infection.

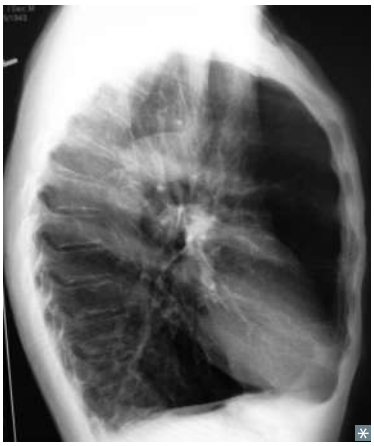


FIGURE 10-35. **Lateral chest film of patient with emphysema.** Note the increased anteroposterior diameter and "barrel-shape" characteristic of emphysema.

MNEMONIC

***Obstructive lung disease*—ABCDE**

Asthma
Bronchiectasis
Chronic bronchitis
Decreased FEV_1:FVC ratio
Emphysema

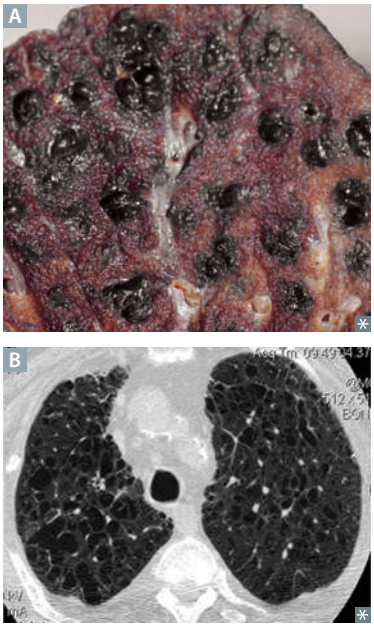


FIGURE 10-36. Centriacinar emphysema. A Gross specimen and B computed tomography cross-section.

KEY FACT

COPD is a broad term encompassing both emphysema and chronic bronchitis, as these two conditions can coexist.

KEY FACT

The term "blue bloater" is sometimes used to describe the clinical picture of chronic bronchitis. These patients are classically overweight ("bloated") and exhibit varying degrees of cyanosis ("blue") due to hypoxemia.

KEY FACT

Emphysema has decreased DL_{CO}, whereas chronic bronchitis has normal DL_{CO}.

Prognosis

Lifelong and chronic. Often coexists with, or may be complicated by, chronic bronchitis. Spontaneous pneumothorax can occur due to rupture of a surface bleb or tear in the airways.

Chronic Bronchitis

Defined clinically as a **productive cough** occurring for at least 3 months per year over at least 2 consecutive years. Characterized by excessive mucus production in the airways. The mucus itself is typically more viscous than normal.

Smoking causes proliferation and hypertrophy of bronchial mucous glands. It also damages cilia lining the bronchial lumen, impeding mucus clearance. There is also an influx of inflammatory cells, leading to airway inflammation.

The increased mucus production and airway wall thickness decreases the cross-sectional area of the lumen, increasing resistance and inhibiting air flow. The obstruction to airflow in chronic bronchitis is in the terminal bronchioles, which is proximal to the obstruction in emphysema.

Presentation

- Chronic cough **productive with copious mucus and sputum.** Blood-tinged mucus can be seen with rupture of pulmonary microvasculature.
- "Blue bloater": Often hypoxemic and cyanotic (**"blue"**) due to decreased ventilation but relatively preserved perfusion; $\dot{V}/\dot{Q}$ mismatch.
- Often obese (**"bloater"**); can have peripheral edema due to RV.
- Dyspnea, chronic smoking history; large overlap with emphysema.

Diagnosis

- **Physical exam:**
  - Often obese and sometimes cyanotic. The fingertips, lips, and tongue in particular may appear purplish blue.
  - Clubbing of fingertips associated with hypoxemia.
  - Rhonchi and wheezing on auscultation.
- **Chest film:** May show increased airway markings (appearing as a "dirty lung"), and there may be evidence of pulmonary hypertension and cor pulmonale.
- **Pulmonary function testing:**
  - **Spirometry:** Airflow obstruction results in decreased FEV_1 and FEV_1:FVC ratio. FVC is often preserved.
  - **Lung volumes:** In patients with dynamic hyperinflation, TLC, FRC, and RV may be increased.
  - **Diffusing capacity (DL_{CO}):** Typically normal. Despite the airway obstruction due to mucus plugging, the alveolar walls function normally.
- **Arterial blood gas testing:** Pa_{O_2} is often decreased, and Pa_{CO_2} is increased. Bicarbonate is elevated by the kidneys in an attempt to compensate for the decreased pH.
- **Pathology:** Increased number of goblet cells. The **Reid index,** which is the ratio of bronchial mucous gland depth to the total thickness of the bronchial wall, is abnormally high in chronic bronchitis.

Treatment

Bronchodilators and corticosteroids are used as in emphysema. Supplemental O_2 can treat hypoxemia, reduce hypoxic vasoconstriction and polycythemia, thereby reducing the incidence of pulmonary hypertension. Supplemental O_2 and cessation of cigarette smoking are the only interventions that have been shown to reduce mortality. Chest physiotherapy (percussion, coughing, and postural changes) can loosen and clear airway secretions, and pulmonary rehabilitation is helpful.

Prognosis

- Chronic hypoxemia increases the risk of developing pulmonary hypertension secondary to pulmonary vasoconstriction. In turn, right-sided heart failure can ensue **(cor pulmonale).**
- In a compensatory effort to increase oxygen delivery to tissues, erythropoietin production is upregulated in the kidneys, resulting in **secondary polycythemia.**

Asthma

Reversible obstructive disease characterized by hyperreactive and hyperresponsive airways that lead to exuberant **bronchoconstriction** with minimal irritation. Prevalence is approximately 9% in the United States, although there is variation between races and sexes. Asthma is frequently seen in patients with a family history of eczema and allergic rhinitis, both of which are also hypersensitivity-mediated conditions. Children exposed to secondhand smoke, as well as infants of mothers who smoke, are at increased risk of developing asthma. Extrinsic and intrinsic subtypes exist, although patients frequently have a combination of the two.

- **Extrinsic asthma:** Mediated by a **type I hypersensitivity** reaction involving IgE and mast cells (see also the section on Allergy at the end of this chapter). Often begins in childhood in patients with a family history of allergies. Common allergens include animal dander (especially cats), pollen, mold, and dust mites.
- **Intrinsic asthma:** Due to nonallergic causes. Precipitating factors include viral URIs, exercise, cold temperatures, air pollutants (eg, cigarette smoke), chronic bronchitis, acid reflux, stress, and medications (especially aspirin).

In both types of asthma, airway inflammation leads to bronchial hyper-responsiveness. Implicated in this inflammation are eosinophils, lymphocytes, histamine, leukotrienes, and IgE (see Table 10-14 for specific mediators). As a result of airway smooth muscle contraction, mucosal edema, and secretions within the lumen, the airway narrows, thereby increasing resistance and reducing airflow, especially during expiration. Unlike COPD, the process in asthma is generally reversible, so between attacks, most asthmatics have relatively normal physiology.

TABLE 10-14. Epithelial-Derived Inflammatory Mediators in Asthma

MEDIATOR	PHYSIOLOGIC EFFECT(S)
Endothelin-1	Bronchoconstriction
NO PGE_2 15-HETE	Vasodilation
Cytokines: ■ GM-CSF ■ IL-8 ■ RANTES ■ Eotaxin	Inflammation
Growth factors: ■ EGF ■ IGF-1 ■ PDGF	Fibrosis Smooth muscle hyperplasia

EGF, epidermal growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IGF-1, insulin-like growth factor-1; 15-HETE, 15-hydroxyeicosatetraenoic acid; IL-8, interleukin-8; NO, nitric oxide; PDGF, platelet-derived growth factor; PGE_2, prostaglandin E_2.

FLASH BACK

In contrast to other organs in the body, such as the brain, the pulmonary circulation actually vasodilates in response to high O_2 and vasoconstricts in response to low O_2.

CLINICAL CORRELATION

"Silent chest" is the absence of wheezing and other breath sounds during an asthma attack due to air flow rates too low to generate sound. It is a marker of disease severity and portends a poor prognosis for an acute asthma exacerbation.

KEY FACT

Not all that wheezes is asthma and not all asthma wheezes. Anaphylaxis, foreign body aspiration, COPD, and cardiac wheeze (pulmonary edema due to HF) may present with wheezing. However, a severe asthma exacerbation can result in respiratory muscle failure or so severely obstruct airways that air flow rates are insufficient to produce audible wheezing.

KEY FACT

Some asthmatics may be sensitive to aspirin, which inhibits cyclooxygenase and favors the production of leukotrienes from arachidonic acid. Leukotrienes play a role in airway inflammation and are potent bronchoconstrictors.

CLINICAL CORRELATION

Samter's triad is characterized by aspirin-induced bronchospasm, asthma, and nasal polyps.

FLASH BACK

Pulsus paradoxus is a decrease in systolic blood pressure by 10 mm Hg or more during inspiration. On board exams, it is most commonly tested in the context of cardiac tamponade but can also be seen in asthma, obstructive sleep apnea, and croup.

KEY FACT

Release of major basic protein (MBP) by eosinophils is a major cause of damage to the alveolar lining in asthma.

FLASH BACK

Immune cytokines:
IL-4 is responsible for B-cell class switching to IgE.
IL-5 is responsible for eosinophil recruitment.

CLINICAL CORRELATION

Asthma exacerbations are typically associated with respiratory alkalosis from tachypnea. Signs of acidosis (eg, decreased pH, increased $Paco_2$) suggest impending respiratory failure as the patient's muscles of respiration become fatigued. This is a potential emergency requiring intubation.

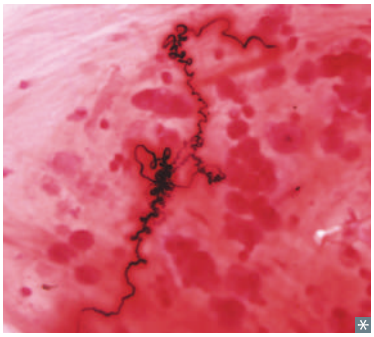


FIGURE 10-37. Curschmann spirals.

Presentation

Acute exacerbation manifests with:

- Sudden-onset dyspnea, wheezing, and tachypnea, usually following an inciting event.
- Patients can also present with coughing, chest tightness, or chest pain.

Diagnosis

- **Physical exam:** Tachypnea. Prolonged expiration and wheezing on auscultation.
- **Methacholine challenge test:** Inhalation of methacholine (direct cholinergic agonist). When performed in asthmatic patients, this precipitates bronchoconstriction at lower doses (hyperreactivity) and increased severity (hyperresponsiveness) compared to normal patients.
- **Pulmonary function testing (PFTs):** During an acute attack, airflow obstruction results in decreased FEV_1 and FEV_1:FVC ratio (FVC is often normal), and dynamic hyperinflation leads to a normal or increased TLC, and an increased FRC and RV. Between attacks, PFTs are often normal, although there may be small changes, such as decreased maximal midexpiratory flow (appearing as a marked concavity on the exhalation curve termed **expiratory coving**) and increased RV (Figure 10-19).
- Patients with asthma can often monitor their own respiratory status with portable peak flow meters.
- **Arterial blood gas testing:** During an attack, Pao_2 is often reduced due to hypoxemia resulting from $\dot{V}/\dot{Q}$ mismatch. $Paco_2$ is also reduced due to hyperventilation. $Paco_2$ levels that normalize or become elevated during an asthma attack may indicate worsening airway obstruction or a tiring individual who can no longer maintain a high minute ventilation rate.
- **Pathology:**
  - Edema of the bronchial walls with **smooth muscle hypertrophy** and cellular infiltrates (eosinophils and lymphocytes).
  - Denuded epithelium, **enlarged mucous glands,** and increased number of goblet cells.
  - **Curschmann spirals** (whorled mucus plugs) containing shed epithelial cells (Figure 10-37) and eosinophilic crystals **(Charcot-Leyden crystals)** on sputum microscopy.
  - Mucus plugging (Figure 10-38).

Treatment

Treatments are listed below. Refer to the Pharmacology section at the end of the chapter for a more detailed discussion of each agent.

- β_2-agonists: albuterol, salmeterol, formoterol
- Corticosteroids: beclomethasone, fluticasone
- Muscarinic antagonists: ipratropium
- Antileukotrienes: montelukast, zafirlukast, zileuton
- Omalizumab
- Magnesium sulfate

Prognosis

May improve with age or be a life-long condition. Avoidance of triggers can avert the worst symptoms. A severe attack that is refractory to bronchodilators **(status asthmaticus)** may require assisted ventilation and can result in death.

Bronchiectasis

Bronchiectasis is irreversible dilation of the airways caused by repeated episodes of infection and/or inflammation with eventual destruction of the bronchi and bronchiole walls. Over time, as the airways lose their elastic recoil, they become unable to expel air. As a

result, air is functionally trapped in the lungs. Also, the damaged airways compromise the ability to fight infection. This allows bacterial colonization, pooling of secretions, and additional inflammation, thus perpetuating a vicious cycle. Bronchiectasis (Figure 10-39) has several causes, including the following:

- **Infection:** May be viral, bacterial, or fungal. Examples include tuberculosis, pertussis, and allergic bronchopulmonary aspergillosis.
- **Obstruction** by tumor, foreign body, or mucus plug.
- Defective airway or ciliary clearance:
  - **Smoking:** Irritants from cigarette smoke paralyze cilia and inhibit their ability to clear secretions.
  - **Primary ciliary dyskinesia (Kartagener syndrome):** Genetic dynein arm defect, resulting in immotile cilia. Affected patients also present with **infertility** (due to immotile sperm in males and dysfunctional fallopian tubes in females) and **situs inversus** (dextrocardia on chest x-ray and right-sided point of maximal impulse [PMI]).
- Patients with **cystic fibrosis** develop bronchiectasis due to the production of thick secretions that are difficult to clear as well as chronic infection with multiple pathogens (Figure 10-39). The lungs of these patients are often colonized with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Haemophilus influenzae*; less common organisms include *Burkholderia cepacia*, which almost exclusively appears in patients with cystic fibrosus.

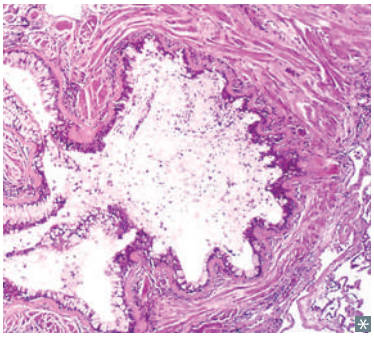


FIGURE 10-38. **Mucus plug.**

KEY FACT

Persistent obstruction of any portion of the respiratory tract (either internal blockage or external compression) can lead to bacterial colonization, inflammation, and eventual destruction of regions distal to the obstruction.

Presentation

Cough; copious mucoid, mucopurulent, or purulent sputum production; dyspnea; rhinosinusitis; hemoptysis.

Diagnosis

- **Physical exam:**
  - Localized crackles or rhonchi may be heard. Some patients also present with wheezing.
  - Clubbing of the fingernails may also be seen in some patients.
- **Chest film:** Often nonspecific abnormal findings, including increased markings, crowded vessels, or "ring" shadows corresponding to the dilated airways.

FIGURE 10-39. **Bronchiectasis.** A Fibrotic lung parenchyma with numerous areas of pneumonia (arrows) and thick inspissated secretions in areas of bronchiectasis (arrowhead) in a patient with cystic fibrosis. B Permanently dilated airways seen with bronchiectasis. C Computed tomography scan cross-section showing dextrocardia and bronchiectasis in a patient with Kartagener syndrome.

- **CT:** Has become the preferred method both to diagnose bronchiectasis and to evaluate location and extent of disease.
- **PFT:** Often normal, but can also show obstructive pattern.
- **Arterial blood gas testing:** Usually normal, except in patients with very diffuse disease, who can exhibit hypoxemia and hypercapnia.
- **Pathology:** Marked dilation of the airways in one of three patterns: cylindrical, varicose, or saccular (Figure 10-39). Increased secretions are also seen. The arteries also enlarge and proliferate. New anastomoses may form, leading to hemoptysis.

Treatment

- Removal of any foreign body or tumor (if possible).
- Inhaled bronchodilators are useful in patients with coexisting causes of airway obstruction.
- Antibiotics for both acute and chronic infections.
- Bronchopulmonary drainage with chest physiotherapy helps to clear secretions from the dilated airways.
- **DNase** is used to break up thick secretions in CF patients.

Prognosis

In severe cases, cor pulmonale can develop. Colonization with *P aeruginosa* is frequent.

KEY FACT

FEV_1:FVC ratio > 80% is characteristic of restrictive lung disease.

CLINICAL CORRELATION

Restrictive lung disease due to poor muscular effort can also arise from diaphragmatic paralysis, in which one or both phrenic nerves are damaged (eg, trauma) or impinged on (eg, tumor).

RESTRICTIVE LUNG DISEASES

Restrictive lung diseases are characterized by reduced lung expansion (decreased lung volume). **TLC and RV are reduced.** In turn, **FEV_1 and FVC are decreased.** FEV_1 and FVC decrease proportionately, resulting in a **normal FEV_1:FVC, or FVC is decreased to a greater degree** than FEV_1, resulting in an **increased FEV_1:FVC.** Restrictive lung disease can develop from both pulmonary and extrapulmonary sources (Figure 10-40).

Extrapulmonary Restrictive Disease (Poor Breathing Mechanics)

The restrictive defect is extrinsic to the lung parenchyma. This includes mainly disorders of the chest wall and neuromuscular disease leading to impaired ability to fully expand the lungs. Hypoxemia develops secondary to **hypoventilation.** There are two broad classes: **poor muscular effort** and **poor structural apparatus.**

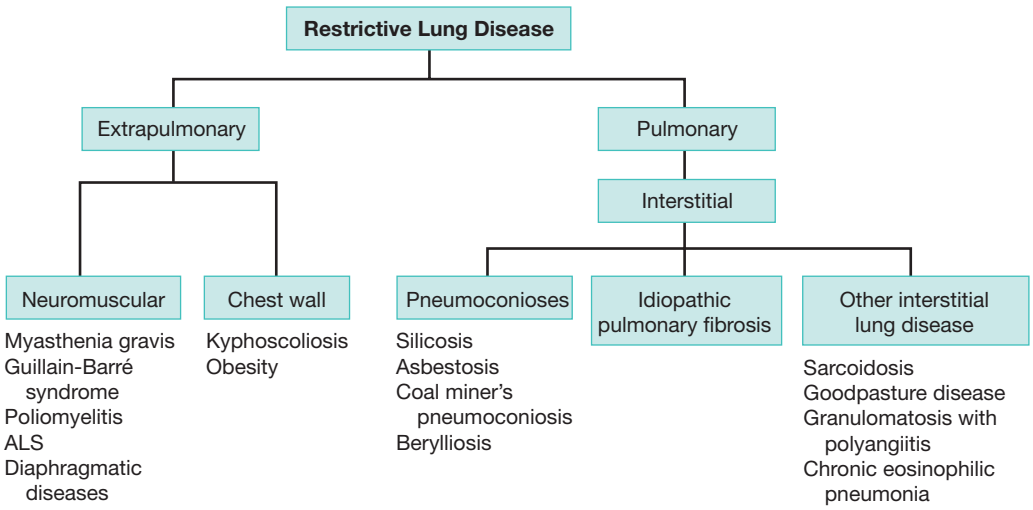


FIGURE 10-40. Classification of restrictive lung diseases. ALS, amyotrophic lateral sclerosis.

Poor Muscular Effort

Poor muscular effort is often due to one of several neuromuscular diseases. In each case, hypoventilation develops as the diaphragm and accessory muscles become fatigued. Patients alter their breathing pattern, taking more frequent, shallow breaths. This increases the V_D:V_T ratio, reducing alveolar ventilation and increasing $PaCO_2$. Ineffective cough can lead to decreased secretion clearance, atelectasis, and recurrent respiratory infections. Common causes of neuromuscular disease include

- **Poliomyelitis (polio):** Picornavirus infection, which leads to ablation of anterior motor neurons and therefore symptoms of lower motor neuron (LMN) paralysis.
- **Myasthenia gravis:** Autoimmune disorder that causes muscle weakness due to autoantibodies targeting nicotinic acetylcholine receptors in the neuromuscular junction.
- **Amyotrophic lateral sclerosis (ALS):** Neurodegenerative motor neuron disease affecting both the lateral corticospinal tracts and anterior horns of the spinal cord, leading to signs of upper motor neuron (UMN) and LMN paralysis, respectively.
- **Guillain-Barré syndrome (GBS):** Transient autoimmune destruction of Schwann cells, leading to peripheral demyelination. Classically presents with symmetric ascending paralysis, starting from the lower extremities; symptoms can also include autonomic dysregulation (eg, cardiac arrhythmias, hypertension, or hypotension). Usually follows gastroenteritis (most commonly caused by *Campylobacter jejuni*).

Poor Structural Apparatus

Commonly due to scoliosis and morbid obesity.

- **Kyphoscoliosis:** Lateral curvature of the spine prevents proper chest wall expansion.
- **Morbid obesity:** The excess weight surrounding the chest wall presses down on the wall and inhibits proper expansion. Obesity is also associated with decreased respiratory rate, which also contributes to hypoventilation (see discussion on obesity hypoventilation syndrome below).

Presentation

Dyspnea, especially with exertion. Other possible signs and symptoms are etiology dependent.

Diagnosis

- A-a gradient: **normal,** because gas exchange in alveoli is **not** impaired.
- **Physical exam:**
  - **Neuromuscular disease:** Etiology dependent, nonpulmonary manifestations of specific disease; assess for UMN and LMN lesions (see Chapter 6).
  - **Diaphragmatic disease:** Paradoxical movement of paralyzed regions of the diaphragm upward during supine inspiration.
  - Assess for kyphoscoliosis.
- **Chest film:** Assess for kyphoscoliosis, diaphragmatic paralysis.
- **PFT:** Variable depending on the specific disease and disease severity. In general, FEV_1, FVC, TLC, and RV are usually decreased, but these are neither sensitive nor specific.

Treatment

Supplemental O_2 or mechanical ventilation may be needed for patients with severe disease. The underlying disorder must be treated, or irreversible pulmonary sequelae will develop.

Prognosis

Extrapulmonary restrictive diseases resulting in hypoxemia can lead to pulmonary hypertension and cor pulmonale. Progressive disease can lead to chronic respiratory acidosis.

Interstitial Lung Diseases

The restrictive defect is due to abnormalities within the lung parenchyma. It is most commonly due to fibrosis, with the exceptions of ARDS and neonatal respiratory distress syndrome (NRDS), which are discussed below. Because diffusing capacity through the alveolar walls is impaired, **A-a gradient is increased.**

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is characterized by acute-onset diffuse alveolar damage and leakage of fluid out of the pulmonary capillaries into the interstitium and alveolar spaces. ARDS is defined by four major criteria, all of which must be met:

1. Reduced arterial oxygen to inspired oxygen ratio Pa_{O_2}/F_{IO_2}:
   - Mild ARDS: 200–300.
   - Moderate ARDS: 100–200.
   - Severe ARDS: < 100.
   - A low ratio reflects poor oxygenation despite ample inspired oxygen; normal ratio is 500 mm Hg.
2. Acute onset.
3. Bilateral lung infiltrates (Figure 10-41).
4. Must not be fully explained by left-sided heart failure or fluid overload.

KEY FACT

Pulmonary edema is an intra-alveolar accumulation of fluid. It can be caused by increased hydrostatic pressure (eg, left ventricular failure), increased capillary permeability (eg, ARDS), or several other mechanisms (eg, high altitude, neurologic injury, or opiate overdose).

Etiologies include pneumonia, inhalation of irritants, O_2 toxicity, heroin overdose, shock, sepsis, aspiration of gastric contents, trauma, uremia, acute pancreatitis, head trauma, multiple transfusions of blood products (transfusion-related acute lung injury [TRALI]), disseminated intravascular coagulation (DIC), and fat or amniotic fluid embolism. In all of these cases, the initial injury in ARDS affects the type I pneumocytes and/or capillary endothelial cells, resulting in leakage of protein-rich fluid. Alveoli become flooded with fluid, inhibiting gas exchange and oxygenation. This leads to hypoxemia in the forms of shunting and $\dot{V}/\dot{Q}$ mismatch, with the latter being exacerbated by altered distribution of pulmonary blood flow due to increased PVR. Additionally, surfactant function and production is altered, resulting in alveolar collapse.

Presentation

Acute-onset dyspnea accompanied by tachypnea and hypoxemia, usually in a critically ill patient.

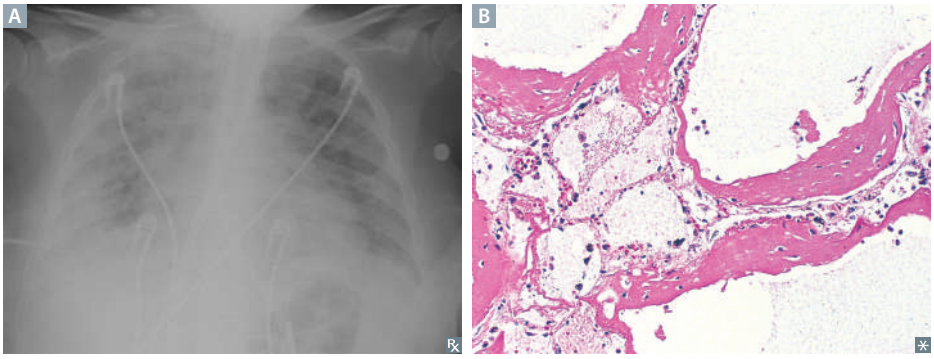


FIGURE 10-41. Acute respiratory distress syndrome. A Chest film shows diffuse, bilateral interstitial and alveolar infiltrates with near-complete opacification of lungs with obscured cardiomediastinal silhouette. B Histology: note alveolar fluid (clear, frothy) and thick hyaline membranes (pink).

Diagnosis

- **Physical exam:** Crackles are often heard on auscultation.
- **Chest film:** Diffuse, symmetrical interstitial and alveolar edema (see Figure 10-41; note that this is criterion 3 from the previous diagnostic criteria). Air bronchograms—visualization of distal bronchioles due to the contrasting opacity of infiltrates around the airway—may be present.
- **PFT:** Not usually performed, but would see a restrictive pattern with a reduced DLCO.
- **Arterial blood gas testing:** Hypoxemia, with a large A-a gradient. Supplemental O_2 may not increase Pa_{O_2} significantly due to shunt.

Pathology

Damage to type I alveolar epithelial cells, with regenerative hyperplasia of type II cells. Interstitial and alveolar fluid is present, with an inflammatory cell infiltrate and areas of alveolar collapse. **Hyaline membranes** (composed of eosinophilic, acellular material), fibrosis, and changes in the pulmonary vasculature can also be seen (Figure 10-42).

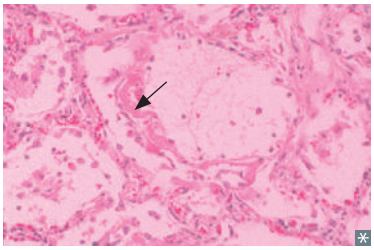


FIGURE 10-42. Alveolar damage in acute respiratory distress syndrome. The alveoli are congested and edematous, and the classic hyaline membrane can be seen (arrow).

Treatment

Treat underlying cause; patients are typically intubated and mechanically ventilated using low tidal volume ventilation and high PEEP in an ICU.

Prognosis

High mortality (30–50%), largely due to the underlying cause rather than the pulmonary effects of ARDS.

Neonatal (Infant) Respiratory Distress Syndrome

Neonatal respiratory distress syndrome (NRDS) is the most common cause of respiratory failure in newborns and the most common cause of death in premature infants. It results from a deficiency of surfactant in immature lungs, leading to atelectasis due to increased surface tension in the air-liquid interface, $\dot{V}/\dot{Q}$ mismatch, and shunting.

Predisposing factors include:

- **Prematurity.**
- **Maternal diabetes:** Excess glucose in the mother's blood reaches the fetus through the placenta. Fetal insulin production increases, which suppresses corticosteroids normally involved in surfactant production.
- **C-section delivery:** During a normal vaginal delivery, maternal uterine contractions compress the fetal head, inducing corticosteroid production. This process is bypassed in a C-section, causing the fetus to produce fewer corticosteroids.

Incidence and mortality decrease dramatically with gestational age, with the most severe disease seen prior to the alveolar stage of lung development.

Presentation

Dyspnea and tachypnea in a newborn, with risk factors described above, especially if premature.

Diagnosis

- **Physical exam:** Tachypnea, often with grunting, cyanosis, and retractions; crackles on auscultation.
- Fetal pulmonary maturity can be assessed by measuring the **ratio of surfactant lecithin to sphingomyelin in the amniotic fluid.** A ratio of 2:1 or greater indicates lung maturity.

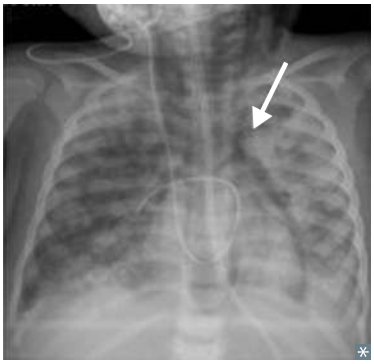


FIGURE 10-43. **Neonatal respiratory distress syndrome.** X-ray of the chest showing pneumomediastinum (arrow).

CLINICAL CORRELATION

Remember your **ABC**s: **A**irway, **B**reathing, **C**irculation. Assess these three parameters and manage them (if needed) before any other physical examination maneuvers are carried out.

MNEMONIC

Adverse effects associated with supplemental O_2 administration in patients with NRDS—

RIB:
Retinopathy of prematurity
Intraventricular hemorrhage
Bronchopulmonary dysplasia

MNEMONIC

Asbestosis is from the roof (roofers), but affects the base (lower lobes).
Silica and coal are from the base (earth), but affect the roof (upper lobes).

- **Chest film:** Low lung volumes, diffuse ground-glass appearance with air bronchograms (Figure 10-43).
- **Arterial blood gas testing:** Hypoxemia, with a large A-a gradient. Hypoxemia may be refractory to supplemental O_2 due to shunting.
- **Pathology:** Lungs are heavier than normal, with alternating atelectatic areas and dilated alveoli. The pulmonary vessels are engorged, with leakage of fluid into the alveoli. Hyaline membranes are also seen (note that neonatal RDS was formerly called hyaline membrane disease).
- **Differential diagnosis:** Transient tachypnea of the newborn (TTN—self-resolving, relatively benign respiratory distress associated with pulmonary edema), bacterial pneumonia, congenital heart disease.

Treatment

Exogenous surfactant administration. Mechanical ventilation with PEEP. Inhaled nitric oxide. Antenatal maternal corticosteroid therapy to promote surfactant production.

Prognosis

Mortality rates have improved dramatically with the use of exogenous surfactant but remain over 10%. NRDS may also be associated with metabolic acidosis, patent ductus arteriosus (PDA), and necrotizing enterocolitis.

Pneumoconiosis

A group of interstitial lung diseases caused by the inhalation of inorganic and organic particulate matter. This produces varying degrees of pulmonary fibrosis, characterized by decreased compliance, reduced lung volumes, and destruction of the alveolar-capillary interface, leading to $\dot{V}/\dot{Q}$ mismatch and hypoxemia. Four common inorganic pneumoconioses are listed in Table 10-15.

Presentation

Dyspnea, especially with exertion.

Diagnosis

- **Physical exam:** Bibasilar crackles heard on auscultation. Clubbing may also be seen.
- **Chest film:** Nodular opacities seen in silicosis, coal worker's pneumoconiosis, and berylliosis. A more linear pattern is seen in asbestosis. Calcified pleural plaques are also seen in asbestosis.
- **PFT:** Decreased TLC, FRC, RV, FEV_1, and FVC, with a normal or increased FEV_1:FVC ratio. D_{LCO} is also decreased.
- **Arterial blood gas testing:** Hypoxemia, often with normo- or hypocapnia.
- **Pathology:** Refer to Table 10-15.

Treatment

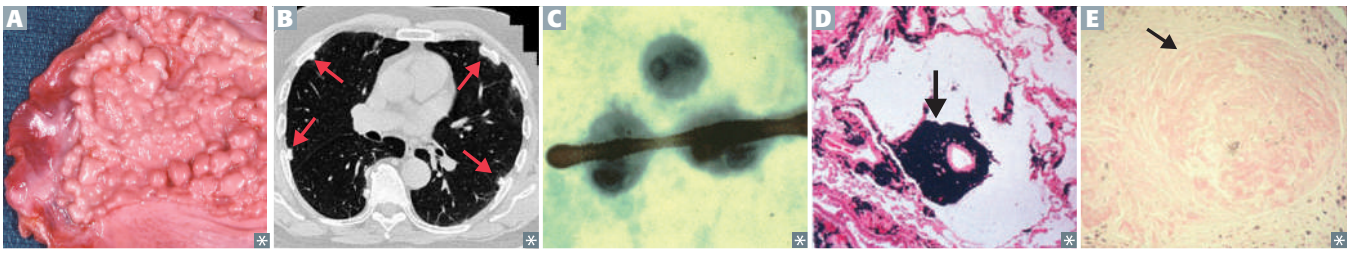
Avoid further exposure. No curative treatment.

Prognosis

- **Silicosis:** Associated with increased susceptibility to tuberculosis (TB).
- **Coal worker's pneumoconiosis (CWP):** Simple CWP is often inconsequential. If CWP is complicated by progressive massive fibrosis (PMF), it can lead to bronchiectasis, pulmonary hypertension, and death from respiratory failure or right-sided heart failure.

TABLE 10-15. Common Inorganic Pneumoconioses

NAME	EXPOSURE	PATHOLOGY	COMMENTS
Asbestosis	Asbestos fibers (associated with shipbuilding, roofing, plumbing, insulation, construction work)	**"Ivory white" calcified pleural plaques** A B are pathognomonic for asbestos exposure but are not precancerous. **Asbestos (ferruginous) bodies** are golden-brown fusiform rods resembling dumbbells C.	Interstitial fibrosis primarily affects the lower lobes. Associated with an increased incidence of bronchogenic carcinoma and mesothelioma (bronchogenic >> mesothelioma). Concomitant cigarette smoking multiplies the risk of developing lung cancer.
Berylliosis	Beryllium (found in aerospace, electronics, nuclear materials, and manufacturing industries)	Noncaseating granulomas.	Interstitial fibrosis primarily affects the upper lobes. Associated with an increased risk of primary lung cancer. **Can mimic sarcoidosis** (granulomas in multiple organ systems).
Coal workers' pneumoconiosis	Prolonged coal dust exposure (coal miners)	Black lungs; coal dust contains silica and carbon D. Progresses from **anthracosis** (mild, asymptomatic form seen in city dwellers and smokers).	Interstitial fibrosis primarily affects the upper lobes and develops secondary to activation of carbon-laden macrophages. **Not associated with lung cancer.**
Silicosis	Silica (associated with sandblasting; also seen in foundries and mines; quartz and other minerals)	**"Eggshell" calcification** of hilar lymph nodes. Silicotic nodules E.	Interstitial fibrosis primarily affects upper lobes. Silica disrupts phagolysosome in macrophages, **increasing susceptibility to tuberculosis.** Associated with increased risk of bronchogenic carcinoma.



Modified with permission from Le T, et al. *First Aid for the USMLE Step 1 2017*. New York, NY: McGraw Hill Education; 2017.

- **Asbestosis:** Predisposes to bronchogenic carcinoma and, less commonly, malignant mesothelioma of the pleura or peritoneum. Concomitant cigarette smoking multiplies the risk of developing cancer.
- **Berylliosis:** Can mimic sarcoidosis, with granulomas in multiple organ systems.

CLINICAL CORRELATION

Caplan syndrome is characterized by rheumatoid arthritis and pneumoconiosis with intrapulmonary nodules.

Sarcoidosis

Inflammatory disease characterized by **noncaseating granulomas,** often involving multiple organ systems. The initial exposure that leads to granuloma formation is unknown.

Presentation

Classic presentation of sarcoidosis is an African-American female in her thirties with progressive dyspnea, often accompanied by a dry or nonproductive cough. More common in women and African Americans. Presents in young adulthood. Often discovered

KEY FACT

Pneumoconiosis associations:
Silicosis → lung nodules, "eggshell" calcification in hilar nodes, tuberculosis
Coal workers' pneumoconiosis → "dust cells" (alveolar macrophages with anthracotic pigment)
Asbestosis → bronchogenic carcinoma >> malignant mesothelioma
Berylliosis → granulomas mimicking sarcoidosis

MNEMONIC

***Causes of hypercalcemia*—CHIMPANZEES**

Calcium excess intake (milk-alkali syndrome)
Hyperparathyroidism and hyperthyroidism
Iatrogenic (thiazides, etc)
Multiple myeloma
Paget disease of bone
Addison disease
Neoplasms (parathyroid hormone-related protein—PTHrP, etc)
Zollinger-Ellison syndrome
Excess vitamin D
Excess vitamin A
Sarcoidosis

in asymptomatic patients on chest film (Figure 10-44A). Less often, presents with extrapulmonary symptoms.

Diagnosis

- **Chest film:** Bilateral hilar lymphadenopathy, diffuse (coarse) reticular densities.
- Reduced sensitivity/anergy to skin test antigens.
- **Laboratory findings:** Hypercalcemia (due to increased 1-α-hydroxylase production by activated macrophages leading to increased 1,25-$(OH)_2$-vitamin D), hypercalciuria, hypergammaglobulinemia, increased ACE activity. Hypercalcemia/hypercalciuria may present as nephrolithiasis.
- **Biopsy** showing noncaseating granulomas in the lung with a negative microbiology work-up is highly suggestive. Granulomas are often seen in other organs as well. The granuloma consists of a core of macrophages surrounded by T lymphocytes, as illustrated in Figure 10-44B.
- **Differential diagnosis:** TB, fungal infections (see Table 10-15), other infectious diseases, malignancy, rheumatologic disease.

Treatment

Many patients do not need treatment. Criteria for receiving treatment include impaired pulmonary function or worsening radiologic findings, systemic symptoms that interfere with activities of daily living, ocular disease, heart disease, neurologic involvement, and hypercalcemia. Treatment consists of systemic corticosteroids or other immunosuppressive drugs.

Prognosis

Natural history varies widely. In some patients, clinical and radiographic manifestations resolve spontaneously. In others, symptoms persist without progression. In a small minority, the disease progresses to widespread pulmonary fibrosis.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) pathogenesis is believed to be precipitated by an unknown agent that causes cytokine release, resulting in repeated cycles of inflammatory lung injury, followed by wound healing. Collagen deposits accumulate in the lungs with each cycle, eventually leading to fibrosis. IPF accounts for approximately 15% of cases of chronic interstitial lung disease.

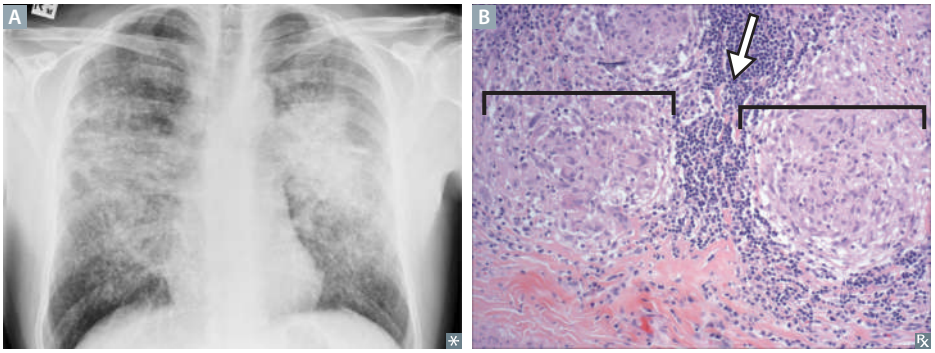


FIGURE 10-44. Sarcoidosis. A X-ray of the chest shows bilateral hilar adenopathy and coarse reticular opacities. B Photomicrograph from a patient with sarcoidosis. Granulomas consist of macrophages and multinucleated giant cells (brackets) surrounded by lymphocytes (arrow).

Presentation

Insidious onset, often between 40 and 70 years of age. Most commonly presents with progressive dyspnea.

Diagnosis

- **Physical exam:** Dry crackles or rales on auscultation, clubbing of fingernails.
- **Chest film and CT:** Diffuse, interstitial pattern bilaterally. Seen more at the bases and peripheral portions of the lung. CT classically shows "honeycombing"—a cavernous network of fibrosis within the lungs (Figure 10-45).
- **Biopsy/pathology:** Provides definitive diagnosis; shows chronic inflammation and fibrosis of the alveolar walls as well as interstitial fibrosis; dilation of bronchioles proximal to fibrotic alveoli produces "honeycomb lung" appearance in UIP.

Treatment

Systemic corticosteroids and other immunosuppressive drugs are not effective. Lung transplantation may be an option for younger patients. Two new drugs can now be considered—pirfenidone and nintedanib.

Prognosis

Rapid disease progression with a mean survival of 2–5 years.

MNEMONIC

Drugs that cause pulmonary fibrosis:

Breathing **A**ir **B**adly [from] **M**edications: **B**leomycin, **A**miodarone, **B**usulfan, **M**ethotrexate

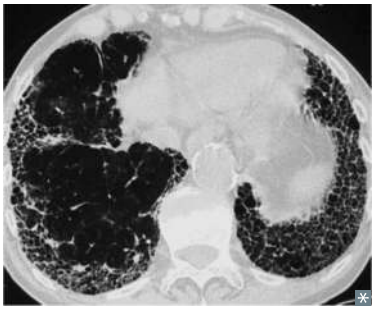


FIGURE 10-45. CT of chest of a patient with idiopathic pulmonary fibrosis. Image demonstrates bibasilar reticular abnormalities with traction bronchiectasis and honeycombing characteristic of usual interstitial pneumonia.

Goodpasture Syndrome

Autoimmune disease targeting the lungs and kidneys. Caused by type II hypersensitivity against the α3-chain of type IV collagen, located in the basement membranes of alveoli and glomeruli.

Presentation

Pulmonary hemorrhage with concomitant nephritic syndrome (hematuria, etc; see Chapter 8).

Diagnosis

- **Anti–type IV collagen autoantibodies.**
- **Kidney biopsy:** Immunofluorescence demonstrates linear, ribbon-like deposition of IgG along the glomerular basement membrane. Lung biopsy may be necessary if renal biopsy is not possible.

Treatment

Plasmapheresis with or without immunosuppressive therapy to reduce the burden of autoantibodies.

Prognosis

Therapy can often control symptoms. However, immune-mediated damage to the lung parenchyma can result in scarring and eventual fibrosis.

FLASH BACK

Both **Goodpasture syndrome** and **granulomatosis with polyangiitis** are causes of **rapidly progressive glomerulonephritis,** which presents as a nephritic syndrome. Histology will reveal crescent-shaped proliferation of glomerular parietal cells and accumulation of fibrin in glomeruli.

Granulomatosis with Polyangiitis (Formerly Wegener Granulomatosis)

Granulomatosis with polyangiitis is an autoimmune vasculitis affecting primarily the upper respiratory tract, lungs, and kidneys, but also affecting the joints, skin, eyes, or nervous system in certain cases. Characterized by vasculitis of small and medium blood vessels in affected organs, with granulomas surrounding these vessels.

Presentation

Extremely varied. Cough, dyspnea, hemoptysis. Persistent rhinorrhea, bloody/purulent nasal discharge, nasal pain. Nonrespiratory symptoms include nephritic syndrome, eye and ear symptoms, arthritis, and cutaneous vasculitis.

Diagnosis

- **CT:** One or several nodules ("coin lesions") and infiltrates, often with cavitation (Figure 10-46).
- **c-ANCA-positive** (antiproteinase 3 autoantibodies).
- **Biopsy:** Necrotizing granulomatous vasculitis.

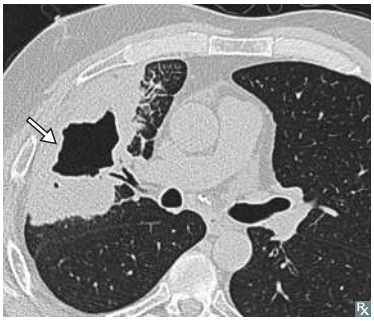


FIGURE 10-46. CT of the lungs of a patient with granulomatosis with polyangiitis. This CT scan shows a large cavitary lesion in the right upper lobe (arrow) (surgically proven).

Treatment

Prednisone used during initial therapy. Cytotoxic agents like cyclophosphamide are also used.

Prognosis

Complete and long-term remission can often be achieved with proper treatment.

Chronic Eosinophilic Pneumonia

Presentation

Presents over weeks to months, with fever, weight loss, dyspnea, and nonproductive cough.

Diagnosis

- **Chest film:** Peripheral pulmonary infiltrates and a pattern suggestive of alveolar filling.
- **Eosinophilia.**
- **Pathology:** Pulmonary interstitium and alveolar spaces infiltrated by eosinophils and macrophages.

Treatment

Administration of corticosteroids.

Prognosis

Clinical improvement can be seen within days to weeks after therapy with steroids is initiated.

PULMONARY VASCULAR DISEASES

The pulmonary vasculature receives the entire cardiac output and is susceptible to a number of disease processes. The four major entities discussed here are deep venous thrombosis (DVT), pulmonary embolism (PE), pulmonary hypertension, and sleep apnea.

MNEMONIC

Virchow triad (**SHE**):

Stasis
Hypercoagulability
Endothelial damage

Deep Venous Thrombosis

DVT refers to the formation of an occlusive blood clot (thrombus) in the deep veins of the lower extremity. The physiologic risk factors that predispose a patient to thrombus formation are described by the **Virchow triad:**

- **Stasis:** Occurs in patients who are immobile for prolonged periods (eg, postoperative state, long plane flights, truck drivers).
- **Hypercoagulability:** Due to defects in coagulation cascade proteins. The most common genetic hypercoagulable condition is factor V Leiden. Other causes include malignancy, multiple bone fractures, and use of oral contraceptive pills (OCPs).
- **Endothelial damage:** Exposure of subendothelial collagen activates the clotting cascade (intrinsic pathway).

Most commonly, DVTs form in the **femoral** and **popliteal** veins, as well as the veins in the **calf.**

Presentation

Sudden-onset unilateral lower extremity pain and swelling (Figure 10-47) in a patient with prolonged immobilization or another risk factor mentioned above.

Diagnosis

- Physical exam:
  - Unilateral lower extremity swelling and tenderness to palpation (Figure 10-47). Pitting edema is also seen in the affected leg due to excessive hydrostatic pressure.
  - Calf pain with passive dorsiflexion of the foot (positive **Homan sign**). This finding is not always present.
- **Compression ultrasound** of the lower extremity can be used for confirmation.

Treatment

- DVTs are initially managed with **unfractionated heparin** or a low-molecular-weight heparin (LMWH), such as **enoxaparin.** This is followed with oral anticoagulants (eg, warfarin, rivaroxaban) for long-term prophylaxis as outpatient therapy.
- Many hospitalized patients are given heparin (unfractionated or LMWH) prophylactically due to increased risk for developing a DVT secondary to immobilization (stasis).

Prognosis

In some cases, DVTs can break off and become lodged in the pulmonary circulation (PE). The majority of PEs arise from the proximal deep veins of the lower extremity.

Pulmonary Embolism

PE is often missed clinically and is seen in > 60% of autopsies. It occurs when a blood clot from a systemic vein lodges in one or more branches of the pulmonary artery. Most often, a PE arises from a deep vein thrombosis (DVT), but it can also result from embolization of fat, air, bacteria (infectious vegetations), amniotic fluid, and tumor cells (Table 10-16). As mentioned earlier, the majority of PEs arise from DVTs. As such, similar risk factors apply.

Decreased perfusion with continued ventilation causes an increase in dead space following a PE. One may expect this to lead to hypercapnia, but patients often hyperventilate and become hypocapnic. The release of inflammatory mediators can lead to bronchoconstriction, $\dot{V}/\dot{Q}$ mismatch, and hypoxemia. Reduced output of the right ventricle can lead to hypotension, syncope, and/or shock.

Presentation

Tachypnea, tachycardia, hypoxia, and **sudden-onset dyspnea** with **pleuritic chest pain** (pain that worsens with breathing) are the classic signs and symptoms, but the presentation is often varied. Can be associated with hemoptysis (secondary to infarcted lung tissue) and syncope. Smaller PEs are often asymptomatic.

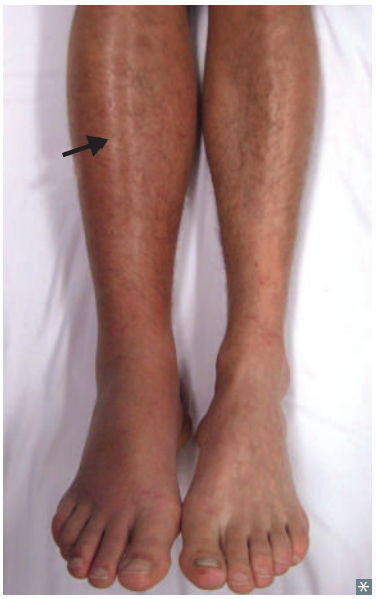


FIGURE 10-47. Deep venous thrombosis in right lower extremity.

CLINICAL CORRELATION

For acute management of DVT, give heparin before transitioning to warfarin. Heparin has a faster onset than warfarin, and this sequence also decreases the risk of warfarin-induced skin necrosis.

FLASH BACK

The differential diagnosis for hypercoagulable states includes primary thrombotic disorders and acquired risk factors. Primary genetic disorders include factor V Leiden, prothrombin G20210A, antithrombin deficiency, protein C or S deficiency, and dysfibrogenemias. Secondary risk factors include antiphospholipid syndrome (APLS), immobility, pregnancy, oral contraceptive use, and obesity.

TABLE 10-16. Types of Emboli

TYPE	COMMENTS	EXAMPLE PRESENTATION
Fat	Associated with long-bone fractures and liposuction. Classic triad: Hypoxemia, neurologic abnormalities, and petechial rash on the chest and truck. Pathology: The emboli stain black with osmium tetroxide.	A 24-year-old patient is hospitalized following a motor vehicle accident. The next day, he develops sudden-onset dyspnea and confusion. On physical examination, a petechial rash is seen across his chest.
Air	Develops in divers when nitrogen bubbles precipitate in their blood as they ascend too rapidly.	A 26-year-old patient develops rapid-onset dyspnea and pleuritic chest pain. On further questioning, patient reports symptoms developed while scuba diving.
Thrombus (DVT)	Develops after prolonged immobilization (usually ≥ 3 days).	Five days after abdominal surgery, a 68-year-old woman develops dyspnea and pleuritic chest pain.
Bacteria	Develops in infective endocarditis, when the bacterial vegetations dislodge from the heart valves. Can travel to brain or lungs, resulting in an abscess.	A 36-year-old IV drug user presents with sudden-onset left-sided weakness. His temperature is 101.6°F. Physical examination shows a heart murmur, painless erythematous nodules on his palms, and nail-bed hemorrhages.
Amniotic fluid	Develops when amniotic fluid leaks into the maternal bloodstream, usually postpartum. Can lead to disseminated intravascular coagulation (DIC).	A 27-year-old woman develops sudden-onset dyspnea shortly after giving birth.
Tumor cells	Be suspicious of malignancy when an adult presents with signs of new-onset hypercoagulability.	A 59-year-old man presents with sudden-onset right-sided weakness. He has a 40 pack-year smoking history. Chest x-ray shows a 4-cm lung nodule.

MNEMONIC

Types of emboli:

An embolus moves like a **FAT BAT** (**F**at, **A**ir, **T**hrombus, **B**acteria, **A**mniotic fluid, **T**umor).

CLINICAL CORRELATION

Lines of Zahn (Figure 10-48B) are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death. As such, they are used to assess whether a thrombus formed pre- or postmortem.

Diagnosis

- **Physical exam:**
  - Tachycardia and tachypnea.
  - Localized crackles or wheezes; however, the lung exam is often normal.
  - A pleural rub may be present. The pleural rub is produced by a fibrinous exudate that is released from the pleural surface overlying the region of ischemic lung tissue.
  - In the case of a massive PE (Figure 10-48A), the sudden increase in vascular resistance can lead to right ventricular overload (acute cor pulmonale), in which case a right-sided S_4 and loud P_2 may be heard (see Heart Sounds, discussed in Chapter 1). Jugular venous distention (JVD) may also be observed.
  - Lower extremity tenderness, swelling, and a palpable cord suggestive of a DVT may be seen.
- **Laboratory results and imaging:**
  - **CT angiography** can show the filling defect due to the thrombus (Figure 10-48C,D). This is the preferred method of definitive diagnosis.
  - **$\dot{V}/\dot{Q}$ scan:** Shows an area of $\dot{V}/\dot{Q}$ mismatch.
  - **Chest film:** Usually nonspecific. Dilation of the pulmonary arteries, **Hampton hump** (wedge-shaped consolidation in the lung periphery adjacent to the pleura), **Westermark sign** (abrupt cutoff of pulmonary vascularity distal to a PE), or a pleural effusion may also be seen.
  - **D-dimer level:** Fibrin degradation product. Elevated levels indicate thrombus formation. Has high sensitivity (hence, used for ruling out PEs).
  - **Arterial blood gas testing:** Decreased Pao_2 due to increased dead space. Decreased $Paco_2$ due to tachypnea. A-a gradient increased due to $\dot{V}/\dot{Q}$ mismatch.

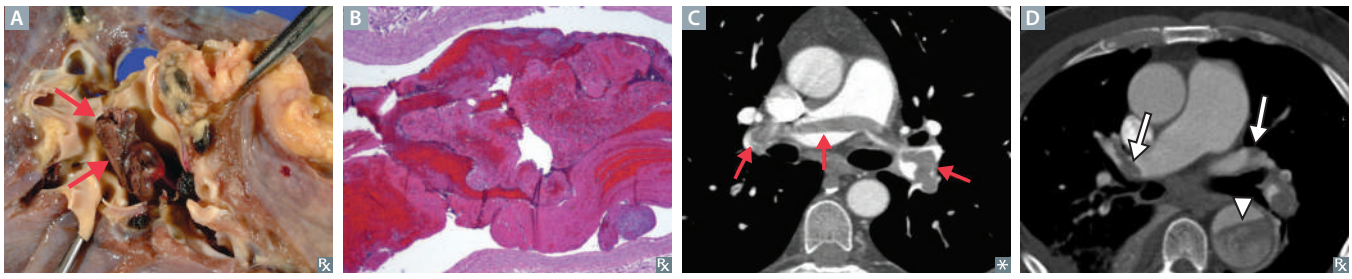


FIGURE 10-48. Pulmonary embolus. A Massive pulmonary embolus. B Lines of Zahn, indicating premortem thrombus formation. C CT angiogram of pulmonary vessels showing a filling defect (arrows). D Bilateral pulmonary emboli (arrows) appear as contrasting regions within the pulmonary vasculature. This axial CT also shows a type B aortic dissection (arrowhead), with the true lumen narrower than the false lumen.

Treatment

Supplemental oxygen if hypoxemic. Anticoagulation therapy, usually with IV heparin or low-molecular-weight heparin followed by oral anticoagulation for 3–6 months. Thrombolytic therapy may be useful in a subset of patients with massive PE and hypotension. Placement of a filtering device in the IVC can be used in patients who cannot tolerate anticoagulation due to an elevated bleeding risk.

Prognosis

Variable, ranging from sudden death to asymptomatic resolution.

Pulmonary Hypertension

Pulmonary hypertension is the elevation of intravascular pressure within the pulmonary circulation and includes pulmonary arterial hypertension (PAH) as well as pulmonary venous hypertension. PAH is defined as a mean pulmonary artery pressure > 25 mm Hg at rest or > 35 mm Hg with exertion. Idiopathic (primary) pulmonary arterial hypertension has no known cause and carries a poor prognosis. It occurs in the absence of underlying heart or lung disease and is more common in women than in men. Primary pulmonary hypertension is associated with mutations in genes linked to transforming growth factor beta (TGF-β) signaling and is characterized by vascular hyperreactivity with proliferation of smooth muscle. Congenital idiopathic pulmonary hypertension is associated with abnormally thickened vasculature.

Secondary pulmonary hypertension is more common and is related to lung or heart disease, including:

- Chronic thromboembolic disease.
- Loss of vessels by scarring or destruction of alveolar walls.
- Chronic hypoxemia.
- Increased flow (left-to-right shunt).
- Elevated left atrial pressure, as in CHF or mitral stenosis.
- Chronic respiratory acidosis (eg, chronic bronchitis, obstructive sleep apnea).
- Meconium aspiration at birth, the most common cause of persistent pulmonary hypertension of the newborn.

Presentation

Dyspnea and exertional fatigue. Substernal chest pain, similar to angina pectoris, is sometimes seen. If cardiac output falls enough, syncope can result.

Diagnosis

- **Physical exam:**
  - Lung examination often normal unless pulmonary hypertension is due to concomitant lung disease.
  - Loud P_2, right-sided S_3 and S_4.
  - JVD.
  - Right ventricular heave.
- **CT:** Increased prominence and size of hilar pulmonary arteries, which rapidly taper off. Enlarged cardiac silhouette (particularly RV and RA enlargement). Redistribution of blood flow to the upper lungs (Figure 10-49).
- **PFT:** Spirometry and lung volumes usually normal, with a decreased DLCO.
- **Arterial blood gas testing:** Useful in determining whether hypoxemia or acidosis plays a role in the disease's cause.
- **Echocardiogram:** Elevated right ventricular systolic pressure with possible right ventricular dysfunction or hypertrophy.
- **Pathology:** Intimal hyperplasia and medial hypertrophy of small arteries and arterioles, leading to obliteration of the lumen. Plexogenic (web-like) lesions are typically seen in idiopathic disease. Thickening of the walls of larger arteries is also seen. Right ventricular hypertrophy is also a feature.

Treatment

Supplemental O_2 therapy, various vasodilators (eg, sildenafil, bosentan, prostacyclins), inhaled nitric oxide, and possibly anticoagulation therapy. See the Pharmacology section of this chapter for a more detailed discussion.

Prognosis

- Right-sided heart failure can occur due to elevated right-sided pressures.
- Idiopathic (primary) pulmonary hypertension: Poor prognosis, often resulting in death within a few years of diagnosis if untreated.

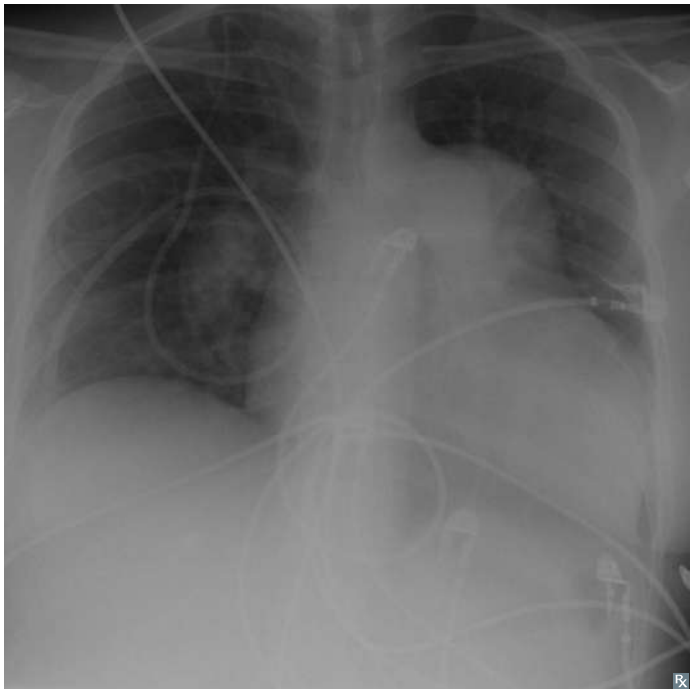


FIGURE 10-49. Pulmonary arterial hypertension. Chest x-ray shows characteristic radiologic features.

Sleep Apnea

Sleep apnea is characterized by repeated cessation of breathing for at least 10 seconds during sleep. Apneic episodes disrupt normal sleep cycles, preventing individuals from getting adequate rest. Thus, **daytime somnolence** is a hallmark presentation of sleep apnea.

Etiology of sleep apnea is classified as either obstructive or central. With **obstructive sleep apnea (OSA),** the airways collapse during sleep. This is due to excess weight of the chest wall pressing down on the airways (associated with obesity) and/or decreased vagal tone, which decreases smooth muscle tone and increases the tendency for the airways to collapse on themselves during sleep. **Central sleep apnea (CSA)** is characterized by a lack of respiratory drive during sleep (airways remain patent) and is associated with central nervous system (CNS) injury/toxicity and congestive heart failure.

KEY FACT

Cheyne-Stokes respirations refer to a cyclic breathing pattern in which a period of apnea is followed by a gradual increase in tidal volume and respiratory rate, then a gradual decrease until the next apneic period. This occurs when damage to the respiratory center causes a delay between the brain stem's detection of changes in blood gas levels (afferent response) and the compensatory adjustments in respiration (efferent response).

KEY FACT

Obesity hypoventilation syndrome (OHS) is a clinical picture in which obese patients have decreased respiratory drive. This condition is characterized by obesity (BMI ≥ 30) and hypercapnia ($Paco_2$ > 45) during the waking hours. Most patients with OHS also have coexisting OSA.

Presentation

- **OSA:** Daytime sleepiness (most common) or fatigue. Patients are **obese** adults with a history of excessive **snoring** (often reported by the patient's spouse or partner). OSA can also present in children with **tonsillar hypertrophy.**
- **CSA:** Daytime sleepiness and morning headaches. The patient's spouse or partner might report seeing the patient stop breathing during the night, sometimes in the context of **Cheyne-Stokes respirations** (see Key Fact). Look for a previous history of CNS injury.

Diagnosis

- **Physical exam:** If OSA is suspected, look for obesity and/or enlarged tonsils. Physical exam is usually unremarkable in patients with CSA.
- **Polysomnography** (sleep study) is the **gold standard.**
- **Arterial blood gas:** Both OSA and CSA are associated with hypoxemia (decreased Pao_2) and hypercapnia (increased $Paco_2$) during sleep secondary to hypoventilation. If associated with obesity hypoventilation syndrome (see Key Fact), these patients will also have increased $Paco_2$ during the waking hours.
- **Chest radiography:** Right ventricular hypertrophy if sleep apnea is complicated by cor pulmonale.

Treatment

The mainstay of treatment for sleep apnea is positive airway pressure (PAP) during sleep.

- Continuous positive airway pressure **(CPAP):** Continuous delivery of positive pressure keeps the airways open in patients with **OSA.**
- Bi-level positive airway pressure **(BiPAP):** Provides a baseline CPAP but also provides additional positive airway pressure whenever the patient initiates a breath. This helps patients with **CSA** take full breaths during sleep. BiPAP can also be programmed to initiate breaths whenever patients fail do so on their own.

Prognosis

If untreated, chronic hypoxemia causes vasoconstriction of pulmonary vessels, leading to pulmonary hypertension and **cor pulmonale.** This is prevented by using PAP during sleep, especially in the case of OSA.

RESPIRATORY TRACT CANCERS

Lung Cancer

Primary lung cancer is the second-most-common cancer by incidence, as well as the leading cause of cancer-related death in both males and females.

Cigarette smoking is clearly related to certain types of lung cancer. While quitting reduces subsequent risk of developing lung cancer, this risk likely never drops to that of a nonsmoker. Family history and occupational exposures, including arsenic, radon, haloethers, hydrocarbons, and agents associated with pneumoconioses (eg, asbestosis, silicosis), can predispose to lung cancer.

Lung cancer is broadly categorized as small cell or non–small cell subtypes. Non–small cell is further classified as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and bronchial carcinoid tumors. The five major types of primary lung cancer are discussed below.

Small Cell Lung Cancer

Small cell lung cancer (SCLC), previously known as oat cell carcinoma, is a neuroendocrine tumor arising from **Kulchitsky cells.** It typically arises centrally in the lung from bronchi and is strongly associated with smoking. Commonly associated with upregulation of **c-Kit** and amplification of the **L-myc (MYCL1)** oncogene (gain-of-function transcription factor mutation), SCLC is composed of undifferentiated cells and is very aggressive. A key feature of SCLC is that it is usually **surgically unresectable** due to lymph node invasion and/or distant metastasis at diagnosis. Treatment is therefore chemotherapy and/or radiation, but the prognosis and long-term survival after diagnosis are grim.

Histology shows **small round "blue" cells with sparse cytoplasm,** finely dispersed chromatin, and no distinct nucleoli (Figure 10-50A) that usually stain positive for **synaptophysin, neuron-specific enolase, and chromogranin A.**

SCLC is commonly associated with paraneoplastic syndromes such as Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), cerebellar ataxia, and **Lambert-Eaton myasthenic syndrome (LEMS).** LEMS is an autoimmune condition involving autoantibodies against presynaptic voltage-gated calcium channels. Inhibition of these channels prevents the release of neurotransmitters. It presents with **proximal muscle weakness** that improves with activity and signs of **autonomic dysfunction,** such as dry mouth and impotence.

Adenocarcinoma

Adenocarcinoma is the most common primary lung cancer (50% of cases) in the overall population, as well as in nonsmokers. It is more common in women than men. There is no clear relationship between adenocarcinoma and smoking. Adenocarcinoma arises from mucin glands located **peripherally** in the lung or old scar sites (usually due to infection or injury and found in a subpleural location). The clinical picture of **hypertrophic osteoarthropathy** is associated with adenocarcinoma of the lung and is characterized by digital clubbing and sudden-onset symmetrical arthropathy, usually involving the wrists and hands.

Adenocarcinoma is associated with activating mutations of *k-ras*, *EGFR*, and *ALK*. On histology, adenocarcinoma shows a **glandular pattern** that often stains positive for **mucin** (Figure 10-50B). Stains such as periodic acid-Schiff (PAS) or mucicarmine are required to demonstrate intracellular mucin.

Bronchioloalveolar adenocarcinoma (BAC) originally described a subtype of invasive adenocarcinoma of the lung characterized by well-differentiated cytology, peripheral location, and growth along intact alveolar walls ("lepidic" growth pattern). BAC has since been reclassified into new subgroups based on histology. BAC is discussed below; however, a detailed description of each subgroup is beyond the scope of this text.

BAC arises from Clara cells (nonciliated columnar epithelium) and grows along alveolar septa, giving the appearance of **thickened alveolar walls** on histology. Many cases of BAC are asymptomatic and detected after incidental imaging. The classic radiologic presentation of BAC is a solitary pulmonary nodule in the lung periphery, appearing as **ground glass** on chest computed tomography or **hazy infiltrates** on chest radiograph. More extensive disease may present with lobar consolidation, mimicking bacterial pneumonia. BAC rarely invades the basement membrane and has a good prognosis. BAC has been traditionally described as having no relationship to smoking. However, newer studies show a definite and direct relationship between smoking and BAC.

Squamous Cell Carcinoma

Squamous cell carcinoma develops **centrally** in the lung, arising from squamous epithelium of proximal large airways. It can be seen on chest radiographs as a hilar mass (sometimes with **cavitation**) arising from the bronchus (Figure 10-50C). Squamous cell carcinoma is strongly associated with smoking and more common in men than women. Classically, squamous cell carcinoma is associated with the paraneoplastic syndrome **hypercalcemia of malignancy** secondary to production of parathyroid hormone–related peptide (**PTHrP**). On histology, **keratin pearls** (Figure 10-50D) and **intercellular bridges** are characteristic. Staining for **desmoglein** is usually positive.

Large Cell Carcinoma

Large cell carcinoma (LCC) is a highly anaplastic undifferentiated tumor with a poor prognosis. LCC is associated with smoking and arises from epithelial cells, commonly in the lung **periphery,** though central tumors sometimes occur. No glandular or squamous differentiation is present in LCC. Thus, LCC is a diagnosis of exclusion and includes all non–small-cell lung carcinomas (NSCLCs) that cannot be further classified. Unlike SCLC, it is less responsive to chemotherapy and is usually **surgically resected.** Histology shows **sheets of pleomorphic giant cells,** polygonal in shape with prominent nucleoli and pale-staining cytoplasm. In some cases, these cells can secrete **β-hCG.**

Bronchial Neuroendocrine (Carcinoid) Tumors

Bronchial neuroendocrine (carcinoid) tumors (NETs) are a group of lung neoplasms that arise from peptide- and amine-producing neuroendocrine cells. There is no clear association with smoking or genetic predisposition, with rare exceptions (eg, multiple endocrine neoplasia, type 1). Bronchial NETs can arise centrally or peripherally in the lung, and growth as a **bronchial polyp-like mass** is a classic description.

CLINICAL CORRELATION

New-onset hypercalcemia is due to primary hyperparathyroidism or hypercalcemia of malignancy in over 90% of cases. Very high Ca^{2+} (> 13 mg/dl) is more commonly due to malignancy.

FLASH BACK

Hypercalcemia commonly presents with nephrolithiasis **(stones),** bone pain **(bones),** constipation **(groans),** and altered mental status (psychiatric over**tones**).

MNEMONIC

Both small cell carcinoma and large cell carcinoma are composed of undifferentiated cells and have a poor prognosis. **Small** cell carcinoma is unresectable because the cells are too **small** for the surgeon to see. **Large** cell carcinoma is surgically resectable because the cells are **large.**

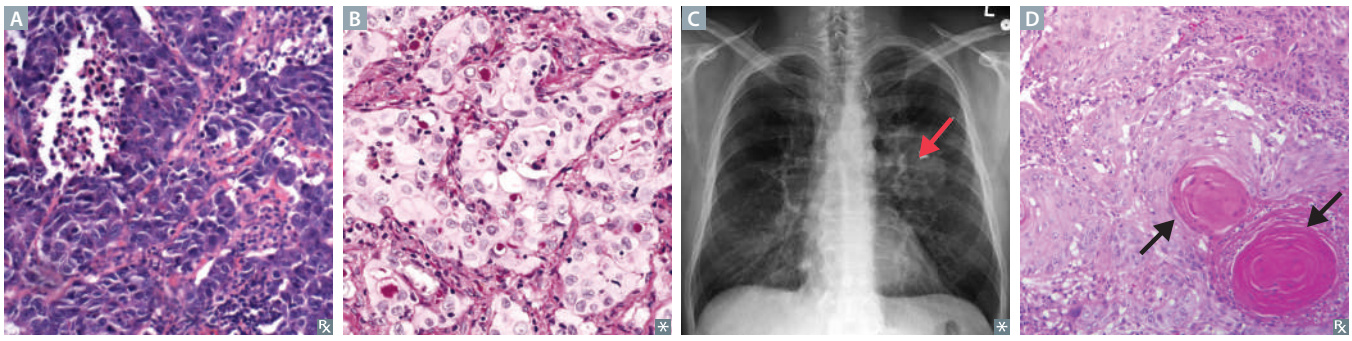


FIGURE 10-50. Lung cancer. A Small dark blue cells in small cell carcinoma. B Glandular pattern in adenocarcinoma. C Squamous cell carcinoma showing hilar mass on chest radiograph and D keratin pearls on histology.

Bronchial NETs are generally low-grade (well-differentiated) benign tumors with an excellent prognosis. Metastasis is rare. While most symptoms are due to mass effect (eg, dyspnea, wheezing), bronchial NETs may be associated with **carcinoid syndrome** (flushing, diarrhea, wheezing) secondary to ectopic serotonin (5-HT) production. Histology shows **nests of neuroendocrine cells** that, similarly to small cell carcinoma, stain positive for **synaptophysin, chromogranin A,** and **neuron-specific enolase.**

MNEMONIC

SPHERE of complications (of lung cancer):
Superior vena cava syndrome
Pancoast tumor
Horner syndrome, **H**oarseness
Endocrine (paraneoplastic)
Recurrent pneumonia
Effusions (pleural or pericardial)

Presentation

Patients with lung cancer generally present with nonspecific complaints, such as coughing, hemoptysis, dyspnea, and wheezing. As with all malignancies, weight loss and anorexia are common. Additionally, lung neoplasms can obstruct airways, causing distal infections (eg, lobar pneumonia). Based on the location and other characteristics (discussed below), lung cancer is also associated with certain clinical syndromes:

- **Superior vena cava (SVC) syndrome:** Tumor compression of the SVC obstructs venous drainage from the head/neck (sometimes causing facial plethora) and upper extremities. This leads to swelling, cyanosis, and venous distension in the aforementioned regions. Blanching can be appreciated in these regions (Figure 10-51A). Patients present with headaches and dizziness due to increased intracranial pressure. Commonly caused by Pancoast tumors (see below) and thrombosis from indwelling catheters (Figure 10-51B). This is a medical emergency, as patients are at increased risk of aneurysm formation/rupture within the intracranial arteries.
- **Pancoast tumor (superior sulcus tumor):** Carcinoma that arises in apex of the lung (Figure 10-51C). Can involve surrounding structures, causing a variety of syndromes (discussed below). These syndromes can coexist in a variety of combinations, collectively referred to as **Pancoast syndrome.**
  - SVC syndrome: Discussed above.
  - Horner syndrome: Ipsilateral ptosis, miosis, and anhydrosis. Due to invasion of cervical sympathetic chain.
  - Sensorimotor deficits: Due to compression of brachial plexus. A commonly tested presentation is Klumpke palsy ("claw hand"), secondary to lower trunk involvement.
  - Thoracic outlet syndrome: Use-dependent ischemic arm pain. Due to compression of subclavian vessels.
  - Hoarseness: From involvement of the recurrent laryngeal nerve (branch of the vagus nerve).
- **Paraneoplastic syndromes:** Includes hypercalcemia (squamous cell carcinoma), Cushing syndrome, SIADH, and Lambert-Eaton syndrome (small cell carcinoma).
- **Recurrent lobar pneumonia:** Due to persistent blockage (either internal obstruction of external compression) of a bronchus segment.
- **Effusions (pleural or pericardial):** Malignancy should always be considered in these cases.

CLINICAL CORRELATION

The recurrent laryngeal nerve provides motor innervation to all of the laryngeal muscles except for the cricothyroid muscle.

KEY FACT

Bronchial hamartoma is the most common benign lung tumor. They contain islands of mature hyaline cartilage (hence the term, "hamartoma") and typically present as a well-defined coin lesion with **"popcorn" calcification** on chest x-ray. Of note, not all coin lesions are hamartomas.

In the event of metastasis, primary lung cancer most commonly spreads to the adrenals, brain, bone, and liver. In many cases, lung cancer is asymptomatic and incidentally detected as a solitary well-defined lung nodule ("coin lesion") on imaging.

Of note, metastasis to the lung (secondary lung cancer) is more common than primary lung cancer, as the lung's extensive vasculature renders it vulnerable to hematogenous seeding from distant sites. Multiple tumors on imaging should raise suspicion for metastatic disease. Metastasis to the lung is most commonly from primary breast cancer. Colon cancer, prostate cancer, and renal cell carcinoma are also frequent primary neoplasm sites.

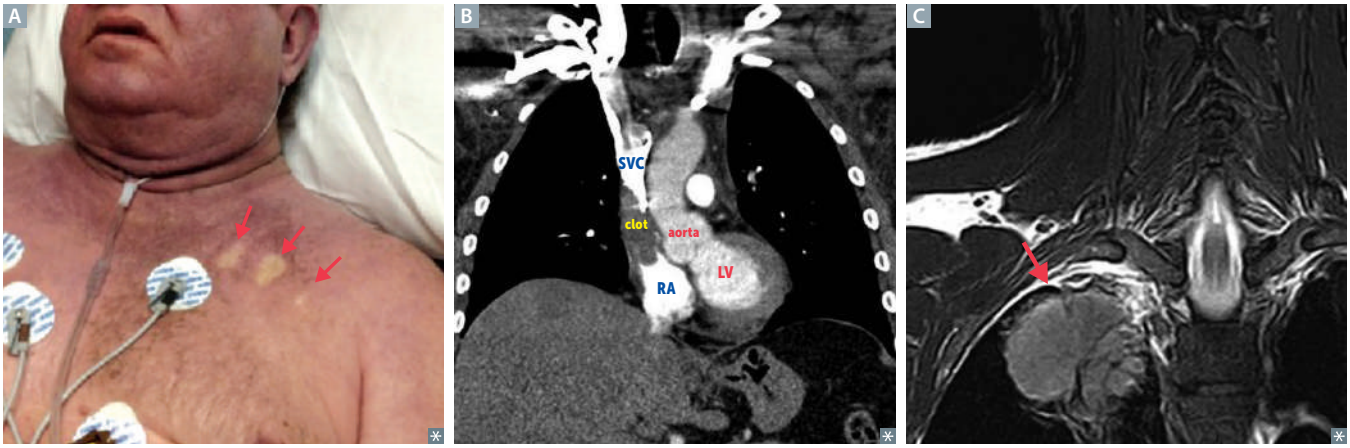


FIGURE 10-51. Superior vena cava and Pancoast tumor. A Blanching after fingertip pressure seen in superior vena cava (SVC) syndrome. B Coronal contrast-enhanced CT of chest showing low-density clot at junction of SVC and right atrium (RA). C Pancoast tumor: Chest MRI shows mass (arrow) at right lung apex. LV, left ventricle.

Diagnosis

- **Chest film:** Nodule or mass within the lung.
  - **Centrally located:** Squamous and small cell.
  - **Peripherally located:** Adenocarcinoma and large cell. Involvement of the hilar lymph nodes or pleura can also be seen.
  - An exception to this is the bronchioloalveolar subtype of adenocarcinoma, which often has a more diffuse radiographic appearance, termed **ground-glass opacity,** similar to pneumonia.
- **CT or positron emission tomography (PET) scans:** To determine location, lymph node involvement, or metastasis for staging.
- **Cytologic examination** of sputum or washings from bronchoscopy, or tissue pathology from a **lung biopsy.**
- **PFT:** To assess whether a patient has the residual capacity to survive surgical resection of a tumor.
- **Pathology:** Multiple tumors arising at once should raise suspicion for metastatic disease from a primary tumor outside the lungs, as the lung's extensive vasculature makes it a nidus for hematogenous seeding.

Treatment

- **Small-cell carcinoma:** Metastases occur very early in the disease course, so surgery is not an option, only chemotherapy and/or radiation.
- **NSCLC:** Surgical resection if there is no distant spread. If metastases are present, then chemotherapy and/or radiation.

Prognosis

Overall 5-year survival is about 14%. Squamous cell carcinoma has the best prognosis, and small-cell carcinoma has the worst. Early-stage disease, while rarely found, has a much better prognosis than late-stage disease.

Mesothelioma

Mesothelioma is a malignancy of the pleura, strongly associated with **asbestosis.** Classically presents with pleural thickening and **recurrent pleural effusions** (often hemorrhagic) on imaging. Electron microscopy is the gold standard for diagnosis and shows tumor cells with numerous **long, slender microvilli** and abundant tonofilaments. **Psammoma bodies** are seen on histology.

MNEMONIC

Squamous and **S**mall cell carcinomas are **S**entral (central) and strongly associated with **S**moking.

KEY FACT

Sites for metastasis of primary lung cancers (ranked by frequency):

1. Hilar lymph nodes
2. Adrenal glands
3. Liver
4. Brain
5. Bone (osteolytic)

KEY FACT

Asbestosis increases the risk for both mesothelioma and bronchogenic carcinoma. While this risk is amplified more in mesothelioma than in bronchogenic carcinoma, the latter is still more common in people with asbestos exposure.

QUESTION

A 40-year-old woman complains of progressive weakness in her right arm over 1 month. She has a 20 pack-year smoking history. Physical exam shows ptosis and miosis on the right side. What is the most likely cause?

MNEMONIC

PSa**MM**oma bodies are seen in
Papilllary carcinoma of the thyroid
Serous papillary cystadenocarcinoma of the ovary
Meningioma
Malignant mesothelioma

Malignancies of the Upper Respiratory Tract

Benign Laryngeal Tumors

The most common clinical presentation is hoarseness.

- **Vocal cord nodules:** Smooth hemispheric protrusions located on the true vocal cords. These occur chiefly in heavy smokers and singers.
- **Laryngeal papilloma:** A benign neoplasm on the true vocal cords that forms a soft, raspberry-like excrescence. Rarely more than 1 cm in diameter.
- **Juvenile laryngeal papillomas:** Usually singular in adults but multiple in children. Associated with human papillomavirus types 6 and 11.

Laryngeal Carcinoma

Accounts for 2% of all cancers. Presents in patients aged > 40 years, more often in men than in women. Associated with smoking, alcohol consumption, and asbestos exposure. Manifests as persistent hoarseness.

- **Glottic tumors:** On the true vocal cords, usually keratinizing.
- **Supraglottic tumors:** Above the vocal cords; one-third metastasize.
- **Subglottic tumors:** Below the vocal cords.

FLASH BACK

EBV produces several proteins that modulate growth signaling in B lymphocytes. This property explains why EBV infection can lead to Burkitt lymphoma, Hodgkin lymphoma, or nasopharyngeal carcinoma, in addition to many other lymphoproliferative disorders.

Nasopharyngeal Carcinoma

Strong link to Epstein-Barr virus (EBV) infection. EBV infects the host by replicating in the nasopharyngeal epithelium and then infecting nearby tonsillar B lymphocytes. High frequency in the Chinese population.

PULMONARY INFECTIONS

Pneumonia

Pneumonia is infection of the lung parenchyma. It is classified as either **community acquired** or **nosocomial** (hospital acquired). This distinction is important because individuals in the hospital setting undergo various interventions (eg, mechanical ventilation, urinary catheterization), which may predispose them to a different set of microorganisms than in the community. Specifically, *Pseudomonas aeruginosa* causes pneumonia almost exclusively in the healthcare setting.

CLINICAL CORRELATION

Because the right mainstem bronchus is positioned more vertically than the left mainstem bronchus, aspiration pneumonia typically affects the right lower and middle lobes.

Community-acquired pneumonia can be further classified according to presentation (typical or atypical) as well as the infiltration pattern seen on chest x-ray (lobar, patchy, or interstitial). These classifications are outlined in Figure 10-52 and elaborated on in the following discussions.

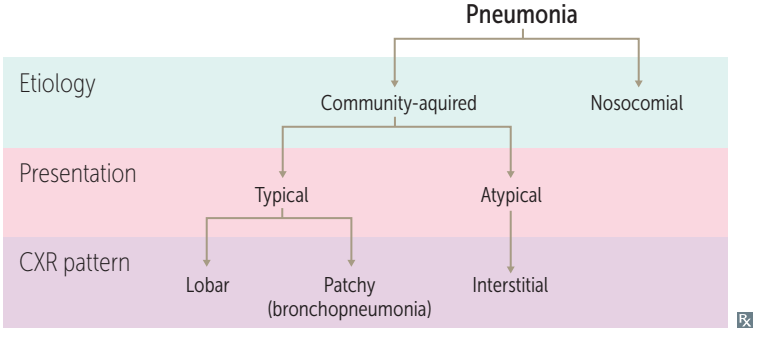


FIGURE 10-52. Pneumonia classifications based on etiology, presentation, and pattern on chest x-ray (CXR).

ANSWER

Pancoast syndrome. Unilateral sensorimotor deficits in the upper extremity and Horner syndrome should raise suspicion for a Pancoast tumor, especially when presenting together. This diagnosis is further supported by the patient's smoking history.

Aspiration pneumonia is another type of pneumonia that develops when oral flora (including anaerobes) are aspirated into the lung. Risk factors for developing aspiration pneumonia include decreased consciousness (eg, in the elderly and alcoholics, and in seizures) and neuromuscular diseases. Aspiration pneumonia can be acquired in the community or in a hospital setting.

The most common causes of pneumonia vary with the patient's age and are associated with specific risk factors. These organisms are listed in Tables 10-17 and 10-18, respectively.

Presentation

- Community-acquired pneumonia:
  - **Typical pneumonia:** Acute onset of fever, dyspnea, and productive cough with purulent sputum. Sputum can also be blood-tinged or "rusty" in appearance due to rupture of pulmonary microvasculature. Pleuritic chest pain can also be present due to inflammation adjacent to the pleura. In some cases, elderly patients can present with epigastric pain rather than chest pain.
  - **Atypical pneumonia:** More indolent course and usually presents with dry cough.
- Nosocomial pneumonia and aspiration pneumonia have a similar presentation to typical pneumonia. Look for additional risk factors, such as an extended hospital stay or decreased consciousness.

Diagnosis

- **Physical exam:**
  - Tachycardia, tachypnea, fever.
  - **Crackles** over the affected area on auscultation.
  - If affected airways are patent, **bronchial breath** sounds (louder, especially during exhalation) can be heard on auscultation. If the airways are completely blocked from consolidation, breath sounds will be decreased in affected areas.
  - **Dullness** to percussion, **increased fremitus,** and **egophony** suggest frank consolidation or associated effusion.
- **Chest x-ray:** Gold standard. Allows classification of pneumonia as lobar, patchy (bronchopneumonia), or interstitial (atypical).
  - **Lobar pneumonia:** Consolidation involves the entire lobe from intra-alveolar exudates. Can involve one or more lobes (Figure 10-53A,B). Most common organism is *Streptococcus pneumoniae*. Also *Legionella* and *Klebsiella*.
  - **Bronchopneumonia:** Patchy consolidation distributed around bronchioles and adjacent alveoli (Figure 10-53C). Often multifocal and bilateral (Figure 10-53D). Most common organisms are *S pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Klebsiella*.

KEY FACT

Mycoplasma, Chlamydia, and *Legionella* are commonly referred to as atypical organisms because they cause atypical pneumonia and do not appear on Gram stain. Their special staining and culture requirements are as follows:

- ***Mycoplasma*—**Eaton agar
- ***Chlamydia*—**Giemsa stain
- ***Legionella*—**Charcoal yeast extract agar (buffered with cysteine and iron)

FLASH BACK

Fremitus refers to the vibrations transmitted through the body whenever the patient vocalizes. With increased fremitus, transmission of the patient's voice will be louder (vocal fremitus) and vibrations will be stronger (tactile fremitus) on lung auscultation and palpation, respectively.

FLASH BACK

Egophony refers to modified voice transmission through the body during lung auscultation. It is classically detected by having the patient produce and hold an "E" sound. In cases of egophony, transmission will be such that the examiner hears an "A" sound through the stethoscope.

TABLE 10-17. Most Common Causes of Pneumonia by Age

NEONATES (< 4 WK)	CHILDREN (4 WK–18 YR)	ADULTS (18–40 YR)	ADULTS (40–65 YR)	ELDERLY (> 65 YR)
Group B streptococci	Viruses (RSV)	*Mycoplasma*	*S pneumoniae*	*S pneumoniae*
Escherichia coli	*Mycoplasma*	*C pneumoniae*	*Haemophilus influenzae*	Influenza virus
	Chlamydia trachomatis (infants–3 yr)	*Streptococcus pneumoniae*	Anaerobes	Anaerobes
	Chlamydophila pneumoniae (school-aged children)		Viruses	*H influenzae*
	S pneumoniae		*Mycoplasma*	Gram-negative rods

TABLE 10-18. Populations Predisposed to Pneumonia with Associated Organisms

POPULATION	ORGANISMS
Alcoholism, IV drug use	*Streptococcus pneumoniae, Klebsiella, Staphylococcus aureus*
Aspiration	Anaerobes (eg, *Peptostreptococcus, Fusobacterium, Prevotella, Bacteroides*)
Cystic fibrosis	*Pseudomonas, S aureus, S pneumoniae*
Immunocompromised	*S aureus,* enteric gram-negative rods, fungi, viruses, *Pneumocystis jirovecii* (with HIV)
Nosocomial	*S aureus, Pseudomonas, Escherichia coli,* other enteric gram-negative rods
Postviral	*S aureus, Haemophilus influenzae, S pneumoniae*

  - **Interstitial (atypical) pneumonia:** Diffuse patchy inflammation localized to the interstitial areas at alveolar walls (Figure 10-53E). Sometimes very subtle on x-ray. Most common organisms are *Mycoplasma*, *Legionella*, *Chlamydia*, and viruses (influenza, respiratory syncytial virus [RSV], adenovirus).
- **Arterial blood gas testing:** Reduced Pa_{O_2} with normal or reduced Pa_{CO_2} due to tachypnea.
- **Sputum Gram stain and culture:** Depends on the infecting organism. Of note, the organisms causing atypical pneumonia do not show up on Gram stain. Hence, they are commonly referred to as "atypical" organisms. The most common organisms associated with pneumonia, along with their distinguishing features and specific treatment options, are outlined in Tables 10-19 and 10-20.

Treatment

Antimicrobial therapy is the mainstay for bacterial and fungal pneumonia.

- Community-acquired pneumonia:
  - In general, patients without comorbidities (eg, diabetes, COPD, heart failure, renal failure, liver failure) should be treated with macrolides (eg, azithromycin, clarithromycin) or doxycycline.
  - The elderly and patients who have comorbidities or require hospitalization should be treated with a fluoroquinolone.
- Nosocomial pneumonia:
  - Treatment should be tailored toward gram-negative rods. This includes cephalosporins (specifically, ceftazidime or cefepime for *Pseudomonas* coverage), carbapenems, or piperacillin/tazobactam.
- Fungal infections:
  - If pneumonia is due to endemic mycoses, treat with itraconazole or fluconazole. Amphotericin B and newer generation -azoles are used in cases of disseminated infection.

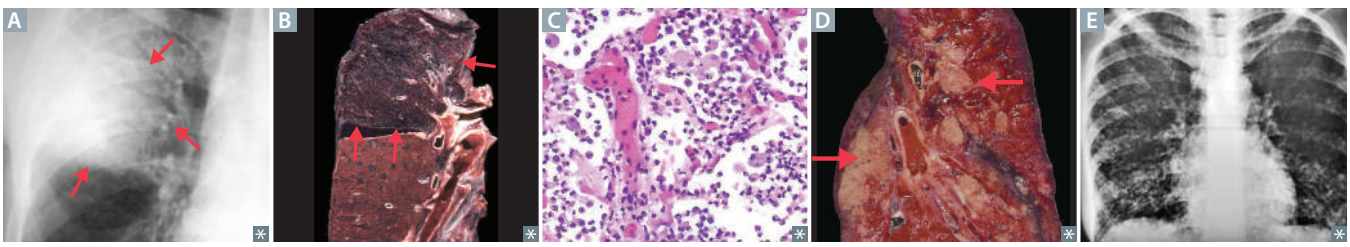


FIGURE 10-53. Pneumonia. A Lobar pneumonia chest x-ray and B gross specimen. C Bronchopneumonia histology showing neutrophils in alveolar spaces and D gross specimen showing multifocal peribronchiolar involvement. E Interstitial pneumonia chest x-ray showing coarse bilateral reticular opacities, worse on the right.

TABLE 10-19. Bacterial Causes of Pneumonia

ORGANISM	CHARACTERISTICS	TREATMENT
Gram-Positive Bacteria		
Streptococcus pneumoniae	Gram-positive cocci (chains). Most common cause of community-acquired pneumonia.	Penicillins First- and second-generation cephalosporins Macrolides (if penicillin allergic) Quinolones
Staphylococcus aureus	Gram-positive cocci (clusters). Usually causes bronchopneumonia.	MSSA: First or second-generation cephalosporins Penicillinase-resistant penicillins MRSA: Vancomycin, ceftaroline, linezolid, tigecycline
Gram-Negative Bacteria		
Haemophilus influenzae	Gram-negative coccobacilli. Requires chocolate agar with hematin (factor X) and NAD+ (factor V) for culture.	Amoxicillin +/– clavulanate Second- or third-generation cephalosporins
Klebsiella pneumoniae	Gram-negative rod. Associated with aspiration pneumonia in diabetics, alcoholics, and IV drug users. Red "currant-jelly" sputum. Large mucoid colonies with abundant polysaccharide capsules.	Aminoglycosides First-, second-, or third-generation cephalosporins
Pseudomonas aeruginosa	Gram-negative rod. Non-lactose fermenting, oxidase (+). Produces pyocyanin (blue-green pigment) and has grape-like odor.	Extended-spectrum β-lactams Carbapenems Aztreonam Ciprofloxacin Aminoglycosides Colistin, polymyxin B (multidrug-resistant strains)
Legionella pneumophila	Gram-negative rod that stains poorly; requires silver stain. Grows on charcoal yeast extract culture with iron and cysteine. Aerosol transmission from environmental water sources (eg, air conditioning systems, hot water tanks, cruise ships). Labs show hyponatremia.	Macrolides Quinolones
Moraxella catarrhalis	Gram-negative diplococcus. Typically associated with otitis media (children) and COPD exacerbations (elderly), but can cause pneumonia in the latter population.	Second- or third-generation cephalosporins Macrolides Quinolones
Other Bacteria (eg, Anaerobes, Intracellular)		
Anaerobes	Part of normal oral flora. Associated with aspiration pneumonia.	Clindamycin
Mycoplasma pneumoniae	No cell wall. Not seen on Gram stain. Cultured on Eaton agar. Classic cause of atypical ("walking") pneumonia. Interstitial pattern on CXR looks worse than patient does. Outbreaks are frequently seen among military recruits and in prisons. Associated with cold-agglutinin (IgM) autoimmune hemolytic anemia.	Macrolides Doxycycline Fluoroquinolone
Chlamydia	Obligate intracellular organisms. Cell wall lacks muramic acid. Does not show up on Gram stain. Giemsa or fluorescent antibody-stained smear shows cytoplasmic inclusions. *C pneumoniae* and *C psittaci* cause atypical pneumonia.	Macrolides Doxycycline
Coxiella burnetii	Rickettsial organism. Obligate intracellular. Causes Q fever, which presents as pneumonia. Transmitted by spore inhalation from cattle/sheep amniotic fluid.	Doxycycline

COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; MRSA, methicillin-resistant *S aureus;* MSSA, methicillin-sensitive *S aureus;* NAD+, oxidized nicotinamide adenine dinucleotide.

TABLE 10-20. Fungal and Viral Causes of Pneumonia

ORGANISM	CHARACTERISTICS	TREATMENT
Pneumocystis jirovecii (PCP)	Causes interstitial pneumonia in immunosuppressed patients (especially AIDS). Diagnosed by lung biopsy or lavage. Disc-shaped yeast seen with methenamine silver stain of lung tissue.	Treatment: TMP-SMX, pentamidine Prophylaxis: TMP-SMX, pentamidine, dapsone, atovaquone
Endemic mycoses	**Histoplasmosis:** Mississippi and Ohio River valleys. Found in bird/bat droppings. Macrophages filled with *Histoplasma*. **Blastomycosis:** States east of Mississippi River and Central America. Broad-based budding. **Coccidiomycosis:** Southwestern United States, California. Spherules filled with endospores. **Paracoccidioidomycosis:** Latin America. Budding yeast with "captain's wheel" formation.	Azoles Amphotericin B (for disseminated infections)
Cryptococcus neoformans	Opportunistic infection (classically HIV patients). Found in soil and pigeon droppings. Acquired through inhalation. Cryptococcosis presents like pneumonia. Can disseminate hematogenously to meninges, causing cryptococcal meningitis. Heavily encapsulated yeast. Culture on Sabouraud agar; stains with India ink and mucicarmine. Definitively diagnosed with latex agglutinin test (detects polysaccharide capsular antigen).	Cryptococcal meningitis: Amphotericin B + flucytosine Non-CNS cryptococcosis: Fluconazole
Viruses	Most commonly influenza virus, RSV, adenovirus. Causes atypical pneumonia.	Paracoccidioidomycosis

CNS, central nervous system; RSV, respiratory syncytial virus; TMP-SMX, trimethoprim-sulfamethoxazole.

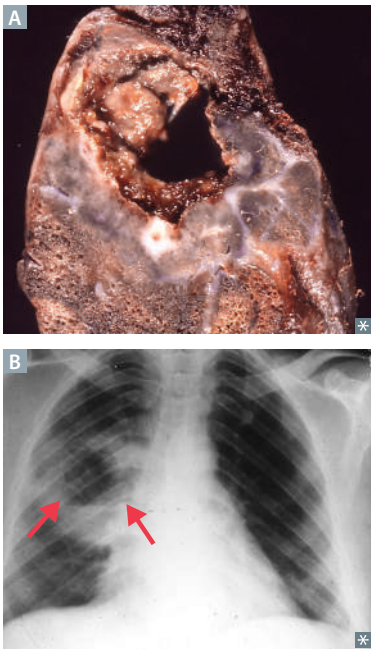


FIGURE 10-54. Lung abscess. A Gross specimen. B Cavitation with air-fluid levels (arrows) visible on x-ray of the chest.

- All HIV patients with a CD4+ count lower than 200 cells/mm^3 should receive prophylaxis against *Pneumocystis jirovecii* (PCP). Therapy can include trimethoprim-sulfamethoxazole (TMP-SMX; most common, except with sulfa allergy), pentamidine, dapsone, or atovaquone. Existing PCP infections can be treated with TMP-SMX or pentamidine.
- Viral pneumonias are usually self-limited, requiring only supportive care, although the use of certain antiviral agents (eg, oseltamivir, zanamavir) has been shown to decrease the duration of influenza infections by approximately 24 hours.
- Refer to Table 10-19 and Table 10-20 for organism-specific treatments.

Prognosis

In most cases, appropriate treatment results in complete recovery without long-term sequelae, but morbidity and mortality increase with age. Complications include:

- **Lung abscess:** Localized pus collection within the lung parenchyma (Figure 10-54A). Common complication of aspiration pneumonia or bronchial obstruction (eg, tumor). Infecting organisms include anaerobic oral flora (eg, *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*) or *S aureus*. Patients typically present with symptoms of pneumonia unresponsive to antibiotics. Chest imaging shows cavitations with air-fluid levels, often in the right lung in the case of aspiration (Figure 10-54B). Treat with clindamycin.
- **Empyema:** Pus in the pleural space. Often caused by anaerobes and staphylococci. Requires drainage.

Tuberculosis

Approximately one-third of the world's population has been infected with TB, which results in 2–3 million deaths each year. The burden of disease is greatest in developing countries.

TB is primarily caused by *Mycobacterium tuberculosis*, an aerobic, rod-shaped, acid-fast bacterium (colloquially termed "red snappers" due to their appearance on Ziehl-Neelsen acid-fast stain), which is transmitted by airborne droplets from infected patients. The disease is so named because of the immune system's attempt to quarantine mycobacteria within dense granulomas ("tubercles") consisting of a core of macrophages surrounded by supporting T lymphocytes. There are three forms of TB: primary, secondary, and miliary.

- **Primary TB:** At initial infection, a **Ghon complex** develops, consisting of a peripheral parenchymal lesion called a **Ghon focus** and granulomas in involved hilar lymph nodes. The Ghon focus develops into a granuloma and eventually undergoes caseating necrosis at its core. Over time, the Ghon complex may calcify and heal into a **Ranke complex.**
- **Secondary (reactivation) TB:** Results from reactivation of a prior site of infection, where the bacteria became dormant but were never cleared. Lesions are localized to the lung apices (region of greatest aeration) with hilar lymph node involvement. Granulomatous lesions form and rupture, resulting in cavitary lesions. Scarring and calcification may be seen.
- **Miliary TB:** Disseminated disease caused by hematogenous spread of bacteria. It may follow from primary or secondary TB. The granuloma-filled lung takes the appearance of being filled with millet seeds, hence the name. Prognosis is very poor without treatment.

Presentation

Pulmonary symptoms include chronic productive cough and hemoptysis. Respiratory function is generally well-preserved, perhaps because of localization of the destructive disease to the Ghon complex in primary TB and to the apices in secondary TB. Systemic symptoms include weight loss, fever, and night sweats.

Diagnosis

- **Physical exam:**
  - **Primary TB:** Fever, chest pain. Often fairly normal physical exam.
  - **Secondary TB:** Cough (evolving into hemoptysis), weight loss, wasting, night sweats.
  - Crackles over the affected area on auscultation.
- **Tuberculin skin test (PPD or Mantoux test):** Acts through a type IV hypersensitivity reaction. A small amount of purified protein derivative (PPD) from *M tuberculosis* is injected subcutaneously. Induration at the site after 48–72 hours indicates prior exposure to TB. This does not differentiate between active and prior infections, and false-positives occur in individuals with prior vaccination with the variably effective BCG (bacillus Calmette-Guérin) vaccine. In contrast, the **interferon-gamma release assay** (IGRA; also known as **QuantiFERON GOLD**) is not affected by the BCG vaccine and can be used as an alternative to the PPD test in individuals who have received BCG vaccination.
- **Chest film:**
  - **Primary TB:** Nonspecific, often lower lobe infiltrate, hilar lymph node enlargement, and pleural effusion.
  - **Secondary TB:** Lesions located in the apices or superior segment of a lower lobe. Infiltrates, cavities, nodules, scarring, and/or contraction may be seen (Figure 10-55).
- Culture of the organism from sputum is needed for a definitive diagnosis. **Acid-fast staining** is useful for quicker results.

MNEMONIC

The **4 R's** of rifampin:
- **R**amps up cytochrome P450 metabolism
- Causes **R**ed or orange urine
- Leads to rapid **R**esistance when used alone
- Acts by inhibiting **R**NA polymerase

Treatment

Six months of treatment with isoniazid (INH), pyridoxine (vitamin B_6), and rifampin, supplemented during the first 2 months with pyrazinamide and ethambutol. A current global challenge is the rise of multidrug-resistant (MDR) and, more recently, extensively drug-resistant (XDR) tuberculosis. MDR-TB is resistant to at least rifampin and isonia-

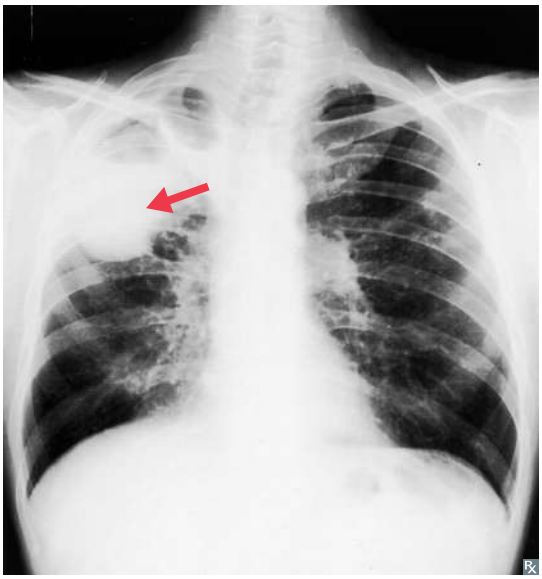


FIGURE 10-55. **Pulmonary tuberculosis.** Plain radiograph shows scarring with cavitation in the right upper lobe (arrow) and ill-defined infiltrates in the lower lobes.

MNEMONIC

Anti-TB drugs—

RIPES:
Rifampin
Isoniazid (INH)
Pyrazinamide
Ethambutol
Streptomycin
Even though streptomycin is no longer a first-line drug for TB, it has historical significance as the first drug to be discovered that could cure tuberculosis.

CLINICAL CORRELATION

The major side effects of **isoniazid** are hepatotoxicity, peripheral neuropathy, and CNS effects. The latter two are due to depletion of pyridoxine (vitamin B_6). Therefore, patients are given pyridoxine supplementation during isoniazid therapy.

FLASH BACK

Acute rheumatic fever (see Pathology section in Chapter 1) may occur following group A streptococcal pharyngitis only, whereas poststreptococcal glomerulonephritis (see section on Nephritic Syndrome in Chapter 8) may occur following pharyngitis or skin infections (eg, impetigo).

zid; XDR-TB is additionally resistant to several second-line therapies. The treatment of drug-resistant TB depends heavily on culture sensitivities.

Latent tuberculosis infection (LTBI) treatment for individuals with a positive PPD but no active disease generally consists of 9 months of INH plus pyridoxine. Note that this is not an appropriate regimen for active TB.

Prognosis

Most patients with primary TB are asymptomatic. Lifetime risk of reactivation is about 10% in immunocompetent patients. This is elevated in patients with AIDS or other immunosuppressive states. Reactivation TB can be complicated by miliary TB, in which distal organs are seeded with innumerable small lesions. Extrapulmonary TB includes tuberculous meningitis, Potts disease of the spine, psoas abscesses, paravertebral abscesses, tuberculous cervical lymphadenitis (scrofula), pericarditis, and kidney and GI involvement.

Upper Respiratory Tract Infections

Patients typically present with fever and sore throat. The age of the patient is also helpful in diagnosis. Physical exam may show a reddened oropharynx.

- **Pharyngitis:** Inflammation of the pharynx; manifests as a sore throat. Viral etiology is more likely than bacterial, but individuals with pharyngitis should be tested for *Streptococcus pyogenes* ("strep throat") because timely treatment with penicillin V is important for the prevention of serious sequelae such as rheumatic fever, although treatment does not prevent poststreptococcal (acute proliferative) glomerulonephritis.
- **Epiglottitis:** Syndrome of young children with an infection of the epiglottis (most frequently caused by *H influenzae*) causing pain and airway obstruction, often manifesting with uncontrollable drooling. The incidence of epiglottitis has fallen dramatically with the introduction of the *H influenzae* type b (Hib) vaccine.
- **Croup (laryngotracheobronchitis):** Croup is a common illness in children caused most often by the parainfluenza virus, influenza viruses, or respiratory syncytial virus (RSV). The typical presentation is a febrile child with barking cough, stridor, and hoarseness.

PLEURAL EFFUSION

Pleural effusion is excess fluid accumulation between the pleural layers (eg, parietal, visceral). Patients develop **dyspnea** as the accumulated fluid restricts inspiratory lung expansion. While there are several causes, workup begins with classifying the effusion as transudate, exudate, or lymphatic (discussed below).

Physical exam shows **dullness** to percussion over affected region (lung base if patient is sitting up). Chest imaging shows fluid within the chest cavity (Figure 10-56). **Thoracentesis** is both diagnostic and therapeutic. Of note, smaller effusions are often asymptomatic and self-resolving.

Transudate

Due to (1) **increased hydrostatic pressure** (ie, excess fluid backup) and/or (2) **decreased oncotic pressure** within the pulmonary vasculature. Because vascular permeability is usually unaffected, most proteins within the blood are too large to pass through the capillary membranes. Thus, transudate is **characterized by decreased protein content** within the accumulated fluid. Congestive heart failure (HF) is a common cause of increased hydrostatic pressure. Liver cirrhosis and nephrotic syndrome are common causes of decreased oncotic pressure.

Exudate

Due to **increased vascular permeability**, which is commonly associated with inflammatory processes (eg, pneumonia, malignancy), collagen vascular diseases, and trauma. Proteins are able to traverse the capillary membranes into the pleural cavity. Thus, an exudate is characterized by **increased protein content**, which may give the fluid a **cloudy** appearance.

Lymphatic

Also known as chylothorax. Leakage of lymphatic fluid (chyle) into the pleural space. Due to disruption of lymphatic flow through the thoracic duct, usually by trauma or malignancy. Lymphatic effusions are characterized by **increased triglycerides**, which gives the fluid a **milky** appearance.

KEY FACT

Pleural effusion: Fluid accumulation in the pleural space.
Pulmonary edema: Fluid accumulation in the alveolar spaces.

CLINICAL CORRELATION

Thoracentesis is a procedure in which a needle or catheter is inserted through the chest wall to drain fluid within the pleural space.

KEY FACT

The thoracic duct is the largest lymphatic vessel in the body, draining lymph from the entire lower body as well as the left upper body (right upper body is drained by the right lymphatic duct). The thoracic duct ascends the posterior mediastinum and empties into the junction of the left subclavian and internal jugular veins.

PNEUMOTHORAX

Pneumothorax is the accumulation of air within the pleural space (Figure 10-57), which restricts inspiratory pulmonary expansion. Generally, pneumothoraces present with **dyspnea** and **unilateral chest pain.** Physical exam shows decreased or absent tactile fremitus, **hyperresonance,** and diminished breath sounds, all on the affected side. Classifications are described below.

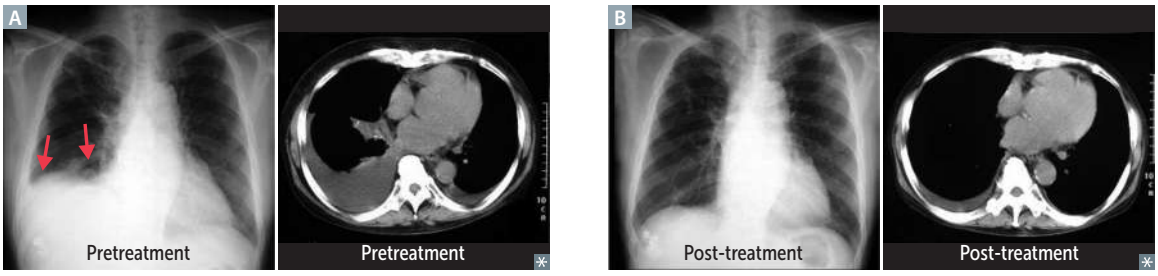


FIGURE 10-56. Pleural effusion. X-ray and CT findings A before and B after treatment.

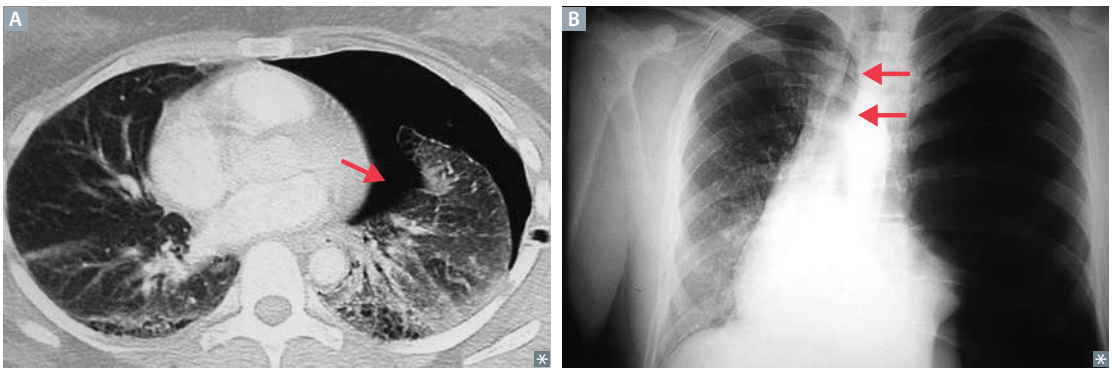


FIGURE 10-57. Pneumothorax. A CT showing collapsed left lung (arrow). B Chest x-ray showing left-sided tension pneumothorax; note the hyperlucent left lung field with low left hemidiaphragm (below the field of view) and rightward mediastinal/tracheal shift (arrows).

Primary Spontaneous Pneumothorax

Due to rupture of apical blebs or cysts within the lung (indicated by the term "spontaneous"). Patients typically have no known history of lung disease. Occurs most frequently in tall, thin, young males.

Secondary Spontaneous Pneumothorax

Also due to rupture of apical blebs or cysts. Develops secondary to lung disease (eg, bullae in emphysema, infections) or mechanical ventilation with excess pressures (causing barotrauma).

Traumatic Pneumothorax

Caused by blunt (eg, rib fracture) or penetrating (eg, gunshot) trauma.

Tension Pneumothorax

Can develop from any of the etiologies above. Air enters pleural space with each inspiration but cannot exit. The amount of air trapped in the pleural space increases rapidly, placing the patient at high risk for respiratory failure and circulatory shock. This is a medical emergency. High air pressure "pushes" the mediastinal contents to the contralateral side, and **contralateral tracheal deviation** is detectable on physical exam and CXR.

Diagnosis

Physical examination findings for pneumothorax, as well as atelectasis, pleural effusion, and consolidation can be found in Table 10-21.

TABLE 10-21. Lung Physical Exam Findings in Atelectasis, Pleural Effusion, Pneumothorax, and Consolidation

ABNORMALITY	BREATH SOUNDS	PERCUSSION	FREMITUS	TRACHEAL DEVIATION
Atelectasis (bronchial obstruction)	↓	Dull	↓	Ipsilateral
Pleural effusion	↓	Dull	↓	Midline or contralateral (if large)
Simple pneumothorax[a]	↓	Hyperresonant	↓	Midline
Tension pneumothorax	↓	Hyperresonant	↓	Contralateral
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles	Dull	↑	Midline

[a]Simple pneumothorax = nonexpanding (in contrast to tension pneumothorax).

Treatment

- Supplemental oxygen to increase the rate of resorption of intrapleural air. In cases of a small asymptomatic pneumothorax, this may be sufficient for spontaneous recovery to occur.
- In larger and/or symptomatic pneumothoraces, air should be evacuated from the intrapleural space via **thoracentesis** (needle aspiration) or chest tube placement (**tube thoracostomy**) with a water seal, which acts as a one-way valve.
- In cases of recurrent pneumothorax, the pleurae may be sealed together through **pleurodesis,** in which chemical or mechanical irritation is employed in order to encourage fibrous scar tissue formation, sealing the visceral and parietal pleurae together. This effectively glues the lung to the chest wall.

ALLERGY

Presentation

The term *allergy* is typically used to refer to type I hypersensitivity, mediated by IgE cross-linking after exposure to an allergen, leading to mast cell degranulation and histamine-mediated vascular permeability. Allergies manifest in a myriad of ways, but many of the symptoms affect the respiratory system, in particular, **allergic rhinitis** ("hay fever"—congestion, sneezing, itching), extrinsic **asthma,** and **anaphylaxis.** Anaphylaxis is the most severe allergy syndrome, characterized by multiorgan involvement including urticaria, edema, airway obstruction, low blood pressure, and GI symptoms. Any airway obstruction must be addressed immediately, usually through epinephrine administration.

Diagnosis

The symptoms of allergies are classic and generally sufficient to establish a diagnosis. However, specific testing for allergen sensitivities may be instructive in certain cases; this is accomplished through either a **radioallergosorbent test** (**RAST**) of the blood for ingestion/inhalation allergies or a skin test for contact allergies.

Treatment

In many cases, the main "treatment" of allergies is allergen avoidance, especially in the case of hypersensitivities to foods, animals, or materials. If this is not possible, several drug classes may be used, which are listed below and discussed further in the Pharmacology section at the end of this chapter.

- **H_1 histamine blockers** (first and second generation) to treat inflammation.
- **α-Adrenergic agonists** (pseudoephedrine, phenylephrine, xylometazoline, oxymetazoline) for nasal decongestion.
- **Epinephrine** for anaphylactic shock.

Another method occasionally employed to treat allergies is **immunotherapy (desensitization),** in which successively escalating doses of allergen are injected with the goal of inducing tolerance. This is particularly useful for unpredictable and difficult-to-avoid allergens such as bee venom.

Prognosis

Most cases of allergy are primarily a lifelong nuisance with seasonal or environmental variation. However, a severe allergic reaction may result in anaphylaxis, which has a poor prognosis unless immediately managed.

HYPERSENSITIVITY PNEUMONITIS

Presentation

Results from inhalation of biological or chemical dust such as aerosolized mold or droppings, leading to a lymphocyte-mediated inflammatory response in the alveoli. Distinguished from asthma in that this is an alveolar disease rather than one of bronchi; additionally, unlike asthma and allergy, this is not a type I hypersensitivity reaction. Symptoms of acute disease include chest tightness, cough, wheezing, fever, and dyspnea, resolving hours after discontinuation of exposure. Symptoms of chronic disease include dyspnea, fatigue, cough, and weight loss.

Diagnosis

- Probable diagnosis made with positive history of exposure, consistent CT scan (reticular, nodular, or ground glass opacities), bronchoalveolar lavage showing increased lymphocytes.
- Definitive diagnosis can be made with lung biopsy (findings include loosely organized granulomas) in conjunction with a consistent history.
- Differential diagnosis includes pneumoconiosis, IPF, COPD, and asthma.

Treatment

Avoid further exposure to offending agents. Glucocorticoids may help resolve symptoms.

Prognosis

Usually complete or near complete recovery of lung function following cessation of antigen exposure.

Pharmacology

HISTAMINE BLOCKERS

First-Generation Histamine Blockers

KEY FACT

1st generation H_1 blocker names usually contain *-en/-ine* or *-en/-ate*.

FLASH BACK

H_1 receptors mediate inflammation, whereas H_2 receptors mediate gastric acid secretion.

Drug Names

Diphenhydramine, dimenhydrinate, chlorpheniramine.

Mechanism

Reversibly inhibit H_1 histamine receptors, which are involved in the inflammatory process. Major effects of H_1 receptor stimulation include:

- Increased nasal and bronchial mucus production
- Contraction of bronchioles
- Increased vascular permeability
- Pruritus
- Pain

Uses

- **Allergies:** Due to anti-inflammatory effects (see above).
- **Motion sickness:** H_1 blockers also competitively inhibit muscarinic receptors, which contribute to the signs and symptoms associated with motion sickness.
- **Sleep aid:** H_1 blockers are lipophilic, which allows them to cross the blood-brain barrier (BBB) and act on the CNS.

Side Effects

- **Sedation:** Due to CNS effects (see above).
- **Muscarinic antagonism:** Blurry vision, dry mouth, urinary retention. Can also cause confusion and hallucinations in the elderly.
- **α-Adrenergic antagonism:** Postural hypotension.

Second-Generation Histamine Blockers

Drug Names

Loratadine, fexofenadine, desloratadine, cetirizine.

Mechanism

- Reversibly inhibit H_1 receptors.
- Unlike first-generation H_1 blockers, second-generation H_1 blockers do not readily cross the BBB and are therefore far less sedating. They also do not act on muscarinic or α-adrenergic receptors.

Uses

Allergies.

Side Effects

Generally well tolerated.

KEY FACT

Second-generation H_1 blocker names usually end in *-adine*.

MUCOACTIVE AGENTS

Subtypes, based on mechanism, include expectorants and mucolytics.

Drug Names

Guaifenesin, N-acetylcysteine, dornase alfa (DNAse).

Mechanism

- **Expectorants** (guaifenesin): Increase the volume of watery airway secretions. This serves to thin out respiratory secretions, making them easier to cough up.
- **Mucolytics:** Loosen mucus plugs. **N-acetylcysteine** acts by cleaving disulfide bonds within the mucus glycoproteins. **Dornase alfa (DNAse)** clears leukocytic debris through hydrolysis of DNA polymers.

FLASH BACK

N-acetylcysteine is also used as an antidote for acetaminophen overdose.

Uses

- Increases clearance of respiratory secretions (eg, common cold, pneumonia, COPD).
- N-acetylcysteine and DNAse are used in cystic fibrosis (CF) patients.

Side Effects

Generally well tolerated.

DEXTROMETHORPHAN

Mechanism

Synthetic codeine analog. Antagonizes N-methyl-D-aspartate (NMDA) glutamate receptors.

Uses

Antitussive agent (suppresses cough).

Side Effects

Mild opioid effects when used in excess (euphoria, respiratory depression, miosis, constipation). Has mild abuse potential. **Naloxone** can be given for overdose.

α-ADRENERGIC AGONISTS

Drug Names

Pseudoephedrine, phenylephrine, xylometazoline, oxymetazoline.

Mechanism

α-Adrenergic agonist.

Uses

- Reduce hyperemia, edema, and nasal congestion.
- Pseudoephedrine is also illicitly used to make methamphetamine.

Side Effects

- Hypertension.
- Pseudoephedrine can also cause CNS stimulation/anxiety.
- Rapid tolerance formation **(tachyphylaxis).**

PULMONARY HYPERTENSION DRUGS

Drug Names

Bosentan, sildenafil, epoprostenol, iloprost.

Mechanisms

FLASH BACK

Sildenafil is also used to treat erectile dysfunction.

- **Bosentan:** Competitively inhibits endothelin-1 receptors, thereby preventing pulmonary vasoconstriction and decreasing pulmonary vascular resistance.
- **Sildenafil:** Inhibits cGMP phosphodiesterase-5 (PDE-5), which normally breaks down nitric oxide. This prolongs the effects of nitric oxide, resulting in arterial vasodilation.
- **Epoprostenol, iloprost:** Prostacyclins (PGI_2). Have direct vasodilatory effects on pulmonary and systemic arterial vasculature. Also inhibit platelet aggregation.

Uses

Pulmonary hypertension.

Side Effects

- **Bosentan:** Hepatotoxic (monitor LFTs).
- **Sildenafil:** Headaches, hypotension.
- **Epoprostenol, iloprost:** Flushing, jaw pain.

ASTHMA DRUGS

Bronchoconstriction in asthma is mediated by (1) inflammatory processes and (2) parasympathetic tone. Therapy is directed at these two pathways, outlined in Figure 10-58.

β_2-Agonists

Drug Names

Albuterol, salmeterol, formoterol.

Mechanism

Facilitate conversion of adenylate cyclase (AC) to cAMP (Figure 10-59B), which relaxes bronchial smooth muscle.

Uses

- **Albuterol:** Short-acting agent used during acute exacerbations.
- **Salmeterol, formoterol:** Long-acting agents used for long-term therapy.

Side Effects

Associated with tremors and arrhythmias.

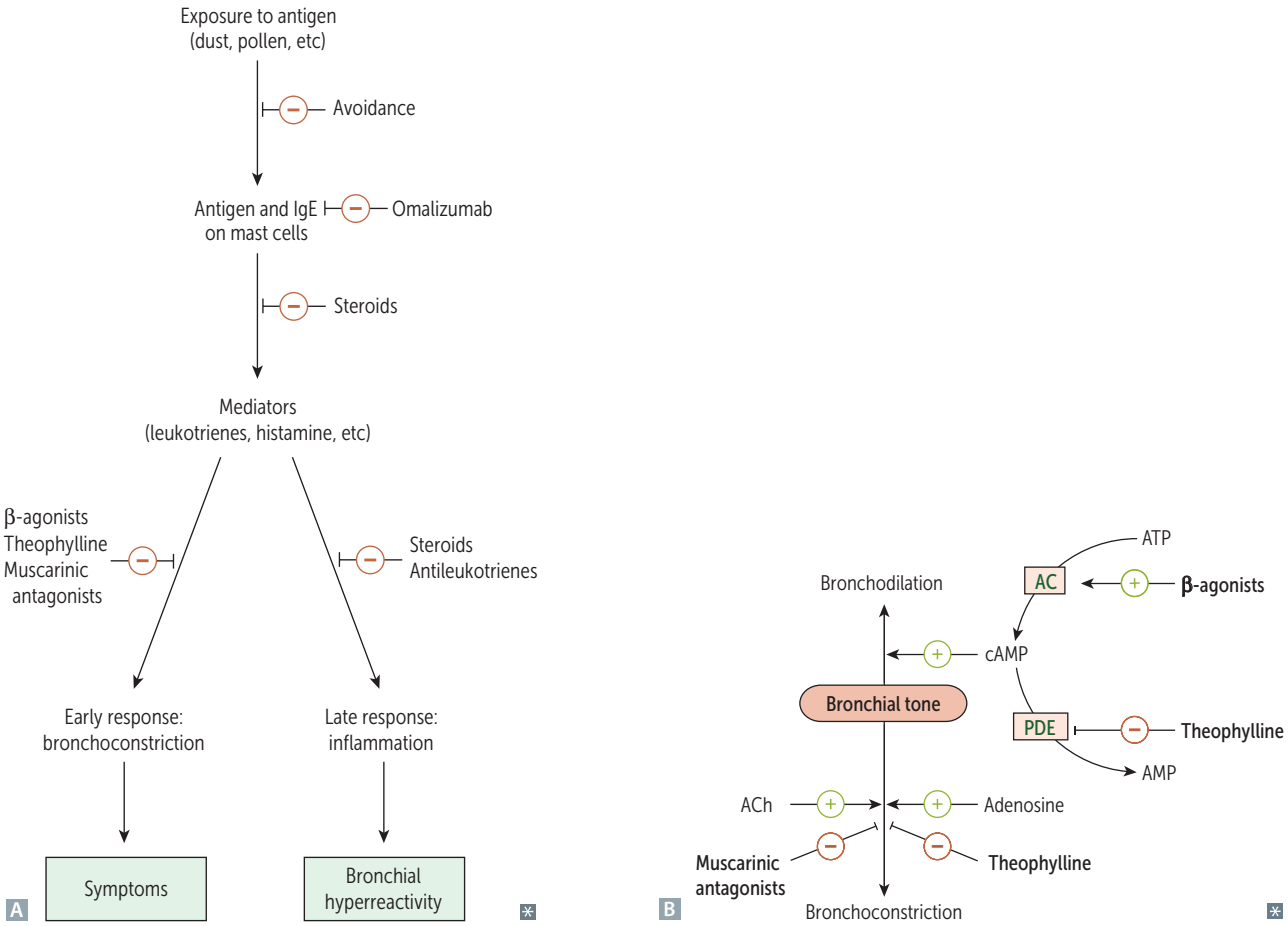


FIGURE 10-58. Pharmacologic targets in asthma. A Inflammatory pathway. B Parasympathetic pathway. AC, adenylyl cyclase; ACh, acetylcholine; PDE, phosphodiesterase.

Corticosteroids

Drug Names

Beclomethasone, fluticasone, flunisolide.

Mechanism

Inhibit the synthesis of virtually all cytokines. Inactivate NF-κB, which is the transcription factor that induces the production of TNF-α and other inflammatory agents.

Uses

First-line therapy for **chronic asthma.**

Side Effects

Oral candidiasis (thrush): Prevented by rinsing mouth following administration.

Muscarinic Antagonists

Drug Names

Ipratropium, tiotropium.

Mechanism

Competitively inhibit muscarinic receptors (M_3), preventing bronchoconstriction. Tiotropium is long acting.

Uses

- COPD.
- Asthma.

Antileukotrienes

Drug Names

Zileuton, montelukast, zafirlukast.

Mechanism

- **Zileuton:** 5-lipoxygenase pathway inhibitor. Blocks the conversion of arachidonic acid to leukotrienes.
- **Montelukast, zafirlukast:** Competitively inhibit leukotriene receptors (CysLT1).

Uses

- Considered when asthma is refractory to long-acting β_2-agonists and inhaled corticosteroids.
- Montelukast and zafirlukast are especially good for aspirin-induced asthma, in which bronchospasms result from increased leukotriene production.

Side Effects

Zileuton is associated with hepatotoxicity.

Omalizumab

Mechanism

Monoclonal anti-IgE antibody. Binds unbound serum IgE at the Fc region (FcεRI).

Uses

Considered when asthma is refractory to long-acting β_2-agonists and inhaled corticosteroids.

Side Effects

Generally well tolerated, but very expensive.

Methylxanthines

Drug Name

Theophylline.

Mechanism

- Inhibits phosphodiesterase, which normally hydrolyzes cAMP (Figure 10-59B). This increases cAMP levels, resulting in bronchodilation.
- Also blocks the actions of adenosine (Figure 10-59B), thereby preventing bronchoconstriction.

Uses

Has limited usage due to narrow therapeutic index.

Side Effects

- Neurotoxicity (eg, seizures).
- Cardiotoxicity (eg, tachycardia, arrhythmias).
- Metabolized by cytochrome P-450.

Magnesium Sulfate

Mechanism

Inhibits calcium influx into airway smooth muscle cells, thereby decreasing airway tone.

Uses

Shown to be helpful, specifically in severe asthma exacerbations.

Methacholine

Mechanism

Muscarinic receptor (M_3) agonist. Causes bronchoconstriction.

Uses

Used in bronchial provocation to help diagnose asthma. Of note, the methacholine challenge test has high sensitivity but low specificity. Therefore, it is useful for ruling out asthma, but a positive result is not diagnostic.

Appendix

Q-Bank

14

Respiratory

CASE 1

While working in a laboratory, a medical student accidentally opens a canister of highly corrosive gas and inhales a large quantity of the gas. He immediately goes to the emergency department for evaluation and treatment. Physical examination shows labored breathing and tachypnea as well as scattered crackles and tachycardia.

What conditions should be included in the differential diagnosis?

Given this patient's history, the differential diagnosis should include noncardiogenic pulmonary edema, acute pneumonitis, and acute respiratory distress syndrome. Onset of symptoms may take up to several days depending on the severity of the insult.

If protein-rich exudate is found in the alveoli, what diagnosis is likely and to what condition could it lead?

Protein-rich exudate in the alveoli suggests diffuse alveolar damage, which may lead to acute respiratory distress syndrome (ARDS). ARDS is a severe and potentially fatal lung disease in which acute inflammation and progressive parenchymal injury leads to hypoxemia. Typical histological presentation (Figure 14-1) involves diffuse alveolar damage and hyaline membrane formation in the alveolar walls.

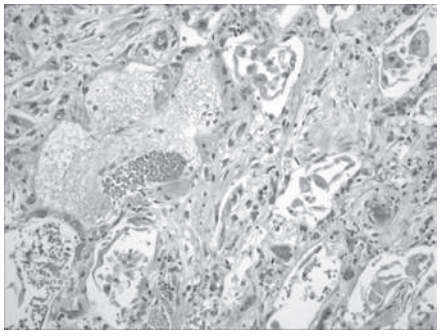


FIGURE 14-1. Histopathology of acute respiratory distress syndrome. (Reproduced, with permission, from USMLERx.com.)

What are the mechanisms of this condition?

Diffuse alveolar damage involves an increase in alveolar capillary permeability because of the damage caused by an inciting agent; in this case, the inciting agent is the corrosive gas and the body's response to it. Initial damage is due to neutrophilic substances that are toxic to tissue, oxygen-derived free radicals, and activation of the coagulation cascade. This insult leads to protein-rich exudates leaking into the lungs and the formation of an intra-alveolar hyaline membrane.

If this condition does not resolve, what complication can arise?

If the inflammation and hyaline membrane formation do not resolve, the damaged tissue can organize, resulting in **fibrosis.**

How are the other conditions in the differential diagnosis characterized?

- Noncardiogenic pulmonary edema is pulmonary edema caused by injury to the lung parenchyma (such as pulmonary contusion, aspiration, or inhalation of toxic gas).
- Acute interstitial pneumonitis is a severe lung disease that begins abruptly with cough, fever, and difficulty breathing and progresses to respiratory failure within days to weeks.

What is the most appropriate treatment for this condition?

Oxygenation is a cornerstone of treatment and usually involves some form of mechanical ventilation in the intensive care unit. Whenever ARDS develops, the underlying cause must be treated, and patients may also need medication to treat infection, reduce inflammation, and remove fluid from the lungs.

CASE 2

A 60-year-old man comes to his primary care physician because of dyspnea on exertion that has been worsening over the past several years. He also reports a nonproductive cough that he has had almost daily in the same period. On questioning, the man says he worked for 30 years stripping insulation on ships. On physical examination, chest expansion appears markedly restricted, and fine inspiratory crackles are heard that are most pronounced at the lung bases. The man also has multiple firm subcutaneous nodules on his hands.

What is the most likely diagnosis?

Asbestosis.

What other conditions should be considered in the differential diagnosis?

Interstitial lung diseases should also be considered, especially those caused by occupational exposure:

- **Silicosis** is caused by exposure to silica dust and characterized by fever, cough, shortness of breath, and cyanosis. X-ray of the chest will usually show multiple small nodules located primarily in the upper lung zones.
- **Coal worker's pneumoconiosis** is due to inhaled coal dust that accumulates in the lungs and, over time, causes inflammation and fibrosis. Symptoms are usually mild at first and include chronic cough and shortness of breath. X-ray of the chest often shows large masses of dense fibrosis in the upper lung zones.
- **Berylliosis** is classically associated with beryllium mining or exposure to fluorescent light bulbs. Patients develop small inflammatory nodules in their lungs (ie, granulomas) that ultimately progress to restrictive lung disease.

Conditions not related to occupational exposure, including idiopathic pulmonary fibrosis, should also be considered.

What is the pathophysiology of this condition?

The pathophysiologic process of asbestosis involves diffuse pulmonary interstitial fibrosis caused by inhaled asbestos fibers. Asbestos fibers penetrate bronchioles and lung tissue, where they are surrounded by macrophages and coated by a protein-iron complex (**ferruginous bodies**); Figure 14-2 shows these phagocytosed bodies. Diffuse fibrosis around the bronchioles spreads to the alveoli, causing lung tissue to become rigid and airways distorted.

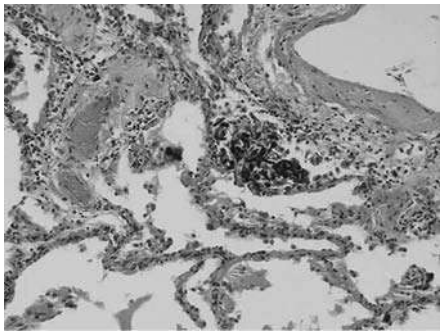


FIGURE 14-2. Asbestos bodies. (Reproduced, with permission, from USMLERx.com.)

What are the most likely x-ray of the chest findings?

In cases of minor exposure, the only findings may be pleural thickening or calcified pleural plaques. In cases of extensive pulmonary fibrosis, reticular or nodular opacities will be seen throughout the lung fields, most prominently at the bases.

CASE 3

A 7-year-old boy is brought to the emergency department (ED) after awakening in the middle of the night with difficulty breathing. He has a 2-day history of worsening productive cough and wheezing. The patient is found to have dyspnea, tachypnea, and a decreased inspiratory/expiratory ratio. Lung examination reveals diffuse rhonchi and expiratory wheezes in addition to pulsus paradoxus. He is afebrile and has no recent history of fever. This is the patient's second visit to the ED with these symptoms; his first visit was 2 years ago.

What is the most likely diagnosis?

Asthma exacerbation. Asthma is a form of obstructive lung disease.

What are other obstructive lung diseases, and how do they differ from this condition?

- **Bronchiectasis** is a disease state in which bronchi become inflamed and dilated, causing obstructed airflow and impaired clearance of secretions. It is often associated with AIDS, cystic fibrosis, and Kartagener syndrome.
- **Emphysema** is a long-term, progressive disease in which the small airways and alveoli (which maintain the lung's functional shape) are destroyed. This is usually the result of smoking.
- **Chronic bronchitis** is chronic inflammation of the bronchi that causes a persistent and productive cough that lasts for at least 3 months in 2 consecutive years. Smoking is almost always the cause.

Unlike these diseases, the airway obstruction seen in asthma is usually reversible.

What is the pathophysiology of this condition?

Acutely, **bronchial hyperresponsiveness** leads to episodic, reversible bronchoconstriction. Specifically, smooth muscle contraction in the airways leads to **expiratory airflow obstruction.** Chronically, **airway inflammation** leads to histologic changes in the bronchial tree.

What histologic findings in the lung are associated with this condition?

Histologic examination reveals smooth muscle hypertrophy, goblet cell hyperplasia, thickening of basement membranes, and increased eosinophil recruitment (in Figure 14-3 the arrow points to plate of cartilage, and the arrowhead points to infiltrate of inflammatory cells). Dilated bronchi are filled with neutrophils and may have mucous plugs.

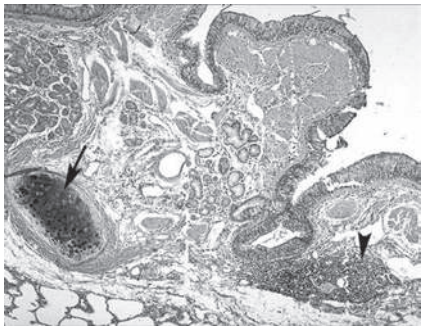


FIGURE 14-3. Histologic findings in asthma. (Reproduced, with permission, from Wilson FJ, et al. *Histology Image Review.* Norwalk, CT: Appleton & Lange, 1997: Figure 19-42.)

What are common triggers of this condition?

Triggers of asthma exacerbation include **stress, cold, exercise, dust and animal dander, mold,** and **viral upper respiratory tract infections.**

What is the appropriate treatment for this condition?

For acute episodes, albuterol, a β_2-agonist, helps relax bronchial smooth muscle and decrease airway obstruction. However, for long-term control of persistent symptoms, inhaled corticosteroids are the best treatment.

CASE 4

A pregnant woman suffering from markedly elevated blood pressure and thrombocytopenia suddenly starts having seizures. She is rushed to the delivery room, where she is determined to have eclampsia, and then immediately taken to the operating room for cesarean section. Her premature baby (< 32 weeks) is delivered and found to have increased work of breathing and an elevated heart rate. The baby is intubated, a drug is administered, and x-ray of the chest is taken (Figure 14-4).

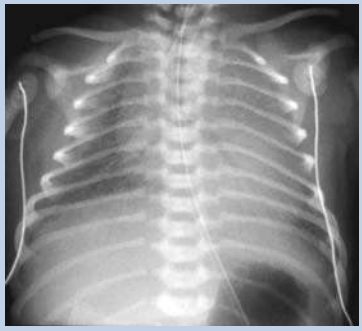


FIGURE 14-4. (Reproduced, with permission, from Tintinalli JE, et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide,* 7th ed. New York: McGraw-Hill, 2008: Figure 4-0.1.)

What drug was most likely given to this baby to promote lung expansion?

Surfactant, normally produced late in fetal life (around week 28), can be given to the baby directly. Surfactant lowers the surface tension between alveoli, helping the lung to expand. Dexamethasone can be used antenatally to aid in surfactant production; it is given to women at risk for preterm delivery to reduce the risk of respiratory distress syndrome.

What is the most likely diagnosis?

The baby is suffering from neonatal respiratory distress syndrome, a disease in which parts of the baby's lungs are deficient in surfactant. This deficiency results in collapsed air spaces, incomplete expansion of the lungs (ie, atelectasis), hyaline membranes (Figure 14-4), and vascular congestion. Clinically, patients present with tachypnea, tachycardia, and cyanosis immediately after birth.

What are the primary types of atelectasis?

- **Adhesive atelectasis** occurs in patients with insufficient surfactant.
- **Obstructive atelectasis** involves obstruction of an airway, commonly at the level of the smaller bronchi, with collapse of the alveoli distal to the obstruction. A common cause for this type of atelectasis is secretions or exudates.
- **Cicatricial atelectasis** occurs in an area of scarred lung tissue.
- **Passive atelectasis** occurs because of poor ventilation (eg, after surgery).
- **Compressive atelectasis** is due to a space-occupying mass in the thorax that compresses a region of lung tissue.

How does obstructive atelectasis differ from compressive atelectasis?

In obstructive atelectasis, the mediastinum shifts toward the atelectasis due to loss of lung volume in that area. By contrast, the mediastinum shifts away from the atelectasis with compression.

During atelectasis, to what is the patient commonly predisposed?

Atelectasis results in mucus trapping and a decrease in ventilation, thereby predisposing the patient to **infections.**

CASE 5

A patient comes to his physician with a hacking cough and purulent sputum. His history is positive for a genetic birth defect called Kartagener syndrome in which ciliary motion is either abnormal or absent. The patient also claims to have a constantly runny nose, a prior diagnosis of chronic bronchitis, and numerous bouts of pneumonia. Before making a diagnosis, the physician orders a high-resolution CT scan of the patient's lungs (Figure 14-5).

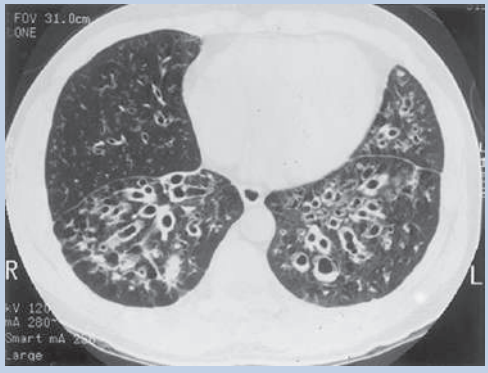


FIGURE 14-5. (Reproduced, with permission, from Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J. *Harrison's Principles of Internal Medicine,* 17th Edition; Fig. 252-1.)

What is the most likely diagnosis?

Bronchiectasis.

What radiologic findings can help diagnose this condition?

In bronchiectasis, a "tree-in-bud" pattern is commonly seen on high-resolution CT scans. This represents the plugging of small airways with mucus and bronchiolar wall thickening.

What are the possible etiologies of this condition?

Etiologies include chronic bronchial necrotizing infections, cystic fibrosis, bronchial obstruction from granulomatous disease or neoplasms, α_1-antitrypsin deficiency, impaired host defense (eg, AIDS), and airway inflammation (eg, bronchiolitis obliterans). Additionally, tuberculosis and primary ciliary dyskinesia should be evaluated.

What complications are associated with this condition?

Complications of bronchiectasis include hemoptysis, hypoxemia, cor pulmonale, dyspnea, and amyloidosis.

What is the appropriate treatment for this condition?

If an infection is thought to be the cause, then antibiotics should be given. If the bronchiectasis is localized, surgery may be an option. For routine management, however, measures include postural drainage and chest percussion.

CASE 6

A 50-year-old woman visits a community health clinic because of a 1-month history of cough productive of yellow sputum. On questioning, she says she has had several periods of cough lasting 4–6 consecutive months each year for the past 5 years. She has smoked two packs of cigarettes per day for the past 30 years. On examination, the woman's breathing is shallow, and she exhales slowly with pursed lips. Her jugular venous pulse is visible to the jawline when she is reclined at an angle of 45°. Auscultation of the chest demonstrates wheezing and distant heart sounds. A positive hepatojugular reflux is demonstrated, as is 2+ pitting edema up to her knees. X-ray of the chest is shown in Figure 14-6.

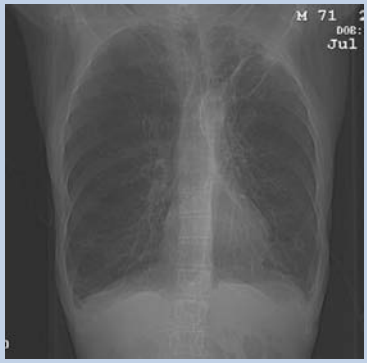


FIGURE 14-6. (Reproduced, with permission, from Tintinalli JE, et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 7th ed. New York: McGraw-Hill, 2011: Figure 73-2.)

What is the most likely diagnosis?

The history of productive cough for at least 3 consecutive months over 2 consecutive years accompanied by emphysema (suggested by pursed-lip breathing) indicates chronic obstructive pulmonary disease (COPD) with features of chronic bronchitis.

What radiologic findings can help diagnose this condition?

In patients with COPD, x-rays of the chest often reveal lung hyperinflation, flattening of the diaphragm, and decreased peripheral vascular markings.

What abnormalities would be expected on pulmonary function testing?

- In COPD, the forced expiratory volume in 1 second (FEV_1) is decreased, forced vital capacity (FVC) is normal or decreased, and the FEV_1/FVC ratio is < 70% of predicted.
- In restrictive lung disease, decreased vital capacity and total lung capacity result in a FEV_1/FVC ratio of > 80%.

How would this condition affect the patient's arterial blood gas levels (pH, PaO_2, $PaCO_2$, and SaO_2)?

The pH decreases as a result of respiratory acidosis. Although pH may be normal in a patient with chronic compensated COPD, it is low in a patient with an acute exacerbation. Arterial oxygen tension (PaO_2) decreases, arterial carbon dioxide tension ($PaCO_2$) increases, and oxygen saturation (SaO_2) decreases secondary to impaired gas exchange (from destruction of alveolar septae and pulmonary capillary bed).

Why is breathing with pursed lips adaptive in this condition?

Breathing with pursed lips maintains positive end-expiratory pressure (PEEP). PEEP prevents alveolar and small airway collapse, which is common in emphysema. Respiratory therapy often provides supplemental oxygen via a mask or nasal prongs. Positive airway pressure can be provided by continuous positive airway pressure, bilevel positive airway pressure, or intubation and ventilatory support.

What complication of this condition is suggested by the patient's enlarged neck veins, hepatomegaly, and edema?

Cor pulmonale. Right heart failure due to chronic pulmonary hypertension leads to systemic venous congestion, which presents with the symptoms mentioned here. This complication occurs only in patients with severe COPD who develop pulmonary hypertension.

CASE 7

A 67-year-old man comes to the emergency department complaining of a 3-day history of cough and fever and a 1-day history of shaking chills. He has smoked about half a pack of cigarettes per day for the past 45 years. For the past 9 months, the man has had an increasingly severe cough that has been productive of clear sputum. His cough now produces rusty sputum. On physical examination, he is found to have a respiratory rate of 24/min and a temperature of 37.8°C (100°F). An x-ray of the chest shows lung consolidation (Figure 14-7).

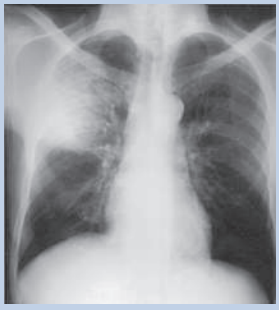


FIGURE 14-7. (Reproduced, with permission, from Le T, et al. *First Aid for the USMLE Step 1: 2011.* New York: McGraw-Hill, 2011: 514.)

What is the most likely diagnosis?

This patient presents with several classic findings of community-acquired pneumonia (CAP): a productive cough, fever, rigors (shaking chills), and tachypnea. His risk factors include an advanced age and a significant smoking history.

What are the likely lung examination findings?

Decreased breath sounds, crackles, dullness to percussion, and increased tactile fremitus are probable findings and can indicate areas of consolidation (ie, areas filled with fluid).

What are the most likely causative organisms?

- *Streptococcus pneumoniae* (20%–60%).
- *Haemophilus influenzae* (3%–10%).
- *Staphylococcus aureus* (3%–5%).
- *Legionella* (2%–8%).
- *Mycoplasma* (1%–6%).
- Viruses (2%–15%).

Gram stain of the sputum reveals gram-positive cocci in pairs and short chains. Additional testing reveals that the organism is optochin sensitive and the Quellung reaction is positive. What is the causative organism?

S pneumoniae is a gram-positive, encapsulated organism, hence the positive Quellung reaction, which is performed by adding anticapsular antisera that cause the capsule to swell. The organism is also catalase negative, α-hemolytic (partial hemolysis; the blood turns greenish), and optochin sensitive (which differentiates it from *Streptococcus viridans*, which is also α-hemolytic).

What are the appropriate treatments for this condition?

Penicillin V and amoxicillin are rarely used in clinical practice because resistance with these drugs is an increasing problem. The typical treatment is either a macrolide in combination with a cephalosporin or fluoroquinolone monotherapy.

What factors would indicate hospitalization for a patient with this condition?

Factors that increase the need for hospitalization include age older than 65 years, altered mental status, underlying chronic illness, elevated blood pressure, elevated temperature, and abnormally high kidney function tests (ie, creatinine and blood urea nitrogen).

CASE 8

A newborn boy has been diagnosed by prenatal ultrasound with a congenital cystic adenomatoid malformation (CCAM) in the right lower lobe of his lung. CCAMs are hamartomas of terminal bronchioles. Because of the risks of CCAM-associated complications, the boy undergoes a right lower lobe resection.

How many segments of lung will be resected if the entire right lower lobe is removed?

There are five segments in the right lower lobe (Figure 14-8): **M**edial, **A**nterior, **L**ateral, **P**osterior, and **S**uperior (mnemonic: **MALPS**).

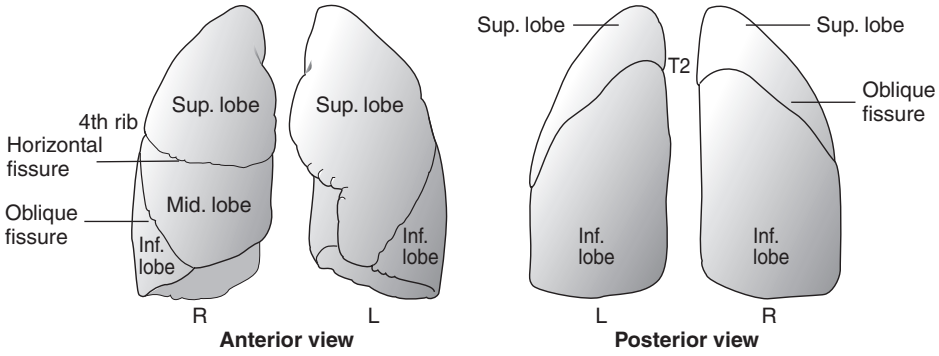


FIGURE 14-8. Lobes of the lung. (Reproduced, with permission, from Le T, et al. *First Aid for the USMLE Step 1: 2011*. New York: McGraw-Hill, 2011: 503.)

Which vessels supply arterial and venous branches to the lungs, and what paths do the branches follow to supply each lung segment?

The lung alveoli are supplied by branches of the pulmonary artery and vein. The bronchial tree also receives its arterial supply from the bronchial arteries (from the aorta) and venous drainage from bronchial veins that feed into the azygos and accessory hemiazygos veins. Pulmonary and bronchial arteries follow the airways into the periphery. Pulmonary veins course in the septa between adjacent lung segments.

When entering the thoracic cavity through an intercostal space, the surgeon preserves the intercostal nerves and vessels. What is the anatomic relationship between the intercostal nerves and vessels and the ribs?

The intercostal nerves and vessels lie in the costal groove inferior to each rib. They are positioned between the innermost intercostal and internal intercostal muscles for the length of those muscles.

During development, the pulmonary arteries arise from which aortic arch?

The sixth aortic arch produces the pulmonary arteries as well as to the ductus arteriosus.

During which week of gestation are the bronchial buds formed from the foregut?

Bronchial buds are formed in the fourth week of gestation. Depending on the histology and other associated anomalies, different types of CCAMs are suspected to result from insults at varying stages of development. For example, **type 2 CCAMs** are associated with anomalies such as esophageal fistulas and bilateral renal agenesis. Thus, type 2 CCAMs are thought to arise early in organogenesis, during the fourth week of gestation.

CASE 9

A 15-year-old girl is brought to the emergency department in acute respiratory distress and is stabilized with treatment. On questioning, she reports an increasingly productive cough over the past few days. Her pulse oximetry shows 93% oxygen saturation on 2 L of oxygen, and she often gasps for air midsentence. Examination shows nostril flaring, subcostal retractions, and clubbing of the fingers. A birth history reveals she had a meconium ileus.

What genetically transmitted condition does this patient likely have?

The patient likely has cystic fibrosis (CF), which is caused by loss-of-function mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel found in all exocrine tissues. As a result of these mutations, secretions in the lung, intestine, pancreas, and reproductive tract are extremely viscous.

What test was likely conducted to confirm the diagnosis?

A genetic screen during the patient's infancy was most likely conducted. A sweat chloride test can also confirm the diagnosis, but it may be difficult to collect an adequate amount of sweat in a baby. Patients with CF have elevated sweat chloride levels.

What is the probable etiology of the patient's current symptoms?

The lungs in patients with CF are colonized at an early age with various bacteria not normally found in the lung. Therefore, patients suffer from repeated pulmonary bacterial infections (*Staphylococcus aureus, Haemophilus influenzae,* and *Pseudomonas aeruginosa* are the most common organisms), which increase production of viscous secretions. These increased secretions lead to increased cough and pulmonary obstruction, which can result in acute respiratory distress.

What vitamin supplements do patients with this condition usually require?

Patients with CF generally require the fat-soluble vitamins A, D, E, and K. The thick secretions block the release of pancreatic enzymes, resulting in pancreatic insufficiency.

What information can be provided if this patient asks for genetic counseling?

The frequency of CF in white people is 1: 2000; the carrier rate of CF in white people is 1:25. CF is an autosomal recessive disease, so all children of a patient with CF will at a minimum become carriers. Approximately 95% of males with CF are infertile because of defects in the transport of sperm. Infertility affects as many as 20% of women as a result of abnormally thick cervical mucus and amenorrhea from malnutrition.

What is the prognosis for patients with this condition?

- Prognosis for patients with CF is generally good.
- Most patients are able to survive into their 30s and lead relatively normal lives.

CASE 10

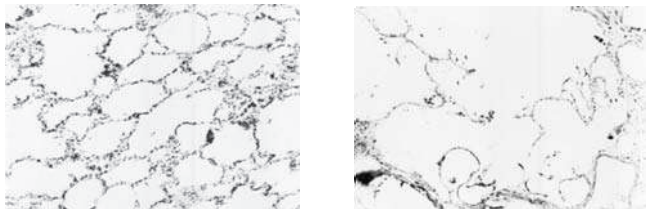
A 70-year-old woman with a 65-pack-year smoking history complains to her physician of worsening dyspnea. The dyspnea has now become so severe that she is experiencing shortness of breath at rest. She also admits that her cough is now occasionally productive of small amounts of thin sputum. Physical examination reveals a thin woman with an increased thoracic anteroposterior diameter. The physician notes that she breathes through pursed lips, has an increased expiratory phase, and is using her accessory muscles to breathe.

What is the most likely diagnosis?

- The most likely diagnosis is COPD with features of emphysema. Other obstructive lung diseases that should be on the differential include chronic bronchitis and asthma.
- By definition, a patient with chronic bronchitis experiences a cough with sputum production on most days for 3 months of a year for at least 2 consecutive years. Patients with chronic bronchitis also experience hypoxia that results in cyanosis of the skin and lips as well as fluid retention.
- Patients with asthma experience reversible and episodic airway obstruction, which is characterized by wheezing, coughing, and shortness of breath. Symptoms usually respond to treatment with an inhaled β_2-agonist and can often be prevented by avoiding triggers, such as allergens and irritants.

What is the pathophysiology of this condition?

Destruction of alveolar walls results in enlargement of air spaces. Compared with a normal lung (Figure 14-9A), the lung in emphysema (Figure 14-9B) shows destruction of lung parenchyma and marked dilatation of terminal air spaces. Destruction of lung parenchyma also decreases elastic recoil, which increases airway collapsibility, causing expiratory obstruction. As a result, patients with emphysema often find it easier to exhale through pursed lips (which maintains a high end-expiratory pressure, thereby stenting the alveoli open)—hence the term "pink puffers." Because of chronic hyperinflation, lungs are expanded close to total lung capacity with little inspiratory reserve, and diaphragms are flattened to a point of significant mechanical disadvantage.



A B

FIGURE 14-9. (A) Normal lung. (B) Lung in emphysema. (Reproduced, with permission, from Chandrasoma P, et al. *Concise Pathology*, 3rd ed. Norwalk, CT: Appleton & Lange, 1997: Figure 35-6.)

What findings are expected on lung and heart examination?

Air trapped in the lungs causes the chest to sound hyperresonant to percussion. Patients with COPD also have decreased breath sounds, wheezing, a prolonged expiratory phase, diminished heart sounds, and a PMI that may be displaced centrally.

What pattern of lung parenchymal destruction is likely to be found in this patient?

Smoking results in a destruction pattern termed **centrilobular emphysema,** which affects the respiratory bronchioles and central alveolar ducts. **Panacinar emphysema** is associated with α_1-antitrypsin deficiency and results in destruction throughout the acinus.

How do pulmonary function test results help distinguish this condition from other lung diseases?

In COPD, pulmonary test results are likely to be consistent with obstructive lung disease findings: dramatically reduced forced expiratory volume in 1 second (FEV_1) and reduced forced vital capacity (FVC), resulting in an FEV_1/FVC ratio of < **70%.** By contrast, in restrictive lung diseases, both the FEV_1 and the FVC are reduced, resulting in a normal FEV_1/FVC.

CASE 11

A 4-year-old boy is brought to the emergency department by his mother because he is lethargic, drooling, and having difficulty breathing. Physical examination reveals an elevated temperature and a high-pitched upper airway wheeze. Further questioning of the patient's mother reveals that the child has not received any immunizations. A lateral x-ray of the neck shows soft tissue swelling.

What is the most likely diagnosis?

The stridor found on lung examination and the drooling—findings consistent with both tracheal and esophageal obstruction—suggest **acute epiglottitis.** The obstruction is due to swelling of the epiglottis caused by infection and is a **medical emergency.** The x-ray shows the classic "thumbprint" sign caused by the thickening and swelling of the epiglottis.

What is the likely source of this infection?

Given the child's unimmunized status, the most likely cause is type b *Haemophilus influenzae* infection. *H influenzae* is considered part of the normal flora of the nasopharynx. The organism may thus be spread by direct contact with respiratory secretions and by airborne droplet contamination. Epiglottitis may also represent a primary infection of the epiglottis rather than invasion from the nasopharynx.

What additional microorganisms can cause this presentation?

Epiglottitis can also be caused by *Pasteurella multocida*, which is often transmitted from dog or cat bites, and herpes simplex virus type 1.

What is the main virulence factor of the causative organism in this case?

The polysaccharide capsule is the major virulence factor of *H influenzae*, which has both encapsulated and nonencapsulated strains. The nonencapsulated forms are limited to local infections such as otitis media in children and mild respiratory infection in adults (Table 14-1). The encapsulated strains are significantly more virulent and can cause disseminated diseases such as meningitis, epiglottitis, and septic arthritis. There are six capsular types of *H influenzae*, designated a through f. The b-type capsule accounts for approximately 95% of serious *H influenzae* infections in children.

TABLE 14-1 Types of Infection Caused by *Haemophilus*

	H INFLUENZAE		*H AEGYPTIUS*	*H DUCREYI*
	TYPE B	NONTYPEABLE		
Type of infection	Meningitis Epiglottitis Bacteremia Cellulitis Septic arthritis	Otitis media Sinusitis Tracheobronchitis Pneumonia	Conjunctivitis Purpuric fever (Brazilian)	Chancroid (painful ulcers of genitals, lymphadenitis)
Treatment	Ceftazidime Cefotaxime Ceftriaxone Gentamicin	Cephalosporin Fluoroquinolone Azithromycin	Rifampin	Azithromycin Cephalosporin Ciprofloxacin

How has the vaccine for this infection been redesigned to improve its efficacy?

The **Hib vaccine** consists of a purified b-type capsule conjugated to diphtheria toxin. The diphtheria toxin activates T lymphocytes, which are required for adequate antibody production against the capsular antigen. The original vaccine consisted only of b capsule and was not effective in eliciting an antibody response.

CASE 12

A 60-year-old man visits his doctor complaining of recurrent fever, chest pain, and difficulty breathing. He states that his symptoms wax and wane but never completely resolve. The patient's occupational history is significant for 30 years as a shipyard worker. Suspecting an occupational exposure to hazardous material, the physician orders a CT scan of the thorax (Figure 14-10).

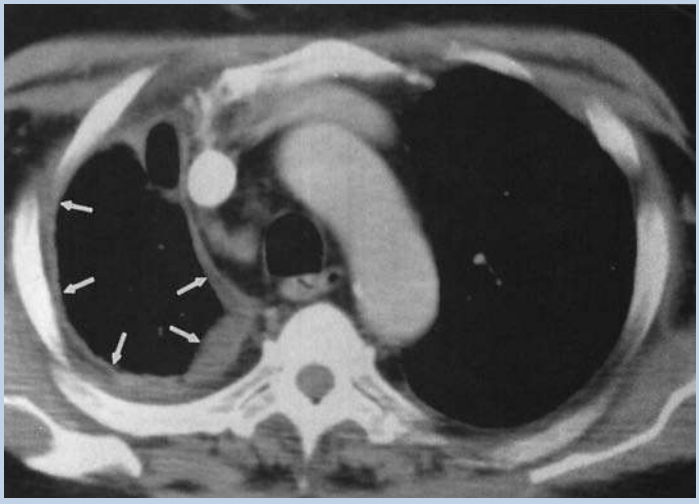


FIGURE 14-10. (Reproduced, with permission, from Chen MYM, et al. *Basic Radiology*. New York: McGraw-Hill, 2004: 101.)

What is the most likely diagnosis?

The pleural thickening (indicated by the arrows in Figure 14-10) in addition to a history of exposure to asbestos makes the diagnosis of **malignant mesothelioma** of high concern. Benign pleural plaques could also present similarly. As the malignant mesothelioma progresses, the lung is surrounded and compressed by a thick layer of tumor. Although mesotheliomas are rare, an exposure history greatly increases the risk. Common features of the disease include dyspnea, chest pain, and pleural effusions.

What occupations put patients at risk for exposure to the suspected agent?

Asbestos exposure is commonly seen in pipe fitters, shipyard workers, welders, plumbers, and construction workers. In addition to malignant mesothelioma, asbestos is associated with benign pleural plaques, interstitial lung disease, pleural effusions, and bronchogenic carcinoma. The diseases typically manifest several decades after asbestos exposure.

What are the typical findings on pulmonary function testing in this condition?

Pulmonary function testing reveals a **restrictive pattern.** Tumor growth decreases lung expansion and total lung capacity. Both forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are decreased, but the FEV_1/FVC ratio is preserved.

What is the prognosis for patients with this condition?

Given only supportive care, the median survival for patients with malignant mesothelioma is approximately 6–12 months. With very aggressive therapies, such as extrapleural pneumonectomy plus chemotherapy and radiation, the median survival can be as high as 34 months.

CASE 13

A 70-year-old man with a history of laryngeal cancer presents to the emergency department with shortness of breath. He complains that for the past 3 days he has been unable to lie flat to sleep, and last night he woke up suddenly gasping for air. A decubitus x-ray of the chest shows layering of fluid (Figure 14-11; arrowhead points to the layer of fluid).

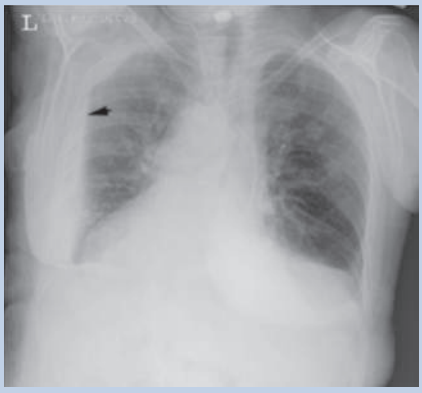


FIGURE 14-11. (Reproduced, with permission, from Tintinalli JE, et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 7th ed. New York: McGraw-Hill, 2011: Figure 56-3.)

What is the most likely diagnosis?

A **pleural effusion** consists of fluid accumulation in the pleural space (between the visceral pleura and the parietal pleura) of the lung. Normally, the pleural space is only a potential space, with a small amount of fluid.

How is this condition classified?

There are two types of pleural effusion:

- **Transudative pleural effusions** are caused by increased hydrostatic pressure of the pleural capillaries (as in congestive heart failure) or by a decrease in plasma oncotic pressure (as in disorders with decreased plasma albumin levels, such as renal and hepatic failure).
- **Exudative pleural effusions** are caused by a change in the permeability of the pleural surface (such as secondary to inflammatory or neoplastic changes). These effusions have a high protein content.

What are the common causes of this condition?

- Common causes of transudative pleural effusion include congestive heart failure, cirrhosis, constrictive pericarditis, nephrotic syndrome, and pulmonary embolism (PE).
- Common causes of exudative pleural effusion include infection (pneumonia, tuberculosis), malignancy (primary or metastatic lung cancer or mesothelioma), collagen vascular disease, and PE (note that PE can cause both transudative and exudative pleural effusions).

What are the typical laboratory findings in this condition?

Analysis of pleural effusion fluid includes measuring pH, total protein, lactate dehydrogenase (LDH), glucose, cell count, gram stain and culture. Cytology can also be performed to identify malignant causes. Meeting any one of the three **Light's criteria** qualifies the effusion as an exudate:

- Protein effusion/serum ratio > 0.5
- LDH effusion/serum ratio > 0.6
- Pleural LDH level greater than two-thirds the upper limit of serum LDH level.

What are the appropriate treatments for this condition?

Thoracentesis performed by needle insertion into the pleural space is both diagnostic and therapeutic. The needle is inserted through an intercostal space superior to the rib to avoid the intercostal nerve and vessels, which lie in the intercostal groove at the inferior border of the rib. Other treatments include **pleurodesis** (in which the pleura is made adherent and closed by chemicals such as talc or doxycycline or physical abrasion) and permanent catheter insertion into the pleural space for periodic fluid drainage.

CASE 14

An 18-year-old man comes to his physician complaining of a 3-week history of worsening dry and nonproductive cough. He also has a throbbing headache and a mild fever and complains of malaise and a sore throat. Treatment with penicillin has not relieved his symptoms.

What is the most likely diagnosis?

Mycoplasma pneumoniae, which causes primary atypical pneumonia (**"walking pneumonia"**), is the most common cause of pneumonia in teenagers (Table 14-2). This organism is the smallest free-living bacterium. It has no cell wall and its membrane is the only bacterial membrane containing cholesterol.

TABLE 14-2 Most Common Causes of Pneumonia According to Age

6 WEEKS–18 YEARS	18–40 YEARS	40–65 YEARS	> 65 YEARS
Viral (respiratory syncytial virus)	*M pneumoniae*	*S pneumoniae*	*S pneumoniae*
Mycoplasma pneumoniae	*C pneumoniae*	*Haemophilus influenzae*	Viral
Chlamydia pneumoniae	*S pneumoniae*	Anaerobes	Anaerobes
Streptococcus pneumoniae		*M pneumoniae*	*H influenzae*

What diagnostic tests can help confirm the diagnosis?

A high titer of cold agglutinins (IgM) and growth on Eaton agar (which is specific for growing *M pneumoniae* and contains penicillin for selectivity) indicate *M pneumonia* infection.

What clinical findings are commonly associated with this condition?

Infection with *M pneumoniae* typically results in mild upper respiratory tract disease including low-grade fever, malaise, headache, and a dry, nonproductive cough. Symptoms gradually worsen over a few days and can last for more than 2 weeks. Less than 10% of patients develop more severe disease with lower respiratory tract symptoms. Classically, x-ray of the chest in these patients looks worse than would be predicted by their physical appearance.

What is the pathogenicity of this organism?

M pneumoniae is an extracellular organism that attaches to respiratory epithelium. As the superficial layer of respiratory epithelial cells is destroyed, the normal ability of the upper airways to clear themselves is lost. As a result, the lower respiratory tract becomes contaminated by microbes and is mechanically irritated. Close contact allows for spread of the organism.

What hematologic condition can develop secondary to this infection?

Autoimmune hemolytic anemia due to **cold agglutinins** (usually IgM autoantibodies that are able to agglutinate RBCs at temperatures below 35°C) can lead to lysis and mild anemia. Cold agglutinin production peaks during the third week of *M pneumoniae* infection and resolves spontaneously.

What are the appropriate treatments for this condition?

Azithromycin is most commonly prescribed to treat *Mycoplasma* infection. Tetracycline, clarithromycin, or erythromycin may be prescribed as well.

CASE 15

A 62-year-old woman presents to the emergency department with acute-onset shortness of breath. She also complains of "stabbing" pleuritic right-sided chest pain. The woman had a stroke 3 months ago but is otherwise healthy. Her temperature is 36.7°C (98.1°F), blood pressure is 90/60 mm Hg, heart rate is 110/min, respiratory rate is 40/min, and oxygen saturation is 80% on room air. Physical examination reveals jugular venous distention, and cardiovascular examination reveals a fast rate with regular rhythm and no murmurs. The woman's lungs are clear bilaterally with decreased breath sounds in the right middle lobe.

What is the most likely diagnosis?

This is a case of pulmonary embolism (also known as pulmonary thromboembolism, or PTE).

What other conditions should be included in the differential diagnosis?

The differential diagnosis includes the following:

- Cardiac: Myocardial infarction, unstable angina, pericarditis (all less likely to present with such a low oxygen saturation).
- Pulmonary: Pneumonia, pneumothorax (tension pneumothorax especially needs to be ruled out), exacerbation of chronic obstructive pulmonary disease.
- Musculoskeletal: Costochondritis (presents with point tenderness reproducible on physical exam).

What is the Virchow triad?

The Virchow triad refers to the three factors that increase the risk for venous thrombosis: local **injury** to the vessel wall, **hypercoagulability,** and **stasis.** It is believed that patients with PTE are predisposed to venous thrombosis; triggers include pregnancy, limb immobility, and surgery.

What test remains the gold standard for diagnosing this condition?

Pulmonary angiography remains the most specific test available for definitively diagnosing PTE. However, because of the invasiveness of angiography, CT of the chest with thin cuts is the most frequently used diagnostic test. A ventilation-perfusion lung scan is still often used. A lung scan showing normal perfusion virtually excludes PTE. An x-ray of the chest can show signs of PTE including Hampton hump (a wedge-shaped indicator of infarction in a region served by an occluded vessel) and Westermark sign (oligemia distal to a PTE) but neither sign is specific and additional imaging is necessary to confirm the diagnosis.

Plasma D-dimer levels have a negative predictive value in cases of low clinical suspicion but are elevated in more than 90% of patients with PTE. This assay is nonspecific and levels may also be elevated in conditions such as myocardial infarction or sepsis. The current strategy for diagnosing PTE and deep venous thrombosis is shown in Figure 14-12.

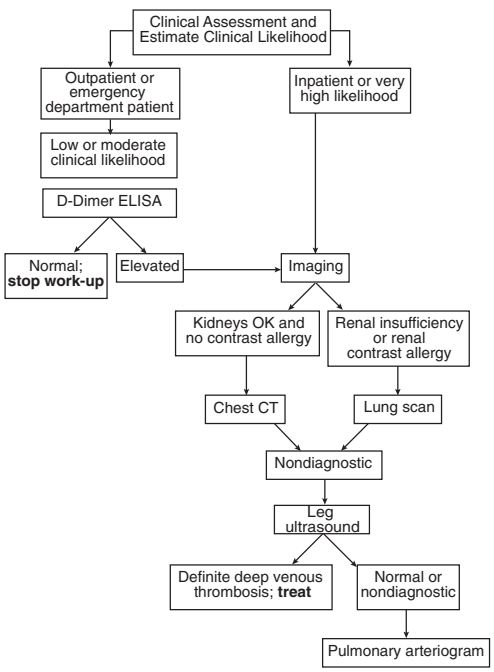


FIGURE 14-12. Diagnosis of PTE. (Adapted, with permission, from Kasper DL, et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1563.)

What is the most likely finding on microscopic examination?

Under low-power magnification, characteristic lines of Zahn (alternating pale lines of platelets and fibrin with RBCs, indicating premortem clot formation) are visible in the thrombus.

What are the appropriate treatments for this condition?

PTE is treated with therapeutic levels of heparin for at least 5 days unless there is a contraindication to anticoagulation (eg, recent surgery). In most patients, warfarin and heparin may be started together and oral anticoagulation continued for at least 3 months. If there is a contraindication to anticoagulation or a high risk of recurrence of PTE, an inferior vena cava filter is recommended.

CASE 16

A 55-year-old woman with a history of chronic obstructive pulmonary disease (COPD) presents to the local hospital complaining of fatigue and weakness. On admission, she is found to have the following laboratory values:

Serum:
Sodium: 144 mEq/L
Chloride: 96 mEq/L
Bicarbonate: 40 mEq/L
Potassium: 4.2 mEq/L
Blood urea nitrogen/creatinine ratio: 18:1.0 mg/dL

Arterial blood gas values: pH of 7.32
Partial pressure of carbon dioxide (P_{CO_2}): 91 mm Hg

What is the most likely cause of these symptoms?

The patient has respiratory acidosis (pH < 7.4 and P_{CO_2} > 40 mm Hg) with compensatory metabolic alkalosis. Respiratory acidosis can be caused by COPD, airway obstruction, and hypoventilation.

What is the most likely diagnosis?

The patient has a chronic respiratory acidosis, as indicated by the large compensatory increase in bicarbonate to correct for an elevated P_{CO_2}. It is most likely due to her underlying COPD since a patient with a more acute process would not be able to compensate as robustly.

In Figure 14-13, which area corresponds to respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis?

Letter A in Figure 14-13 refers to respiratory acidosis, and letter B refers to metabolic acidosis. Letter C refers to respiratory alkalosis, and letter D refers to metabolic alkalosis.

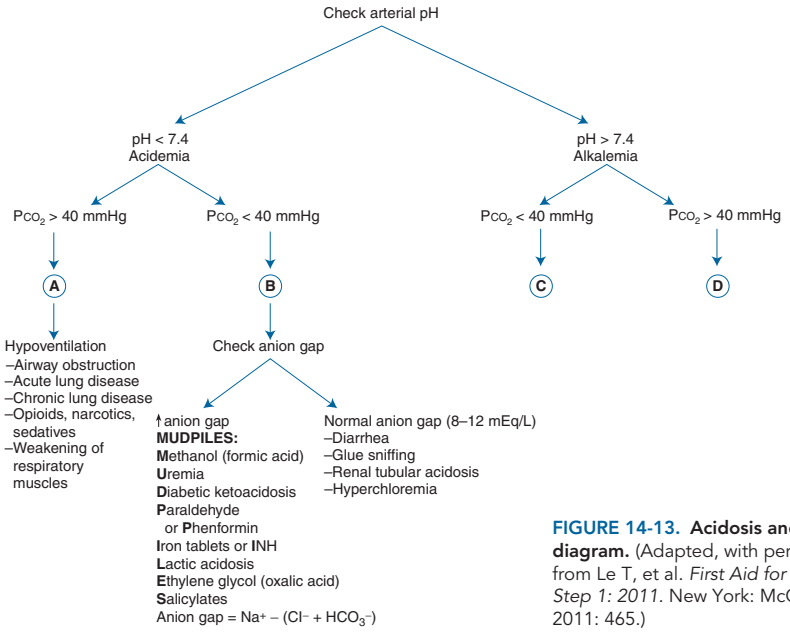


FIGURE 14-13. Acidosis and alkalosis diagram. (Adapted, with permission, from Le T, et al. *First Aid for the USMLE Step 1: 2011*. New York: McGraw-Hill, 2011: 465.)

How is this condition distinguished from metabolic acidosis?

In respiratory acidosis, the primary disturbance is an increase in P_{CO_2} to which the body responds by increasing renal bicarbonate reabsorption. In metabolic acidosis, the primary disturbance is a decrease in bicarbonate, which is compensated for by hyperventilation, resulting in a decreased P_{CO_2}.

What is the anion gap, and what factors can increase the anion gap in this condition?

Anion gap is defined as $[Na+] - ([HCO_3^-] + [Cl^-])$. In this case it is [144] – ([40] + [96]) = 8, which is within the normal range (8–12). Causes of increased anion-gap metabolic acidosis include renal failure, diabetic ketoacidosis, lactic acidosis, and salicylate ingestion. Causes of normal anion-gap metabolic acidosis include diarrhea, renal tubular acidosis, and hyperchloremia.

CASE 17

A 35-year-old African-American man presents to his primary care physician with progressive dyspnea on exertion. He has no history of congestive heart failure or asthma and has had no known contact with any individuals known to have tuberculosis. His laboratory results reveal normal creatinine kinase (CK), CK-MB fraction, and troponin levels. An x-ray of the chest shows bilateral hilar lymphadenopathy and evidence of interstitial lung disease (ILD). A bronchoscopic lung biopsy reveals the presence of several small, noncaseating granulomas.

What is ILD and what are the common causes?

The term ILD is generically used to describe a collection of diseases that involve diffuse scarring and/or inflammation of lung tissue. Common causes of ILD are as follows:

- Prolonged exposure to occupationally inhaled inorganic agents such as silicone, coal, asbestos, talc, mica, aluminum, and beryllium.
- Idiopathic pulmonary fibrosis.
- Connective tissue disease (eg, Wegener granulomatosis, systemic lupus erythematosus, scleroderma, Sjögren disease).
- Sarcoidosis.
- Hypersensitivity pneumonitis, such as "farmer's lung" or "bird-breeder's lung," in which an immune reaction to an organic dust induces a type III or type IV hypersensitivity reaction.
- Radiation-induced disease.
- Antitumor drugs (eg, bleomycin).

What is the most likely cause of ILD in this patient?

Sarcoidosis is the most likely cause. This diagnosis is supported by the patient's race, the presence of **noncaseating granulomas** (discrete collections of tissue macrophages termed *histiocytes* often organized into multinucleated giant cells without central necrosis), and the bilateral hilar lymphadenopathy on x-ray of the chest.

What laboratory abnormalities may be found in this patient?

Vitamin D is secreted by the macrophages of the granulomas and is therefore elevated in serum. Angiotensin-converting enzyme is also secreted by the macrophages of the granulomas and is also elevated.

What pulmonary function testing findings are expected?

In ILD, lung compliance is decreased, reflecting increased stiffness from alveolar wall inflammation and fibrosis. Tidal volume and total lung capacity are typically decreased. Diffusion capacity is also decreased as a result of inflammatory destruction of the air-capillary interface. Unlike most ILDs, sarcoidosis has features of both obstruction and restriction.

What are some extrapulmonary manifestations of this patient's ILD?

Common extrapulmonary manifestations of sarcoidosis are in the eye (anterior uveitis) and skin (papules and erythema nodosum), but granulomas can also occur in the heart, brain, lung, and peripheral lymph nodes.

What is the appropriate treatment for this condition?

Corticosteroids.

CASE 18

A 56-year-old man presents to his physician complaining of generalized weakness, cough, and a 9.1-kg (20-lb) weight loss that has occurred over the past 8 weeks. His voice is hoarse and he is unable to keep up with his work as a construction worker. The patient has a 30-pack-year smoking history. Serum sodium is 119 mEq/L. The physician orders posteroanterior and lateral chest radiographs (Figure 14-14).

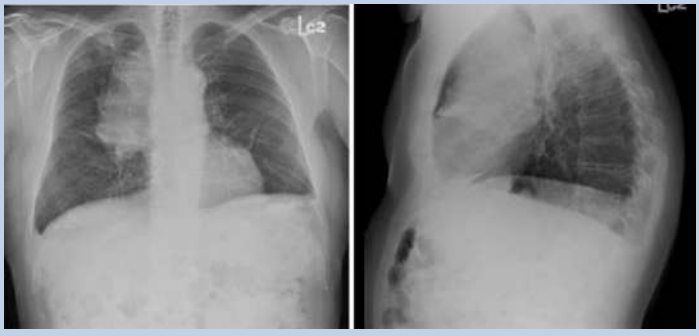


FIGURE 14-14. (Reproduced, with permission, from Kantarjian HM, et al. *MD Anderson Manual of Medical Oncology*. New York: McGraw-Hill, 2006: 239.)

What is this most likely diagnosis?

Small cell lung carcinoma is strongly suggested by the central, hilar nature of the lung mass; a significant weight loss; and a serum sodium of 119 mEq/L, as a result of syndrome of inappropriate antidiuretic hormone (SIADH) as part of the paraneoplastic process.

Which other paraneoplastic processes are associated with this condition?

Small cell lung carcinoma is known to cause hormonally mediated Cushing syndrome due to ectopic secretion of adrenocorticotropic hormone. In addition, up to 3% of patients with small cell lung carcinoma develop Lambert-Eaton myasthenic syndrome.

What additional symptoms can arise from an intrathoracic cancer?

Symptoms for tumors within the thoracic cavity derive from their location and the structures they displace or disrupt, and include superior vena cava obstruction, hoarseness of the voice due to recurrent laryngeal nerve compression, phrenic nerve palsy resulting in dyspnea, dysphagia from esophageal compression, and stridor due to tracheal compression.

To which areas does this condition commonly metastasize?

Small cell lung carcinoma is notable for its metastases to the central nervous system, liver, and bone. As a result, patients may present with bone pain, neurologic symptoms such as seizures or focal deficits, and pain in the right upper quadrant.

What is the prognosis for patients with this condition?

Untreated patients with this disease have a median survival of only 6–17 weeks. However, with combination chemotherapy, median survival may increase to up to 70 weeks. The prognosis largely depends on the tumor's reaction to chemotherapy; drugs include etoposide and cisplatin. Surgery is not an option in small cell carcinoma because of its early and highly aggressive metastasis.

CASE 19

A 55-year-old man comes to the emergency department after suddenly experiencing severe right-sided chest pain followed by profound difficulty breathing. He informs the physician that he has severe emphysema due to an extensive history of tobacco use. On physical examination, the patient is markedly tachypneic and tachycardic. His breath sounds are diminished at the right apex, and his chest wall is hyperresonant to percussion. No tactile fremitus is noted. Arterial blood gas analysis demonstrate a partial pressure of oxygen (PO_2) of 60 mm Hg and a partial pressure of carbon dioxide (PCO_2) of 50 mm Hg.

What is the most likely diagnosis?

Pneumothorax—more specifically, secondary spontaneous pneumothorax. Whereas primary spontaneous pneumothorax occurs in the absence of underlying lung disease, secondary spontaneous pneumothorax occurs in the setting of chronic lung parenchymal disruption.

What is the pathophysiology of this condition?

Spontaneous pneumothorax is most likely caused by rupture of a **subpleural bleb** (a pocket of air caused by destruction of lung parenchyma near the pleural surface), which allows air to escape into the pleural cavity. A tension pneumothorax ensues when a one-way valve is created, allowing air to progressively accumulate with each inspiration. This expanded and pressurized pleural compartment shifts and compresses other intrathoracic structures.

What diseases most often underlie this condition?

The most common underlying condition is chronic obstructive pulmonary disease. Additionally, patients with AIDS, *Pneumocystis jiroveci* (formerly *carinii*) pneumonia, cystic fibrosis, and tuberculosis are at higher risk for spontaneous pneumothorax.

What is the most common clinical presentation of this condition?

Dyspnea with pleuritic chest pain on the same side of the pneumothorax is a common presentation. Typical physical examination findings include diminished breath sounds, hyperresonance, and absent fremitus over the pneumothorax. Arterial blood gas testing typically shows hypoxia and hypercapnia.

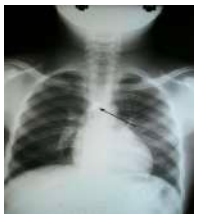
What are the typical radiologic findings in this condition?

Partial collapse of the lung on the side of the pneumothorax with a thin line parallel to the chest wall is usually visible. In a **tension pneumothorax,** tracheal and mediastinal deviation can be present away from the pneumothorax. In a **nontension pneumothorax,** however, the trachea and mediastinum will remain unchanged or shift toward the side of the collapsed lung.

What is the appropriate treatment for this condition?

For a tension pneumothorax, needle decompression at the second intercostal space at the midclavicular line is the initial treatment. Then, as with other pneumothoraces, a chest tube (thoracotomy) is placed at the fifth intercostal space at the midaxillary line. Small pneumothoraces may be treated with high concentration oxygen to facilitate nitrogen resorption and followed clinically and radiographically. In the case of repetitive pneumothoraces, parenchymal sclerosing agents such as physical and chemical irritants are used to adhere to layers of the pleura to prevent future pneumothoraces by a process called pleurodesis.

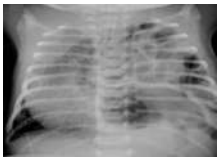
A 3-year-old boy is brought to the hospital with acute shortness of breath. He was sitting in the playground, playing with his building bricks, when his mother noticed him coughing and becoming acutely short of breath. As the boy was continuing to struggle to breathe, he was brought to the hospital. Prior to this incident he was healthy. His vaccinations are up-to-date, and he takes no medications. On X-ray of the chest, which portion of t he lung most likely to appear abnormal?



A-Left lower lobe.
B-Left upper.
C- Lingulalobe
D-Lower portion of right lower lobe
E. Right upper lobe.

- The correct answer is D..Acute shortness of breath in healthy young children is most often due to aspiration of small objects, like that indicated by the arrow in the image. The right main bronchus wider than the left and aspirated objects are more likely to lodge there. If the object is sufficiently small it may continue inferiorly into the intermediate bronchus, a common stem for the right middle lobar and inferior lobar bronchi. Because of this, aspiration pneumonia contracted when an individual is in an upright position is most common in the right lower and middle lobes. On X-ray, the right lower lobe may appear collapsed as a result of foreign object aspiration.
- A is not correct. 5°/o chose this.The left main bronchus is narrower and less vertical than the right main bronchus. The right main bronchus is more vertical and wider than the left, and aspirated objects are more likely to lodge at the junction of the right inferior and right middle bronchi.
- B is not correct. 6°/o chose this.The left main bronchus is narrower and less vertical than the right main bronchus. The right main bronchus is more vertical and wider than the left, and aspirated objects are more likely to lodge at the junction of the right inferior and right middle bronchi .
- C is not correct. 4°/o chose this .The lingula is in the left lung, and the left main bronchus is narrower and less vertical than the right main bronchus. The right main bronchus is more vertical and wider than the left, and aspirated objects are more likely to lodge at the junction of the right inferior and right middle bronchi.Bronchus lingula lung
- E is not correct. 16% chose this .When a person is supine, aspirated particles may affect the upper lobes and posterior segments of the lungs, since they become the gravity-dependent regions when a person lies flat. So if the child had aspirated a small object while lying down, it would probably be lodged in the right upper lobe instead of the lower lobe .Supine Supine position Aspirated consonant
- Bottom Line:The right main bronchus is more vertical and wider than the left, so aspirates are more likely to enter the right middle or inferior lobe if the patient is positioned vertically

A child born prematurely is in respiratory distress and is emergently intubated. Synthetic pulmonary surfactant is administered, with no improvement in pulmonary function. On auscultation, breath sounds are absent over the left hemithorax, and heart sounds are best heard to the right of the sternum. A chest X-ray was obtained and the results are shown below.What physical examination finding would support the most likely diagnosis in this child?



A-Continuous cardiac murmur
B-Marked splenomegaly
C.Thoracic bowel sounds.
D-Tracheal deviation to the left
E-Yellowish coloring to umbilical cord and nail beds

- The correct answer is C. This child suffers from a congenital diaphragmatic hernia caused by the failure of the diaphragm to properly form and close. Herniation of bowel into the thorax may cause a shift in mediastinal structures to the contralateral hemithorax, which may manifest as heart sounds best appreciated in the right hemithorax. A scaphoid abdomen may be apparent on physical exam in the supine position because abdominal contents are present in the chest. Chest auscultation on this child could also help point to this diagnosis because it is possible that bowel sounds could be heard in the chest region; the presence of bowel sounds in a lung zone indicates that abdominal contents have herniated past the boundary of the diaphragm into the thorax. The developing diaphragm is derived from the septum transversum, pleuroperitonea ! folds, body wall, and dorsal mesentery of the esophagus
- A is not correct. 8°/o chose this •A continuous cardiac murmur (ie, present during both systole and diastole) could be the consequence of a patent ductus arteriosus, but is not related to the pleuroperitonea! folds and is unlikely to cause the presentation in this patient .
- B is not correct. 4°/o chose this •Marked splenomegaly in children has many causes, but is unlikely to be consistent with the features of this vignette. Causes of splenomegaly include congenital infections and metabolic genetic disorders. Congenital infections include the ToRCHeS infections, which include Toxoplasmosis, Rubella, Cytomegalovirus, Herpesvirus/ HIV, and Syphilis. These infections often cause hepatosplenomegaly, jaundice, intellectual disability, and intrauterine growth retardation . Lysosomal storage diseases such as Gaucher disease, Niemann-Pick disease hunter syndrome and hurler syndrome also have symptoms of heptosplegmomegaly.
- D is not correct. 12% chose this •Deviation of the trachea is commonly associated with pneumothorax or space-occupying lesions of the cervical region. Mediastinal deviation can also occur with a diaphragmatic hernia, with mediastinal deviation away from the side of the herniation, almost always the left hemithorax. Therefore, we would expect deviation to the right on X-ray, not to the left, where the herniated bowel will be found . (Pneumothorax Trachea Hernia Mediastinum Diaphragmatic hernia X-ray Cervical vertebrae Gastrointestinal tract NeckE)
- E is not correct. 3°/o chose this •Meconium aspiration syndrome (MAS) can occur when fetal meconium (first stool) is passed prior to delivery instead of after delivery. Usually this is a response to fetal distress and hypoxic conditions in utero. If the meconium is expelled before delivery, the infant may have aspirated it prior to birth . As a result, the infant will present in respiratory distress immediately after delivery. The infant's skin, umbilical cord, and nail beds may show yellow or green discoloration due to staining from the expelled meconium in the amniotic fluid. Chest Xray may show patchy infiltrate or consolidation. Surfactant administration may improve outcomes .
- Bottom Line:Failure of the pleuroperitonea! folds to form leads to diaphragmatic hernias, with bowel sounds in lung zones

An infant is born to a mother with poorly controlled type II diabetes. Shortly after delivery, the infant develops tachycardia, chest wall retractions, and expiratory grunting. The medical team begins treatment presuming that the infant is not producing a substance that decreases alveolar surface tension and prevents alveolar collapse.
After acute lung injury, the cells that normally secrete this substance can regenerate. which of the following cell types:

A-Alveolar macrophages
B-.Goblet cells
C-Type I pneumocytes only
D-Type II pneumocytes only
E-Type I and type II pneumocytes

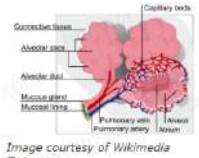
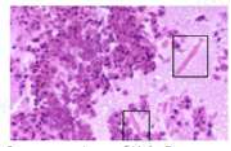


Image courtesy of Wikimedia Commons

- The correct answer is E. 55°/o chose this.This infant is lacking pulmonary surfactant. Surfactant deficiency can be seen in the setting of various conditions, including prematurity and maternal diabetes, and it gives rise to neonatal respiratory distress syndrome. Surfactant is secreted by type II pneumocytes, which are irregularly shaped or rounded cuboidal cells that form bulges off of the basal lamina layer of the alveolar epithelium. Type II pneumocytes contain lamellar bodies with surfactant, which helps to lower the surface tension in the alveoli. They are small and more numerous than type I pneumocytes, but cover less surface area and can regenerate both type I and type II pneumocytes in the setting of lung injury. Type I pneumocytes, by contrast, are simple squamous epithelial cells that line the alveoli and facilitate gas exchange. They are larger and less numerous than type II pneumocytes, but cover more surface area .The diagram illustrates the anatomic structure of an alveolus(The diagram illustrates the anatomic structure of an alveolus .)
- A is not correct. 2°/o chose this . Alveolar macrophages, known as dust cells, phagocytose debris and other irritants in the alveoli. These macrophages do not arise from type II pneumocytes, but rather from monocytes that have extravasated from blood vessels within the alveoli .
- B is not correct. 2°/o chose this .Mucus-secreting goblet cells are found only in larger bronchioles. They are not found in respiratory bronchioles or alveoli under normal conditions, and they are thus not derived from type II pneumocytes
- C is not correct. 14% chose this .Type II pneumocytes can regenerate their own population and also differentiate to give rise to type I pneumocytes.
- D is not correct. 27% chose this .Type II pneumocytes do proliferate during acute lung injury to produce additional type II pneumocytes. However, they also differentiate into type 1 cells, which are thin squamous cell, across which gas diffusion occurs .
- Bottom Line:Surfactant, secreted by type II pneumocytes, decreases surface tension in alveoli. Lack of surfactant gives rise to neonatal respiratory distress syndrome, which is commonly seen in premature infants and infants born to diabetic mothers. Type II pneumocytes can proliferate following acute lung injury, giving rise to more type II cells, in addition to type 1 pneumocytes .

A middle-aged man comes to the clinic for a physical exam. He has been in and out of work and hopes to be cleared to start work as a truck driver. He moved to the area 6 months ago after a complicated divorce. Other than some recent difficulty breathing, which he says occurred around the time when he moved to the area, he states that he has no major health concerns. A sputum sample from this patient shows a prominent infiltrate of eosinophils. Hazy whorls of mucus and rhomboid-shaped crystals are also present. Which of the following is the most likely diagnosis?



A-Asbestosis
B-Bronchial asthma
C-Chronic bronchitis
D-Cystic fibrosis
E-Lobar pneumonia

- The correct answer is B. This patient likely has bronchial asthma, a chronic inflammatory disease of the airways. Asthma can be triggered by environmental causes, so the patient's observation that he experienced increased difficulty breathing when he moved to the area is a clue here. Eosinophilia can be due to a number of disease processes, including Neoplasia, A llergic processes, Asthma, Chronic adrenal insufficiency, and Parasites (remember the mnemonic "NAACP"). If eosinophils are present in the sputum of a patient along with hazy whorls of mucus known as Curschmann spirals as well as Charcot-Leyden crystals (breakdown products of eosinophils, indicated in the image by the squares), bronchial asthma is the most likely diagnosis.
- A is not correct. 11 °/o chose this . A is not correct. 11 °/o chose this . Asbestosis is generally associated with pulmonary fibrosis and a dry , anonproductive cough.The needle chapped asbestosis fibers are typically covered with beaded deposits and are not generally recovered in sputum.
- C is not correct. 6°/o chose this . The predominant cell type seen in sputum associated with chronic bronchitis is macrophages. In an acute exacerbation, the sputum can be purulent with neutrophils and a variety of organisms .
- D is not correct. 2°/o chose this.Cystic fibrosis is associated with prominent mucus production, but eosinophils are not a characteristic feature .
- E is not correct. 4°/o chose this .A lobar pneumonia is commonly associated with rusty, purulent sputum filled with neutrophils .
- Bottom Line: Sputum of asthma patients contains eosinophils, Charcot-Leyden crystals, and Curschmann spirals .

A 1-hour-old infant who was born full-term and without complications develops cyanosis and dyspnea. Physical examination reveals absent breath sounds on the left, with bowel sounds present in the left hemithorax. Heart sounds are distant on the left but heard well on the right.
Abnormal development of which of the following would best account for this infant's presentation?

A-Mesencephalon
B-Midgut loop
C-Pleuroperitonea Folds
D-Respiratory diverticulum
E-Tracheoesophageal septum

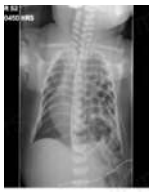
- The correct answer is C. The clinical picture presented is one of a congenital diaphragmatic hernia with pulmonary hypoplasia. When bowel protrudes up through an open diaphragm (usually on the left), the lungs cannot develop fully and the mediastinum is pushed to the right (which wou ld account for the abnormal location of this infant's heart sounds) . This occurs most commonly as a result of the pleuroperitonea! folds either failing to fuse with the other components of the diaphragm or failing to develop altogether. The diaphragm derives from four fetal structures: the Septum transversum, the Pleuroperitonea! folds, the Body wall, and the Dorsal mesentery of the esophagus. This can be remembered by the mnemonic " Several Parts Build Diaphragm. "
- A is not correct. 4°/o chose this .The mesencephalon gives rise to the midbrain, which is not at all implicated in this scenario.
- B is not correct. 8°/o chose this .The midgut loop is the precursor to a stretch of the gastrointestinal tract from the distal portion of the second part of the duodenum to the proximal two-thirds of the transverse colon. Abnormal development of the midgut loop would not account for the thoracic findings in this infant .
- D is not correct. 10% chose this. The respiratory diverticulum is an outpouching of the foregut that is the first step in the development of the respiratory system, eventually enlarging to generate the lung bud. Although the lungs are not properly developed in this scenario, it is the result of the diaphragmatic hernia and is not itself the underlying cause of the pathology. This can be deduced from the presence of bowel in the chest; this would not happen if the pathology were strictly in the development of the lungs.
- E is not correct. 6°/o chose this .Abnormal development of the tracheoesophageal septum might give rise to a tracheoesophageal fistula . I nfants with tracheoesophageal fistulas most commonly present with cyanosis and with choking and vomiting with feeding. A tracheoesophageal fistula would not account for a number of findings in this patient, including bowel loops in the thorax, dextrocardia, and pulmonary hypoplasia .
- Bottom Line:The human diaphragm is derived from four parts: the septum transversum, pleuroperitonea! folds, body wall, and dorsal mesentery of the esophagus. Congenital diaphragmatic hernias result most commonly from failure of the pleuroperitonea l folds to fuse or from absence of development of the remaining diaphragmatic components.

A 37-year-old man is brought to the emergency department after being stabbed superior to his right nipple with a knife. His blood pressure is 100/60 mm Hg, heart rate is 126/min, respiratory rate is 26/min, and oxygen saturation is 90% on 100% oxygen facemask. The wound is bubbling, and the skin immediately around the wound is moving in and out with respirations. Bilateral percussion of the chest revealed the right side to be more resonant.
Which of the following will most like tybe found on the right-side during x-ray of this patient's chest?

A-Hemothorax
B-Ninth rib fracture
C-Pleural effusion
D-Pneumothorax
E-Upper lobe consolidation

- The correct answer is D. This question requires knowledge of both the anatomy and the physiology of the sucking chest wound, as described in this patient. A penetrating wound to the chest can puncture the pleura, making an opening for air to be sucked into the pleural space. Wit h inspiration, the diaphragm descends, lowering the intrapleural pressure. If t here is a communication directly between the pleural space and the outside world, air is sucked into this negative-pressure space and collapses the lung. Pneumothorax is seen on x-ray of the chest as a collapsed lung. In tension pneumothorax, the mediastinum is shifted away from the collapsed lung due to a build up of positive pressure in t he pleural space. This finding is a medical emergency. With pneumothorax, the patient should be assessed for signs and symptoms of hemodynamic compromise. This patient, for example, is hypotensive, tachycardic, and tachypnic, and therefore requires urgent management .
- A is not correct. 14% chose this .Stab wounds to the chest can result in either a hemothorax or pneumothorax. This vignette describes a pneumothorax inju ry with the characteristic sucking chest wound (skin moving in and out with respiration) and bubbling at the wound. A hemothorax is defined as blood in the t horacic cavity and would present with blood oozing out of the wound. Additionally, percussion of a chest affected by hemothorax would be dull and not hyper-resonant as described in the stem .
- B is not correct. 1 °/o chose this .The stab wound is above the nipple, which is about the level of the fourth and fifth ribs, superior to the ninth and tenth ribs. It is possible that the man has also sustained injury to his lower ribs, but this would not be related to the knife injury and is not described in this vignette. Of note is the risk that a fractured lower rib (11th or 12th) mav puncture t he kidney, leadina to retroperitoneal bleedina.
- C is not correct. 3°/o chose this.A pleural effusion is seen on radiographs as a fluid collection in the dependent portions of the thorax. Pleural effusions can occur in heart failure, pneumonia, or iatrogenic fluid overload (eg, improper fluid management of a hospitalized patient) .
- E is not correct. 2°/o chose this .Right upper lobe consolidation would be consistent with right upper lobe pneumonia, which is not described in this vignette. One would expect to see a history of fever and other signs of infection, which is not the case here . Also, radiographs would show an uninterrupted opacity .
- Bottom Line:Air in the pleural space is known as a pneumothorax and is seen on x-ray of the chest as a collapsed lung with a mediastinum shifted away from the collapsed lung .

A neonatologist receives an emergency call from the nursery about an infant girl who just became dyspneic and cyanotic on her arrival from the delivery room. The mother of the girl never received prenatal care;however, the infant was born at 39 weeks' gestation and was the product of a normal delivery. During the physical examination, severe dyspnea and intercostal retractions are noted, as well as absent breath sounds and positive peristaltic bowel sounds in the left chest. What isthe underlying anatomic malformation that led to the development of symptoms seen in this patient?



A-Failure of the pleuroperitonea! canal (foramen of Bochdalek) to close
B-Patent ductus arteriosus
C-Persistent pulmonary hypertension of the newborn
D-Pulmonary hypoplasia
E-Transposition of the great vessels of the heart

- The correct answer is A.. Congenital diaphragmatic hernia (shown in the image) usually represents failure of the pleuroperitonea! canal to close completely, leading to protrusion of the abdominal viscera into the chest. It is usual ly located on the left side. Pulmonary hypoplasia is the most common cause of death in these patients, which develops secondary to lack of space for the lung to grow
- B is not correct. 5°/o chose this .A patent ductus arteriosus produces a left-to-right shunt. In other words, it allows blood to go from the systemic circulation to the pulmonary circulation. Therefore, pulmonary blood flow is excessive. The ductus arteriosus is normally patent during fetal life. This patency is promoted by continual production of prostaglandin E 2 by the ductus. Prostaglandin antagonism, such as maternal use of nonsteroidal anti-inflammatory medications, can cause fetal closure of the ductus arteriosus. This can be associated with severe fetal cardiovascular compromise. Normal ly, functional closure of the ductus arteriosus occurs by about 15 hours of life in healthy infants born at term. This occurs by abrupt contraction of the muscular wall of the ductus arteriosus, which is associated with increases in the partial pressure of oxygen coincident with the first breath
- C is not correct. 4°/o chose this .Persistent pulmonary hypertension of the newborn (PPHN) is failure of the normal circulatory transition that occurs after birth. It is a syndrome characterized by marked pulmonary hypertension that causes hypoxemia and right-to-left extrapulmonary shunting of blood. With inadequate pulmonary perfusion, neonates develop refractory hypoxemia, respiratory distress, and acidosis. Respiratory failure and hypoxemia in the term newborn results from a heterogeneous group of disorders, and the therapeutic approach and response often depend on the underlying disease. PPHN often results when structurally normal pulmonary vessels constrict in response to alveolar hypoxia due to hypoventilation or parenchymal disorders, such as hyaline membrane disease or meconium aspiration syndrome. However, PPHN can also occur idiopathically in the absence of underlying parenchymal disease. In these cases, the syndrome is believed to be the result of an abnormal ly remodeled vasculature that develops in utero in response to prolonged fetal stress, hypoxia, and/ or pulmonary hypertension. Excessive and peripheral muscularization of pulmonary arterioles can be seen in these cases .
- D is not correct. 20% chose this. Pulmonary hypoplasia or aplasia is part of the spectrum of malformations characterized by incomplete development of lung tissue. Pulmonary hypoplasia can result secondary to a diaphragmatic hernia, where space for lung growth is limited . The severity of the lesion depends on the timing of the insult in relation to the stage of lung development and the presence of other anatomic anomalies. The hypoplastic lung consists of a carina, a malformed bronchial stump, and absent or poorly differentiated distal lung tissue. I n more than 50% of these cases, coexisting cardiac, gastrointestinal, genitourinary, and skeletal malformations are present, as well as variations in the bronchopulmonary vasculature. Typically, in the physical examination the external chest may appear normal or may be small and bell shaped, with or without scoliosis. A mediastinal shift is observed toward the involved side, and dullness on percussion is heard over the displaced heart. I n right-sided hypoplasia the heart is displaced to the right, which may lead to a mistaken diagnosis of dextrocardia. Breath sounds may be decreased or absent on the side of hypoplasia, especially over the bases and axilla.
- E is not correct. 6°/o chose this .Transposition of the great arteries (TGA) is a cyanotic congenital heart lesion that presents in neonates. The hallmark of TGA is ventriculoarterial discordance, in which the aorta arises from the morphologic right ventricle and the pulmonary artery arises from the morphologic left ventricle. The pulmonary and systemic circulations function in parallel, rather than in series. Oxygenated pulmonary venous blood returns to the left atrium and left ventricle but is recirculated to the pulmonary vascular bed via the abnormal pulmonary arterial connection to the left ventricle. Deoxygenated systemic venous blood returns to the right atrium and right ventricle, where it is subsequently pumped to the systemic circulation, effectively bypassing the lungs. This parallel circulatory arrangement results in a deficient oxygen supply to the tissues and an excessive right and left ventricular workload . It is incompatible with prolonged survival unless mixing of oxygenated and deoxygenated and deoxygenated blood occurs at some anatomic level .
- Bottom Line :Congenital diaphragmatic hernia usually represents failure of the pleuroperitonea! canal to close completely, leading to protrusion of the abdominal viscera into the chest. Secondary pulmonary hypoplasia is the most common cause of death in these patients .

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A group of medical students is assigned to an educational outreach event at a high school summer science camp. They decide to present some basic lung anatomy as part of a broader lesson on the harmful effects of smoking on the lungs. The students present an overview of the lungs and teach the campers that each bronchopulmonary segment in the lung is supplied by a tertiary bronchus, two arteries, veins, and lymphatics.
What is the relationship of the arteries to the airway in a bronchopulmonary segment?

A-Arteries run alone in the center of the segments
B-Arteriesrun with the airways at the periphery in the intersegmental space
C-Arteries run with the airwaysin the center of the segments
D-Arteries run with the lymphaticsat the periphery in the intersegmental space
E-Arteries run with the veins in the center of the segments

- The correct answer is C..The left lung and the right lung have 8 and 10 bronchopulmonary segments, respectively. Each segment functions as a separate unit and is supplied by a tertiary bronchus and two arteries (a bronchial and a pulmonary artery, as shown in the right-hand illustration), all of which run together in the center of the segments. Veins and lymphatics drain together along the edges of the segments..
- A is not correct. 5˚/o chose this. The arteries run with the airways, not alone in the center of the segments. A way to rule out this answer choice would be to consider the function of the vasculature of the lungs- it would not make sense from a gas-exchange perspective to have the blood supply to the lungs running independently from the airways .
- B is not correct. 20% chose this.The arteries run with the airways in the center of the segments, not at the periphery. This answer choice can be ruled out with consideration to the structure and function of the lungs. It would be difficult to imagine the airways running only along the borders of the lung segments, and additionally this would probably make respiration more difficult a process if the lungs were structured this way .
- D is not correct. 12% chose this .The arteries run with the airways in the center of the segments, not with the lymphatics at the periphery. The lymphatics serve to drain toxins from the lungs, and so it follows that they would be situated at borders and drainage sites. The lungs have a vested interest in maximizing respiration, however, and in order to maximize function, the lung segments themselves need to be supplied with arteries, so the arteries run with the airways in the center of segments and branch out into the alveoli where respiration occurs .
- E is not correct. 17% chose this .The arteries run with the airways, not the veins, in the center of the segments. It can be a bit t ricky to think about and differentiate the blood supply to the lung tissue versus the blood going in to the lungs to participate in respiration. I n this case the question is asking about blood supply to the lung segments themselves. It follows that the lung segments need their own arterial blood supply to maintain activity and function, so the arteries run with the airways in each lung segment .
- Bottom Line:Each segment is supplied by a tertiary bronchus and two arteries (one bronchial and one pulmonary), all of which run together in the center of the segments. Veins and lymphatics drain together along the edges of the segments .

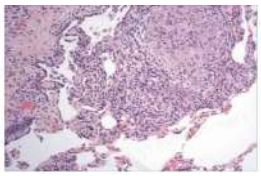
A full-term infant develops respiratory distress within the first few hours of life. Physical a barrel-shaped chest, scaphoid abdomen, and absence of breath sounds and presence the left side. X-ray of the chest is shown here.
What is the most likely cause of this patient's condition?

A-Altered development of the third and fourth branchial pouches
B-Cervical rib
C-Congenital diaphragmatic hernia
D-Dextrocardia

The correct answer is C..This child has pulmonary hypoplasia secondary to a developmental defect in the diaphragm that allows abdominal viscera to herniate into the chest. A congenital diaphragmatic hernia coincides with a critical period of lung development, and lung compression by the herniated bowel results in underdevelopment. This hypoplasia results in immediate respiratory distress following delivery. Diaphragmatic hernia usually occurs on the left side (80%-85% of the cases) due to the presence of liver on the right side. Notice in the stem image that there is no visible aerated lung on the left side but a normal appearing lung on the right side.

- A is not correct. 6˚/o chose this.This abnormality is associated with DiGeorge syndrome, which is characterized by thymic and parathyroid hypoplasia . Lung development is typically not affected.
- B is not correct. 3˚/o chose this.Cervical ribs are common and typically asymptomatic, but they may also contribute to thoracic outlet syndrome. This syndrome results in obstruction of the neurovascular bundle of the arm as it passes from the thoracocervical region to the axilla, causing vascular or neurologic symptoms.
- D is not correct. 6˚/o chose this.Dextrocardia is the presence of the heart on the right side of the body as a result of malrotation . Although associated with many other conditions (particularly Kartagener syndrome), dextrocardia alone does not contribute to pulmonary hypoplasia.
- Bottom Line:Congenital diaphragmatic hernia usually represents failure of the pleuroperitonea! canal to close completely, leading to protrusion of the abdominal viscera into the chest. Pulmonary hypoplasia is the most common cause of death in these patients.

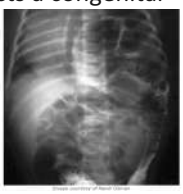
A 32-year-old African-American woman presents to her physician complaining of a cough for the past 2 months and increased shortness of breath over the past year. After completing a full physical exam, her physician orders an x-ray of the chest, which shows enlarged hilar nodes bilaterally as well as lung nodules. Results of a lung biopsy are shown in the image. Which of the following is the first-line treatment for this patient's disease?



A-Cisplatin
B-Cyclophosphamide
C-Dexamethasone
D-Hydroxychloroquine
E-Rifampin

- The correct answer is C. . This image shows noncaseating granulomas (indicated by the circle) involving lung septae Noncaseating granulomas are characteristic of sarcoidosis. Sarcoidosis is a multiorgan inflammatory disorder of unknown origin. It is thought to be immune mediated. The lung is the most frequently involved organ, but other commonly affected organs are lymph nodes, skin, eyes, kidneys, the heart, and the central nervous system. Findings that might be expected in a patient with sarcoidosis include y-Giobulinemia, Rheumatoid arthritis, elevated Angiotensin-converting enzyme levels, Interstitial fibrosis, and Noncaseating granulomas (remember the mnemonic "GRAIN"), as well as bilateral hilar lymphadenopathy in the lungs, as seen in this patient. Initial treatment of sarcoidosis includes a short course of glucocorticoids, such as dexamethasone if the patient is symptomatic. For chronic disease, glucocorticoids may be continued or alternative agents, such as methotrexate, may be used .
- A is not correct. 7˚/o chose this .Small cell lung cancer is recognized by numerous small blue neoplastic cells on histologic exam. Small cell lung cancer is treated with chemotherapy (etoposide + cisplatin) and possibly radiation . There is no survival benefit with surgery; therefore, surgery is not indicated in the treatment of small cell lung cancers. The image shows noncaseating granulomas, which are characteristic of sarcoidosis and wou ld not be treated with chemotherapy .
- B is not correct. 16% chose this.Goodpasture syndrome is caused by antibasement membrane antibodies, which can be demonstrated on immunofluorescence. It is not associated with noncaseating granulomas. Initial treatment of Goodpasture syndrome is a 5-day course of methylprednisolone followed by a long taper and maintenance. However, if the disease is particularly severe, immunosuppressive agents, such as cyclophosphamide or azathioprine, may be started.
- D is not correct. 6˚/o chose this. Systemic lupus erythematosus (SLE) can be associated with pleuritis, but it is not associated with noncaseating granulomas. Initial treatment of non-life-threatening SLE includes analgesics and antimalarials such as hydroxychloroquine. Since this patient has sarcoidosis, not lupus, hydroxychloroquine would not be the first-line treatment for her. Nonetheless, hydroxychloroquine can be used to control symptoms of sarcoidosis in patients who fail to respond to corticosteroids or develop severe side effects .
- E is not correct. 14% chose this .Tuberculosis is characterized by caseating granulomas, a type of granuloma with a form of necrosis in which diseased tissue central to the granuloma forms a firm, dry mass with cheese-like appearance. Bacteria within the granuloma may not be destroyed, but may rather be dormant only to be later reactivated . This is more likely if the patient is immunosuppressed at any time. Tuberculosis is treated with a multidrug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by a 4-month course of isoniazid and rifampin .
- Bottom Line:Sarcoidosis, a multiorgan inflammatory disorder, is characterized by noncaseating granulomas. Other findings include y globulinemia, rheumatoid arthritis, elevated levels of angiotensin-converting enzyme, and interstitial fibrosis. Initial treatment of sarcoidosis is glucocorticoids .

A 19-year-old migrant worker presents to the hospital in labor. This is her first pregnancy and she has had very little prenatal care due to work-related migration patterns and lack of reliable health insurance. Her baby is delivered vaginally, but is cyanotic at birth and struggles to breathe independently. The neonatologist begins ventillation and once the baby is stabilized, a breathing tube is inserted . Plain films are done, and the neonatology team suspects a congenital condition. The X-ray results are shown in the image below.



A-Cardiac tamponade
B-Coarctation of the aorta
C-Mediastinal shift
D-Pneumothorax
E-Pulmonary hypoplasia

- The correct answer is E.. Pulmonary hypoplasia is the most common cause of death in infants born with congenital diaphragmatic hernia. When the pleuroperitonea! folds fail to fusewith the other components of the diaphragm during development, a hole is created that allows bowel into the thorax (red circle in image). The physical compression of the bowels on the lung buds then prevents full development of the respiratory system. The blue arrows indicate the small bowel pushing the heart to the right. This compression leads to a common presentation of dyspnea and cyanosis, which, unless it can be repaired surgically, eventually leads to death.
- A is not correct.with a pericardia! effusion. This is not a common complicationCardiac tamponade is most frequently associated of congenital diaphragmatic hernia .
- B is not correct. 7˜/o chose this.Cardiac abnormalities such as ventriculoseptal defects, vascular rings, and coarctation of the aorta are associated with congenital diaphragmatic hernias; however, they are not the most common cause of death .
- C is not correct . 12% chose this .Mediastinal shift does occur in congenital diaphragmatic hernia, as the bowel invades the thorax and pushes the mediastinum to the right. However, this in itself is not a cause of death .
- D is not correct. 10% chose this .Pneumothorax is characterized by an abnormal collection of air in the pleural space, leading to collapse of the lung. It is commonly associated with trauma and other underlying disorders such as cystic fibrosis, necrotizing pneumonia, chronic obstructive pulmonary disease, etc. It is not associated with diaphragmatic hernia .
- Bottom Line:Pulmonary hypoplasia is the most common cause of deat h in infants born with congenital diaphragmatic hernia .

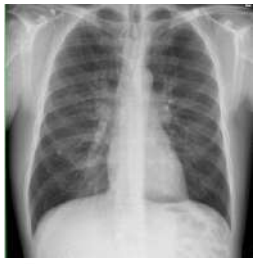
A 56-year-old intensive care unit patient develops sudden-onset dyspnea, and his oxygen saturation drops from 97% to 82%. His blood pressure is 144/89 mm Hg, pulse is 94/min, and respiratory rate is 30/min. Aportable radiograph of the chest reveals bilateral pulmonary infiltrates. His physician suspects acute respiratory distress syndrome, a condition in which a massive inflammatory response damages the alveolar endothelium.

Damage to which of the following cell types is primarily responsible for protein-rich fluid to leak into thealveoli?

A-Club (Clara) cells
B-Dust cells
C-Goblet cells
D-Pseudostratified columnar ciliated
E-Type I pneumocytes

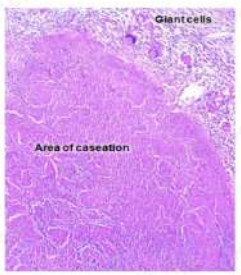
- The correct answer is E. . Acute respiratory distress syndrome (ARDS) is a clinical syndrome of acute-onset dyspnea, hypoxemia, and diffuse pulmonary infiltrates that leads to respiratory failure. It is associated with a wide range of underlying disorders, including pancreatitis. ARDS is characterized by diffuse alveolar damage, which leads to alveolar capillary permeability and protein-rich leakage into alveoli, and ultimately the formation of an intra-alveolar hyaline membrane, indicated by the arrow in the image. The alveoli are therefore the lung structures most affected by this syndrome. Although, many cell types are damaged and likely participate in the pathogenesis of ARDS, type I pneumocytes line 97% of the surface of the alveoli, and are therefore primarily involved.
- A is not correct. 15°/o chose this . Club cells are found in the terminal bronchioles, not the alveoli, where t he cytokine-mediated associated wit h ARDS occurs .
- B is not correct. 5°/o chose this . Dust cells are alveolar macrophages,which are not part of the alveolar lining .
- C is not correct. 8°/o chose this.Goblet cells extend only to the terminal bronchioles and are therefore not found in the alveoli, where the cytokine-mediated damage associated with ARDS occurs.
- D is not correct. 8°/o chose this. Pseudostratified columnar ciliated cells extend only to the respiratory bronchioles and are therefore not found in the alveoli, where the cytokine-mediated damage associated with ARDS occurs .
- Bottom Line:Type I pneumocytes line approximately 97% of the surface of alveoli of the lung and are primarily damaged by the massive inflammatory reaction in the lungs during ARDS .

A man presents for a follow up after a concerning finding on his pre-employment health screen. The patient was incarcerated recently. He is asymptomatic, and he is not HIV positive. A chest X-ray demonstrates perihilar adenopathy and a 1-cm peripheral nodule that is calcified (similar to those shown in the image). The radiologist identifies the lesion as a Ranke complex.



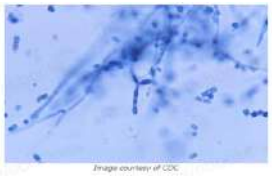
Which of the following describes the lung histology of the most likely diagnosis?

A-Abundant 2-mm foci of consolidation on gross pathology that represent caseating granulomas
B-Laminated, concentric, calcific spherules
C-Multinucleated giant cells and epithelioid cells surrounding central caseation and calcification
D-Noncaseating granuloma with nodal aggregates of epithelioid cells
E-Peroxidase-positive cytoplasmic inclusions in granulocytes
F-Poorly formed granulomas surrounded by lymphocytes, and plasma cells, in addition to epithelioid and giant cells surrounding a small artery



Courtesy of Dr. Robert W. Novak

- The correct answer is C. . A Ranke complex is the evolution of a Ghon complex, with radiographic calcification of the nodule inside the complex (shown in the vignette image). Ghon complexes evolve from Ghon foci (the incipient mass of inflammation with caseation) and represent a primary tuberculosis infection in which caseating granulomas have formed in the lung parenchyma and the hilar lymph nodes. Histologically, a caseating granuloma has multinucleated giant cells and epithelioid cells surrounding an area of central necrosis (as shown in this image).
- A is not correct. 15°/o chose this . This is a description of miliary tuberculosis, which often occurs in elderly or immunocompromised patients who have had inadequate treatment. The infection can disseminate from lung lesions through the airway, vessels, or lymph channels. Gross pathologic specimens of the lung will have numerous small foci of consolidation. These lesions can coalesce to form consolidations that may manifest clinically as a serous pleural effusion, tuberculous empyema, or an obliterative fibrous pleurisy.
- B is not correct. 10% chose this.Psammoma bodies (laminated, concentric, calcific spherules) are seen in papillary adenocarcinoma of the thyroid, serous papillary cystadenocarcinoma of the ovary, meningioma, and malignant mesothelioma.
- D is not correct. 15% chose this.Sarcoidosis can manifest with symptoms such as fever, anorexia, dyspnea on exertion, chest pain, and, rarely, bilateral hilar lymphadenopathy, so the clinical picture could be somewhat similar to this vignette. However, the diagnosis of sarcoidosis requires lung biopsy, and the hal lmark feature is noncaseating granulomas. The distinction between caseating and noncaseating granulomas is key as this distinguishes infectious (causing caseating granulomas) causes from noninfectious (causing noncaseating granulomas) causes.
- E is not correct. 4°/o chose this .Auer bodies (or rods) are peroxidase-positive cytoplasmic inclusions in granulocytes and myeloblasts. Cells containing Auer rods are seen in the blood of patients with acute myelogenous leukemia .
- F is not correct. 7°/o chose this.This is a histologic description of the lung pathology for granulomatosis with polyangiitis (formerly called Wegener). These patients have a necrotizing vasculitis affecting three organ systems : the respiratory tract, the small- to medium-sized vessels (capillaries, venules, arterioles, and arteries), and the kidneys. Patients typical ly have both renal disease and upper or lower respiratory involvement, often manifesting as pneumonitis with nodular and cavitary infiltrates. Most patients will be positive for circulating antineutrophilic cytoplasmic antibodies.
- Bottom Line:A Ghon complex is composed of a Ghon focus and associated lymph-node involvement



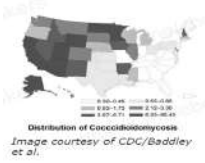
This is an image of a dimorphic soil fungus with barrel-shaped arthroconidia. If inhaled, it can infect the lungs. From there, it may enter the bloodstream and infect the skin, bones, joints, lymph nodes, adrenal glands, or central nervous system. Where in the UnitedStates is a person most likely to be exposed to this fungus?

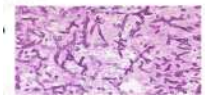
A-Anywhere (ubiquitous)

B-Mississippi, Ohio, and Missouri river valleys

C-Southern Arizona

D-Tennessee-Ohio-Mississi

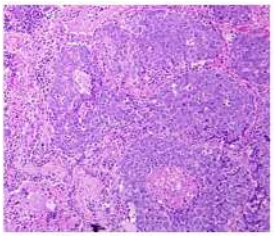




- The correct answer is C.. Coccidioidomycosis is a disease caused by the spores of the fungus Coccidioides immitis, shown in the vignette image. This fungus is endemic to the soil in California's Central Valley; southern Arizona; and parts of Utah, Nevada, New Mexico, and Texas (see map). The risk of contracting coccidioidomycosis just from traveling to the endemic regions is low; the risk of infection increases in particularly dusty settings and after major environmental events such as earthquakes. Any age group can be affected, but usually the higher-risk groups are patients over the age of 60 and immunocompromised individuals. In the image, a blue stain from cultured material shows the typical barrel-shaped arthroconidia and 90-degree branching pattern of C. immitis. Although not the classic image of spherules with endospores, it is another way C. immitis may be shown on an exam.
- A is not correct. 13°/o chose this.Aspergillus species (shown in this image) are ubiquitous molds found in organic matter. Most human illness is caused by Aspergillus fumigatus, A. niger, A. flavus, and A. c/avatus. Humans become infected through inhalation of fungal spores. Aspergillus may cause a broad spectrum of disease in the human host, from hypersensitivity reactions to direct invasion into the bloodstream. It can cause various pulmonary syndromes, including allergic bronchopulmonary aspergillosis, chronic necrotizing Aspergillus pneumonia, aspergilloma, and invasive aspergillosis .
- 8 is not correct. 33°/o chose this.Blastomyces dermatitidis is a dimorphic fungus that grows within humans as budding, round yeast-like cells. I n the mold form it possesses small spores on its hyphae. It is found in the Mississippi, Ohio, and Missouri river valleys (see map) .
- D is not correct. 15% chose this.Histoplasmosis is an infection caused by Histoplasma capsulatum, a dimorphic fungus found in soil contaminated with bird or bat droppings. Endemic areas are the Tennessee-Ohio-Mississippi river basins (see map). It usually causes acute or chronic pulmonary infections.
- Bottom Line:Coccidioides immitis, the fungus that causes coccidioidomycosis, is endemic to the soil in California's Central Valley; southern Arizona; and parts of Utah, Nevada, New Mexico, and Texas .

A 56-year-old man of the chest reveals tests show:presents with fatigue, fever, weight loss, and hemoptysis of 5 weeks' duration. Imaging a centrally located mass. Results of a lung biopsy are shown (see image). Laboratory tests show :

Sodium: 130 mEq/ L.	Potassium: 3.9 mEq/ L	Chloride: 101 mEq/ L.
Bicarbonate: 24 mEq/ L.	Calcium: 9.8 mg/ dl .	WBC count: 11,600/ mm
Hemoglobin: 12 g/ dl.	Hematocrit: 38.1%	Platelet count: 420,000/ mm 3.
Blood urea nitrogen: 8 mg/dl	Creatinine : 0.8 mg/dl	Glucose: 108 mg/dl



What is the reasoning behind the best management for this patient?

A-Surgery carries a risk of provoking para-neoplastic syndromes

B-Surgery has not been shown to improve survival.

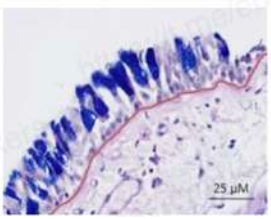
C-Surgery is palliative but not curativeon removal of the mass

D-Surgery often is curative in every lung cancer without identifiable metastases

E-This lesion is likely to regress in 7 years

- The correct answer is B. .The stem image is representative of small (oat) cell lung cancer, characterized by small, dark-blue cells known as Kulchitsky cells. The patient has hyponatremia, which can be attributed to the syndrome of inappropriate ADH secretion from a presenting para-neoplastic phenomenon, which is more common in small cell than non-small cell lung cancers. Lung cancer management initially involves distinguishing small cell from non-small cell carcinomas. Early small cell carcinoma management entails chemotherapy; early non-small cell carcinomas can be treated via surgical resection . Survival time for those with untreated small cell carcinoma is 6-17 weeks. With chemotherapy, median survival increases to 18 months
- A is not correct. 14% chose this.Surgery does not carry a risk of provoking para-neoplastic syndromes in small cell carcinoma of the lung. In pheochromocytoma, however, manipulation of the tumor during surgical resection is known to stimulate catecholamine release.
- C is not correct . 19% chose this . Surgical resection has not been shown to improve morbidity or mortality for small cell lung cancer, and is thus contraindicated because of increased and unnecessary morbidity. Resection may be more effective for non-small cell lung carcinoma . Some patients with very advanced gastrointestinal tumors benefit from surgical resection to relieve obstructive symptoms .
- D is not correct. 10% chose this.Surgical resection is more effective for non-small cell lung carcinoma. It leads to increased morbidity and no improvement in survival in patients with small cell carcinoma.
- E is not correct. 3°/o chose this.This explanation would suggest that no therapy is the best course of action, which is false. There are few masses for which nothing is done; an example is the cutaneous hemangioma seen in pediatric patients.
- Bottom Line: Small cell lung cancer is the lung neoplasm most likely to be associated with para-neoplastic syndromes such as Lambert-Eaton syndrome, para-neoplastic cerebellar degeneration, syndrome of inappropriate secretion of ADH, and Cushing's syndrome. I ntuitively it may seem obvious that removing a bulky tumor would help a patient, but surgery is not indicated in patients with small cell lung cancer, because it does not improve survival.

A 65-year-old man presents to the physician with a 4-month history of a productive cough with white sputum. He reports that he had similar symptoms last year. His FEV 1 :FVC ratio is 60%. Physical examination reveals wheezing and crackles. X-ray of the chest reveals cardiomegaly. He says that both of his children are healthy.



A lung biopsy of this patient would most likely show which of the following?

A-Air space enlargement

B-Desquamationof epithelium

C-Hyperplasia of mucus-secretingglands

D-Mucus plugs with whorls of shed epithelium

E-Smooth muscle hyperplasia

- The correct answer is C.. The patient presents with a classic case of chronic bronchitis, which is defined as a productive cough for 3 or more consecutive months in 2 or more years. Chronic bronchitis is an obstructive lung disease characterized by an FEV1 /FVC ratio < 80% . Pathology reveals both mucus-secreting gland hypertrophy (as shown in the image) and hyperplasia . These changes are reflected by the Reid index, which is the ratio of the t hickness of the mucus gland layer to t he thickness of the entire airway wal l (from end of epit helium to the start of the cartilage). The Reid index, which is normally 0.4, is increased in chronic bronchitis (>0.5) . Chronic bronchitis is associated with smoking and is an obstructive lung disease. Physical findings include wheezing, cyanosis, and lung crackles. Cor pulmonale, or right heart failure, is a common complication.
- A is not correct. 17% chose this . Air space enlargement occurs in emphysema. Like bronchitis, emphysema is an obstructive lung disease that is closely associated with smoking. Destruction of alveoli leads to enlarged air spaces. Clinical findings of emphysema include increased anteroposterior chest diameter (barrel-shaped chest), increased total lung capacity, tachycardia, and respiratory acidosis. A productive cough for 2 years in a row is more consistent with chronic bronchitis .
- B is not correct. 6°/o chose this.Bronchiectasis is also an obstructive lung disease in which bronchi and bronchioles are permanently dilated from chronic necrotizing infections that have destroyed muscle and elastic tissue. The patient typically presents with cough, fever, and production of purulent sputum, and usually will have either an infection or an obstruction in the lung. On histology, there can be inflammatory exudation, desquamation of the lining epithelium, necrotizing ulceration, and pseudostratification of the columnar cells. This patient's history and presentation is not typical for bronchiectasis.
- D is not correct. 14% chose this. Mucus plugs with whorls of shed epithelium, or Curschmann spirals, are histologic findings of asthma. Although there are variants of asthma that manifest with coughing, the cough is not typically productive. Cardiomegaly is also not associated with asthma .
- E is not correct. 7°/o chose this .Smooth muscle hyperplasia is a predominant histologic finding in asthma, which is also an obstructive disease . Cardiomegaly is not associated with asthma .
- Bottom Line:Pathologic findings of chronic bronchitis include mucus-secreting gland hypertrophy and hyperplasia .

A 40-year-old woman presents with a chief complaint of progressive dyspnea and a nonproductive cough. She has a 40-pack-year smoking history. X-ray of the chest reveals a honeycomb appearance, and a CT image shows cystic lesions. An electron micrograph of her tissue biopsy is shown. This patient's defective cells are most likely to stain positive for which of the following

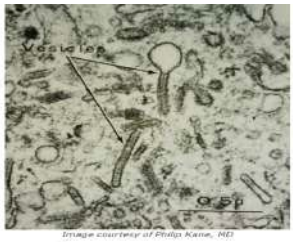


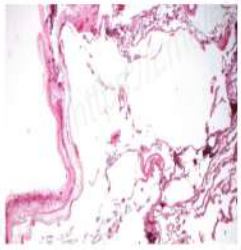
Image courtesy of Philip Kane, MD

A-CD20
B-CD30
C-CD5
D-S-100
E-TdT

- The correct answer is D.This woman has histiocytosis X, a condition characterized by the abnormal proliferation of cells of mononuclear phagocytic origin, which are called histiocytes. The histiocytes that proliferate in this condition are dendritic cells that are related in lineage to Langerhans cells (the dendritic cells of the skin), and for this reason, the disease is also called Langerhans histiocytosis. Patients with this disease can present with hepatosplenomegaly, lymphadenopathy, cystic lung and lytic bone lesions, and cutaneous eruptions. The histiocytes are stellate (dendritic) cells with an oval or irregular pale nucleus, pale cytoplasm, and characteristic cytoplasmic granules Birbeck granules). Birbeck granules are pathognomonic of Langerhans cell histiocytosis. They are said to resemble tennis rackets, as seen in the electron micrograph in the vignette. The defective dendritic cells in this disease stain positively for S-100 and CDla. Of note, Hand-Schuller-Christian disease is a pediatric variant of histiocytosis X and is associated with lytic lesions in the skull.
- A is not correct. 11% chose this.CD20 is a 8-lymphocyte marker. It can be helpful in diagnosing 8-lymphocyte-derived malignancies such as follicular lymphoma, diffuse large 8-cell lymphoma, or chronic lymphocytic leukemia.
- B is not correct. 13% chose this .CD30 is present on Reed-Sternberg cells (the characteristic cells of Hodgkin lymphoma) .
- C is not correct. 14% chose this.CDS is aT-cell marker. However, it is also a tumor marker for chronic lymphocytic leukemia (CLL) cells. CLL cells are negative for cyclin D1 and are often postive for CD23. Additionally, CDS is a tumor marker for mantle cell lymphoma, which is caused by the t(ll; 14) translocation . Mantle cell lymphomas express high levels of cyclin D1 and tend to manifest in men in their 50s and 60s as painless lymphadenopathy.
- E is not correct. 11% chose this.TdT + cells are seen in acute lymphoblastic leukemia. TdT stands for terminal deoxynucleotidyl transferase, which is a special DNA polymerase expressed in B- and T-lymphocyte precursors.
- Bottom Line:Langerhans cells contain characteristic Birbeck granules. Dendritic cells in Langerhans cell histiocytosis stain positive for S-100 and CD1a .

A 34-year-old man presents to the physician with progressive shortness of breath of several years' duration. Physical examination shows an increase in the anteroposterior diameter of the chest, hyperresonance to percussion, and diffuse wheezes. The patient is administered a combination nebulizer treatment of albuterol and ipratropium with only modest relief of symptoms. Laboratory studies are remarkable for elevated aspartate aminotransferase and alanine aminotransferase. A detailed history reveals that the patient has never smoked cigarettes or cigars, drinks one to two beers per week maximum, and has no history of illicit drug use. He has never traveled outside of the United States and works in billing. His mother is healthy, and his father died recently of liver failure.
Which of the following parts of the respiratory pathway is most affected by his disease?

A-the central acinus
B-the distal acinus
C-the entire size of the mucous glands
E-the sub pleural region



- The correct answer is C.. There are two main clinically significant kinds of emphysemas: centriacinar and panacinar. Each affects a different part of the acini, which are the approximately spherical units of the lung containing the alveoli, distal to the conducting bronchioles. Panacinar emphysema enlarges the acini uniformly from the respiratory bronchiole to the alveoli (as shown in the image) . It is associated with a deficiency of properly folded a1 -antitrypsin. Normally, ar antitrypsin is released into the bloodstream and travels to the lung, where it protects the lungs from destruction via excess protease activity. However, individuals with the PiZZ genotype have less than 15% of the normal amount of a 1 -antitrypsin and will develop panacinar emphysema at a young age. (To remember the genotype-phenotype association, think about PiZZa in the PAN !) This lack of normal a1 -antit rypsin leads to progressive and unregulated Image courtesy of Yale Rosen, lung damage by proteases. Symptoms include chronic cough and shortness of MD breath that initially occurs only upon exertion, and then gradually occurs at rest as well. These symptoms usually develop over 15-20 years and can eventually lead to respiratory failure and premature death. Additionally, as the misfolded enzyme cannot be secreted, it accumulates within the liver, which can lead to hepatocyte destruction and associated transaminitis..
- A is not correct. 12°/o chose this .entriacinar emphysema affects the central and proximal parts of the acini. It tends to occur in the upper lung lobes of heavy smokers. However, the patient does not smoke, so centriacinar emphysema is unlikely .
- B is not correct. 15% chose this.Distal acinar emphysema is also known as paraseptal emphysema . It can occur as part of COPD or independently, in which case it is usually associated with spontaneous pneumothorax in young adults. It may occur by itself or in combination with proximal acinar and panacinar emphysema .
- D is not correct. 3°/o chose this.An increase in the size of the mucous glands is a feature of bronchitis. This increase can be quantified by measuring the ratio between the thickness of the gland and the thickness of the airway wall. This ratio, the Reid index, is normal ly 0.4 or less. A value >0.5 indicates bronchitis. The primary symptom of chronic bronchitis is productive cough, which this patient does not have.
- E is not correct. 2°/o chose this.The subpleural region, between the pleural membrane and the parenchyma, is a focus of fibrosis in the case of idiopathic pulmonary fibrosis. Like emphysema, it begins with dyspnea on exertion. However, idiopathic pulmonary fibrosis usually presents later in life, between the ages of 40 and 70, and is accompanied by a dry cough.
- Bottom Line:a1 Antitrypsin deficiency manifests as panacinar emphysema in relatively young nonsmokers .

At a check-up during week 22 of her fourth pregnancy, a woman tells her doctor that she feels like she is " abnormally large" compared with prior pregnancies. The doctor agrees, and ultrasonography reveals excess fluid in the uterus. In addition, the fetus's stomach, spleen, and a portion of the small intestine are visible in the fetal thorax.
What structure(s) most likely has failed to form completely in the fetus?

A-Dorsal mesentery of the esophagus
B-Foregut
C-Lateral body wall
D-Pleuroperitonea! Folds
E-Septum transversum

- The correct answer is D. .The ultrasound reveals a congenital diaphragmatic hernia (CDH) in the fetus. The diaphragm is derived from four embryologic structures: the septum transversum, the pleuroperitonea! folds, the dorsal mesentery of the esophagus, and a muscular outgrowth of the lateral body wall. The pleuroperitonea! folds form a large portion of the fetal diaphragm; if they fail to form completely, the thorax and the abdomen are incompletely separated posterolaterally, and the abdominal contents often herniate into the thorax (known as a Bochdalek hernia). Pressure from abdominal organs results in lung hypoplasia . The polyhydramnios could result either from mechanical compression of the esophagus by the herniated viscera (most likely), and/or from the lung hypoplasia, as the lungs may offer a resorptive surface for the recycling of amniotic fluid. Newborns with CDH typically have a flat stomach and a heart displaced to the right.
- A is not correct. 7°/o chose this.The dorsal mesentery of the esophagus forms the central part of the fetal diaphragm. Postembryonically, this structure becomes the crura of the diaphragm. It is not normally defective in congenital diaphragmatic hernia.
- B is not correct. 9°/o chose this.00Although the foregut is displaced from the abdomen into the thorax in the presence of a congenital diaphragmatic hernia, its formation is normal. The foregut is the embryonic precursor to the lungs, esophagus, stomach, duodenum, liver, gallbladder, and part of the pancreas. Arterial supply to all these structures except for the lungs is from the celiac trunk.
- C is not correct. 10% chose this.Muscular outgrowths of the lateral body wall form the lateral edge of the diaphragm, bordering the left and right costodiaphragmatic recesses. These structures are not commonly defective in congenital diaphragmatic hernia.
- E is not correct. 16% chose this.The septum transversum grows out from the ventrolateral body wall and separates the heart from the liver in the embryo. Ultimately it gives rise to the central tendon of the diaphragm. However, defects in the septum transversum are rarely the cause of congenital diaphragmatic hernia.
- Bottom Line:Polyhydramnios is common with congenital diaphragmatic hernia due to failure of the pleuroperitonea! folds to form.
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Main References

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